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VIEWPOINT

Risk and risk reduction in trials of heart failure with reduced ejection fraction: absolute or relative?

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Randomized clinical trials (RCTs) of heart failure with reduced ejection fraction (HFrEF) typically recruit patients at high risk of clinical outcomes during the follow-up period by including those with severe symptoms, comorbidities, elevated cardiac biomarkers, or a recent hospitalization.[1] By recruiting patients who will likely respond to the intervention and commonly experience outcomes without it, trials can demonstrate treatment efficacy with smaller sample sizes or shorter periods of follow-up. For example, in the CONSENSUS RCT of enalapril in patients with severe symptoms, 253 enrolled patients demonstrated a 40% relative risk reduction (RRR) in 6-month mortality.[2] In contrast, in the SOLVD trial of enalapril in younger patients with less severe symptoms, 2569 patients were enrolled to demonstrate a 16% RRR in 4-year mortality[3] (*Table 1*).

Some have argued that recruiting high-risk patients in an RCT can have drawbacks – patients may be too advanced in their disease trajectory for treatment to improve physiologic and clinical endpoints.[4] Another concern is that higher-risk patients may experience adverse effects more commonly. The VICTORIA trial showed that vericiguat caused a 10% RRR [hazard ratio (HR) 0.90; 95% confidence interval (CI) 0.82, 0.98] in the composite endpoint of cardiovascular death or heart failure hospitalization.[5] VICTORIA enrolled higher-risk patients (37.8 events/100 patient-years) than a majority of pharmacotherapy trials in patients with HFrEF, a reason proposed by some to explain its modest effect; the absolute risk reduction (ARR) (3.0%) and RRR were lower than in the PARADIGM-HF trial, which recruited lower-risk patients (13.2 events/100 patient-years) and demonstrated that sacubitril-valsartan caused a RRR of 20% (HR 0.80; 95% CI 0.73, 0.87) and ARR of 4.7 vs. enalapril on the same composite endpoint.[6] Furthermore, subgroup analysis in a few HFrEF trials demonstrated the possibility of attenuated treatment effect in higher-risk patients.[6–8] To some, this evidence represents the possibility of a risk threshold within RCTs beyond which pharmacotherapies may provide minimal incremental benefit.

How does the risk of a trial population influence ARR and RRR, and how can these measures be used to guide inferences about treatment effect? Is there a threshold of risk beyond which it is difficult to demonstrate treatment effect in HFrEF RCTs?

Absolute vs. relative risk

Risk is the ratio of individuals developing an undesirable outcome during a follow-up period. Risk comparisons can be described in relative or absolute terms. Often, treatments with a large RRR also offer a large ARR. However, for any given RRR, higher event rates in the trial population will translate to a higher ARR (*Figure 1*). For fair comparisons to be made across populations, it is important to express risk over a standard duration of follow-up, and measures such as annualized mortality can be useful. Incidence rate ratio and HRs are measures of relative risk; the former assumes constant risk over time, while the latter assumes proportional hazards but not constant risk.

With the same relative risk reduction, the absolute risk reduction is greater when higher-risk patients are included

Randomized clinical trials in patients with HFrEF demonstrate an association between baseline risk of death – as measured by annualized mortality – and ARR offered by an intervention. *Table 1* describes the clinical risk profile, annualized mortality, and absolute and relative risk reduction across pivotal trials in HFrEF. The RRR offered by pharmacotherapies in the same class may be consistent across trials, but the ARR varies according to risk of the trial population, which is a reflection of inclusion

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Table 1 **A comparison of patient risk profiles and events in trials of heart failure with reduced ejection fraction**

