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SYSTEMATIC REVIEW AND META-ANALYSIS

Cancer Mortality in Trials of Heart Failure With Reduced Ejection Fraction: A Systematic Review and Meta-Analysis

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BACKGROUND: The burden of cancer in heart failure with reduced ejection fraction is apparently growing. Randomized controlled trials (RCTs) may help understanding this observation, since they span decades of heart failure treatment.

METHODS AND RESULTS: We assessed cancer, cardiovascular, and total mortality in phase 3 heart failure RCTs involving ≥90% individuals with left ventricular ejection fraction <45%, who were not acutely decompensated and did not represent specific patient subsets. The pooled odds ratios (ORs) of each type of death for the control and treatment arms were calculated using a random-effects model. Temporal trends and the impact of patient and RCT characteristics on mortality outcomes were evaluated by meta-regression analysis. Cancer mortality was reported for 15 (25%) of 61 RCTs, including 33 709 subjects, and accounted for 6% to 14% of all deaths and 17% to 67% of noncardiovascular deaths. Cancer mortality rate was 0.58 (95% CI, 0.46–0.71) per 100 patient-years without temporal trend (P=0.35). Cardiovascular (P=0.001) and total (P=0.001) mortality rates instead decreased over time. Moreover, cancer mortality was not influenced by treatment (OR, 1.08; 95% CI, 0.92–1.28), unlike cardiovascular (OR, 0.88; 95% CI, 0.79–0.98) and all-cause (OR, 0.91; 95% CI, 0.84–0.99) mortality. Meta-regression did not reveal significant sources of heterogeneity. Possible reasons for excluding patients with malignancy overlapped among RCTs with and without published cancer mortality, and malignancy was an exclusion criterion only for 4 (8.7%) of the RCTs not reporting cancer mortality.

CONCLUSIONS: Cancer is a major, yet overlooked cause of noncardiovascular death in heart failure with reduced ejection fraction, which has become more prominent with cardiovascular mortality decline.

Key Words: cancer ■ comorbidities ■ heart failure ■ mortality

In the past years, analyses of community-based cohorts in the United States,[1,2] Europe,[3] and Japan[4,5] highlighted a higher frequency of newly diagnosed cancer in subjects with heart failure (HF), as compared with those without HF. Although residual confounding cannot be excluded, these studies indicated an increased incidence of cancer in patients with HF, even after taking into account shared risk factors and cardiovascular medications. Furthermore, the higher rate of cancer diagnosis in individuals with HF did not appear to result from a surveillance bias, that is, a higher likelihood of tumor detection secondary to increased medical attention for subjects with HF.[3] Mortality of patients with HF and cancer was also reported to be increased.[1–5] The association with cancer was primarily observed in HF with reduced left ventricular ejection fraction (HFrEF) and was consistent for most common cancer types.[1,3] This epidemiologic evidence is strengthened by preclinical data indicating that the failing heart may promote neoplastic development and

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CLINICAL PERSPECTIVE

What Is New?

- When evaluated, cancer mortality accounted for 6% to 14% of deaths in randomized controlled trials of heart failure with reduced ejection fraction and was not affected by treatments, which instead decreased cardiovascular mortality.
- However, cancer mortality was not assessed in the majority of heart failure with reduced ejection fraction randomized controlled trials.

What Are the Clinical Implications?

- Cancer is a major, yet overlooked cause of noncardiovascular death in heart failure with reduced ejection fraction, which has become more prominent with cardiovascular mortality decline.

Nonstandard Abbreviations and Acronyms

HF	heart failure
HFpEF	heart failure with preserved left ventricular ejection fraction
HFrEF	heart failure with reduced left ventricular ejection fraction
OR	odds ratios
RCTs	randomized controlled trials

progression.[6] Nonetheless, one investigation based on the Physicians' Health Studies I and II population did not observe any relationship between HF and incident cancer among males.[7]

Clearly, recognition of the potential relation of HFrEF with cancer is growing, but understanding of the interconnection between these 2 entities remains limited.[8]

It is possible that cancer has gained importance in HFrEF because of the changes that occurred in the natural history of this syndrome over time. Advances in pharmacologic and device treatment have led to a significant decline in HF-related cardiovascular mortality, to the extent that overall mortality has also decreased.[9] By contrast, HFrEF therapies do not affect noncardiovascular disorders, which have therefore progressively become more prominent.[9–11] This may also be the case with cancer. Indeed, cancer has been recently pinpointed as a major cause of noncardiovascular death in contemporary HFrEF populations.[9,11,12]

To better describe the relevance of cancer in HFrEF throughout the last decades, we systematically assessed cancer mortality in phase 3 randomized controlled trials (RCTs) and investigated whether it has been influenced by HFrEF therapies as compared with cardiovascular and total mortality.

METHODS

The authors declare that all supporting data are available within the article and its online supplementary files.

Search Strategy

We systematically searched the MEDLINE, Embase, Scopus, and Cochrane Library databases for phase 3 RCTs in HFrEF using the search strings "heart failure," "congestive heart failure," and "randomized controlled trial." 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 April 30, 2019.

Inclusion and Exclusion Criteria

We focused on HFrEF because this type of HF has primarily been the object of RCTs as well as of the investigations about comorbid cancer.[1,3,8] After selecting phase 3 RCTs involving individuals with left ventricular ejection fraction <45%, we excluded those that included >10% of patients with HF with preserved left ventricular ejection fraction (HFpEF), enrolled subjects with or recently discharged after acutely decompensated HF, were not broadly representative of the HFrEF population (ie, investigating only specific subsets of patients), or did not have sufficient information about mortality. Two investigators (G.T., E.B.) independently reviewed the retrieved articles and collected information regarding number, sex and age of participants, follow-up duration, HF therapy including implantable cardioverter defibrillator and cardiac resynchronization therapy with defibrillator capacity, enrollment criteria with special attention to those regarding malignancy, and cause-specific and total mortality.

Data Synthesis and Statistical Analysis

Mortality rates were calculated per 100 patient-years with 95% CI. The odds ratios (ORs) of cancer, cardiovascular, and all-cause death were obtained from the number of events and the total number of patients in the control and treatment arms. The ORs were then pooled together using the random-effects model based on the method of DerSimonian and Laird. The estimate of heterogeneity was derived from the Mantel-Haenszel model and was reported using the I-square coefficient. Since the number of cancer deaths was low in several RCTs, the Mantel-Haenszel exact test on log OR was also used to evaluate the effect of treatment on cancer mortality. A random-effects

