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Original article

Comparison of impact of medical therapy and surgical treatment on overall mortality in patients with severe chronic heart failure: a meta-analysis

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Abstract: *Aim* — Meta-analysis of clinical trials comparing the efficacy of medical therapy (MT) and surgical treatment, including cardiac resynchronization therapy with and without cardioversion-defibrillation (CRT and CRT-D), circulatory support system (CSS) and heart transplantation (HT), in terms of decreasing overall mortality in patients with severe chronic heart failure (CHF).
Material and Methods — Meta-analysis included 39 clinical trials with a total number of 30,257 patients. Search was performed in MEDLINE, Medscape, Pubmed databases and on web resources, dedicated to clinical trials (National Institutes of Health, Clinical Center, ClinicalStudyResults.org, ClinicalTrials.gov).
Results — There was no significant overall mortality reduction in patients receiving MT when compared to control group: OR=0.97 (95% CI: 0.85-1.10), p=0.211. Treatment with CRT and CRT-D, as well as CSS implantation and HT reduced overall mortality: OR=0.67 (95% CI: 0.57–0.79), p < 0.001 for CRT/CRT-D and OR=0.46 (95% CI: 0.24–0.86), p = 0.018 for CSS/HT.
Conclusion — Superiority of surgical treatment over traditional MT in terms of overall mortality was observed in patients with severe CHF.

Keywords: chronic heart failure, medical therapy, cardiac resynchronization therapy, circulatory support system, heart transplantation

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Introduction

In the last decades problem of choosing how to manage patients with chronic heart failure (CHF) is becoming more and more relevant, because new approaches to this condition are being developed and included in clinical guidelines [1-5]. Standard models of organizing care for patients with CHF are also being developed [6], methods of evaluating its quality and efficacy are being perfected [7] and CHF registries are created [8-14]. Researchers turn their attention to different aspects of CHF: from influence of low-intensity electromagnetic fields on endothelium function [15] and genetic determinants of CHF [16] to vegetative [17] and cognitive dysfunction [18].

Defining optimal treatment for patients with severe CHF to improve their short-term and long-term prognosis remains an unsolved problem for modern cardiology and cardiac surgery, as condition of many patients worsens even while receiving medical therapy (MT). This fact has stimulated the development of surgical techniques for management of severe CHF, such as cardiac resynchronization therapy (CRT), cardiac resynchronization therapy combined with cardioversion-defibrillation (CRT-D), circulatory support system implantation (CSS) and heart transplantation (HT), which have their efficacy already proven [19-24].

Earlier we have conducted a five year prospective clinical trial to evaluate long-term results of medical and surgical treatment in 90 patients with New York Heart Association (NYHA) functional class III-IV of CHF, who have received treatment in A.N. Bakoulev Scientific Center for Cardiovascular Surgery in 2007 [25]. Advantage of surgical treatment over traditional MT in setting of severe CHF was shown.

Despite great interest towards surgical and medical management of severe CHF, we found no comparative meta-analyses on this topic in available literature.

Aim of this study was to perform a meta-analysis of major clinical trials which compared the efficacy of MT and surgical treatment (CRT, CRT-D, CSS and HT) of patients with severe CHF.

Material and Methods

The meta-analysis included 39 clinical trials [25-67] with a total number of 30257 patients. Search was performed in MEDLINE, Medscape, Pubmed databases and on web resources, dedicated to clinical trials (National Institutes of Health, Clinical Center, ClinicalStudyResults.org, ClinicalTrials.gov).