	CONSEN -SUS (n = 253)	SOLVD (n = 2569)	DIG (n = 6800)	MERIT-HF (n = 3991)	COPER -NICUS (n = 2289)	CHARM-Added (n = 2548)	CHARM-Alternative (n = 2028)	RALES (n = 1663)	EMPHA-SIS-HF (n = 2737)	SHIFT (n = 6508)	PARA-DIGM HF (n = 8399)	DAPA-HF (n = 4744)	EMPEROR-Reduced (n = 3730)	VICTORIA (n = 5050)	GALAC-TIC- HF (n = 8256)
Inclusion criteria	NYHA IV HF	HF and EF < 35%	HF, EF < 45%, and normal sinus rhythm	NYHA II-IV HF and EF < 40%	NYHA IV HF and LVEF < 25%	NYHA II-IV HF, LVEF < 40%, and treated with an ACE inhibitor	NYHA II-IV HF, LVEF < 40%, and intoler-ant to ACE inhibitors	NYHA III-IV HF and EF < 35%	NYHA II HF and EF < 30%	HF with LVEF < 35%, sinus rhythm, resting heart rate > 70 bpm, and HF admi-ssion in prior 12 months	NYHA II-IV HF, LVEF < 35%, and: BNP > 150 pg/mL or NT-proBNP > 600 pg/mL; or hospital-ization in the prior 12 months and BNP > 100 pg/mL or NT-proBNP > 400 pg/mL	NYHA II-IV HF with EF < 40% and: NT-proBNP > 600 pg/mL; or NT-proBNP > 400 pg/mL if hospitalized for HF in the past year	NYHA II-IV HF with: EF < 30% or hospital-ization for HF in the past year; and EF 31–35% and NT-proBNP > 1000 pg/mL; or EF 36–40% and NT-proBNP > 2500 pg/mL	NYHA II-IV HF with EF < 45% and NT-proBNP > 1000 pg/mL within 30 days and: hospitaliza-tion within 3-6 months; or IV diuretics without hos-pitalization within 3 months	Adults aged 18-65 with NYHA II-IV HF, EF < 35%, optimally treated with medical and device therapy, NT-proBNP ≥400 pg/mL, and currently hospita-lized; or presented to ED or hospita-lized within 1 year for HF
Intervention	Enalapril up to 20 mg BID vs. placebo	Enalapril up to 10 mg BID vs. placebo	Digoxin 0.25 mg daily vs. placebo	Metoprolol XL up to 200 mg daily vs. placebo	Carvedilol up to 25 mg BID vs. placebo	Candesartan up to 32 mg daily vs. placebo	Candesartan up to 32 mg daily vs. placebo	Spironolactone 25 mg daily vs. placebo	Eplerenone up to 50 mg daily vs. placebo	Ivabradine up to 7.5 mg BID vs. placebo	Sacubitril-valsartan 200 mg BID vs. enalapril 10 mg BID	Dapagliflozin 10 mg daily vs. placebo	Empagliflozin 10 mg daily vs. placebo	Vericiguat up to 10 mg daily vs. placebo	Omecamtiv mecarbil 25 mg BID, 37.5 mg BID, or 50 mg BID based on 4-week trough level vs. placebo
Age, mean	70.0[a]	61.0[a]	63.5[a]	63.7[a]	63.4[a]	64.1[a]	66.8[a]	65.0[a]	68.6[a]	60.1[a]	63.8	66.4	66.9	67.3	64.5
NT-proBNP, median	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported	1608.0	1437.0	1926.0	2816.0	1971.0
LVEF, mean	Not reported	24.9[a]	28.4[a]	28.0[a]	19.8[a]	28.0[a]	30.0[a]	25.2[a]	26.1[a]	29.0[a]	29.5	31.1	27.5	28.9	26.6
eGFR, mean or serum creatinine, mean	124.0 μmol/L[a]	106.1 μmol/L[a]	Not reported	Not reported	Creatinine: 134.0 μmol/L[a]	Not reported	Not reported	Not reported	70.4 mL[a]/ min/1.73 m^2	74.8 mL[a]/ min/1.73 m^2	70.0 mL/ min/1.73 m^2	65.8 mL/ min/1.73 m^2	62.0 mL/ min/1.73 m^2	61.5 mL/ min/1.73 m^2	60.3 mL/min/ 1.73 m^2
CKD (%)	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported	34.5[a]	Not reported	33.0	40.2	48.3	52.0	52.5