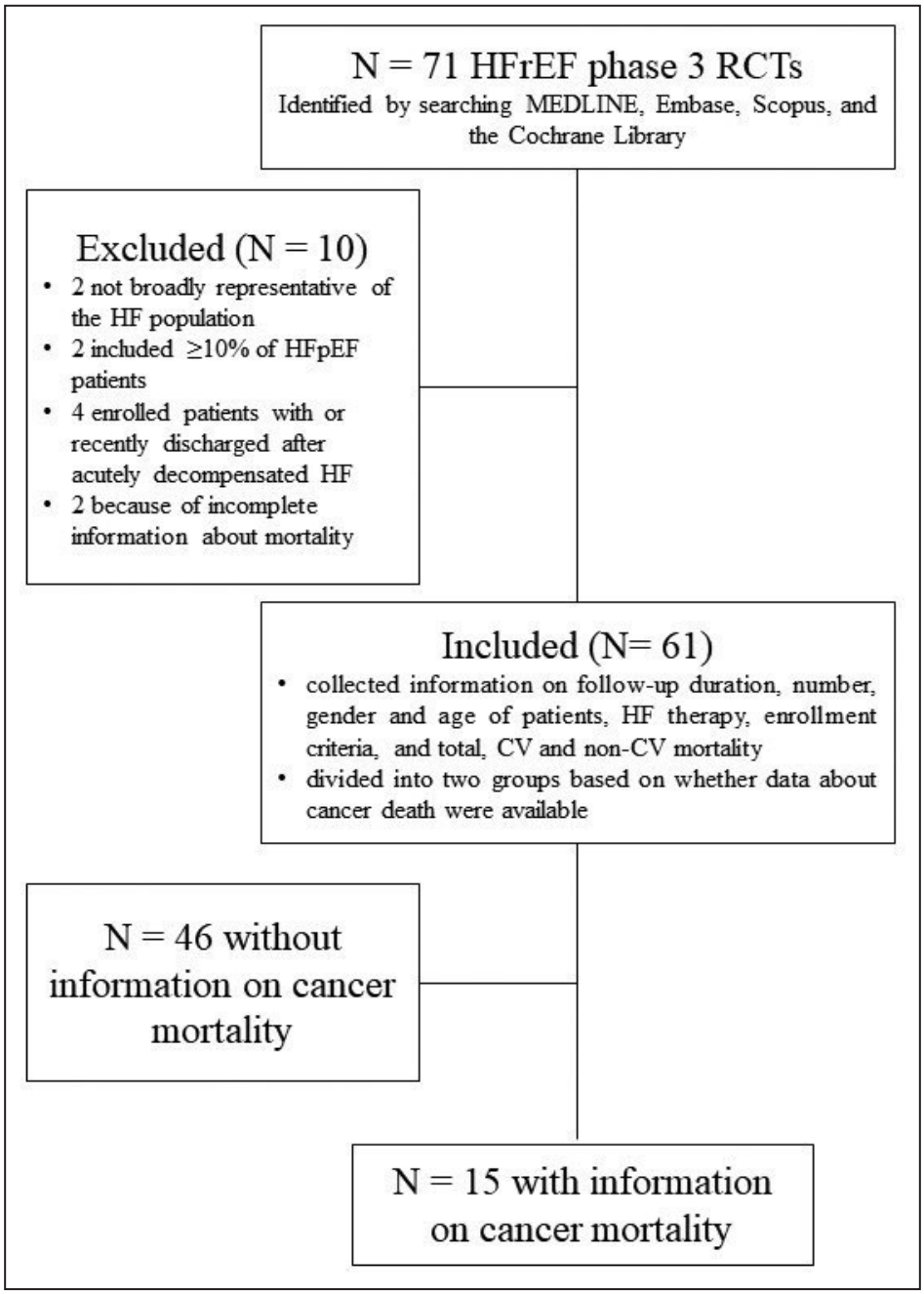

Figure 1. Preferred Reporting Items for Systematic Reviews and Meta-Analyses flow diagram of the systematic search and selection process.
CV indicates cardiovascular; HF, heart failure; HFpEF, heart failure with preserved left ventricular ejection fraction; HFrEF, heart failure with reduced left ventricular ejection fraction; and RCTs, randomized controlled trials.

meta-regression analysis, with the between-studies variance (tau-squared) estimated by residual maximum likelihood, was performed to assess possible temporal trends of the mortality rates and to determine whether the following patient and trial characteristics had an impact on mortality outcomes: age and sex of recruited subjects; length of follow-up; number of disease-modifying drug classes in the background therapy (0–3: beta-blockers; inhibitors of the renin-angiotensin system including aliskiren, angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, and mineralocorticoid receptor antagonists); and proportion of patients with implantable cardioverter defibrillator or cardiac resynchronization therapy with defibrillator capacity. Statistical analysis was done using Stata (v.14; StataCorp, College Station, TX).

Table 1. HFrEF RCTs With Published Cancer Mortality

Trial name and period	N (males) and age of patients	Follow-up y	Tested therapy Background disease-modifying therapy	All-cause mortality N n/100 pts/y (95% CI)	Cardiovascular mortality N n/100 pts/y (95% CI)	Cancer mortality N n/100 pts/y (95% CI)	Non cardiovascular noncancer mortality N n/100 pts/y (95% CI)	Non cardiovascular deaths attributable to cancer
CONSENSUS 1985–1986[13]	253 (178) 70 y	1	Enalapril vs placebo	118	117	0	1	0%
			BB: 3%	46.6 (40.6–52.8)	46.3 (40.2–52.4)	0	0.4 (0.1–2.2)	
			MRA: 53%					
V-HeFT II 1986–1990[14]	804 (804) 60.6 y	2.5	Enalapril vs hydralazine-isosorbide	285	249	18	18	0%
			ACEi: 61%	14.2 (12.7–15.8)	12.4 (11–13.9)	0.9 (0.6–1.4)	0.9 (0.6–1.4)	
GESICA 1989–1993[15]	516 (417) 58.8 y	1.1	Amiodarone vs standard therapy	193	185	2	6	25%
			ACEi: 90%	34 (30.2–38)	32.6 (28.9–36.6)	0.4 (0.1–1.3)	1.1 (0.5–2.3)	
CABG Patch 1993–1997[16,74]	900 (759) 63.5 y	2.7	ICD vs standard therapy	198	163	13	22	37.1%
			BB: 21%	8.2 (7.1–9.3)	6.7 (5.8–7.8)	0.5 (0.3–0.9)	0.9 (0.6–1.4)	
			ACEi: 54%					
			ICD: 50%					
DEFINITE 1998–2003[17]	458 (326) 58.3 y	2.4	ICD vs standard therapy	68	43	10	15	66.7%
			BB: 86%	6.2 (4.9–7.8)	3.9 (2.9–5.2)	0.9 (0.5–1.7)	1.4 (0.8–2.2)	
			ACEi: 86 %					
			ARB: 11%					
			ICD: 50%					
CHARM-Alternative 1999–2003[18,75]	2028 (1382) 66.6 y	2.8	Candesartan vs placebo	561	471	43	47	47.8%
			BB: 55%	9.9 (9.1–10.7)	8.3 (7.6–9.0)	0.8 (0.6–1)	0.8 (0.6–1.1)	
			MRA: 24%					
			ICD: 3%					
CHARM-Added 1999–2003[19,75]	2548 (2006) 64.1 y	3.4	Candesartan vs placebo	789	649	54	86	38.6%
			BB: 56%	9.1 (8.5–9.7)	7.5 (7–8.1)	0.6 (0.5–0.8)	1 (0.8–1.2)	
			ACEi: 100%					
			MRA: 17%					
			ICD: 4%					
AF-CHF 2001–2007[20]	1376 (1122) 67 y	3.1	Rhythm control vs rate control	445	357	34	54	38.6%
			BB: 79%	10.4 (9.6–11.4)	8.4 (7.6–9.2)	0.8 (0.6–1.1)	1.3 (1–1.7)	
			ACEi: 86%					
			ARB: 11%					
			MRA: 45%					
			ICD: 7%					

(*Continued*)

Table 1. Continued

Trial name and period	N (males) and age of patients	Follow-up y	Tested therapy Background disease-modifying therapy	All-cause mortality N n/100 pts/y (95% CI)	Cardiovascular mortality N n/100 pts/y (95% CI)	Cancer mortality N n/100 pts/y (95% CI)	Non cardiovascular noncancer mortality N n/100 pts/y (95% CI)	Non cardiovascular deaths attributable to cancer
GISSI-HF 2002–2008[21]	6975 (5459) 67 y	3.9	n-3 PUFA vs standard therapy	1969	1477	219	273	44.5%
			BB: 65%	7.2 (6.9–7.5)	5.4 (5.1–5.7)	0.8 (0.7–0.9)	1 (0.9–1.1)	
			ACEi: 77%					
			ARB: 19%					
			MRA: 39%					
			ICD: 7%					
STICH 2002–2010[22,76]	1212 (1064) 60 y	4.7	CABG vs standard therapy	462	351	35	76	31.5%
			BB: 86%	8.1 (7.4–8.9)	6.2 (5.6–6.8)	0.6 (0.4–0.9)	1.3 (1.1–1.7)	
			ACEi: 82%					
			ARB: 9.5%					
			MRA: 46%					
CORONA 2003–2007[23]	5001 (3821) 73 y	2.7	Rosuvastatin vs placebo	1487	975	102	410	19.9%
			BB: 75%	11 (10.5–11.5)	7.2 (6.8–7.7)	0.8 (0.6–0.9)	3 (2.8–3.3)	
			ACEi/ARB: 92%					
			MRA: 39%					
			ICD: 3%					
REVERSE 2004–2006[24]	610 (479) 62.4 y	1	CRT vs standard therapy	12	6	1	5	16.7%
			BB: 95%	2 (1.1–3.4)	1 (0.5–2.1)	0.2 (0.1–0.9)	0.8 (0.4–1.9)	
			ACEi: 79%					
			ARB: 21%					
			ICD: 84%					
MADIT-CRT 2004–2008[25,77]	1820 (1367) 64.5 y	4	CRT-D vs ICD	169	108	19	42	31.1%
			BB: 92%	2.3 (2–2.7)	1.5 (1.2–1.8)	0.3 (0.2–0.4)	0.6 (0.4–0.8)	
			ACEi: 74%					
			ARB: 20%					
			MRA: 30%					
			ICD: 50%					
ECHO-CRT 2008–2013[26]	809 (585) 58 y	1.6	CRT vs standard therapy	71	48	5	18	21.7%
			BB: 97%	5.5 (4.4–6.9)	3.7 (2.8–4.9)	0.4 (0.2–0.9)	1.4 (0.9–2.2)	
			ACEi/ARB: 95%					
			MRA: 60%					
			ICD: 50%					

(*Continued*)

Table 1. Continued

Trial name and period	N (males) and age of patients	Follow-up y	Tested therapy Background disease-modifying therapy	All-cause mortality N n/100 pts/y (95% CI)	Cardiovascular mortality N n/100 pts/y (95% CI)	Cancer mortality N n/100 pts/y (95% CI)	Non cardiovascular noncancer mortality N n/100 pts/y (95% CI)	Non cardiovascular deaths attributable to cancer
PARADIGM-HF 2009–2014[27,78]	8399 (6567) 63.8 y	2.3	ARNI vs ACEi	1546	1251	82	213	27.8%
			BB: 93%	8 (7.6–8.4)	6.5 (6.1–6.8)	0.4 (0.3–0.5)	1.1 (1–1.3)	
			ACEi: 77.8%					
			ARB: 22.6%					
			MRA: 56%					
			ICD: 15%					

CORONA included only >60 year-old patients.

