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REVIEW

The effect of beta-blocker therapy on quality of life in heart failure patients: a systematic review and meta-analysis†

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SUMMARY

Purpose To assess the impact of β-blocker therapy on quality of life (QoL) in chronic heart failure (CHF) patients receiving optimal standard medication.

Methods Randomised controlled trials (RCT) assessing QoL with a generic or disease specific instrument were identified by searching Medline, Embase, Pascual, Cochrane Controlled Trial database, and the bibliographies of the published articles. Studies published between 1985 and 2002 were included, regardless of language of publication. Cochrane Review Manager 4.2 software was used to analyse the data and standardised mean difference (SMD) was calculated to assess the effect on QoL.

Results A total of 9 trials involving 1954 patients fit into the inclusion criteria for the analysis. QoL improved more in the β-blocker group compared to the control arm, but the SMD did not reach statistical significance (SMD, 0.07; 95%CI [−0.16, 0.02]; $p = 0.13$). Subgroup analysis, per type of β-blocker and various treatment follow-up showed similar results.

Conclusions In this meta-analysis there is evidence that β-blocker therapy, on top of standard medication, does not impair QoL. Clinicians may add β-blockers to standard therapy without concerns of impairing QoL in patients with CHF.

KEY WORDS — beta adrenergic antagonists; congestive heart failure; quality of life; clinical trials

INTRODUCTION

Chronic heart failure (CHF) is a debilitating disorder, with a poor prognosis.[1,2] Accordingly, current treatment goals aim to improve survival, as well as quality of life (QoL) of the patients.[3] Previous meta-analysis of randomised controlled trials (RCT) showed a favourable effect of β-blockers on mortality and hospitalisations in patients with CHF.[4,5] However, despite established clinical benefits, it is uncertain to what extent β-blockers affect QoL in CHF patients receiving optimal standard therapy.

QoL refers to physical, psychological, and social domains of health, as distinct areas influenced by person's beliefs and perceptions.[6] Patients with CHF have significant impairment of all domains of QoL compared to general population and poorer perception

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of most areas of QoL compared to patients with other chronic disorders.[7,8] A previous study showed that half of CHF patients were willing to select therapies that improved their QoL even at the expense of shortening life.[9]

There are conflicting hypotheses regarding the impact of β-blocker therapy on QoL in CHF patients. Primarily, an improvement in QoL is expected in these patients, due to beneficial effects on cardiac function and hospitalisations.[4,5] On the other hand, physicians fear that QoL might be adversely affected in such patients due to the side effects of β-blocker medication, especially during the initiation of therapy.[10,11]

A previous literature review shows that one of eight RCT using a QoL questionnaire found a significant beneficial effect of β-blockers on QoL when compared to the placebo group.[12] Seven other trials found no significant difference, although six trials reported a trend for a better effect on QoL in the β-blocker arm.

We performed a meta-analysis of RCT to quantify the impact of β-blocker therapy on QoL in CHF patients receiving optimal standard therapy. None of the preceding meta-analysis included QoL as an end point evaluation.

METHODS

Identification of trials

We included RCT that assessed the impact of β-blocker therapy on QoL in CHF patients receiving optimal standard therapy. Standard therapy consists of an Angiotensine converting enzyme inhibitor (ACEI) or an Angiotensin receptor blocker (ARB), together with diuretics and/or digitalis, when recommended. Studies were selected if QoL was assessed with a generic or disease specific QoL questionnaire. Studies that assessed QoL with symptom scores (NYHA class or other symptom questionnaires) were not included into analysis.

We searched Medline, Embase, Pascual, and Cochrane Trial databases from 1985 to 2002 using the key words *Beta Adrenergic Antagonists, Clinical Trials* and *Congestive Heart Failure*. The reference lists of all retrieved studies were hand-searched for additional relevant studies. Qualifying studies were selected regardless of language of publication, type of β-blocker or duration of treatment.