Table 1 (Continued)

	CONSEN -SUS (*n* = 253)	SOLVD (*n* = 2569)	DIG (*n* = 6800)	MERIT-HF (*n* = 3991)	COPER -NICUS (*n* = 2289)	CHARM-Added (*n* = 2548)	CHARM-Alternative (*n* = 2028)	RALES (*n* = 1663)	EMPHA-SIS-HF (*n* = 2737)	SHIFT (*n* = 6508)	PARA-DIGM HF (*n* = 8399)	DAPA-HF (*n* = 4744)	EMPEROR-Reduced (*n* = 3730)	VICTORIA (*n* = 5050)	GALAC-TIC- HF (*n* = 8256)
At least one prior ED visit in preceding year	Not reported	Not reported	Not reported	Not reported	65.0	Not reported	Not reported	Not reported	Not reported	100.0	42.0	27.0	31.0[a]	83.9	74.5
Follow-up duration	Mean: 188.0 days	Mean: 41.4 months	Mean: 37 months	Mean: 1.0 years	Mean: 10.4 months	Median: 41.0 months	Median: 33.7 months	Mean: 24.0 months	Median: 21.0 months	Median: 22.9 months	Median: 27.0 months	Median: 18.2 months	Median: 16.0 months	Median: 10.8 months	Median: 21.8 months
Primary outcome	6-month all-cause mortality	4-year all-cause mortality	All-cause mortality	All-cause mortality	All-cause mortality	Composite of CV death or HF hospital-ization	Composite of CV death or HF hospital-ization	All-cause death	Composite of CV death or HF hospital-ization	Composite of CV death or HF hospital-ization	Composite of CV death or HF hospital-ization	Composite of CV death or worsening HF (hospital-ization for HF or visit resulting in IV diuretic use)	Composite of CV death or HF hospital-ization	Composite of CV death or HF hospital-ization	Composite of CV death or HF event (clinic or ED visit or admiss-ion for HF)
CV death or HF decompen-sation hospital-ization events, *n* (%)	Not reported	1274 (49.6)	2332 (34.3)	750 (18.8)	628 (27.4)[b]	1021 (40.1)	740 (36.5)	893 (53.7)	605 (22.1)	1730 (26.6)	2031 (24.2)	877 (18.5)	823 (22.1)	1869 (37.0)	3130 (38.0)
Annualized CV death or HF decompen-sation or hospi-talization events per 100 patient years	Not reported	26.0[b]	17.0[b]	23.9[b]	46.5[b]	16.6	18.2	45.4[c]	16.7[c]	20.0[b]	13.2[b]	15.3	21.0	37.8	26.3
RR (95% CI) or HR (95% CI) for composite CV death or HF decompen-sation or hospi-talization	Not reported	RR 0.74 (0.66, 0.82)	RR 0.75 (0.69, 0.82)	RR 0.69 (0.60, 0.80)	RR 0.74 (0.65, 0.85)	HR 0.85 (0.75, 0.96)	HR 0.70 (0.60, 0.81)	RR 0.67 (0.59, 0.77)[c]	HR 0.63 (0.54, 0.74)	HR 0.82 (0.75, 0.90)	HR 0.80 (0.73, 0.87)	HR 0.75 (0.65, 0.85)	HR 0.75 (0.65, 0.86)	HR 0.90 (0.82, 0.98)	HR 0.92 (0.86, 0.99)
ARR for CV death or HF decom-pensation or/hospitali-zation	Not reported	10.3	HF death or HF hospitaliza-tion 7.3	6.3	8.1	4.4	7.0	14.5[c]	7.6	4.2	4.7	4.8	5.3	3.0	2.1
ARR for CV death or HF decompensa-tion or hospitalization per 100 patient years	Not reported	7.6[b]	4.3[c]	7.4[b]	13.5[b]	2.5	4.4	16.0[c]	6.2[c]	3.7[b]	2.7[b]	3.9	5.2	4.2	2.1
CV deaths, *n* (%)	110 (43.5)	860 (33.5)	2020 (29.7)	331 (8.3)	Not reported	649 (25.5)	471 (23.2)	540 (32.5)	332 (12.1)	940 (14.4)	1251 (14.9)	500 (10.5)	389 (10.4)	855 (16.9)	1606 (19.5)