Age and follow-up duration are mean or median, as published. When presented in months, follow-up duration was converted into years by dividing by 12.

ACEi indicates angiotensin-converting enzyme inhibitor; AF-CHF, atrial fibrillation and congestive heart failure; ARB, angiotensin receptor blocker; ARNI, angiotensin receptor neprilysin inhibitor; BB, beta-blocker; CABG, coronary artery bypass graft; CHARM-Added, candesartan in heart failure assessment of reduction in mortality and morbidity-added; CHARM-Alternative, candesartan in heart failure assessment of reduction in mortality and morbidity-alternative; CONSENSUS, cooperative north scandinavian enalapril survival study; CORONA, controlled rosuvastatin multinational trial in heart failure; CRT(-D), cardiac resynchronization therapy (and ICD); DEFINITE, defibrillators in non-ischemic cardiomyopathy treatment evaluation; ECHO-CRT, echocardiography guided cardiac resynchronization therapy; GESICA, grupo de estudio de la sobrevida en la insuficiencia cardiaca en Argentina GISSI-HF, gruppo Italiano per lo studio della sopravvivenza nell'insufficienza cardiaca heart failure; HFrEF, heart failure with reduced left ventricular ejection fraction; ICD, implanted cardioverter defibrillator; MADIT-CRT, multicenter automatic defibrillator implantation trial with cardiac resynchronization therapy; MRA, mineral receptor antagonist; PARADIGM-HF, prospective comparison of ARNI with ACEI to determine impact on global mortality and morbidity in heart failure trial; PUFA, polyunsaturated fatty acids; RCTs, randomized controlled trials; REVERSE, resynchronization reverses remodeling in systolic left ventricular dysfunction; STICH, surgical treatment for ischemic heart failure; and V-HeFT II, vasodilator-heart failure trial II.

RESULTS

A total of 61 HFrEF RCTs were included in the analysis[13–73]; Figure 1 shows the flow diagram of the selection process.

Cancer mortality was reported for 15 (25%) RCTs.[13–27,74–78] These studies covered 29 years, from 1985 to 2014, and involved a total of 33 709 subjects aged between 58 and 70 years, with the exception of CORONA[23] that included ≥60-year-old patients and, thereby, consisted of an older cohort (Table 1; risk of bias is summarized in Table S1). The number of participants, as well as the complexity of HFrEF treatment, progressively increased from the earliest to the latest RCTs. Duration of follow-up ranged from 1 to 4.7 years (Table 1). The proportion of patients with cancer at the enrollment was available for 3 RCTs and always small: CHARM Alternative[18] (134 patients, 6.6% of total), CHARM Added[19] (153 patients, 6%), and GISSI-HF[21] (256 patients, 3.7%).

Except for 2 of the earliest RCTs with published information about cancer mortality (CONSENSUS[13] and GESICA[15]), cancer accounted for 6% to 14% of all deaths and 17% to 67% of noncardiovascular deaths (Table 1). The inferred mortality rate was 0.58 (95% CI, 0.46–0.71) per 100 patient-years (I2 for heterogeneity, 83.4%) and did not have a clear temporal trend (P=0.35; Figure 2). The cancer mortality rates for the population of corresponding age in the United States, provided in Table S2, were in general lower than in RCTs before the 2000s and then comparable. Similar to cancer mortality, no significant trend was noted for noncardiovascular noncancer mortality rates (P=0.24; Table 1). Conversely, cardiovascular (P=0.001) and total (P=0.001) mortality rates decreased over time (Table 1 and Figure 2). Furthermore, HFrEF therapies did not modify cancer mortality (OR, 1.08; 95% CI, 0.92–1.28; Figure 3A), but significantly diminished cardiovascular (OR, 0.88; 95% CI, 0.79–0.98; Figure 3B) and all-cause (OR, 0.91; 95% CI, 0.84–0.99; Figure 3C) mortality. The Mantel-Haenszel exact test for cancer mortality yielded similar results (OR, 1.09; 95% CI, 0.92–1.27). None of the patient or RCT characteristics taken into consideration reduced heterogeneity in the meta-regression analysis of treatment effect (Table S3). However, part of the heterogeneity for the cardiovascular death outcome was imputable to the ECHO-CRT and V-HeFT-II studies, since removing these 2 RCTs decreased heterogeneity from 64.5% to 54.4% and 57.9%, respectively. The leave-one-out approach with the other RCTs did not substantially modify the heterogeneity for cardiovascular death.

Information about cancer mortality was not given for 46 (75%) RCTs.[28–73,79–91] The main features of these RCTs are presented in Table S4. Of note, only 4 of these studies[43,44,63,72] (8.7% of the RCTs without

