European Journal of Internal Medicine 134 (2025) 51–58

Contents lists available at ScienceDirect

European Journal of Internal Medicine

journal homepage: www.elsevier.com/locate/ejim

Original Article

Characterization of ischemic etiology in heart failure with reduced ejection fraction randomized clinical trials: A systematic review and meta-analysis

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ARTICLE INFO

Keywords:
Heart failure
Ischemic heart disease
Randomized controlled trials

ABSTRACT

Aims: We investigated how ischemic etiology has been assigned in heart failure with a reduced ejection fraction (HFrEF) randomized controlled trials (RCTs).

Methods and results: We performed a systematic review and meta-analysis of definitions, rates of ischemic etiology and of each ischemic definition component: i) coronary artery disease (CAD), ii) myocardial infarction (MI), iii) coronary revascularization, and iv) prior/current angina. A total of 145 HFrEF RCTs were selected, of which 133 (91.7 %) enrolling both ischemic and non-ischemic patients (629 patients/study on average, median age 64.8 years and ejection fraction 28.2 %). The majority of these RCTs (84.2 %) lacked of clear ischemic etiology definition. Rate of ischemic etiology was 57.8 % (122 RCTs, 169,855 patients), of CAD 53.8 % (25 RCTs, 18,756 patients), of prior MI 46.7 % (57 RCTs, 80,582 patients), of prior revascularization 39.9 % (32 RCTs, 30,730 patients), and of prior/current angina 25.5 % (22 RCTs, 25,572 patients). In studies presenting both variables, prior MI showed the strongest correlations with assigned ischemic etiology ($\beta = 0.84$, $p < 0.0001$, 49 RCTs), followed by prior/current angina ($\beta = 0.84$, $p < 0.0001$, 20 RCTs), prior revascularization ($\beta = 0.30$, $p = 0.006$, 28 RCTs), whereas CAD had no significant correlation ($\beta = 0.29$, $p = 0.162$, from 17 RCTs). Rate of prior MI decreased over time (1986–2007: 51.4 ± 11.6 %; 2008–2016: 48.2 ± 8.8 %; 2017–2023: 41.4 ± 16.6 %; $p = 0.057$), whereas the one of prior revascularization increased (28.3 ± 11.2 %; 40.7 ± 19.6 %; 49.3 ± 19.4 %; $p = 0.048$).

Conclusions: An accurate definition of ischemic etiology is mostly lacking in HFrEF RCTs, and primarily assigned based on investigators clinical judgment, sometimes in the presence of a prior MI, although the rate of this component showed a decline over time.

1. Introduction

Heart failure (HF) is a major cause of cardiovascular (CV) morbidity and mortality in developed countries with rising prevalence due to the aging of the population, the poor control of CV risk factors, and the increased survival of patients with acute coronary syndromes (ACS) or other cardiac diseases [1]. Data suggest that the incidence of HF is mostly flat or declining but that the burden of mortality and hospitalization remains mostly unabated despite significant ongoing efforts to treat and manage HF [2]. About half of subjects with HF have a reduced ejection fraction (HFrEF), as defined by a left ventricular ejection fraction (LVEF) equal to or below 40 % [3]. Ischemic heart disease (IHD) is the most common cause of HFrEF [4,5], and the initial diagnostic work-up for newly diagnosed HFrEF aims at distinguishing between ischemic and non-ischemic etiology [3,6]. This dichotomous categorization is primarily based on patient's medical history and on the presence and extent of epicardial coronary artery disease (CAD) [5]. Nonetheless, a standardized definition of ischemic etiology of HFrEF is

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https://doi.org/10.1016/j.ejim.2025.02.004
Received 16 November 2024; Received in revised form 2 February 2025; Accepted 3 February 2025
Available online 11 February 2025
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lacking.

The recent universal definition of HF does not cover aspects related to the etiological classification of the syndrome [3]. Recent clinical consensus and scientific documents have mainly focused on diagnostic criteria for non-ischemic forms of HFrEF, such as those due to toxins or genetic mutations [4,7]. In 2021, the American College of Cardiology (ACC) and the American Heart Association (AHA) published a document on key data elements and definitions for HF, with the goal of creating a common vocabulary to be adopted both in clinical practice and in research. In this document, it is stated that an "ischemic cause of HF usually develops in the setting of significant ≥1 CAD with ≥75 % stenosis and/or in patients with history of myocardial infarction (MI) and/or history of coronary revascularization" [6]. Nonetheless, the proportion of patients enrolled in randomized controlled trials (RCTs) receiving a diagnosis of ischemic HFrEF according to each of these components is unknown. This gap limits the comparability of different studies, halts research in the field and has practical implications, since the prognosis of HF varies depending on whether it is underlaid by CAD/IHD or not. Furthermore, the distribution of these ischemic definition components has likely changed over time, considering that i) the incidence of HFrEF following an ACS is declining [8] ii) CAD is increasingly detected in the absence of an overt history of myocardial ischemia [9] and iii) the use of percutaneous coronary intervention (PCI) in HFrEF has increased over time [10].

We herein performed a systematic review and meta-analysis of definitions, rates of ischemic etiology and of each component of the ischemic definition (namely CAD, MI, coronary revascularization, and angina - see below) in RCTs in HFrEF.

