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Clinical research

Six minute corridor walk test as an outcome measure for the assessment of treatment in randomized, blinded intervention trials of chronic heart failure: a systematic review

Lars G. Olsson[1], Karl Swedberg[1]*, Andrew L. Clark[2], Klaus K. Witte[2], and John G.F. Cleland[2]

[1] *Department of Medicine, Sahlgrenska University Hospital/Östra, SE-416 85 Göteborg, Sweden*
[2] *Department of Academic Cardiology, Castle Hill Hospital, Cottingham, Kingston upon Hull, UK*

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KEYWORDS
Chronic heart failure;
Six minute walk test;
Submaximal exercise;
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Aims The 6 min walk test (6MWT) is commonly used in clinical trials to assess treatments for heart failure, but its ability to distinguish between effective and ineffective treatments is questionable. The aim of this study is to investigate, using a systematic literature review, the utility of the 6MWT as a measure of the effectiveness of treatment in randomized controlled trials of heart failure.

Methods and results A literature search was performed using Medline, EMBASE, CINAHL, and Biological abstracts for randomized controlled trials that measured 6MWT between 1988 and 31 May 2004. A significant increase in 6MWT distance was observed in only 9 of 47 randomized controlled trials of pharmacological therapy; 2 of 6 trials of ACE-inhibitors; 3 of 17 trials of beta-blockers; 1 of 4 trials of digoxin; one trial of ibopamine; one trial of L-arginine; one trial of beriberine; and one trial showed superiority of captopril over flosequinan. A significant increase in 6MWT was observed in four out of six placebo-controlled trials of cardiac resynchronization. Smaller pharmacological trials with fewer centres were more likely to be positive; six out of nine positive pharmacological trials had four or less participating centres, raising the possibility of publication bias. Pharmacological trials including patients with more severe heart failure were more likely to show a significant improvement with therapy than trials of milder heart failure. Five out of seven pharmacological trials that reported an improvement in symptoms also reported an improvement in 6MWT distance. Of 30 pharmacological trials, 29 that reported no improvement in symptoms also reported no improvement in 6MWT. Using mean values in these trials, the age of patients appeared a more important determinant of 6MWT distance than New York Heart Association classification.

Conclusion The 6MWT has not yet been proven to be a robust test for the identification of effective pharmacological interventions although it appears useful for the assessment of cardiac resynchronization therapy. The results of the 6MWT were concordant with changes in symptoms, suggesting that it may be used as supportive evidence for symptom benefit. The test may be of greater value in patients with more advanced heart failure, where it may function as a maximal exercise test.

* Corresponding author. Tel: +46 313434000; fax: +46 31258933.
E-mail address: karl.swedberg@hjl.gu.se

Introduction

Chronic heart failure is a major health problem.[1] During the last 25 years, several new therapies have been introduced that can prolong life and delay hospitalizations for heart failure.[2–5] The prevalence of heart failure is rising partly due to ageing of the population and partly due to increased longevity of even patients with severe heart failure.[6] Accordingly, there is growing need for further innovations in care for patients with heart failure and for tools with which to evaluate treatment.

The objective of managing patients with heart failure is generally to improve well being and increase longevity. The relative importance of these outcomes will vary among patients and their circumstances. Evaluating the effects of treatment on mortality usually requires large, long-term trials and, when adequately powered, provides robust evidence of the presence and magnitude of effect. It is generally accepted that there are no adequate surrogate measures for mortality. Evaluating well being in patients with heart failure appears more complex, as the patients perceptions will be coloured by their previous health state, future expectations, mood, intercurrent illnesses, and the way in which they are asked questions. Equally, knowledge of the severity of cardiac dysfunction, age, and prognosis will affect the investigator's assessment, consciously or unconsciously. Accordingly, researchers have turned to surrogate measures in an attempt to identify an accurate, objective, and reproducible method of assessing patients' well-being. Bicycle and treadmill exercise tests have been used to assess the effects of therapy in heart failure for at least 40 years.[7–9] Brief, high-intensity exercise tests may be used to assess cardiorespiratory reserve, while longer, lower intensity protocols can be used to assess submaximal exercise endurance, which is determined by complex interactions among the lungs, heart, circulation, and muscle. However, formal exercise testing, especially when coupled with assessment of gas exchange, is complex to administer, may be a poor measure of limiting symptoms during daily activity, and may have limited reproducibility unless patients and staff are rigorously trained. Moreover, many patients are unable or unwilling to exercise adequately on such equipment and training effects may be substantial. On the other hand, all ambulatory patients can manage a self-paced 6 min walk test (6MWT).[10,11] It is simple, inexpensive, and carries important prognostic information.[12–14] As the patient determines the distance walked and because such activity is familiar, it may be more representative of patients' everyday experience.

The 6MWT has been used as an outcome measure in clinical trials since 1988, but its ability to distinguish between effective or ineffective interventions in patients with heart failure has not been assessed in detail. The purpose of this review is to evaluate the utility of the 6MWT for the evaluation of therapy in randomized controlled trials of heart failure, features of trial design that may influence its success, and whether or not the results of 6MWT were concordant with other trial outcomes.

Methods

A literature search was performed using Medline, EMBASE, CINAHL, and Biological abstracts. Additional searches were performed using the Science Direct™ database, where the used phrases were 'walk' or 'walking' in full-text and 'heart failure' and 'ventricular dysfunction' in the title–abstract–keyword section. Reference lists of papers identified were read to identify additional papers. Additional information was gathered through authors, expert colleagues, and study sponsors. Trials published only in abstract form at scientific meetings were also included.

For inclusion, the trials had to be randomized, blinded (patient, supervisor, or both), report the results of the 6MWT, administer at least daily doses of treatment or have devices implemented, and comprise patients with diagnosed heart failure with or without major left ventricular (systolic) dysfunction who had stable symptoms or were asymptomatic. Trials appearing on the above searches prior to 31 May 2004 were included.

Analysis

For each trial, change in distance walked in 6MWT was noted and whether this was significant compared with the control group. Delta 6MWT was the difference (in meters) between the active and the control group. The impact of repeated baseline tests, intervention type, number of centres involved, study size, blinding, age, and severity of heart failure was analysed together with publication form and presence of diastolic heart failure. In placebo-controlled trials with more than one comparator group, each comparison between active and placebo was treated as a separate analysis for this evaluation. The severity of heart failure was defined as the per cent of patients in different New York Heart Association (NYHA) classes. Trials were analysed according to the number of participating centres: one, two to four, or more than four centres involved. The concordance between 6MWT and maximal exercise testing (ETT), peak oxygen uptake (pVO_2), symptoms, and left ventricular ejection fraction (LVEF) was analysed. Positive concordance between two measures was defined as both measures showing significant improvement with therapy. Neutral concordance was defined as both measures showing a non-significant treatment effect. The placebo response was assessed by analysing results after excluding 'withdrawal' trials. Trials were also analysed according to whether the intervention was considered effective for the improvement in symptoms or prognosis according to European Society of Cardiology Guidelines or based on large clinical trials reported since the Guidelines were last published.[15]

