Heart

Do beta-blockers and RAAS inhibitors improve outcomes in patients with heart failure and left ventricular ejection fraction greater than 40 percent?

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Do beta-blockers and inhibitors of the renin-angiotensin aldosterone system improve outcomes in patients with heart failure and left ventricular ejection fraction greater than 40 percent?

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BACKGROUND

Approximately half of all patients with heart failure have preserved left ventricular ejection fraction, yet in contrast to heart failure with reduced ejection fraction (HFrEF), no treatments have yet been shown to be effective at improving outcomes [1]. Neurohumoral activation is observed in heart failure across the full spectrum of left ventricular function [2], however pharmacological inhibition of the renin-angiotensin aldosterone system (RAAS) has only be demonstrated improve survival and reduce hospitalisation in HFrEF [1]. There is some evidence suggesting that LVEF is an effect modifier for treatment effects of inhibitors of the renin-angiotensin aldosterone system (RAAS) in heart failure, with greater benefit observed in patients with lower LVEF [3]. We therefore performed a Cochrane systematic review and meta-analysis to synthesis all available evidence to test whether pharmacological inhibition of RAAS would be of benefit in heart failure with a left ventricular ejection fraction greater than 40%. This patient population comprises both heart failure with mid-range (HFmrEF, 40-49%) and preserved ejection fraction (HFpEF, >50%).

METHODS

We searched for randomised controlled trials (RCTs) investigating pharmacological neurohumoral inhibition with beta-blockers, angiotensin converting enzyme inhibitors, angiotensin receptor blockers, mineralocorticoid receptor antagonists, and angiotensin receptor-neprilysin inhibitors, in patients with HFpEF, defined by a left ventricular ejection fraction greater than 40%, in adult patients (≥18 years old). We searched MEDLINE, Embase, and the Cochrane Central Register of Controlled Trials (CENTRAL) on 25 July 2017. The primary outcomes were cardiovascular mortality, heart failure hospitalisation, and hyperkalaemia; and the secondary outcomes were all-cause mortality, quality of life (measured using either the Minnesota Living with Heart Failure Questionnaire or *Kansas City Cardiomyopathy Questionnaire)*. Where possible, we undertook meta-analysis for each drug class and outcome using a fixed-effect model except where heterogeneity was high ($I^2 \geq 50\%$) when a random-effect model was used. We evaluate the quality of evidence for each comparison using GRADE and the review was conducted in accordance with the guidelines provided in the Cochrane Handbook [4], and reported findings using standardised terminology [5]. Given the high absolute risk for mortality and hospitalisation outcomes in heart failure, we interpreted a modest reduction in relative risk (>15%) as a clinically meaningful effect.

RESULTS

Database searches retrieved 57890 unique records from which we identified 207 records from 37 RCTs that met our inclusion criteria. These studies reported data for 18,311 participants and enrolment periods ranged from 1997 to 2012. The threshold of left ventricular ejection fraction, used to classify heart failure patients for inclusion in studies, was between 40-50%. A minority of studies specified inclusion criteria that included corroboration of clinical heart failure (prior heart failure hospitalisation or elevated natriuretic peptides) or echocardiographic markers of diastolic dysfunction or elevated filling pressures. Notable differences in patient characteristics were observed with respect to co-morbid cardiovascular disease and baseline medication. We performed a quantitative synthesis of 22 trials investigating the effects of four classes of pharmacological renin-angiotensin aldosterone system inhibitors: beta-blockers (BB), angiotensin converting enzyme inhibitors (ACEI), angiotensin receptor blockers (ARB), or mineralocorticoid receptor antagonist (MRA). We pooled quality of life data from the Minnesota Living with Heart Failure (MLHF) questionnaire however our findings were inconclusive due to a quality of evidence that was either low or very low, except for ARB where there was no effect. The results of these interventions on the cardiovascular (CV) mortality, heart failure hospitalisation, and all-cause mortality are summarised in **Table 1**.