Table 1. Brief description of studies which evaluated efficacy of MT in patients with severe CHF

Year	*Ref.*	*Name of study*	*Study group, n*	*Control group, n*	*Study design*	*Drug class*
2013	[66]	ASTRONAUT study	808	807	aliskiren vs placebo	DRIs
2001	[47]	BEST study	1,354	1,354	bucindolol vs placebo	β-blockers
1987	[27]	Bussmann study	12	11	captopril vs placebo	ACEIs
1999	[45]	CIBIS II study	1,327	1,320	bisoprolol vs placebo	β-blockers
1994	[35]	CIBIS study	320	321	bisoprolol vs placebo	β-blockers
1997	[42]	Cohn study	70	35	carvedilol vs placebo	β-blockers
1987	[30]	CONSENSUS study	127	126	enalapril vs placebo	ACEIs
1994	[36]	Cowley study	75	76	enoximone vs placebo	PDEIs
1995	[40]	Dickstein et al. study	108	58	losartan vs enalapril	AngRBs
2007	[62]	EMOTE study	101	100	enoximone vs placebo	PDEIs
2003	[53]	EPHESUS	3,319	3,313	eplerenone vs placebo	AldRBs
2009	[64]	ESSENTIAL II	472	478	enoximone vs placebo	PDEIs
1994	[37]	Fisher study	25	25	metoprolol vs placebo	β-blockers
1993	[34]	Ghose study	50	51	hydralazine, isosorbide dinitrate vs placebo	Vasodilators
1999	[46]	Hamroff et al. study	16	17	losartan+ACEI vs ACEI	AngRBs
1991	[31]	IRG study	103	44	imazodan vs placebo	PDEIs
1987	[28, 29]	Kassis study	10	10	felodipine vs placebo	CCBs
1995	[39]	Krum study	33	16	carvedilol vs placebo	β-blockers
1991	[32]	Lechat study	6	6	nebivolol vs placebo	β-blockers
1991	[40]	Maass-a study	87	45	ramipril vs placebo	ACEIs
1991	[41]	Maass-c study	47	48	ramipril vs placebo	ACEIs
1986	[26]	Packer study	21	21	captopril vs enalapril	ACEIs
2000	[56, 67]	PRAISE II study	826	826	amlodipine vs placebo	CCBs
1996	[41]	PRAISE study	571	582	amlodipine vs placebo	CCBs
1997	[43]	PRIME II study	953	953	ibopamin vs placebo	PDEIs
1991	[33]	PROMISE study	561	527	milrinone vs placebo	PDEIs
1998	[44]	VEST study	2,550	1,283	vesnarinon vs placebo	PDEIs

ACEIs, angiotensin-converting enzyme inhibitors; AldRBs, aldosterone receptor blockers; AngRBs, angiotensin receptor blockers; CCBs, calcium channel blockers; DRIs, direct renin inhibitors; PDEIs, phosphodiesterase-3 inhibitors.

Following keywords were used during the search: “heart failure”, “ventricular dysfunction”, “cardiac resynchronization therapy”, “heart transplantation”, “mechanical assist devices”, “LVAD”, “randomized controlled trial”, “congestive heart failure”, “biventricular pacing,” “chronic cardiac failure resynchronization therapy,” “Medtronic,” “InSync,” “Guidant,” “St. Jude,” “implantable defibrillators,” “ICD,” “single chamber ICD,” “dual chamber ICD,” “congestive heart failure,” “CHF,” “chronic heart failure,” “biventricular assist device implantation”, “continuous-flow LVAD”, “ambulatory pts with HF”, “quality of life”, “exercise capacity”, “peak oxygen consumption”, “controlled clinical trial,” “meta-analysis”.

Inclusion criteria for the trials to be included in meta-analysis were:

- papers published in 1977-2014 (however, one trial was completed in 2014, but its results were published later, and it was included in meta-analysis [25]);
- randomized clinical trials (RCT), observational studies (prospective and retrospective, case-control studies), which included patients with NYHA class III-IV CHF and contained data on control / comparison groups;
- trials which compared one of single or combined treatments (MT, CRT, CRD-D) with lack of treatment or absence of one of treatment components (for combined treatment), and trials which compared efficacy and safety of CSS usage (based on pulse-style pumps) with MT, and trials which evaluated orthotopic HT;
- trials which included data on overall mortality.

Exclusion criteria for trials: conference reports, clinical cases, case series, expert reports and opinions.

Primary endpoints: overall mortality.