2. Material and methods

2.1. Search strategy

We systematically searched MEDLINE/Pubmed for RCTs in HFrEF using the keywords and medical subject headings (MESH) "heart failure with reduced ejection fraction", OR "heart failure" AND "reduced ejection fraction", OR "HFrEF" and applying the "randomized controlled trial" filter. Moreover, we thoroughly screened the bibliographies of original research articles, guidelines, reviews, and meta-analyses to identify additional eligible studies. The search was limited to English language peer-reviewed publications and is updated to July 31, 2023.

2.2. Inclusion and exclusion criteria and study selection

Supplemental Figure 1 shows the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow diagram of the selection process. Selection of primary manuscript of RCTs with 100 or more patients per arm was performed by two independent reviewers (GA and MC), with differences resolved by consensus and involvement of a third author (PA). We excluded studies enrolling patients with post-acute MI LV systolic dysfunction (N = 9), or exclusively enrolling patients with new-onset HF (N = 3). Studies of patients with acute decompensation of chronic HFrEF were instead included (e.g. ASTRONAUT [11], ATHENA-HF [12], SURVIVE [13], PROTECT [14], REVIVE [15] and others). Studies with >30 % of the participants with HF with preserved ejection fraction were also excluded (N = 11). Ten studies out of the remaining 155 (6.4 %) were excluded at the final step of study selection because they did not contain any information on ischemic etiology or any ischemic component (namely CAD, MI, coronary revascularization, and angina - see below). Detailed lists of include and excluded studies are presented in **Supplemental Table 1** and **Supplemental Table 2**, respectively.

2.3. Data synthesis and statistical analysis

Data collection and study appraisal were performed by the same two independent reviewers (GA and MC) and revised by a third (PA), who searched throughout the whole main study manuscript, tables and figures.

Studies were categorized into three main groups (ischemic-only, non-ischemic-only, ischemic/non-ischemic) based on their enrollment criteria. Whenever available, definitions used to assign an ischemic etiology were extracted from the text. The absence of a clear definition of ischemic etiology ("no definition") and the assignment of an ischemic etiology overtly left at the judgment of study investigators ("investigator-based") were also recorded.

Rates of ischemic etiology were extracted from RCTs enrolling ischemic/non-ischemic HFrEF patients, either from the main table or from the text of the manuscript, regardless of the availability of an ischemic HF definition. Rates of each component of the definition of ischemic etiology were also extracted using the same methodology whenever provided in the original source publication. Data availability is shown in **Supplemental Figure 2** and discussed in the Results and Discussion section. The presence of CAD was generally reported as "CAD", "known CAD", or "history of CAD", whereas a history of MI as "history of/prior MI" or "history of/prior ACS". Angina was usually reported either as current, prior or a combination of the two; we combined these features in a unique "prior/current angina" variable. Finally, rates of coronary revascularization procedures were variably reported as "any prior revascularization", "prior PCI", "prior coronary artery bypass grafting (CABG"), or a combination of "prior PCI and/or CABG". For the sake of convenience and practical feasibility, these variables were incorporated into a single cumulative variable named "prior revascularization" using either i) the rate of "any prior revascularization" in the manuscript, or ii) the sum of the rate of "prior PCI" and of "prior CABG" when both were available, or iii) the percentage of either "prior PCI" or "prior CABG" when only one was reported.

The following study and patient characteristics were also extracted from the original source publication: i) year and journal of main study publication and drug/procedure/device under investigation, ii) study sample size and characteristics of the treated-arm study population (age, LVEF, proportion of male sex, frequency of diabetes, hypertension, and hyperlipidemia).

Means and percentages were obtained from the treatment group, under the assumption that they were similar in the control one by virtue of the randomization process.

Since most variables were normally distributed at Shapiro-Wilk test, aggregate data were reported as mean with standard deviation. Age and LVEF had non-normal distribution, hence sensitivity analysis using median with 25th and 75th interquartile range were performed.

Publication bias was assessed using Funnel plots and Egger's test (see **Supplemental Figure 3**, p value for Egger's test = 0.032). Heterogeneity was assessed by Higgins and Thompsons' I^2 statistic, with <25 %, 25–50 % and >50 % I^2 suggesting low, moderate or high heterogeneity, respectively. A significant heterogeneity was confirmed (I^2 for heterogeneity = 98.8 %). Based on heterogeneity, a random effects model was used. We used restricted maximum likelihood random effects models to analyze the prevalence of ischemic etiology and of each components of the ischemic etiology definition.

To understand the relative contribution of the different components of the ischemic HF definition (i.e. CAD, prior revascularization, prior MI, prior/current angina), we firstly estimated the difference between the rate of ischemic etiology and the rate of each ischemic definition component reported in each study. Significance of differences between continuous variables was tested with T test or non-parametric Mann-Whitney test. We subsequently used a meta-regression model to investigate the relationship between the rate of ischemic HF and the rate of each ischemic definition component reported in each study. Values of beta coefficient and R-squared were attained and correlation plots were generated. To investigate the association of CV risk factors with ischemic etiology and with each ischemic definition component, we performed multiple separate meta-regression analyses selecting ischemic etiology

and each ischemic definition component as outcome prevalence variable and each CV risk factor as independent variable.