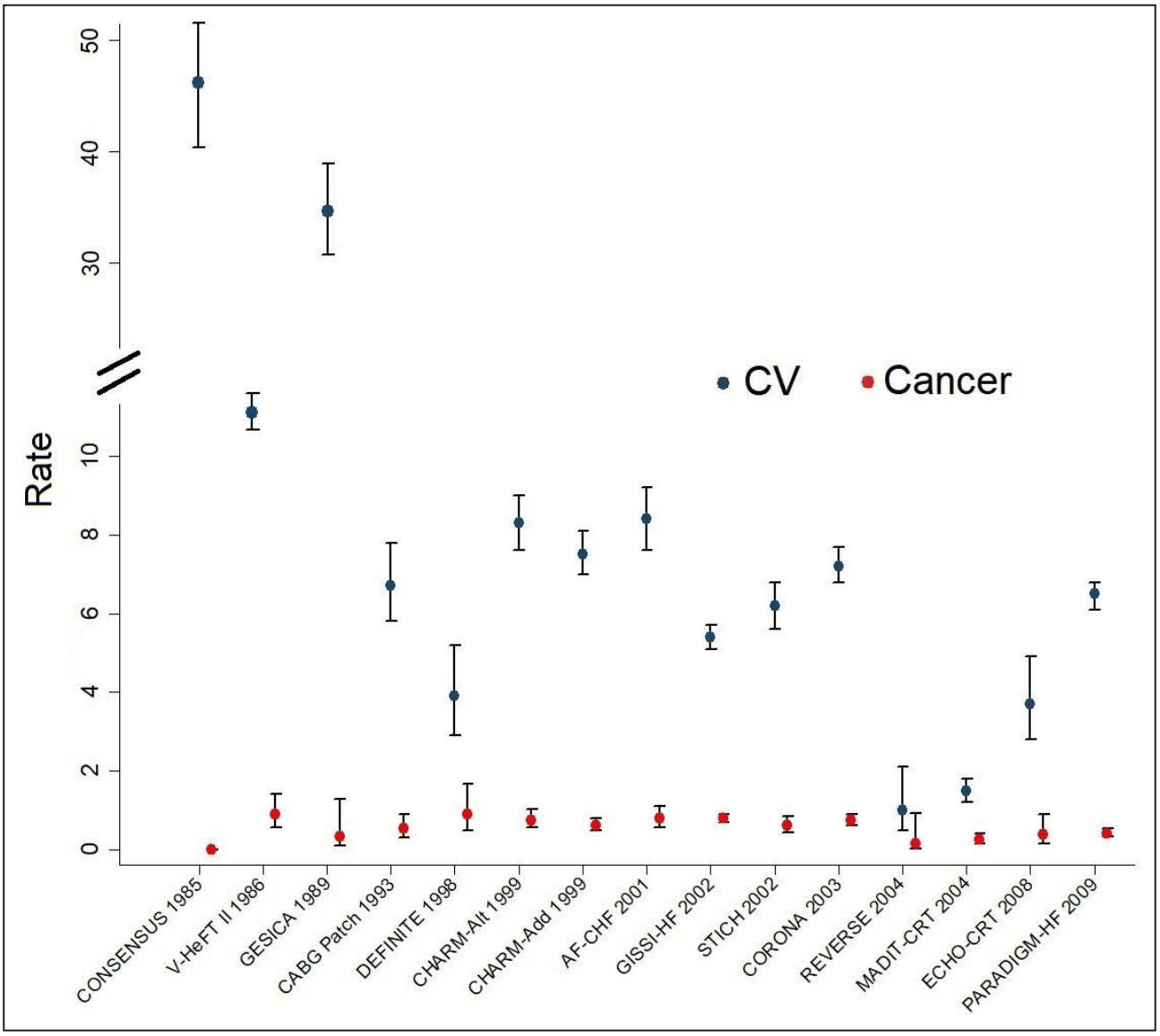

Figure 2. Cancer and CV mortality in HFrEF RCTs with cancer mortality data available.
AF-CHF indicates atrial fibrillation and congestive heart failure; CABG, coronary artery bypass graft; CHARM-Added, candesartan in heart failure assessment of reduction in mortality and morbidity-added; CHARM-Alternative, candesartan in heart failure assessment of reduction in mortality and morbidity-alternative; CONSENSUS, cooperative north scandinavian enalapril survival study; CORONA, controlled rosuvastatin multinational trial in heart failure; CV, cardiovascular; DEFINITE, defibrillators in non-ischemic cardiomyopathy treatment evaluation; ECHO-CRT, echocardiography guided cardiac resynchronization therapy; GESICA, grupo de estudio de la sobrevida en la insuficiencia cardiaca en Argentina; GISSI-HF, gruppo Italiano per lo studio della sopravvivenza nell'insufficienza cardiaca heart failure; HFrEF, heart failure with reduced left ventricular ejection fraction; MADIT-CRT, multicenter automatic defibrillator implantation trial with cardiac resynchronization therapy; PARADIGM-HF, prospective comparison of ARNI with ACEI to determine impact on global mortality and morbidity in heart failure trial; RCTs, randomized controlled trials; REVERSE, resynchronization reverses remodeling in systolic left ventricular dysfunction; STICH, surgical treatment for ischemic heart failure; and V-HeFT II, vasodilator-heart failure trial II.

published cancer mortality) formally excluded patients with current and/or prior malignancy (Figure 4 and Table S5). Most RCTs did not enroll individuals who might have had cancer, based on limited life expectancy (12 RCTs[†]; 26% of those without data on cancer mortality), a predicted survival below a specific cutoff between 6 months and 5 years (11 RCTs[§]; 24%), the presence of concomitant "major noncardiac diseases" (4 RCTs[41,51,66,69] 9%), or the assumption that complete follow-up would not be feasible (3 RCTs[49,60,65] 6.5%). In 12 studies,[¶] (26%) there was not even indirect indication that patients with cancer could not be recruited

[†]References 13, 29, 32, 35, 36, 38–40, 42, 47, 48, 59.

[§]References 28, 33, 46, 52, 54–56, 58, 64, 71, 73.

[¶]References 31, 34, 37, 45, 50, 53, 57, 61, 62, 67, 68, 70

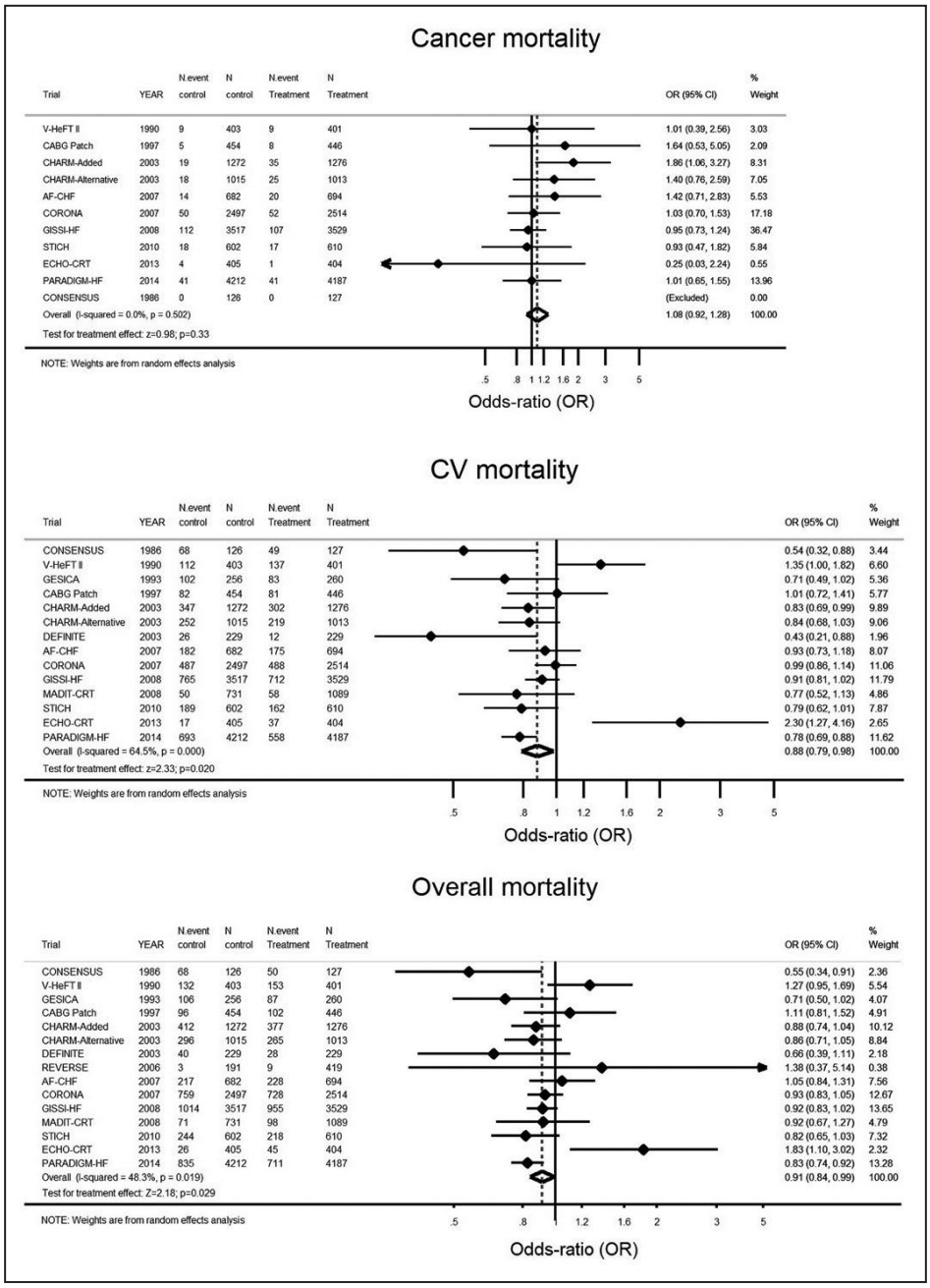

Figure 3. Pooled OR for cancer, CV, and total mortality in HFrEF RCTs with published information about cancer mortality.

AF-CHF indicates atrial fibrillation and congestive heart failure; CABG, coronary artery bypass graft; CHARM-Added, candesartan in heart failure assessment of reduction in mortality and morbidity-added; CHARM-Alternative, candesartan in heart failure assessment of reduction in mortality and morbidity-alternative; CONSENSUS, cooperative north scandinavian enalapril survival study; CORONA, controlled rosuvastatin multinational trial in heart failure; CRT(-D), cardiac resynchronization therapy (and ICD); CV, cardiovascular; DEFINITE, defibrillators in non-ischemic cardiomyopathy treatment evaluation; ECHO-CRT, echocardiography guided cardiac resynchronization therapy; GESICA, grupo de estudio de la sobrevida en la insuficiencia cardiaca en Argentina; GISSI-HF, gruppo Italiano per lo studio della sopravvivenza nell'insufficienza cardiaca heart failure; HFrEF, heart failure with reduced left ventricular ejection fraction; MADIT-CRT, multicenter automatic defibrillator implantation trial with cardiac resynchronization therapy; PARADIGM-HF, prospective comparison of ARNI with ACEI to determine impact on global mortality and morbidity in heart failure trial; RCTs, randomized controlled trials; REVERSE, resynchronization reverses remodeling in systolic left ventricular dysfunction; STICH, surgical treatment for ischemic heart failure; and V-HeFT II, vasodilator-heart failure trial II.