Results

Sixty-three randomized, controlled trials reporting the results of 6MWT published between 1988 and May 2004 were identified. Four papers duplicated results from an already published trial.[16–19] Two short-term trials were excluded.[20,21] One trial decided treatment on symptomatic improvement.[22] The Australia–New Zealand Heart Failure Research Collaborative Group trial reported short-term and long-term effects of carvedilol.[23,24] Of the remaining 56 trials, 46 were placebo-controlled, 7 parallel active-controlled, and 3 crossover group comparisons with a total of 9861 patients. Forty-nine trials

Table 1 Single- or double-blinded placebo-controlled clinical trials

Trials	No. centres (blinding)	Study groups	*n*	NYHA class I/II/III/IV (%)	Age (years)	Study duration	Baseline exercise distance (m)[a]	SD or CI	Change (m)	SD or CI[b]	Delta 6MWT (m)	Significant changes		
												6MWT	Symptoms	ETT
ACE-inhibitors (or ARBs for ACE-inhibitor-intolerant patients)														
Barabino 1991[25]	1	Placebo	49	0/41/45/14	75	12 months	283R/NE	32	+19	3–36[c]				
	(D)	Captopril 37.5–75 mg	52	0/37/46/17			300R/NE	35	+104	90–118[c]	+85	S	S	NA
		Ibopamine 150–300 mg	49	0/35/43/22			282R/NE	32	+100	75–125[c]	+81	S	S	NA
DeBock 1994[27]	1	Placebo	25	0/36/30/34	84	6 months	242R/NA	130	+20	NA				
	(D)	Captopril 25 mg bid	25				164R/NA	119	+64	NA	+44	NS	NA	NA
Dosegger 1995[28]	>4	Placebo	114	0/57/41/1	63	12 weeks	NA/R/NA	NA	+23					
	(D)	Cilazapril 1–2.5 mg	221	0/62/36/1			NA/R/NA	NA	+33	4	+10	NS	NS	S
		Captopril 25–50 mg	108	0/57/42/1			NA/R/NA	NA	+30	6	+7	NS	NS	S
SPICE 2000[31]	>4	Placebo	91	0/47/50/3	66	12 weeks	NA/NA	NA	+31	NA				
	(D)	Candesartan 16 mg	179	0/57/36/7			NA/NA	NA	+20	NA	−11	NS	NS	NA
Hutcheon 2002[26]	4	Placebo	35	3/34/60/3	81	10 weeks	277R/E	NA	−0.3	NA				
	(D)	Perindopril	31	3/48/45/3			275R/E	NA	+37	NA	+37	S	NS	NA
Zi 2003[29]	2	Placebo	38	0/74/26/0	78	6 months	215R/E	114	+53	NA				
	(D)	Quinapril 40 mg	36	5/78/17/0			241R/E	132	+26	NA	−27	NS	NS	NA
Summary results												2/7	1/7	1/7
Beta-blockers														
Bristow 1994[39]	>4	Placebo	34	0/47/47/3	52	12 weeks	499R/NA	15	+11	17				
	(D)	Bucindolol 12.5 mg	38	0/42/55/0	55		484R/NA	18	+0	12	−10	NS	NS	NS
		50 mg	32	0/38/63/0	56		478R/NA	22	+55	24	+45	NS	NS	NS
		200 mg	35	3/40/57/0	56		488R/NA	16	+34	22	+23	NS	NS	NS[d]
Krum 1995[36]	2	Placebo	16	0/31/62/6	53	14 weeks	406R/NA	23	−51	NA				
	(D)	Carvedilol 25 mg bid	33	0/24/64/2	56		391R/NA	19	+53	NA	+104	S	S	NA
PRECISE 1996[37]	>4	Placebo	145	0/42/54/4	61	6 months	347R/NA	70	−3	NA				
		Carvedilol 25 mg bid	133	0/38/59/3	59		345R/NA	64	+9	NA	+12	S	S	NA
MOCHA 1996[40]	>4	Placebo	84	0/42/57/1	60	6 months	354R/NA	74	NA	NA				
	(D)	Carvedilol 6.25 mg bid;	83	0/49/47/4	58		363R/NA	72	NA	NA	NA	NS	NS	NA
		12.5 mg bid	89	0/39/57/3	60		356R/NA	71	NA	NA	NA	NS	NS	NA
		25 mg bid	89	0/53/47/0	60		356R/NA	72	NA	NA	NA	NS	NS	NA
Cohn 1997[41]	>4	Placebo	35	0/0/83/17	61	6 months	NA/NA/NA	NA	+28	NA				
	(D)	Carvedilol 25 mg bid	70	0/1/87/11	60		NA/NA/NA	NA	+19	NA	−9	NS	NS	NA
ANZ Short-term 1995[23]	>4	Placebo	208	30/49/21/0	67	6 months	394R/NA	5	+12	NA				
	(D)	Carvedilol 25 mg bid	207	29/59/11/0	67		390R/NA	5	+6	NA	−6	NS	NS[e]	NS
ANZ Long-term 1997[24]	>4	Placebo	208	30/49/21/0	67	12 months	394R/NA	5	NA	NA				
	(D)	Carvedilol 25 mg bid	207	29/59/11/0	67		390R/NA	5	NA	NA	−3	NS	NS	NS
Sanderson 1998[42]	1	Placebo	10	0/50/50/0	61	12 weeks	430R/NA	23	+31	NA				
	(D)	Celiprolol 200 mg	21	0/43/48/9	67		393R/NA	18	+22	NA	−9	NS	NS	NA
		Metoprolol 50 mg bid	19	0/42/58/0	56		411R/NA	18	+52	NA	+21	NS	NS	NA