Twenty seven trials were dedicated to analysis of MT efficacy (*Table* 1). This group included 7 trials which evaluated the impact of using β-blockers [32, 35, 37, 39, 42, 45, 47], one trial which evaluated usage of aldosterone receptor blockers (AldRBs) [53], 5 trials which evaluated angiotensin-converting enzyme inhibitors (ACEIs) [26, 27, 30, 40], 2 trials on effects of angiotensin receptor blockers (AngRBs) [38, 46], 3 trials on effects of calcium channel blockers (CCBs) [28, 29, 41, 56, 67], 7 trials which evaluated effects of phosphodiesterase-3 inhibitors (PDEIs) [31, 33, 36, 43, 44, 62, 64], one trial on direct renin inhibitors (DRIs) [66] and one trial on vasodilator usage [34].

Thirteen trials described the effect of CRT in patients with severe CHF (*Table* 2). Seven trials evaluated efficacy of CRT only [48, 50-52, 57, 58, 60, 63, 65]. One trial [54] compared efficacy of cardiac resynchronization therapy combined with cardioversion-defibrillation (CRT-D) and efficacy of cardioversion-defibrillation only. Two trials compared efficacy of CRT-D with no resynchronization therapy [55, 61]. COMPANION (CRT vs MT) trial [55, 59] evaluated CRT with optimal MT. One trial (Kotsoeva-Bockeria) [24, 25] evaluated efficacy of CRT and CRT-D compared with MT in patients with severe CHF.

Also, meta-analysis included 2 trials on evaluation of efficacy and safety of surgical treatment for terminal CHF: REMATCH study [49] and Kotsoeva-Bockeria study (CSS, HT vs MT) [25, 68]. In these trials efficacy and safety of CSS usage, orthotopic HT and MT in patiens with NYHA class III-IV CHF were compared.

Meta-analysis was performed using Meta-analysis Comprehensive V.2.0 software (Biostat Inc., USA). In cases of insignificant statistical heterogeneity in trials (I^2 <50%) the analysis was performed using fixed effects model. High statistical heterogeneity (I^2 >50%) required us to use random effects model. Treatment effects were evaluated by calculating odds ratio (OR) and 95% confidence interval (95% CI).

Table 2. Brief description of studies which evaluated efficacy of CRT in patients with severe CHF

Year	*Ref.*	*Name of study*	*Study group, n*	*Control group, n*	*Study design*
2005	[57, 63, 65]	CARE-HF study	409	404	CRT vs non-CRT
2004	[55, 59]	COMPANION (CRT vs MT) study	617	154	CRT vs MT
2004	[55]	COMPANION (CRT+ICD vs CRT) study	595	617	CRT-D vs CRT
2004	[55, 59]	COMPANION (CRT+ICD vs MT) study	595	154	CRT-D vs MT
2006	[60]	HOBIPACE	16	16	CRT vs non-CRT
2002	[58]	MIRACLE study	228	225	CRT vs non-CRT
2003	[54]	MIRACLE-ICD-I study	187	182	CRT-D vs CVDF
2002	[51]	MUSTIC AF study	25	18	CRT vs non-CRT
2001	[48]	MUSTIC-SR study	29	29	CRT vs non-CRT
2002	[50]	PATH-CHF study	24	17	CRT vs non-CRT
2003	[52]	RD-CHF study	22	22	CRT vs non-CRT
2007	[61]	RethinQ study	85	85	CRT-D vs non-CRT
2014	[25, 68]	Kotsoeva-Bockeria (CRT, CRT-D vs MT)	30	30	CRT, CRT-D vs MT

CRT, cardiac resynchronization therapy; CRT-D, cardiac resynchronization therapy combined with cardioversion-defibrillation; CVDF, cardioversion-defibrillation; MT, medical therapy; non-CRT, patients without cardiac resynchronization therapy.