(Figure 4 and Table S5). Strikingly, very similar exclusion criteria were applied in the RCTs that instead reported cancer mortality, with a comorbidity expected to shorten life expectancy to less than the duration of follow-up or a variable amount of time being the most common reason to preclude the participation of patients with active cancer (Figure 4 and Table 2). In CONSENSUS[13] and DEFINITE,[17] noncardiac diseases leading to exclusion were explicitly listed, and cancer was not mentioned (Table 2).

DISCUSSION

There is increasing attention toward cancer in HFrEF. Contemporary registries suggest that at minimum 1 in 10 patients with HFrEF also has a malignant tumor at the first observation[11,92,93] or is diagnosed with and dies from cancer during follow-up.[1–5,11,12,92,93]. In fact, the risk of malignancy may be even higher in subjects with than without HFrEF.[1–4]

Since RCTs provide robust and high-quality data, we systematically reviewed these studies to better define the burden of cancer in HFrEF. In the 15 HFrEF RCTs with published cancer mortality, the proportion of deaths ascribed to malignancy was not negligible, being 6% to 7% and peaking at over 14%. Up to 67% of noncardiovascular deaths were attributable to cancer. These results are consistent with those of recent investigations assessing cancer in HF out of RCTs. By reviewing the electronic health records from a representative sample of the UK population, Conrad and colleagues showed that cancer caused 15% of deaths within 1 year from HF diagnosis in 2013.[11] Of about 1800 patients with HFrEF followed at one HF clinic in Spain and >2000 from another single center in Japan, 15% and 16%, respectively, died from cancer.[92,93] Thus, our work confirms that cancer is a relevant cause of death in HFrEF, by integrating retrospective analyses of real-world cohorts with data from prospective RTCs, which have been extracted and examined here for the first time.

While there was no consistent trend in cancer mortality throughout HFrEF RCTs, cardiovascular and all-cause mortality decreased. This reduction has already been described for HFrEF RCTs in general[9,94] and in population studies,[9,11,12] and is explained by the sequential implementation of drugs and devices halting HF progression and death. In fact, the decline in cardiovascular and overall mortality in our analysis was driven by the 3 oldest RCTs,[13–15] in which HF-specific therapy was simpler than in the following ones. By contrast, cancer mortality was not influenced by treatment, in line with the epidemiologic evidence that neurohormonal inhibitors do not substantially affect the risk of dying from malignant tumors.[95] Hence, the emerging issue of cancer in HFrEF may be, at least in part, the consequence of curtailed cardiovascular death by virtue of therapeutic advances. This paradigm has also been proposed for other comorbidities that nowadays compete with HFrEF per se in dictating prognosis more than in the past and has prompted questions about the appropriateness of some treatment choices.[10,17] It must be acknowledged that this interpretation of the results is speculative and needs to be verified. Nevertheless, the data presented here corroborate the debate and emphasize that cancer is a noncardiovascular disease complicating HFrEF, which deserves careful consideration.

Interestingly, a specular trend has been shown for cardiovascular mortality among oncologic patients,

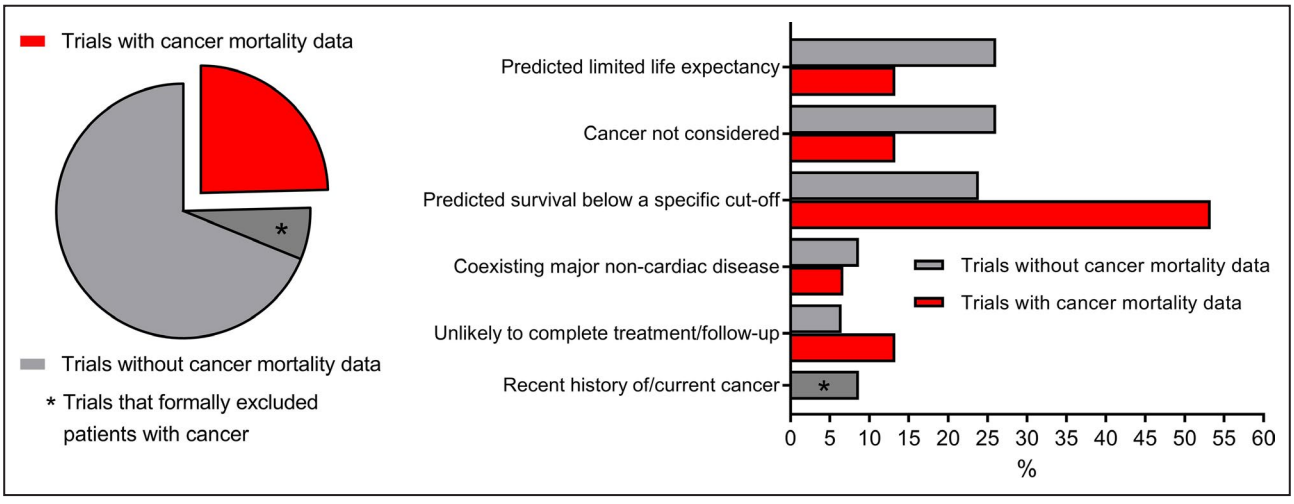

Figure 4. Potential reasons for exclusion of patients with malignancy from HFrEF RCTs.
Note the overlap of criteria between trials for which cancer mortality was or was not reported. *Cancer not considered* means that cancer was not a direct or indirect cause of exclusion.

where cardiovascular deaths have become more frequent with the improvement of cancer prognosis.[96] Thus, the reciprocal impact of the evolving epidemiology of cardiovascular disease and cancer must be borne in mind when addressing their interrelation.

Three RCTs reported the percentage of patients having cancer at baseline, which was 3.7% to 6.6%[18,19,21] and lower than the ones found in the general population. Among subjects with incident HF in the United Kingdom between 2011 and 2013, 29% also had a history of cancer.[11] In the United States, comorbid nonmetastatic cancer was recorded for 11% of all the admissions between 2003 and 2015 with a primary discharge diagnosis of HF.[92,93] This discrepancy may depend on the inaccurate definition of HF in population studies, with no distinction between HFrEF and HFpEF. It is also likely that oncologic patients were somehow excluded from RCTs, but not from registries. However, it should also be noted that the representation of subjects with malignancy in HFrEF RCTs is largely unknown. Only 4 RCTs[43,44,63,72] explicitly excluded these patients. In the great majority of RCTs, participation was precluded to individuals with a concomitant noncardiovascular condition, which would jeopardize follow-up or substantially decrease life expectancy according to the recruiting investigators. Obviously, such conditions could have been, but were not necessarily limited to, cancer. Therefore, it is conceivable that a number of individuals were enrolled in HFrEF RCTs in spite of having malignant tumors, although apparently cured or deemed indolent.

The majority of HFrEF RCTs also lack information about how many patients died from cancer. Modes of death were reported as cardiovascular or noncardiovascular, without further distinction of the noncardiovascular causes of death. This methodologic limitation generates a gap in knowledge about cancer in HFrEF and has negative implications for clinical practice. Since guidance may not be derived from RCTs, the management of patients with cancer in addition to HFrEF remains empirical and based on personal experience, when evidence-based data are instead warranted given the challenges portended by the co-occurrence of cancer and HF.[97] We advocate for future RCTs better describing and adjudicating noncardiovascular events and mortality, including incident and fatal cancer.