RESOLVD Substudy 2000[44]	>4	Placebo	212	9/65/26/0	61	24 weeks	399R/NA	85	−3	NA				
	(D)	Metoprolol CR 135 mg	214	5/73/21/1	62		398R/NA	84	−1	NA	+2	NS	NS	NA
Refsgaard 2000[38]	1	Placebo	20	II–III	64	23 weeks	NA/R/NA	NA	+7	NA				
	(D)	Carvedilol 25 mg bid	40				399/R/NA	110	+31	NA	+24	S	NA	NS[f]
MIC 2000[43]	3	Placebo	26	0/46/54/0	55	6 months	462NA/NA	102	+50	NA				
	(D)	Metoprolol 135 mg	26	0/69/31/0	53		412NA/NA	60	+40	NA	−10	NS	NS	NS
Beanlands 2000[45]	(D)	Placebo	19	2.0 ± 0.5	63		454NA/NA	105	+1	NA	+1	NS	NS	NA
		Metoprolol 50 mg tid	14											
TIDES 2002[46]	2	Placebo	9	2.4 ± 0.5	68	9 months	332NA/NA	100	+10	NA				
	(D)	Metoprolol XL	9	2.3 ± 0.5			332NA/NA	101	−5	NA	−14	NS	NS	NA
DeMilliano 2002[47]	1	Placebo	11	55% class III	64	6 months	414NA/NE	66	+7	NA				
	(D)	Metoprolol 50–150 mg	43	44% class III	65		420NA/NE	81	+1	NA	−6	NS	NS	NA
Khand 2003[48]	2	Placebo	23	4/70/26/0	68	4 months	354NA/E	109	60	NA				
	(D)	Carvedilol 25 mg bid	24	4/46/39/13	69		353NA/E	143	41	NA	−19	NS	S	NA
Summary results												3/15	3/14	0/5
Digoxin, diuretics and exercise training														
Guyatt 1988[52]	1	Placebo	20(XO)	10/50/40/0	63	7 weeks	NA/R/E		XO	XO	+19	NS	NS	NA
	(D)	Mean digoxin dose 0.39 mg												
RADIANCE 1993[51]	>4	Placebo (withdrawal)	93	0/75/25/0	59	12 weeks	NA/R/NA	NA	NA	NA				
	(D)	Mean digoxin dose 0.38 mg	85	0/71/29/0	61		NA/R/NA	NA	NA	NA	+41	S	S	S
PROVED 1993[53]	>4	Placebo (withdrawal)	46	0/83/17/0	64	12 weeks	NA/R/NA	NA	NA	NA				
	(D)	Mean digoxin dose 0.38 mg	42	0/83/17/0	64		NA/R/NA	NA	NA	NA	NA	NS	NS	S
Van Kraaij 2000[55]	2	Placebo (withdrawal)	21	I–III	75	3 months	NA/NA/NA	NA	NA	NA				
	(D)	Furosemide 35 ± 12 mg	11		75		NA/NA/NA	NA	NA	NA	NA	NS	NA	NA
EXERT 2002[56]	4	Control	91	1/66/33/0	66	12 months	421R/E	8	+20	9				
	(S/superv.)	Exercise training	90	2/67/31/0	65		434R/E	7	+17	8	−3	NS	NS	NA
DIG substudy 2002[54]	>4	Placebo	291	14/54/30/3	65	12 months	323R/NA	115	+17	NA				
	(D)	Digoxin 0.25 mg	289	13/55/31/2	65		316R/NA	123	+20	NA	+3	NS	NS	NA
Summary results												1/6	1/5	2/2

Continued

Table 1 Continued

Trials	No. centres (blinding)	Study groups	*n*	NYHA class I/II/III/IV (%)	Age (years)	Study duration	Baseline exercise distance (m)[a]	SD or CI	Change (m)	SD or CI[b]	Delta 6MWT (m)	Significant changes		
												6MWT	Symptoms	ETT
Miscellaneous interventions														
Pizzorni 1991[57]	1	Placebo	20	0/100/0/0	75	12 weeks	272R/E	20	+68	NA				
	(D)	Ibopamine 300 mg	20	0/100/0/0			301R/E	16	+106	NA	+38	NS	NA	NS
Abrams 1993[58]	>4	Placebo	34	III/IV	36–87	4 months	NA/NA/NA	NA	+29	NA				
	(D)	Nicardipine 30 mg	39				NA/NA/NA	NA	+55	NA	+27	NS	NA	NS
Rector 1996[69]	1	Placebo	15(XO)	NA	56	6 months	390NA/E	91	XO	XO	+32	S	S	NA
	(D)	5.6–12.6 g L-arginine												
Osterziel 1998[60]	3	Placebo	25	8/76/16/0	54	12 weeks	441R/NA	108	+20	76				
	(D)	2 IU rhGH sc	25	8/48/36/4	54		469R/NA	106	−17	86	−37	NS	NS	NA
Benatar 1998[59]	2	Placebo	10	III/IV	55	4 months	490NA/NA	8	+91	NA				
	(D)	Nicardipine 60 mg, 90 mg	10				484NA/NA	101	+62	NA	−29	NS	NA	NS
Cleland 1998[61]	>4	Placebo	279	0/73/27/0	64	10 weeks	NA/NA/NA	NA	NA	NA	NA			
	(D)	Ecadotril 50, 100, 200, and 400 mg bid					NA/NA/NA	NA	NA	NA	NA	NS	NS	NA
							NA/NA/NA	NA	NA	NA	NA	NS	NS	NA
							NA/NA/NA	NA	NA	NA	NA	NS	NS	NA
							NA/NA/NA	NA	NA	NA	NA	NS	NS	NA
Udelson 2000[62]	>4	Placebo	233	0/60/39/1	65	12 weeks	NA/NA/NA	NA	+13	NA				
	(D)	Amlodipine 10 mg	214	0/55/38/7	63		NA/NA/NA	NA	+7	NA	−5	NS	NS	NS
EARTH 2002[63]	>4	Placebo	642	II–IV	60	6 months	356NA/NA	113	+17	68				
	(D)	Darusentan 10 mg					359NA/NA	113	+18	76	+1	NS	NS	NA
		25 mg					356NA/NA	130	+19	65	+2	NS	NS	NA
		50 mg					346NA/NA	116	+18	71	+1	NS	NS	NA
		100 mg					351NA/NA	118	+20	93	+3	NS	NS	NA
		300 mg					336NA/NA	108	+30	69	+13	NS	NS	NA
Mancini 2003[64]	1	Placebo	8	III/IV	55	3 months	307NA/NE	118	+41	118				
	(S/patient)	EPO (15 000–30 000 units)	15		60		392NA/NE	93	+47	92	+6	NS	NA	NS
Immune Modulation Therapy trial 2003 [65]	>4	Placebo	37	III/IV	62	6 months	NA/NA/NA	NA	NA	NA	NA			
	(D)	Immune modulation therapy	36				NA/NA/NA	NA	NA	NA	NA	NS	NS	NA
Keogh 2003[66]	2	Placebo	18	2.7 ± 0.2	61	3 months	345NA/NA	33	−16	NA				
	(D)	Coenzyme Q10 150 mg	17	2.9 ± 0.06	62		351NA/NA	25	+21	NA	+38	NS	S	NS

Zeng 2003[70]	1	Placebo	77	0/32/48/20	64	8 weeks	125NA/NA	54	+39	NA				
	(D)	Beriberine 1.2–2.0 g	78	0/28/52/20			125NA/NA	53	+68	NA	+28	S	S	NA
Laufs 2004[67]	>1	Placebo	7	II/III	49	20 weeks	NA/NA/NA	NA	NA	NA				
	(D)	Cerivastatin 0.4 mg	8		53		264/NA/NA	58	+53	NA	NA	NS	NS	NA
Summary results												2/12	2/8	0/6
Cardiac resynchronization therapy														
MUSTIC SR 2001[71]	>4	No pacing	67(XO)	0/0/100/0	63	3 months	320R/NA	97	326	134				
	(S/patient)	Biventricular pacing							399	101	+74	S	S	NA
MIRACLE 2002[72]	>4	Placebo	225	0/0/100/0	65	12 months	291R/NA	105	+10	0–25[c]				
	(D)	CRT	228	0/0/100/0	64		305R/NA	85	+39	26–54[c]	+29	S	S	S
MIRACLE ICD 2003[76]	>4	ICD only	182	0/0/90/10	68	6 months	243R/NA	117	+52	43–75[c]				
	(D)	ICD + CRT	187	0/0/82/18	67		243R/NA	129	+55	44–79[c]	+3	NS	S	S
MIRACLE ICD II 2003[75]	>4	ICD only	100	0/100/0/0	NA	6 months	385NA/NA	105	+33	NA				
	(D)	ICD + CRT	85	0/100/0/0			363NA/NA	123	+38	NA	+5	NS	NS	NA
PATH CHF II 2003[73]	>4	Placebo	86(XO)	33% II–III	60	3 months	407NA/NA	81	427	NA				
	(S)	LVP		67% IV					453	NA	+26	S	S	NA
CONTAK CD 2003[74]	>4	ICD only	253	0/33/57/10	66	6 months	317NA/NA	5	+15	8				
	(D)	ICD + CRT	248	0/32/60/7	66		317NA/NA	5	+36	8	+21	S	NS	NA
Summary results												4/6	3/6	2/2