Table 1 (Continued)

	CONSEN -SUS (*n* = 253)	SOLVD (*n* = 2569)	DIG (*n* = 6800)	MERIT-HF (*n* = 3991)	COPER -NICUS (*n* = 2289)	CHARM-Added (*n* = 2548)	CHARM-Alternative (*n* = 2028)	RALES (*n* = 1663)	EMPHA-SIS-HF (*n* = 2737)	SHIFT (*n* = 6508)	PARA-DIGM HF (*n* = 8399)	DAPA-HF (*n* = 4744)	EMPEROR-Reduced (*n* = 3730)	VICTORIA (*n* = 5050)	GALAC-TIC- HF (*n* = 8256)
Annualized CV deaths per 100 patient years	Not reported	13.0	10.1[b]	10.3	Not reported	9.3[d]	9.8[d]	21.6[b]	7.9[b]	8.5[b]	7.5[b]	7.9	8.1	13.9	10.8
RR (95% CI) or HR (95% CI) for CV death	Not reported	RR 0.82 (0.72, 0.94)	RR 1.01 (0.93, 1.10)	RR 0.62 (0.50, 0.78)	Not reported	HR 0.83 (0.71, 0.97)	HR 0.80 (0.66, 0.96)	RR 0.69 (0.58, 0.82)	HR 0.76 (0.61, 0.94)	HR 0.91 (0.80, 1.03)	HR 0.80 (0.71, 0.89)	HR 0.82 (0.69, 0.98)	HR 0.92 (0.75, 1.12)	HR 0.93 (0.81, 1.06)	HR 1.01 (0.92, 1.11)
ARR for CV death	Not reported	4.8	−0.4	3.7	Not reported	3.6	3.2	9.8	2.7	1.2	3.2	1.9	0.8	1.1	-0.2
ARR for CV death per 100 patient years	Not reported	2.3[b]	0.2[b]	3.9	Not reported	1.4[d]	1.6[d]	6.8[b]	1.8[b]	0.8[b]	1.5[b]	1.4	0.5	1.0	-0.1
All-cause deaths, *n* (%)	118 (46.6)	962 (37.4)	2375 (34.9)	362 (9.1)	320 (14.0)	789 (40.0)	561 (27.7)	670 (40.3)	384 (14.0)	1055 (16.2)	1546 (18.4)	605 (12.8)	515 (13.8)	1046 (20.7)	2132 (25.8)
Annualized all-cause death per 100 patient years	52.0	14.4[b]	12.0[c]	11.0	19.7	11.1[d]	11.5[d]	26.6[b]	9.1[b]	9.6[b]	9.0[b]	9.5	10.7	16.9	14.4
RR (95% CI) or HR (95% CI) for all-cause death	RR 0.60 (95% CI not reported)	RR 0.84 (0.74, 0.95)	RR 0.99 (0.91, 1.07)	RR 0.66 (0.53, 0.81)	RR 0.65 (0.52, 0.81)	HR 0.89 (0.77, 1.02)	HR 0.83 (0.70, 0.99)	RR 0.70 (0.60, 0.82)	HR 0.76 (0.62, 0.93)	HR 0.90 (0.80, 1.02)	HR 0.84 (0.76, 0.93)	HR 0.83 (0.71, 0.97)	HR 0.92 (0.77, 1.10)	HR 0.95 (0.84, 1.07)	HR 1.00 (0.92, 1.09)
ARR for all-cause death	15.0	4.5	0.3	3.6	5.5	2.8	3.0	11.3	3.0	1.4	2.8	2.3	0.8	0.8	0.0
ARR for all-cause death per 100 patient years	16.0	2.3[b]	0.0[c]	3.8	7.0	1.3[d]	1.5[d]	8.1[b]	2.0[b]	0.9[b]	1.3[b]	1.6	0.6	0.9	0.0