Quality of life assessment

A generic QoL questionnaire is used to assess a wide range of domains applicable to a variety of health states and diseases. Disease specific instruments focus on the domains most relevant to the disease under study. Two CHF-specific QoL questionnaires are used most often in RCT, the Minnesota Living with Heart Failure questionnaire (MLHF) and the Quality of Life with Heart Failure questionnaire (QLHF). MLHF is a 21-item questionnaire that assesses physical, emotional, and social-economic impairments. Each item has a six-point scale from 0 to 5. Higher scores indicate poorer QoL.[13] QLHF is a 27-item questionnaire that utilises a six-grade scale to describe physical activity and a visual analogue scale to depict somatic symptoms, emotions, and life satisfaction. Similar to the MLHF, higher scores indicate worse QoL.[14]

Data extraction and quality assessment

We considered the QoL outcome at the end point of the study and we did not include intermediary measurements. Also, we selected the QoL effect of optimal dose of β-blocker medication.

Two independent investigators assessed methodological quality according to Delphi list criteria for RCT.[15] A quality score was not allocated to each study. Rather, a judgement was made taking into account the context of identified studies. For instance, we included studies if QoL data were provided for at least 70% of the patients included in the QoL sample. QoL data at end point study could include both actual values and values obtained through carry forward analysis.

If all the necessary data to perform a meta-analysis (sample size at end point assessment, QoL scores and their standard deviations) were not specified within the articles, authors or sponsors were contacted. First, the primary author of the study was contacted and asked for the additional QoL data. If the authors did not have the data, they put us in contact with the sponsor of the study.

Statistical methods

The outcome of the study was the impact on QoL of β-blocker therapy in addition to standard medication in comparison to standard medication alone. The data were analysed using Cochrane Review Manager 4.2 software and standardised mean difference (SMD) was calculated as a measure of effect size.[16] SMD is the difference between mean QoL in treatment and placebo groups divided by the pooled standard deviation. We calculated SMD instead of simply mean QoL difference because QoL was assessed with

different questionnaires across the studies. We calculated SMD using both a random and a fixed effect model. We assessed the impact of β-blocker therapy on overall QoL, as well as on physical and emotional domains. Subgroup analysis per type of β-blocker, duration of treatment, and disease severity were performed as well.

RESULTS

Study inclusion

The Medline search revealed 401 RCT, seven relevant for our study. Embase database was searched (657 articles) and one additional study was identified. Finally, three more studies were selected from the references of the identified articles. The Pascual and Cochrane databases did not provide any additional studies.

In seven studies additional data were obtained through direct communication with the authors or sponsors.[17–23]

Two studies were excluded from the analysis.[24,25] In the case of first one, QoL scores could not be obtained. However, this study included a small sample size (40 patients). The second study was excluded because QoL data were provided for about half of the patients at final 6 months evaluation, even though a carry forward analysis was performed for the patients lost to follow-up.

One study included patients enrolled for two different study periods, 18 months and 12 months, respectively.[26] We included this study (18 months sample) because QoL data were available for more than 70% of patients enrolled for this study period. Finally, nine trials remained eligible for inclusion.

Study characteristics

Table 1 shows the main characteristics of the studies. Most trials included patients with CHF caused by both coronary artery disease (CAD) and idiopatic dilatated cardiomiopathy (IDC), with NYHA class I-IV. Second generation selective β_1 blocker metoprolol, third-generation non-selective β_1/β_2 blocker celiprolol as well as non-selective $\beta_1/\beta_2/\alpha_1$ blockers carvedilol and bucindolol have been assessed within the trials and the duration of treatment varied from 3 months to 20 months. Baseline characteristics of study patients were similar across the studies (mean age 60 years, male sex around 75%, treatment with ACEI around 90%). One study differed in standard therapy (ACEI, ARB or a combination of the two drugs)[23] and another study included relatively younger patients (mean age 50 years).[26] The percentage of severe CHF patients differed slightly across studies; two trials included mostly NYHA I-II patients,[18,23] while two trials included more than 60% NYHA III-IV patients.[17,20]

QoL was mainly assessed with MLHF and in the case of one study with QLHF questionnaire. QoL was a secondary outcome in all the studies included. β-blocker therapy did not have a significant beneficial effect on QoL when compared to the placebo group in any of the studies included. Nevertheless, all studies but one[19] showed a trend for a better QoL in the β-blocker arm.