R, repeated walk tests at baseline; E, encouragement used; NE, encouragement not used; NA, not available; D, double-blind; S, single-blind; SPICE, Study of Patients Intolerant to Converting Enzyme inhibition investigators; SD, standard deviation; CI, confidence intervals; ANZ, Australia/New Zealand heart failure research collaborative group; MOCHA, Multicentre Oral Carvedilol Heart Failure; PRECISE, Prospective Randomised Evaluation of Carvedilol on Symptoms and Exercise; RESOLVD, Randomised Evaluation of Strategies Of Left Ventricular Dysfunction; MIC, Metoprolol in Cardiomyopathy trial; TIDES, Trial to Improved Diastole in the Elderly Study; DIG, Digitalis Investigation Group; PROVED, Prospective Randomised study of Ventricular failure and the Efficacy of Digoxin; RADIANCE, Randomised Assessment of Digoxin on Inhibitors of the Angiotensin-Converting Enzyme; EARTH, Endothelin A Receptor Trial in Heart failure; EXERT, EXErcise Rehabilitation Trial; MIRACLE, Multi-centre InSync Randomized Clinical Evaluation; MUSTIC-SR/AF, MUltiSite STimulation in Cardiomyopathy-Sinus Rhythm/Atrial Fibrillation; PATH-CHF, Pacing therapies in Heart Failure.

[a]Baseline exercise distance is presented in relation to the use of repeated testing and encouragement.

[b]Standard deviation unless indicated.

[c]Confidence interval.

[d]Patients exercised significantly longer on placebo than bucindolol when the three dose groups were evaluated together.

[e]Patients symptoms significantly worsened on 6 months on active therapy.

[f]Maximal exercise testing significantly decreased on active therapy.

Table 2 Randomized, blinded trials with an active control

Trials	No. centres (blinding)	Study groups	*n*	NYHA class I/II/III/IV (%)	Age (years)	Study duration	Baseline exercise (m)	SD or CI	Change (m)	SD or CI	Delta 6MWT (m)	Significant changes		
												6MWT	Symptoms	ETT
ACE-inhibitors and ARBs														
Cowley 1992[30]	>4	Captopril 25 mg tid	107	III/IV	64	12 months	NA/NA/NA	NA	+62	9	+37	S	NA	NS
	(D)	Flosequinan 150 mg	102		64		NA/NA/NA	NA	+40	10				
Dickstein 1995[32]	>4	Enalapril 20 mg	58	0/0/90/10	64	8 weeks	397R/E	109	+14	NA				
	(D)	Losartan 25 mg	52	0/0/83/17	66		378R/E	174	+18	NA	+4	NS	NS	NA
		Losartan 50 mg	56	0/0/80/20	64		395R/E	111	+12	NA	−2	NS	NS	NA
Lang 1997[33]	>4	Enalapril 20 mg	38	0/34/66/0	60	12 weeks	393R/E	79	±0	63				
	(D)	Losartan 25 mg	38	0/53/47/0	57		383R/E	75	+9	48	+3	NS	NS	NS
		Losartan 50 mg	40	0/55/40/0	56		394R/E	71	+3	71	+9	NS	NS	NS
RESOLVD 1999[34]	>4	Enalapril 20 mg	109	0/56/40/4	63	43 weeks	374R/NA	8	+13	NA				
	(D)	Candesartan 4,8,16 mg	327	0/66/33/1	63		379R/NA	5	+11	NA	−2	NS	NS	NA
		Candesartan/Enalapril	332	0/56/40/4	64		386R/NA	5	−1	NA	−12	NS	NS	NA
HEAVEN 2002[35]	4	Enalapril 20 mg	71	0/70/30/0	67	12 weeks	426R/NE	142	±0	80				
	(D)	Valsartan 160 mg qd	70	0/71/29/0	68		421R/NE	119	+1	48	+1	NS	NS	NA
Summary results												1/5	0/4	0/2
Comparisons between beta-blockers														
Sanderson 1999[49]	1	Carvedilol 25 mg bid	25	0/40/56/4	59	12 weeks	384R/NA	15	+24	NA				
	(D)	Metoprolol 50 mg bid	26	0/27/73/0	60		370R/NA	17	+33	NA	+9	NS	NS	NA
Metra 2000[50]	2	Metoprolol 124 ± 55 mg	75	0/36/59/5	58	15 months	416R/NA	121	+63	NA	+15	NS	NS	NS
	(D)	Carvedilol 49 ± 18 mg	75	0/30/66/4	55		447R/NA	136	+50	NA				
Overall results												0/2	0/2	0/1
Comparisons between univentricular and biventricular pacing														
PATH-CHF 2002[77]	>4	Left ventricular pacing	42(XO)	0/0/86/14	60	4 weeks	NA/R/E	NA	401	16				
	(S/patient)	Biventricular pacing							402	16	+1	NS	NS	NA
MUSTIC-AF 2002[79]	>4	Left ventricular pacing	59(XO)	0/0/100/0	66	3 months	329R/NA	85	341	100				
	(S/patient)	Biventricular pacing							359	121	+14	NS	NS	NS
Garrigue 2002[78]	1	Left ventricular pacing	13(XO)	III–IV	62	2 months	NA/NA/NA	NA	428	68				
	(S/patient)	Biventricular pacing							437	59	+9	NS	NA	S
Overall results												0/3	0/2	1/2

HEAVEN, HEArt failure Valsartan Exercise capacity Evaluation.

were published in article form and seven as abstracts or in meeting reports. Fifty-three trials evaluated treatment in patients with reduced systolic function and three in patients with preserved systolic function. Seven were single blind and 49 double blind. Forty-six placebo-controlled trials included 102 randomized arms, allowing 58 comparisons against placebo; 10 active-controlled trials included 23 randomized arms, allowing 13 comparisons against control. Trials are listed in *Tables 1* and *2*. Captopril was compared with ibopamine and placebo in one trial and to flosequinan in another.