As a sensitivity analysis, we investigated the temporal trends in the rate of ischemic etiology and each component of the ischemic definition by dividing the selected studies in three temporal periods including a similar number of RCTs per period. Differences in time in clinical characteristics, ischemic etiology and ischemic definition components were evaluated for parametric and non-parametric variables with ANOVA and Kruskal-Wallis tests, respectively. Likelihood test was used to underline differences comparing a regression model with and without interactions of time with ischemic etiology rate and ischemic definition component rates. Statistical analysis was performed using STATA/SE 18.0.

3. Results

A total of 145 HFrEF RCTs conducted between 1986 and July 2023 were included in the final database. **Supplemental Figure 1** shows the flow diagram of the selection process and **Supplemental Table 1** provides a detailed list with references of the included studies. Nine studies (6.2 %) enrolled only patients with ischemic HF and 3 studies (2.1 %) enrolled only patients with non-ischemic HF. The remaining 133 studies (91.7 %) enrolled both ischemic and non-ischemic patients. Most studies tested a pharmacological medical intervention (N = 92, 63.4 %), others tested a procedure (N = 23, 15.9 %) or a device (N = 30, 20.7 %).

Definitions of ischemic etiology. Most studies enrolling either ischemic-only or non-ischemic-only HFrEF patients had a definition of ischemic etiology within their inclusion/exclusion criteria (**Supplemental Table 3**). On the contrary, a definition of ischemic etiology was given for only 12 (9.0 %) of the 133 studies that enrolled both ischemic and non-ischemic HFrEF patients, (**Supplemental Table 3**). In another 9 studies (6.8 %) the definition of ischemic HFrEF was investigator-based (ALOFT [16], TIME-CHF [17], CORONA [18], PARADIGM-HF [19], DAPA-HF [20], EMPEROR-Reduced [21], BLOCK-HF [22], CHARM-Added [23], CHARM-Alternative [24]). The remaining 112 (84.2 %) studies did not have a definition of ischemic etiology published in their article.

Characteristics of study populations. The 133 ischemic/non-ischemic RCTs enrolled a median of 629 patients per study (min 201, max 8399), with a median age of 64.8 years, a median LVEF of 28.2 %, a 73.3 % prevalence of male subjects, a 36.1 % of diabetes, a 62.3 % of hypertension, and a 58.0 % of dyslipidemia (Table 1). A comparison of these studies characteristics with those who enrolled either ischemic-only or non-ischemic-only HFrEF patients is presented in Table 1. Ischemic-only studies enrolled older populations with greater prevalence of male subjects and CV risk factors as compared to general ones, whereas non-ischemic-only studies had opposite characteristics. Lower LVEF values were found in studies of non-ischemic-only patients (Table 1).

When analyzing studies including both ischemic and non-ischemic patients, no clear relationship was found between the rate of ischemic etiology (or of each component of the ischemic definition) and age, sex, traditional CV risk factors and LVEF (**Supplemental Table 4**).

Ischemic etiology and ischemic definition components data availability and prevalence. **Supplemental Figure 2** shows the number of studies out of the initial 133 ischemic/non-ischemic RCTs with available information regarding the rate of ischemic etiology (N = 122, 91.7 %), of CAD (N = 25, 18.8 %), of prior MI (N = 57, 42.9 %), of prior revascularization (N = 32, 24.1 %), of prior/current angina (N = 22, 16.5 %), and the availability of different combinations of these variables. Fig. 1 and Table 1 present the prevalence of ischemic etiology and of each ischemic definition component in these studies. In aggregate, ischemic HF was reported in 57.8 % of patients, CAD in 53.8 %, prior MI in 46.7 %, prior revascularization in 39.9 %, and prior/current angina in 25.5 %.

Differences and correlations between ischemic etiology and ischemic definition components. In studies that presented both the rate of ischemic etiology and the rate of at least one ischemic definition component, the former was always higher than the latter, as expected. Compared to the rate of ischemic etiology, the percentage of CAD was 5.2 % lower (N = 17), of prior MI was 10.1 % lower (N = 49), of prior revascularization was 20.0 % lower (N = 28), and of prior/current angina was 32.3 % lower (N = 20) (Fig. 2).

Fig. 3 shows the correlations between rates of ischemic etiology and rates of each component of the ischemic definition. Rate of ischemic etiology had the strongest and most significant correlation with rate of prior MI (β=0.84, R-sq = 74.6 %, N = 49, $p < 0.0001$), followed by with rate of prior/current angina (β = 0.84, R-sq = 42.7 %, N = 20, $p < 0.0001$) and of prior revascularization (β = 0.30, R-sq = 20.3 %, N = 28, $p = 0.006$). There was a non-significant correlation with the rate of CAD (β = 0.29, R-sq = 6.1 %; N = 17, =0.162), although the contemporary availability of rate of ischemic etiology and rate of CAD was limited to 17 studies. Correlations among rates of each ischemic definition components are reported in **Supplemental Table 4**.