Intervention	Outcome	RCTs (n)	Participants (n)	Follow-up range (months)	Anticipated absolute effects (95% CI)		RR - all studies (95% CI)	Certainty of the evidence (GRADE)	Sensitivity anaylsis (low risk of bias studies)		Important effect (RR < 0.85)	Interpretation
					Control (events per 1000)	Intervention (events per 1000)			RCTs (n)	RR (95% CI)		
Beta-blocker	Cardiovascular mortality	3	1046	21 to 38	173	135 (107, 171)	0.78 (0.62, 0.99)	●●○○ LOW	1	0.81 (0.50, 1.29)	YES	May reduce CV mortality
	All-cause mortality	4	1105	21 to 38	243	199 (163, 243)	0.82 (0.67, 1.00)	●●○○ LOW	1	0.93 (0.63, 1.35)	NO	May have little or no effect
	Heart failure hospitalisation	4	449	6 to 38	117	86 (55, 133)	0.73 (0.47, 1.13)	●○○○ VERY LOW	0	-	YES	Effects uncertain
Mineralocorticoid receptor antagonists	Cardiovascular mortality	3	4070	12 to 40	88	79 (65, 97)	0.90 (0.74, 1.11)	●●●○ MODERATE	1	0.91 (0.74, 1.11)	NO	Probably little or no effect
	All-cause mortality	5	4207	9 to 3840	133	121 (104, 141)	0.91 (0.78, 1.06)	●●●○ MODERATE	2	0.92 (0.79, 1.08)	NO	Probably little or no effect
	Heart failure hospitalisation	3	3714	24 6 to 40	136	112 (94, 134)	0.82 (0.69, 0.98)	●●●○ MODERATE	1	0.84 (0.71, 1.00)	YES	**Probably reduces heart failure hospitalisation**
Angiotensin converting enzyme inhibitor	Cardiovascular mortality	2	945	12 to 26	86	81 (53, 123)	0.93 (0.61, 1.42)	●●●○ MODERATE	1	0.95 (0.63, 1.46)	NO	Probably little or no effect
	All-cause mortality	4	1079	6 to 26	119	119 (84, 166)	0.99 (0.71, 1.38)	●●●○ MODERATE	1	1.06 (0.75, 1.51)	NO	Probably little or no effect
	Heart failure hospitalisation	3	1019	6 to 26	13	11 (8, 15)	0.86 (0.64, 1.15)	●●●○ MODERATE	1	0.88 (0.65, 1.20)	NO	Probably little or no effect
Angiotensin receptor blocker	Cardiovascular mortality	3	7254	12 to 50	131	133 (118, 149)	1.02 (0.90, 1.14)	●●●● HIGH	2	1.02 (0.90, 1.14)	NO	Little or no effect

	All-cause mortality	4	7964	12 to 53	72	73 (66, 80)	1.01 (0.92, 1.11)	●●●● HIGH	2	1.02 (0.93, 1.12)	NO	Little or no effect
	Heart failure hospitalisation	3	7254	12 to 50	171	157 (142, 174)	0.92 (0.83, 1.02)	●●●● HIGH	2	0.92 (0.83, 1.02)	NO	Little or no effect

Table 1. Summary of effect of inhibitors of the renin-angiotensin aldosterone system in heart failure with ejection fraction greater than 40 percent

Beta-blockers

We performed meta-analyses of up to four studies and 1105 participants. The quality of evidence was low or very low due to high risk of bias and imprecision. The analysis of all studies suggested an BB may improve CV mortality however these effects were attenuated upon sensitivity analysis, including only studies with a low risk of bias, where the results could be consistent with little or no effect. The results were similar for all-cause mortality. For heart failure hospitalisation, the quality of evidence was very low and the effects on this outcome remain uncertain. High rates of discontinuation due to intolerance were reported for the two largest studies (J-DHF and SENIORS) due to intolerance rather than adverse events and this may have attenuated any effects.

Mineralocorticoid receptor antagonists

We performed meta-analysis of up to six trials with 4291 participants and our results suggest that treatment with MRA probably reduces the risk of heart failure hospitalisation but has little or no effect on cardiovascular or all-cause mortality. The quality of evidence was moderate, and uncertainty remains over treatment effects.