Placebo response

There were small differences in placebo response between trials reporting more than one baseline test and those that did not (*Figure 1A*). Trials showing a difference between the active intervention and placebo had a smaller placebo group response (median 8.5 m compared with 24.2 m) (*Figure 1B*). The placebo response was greater in trials with fewer patients and fewer centres with small differences regarding severity of heart failure (*Figure 1C–E*).

Treatment effects

Twelve out of 46 placebo-controlled trials of pharmacological and non-pharmacological interventions (26%) showed a significant improvement in the 6MWT with intervention and 1 out of 10 trials (10%) showed differences between interventions. Two out of five placebo-controlled trials[25,26] (two of six comparisons between active treatment and control) of ACE-inhibitors[27–29] showed an improvement in 6MWT distance. However, one was a single centre study, which also investigated the effects of ibopamine.[25] The only, large multicentre, placebo-controlled trial of an ACE inhibitor failed to show an effect in either of its two active treatment arms, but comprised mostly NYHA II patients.[28] One large multicentre study comparing captopril and flosequinan in patients with severe heart failure suggested that the latter was inferior.[30] Whether this reflects worsening with flosequinan or improvement with captopril cannot be resolved owing to the lack of a placebo group. The only trial comparing an angiotensin receptor blocker (ARB) with placebo in the absence of an ACE-inhibitor also showed no effect.[31] ARBs were compared with enalapril in four active-controlled trials,[32–35] with no significant differences in exercise capacity or symptoms regardless of agent or dosage.

Only 3[36–38] of 15 placebo-controlled trials[23,24,39–48] (3 of 20 comparisons) of beta-blockers showed an improvement in 6MWT distance, all with carvedilol (three of eight trials, 3 of 10 comparisons). Only one[37] of five comparisons[23,24,40,44] in substantial multicentre trials showed a difference. Two trials[49,50] comparing metoprolol and carvedilol showed no difference between agents.

Only one[51] of four trials[52–54] of digoxin showed an improvement in 6MWT distance. This trial was a substantial multicentre trial with a withdrawal design. A trial evaluating furosemide withdrawal in elderly patients with preserved systolic function showed no significant changes in distance walked between groups.[55] A trial evaluating aerobic exercise showed no significant difference in distance walked between groups.[56]

The 6MWT distance did not improve in 12 trials[30,57–67] of agents that are not yet generally accepted as effective. One single-centre trial investigating ibopamine was positive,[25] while outcome trials have suggested harm.[68] Two single-centre studies, one of L-arginine[69] and one of beriberine,[70] two interventions for which conclusive evidence of an effect are awaited, were also positive.

Four[71–74] of six trials[75,76] of cardiac resynchronization, two of which were large multicentre trials, showed an improvement in the 6MWT, and results were concordant with the effect on symptoms. In three trials,[77–79] where bi-ventricular pacing was compared with left ventricular pacing, 6MWT was not significantly improved.

Concordance between changes in 6MWT and changes in other measures

Comparison between 6MWT and other endpoints are listed in *Table 3*. Overall, there was concordance in 107 of 139 (77%) comparisons, of which 85 showed neutral and 22 showed positive concordances. No trial showed a significant reduction in 6MWT on active therapy compared with control.

The 6MWT showed positive concordance with symptoms in 9 of 47 trials[25,36,37,51,69–73] (10 of 62 comparisons), neutral concordance in 33 of 47 trials[23,24,28,29,31–35,39–47,49,50,52–54,56,60–63,65,67,75,78,79] (48 comparisons), and discordance in 11% of trials. 6MWT was significantly improved while symptoms remained neutral in two trials[26,74] (two comparisons) and neutral when symptoms significantly improved in three trials[48,66,76] (three comparisons). In placebo-controlled trials where treatments were considered to be effective, symptoms improved in only 9 of 32 and 6MWT in 10 of 34 trials, with a positive concordance in 9 of 32 trials.

The 6MWT showed positive concordance with ETT in 2 of 21 trials[51,72] (2 of 25 comparisons), neutral concordance in 13 trials[23,24,33,39,43,50,52,57–59,62,64,66] (17 comparisons), and discordance in 29% of trials. 6MWT was significantly improved while ETT remained neutral in 2 trials[30,38] (two comparisons) and neutral when ETT significantly improved in four trials[28,53,76,78] (five comparisons).

The 6MWT showed positive concordance with peak oxygen uptake (pVO_2) in 4 of 14 trials[71–74], neutral concordance in 7 of 14 trials[43,47,56,64,77–79] (seven comparisons), and discordance in 21% of trials. 6MWT was significantly improved while pVO_2 remained neutral in one trial[36] (one comparison) and neutral when pVO_2 significantly improved in two trials[50,76] (two comparisons).

The 6MWT showed positive concordance with LVEF in 6 of 30 trials[36,37,51,70,72,74] (6 of 34 comparisons), neutral concordance in 9 of 30 trials[32–34,47,56,59,60,67,76] (9 comparisons), and discordance in 50% of trials. 6MWT was significantly improved while LVEF remained neutral in