Table 3. Data on lethality in patients with severe CHF on different modes of treatment (results of randomized clinical studies)

Treatment option	*Name of study*	*Study group, n*		*Control group, n*	
		Total number of patients	*Event frequency*	*Total number of patients*	*Event frequency*
MT	BEST study	1,354	411	1,354	449
MT	Bussmann study	12	2	11	3
MT	Kassis study	10	5	10	3
MT	CIBIS study	320	53	321	67
MT	CIBIS II study	1,327	156	1,320	228
MT	Colin study	70	2	35	2
MT	CONSENSUS study	127	50	126	68
MT	Cowley study	75	27	76	18
MT	Dictntein et al. study	108	2	58	2
MT	EMOTE study	101	38	100	31
MT	EPHESUS	3,319	478	3,313	554
MT	ESSENTIAL	472	157	478	144
MT	Fisher study	25	1	25	2
MT	Gime study	50	11	51	14
MT	Hamroff et al. study	16	0	17	1
MT	IRG study	103	8	44	3
MT	Krum study	33	3	16	2
MT	Mans-a study	87	8	45	4
MT	Mans-c study	47	1	48	1
MT	Pater study	21	1	21	1
MT	PRAISE study	571	190	582	223
MT	PRAISE II study	826	278	826	262
MT	PRIME II study	953	232	953	193
MT	PROMISE study	561	168	527	127
MT	VEST study	2,550	560	1,283	242
CRT	CARE-HF study	409	82	404	120
CRT	COMPANION (CRT vs MT) study	617	131	154	39
CRT	COMPANION (CRT-ICD vs CRT) study	595	105	617	131
CRT	COMPANION (CRT-ICD vs MT) study	595	105	154	39
CRT	HOBIPACE	16	1	16	1
CRT	MIRACLE study	728	12	225	16
CRT	MIRACLE-ICD-1 study	187	4	182	5
CRT	MUSTIC AF study	25	1	18	0
CRT	MUSTIC-SR study	29	1	29	0
CRT	PATH-CHF study	24	2	17	0
CRT	RD-CHF study	22	2	22	4
CRT	RethinQ study	85	5	85	2
CRT	Kotsoeva-Bockeria (CRT, CRT-D vs MT)	30	2	30	11
HT	REMATCH study	66	41	68	54
HT	Kotsoeva-Bockeria (CSS, HT vs MT)	30	7	30	11

CRT, cardiac resynchronization therapy; CSS, circulatory support system; HT, heart transplantation; MT, medical therapy.