Temporal trend analysis. A definition of ischemic etiology was more frequently detailed in older than more recent HFrEF studies, in which either no definition or an investigator-based definition prevailed (**Supplemental Figure 4**). The rate of ischemic etiology showed a non-significant decline with time (1986–2007: 58.9 ± 9.4 %; 2008–2016: 59.8 ± 10.7 %; 2017–2023: 53.9 ± 14.6 %; $p = 0.081$) (Fig. 4,

Table 1
Characteristics of HFrEF study populations included in the analysis by ischemic/non-ischemic status at study enrollment.

	RCTs enrolling both ischemic and non-ischemic HFrEF (133 RCTs, 178,907 patients)	RCTs enrolling ischemic HFrEF only (9 RCTs, 25,957 patients)	RCTs enrolling non-ischemic HFrEF only (3 RCTs, 3228 patients)	P value
Sample size (median, min, max)	629 (201–8399)	1212 (259–10,917)	787 (458–1654)	0.175
Age (years)	64.8 ± 4.5 (*n* = 132)	66.4 ± 3.7 (*n* = 9)	61.0 ± 4.2 (*n* = 2)	0.289
Male (%)	73.3 ± 9.6 (*n* = 126)	85.0 ± 5.5 (*n* = 9)	73.0 ± 0 (*n* = 2)	0.026
Hypertension (%)	62.3 ± 15.9 (*n* = 80)	63.7 ± 8.9 (*n* = 8)	33.0 (*n* = 1)	0.263
Diabetes (%)	36.1 ± 12.5 (*n* = 101)	35.4 ± 4.6 (*n* = 9)	20.5 ± 3.5 (*n* = 2)	0.125
Dyslipidemia (%)	58.0 ± 15.4 (*n* = 23)	78.0 (*n* = 1)	–	0.0001
LVEF (%)	28.2 ± 4.3 (*n* = 124)	29.5 ± 3.7 (*n* = 8)	22.3 ± 2.3 (*n* = 3)	0.039
Ischemic etiology (%)	57.8 ± 11.8 (*n* = 118)	100 (*n* = 7)	–	0.0001
CAD (%)	53.8 ± 12.2 (*n* = 25)	100 (*n* = 4)	–	0.0001
Prior MI (%)	46.7 ± 13.4 (*n* = 57)	81.0 ± 17.5 (*n* = 9)	–	0.0001
Prior revascularization (%)	39.9 ± 18.9 (*n* = 32)	47.5 ± 31.5 (*n* = 8)	–	0.364
Prior/current angina (%)	25.5 ± 12.8 (*n* = 22)	61.0 ± 23.4 (*n* = 3)	–	0.0001

Data are reported as mean and standard deviation. RCTs = randomized controlled trials; pts = patients; "*N*=" represents the number of studies from which the data were calculated. HFrEF = heart failure wih reduced ejection fraction; LVEF = left ventricular ejection fraction; CAD = coronary artery disease; MI = myocardial infarction.
tion fraction; CAD = coronary artery disease; MI = myocardial infarction.

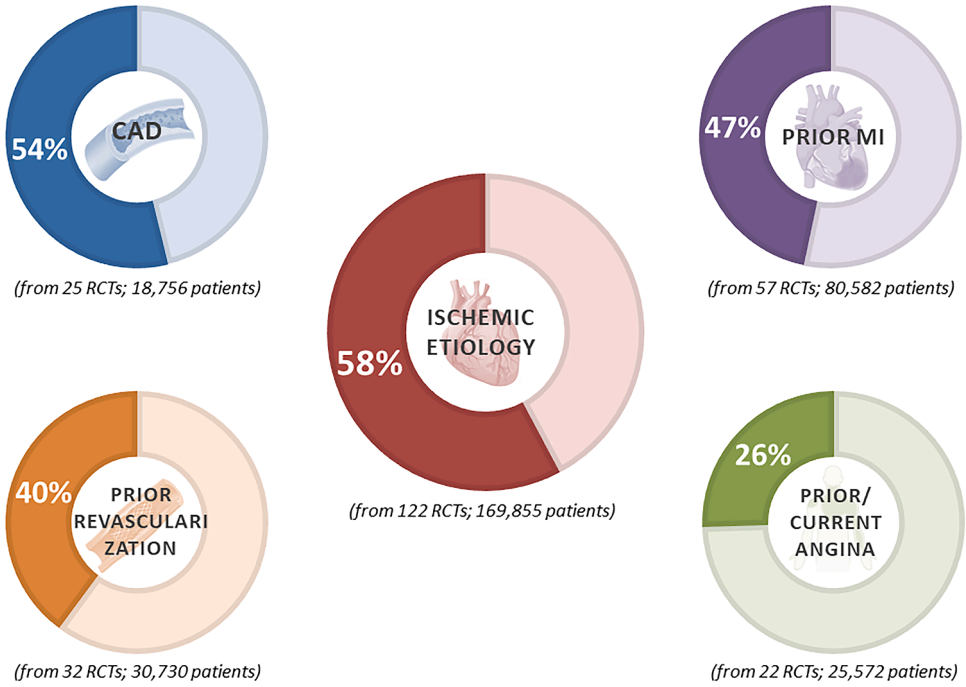

Fig. 1. Prevalence of ischemic etiology and its components in RCTs including both ischemic and non-ischemic HFrEF patients.
RCTs = randomized controlled trials; HF = heart failure; CAD = coronary artery disease; MI: myocardial infarction.