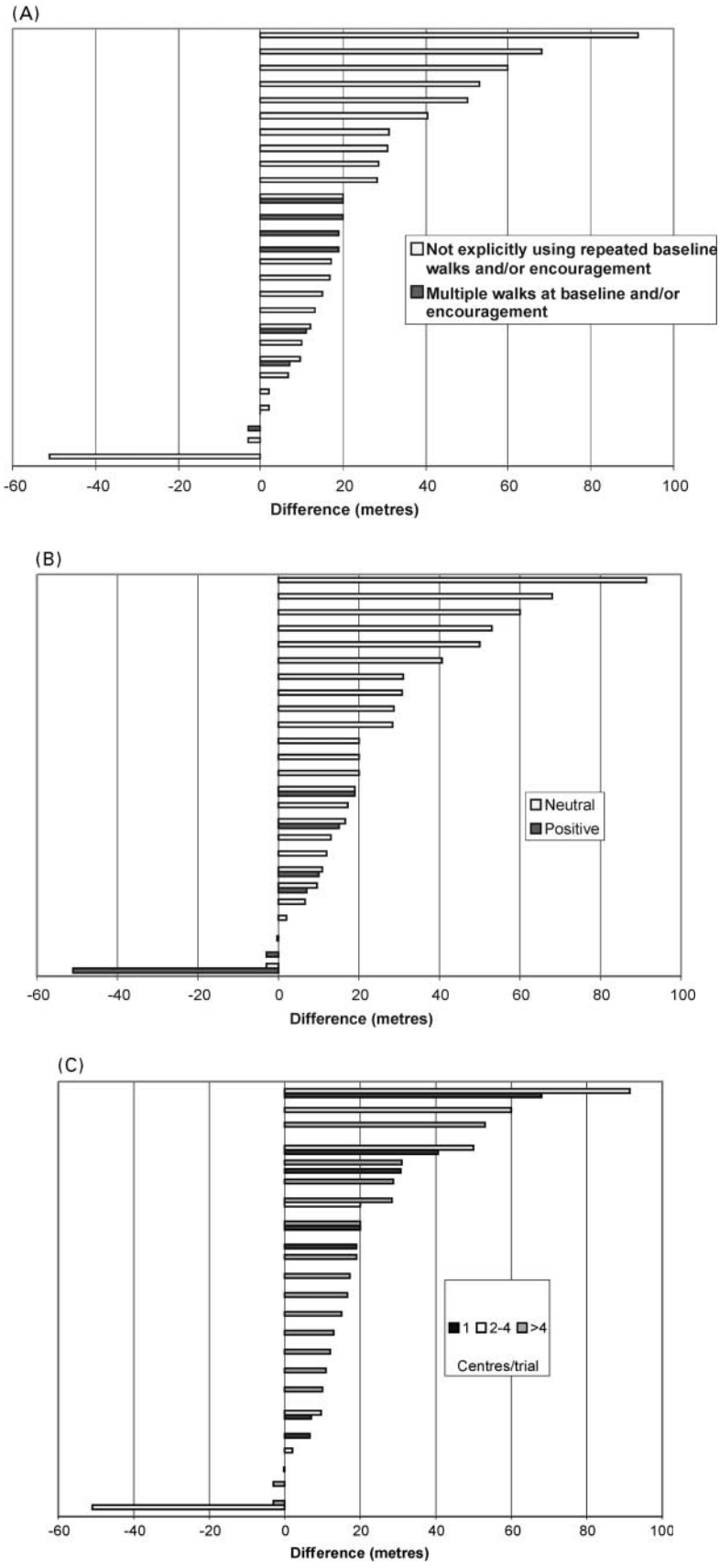

Figure 1 (*A*) Change in mean 6MWT distance in the placebo group in trials performing multiple baseline tests and/or using encouragement; (*B*) by significant results from an intervention; (*C*) by number of participating centers; (*D*) by median placebo group size ($n = 34$); and (*E*) by per cent patients in NYHA class III/IV.

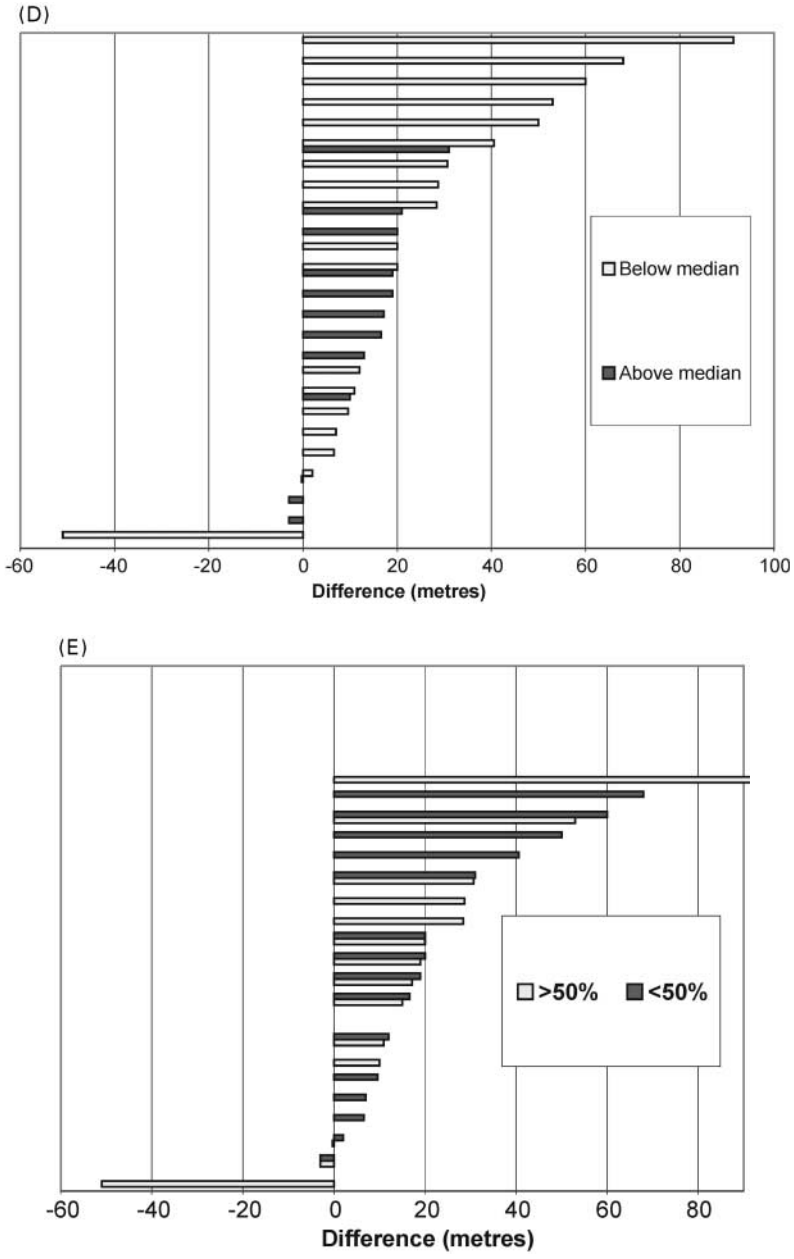

Figure 1 Continued.

no trial and neutral when LVEF improved in 15 trials[23,24,39–44,48–50,53,58,62,75] (19 comparisons).

Standardization

Table 4 shows information concerning the standardization of the trials. Three[30,70,74] (20%) of 15 trials[41,43,46,58,59,61–63,65,66,75,78] (two comparisons) not offering any information about 6MWT methodology showed significant improvements. Two[26,69] (40%) of five trials[48,52,56] (two of five comparisons) that stated the use of encouragement and 4[25,38,51,71] (24%) of 17 trials[28,31–35,39,40,44,49,50,56,60] (five comparisons) stating the use of more than one baseline 6MWT showed significant improvements with 6MWT.

Number of centres and study size

Four[25,38,69,70] of 12 single-centre trials[27,42,47,49,52,57,64,67,78] (33%) showed a significant improvement in 6MWT (5 of 14 comparisons), 2[26,36] of 14 trials (14%) (2 of 14 comparisons)[29,35,43,45,46,48,50,55,56,59,60,66] with two to four participating centres, and 7[30,37,51,71–74] of 29 multicentre trials (24%) (7 of 39 comparisons).[23,24,28,31–34,39–41,44,53,54,58,61–63,65,75–77,79] However, the intervention was cardiac resynchronization in four of these seven trials. Only 3 of the remaining 23 multicentre

Table 3 Concordance between 6MWT and other endpoints

Endpoints	Symptoms	ETT	pVO_2	LVEF
Number of trials	47	21	14	30
Studies with both measures positive	9/47 (19%)	2/21 (10%)	4/14 (29%)	6/30 (20%)
Studies with both measures neutral	33/47 (70%)	13/21 (62%)	7/14 (50%)	9/30 (30%)
Studies with only 6MWT positive	2/47 (4%)	2/21 (10%)	1/14 (7%)	0/30 (0%)
Studies with only other endpoint positive	3/47 (6%)	4/21 (19%)	2/14 (14%)	15/30 (50%)
Total concordance	42/47 (89%)	15/21 (71%)	11/14 (79%)	15/30 (50%)

In no study was delta 6MWT significantly negative; carvedilol significantly worsened NYHA classification in one trial;[23] carvedilol significantly decreased ETT over placebo in one study while it significantly improved 6MWT;[38] placebo significantly improved ETT over treatment with bucindolol in a dose-ranging study while 6MWT remained neutral[39].