ACE, angiotensin-converting enzyme; ARR, absolute risk reduction; BNP, B-type natriuretic peptide; CI, confidence interval; CKD, chronic kidney disease; CV, cardiovascular; ED, emergency department; EF, ejection fraction; eGFR, estimated glomerular filtration rate; HF, heart failure; HR, hazard ratio; IV, intravenous; LVEF, left ventricular ejection fraction; NT-proBNP, N-terminal pro B-type natriuretic peptide; NYHA, New York Heart Association; RR, relative risk.

[a]Data for comparator group; baseline characteristics for entire trial population not presented.

[b]Derived using the methods described by Skali H, Pfeffer MA, Lubsen J, Solomon SD. Variable impact of combining fatal and nonfatal end points in heart failure trials. Circulation 2006;114:2298–2303.

[c]As per Ferreira JP, Docherty KF, Stienen S, Jhund PS, Claggett BL, Solomon SD, Petrie MC, Gregson J, Pocock SJ, Zannad F, McMurray JJV. Estimating the lifetime benefits of treatments for heart failure. JACC Heart Fail 2020;8:984–995.

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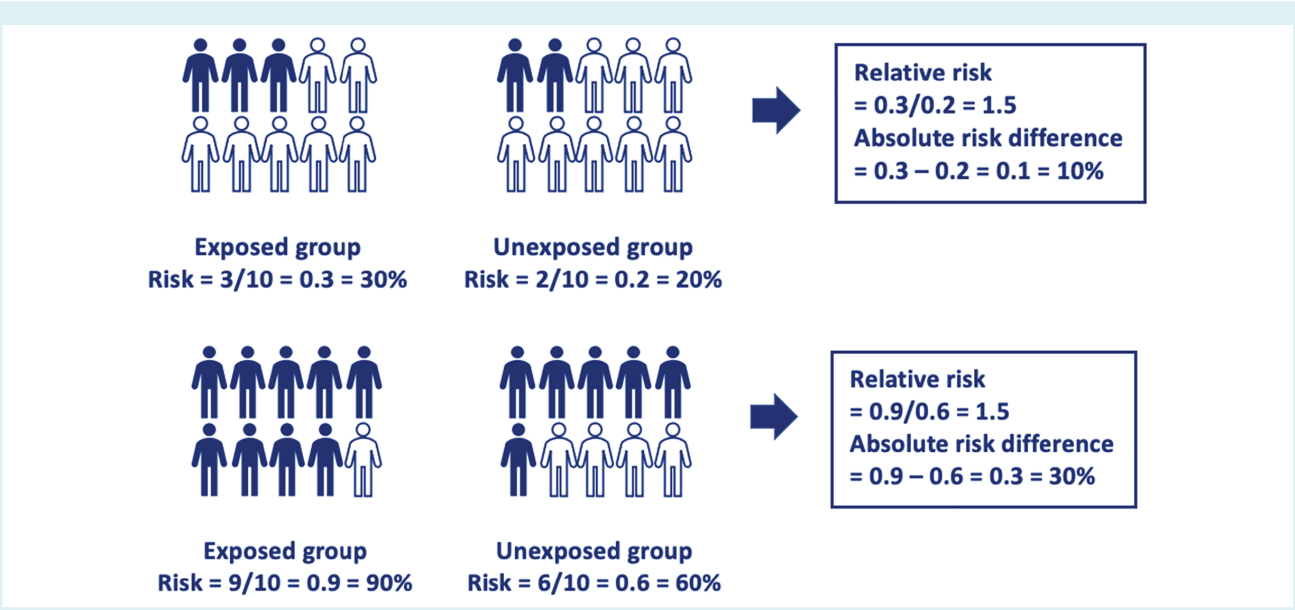