One trial assessed the impact on QoL of two different β-blockers (metoprolol and celiprolol) by using one control group.[21] Therefore, we divided the number of control patients to half when presenting the effects of metoprolol and respective celiprolol on QoL. We applied this procedure to preserve the

Table 1. Characteristics of the RCT included in the review

Study (Reference)	Year	Nb Pat QoL sample	Drug	Cause of heart failure*	NYHA class	Duration of therapy, months†	QoL instrum‡
Pollock *et al.*[17]	1990	19	Bucindolol	IDC/CAD	II-IV	3	MLHF
Colucci *et al.*[18]	1996	366	Carvedilol	IDC/CAD	II-III	≤15 (7)	MLHF
MOCHA[19]	1996	345	Carvedilol	IDC/CAD	II-IV	6.5–7.5 (7)	MLHF
PRECISE[20]	1996	278	Carvedilol	IDC/CAD	II-IV	6.5–7.5 (7)	MLHF
MDC[26]	1996	173	Metoprolol	IDC	I-IV	18	QLHF
Goldstein *et al.*[27]	1999	60	Metoprolol	IDC/CAD	II-IV	6	MLHF
Sanderson *et al.*[21]	1999	50	Metoprolol	IDC/CAD	II-III	3	MLHF
			Celiprolol	IDC/CAD	II-IV	3	MLHF
MERIT HF[22]	2000	741	Metoprolol	IDC/CAD	II-IV	≤20 (12)	MLHF
RESOLVD[23]	2000	426	Metoprolol	IDC/CAD	I-IV	6	MLHF

*IDC, idiopatic dilatated cardiomiopathy; CAD, coronary artery disease.
†The average duration of the blinded therapy is mentioned between brackets.
‡MLHF, Minnesota Living with Heart Failure questionnaire; QLHF, quality of life with Heart Failure questionnaire.
p-value β-blocker treatment versus control group non-significant for all trials included.

number of patients allocated to control and treatment groups when the data were pooled for meta-analysis.

The impact of β-blocker therapy on overall QoL

Despite the inclusion of trials that assessed the impact of different β-blockers, with various treatment duration, there was no significant heterogeneity among the nine studies ($\chi^2 = 6.40$; $p = 0.70$) or among subgroups (Fig. 1). QoL improved more in the β-blocker group compared to the control arm, but the SMD did not reach statistical significance (SMD = −0.07; 95%CI [−0.16, 0.02]; $p = 0.13$) under random effect model (Fig. 1). The fixed effect model showed similar results.

The impact of selective and non-selective β-blockers

Sensitivity analysis per type of β-blocker (selective and non-selective) showed also a non-significant effect on QoL in both groups (Metoprolol, SMD = −0.07; 95%CI [−0.18, 0.04]; $p = 0.20$; Carvedilol, Celiprolol and Bucindolol, SMD = −0.07; 95%CI [−0.22, 0.09]; $p = 0.40$) (Fig. 1). We also analysed the separate effects of carvedilol on QoL; the results were similar (SMD = −0.04; 95%CI [−0.20, 0.11]; $p = 0.58$).

The impact of β-blockers according to treatment duration

Analysis of QoL at 3 months, 6–8 months, and 12 months β-blocker therapy showed a non-significant effect on medium and long-term (Fig. 2). The most important impact on QoL (borderline significance) was on short-term medication, 3 months (SMD = −0.61; 95%CI [−1.22, 0.00]; $p = 0.05$).