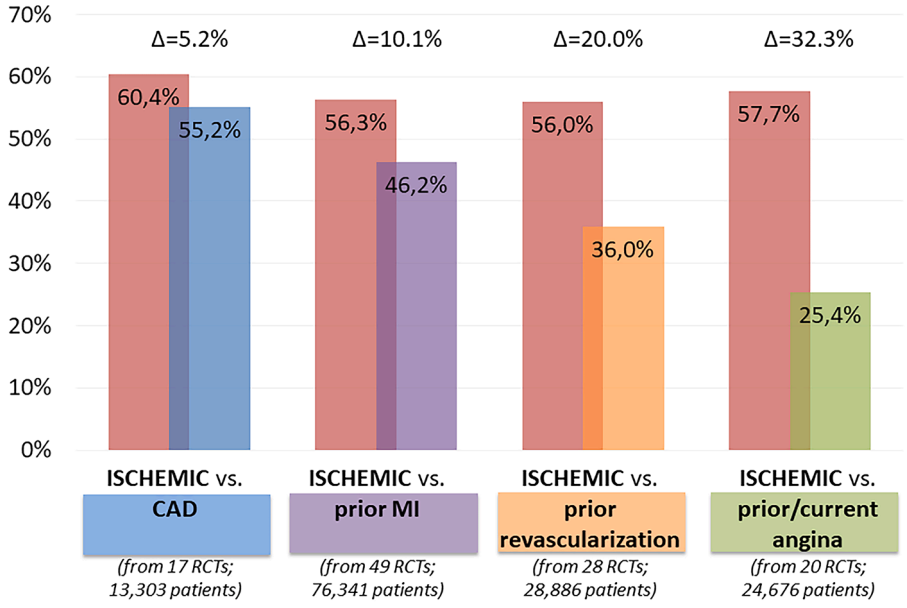

Fig. 2. Prevalence of ischemic etiology and of each ischemic definition component in RCTs reporting both these variables.
RCTs = randomized controlled trials; CAD = coronary artery disease; MI: myocardial infarction. Δ represents the difference obtained by subtracting the rate of each ischemic component from the rate of ischemic etiology in the indicated HFrEF RCTs in which both these values were available.

Supplemental Table 5). The rate of CAD was found substantially stable over time, although somehow higher in the years 2008–2016 (1986–2007: 51.2 ± 14.5 %; 2008–2016: 57.0 ± 8.3 %; 2017–2023: 51.9 ± 14.8 %; $p = 0.59$). Interestingly, the rate of prior MI decreased over time (1986–2007: 51.4 ± 11.6 %; 2008–2016: 48.2 ± 8.8 %; 2017–2023: 41.4 ± 16.6 %; $p = 0.057$), whereas the one of prior revascularization increased over time (1986–2007: 28.3 ± 11.2 %; 2008–2016: 40.7 ± 19.6 %; 2017–2023: 49.3 ± 19.4 %; $p = 0.048$), surpassing that of prior MI in the late time period 2017–2023 (Fig. 4).

4. Discussion

Our present analysis shows that a definition of ischemic etiology is mostly lacking in manuscripts of RCTs in HFrEF patients published over the last 40 years, and especially in those published most recently. It also shows that about 58 % of patients enrolled in these HFrEF RCTs are categorized as ischemic, and that this etiology is primarily assigned based on the clinical judgment of study investigators. This approach does capture a subpopulation enriched for features associated with IHD, such as older age, male sex and prevalent CV risk factors. We also