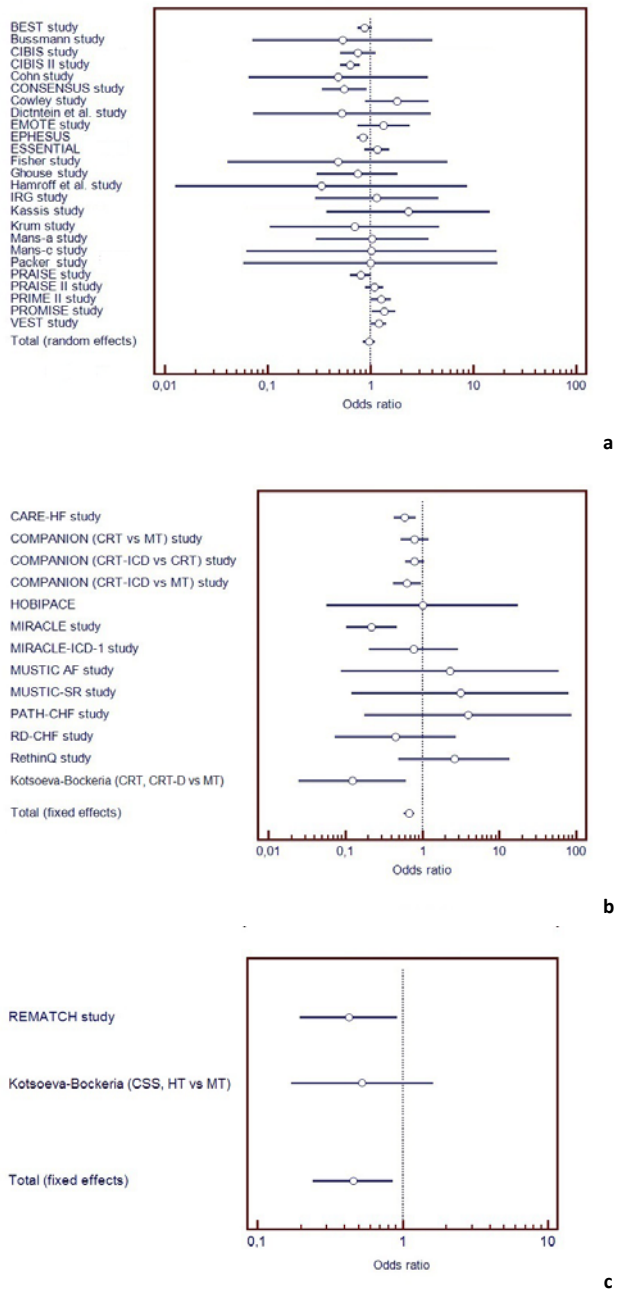

Figure 1. A metagraph of overall mortality in patients with severe CHF on MT (a), CRT / CRT-D (b) and CSS usage / after HT (c) compared to control group.

Left column shows names of the trials (brief description of trials is given in *Tables* 1, 2 and text). «Total» – total evaluation of odds ratios.

Results

Meta-analysis of overall mortality in patients with severe CHF was performed by each treatment type (*Table* 3). There was no significant decrease of overall mortality risk in patients who received MT when compared to control group: OR=0.97 (95% CI: 0.85-1.10), p=0.211 (*Figure* 1a). Treatment of patients with severe CHF using CRT and CRT-D and also by CSS implantation and HT significantly decreased overall mortality: OR=0.67 (95% CI: 0.57–0.79), p<0.001 (*Figure* 1b) for CRT/CRT-D and OR=0.46 (95% CI: 0.24–0.86), p=0.018 (*Figure* 1c) for CSS/HT. No significant difference was onserved between CRT/CRT-D and CSS/HT in terms of overall mortality decrease.

Discussion

Results obtained in this meta-analysis complement existing knowledge on value of various options of surgical treatment for severe CHF. Evidence on a certain degree of superiority of surgical management over traditional MT in terms of decrease in overall mortality was gained.

CRT is studied most comprehensively of all surgical options. It is known that effect of CRT is pathogenetically based on its influence on interventricular dyssynchrony, which elevates personal risk level in patients with severe CHF [69]. Meta-analysis of CRT and CRT-D efficacy in patients with CHF is known, where it was demonstrated that CRT decreases overall mortality and hospitalization rate due to CHF, irrespective of NYHA class [70]. However, patients with I-II NYHA class CHF had too many adverse events, so is is advised to use CRT only for III-IV NYHA class patients [70]. It is important to note that CRT is seen by some authors as a temporary alternative solution for patients who will inevitably require transplantation [71, 72].

CSS implantation allows to improve quality of life of patients with severe CHF for a prolonged period, which is especially important for those who are in line for HT. M.S. Slaughter et al. [73] have demonstrated a relative safety of modern CSS in terms of stroke risk. A relatively favorable prognosis in patients with severe CHF with active CSS is confirmed by several literature reviews [74].

HT surgery is also a treatment of choice for selected patients with terminal CHF, especially when other options fail. Of course, HT is unable to radically change the situation with CHF on a population level [75].

It is out of the question that clinical decision making and personal risk evaluation for surgical management of severe CHF should be done with consideration of other risk factors, already well studied for cardiosurgical patients [76-80].

Of all trials included in this meta-analysis, none evaluated gender-specific effects of treating severe CHF on long-term prognosis. This problem requires thorough research in the future, with results by S. Zabarovskaja et al. taken into account [24], which provide evidence of lower long-term mortality in women who were treated with CRT when compared to men.

Study Limitations

An important limitation of this study was small number of trials on HT included for analysis.

Conclusion

Primarily, this meta-analysis has demonstrated the advantages of surgical options for treatment of severe CHF (such as CRT, CRT-D, CSS and HT) over traditional MT in terms of decrease of overall mortality.

Conflict of interest: none declared.

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