Table 4 Information regarding standardization in the trials

Protocol referred to with no further information on the exertion	No information about the exertion	Encouragement used?		Multiple walk tests performed at least at baseline
		Yes	No	
Guyatt protocol ANZ short and long-term, PRECISE[a], Krum[a], Beanlands, PROVED, MIRACLE[a], MIRACLE ICD, VanKraaij, DIG substudy, MUSTIC AF, Pizzorni, Laufs Yusuf protocol Sanderson 1998 Bittner protocol PATH CHF, PATH CHF II Lipkin protocol DeBock	Cohn, MIC, Benatar, Udelson, Cleland, Cowley[a], Abrams, TIDES, Garrigue, CONTAK CD[a], EARTH, Immune modulation therapy trial, Keogh, MIRACLE ICD II, Zeng	Guyatt, Rector[a]; Hutcheon[a], EXERT, Khand	Barabino[a]; DeMilliano, Mancini	Barabino[a], RADIANCE[a], Bristow 1994, Dickstein, Lang, Dosegger[b], MOCHA[c], Osterziel, Sanderson 1999[b], Metra[c], SPICE, HEAVEN, MUSTIC-SR[a], RESOLVD substudy[d], RESOLVD[d], Refsgaard[a,d], EXERT[d]

[a]Δ 6MWT significant.
[b]Baseline, average value of last two walks.
[c]The last walk had to be within ±10% from the second last.
[d]Both at baseline and at follow-up, average value.

trials (13%) using pharmacological interventions showed an improvement in 6MWT.

All trials except two disclosed information on study group size.[61,63] Study group size ranged between 9 and 298 patients, with median size of 52. Five[25,26,36,38,69] (17%) out of 29 trials[27,29,33,39,42,43,45–49,52,53,55,57–60,64–67,77,78] (6 of 35 comparisons) with study arms below median size showed significant improvement. Eight[30,37,51,70–74] (32%) out of 25 trials[23,24,28,31,32,34,35,40,41,44,50,54,56,62,75,76,79] (6 of 33 comparisons) with study arms above median size showed significant improvement with 6MWT.

Age

All but two trials reported the mean age of the study population.[58,75] An inverse relationship between baseline 6MWT and mean age was observed ($r = -0.59$; $P < 0.0001$) (*Figure 2*). 6MWT distance improved significantly in two[25,26] of six trials[27,29,55,57] (three of seven comparisons) where the mean age of the study population was >70 years. These studies evaluated captopril, ibopamine, and perindopril, with none including more than 52 patients per treatment arm.

Severity of heart failure

All but one trial reported information on NYHA class.[69] There was a weak inverse relationship between per cent of patients in NYHA class III/IV and baseline 6MWT distance ($r = -0.26$; $P = 0.02$) as shown in *Figure 3*. Mean baseline walk test for trials including 100% NYHA class III/IV patients ranged between 243 and 490 m. Ten[25,26,30,36,37,70–74] (34%) of 29 trials[27,32,39–42,46,48–50,58,63–66,76–79] (11 of 38 comparisons) that included >50% of patients with NYHA class III/IV showed an improvement in 6MWT distance with treatment [captopril[25,30] (two treatment arms), ibopamine,[25] perindopril,[26] carvedilol[36,37] (two treatment arms), beriberine[70] (one treatment arm) cardiac resynchronization therapy[71–74] (four treatment arms)]. Only 2[38,51] of 25 trials[23,24,28,29,31,33–35,43–45,47,52–57,59–62,75] (2 of 32 comparisons) that included <50% of patients with NYHA

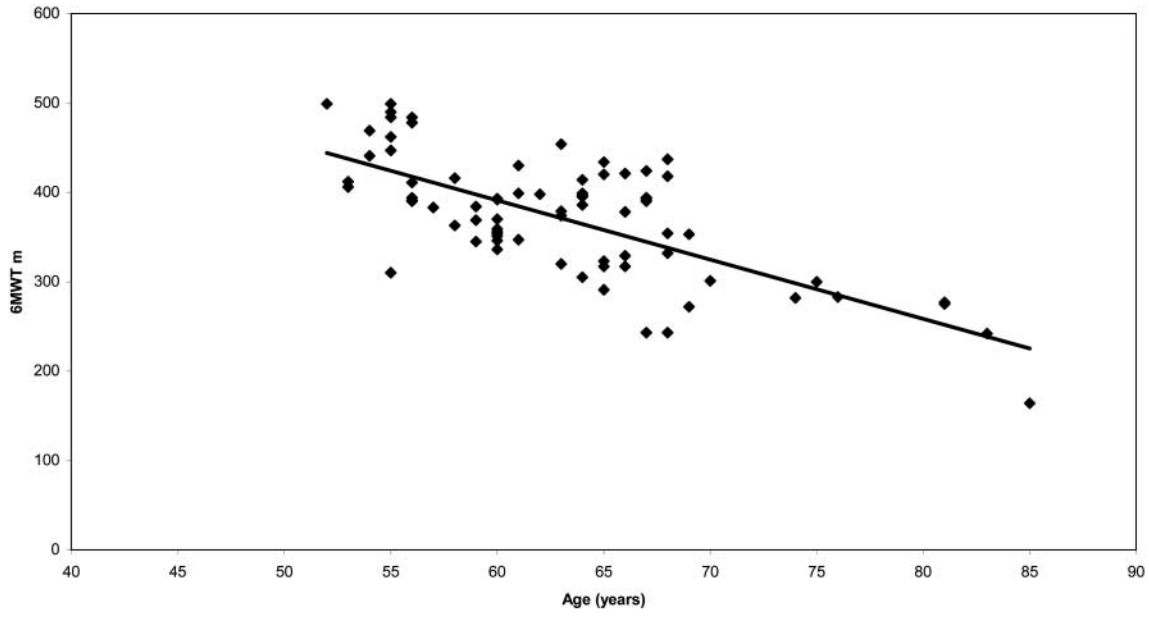

Figure 2 Baseline 6MWT distance by age in 37 trials.