The impact of β-blockers according to disease severity

Analysis of QoL within different classes of severity, including trials with less than 40% NYHA I-II patients, 40–60% NYHA I-II patients and more than

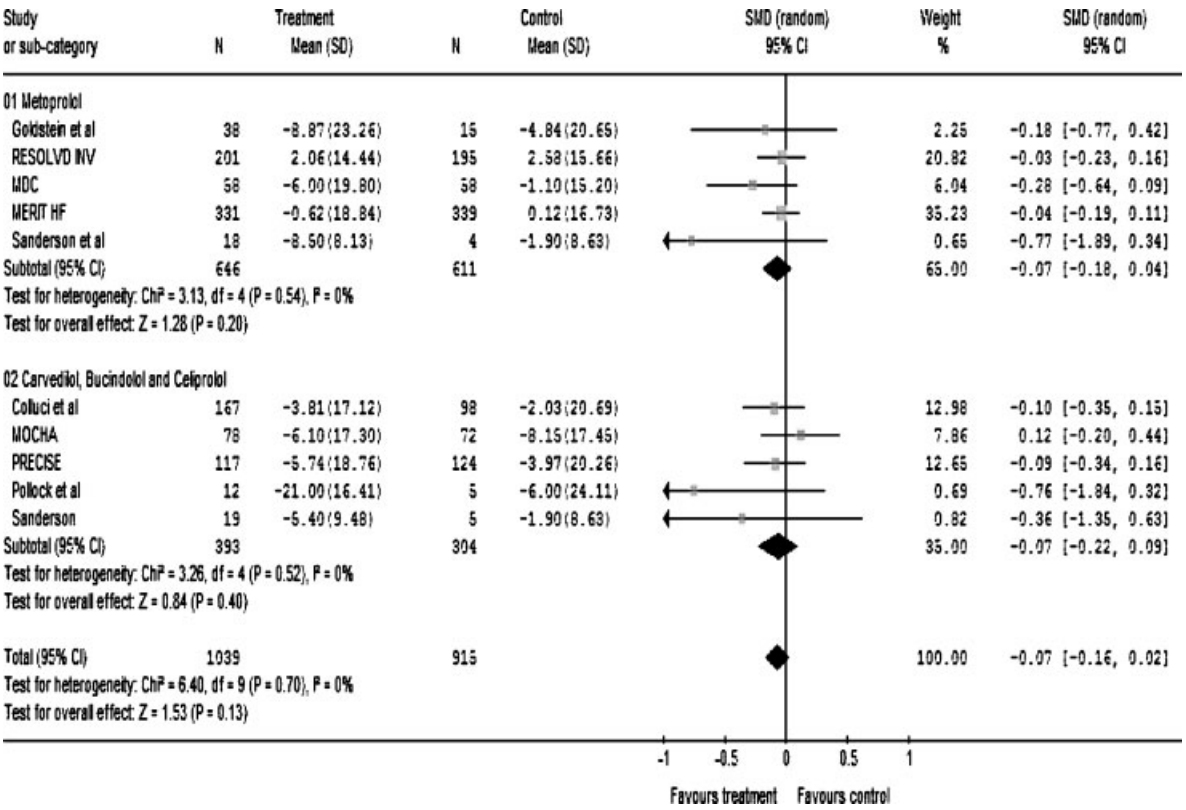

Figure 1. Effectiveness of β-blocker therapy using SMD. Mean change in QoL score is presented relative to the baseline score. A decrease in the mean score shows an improvement in QoL. SD stands for the standard deviation of the mean change in QoL score. SMD stands for the standardised mean difference in QoL between β-blocker and control groups