Angiotensin converting enzyme inhibitors

We combined evidence from up to four trials and 1079 participants through meta-analysis. No large RCTs were available (>1000 participants) have been conducted and the quality of evidence was moderate due to imprecision. Our results, however, suggest that there was probably little or no effect of ACEI on cardiovascular mortality, all-cause mortality, heart failure hospitalisation.

Angiotensin receptor blocker

We performed meta-analyses from up 7964 participants from four trials, two of which were well large and well designed (I-PRESERVE and CHARM preserved). We found little or no effect of ARB on the outcomes of cardiovascular mortality, all-cause mortality, and heart failure hospitalisation.

DISCUSSION

In this review, we sought to determine the effects of pharmacological inhibition of the renin-angiotensin aldosterone system in patients with heart failure and left ventricular ejection fraction over 40%. Our systematic review highlighted a persistent lack of RCT evidence to inform treatment approaches for this disease. When we pooled data from multiple RCTs, we found that MRA probably reduce heart failure hospitalisation, however for other outcomes and intervention comparisons we found that there was either no effect (ARB), or there was insufficient evidence to detect a modest beneficial effect (BB, ACEI).

We noted significant differences in the inclusion and exclusion criteria used to specify the patient population across RCTs for HFpEF, reflecting a lack of a durable definition for this condition; the resulting heterogeneity of study populations with respect to disease phenotype and/ or stage may account differences in the placebo event rates that were observed across studies. The symptoms and signs of heart failure are non-specific and, in absence of overt left ventricular systolic failure, distinguishing a primary causal role for cardiac dysfunction from commonly associated non-cardiac causes remains challenging. With few exceptions, trials did not specify a requirement for prior heart failure hospitalization, elevated plasma natriuretic peptides, or echocardiography measures of elevated filling pressures, and it is possible that the patient populations included subjects who did not have significant cardiac dysfunction.

Two important outcomes trials are currently underway that should significantly advance our understanding of whether RAAS inhibition is beneficial in all patients with heart failure or only those with reduced LVEF. Firstly, the SPIRRIT trial is a registry-randomised clinical outcomes trial of spironolactone for HFpEF that aims to enrol 3200 patients in Sweden and the United States (NCT02901184). Secondly, the PARAMOUNT trial will investigate the effects of angiotensin receptor neprilysin inhibition with sacubitril-valsartan (NCT00887588)[6]. Both of these trials carefully define the study population and include a requirement for elevated N-terminal pro-brain natriuretic peptide.

Although heart failure patients share common phenotypic characteristics such as elevated left ventricular filling pressures and fluid congestion, important differences in the underlying pathophysiology may

influence treatment effects [7]. New treatment paradigms that go beyond RAAS inhibition are emerging, including therapies that target causal mechanisms for disease onset. For example, observational studies have shown that over one in every seven patients with HFpEF have evidence of wild-type transthyretin (TTR) amyloidosis [8]. The ATTR-ACT trial (n = 441) found that treatment with a selective TTR stabilizer lead to a reduction in all-cause mortality (hazard ratio 0.70, confidence interval (CI) 0.51 – 0.96) and hospitalisation for heart failure (relative risk 0.68, CI 0.56 – 0.81)[9].

CONCLUSION

The evidence exploring the effects of RAAS inhibition in HFpEF remains largely inconclusive however we did find evidence to suggest a probable benefit from MRA in reducing heart failure hospitalisation. The lack of large clinical trials means that a modest beneficial (or harmful) effect from RAAS inhibition cannot be excluded for this patient group and the results of ongoing studies will be informative. Whether or not RAAS inhibition will come to have a role in the treatment of heart failure patients with LVEF >40%, it is likely that a significant unmet need will remain for this group. New treatment approaches are required that target the underlying causal biology as exemplified by TTR stabiliser therapy. The application of precision phenotyping of heart failure at population scale using molecular measures and advanced cardiac imaging are likely to yield insights into modifiable disease mechanisms that may inform new therapeutic approaches.

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COMPETING INTERESTS

CD has received sponsorship from Servier, Roche and Novartis to attend cardiology conferences, payment from GE Healthcare to give lectures on heart failure and has served as a paid consultant to Servier and

Vifor. RTL: has received research grants from Pfizer and has served as an unpaid consultant to GSK.