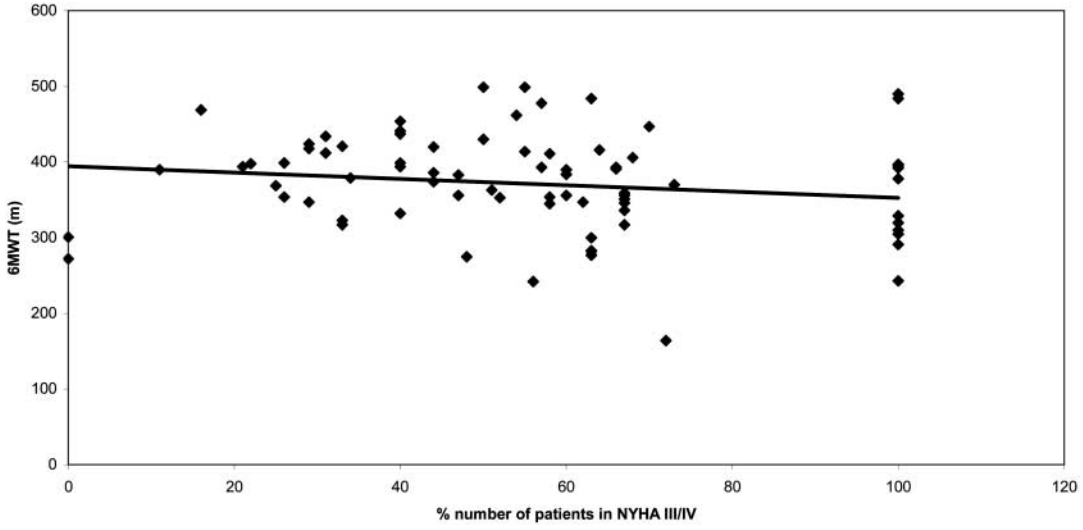

Figure 3 Baseline 6MWT distance by severity of NYHA class (% NYHA III/IV) in 37 trials.

class III/IV showed significant delta 6MWT. These trials evaluated carvedilol[38] and digoxin withdrawal.[51]

Publication form

One[38] of seven trials[46,58,61,63,65,75] (14%) published as abstracts or meeting reports showed a significantly improved 6MWT compared with 11 of 49 trials published in article form (22%). This trial evaluated carvedilol. Four[58,61,63,65] of seven trials evaluated treatment currently not recommended for heart failure patients (57%) compared with 12 of 49 trials in article form (24%).

Trials evaluating treatment in patients with preserved systolic function

Three of 56 trials evaluated treatment in patients with diastolic dysfunction,[29,46,55] with none of them showing a significantly improved 6MWT with therapy.

Discussion

This review of the utility of the 6MWT for the evaluation of therapy in randomized controlled trials in heart failure indicates uncertainty about the utility of this test. The 6MWT improved in the majority of trials of cardiac resynchronization, a promising intervention. There was no

improvement in the majority of studies of ACE-inhibitors and beta-blockers, agents with limited impact on exercise performance. It improved with at least one intervention (ibopamine) that is now generally considered deleterious. However, positive and neutral evaluations by the 6MWT showed a high concordance with the results of symptom assessment and formal exercise testing.

The failure of ACE-inhibitors and beta-blockers to improve symptoms or exercise capacity in the majority of comparisons in this review could reflect problems with the size or design of the trials, the inclusion of patients with milder symptoms or an inability of treatment to alter these outcomes. The relative success of the 6MWT in trials of cardiac resynchronization may reflect a selection of patients with more severe symptoms. As in other device clinical research, there may be a problem in maintaining both patient and investigator blind to treatment allocation. The improvement in symptoms but not the 6MWT in MIRACLE ICD may be due to a marked placebo response. This may have been influenced by the inclusion primarily of patients with mild symptoms and ventricular dyssynchrony in MIRACLE ICD II who received an implantable cardioverter defibrillator (ICD) device to reduce risk rather than primarily to improve heart failure symptoms by cardiac resynchronization therapy (CRT).

Part of the rationale for using the 6MWT rather than the bicycle or treadmill exercise in clinical trials is that it is a more natural form of exercise that may better reflect daily activity. The present analysis shows that there is considerable placebo response and, where repetitive tests are performed, evidence of a learning experience[10,11,80–85]. Trials reporting the use of multiple tests prior to randomization were more likely to show differences than those that did not use this approach. However, this may reflect reporting bias, as the methodology in positive trials was reported in greater detail. It is likely that improved standardization of test procedures and conditions would improve the reliability of the test.

Study size was not a major determinant of the ability of the 6MWT to show differences between effective pharmacological treatments and placebo. This finding is at variance with a previous analysis on ETT in ACE-inhibitor trials.[7] Large multicentre trials are powered to detect small differences, but with the self-paced, time-limited 6MWT, the environment in which the test is conducted and the person supervising the test may introduce greater variability in test results. These factors may be more easily controlled in single-centre trials, but such trials are often underpowered. With the 6MWT design, there may also be a 'ceiling' effect leaving those walking longer at baseline with less room for improvements. In large multicentre trials of pharmacological treatments that are presently considered effective, formal ETT (five of seven comparisons) seemed slightly superior to the 6MWT (three of seven comparisons).

There was little relationship between the 6MWT distance and symptom severity, judged by NYHA class. This may reflect problems with the assessment of NYHA or with the 6MWT. NYHA classification may not be consistent between investigators and is probably influenced by extraneous factors such as knowledge of the patients LVEF and likely prognosis, although it is meant to be a purely functional classification. Moreover, clinical trials often require a certain NYHA classification severity as an entry criterion and this may influence investigator judgement. Age was correlated with 6MWT, perhaps reflecting more problems with balance and joints and reduced skeletal muscle strength. When younger and older patients are matched for the severity of symptoms, older patients have a higher LVEF and lower natriuretic peptide concentrations, implying a contribution of age itself, in addition to cardiac dysfunction, to the subjective severity of symptoms.[86]

Greater severity of heart failure was the main determinant of whether the walk test performance improved, as has been noted with treadmill exercise.[87] Apart from the high success rate in CRT trials, modern pharmacological treatment for heart failure blunts the neurohormonal response to exercise but may improve haemodynamics so that exercise capacity is improved anyway. These effects may be more apparent in patients with severe heart failure. The greater ability of the 6MWT to show differences in patients with more severe heart failure who probably are exercising near their peak oxygen consumption suggests that the 6MWT may also be best viewed as an ETT.[84,88,89]

There is a widely held belief that exercise testing is a more objective measure of outcome than patient-reported symptoms. It is not clear whether this is true. Encouragement may improve distance walked.[90] The outcome of both exercise testing and symptom evaluation are highly dependent on the motivation of the patient and of the person administering the test, and motivation is likely to be affected by whether the patients feels that their symptoms have improved. Ultimately, exercise testing is a surrogate outcome measure for symptoms and, similar to surrogate outcome measures for mortality, may be no substitute for a more direct measurement of the patient perceived and self-rated experience.

Limitations

Sex and different aetiology of heart failure are factors known to influence prognosis and/or response to treatment. Whether this also affects walk test result cannot be resolved, because of the nature of the information presented in these studies.

Conclusion

The 6MWT has not yet been proven to be a robust test for the identification of effective pharmacological interventions, although it appears useful for the assessment of cardiac resynchronization therapy. Improved standardization of testing may improve performance. The results of the 6MWT were concordant with changes in symptoms, suggesting that it may be used as supportive evidence for

symptom benefit. The test may be of greater value in patients with more advanced heart failure, where it may function as an ETT.

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