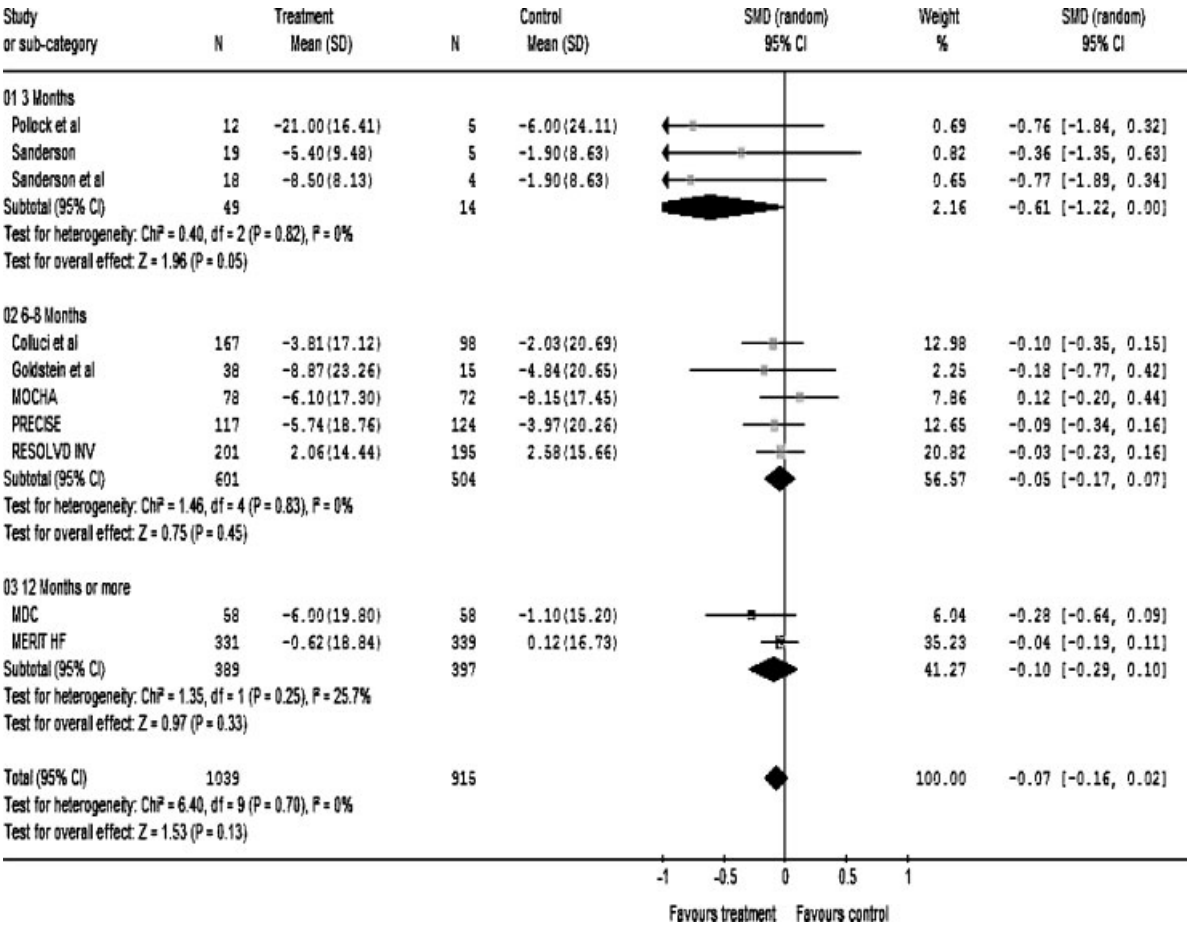

Figure 2. Effectiveness of β-blocker therapy according to treatment duration

60% NYHA I-II patients, showed also a non-significant effect (Fig. 3). However, the largest impact on QoL appeared to be in severe CHF patients (trials with less than 40% NYHA I-II patients).

The impact of β-blockers on physical and emotional domains of QoL

QoL scores per physical and emotional domains were provided for only two[26,27] out of the nine studies included, and we were able to obtain relevant data from another five trials.[18–20,22,23] The two trials excluded from the analysis[17,21] were of smallest sample size. The analysis showed better results on physical domain than on emotional dimension, but without statistical significance (results not shown).

DISCUSSION

We found a trend towards improvement on QoL in CHF patients receiving β-blocker therapy, but the effect was small and did not reach statistical significance. This result was independent of the type of β-blocker. The results did not change with the exclusion of one trial that showed better effects on standard medication or inclusion of one moderate size trial with positive effect on QoL.