From a conceptual standpoint, the results presented here lend support to the statement that the discipline of cardio-oncology should broaden goals and perspectives. The interfaces between cancer and HF and other cardiovascular disorders are manifold and not limited to the side effects of antitumor therapies. Basic and clinical science efforts are awaited to dissect these multiple levels of interaction and provide insights, which may be in turn translated into clinical improvements. Our analysis highlights how the extensive phenotyping offered by RCTs has

Table 2. Potential Reasons for Exclusion of Patients With Malignancy From HFrEF RCTs With Cancer Mortality Data Available

	Exclusion Criteria Possibly Regarding Patients With Cancer
CONSENSUS[13]	*Cancer not a direct or indirect reason for exclusion*
V-HeFT II[14]	"Diseases likely to limit life expectancy"
GESICA[15]	"Concomitant serious disease"
CABG Patch[16,74]	"A noncardiovascular condition with expected survival of less than two years"
DEFINITE[17]	*Cancer not a direct or indirect reason for exclusion*
CHARM Alternative[18,75]	"Presence of any noncardiac disease (eg, cancer) that is likely to significantly shorten life expectancy to <2 years."
CHARM Added[19,75]	"Presence of any noncardiac disease (eg, cancer) that is likely to significantly shorten life expectancy to less than 2 years."
AF-CHF[20]	"An estimated life expectancy of less than 1 year"
GISSI-HF[21]	"Presence of any noncardiac comorbidity (eg, cancer) unlikely to be compatible with a sufficiently long follow-up"
STICH[22,76]	"Noncardiac illness with a life expectancy of less than 3 years" "Noncardiac illness imposing substantial operative mortality"
CORONA[23]	"Any other condition that would substantially reduce life expectancy or limit compliance with the protocol"
REVERSE[24]	Life expectancy ≤12 months
MADIT-CRT[25,77]	"Presence of any disease, other than the subject's cardiac disease, associated with a reduced likelihood of survival for the duration of the trial, eg, cancer, uremia (BUN >70 mg/dL or creatinine >3.0 mg/dL), liver failure, etc"
ECHO-CRT[26]	"Have a life expectancy of <6 months. Presence of any disease, other than the subject's cardiac disease associated with a reduced likelihood of survival for the duration of the trial, (eg, cancer)"
PARADIGM-HF[27,78]	"Presence of any other disease with a life expectancy of <5 years"

AF-CHF indicates atrial fibrillation and congestive heart failure; BUN, blood urea nitrogen; CABG, coronary artery bypass graft; CHARM-Added, candesartan in heart failure assessment of reduction in mortality and morbidity-added; CHARM-Alternative, candesartan in heart failure assessment of reduction in mortality and morbidity-alternative; CONSENSUS, cooperative north scandinavian enalapril survival study; CORONA, controlled rosuvastatin multinational trial in heart failure; DEFINITE, defibrillators in non-ischemic cardiomyopathy treatment evaluation; ECHO-CRT, echocardiography guided cardiac resynchronization therapy; GESICA, grupo de estudio de la sobrevida en la insuficiencia cardiaca en Argentina; GISSI-HF, gruppo Italiano per lo studio della sopravvivenza nell'insufficienza cardiaca heart failure; HFrEF, heart failure with reduced left ventricular ejection fraction; MADIT-CRT, multicenter automatic defibrillator implantation trial with cardiac resynchronization therapy; PARADIGM-HF, prospective comparison of ARNI with ACEI to determine impact on global mortality and morbidity in heart failure trial; RCTs, randomized controlled trials; REVERSE, resynchronization reverses remodeling in systolic left ventricular dysfunction; STICH, surgical treatment for ischemic heart failure; and V-HeFT II, vasodilator-heart failure trial II.

been minimally exploited to characterize cancer in HFrEF. In parallel, investigations are needed to understand whether a mechanistic link exists between the 2 conditions.[95,98,99]

Limitations

This systematic review collected information from RCTs, which were not specifically designed to evaluate cancer mortality in HFrEF. As such, adjudication and proper event description, by default, was of mediocre quality. Second, the competing risk explanation for the increasing relevance of cancer in HFrEF is strongly hampered by the lack of any analysis that directly address it. In this regard, this work should be considered hypothesis-generating. Third, we did not assess the burden of malignancy in HFpEF. However, a recent comprehensive paper examined noncardiovascular death in HFpEF RCTs and found that detailed data were available only for 3 studies.[100] In these RCTs, 30% to 40% of noncardiovascular mortality was attributable to cancer, suggesting that death attributable to malignancy is also noticeable in this setting.

CONCLUSIONS

When assessed, cancer was a primary cause of noncardiovascular death in RCTs in patients with HFrEF, and it was unaffected by HF treatments. However, cancer mortality was often unreported. Given the increasing number of subjects with HF and cancer, restrictive exclusion criteria or inadequate data collection may hinder the appropriate representation of a relevant population in RCTs. A similar observation has been made for RCTs of anticancer therapies, where concomitant cardiovascular disease and especially HF are a common reason for exclusion.[101] Upcoming HFrEF RCTs should consider including at least a subset of patients with thorough information about the prevalence, characteristics, and mortality of cancer, as this would allow better positioning of new therapies.

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Disclosures

None.

Supplementary Materials

Tables S1–S5

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SUPPLEMENTAL MATERIAL

Table S1. Risk of bias in HFrEF RCTs with published cancer mortality.

	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding of participants and personnel (performance bias)	Blinding of outcome assessment (detection bias)	Incomplete outcome data addressed (attrition bias)	Selective reporting (reporting bias)
CONSENSUS [13]	Low	Low	Low	Low	Low	Low
V-HeFT [14]	Low	Low	Low	Low	Low	Low
GESICA [15]	Low	Low	High	High	Low	Low
CABG Patch [16,74]	Low	Low	High	Low	Low	Low
DEFINITE [17]	Low	Low	High	Low	Low	Low
CHARM-Alt [18,75]	Low	Low	Low	Low	Low	Low
CHARM-Add [19,75]	Low	Low	Low	Low	Low	Low
AF-CHF [20]	Low	Low	High	Low	Low	Low
GISSI-HF [21]	Low	Low	Low	Low	Low	Low
STICH [22,76]	Low	Low	High	Low	High	Low
CORONA [23]	Low	Low	Low	Low	Low	Low
REVERSE [24]	Low	Low	Low	Low	Low	Low
MADIT-CRT [25,77]	Low	Low	Low	Low	High	Low
ECHO-CRT [26]	Low	Low	Low	High	High	Low
PARADIGM-HF [27,78]	Low	Low	Low	Low	Low	Low

HFrEF indicates heart failure with reduced left ventricular ejection fraction; RCTs**,** randomized controlled trials.

Table S2. Cancer mortality rates in HFrEF RCTs and in the general population of the United States.

Trial name and period	**Cancer mortality in the trial** *n/100 pts/yr*	**Cancer mortality in the US population *** *n/100 pts/yr (year)*	**Cancer mortality in the US population of corresponding age **** *n/100 pts/yr (age range; year)*
CONSENSUS 1985-1986 [13]	0	0.2 (1985)	*Not available*
V-HeFT II 1986-1990 [14]	0.9	0.2 (1986)	0.5 (50-69 yrs; 1990)
GESICA 1989-1993 [15]	0.4	0.2 (1989)	0.5 (50-69 yrs; 1990-1993)
CABG Patch 1993-1997 [16,74]	0.5	0.2 (1993)	0.4 (50-69 yrs; 1993-1997)
DEFINITE 1998-2003 [17]	0.9	0.2 (1998)	0.4 (50-69 yrs; 1998-2003)
CHARM-Alternative 1999-2003 [18,75]	0.9	0.2 (1999)	0.4 (50-69 yrs; 1999-2003)
CHARM-Added 1999-2003 [19,75]	0.6	0.2 (1999)	0.4 (50-69 yrs; 1999-2003)
AF-CHF 2001-2007 [20]	0.8	0.2 (2001)	0.4 (50-69 yrs; 2001-2007)
GISSI-HF 2002-2008 [21]	0.8	0.2 (2002)	0.3 (50-69 yrs; 2002-2008)
STICH 2002-2010 [22,76]	0.6	0.2 (2002)	0.3 (50-69 yrs; 2002-2010)
CORONA 2003-2007 [23]	0.8	0.2 (2003)	1.3 (>70 yrs; 2003-2007)
REVERSE 2004-2006 [24]	0.2	0.2 (2004)	0.3 (50-69 yrs; 2004-2006)
MADIT-CRT 2004-2008 [25,77]	0.3	0.2 (2004)	0.3 (50-69 yrs; 2004-2008)
ECHO-CRT 2008-2013 [26]	0.4	0.2 (2008)	0.3 (50-69 yrs; 2008-2013)
PARADIGM-HF 2009-2014 [27,78]	0.4	0.2 (2009)	0.3 (50-69 yrs; 2009-2014)

* source: https://seer.cancer.gov/archive/csr/1975_2015/

** source: https://ourworldindata.org/cancer, in which cancer mortality rates are provided per each calendar year stratified according to age (all ages, 50-69 years or >70 years). The values presented in the table are the mean of the mortality rates in the years when the RCT was performed, for the corresponding age group. For

example, PARADIGM-HF was conducted from 2009 to 2014, and the mean age of the participants was 63.8 years: thus, 0.3/100 pts/yr is the mean of the cancer mortality rates in the US population aged 50 to 69 years in 2009, 2010, 2011, 2012, 2013 and 2014.