Figure 1 Hypothetical example of two studies (top and bottom panel), each with 20 participants: 10 in the exposed and 10 in the unexposed group. Participants who experienced the outcome (blue) and no outcome (white) after 1 year of follow-up are depicted. The lower panel depicts a higher-risk population with a higher proportion experiencing events. Although the relative risk of the outcome in both studies is the same, the absolute risk difference in the higher-risk population is greater.

criteria.[7,8] In the COPERNICUS trial of patients with New York Heart Association (NYHA) class III–IV symptoms, carvedilol decreased all-cause mortality[7] [relative risk (RR) 0.65; 95% CI 0.52, 0.81] with a similar RRR as metoprolol XL in MERIT-HF[8] (RR 0.66; 95% CI 0.53, 0.81), which enrolled patients with milder symptoms. COPERNICUS had a higher annualized all-cause death (19.7 vs. 11.0 events/100 patient-years) and a greater ARR (7.0 vs. 3.8 events/100 patient-years) for all-cause death than MERIT-HF. Similarly, in the RALES trial in patients with NYHA class III–IV symptoms, spironolactone reduced all-cause mortality[9] (RR 0.70; 95% CI 0.60, 0.82) with a similar magnitude as eplerenone in the EMPHASIS-HF trial (HR 0.76; 95% CI 0.62, 0.93) which enrolled patients with milder symptoms.[10] RALES had higher annualized all-cause deaths than EMPHASIS-HF (26.6 vs. 9.1 events/100 patient-years) and the ARR for RALES was greater than EMPHASIS-HF (8.1 vs. 2.0 events/100 patient-years), reflecting the differing baseline risk of enrolled patients. Thus ARR is sensitive to the baseline risk of a population (*Figure 1*).

The absolute risk reduction must be interpreted in the context of baseline risk

Most trials report their primary outcomes as RRR, an important measure of treatment effect that remains relatively stable across baseline risk. This measure is intuitive, although the number of events during the follow-up period and the modelling assumptions need to be borne in mind when making inferences. Effect sizes look larger when presented as RRR rather than ARR; for example, 'this treatment reduced death by 50%' looks more impressive than 'this treatment reduced death from 2% to 1%'.[11] Adverse effects are often presented as absolute risk, and they look smaller this way. While RRR is a stable measure that reflects the magnitude of treatment effect, it does not adequately reflect effect at the population level. A treatment with an RRR of 50% will have a greater impact on the population health if it reduces risk from 20% to 10% than from 2% to 1%. In a common disease or one with high event rates, however, even a small ARR can have a large impact on the population health.

An important benefit of ARR over RRR is that it can be used to estimate the number of patients needed to treat (NNT) to prevent one event. Because both ARR and RRR reflect treatment at the end of the follow-up period – which varies across trials – ARR can be annualized to estimate NNT for a year to prevent one event. As with RRR, this must be contextualized according to the other findings of the study. For example, from VICTORIA and PARADIGM-HF we can extrapolate that 24 patients need to be treated with vericiguat vs. placebo and 37 patients need to be treated with sacubitril-valsartan vs. enalapril for 1 year to prevent one primary composite event. However, this is not an appropriate comparison as vericiguat was a less effective treatment overall; it offered a higher annualized ARR in a higher-risk population than did sacubitril-valsartan, but offered a lower RRR for the primary composite outcome and had no significant reduction in death.