Our study is the first to assess the impact of β-blocker medication on QoL in CHF patients through a systematic review and meta-analysis. To perform the analysis we collected unpublished data in seven of the nine trials included.

Our analysis shows a trend towards improvement on QoL irrespective of treatment duration. However, the

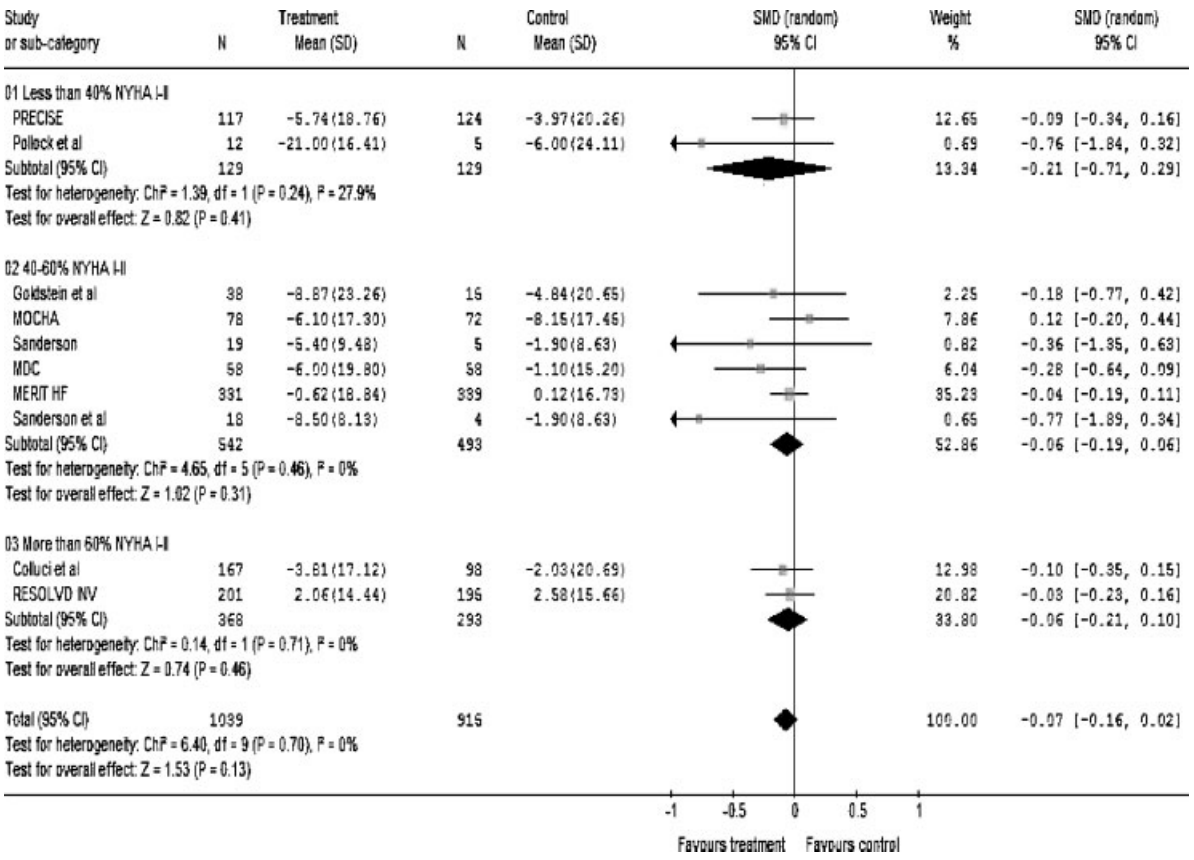

Figure 3. Effectiveness of β-blocker therapy according to disease severity

highest impact on QoL appears at 3 months therapy. This effect may be attributed to multiplicity, that is, it is one of several groups considered and by chance it shows a significant result. We expected better results with long-term β-blocker treatment than with short-term therapy, as it is well documented in the literature that initial treatment with β-blockers can have deleterious effects and beneficial effects begin after approximately 1 month, becoming clearly apparent at 3 months.[11] Nevertheless, it may be also possible that a significant improvement in QoL is achieved at 3 months of therapy and a gradual adaptation to the treatment occurs over time. Patients may be more aware of treatment effects at the beginning of the treatment rather than during follow-up, when progression of the disease or other life events may affect their QoL.