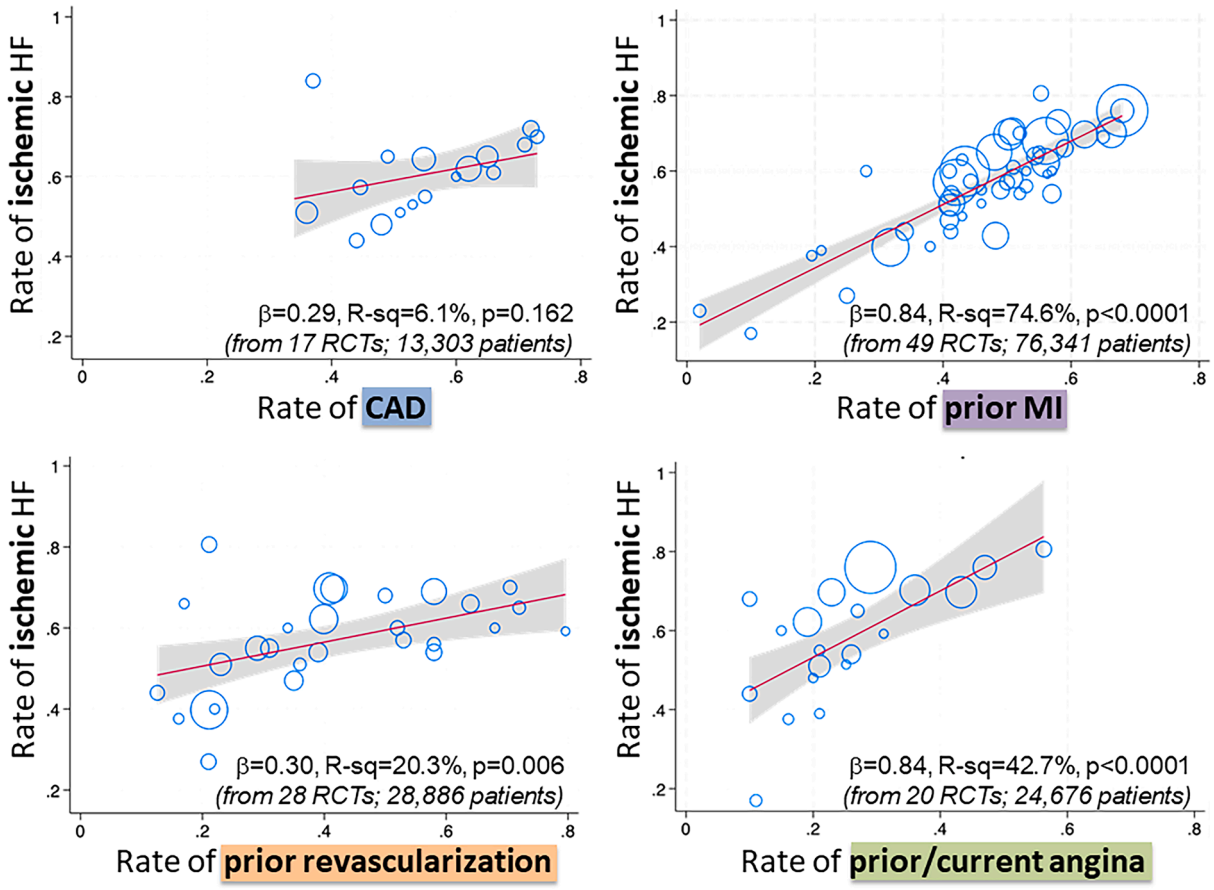

Fig. 3. Relationships between ischemic etiology and each ischemic component in RCTs reporting both these variables.
Each panel shows the relationship between the rate of ischemic etiology and the rate of each ischemic component in studies where both these variables were simultaneously reported (see data availability plot showed in Supplemental Figure 2). These relationships were used to suggest how much a determinate component has been considered for the assignment of an ischemic etiology of HF.
RCTs = randomized controlled trials; HF = heart failure; CAD = coronary artery disease; MI: myocardial infarction.

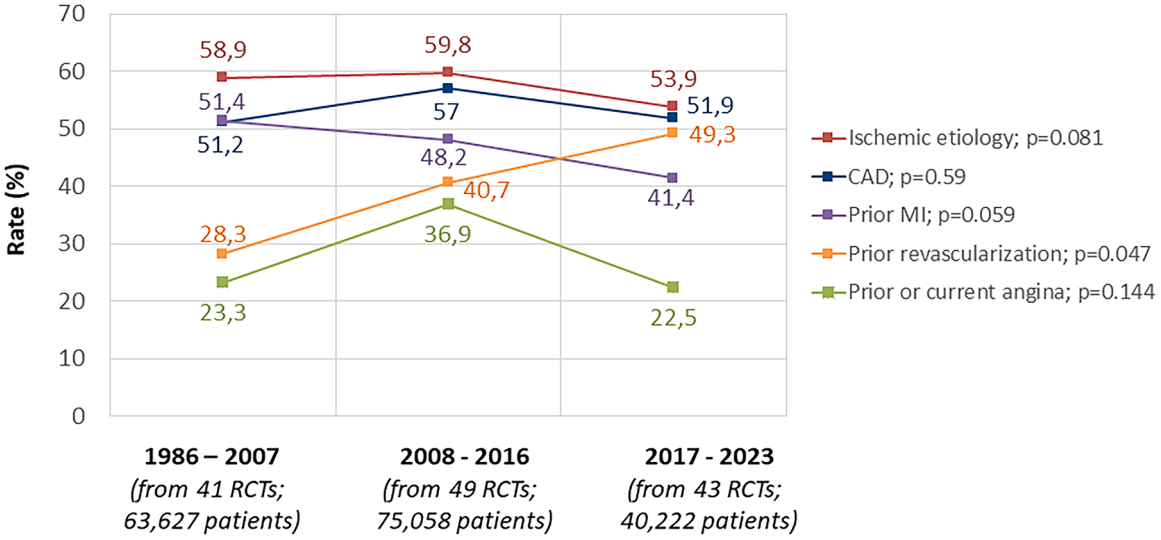

Fig. 4. Temporal trend in the rate of ischemic etiology and each ischemic definition component.
RCTs = randomized controlled trials; CAD = coronary artery disease; MI: myocardial infarction.

demonstrate that the frequency of the ischemic definition components possibly leading to the assignment of an ischemic etiology is variable across RCTs and only partially related to the frequency of ischemic etiology. In particular, we show a strong direct correlation of assigned ischemic etiology with prior MI but a modest one with prior revascularization, which is notable since the proportion of patients with a

history of MI has decreased and with a history of coronary revascularization has increased over time in HFrEF RCTs [9,11]. The rate of CAD, another common criterion to identify HF as ischemic, is even not associated with the rate of reported ischemic etiology in HFrEF RCTs.