The limitations of RRR and annualized ARR can be bridged by utilizing both measures. *Figure 2A* depicts the relationship between baseline risk of cardiovascular death or heart failure hospitalizations in the control groups and the ARR in pivotal RCTs. Among effective pharmacotherapies, there is a linear association between

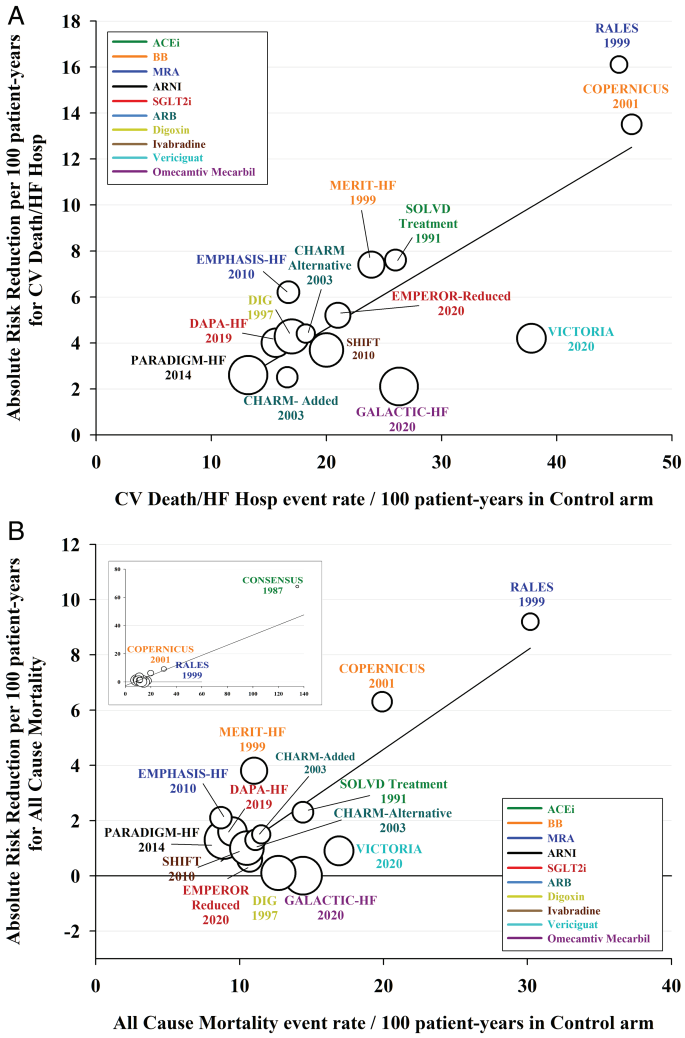

Figure 2 (*A*) Absolute risk reduction (ARR) as a function of baseline risk of the primary composite outcome [cardiovascular (CV) death or heart failure (HF) hospitalization] in the control group in pivotal trials of HF with reduced ejection fraction (HFrEF). (*B*) ARR as a function of baseline risk of all-cause mortality in the control group in pivotal trials of HFrEF. The insert shows data from the CONSENSUS trial, which was an outlier relative to other trials (Cook's distance >1.0) and therefore not included in the regression plot in the main figure. Data were extracted from the original publications or retrospective analyses, if presented, or were estimated from Kaplan–Meier survival curves. Size of circles in panels reflect trial sample size. The regression line in each plot was constructed by simple linear regression based on study level data and added for visualization rather than quantification of the association. Robust regression analyses were carried out to evaluate possible confounding data-points. For the outcome of all-cause mortality, the standardized β was 0.80 ($P < 0.01$), and for the outcome of CV death or HF hospitalization, the standardized β was 0.79 ($P < 0.01$). COPERNICUS and MERIT-HF depict all-cause death/HF hospitalization, and DIG depicts HF death/HF hospitalization in panel *A*. PARADIGM-HF, designed to test the effect of neprilysin inhibition, had an active comparator of enalapril. With improved treatments and prognosis over time in the control group, risk (events/100 patient-years) in HFrEF trials has decreased overall, with small variations in risk related to trial risk enrichment strategies. A greater ARR for a given level of risk denotes greater treatment efficacy. For any given outcome and level of risk, interventions that are more efficacious are along or above the regression line and those that are less efficacious are far below the regression line. There was no evidence of outliers among the trials listed in the main plot (Cook's distance in robust regression analysis <1.0). Angiotensin-converting enzyme inhibitors/angiotensin receptor blockers (ACEi/ARB), angiotensin receptor–neprilysin inhibitors (ARNI), beta-blockers (BB), mineralocorticoid receptor antagonists (MRA) and sodium–glucose co-transporter 2 inhibitors (SGLT2i) remain among the most effective pharmacotherapies at reducing CV death or worsening HF as well as all-cause mortality (*Table 1*). Data from CONSENSUS (all-cause mortality), DIG (HF death/HF hospitalization) and SHIFT (both endpoints) extracted according to Skali *et al.*[14]