Our study shows that β-blocker therapy does not impair QoL in CHF patients, and there is not a reduced QoL at the expense of longer survival and reduced morbidity. This neutral effect may be due to several reasons. First, the side effects of β-blocker medication may affect QoL in these patients. Dizziness, hypotension, and bradycardia, as well as worsening of HF are among the most frequent side effects reported.[28] Nevertheless, recent evidence suggests that metoprolol CR/XL can be given safely to patients with stable to mild heart failure, with minimal side effects or deterioration.[29] Our results also suggest that QoL is not affected in short term. Given the actual evidence, it is difficult to draw a definite conclusion regarding the impact of the side effects of the medication on QoL in these patients.

Second, baseline QoL values among CHF patients have been relatively favourable in the MDC trial, indicating that these patients perceived themselves as not being severely affected. The reason of this favourable scoring might be that IDC follows a slow and progressive course, which may determine mental adaptation over time.[26] Favourable QoL scores are

also reported in studies including mostly NYHA II patients.[17,23] Hence, it was relatively more difficult in these patients to improve QoL.

Third, although MLHF is widely used in clinical trials of CHF, there are concerns about its sensitivity.[30] It is possible that a true/small change in QoL was simply not captured by the instrument.

Fourth, it may be that β-blocker therapy does not change QoL significantly when used on top of standard medication, due to a kind of 'saturation level'.

However, a positive effect of ACEI on QoL when used on top of diuretics and/or digoxin is also not evident[31,32], although a meta-analysis has not been performed so far. In contrast, the Valsartan trial showed that prescription of ARB Valsartan on top of ACEI improves QoL in patients with CHF.[33] The main differences between Valsartan trial and β-blocker trials were inclusion in the former one of a large number of patients (approximately 2000), and a long duration of follow-up (average 2 years). Vesnarinone, an inotropic agent, on top of ACEI/diuretics/digoxin was shown to improve significantly QoL in patients with severe CHF, however at the risk of increased mortality.[34] Device therapy on top of optimal medication was shown to improve significantly both survival and QoL in patients with severe CHF, but its indication is limited to a certain subgroup of patients with CHF.[35]

Our results indicate that more studies, especially with long follow-up have to be conducted to reach a definite conclusion regarding the impact of β-blocker medication on QoL. As patient enrolment in new RCT may be not ethical, cohort studies might be more appropriate. A meta-analysis that includes both RCT and cohort studies might be therefore a solution for further investigation on the topic. Finally, a more sensitive QoL questionnaire may be required to perform accurate analysis.

This study has some limitations. First, we could not include one study because appropriate data had not been published/provided. However, it is unlikely that the outcome would have been changed significantly, due to the small sample size of that study ($N = 40$). Second, QoL scores for patients lost to follow-up were provided through carry forward analysis, certainly less accurate than actual scores. Finally, we included a relatively small number of patients (approximately 2000), as only a limited number of β-blocker trials included QoL as an outcome, or QoL was assessed only in a sub-sample of the initial trial.

In conclusion, the present study demonstrates that QoL is not adversely affected by β-blocker medication. Clinicians may add β-blockers to standard therapy without concerns of impairing QoL in CHF patients.

KEY POINTS

- Conflicting hypotheses regarding the impact of β-blocker therapy on QoL in patients with CHF.
- A total of 9 trials, involving 1954 patients were included in a meta-analysis to quantify the impact of β-blocker therapy on QoL.
- β-blocker therapy, on top of standard medication, does not impair QoL. Moreover, there is a trend towards improvement on QoL in CHF patients additionally treated with β-blockers.
- Clinicians may add β-blockers to standard therapy without concerns of impairing QoL in patients with CHF.

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