Traditional binary classification assign an ischemic etiology to HF based on the presence of i) a coronary vessel stenosis ≥75 % and/or ii) a history of MI and/or iii) a history of coronary revascularization [6,25]. Very few HFrEF RCTs included in our meta-analysis enrolling both ischemic and non-ischemic patients report a definition of ischemic etiology (summarized in Supplemental Table 3), which largely refers to these traditional criteria. Studies enrolling only ischemic or only non-ischemic patients provide more detailed definitions. For example, in some ischemic-only HFrEF RCTs (e.g. MADIT II [26] and COMMANDER-HF [27]), a diagnosis of prior MI was required and had to be reinforced by the presence of pathological Q waves at ECG and/or evidence of wall motion abnormalities at imaging. Some ischemic-only HFrEF RCTs also included in their definition CAD amenability to either percutaneous or surgical revascularization as a standalone criterion for classifying HF as ischemic (e.g. STICH [28] and REVIVED-BCIS2 [29]). Surprisingly, little effort has been done to improve the method for classifying ischemic vs. non-ischemic HF, and traditional criteria proposed >20 years ago are still used as reference at present [6,30]. This has determined a great heterogeneity and inconsistency in the assignment of ischemic HF etiology in clinical research and, thereby, guidance documents and clinical practice [25]. Out of a total of 145 HFrEF RCTs published over the last 40 years and examined here, almost 90 % left the assignment of an ischemic HF etiology to the judgment of the study investigators. Furthermore, despite the absence of clear definition for uniformly categorizing patients with ischemic HF, some of these RCTs tested interactions for ischemic vs. non-ischemic etiology or performed sub-group analyses by ischemic etiology (e.g. amongst the most recent, VICTORIA [31], PARADIGM-HF [19], DAPA-HF [20], EMPEROR-Reduced [21]).

Our meta-analysis suggests that prior MI is the item mostly relied upon by trial investigators to define HFrEF as ischemic. MI is considered the primary clinical intermediate between CAD and HF [30,32]. However, the number of patients developing HF after an acute MI has been decreasing with time [8,33], due to the earlier diagnosis and treatment of MI patient with wider availability of increasingly sensitive troponin biomarker and PCI. On the other hand, the use of PCI in chronic HFrEF has increased over time due to the improvement in outcomes demonstrated in numerous observational studies [10]. In accordance with these observations, our temporal analysis shows a progressive significant reduction in the rate of prior MI and an increase in the rate of coronary revascularization reported in HFrEF RCTs (Fig. 4). This trend in the rate of coronary revascularization will likely change due to the failure of recent RCTs investigating myocardial ischemia or viability testing for revascularization treatment guidance in HFrEF [34]. In particular, the very recent trial REVIVED-BCIS2 testing PCI in HFrEF patients with extensive CAD amenable to PCI and demonstrable myocardial viability failed to demonstrate a benefit of PCI on survival and HF hospitalization [29], marking a turning point in the use of coronary revascularization in this setting.

The rate of CAD was not associated with the rate of reported ischemic etiology in HFrEF RCTs, despite CAD having the highest rate of all the ischemic definition components (54 % in 25 RCT reporting this variable) and the lowest difference with the rate of ischemic etiology (5.2 % in 17 HFrEF RCTs reporting both these variables, Fig. 2). Overall, this suggests that investigators do not consider the simple presence of CAD as a sufficient criterion to assign an ischemic etiology. Extension and severity of CAD become of greater importance, particularly in the absence of a history of MI or coronary revascularization. In a single-center retrospective analysis from Duke University Medical Center published >20 years ago, considering patients with single-vessel CAD not involving the left main or the proximal left anterior descending artery as non-ischemic rather than ischemic resulted in better prognostication [25]. On the same line, recent non-ischemic HFrEF RCTs also enrolled patients with CAD "if the extent of CAD was not considered to be sufficient to account for the reduced LVEF (e.g. DANISH [35] and AMIOVIRT [36])".

Prevalence of CAD was estimated 62 % in a previous summary analysis including 24 HF RCTs from 1986 to 2005 [37], while it was found 53 % in our present systematic meta-analysis including 25 carefully selected HFrEF RCTs from 1986 to 2023 reporting this component of the ischemic definition. These percentages are probably an underestimate of the true prevalence of CAD among unselected HF patients, one of the reasons being the absence of systematic CAD investigation in the majority of these studies. Data from a large administrative claims American database from 2004 to 2019 showed that CAD testing was performed in only about half of patients presenting with a first diagnosis of HFrEF [38], with higher rates found in the years 2011–2016 from before to after STICHES publication [28]. Similar rates of CAD testing were found when analyzing 17,185 new-onset HF patients hospitalized from 2009 to 2015 and enrolled in the Get With The Guidelines–Heart Failure registry, with higher rates found in HFrEF vs. HFpEF (53 % vs. 31 %) [39]. This scenario will likely change in the near future. Indeed, most recent guideline documents recommend performing CAD testing through non-invasive modalities, particularly coronary computed tomography [4,5], and this will likely represent a significant advancement in our understanding of the prevalence and significance of CAD in HF in the next future. Nonetheless, significant geographical variations in the rates of CAD in HFrEF will probably remain. For example, in the ASCEND-HF trial (included in the present meta-analysis), CAD was found being more prevalent in Central/Western Europe and North America vs. Asia/Pacific and Latin America, but previous PCI being most common in North America and Western Europe vs. other regions despite the latter had similar prevalence of CAD and previous MI [40]. These regional differences in the diagnostics of ischemic HF need to be considered in the context of the progressive globalization of HF clinical trials [41]. In spite of the presence of well-defined enrollment criteria, geographic variations in patient characteristics and event rates have been shown in several RCTs (see for example the recent PARADIGM-HF trial [42]), sometimes with important consequences on treatment effects (as exemplified by the TOPCAT trial experience [43]). These aspects further hamper the adoption of a uniform definition for ischemic HF in RCTs.