HFrEF indicates heart failure with reduced left ventricular ejection fraction; RCTs**,** randomized controlled trials.

Table S3. Univariate meta-regression analysis.

	Coefficient (95% CI)*	*P* value
Cancer mortality		
Age, 1-year increase	-0.0017 (-0.0491 to 0.0456)	0.94
Male sex	-0.0038 (-0.0469 to 0.0393)	0.86
Ischemic etiology, 10-unit increase	0.0036 (-0.0084 to 0.0091)	0.94
Follow-up (years)	-0.0398 (-0.2775 to 0.1978)	0.74
DMD control	-0.1138 (-0.3861 to 0.1585)	0.41
DMD treatment	-0.1421 (-0.5335 to 0.2492)	0.48
CRT-D/ICD control (%)	-0.0152 (-0.0355 to 0.0052)	0.14
CRT-D/ICD treatment (%)	-0.0013 (-0.0128 to 0.0103)	0.83
CV mortality		
Age, 1-year increase	-0.0051 (-0.0349 to 0.0247)	0.74
Male sex	0.0013 (-0.0162 to 0.0188)	0.89
Ischemic etiology, 10-unit increase	0.0020 (-0.0027 to 0.0068)	0.40
Follow-up (years)	-0.0007 (-0.1254 to 0.1239)	0.99
DMD control	-0.0300 (-0.1731 to 0.1131)	0.68
DMD treatment	-0.0360 (-0.2318 to 0.1598)	0.72
CRT-D/ICD control (%)	0.0030 (-0.0015 to 0.0076)	0.19
CRT-D/ICD treatment (%)	0.0010 (-0.0024 to 0.0044)	0.57
Overall mortality		
Age, 1-year increase	-0.0033 (-0.0228 to 0.0162)	0.74
Male sex	0.0021 (-0.0113 to 0.0156)	0.76
Ischemic etiology, 10-unit increase	0.0005 (-0.0027 to 0.0037)	0.75
Follow-up (years)	0.0071 (-0.0757 to 0.0898)	0.87
DMD control	-0.0518 (-0.1261 to 0.0225)	0.17
DMD treatment	-0.0791 (-0.1756 to 0.0174)	0.11
CRT-D/ICD control (%)	0.0025 (-0.0006 to 0.0057)	0.12
CRT-D/ICD treatment (%)	0.0016 (-0.0007 to 0.0039)	0.18

DMD indicates number of disease-modifying drug classes in the background therapy; CRT-D, cardiac resynchronization therapy with defibrillator; ICD, implanted cardioverter defibrillator.

Table S4. HFrEF RCTs without published cancer mortality.

Trial name and period	**N. (males) and age of pts**	**Follow-up** *Yrs*	**Tested therapy** **Background disease-modifying therapy**	**All-cause mortality** *N.*	**CV mortality** *N.*	**Non-CV mortality** *N.*
V-HeFT I 1980-1985 [28]	642 58.3 yrs	2.3	*Prazosin vs hydralazine + isosorbide dinitrate vs placebo* None	283	267	16
SOLVD-T 1986-1989 [29]	2569 61 yrs	3.4	*Enalapril vs placebo* BB: 8% MRA*: 9%	962	860	102
SOLVD-P 1986-1991 [30]	4228 59.1 yrs	3.1	*Enalapril vs placebo* BB: 24% MRA*: 4%	647	563	84
PROMISE 1989-1990 [31]	1088 63.7 yrs	0.5	*Milrinone vs placebo* ACEi: 100%	295	284	11
CIBIS-I 1989-1993 [32]	641 59.7 yrs	1.9	*Bisoprolol vs placebo* ACEi: 90%	120	99	7
CHF-STAT 1991-1994 [33]	674 66 yrs	3.8	*Amiodarone vs placebo* BB: 4% ACEi: 78%	274	163	45
DIG 1991-1995 [34,79]	6800 63.5 yrs	3.1	*Digoxin vs placebo* ACEi: 95%	2375	2020	355
V-HeFT III 1991-1995 [35,80]	450 63 yrs	1.5	*Felodipine vs placebo* ACEi: 97%	60	48	12

PRAISE I 1992-1994 [36,81]	1153 64.7 yrs	1.2	*Amlodipine vs placebo* ACEi: 99%	413	368	45
PRIME II 1992-1995 [37]	1906 64.7 yrs	1	*Ibopamine vs placebo* ACEi: 92%	425	386	32
AUST-NZ 1992-1995 [38]	415 67 yrs	1.5	*Carvedilol vs placebo* ACEi: 86%	46	38	8
ATLAS 1992-1997 [40]	3164 63.6 yrs	3.8	*Lisinopril low-dose vs high-dose* ACEi: 100%	1383	1224	146
USCP 1993-1995 [39]	1094 58 yrs	0.5	*Carvedilol vs placebo* ACEi: 95%	53	51	2
MACH-I 1994-1996 [41]	2590 62.8 yrs	1.6	*Mibefradil vs placebo* ACEi: 99% BB: 16%	669	599	70
ELITE I 1994-1996 [42]	722 73.5 yrs	0.9	*Losartan vs captopril* BB: 59%	49	36	13
VEST 1995-1996 [43]	3833 63 yrs	0.8	*Vesnarinone vs placebo* ACEi: 90%	802	750	52
RALES 1995-1998 [44]	1663 65±12 yrs	2	*Spironolactone vs placebo* ACEi: 95% BB: 11%	670	565	70
CIBIS-II 1995-1998 [45]	2647 61 yrs	1.3	*Bisoprolol vs placebo* ACEi: 96%	384	280	51
BEST 1995-1999 [46]	2708 60 yrs	2.0	*Bucindolol vs placebo*	860	731	93

			ACEi: 98% MRA: 4%			
PRAISE II 1995-2000 [47]	1654 59 yrs	2.8	*Amlodipine vs placebo* ACEi: 100%	540	454	86
COMET 1996-2000 [48]	3029 62 yrs	4.8	*Carvedilol vs metoprolol* ACEi: 93% ARB: 6% BB: 4% MRA: 11%	1112	972	140
MERIT-HF 1997-1998 [49]	3991 63.8 yrs	1	*Metoprolol vs placebo* ACEi/ARB: 96% MRA: 8%	362	331	31
ELITE II 1997-1999 [50]	3152 71.5 yrs	1.5	*Losartan vs captopril* BB: 22% MRA*:22%	530	429	101
COPERNICUS 1997-2000 [9,51]	2289 63.3 yrs	0.9	*Carvedilol vs placebo* ACEi/ARB: 97% MRA: 19%	323	282	23
Val-HeFT 1997-2000 [52]	5010 62.7 yrs	1.9	*Valsartan vs placebo* ACEi: 93% BB: 35%	979	763	124
SCD-HeFT 1997-2003 [9,53,82]	2521 60.1 yrs	3.8	*Amiodarone vs ICD vs placebo* ACEi/ARB: 96% BB: 69% MRA*: 20%	666	484	122
MOXCON 1998-1999 [54]	1934 64.2 yrs	NA	*Moxonidine vs placebo*	86	80	6

			ACEi: 87% BB: 1% MRA: 7%			
CONTAK-CD 1998-2000 [55,83]	490 66 yrs	0.5	*CRT vs standard therapy* ACEi/ARB: 88% BB: 47% ICD: 100%	109	60	21
COMPANION 2000-2002 [9,56,84]	1520 67 yrs	1.3	*CRT-D vs* *CRT-P vs standard therapy* ACEi/ARB: 89% BB: 68% CRT: 80% ICD: 39%	313	251	46
CARMEN 2000-2003 [57,85]	572 62.3 yrs	1.7	*Carvedilol vs enalapril vs carvedilol + enalapril* ACEi/ARB: 66% BB: 67% MRA:13%	42	38	4
CARE-HF 2001-2004 [58,86]	813 67 yrs	2.4	*CRT vs standard therapy* ACEi/ARB: 95% BB: 72% MRA: 56%	202	167	34
HEAAL 2001-2009 [59,87]	3846 66 yrs	4.7	*Losartan low dose vs high dose* BB: 72% MRA: 38%	1300	926	374
CIBIS-III 2002-2005 [9,60,88]	1010 72.4 yrs	1.3	*Bisoprolol followed by enalapril vs opposite sequence*	138	107	27