baseline risk and annualized ARR. Cornerstone treatments of HFrEF [angiotensin-converting enzyme inhibitors/angiotensin receptor blockers (ACEi/ARB), angiotensin receptor–neprilysin inhibitors (ARNI), beta-blockers (BB), mineralocorticoid receptor antagonists (MRA), sodium–glucose co-transporter 2 inhibitors (SGLT2i)] are at or above the regression line. In contrast, the treatment effects of vericiguat and omecamtiv mecarbil are small, particularly given the large number of baseline events relative to other HFrEF trials; the annualized ARR achieved with each of these pharmacotherapies is lower than expected. Subgroup analyses from the VICTORIA5 and GALACTIC-HF12 trials reveal conflicting data regarding the association between baseline risk and treatment effect, and have served as arguments for targeting therapies to specific groups. However, subgroup analyses are hypothesis-generating, limited by multiple testing, and ill-justified in guiding treatment, especially when a pharmacotherapy has little overall effect in a trial with a large number of events.

The linear association between baseline risk and annualized ARR among effective pharmacotherapies is also evident for the outcome of all-cause mortality. While a majority of trials were not adequately powered for mortality, the cornerstones of HFrEF treatment all showed reductions in mortality. In contrast, interventions such as digoxin,[13] vericiguat,[5] and omecamtiv mecarbil[12] did not reduce mortality despite adequate trial event rates. For any given outcome and level of risk, then, more efficacious therapies are along or above the regression line of annualized ARR to annualized events (*Figure 2*) and less efficacious therapies are below the regression line. As evident, ACEi/ARB, ARNI, BB, MRA, SGLT2i remain among the most effective pharmacotherapies at reducing composite cardiovascular death or worsening heart failure as well as all-cause mortality (*Figure 2B*). With improved uptake of evidence-informed treatments, there has been an overall reduction in absolute risk (events/100 patient-years) in control groups over time, with variations in baseline risk partly related to trial inclusion criteria.

Without reasonable trial risk enrichment strategies, current-era trials would need to be much longer to accrue the events required to demonstrate treatment effect. Within the context of HFrEF RCT populations – haemodynamically stable, ambulatory patients in whom treatment is not futile and comorbidities not so severe as to pose risk of harm with treatment – higher risk makes it easier to demonstrate treatment efficacy with efficiency. Pharmacotherapies that are considered first-line treatments in HFrEF have demonstrated efficacy across a range of risk. In the context of RCT populations, there is no evidence of a threshold beyond which risk is too high for treatment efficacy to be demonstrated. To date, there is no pharmacotherapy that has demonstrated a greater treatment effect in a HFrEF trial population with lower baseline event rates than in one with higher event rates.

Summary

The clinician is left with a few key concepts from this evidence. First, risk enriched RCT populations with high event rates make it easier – not harder – to efficiently demonstrate treatment effect. Second, ARR or NNT cannot be interpreted or compared across trials without adjusting for the baseline risk, which is estimated using annualized events/100 patient-years. For any given RRR, ARR has a linear association with baseline risk, providing insights into treatment effect at the risk level of the trial population. RRR is less sensitive to changes in baseline risk, reflecting treatment effect at the individual level. Both ARR and RRR should be considered in the context of the number of events accrued in the trial; the larger the number of events, the greater the statistical power to demonstrate an effect with precision. Subgroup analyses are hypothesis-generating and should not direct treatment, especially the intervention has little or no effect overall in a trial population with a large number of events.

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