Given the lack of a standard definition of ischemic HF in relevant RCTs, one could question the validity of the results of some HFrEF RCTs testing therapeutic interventions with anticipated benefit in patients with IHD. For example, statins are of proven benefit in CAD patients, and HF patients with CAD are also expected to benefit from statins. Surprisingly, the efficacy of statins in ischemic HF was not confirmed in subgroup analysis of the GISSI-HF [44] or in the CORONA study enrolling exclusively ischemic HFrEF patients [18]. Notably, in both these studies, ischemic HF etiology was assigned by study investigators without specific criteria or definitions. It is possible that other unknown or unmeasured confounders beyond ischemic etiology are responsible for these unexpected findings. Even so, in real world statins are prescribed in more than half of HF patients [45] and recommended by guidelines in patients with HF who have other indications for their use, among which is CAD [4]. In contrast to the abovementioned results with statins, the DANISH trial represents an excellent example of the importance of deep phenotyping ischemic HFrEF patients. Initial meta-analysis that supported the beneficial effect of ICD implantation on the survival of patients with both ischemic and non-ischemic HF used data from RCTs with scarce definition of the HF etiology [46]. The DANISH trial enrolled non-ischemic HFrEF patients who underwent a systematic exclusion of ischemic HF etiology (i.e. all patients underwent specific testing, including 97 % coronary angiography, see Supplemental Table 3). The trial showed a non-significant impact of ICD implantation on survival in this carefully selected non-ischemic HFrEF population [35].

5. Study limitations

The present analysis has limitations that should be acknowledged.

Detailed definitions of ischemic etiology were collected, when reported, searching the methodology study section of manuscripts published in the medical literature. It is possible that detailed standard operative procedure for the assignment of ischemic HF etiology were given in the main study protocol available to each study center/investigator, but not included in the final study publication.

All analyses were study-level and only the rates of some components of the ischemic HF definition were available in most cases (see Supplemental Figure 3 for data availability details). Nevertheless, a meta-analysis limited to RCTs reporting simultaneously all four components of the ischemic definition (i.e. CAD, prior MI, prior revascularization, prior/current angina) would have included only a hand of studies and become irrelevant. Similarly, very few (if none) RCTs included in our work reported detailed information regarding extension and severity of CAD, type and extent of prior MI and prior revascularization, frequency of angina, use of imaging (particularly echocardiography and/or cardiac magnetic resonance imaging) to strengthen a diagnosis of ischemic HFrEF. Thus we could not investigate any relationship between these variables and their contribution to the definition of ischemic etiology. According to the goals of our analysis, we used main study manuscripts as a primary source of data and discarded secondary manuscripts with post-hoc analyses; thus we did not perform a prevalence meta-analysis stratified by ischemic/non-ischemic HF. Selecting only RCTs providing patients' characteristics and outcomes by ischemic/non-ischemic etiology would have significantly limited the number of included studies and altered the design of our main analysis. We acknowledge that IHD is emerging as an important risk factors for HFpEF [47], but this setting was out of the scope of the present analysis. On the other hand, we could not estimate the percentage of patients with HF with mildly-reduced EF (HFmrEF) that accidentally fell into our analysis. HFmrEF has been recognized only recently as a separate entity from HFrEF and HFpEF [4], and resembles HFrEF rather than HFpEF with regard to both a higher prevalence of IHD and a greater risk of new IHD events [48].

6. Conclusions

In conclusion, defining ischemic etiology of HFrEF represents a challenge, which in the case of HFrEF RCTs has been largely left at the judgment of study investigators. A standardization of ischemic etiology definition is needed, and should be achieved by detailing its components, in particular the presence and severity of CAD and a history of MI and/or coronary revascularization. A more rigorous characterization of ischemic HFrEF patients is expected to improve the design of future RCTs, the allocation of therapeutic interventions to the right patients and, eventually, clinical care in HFrEF.

Funding

The author(s) received no financial support for the research, authorship, and/or publication of this article.

Conflict of interest

MC received speaker and advisor fees in the last 2 years from Akcea Therapeutics, Alnylam, Amicus Therapeutics, Astrazeneca, Boehringer Ingelheim, Boston Scientific, Bristol-Myers Squibb, Novartis, Pfizer, Sanofi and Sanofi Genzyme, Takeda and two investigator-initiated grants from Pfizer.

PA received speaker and/or advisor fees in the last 2 years from Astra Zeneca, Boehringer-Ingelheim, Bayer, Daiichi-Sankyo, MSD and Janssen, and travel support from Daiichi-Sankyo.

All other authors have no disclosures directly related to the content of this work.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.ejim.2025.02.004.

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