			MRA: 13%			
HHH 2002-2005 [61]	461 60 yrs	1	*Home telemonitoring ± transmission of vital signs ± periodic monitoring of cardio-respiratory activity* ACEi/ARB: 87% BB: 84%	33	30	3
OPT-CHF 2003-2004 [62,89]	405 64.5 yrs	0.5	*Oxypurinol vs placebo* ACEi/ARB: 96% BB: 92% MRA: 35%	16	12	4
ACCLAIM 2003-2005 [63,90]	2426 64.3 yrs	0.8	*Immuno-modulation therapy vs placebo* ACEi/ARB: 94% BB: 87% MRA: 49%	245	202	43
SADHART-CHF 2003-2008 [64]	469 62.2 yrs	0.3	*Sertraline vs placebo* ACEi/ARB: 79% BB: 84% ICD: 19%	33	26	7
HF-ACTION 2003-2008 [65]	2331 59 yrs	2.5	*Aerobic exercise training vs standard therapy* ACEi/ARB: 94% BB: 95% CRT: 18% ICD: 40% MRA: 45%	387	274	113
RAFT 2003-2009 [66]	1798 66.2 yrs	3.3	*ICD vs CRT-D*	422	292	130

			ACEi/ARB: 97% BB: 90% MRA: 42%			
FUSION-II 2004-2006 [67]	911 65 yrs	0.3	*Nesiritide vs placebo* ACEi/ARB: 59% BB: 65% CRT: 24% ICD: 39% MRA: 37%	85	74	11
SHIFT 2006-2010 [68,91]	6505 60.4 yrs	1.9	*Ivabradine vs placebo* ACEi/ARB: 93% BB: 90% CRT: 1% ICD: 3% MRA: 60%	1055	940	115
EMPHASIS-HF 2006-2010 [69]	2737 68.8 yrs	1.8	*Eplerenone vs placebo* ACEi/ARB: 93% BB: 87% CRT: 9% ICD: 13% MRA: 50%	384	332	52
IN-TIME 2007-2010 [70,92]	664 65.5 yrs	1	*Tele-monitoring vs standard therapy* ACEi/ARB: 89% BB: 92% CRT: 41% ICD: 59%	37	29	8
TIM-HF 2008-2009 [71]	710 66.9 yrs	2.2	*Remote telemedical management vs standard therapy*	109	86	23

			ACEi/ARB: 95% BB: 93% CRT: 16% ICD: 46% MRA: 64%			
			ICD vs standard therapy			
DANISH 2008-2014 [72]	1116 64 yrs	5.6	ACEi/ARB: 97% BB: 92% CRT: 58% MRA: 58%	251	172	79
			Primary care vs HF clinic			
COACH-2 2012-2014 [73]	189 72 yrs	1	ACEi/ARB: 92% BB: 92% MRA: 48%	20	13	7

HFrEF indicates heart failure with reduced left ventricular ejection fraction; RCTs**,** randomized controlled trials; CV, cardiovascular; BB, beta blocker; MRA, mineral receptor antagonist; ACEi, angiotensin-converting enzyme inhibitor; ICD, implanted cardioverter defibrillator; ARB, angiotensin receptor blocker; CRT(-D), cardiac resynchronization therapy (and ICD).

* potassium-sparing diuretics, may have not been MRA

Table S5. Potential reasons for exclusion of patients with malignancy from HFrEF RCTs without cancer mortality data available.

	Exclusion criteria possibly regarding patients with cancer
V-HeFT I 1980-1985 [28]	"Disease likely to limit 5 year survival"
SOLVD-T 1986-1989 [29]	"Any other disease that may substantially shorten survival". 39,924 patients identified, 12% excluded because of cancer or other life-threatening disease
SOLVD-P 1986-1991 [30]	Same as SOLVD-P
PROMISE 1989-1990 [31]	*Cancer not considered among exclusion criteria*
CIBIS-I 1989-1993 [32]	"Patients whose life expectancy was shortened by a severe illness such as malignant disease"
CHF-STAT 1991-1994 [33]	"Serious disease other than heart disease that was likely to be fatal within three years"
DIG 1991-1995 [34,79]	*Cancer not considered among exclusion criteria*
V-HeFT III 1991-1995 [35,80]	"Significant comorbidity which, in the investigator's opinion, makes survival for the duration of the study unlikely or would otherwise interfere with adherence to the protocol"
PRAISE I 1992-1994 [36,81]	"Other significant comorbidity that made survival or compliance with the protocol unlikely"
PRIME II 1992-1995 [37]	*Cancer not considered among exclusion criteria*
AUST-NZ 1992-1995 [38]	"Any other life-threatening non-cardiac disease"
ATLAS 1992-1997 [40]	"Any non-cardiac disorder that could limit survival"
USCP 1993-1995 [39]	"Any condition other than heart failure that could limit exercise or survival"
MACH-I 1994-1996 [41]	"Any clinically significant disease other than HF"
ELITE I 1994-1996 [42]	"Unlikely survival for length of study or risk to patient"
VEST 1995-1996 [43]	"Cancer likely to limit life expectancy"

RALES 1995-1998 [44]	"Active cancer"
CIBIS-II 1995-1998 [45]	*Cancer not considered among exclusion criteria*
BEST 1995-1999 [46]	"Life expectancy of less than 3 years (..) or if they had hematologic, gastrointestinal, immunologic, endocrine, metabolic, or central nervous system disease that could adversely affect the safety or the efficacy of the study drug"
PRAISE II 1995-2000 [47]	"Any disease (other than heart failure) that might have limited survival"
COMET 1996-2000 [48]	"Any other serious systemic disease that might complicate management and reduce life expectancy"
MERIT-HF 1997-1998 [49]	"Any other serious disease that might complicate management and follow-up according to the protocol"
ELITE II 1997-1999 [50]	*Cancer not considered among exclusion criteria*
COPERNICUS 1997-2000 [9,51]	"Severe primary pulmonary, renal, or hepatic disease"
Val-HeFT 1997-2000 [52]	"Malignancies likely to limit 5-year survival"
SCD-HeFT 1997-2003 [9,53,82]	No information available
MOXCON 1998-1999 [54]	"Severe concomitant disease likely to reduce life expectancy to less than 5 years"
CONTAK-CD 1998-2000 [55,83]	"Life expectancy <6 months due to other medical conditions"
COMPANION 2000-2002 [9,56,84]	"Life expectancy <6 months because of any other medical conditions"
CARMEN 2000-2003 [57,85]	*Cancer not considered among exclusion criteria*
CARE-HF 2001-2004 [58,86]	"Life expectancy <1 year for disease unrelated to heart failure"
HEAAL 2001-2009 [59,87]	"Life-limiting disease other than heart failure"
CIBIS-III 2002-2005 [9,60,88]	"Significant disease, which in the investigator's opinion would exclude the patient from the study"
HHH 2002-2005 [61]	*Cancer not considered among exclusion criteria*

OPT-CHF 2003-2004 [62,89]	*Cancer not considered among exclusion criteria*
ACCLAIM 2003-2005 [63,90]	"Malignancy: evidence of disease within the previous five years. Exceptions: basal cell carcinoma, provided it was neither infiltrating nor sclerosing, or carcinoma in situ of the cervix"
SADHART-CHF 2003-2008 [64]	"Life-threatening comorbidity (estimated 50% mortality within 1 year)"
HF-ACTION 2003-2008 [65]	"Comorbid disease or behavioral or other limitations that interfere with performing exercise training or prevent the completion of 1 y of exercise training"
RAFT 2003-2009 [66]	"Major coexisting illness"
FUSION-II 2004-2006 [67]	*Cancer not considered among exclusion criteria*
SHIFT 2006-2010 [68,91]	*Cancer not considered among exclusion criteria*
EMPHASIS-HF 2006-2010 [69]	"Any other clinically significant, coexisting condition"
IN-TIME 2007-2010 [70,92]	*Cancer not considered among exclusion criteria*
TIM-HF 2008-2009 [71]	"Any disease (HF excluded) reducing life expectancy to less than 1 year"
DANISH 2008-2014 [72]	"Receiving or having received cytotoxic or cytostatic chemotherapy and/or radiation therapy for treatment of a malignancy within 6 month before randomization or clinical evidence of current malignancy"
COACH-2 2012-2014 [73]	"The patient had a life expectancy < 6 months"

HFrEF indicates heart failure with reduced left ventricular ejection fraction; RCTs**,** randomized controlled trials; HF, heart failure.