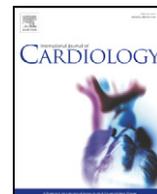




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Review

Cardiac resynchronization therapy in the elderly: A realistic option for an increasing population?

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ABSTRACT

Cardiac resynchronization therapy (CRT) has become a mainstay of heart failure treatment. Since heart failure is a disease primarily affecting older patients it is important to evaluate the performance of CRT in this population.

Elderly has been suggested as a subgroup less likely to benefit from CRT. This is an important issue that should be clarified, because most patients with heart failure are old.

The present review discusses the available data concerning cardiac resynchronization therapy in the elderly, focusing on efficacy, indication, safety, and impact of co-morbidities.

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1. Introduction

Heart failure (HF) is the fastest growing cardiovascular disease and it carries a poor prognosis, even with optimal pharmacotherapy [1]. Additionally, HF is a condition that dramatically impairs the quality of life, particularly in older patients and mostly when it is associated with typical age-associated comorbidities.

The prevalence of HF rises sharply with age, so the prevalence in 70- to 80-year-old people is between 10 and 20% [2]. Probable reasons are the age-related changes in ventricular function, the cumulative effects of chronic risk factors (particularly arterial hypertension), in addition to the enhanced therapy for acute myocardial infarction and acute HF [3].

HF is a condition that dramatically impairs the quality of life, particularly in older patients and mostly when it is associated with typical age-associated comorbidities. In patients older than 65, at least 20% of hospital admissions are due to HF [4].

Several randomized controlled trials have shown improved outcomes with CRT in appropriately selected patients with systolic HF and evidence of dyssynchrony [5,6]. Potential mechanisms of benefit include improved contractile function and reverse ventricular remodeling. The usual inclusion criteria include NYHA classes III to IV HF despite optimal medical therapy, left ventricular ejection fraction (LVEF) <35%, and QRS duration of >120 ms [2].

Despite the encouraging results from CRT in recent trials, patients' responses to CRT vary significantly and up to 30% of patients receiving

CRT are “non-responders” [7]. Concerns about costs have encouraged the search for patient's subgroups more likely to benefit from CRT. Of note, elderly has been suggested as a subgroup of patients less likely to benefit from CRT. This is an important issue that should be clarified, because most patients with HF are old.

Although HF is a disease of the elderly, data on the efficacy and safety of CRT in this population are scarce. Older patients are poorly represented in almost all large-scale CRT trials and little data exists on the effects of CRT in the elderly [8].

In this review, we tried to summarize the current knowledge regarding the use of CRT devices in elderly HF patients based on subgroup analyses of prospective randomized trials, and based on published cohort studies.

1.1. CRT efficacy and indications in the elderly

Heart failure patients in clinical practice are almost a decade older than the trial participants [1].

To date, it remains unclear, whether the favorable results of CRT therapy are generalizable to elderly patients, because few old patients have been included in clinical trials as summarized in Table 1. Additionally, randomized trials have not specifically addressed the benefit of CRT in elderly patients.

In two major CRT trials (CARE-HF and COMPANION), the mean age was about 65 years and the benefit from CRT was similar in patients above and below the mean age [6,9].

The COMPANION trial randomized 1520 patients (mean age 67) with advanced heart failure to receive CRT alone or CRT with prophylactic ICD back-up (CRT-D) in a 1:2:2 ratio [9]. At a mean follow-up of 12 months, there was a significant reduction in the incidence of the primary composite end point of all-cause mortality

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Table 1
Important prospective CRT trials with subgroup analysis by age.

Study	Year	Age	Number of patients	Results
COMPANION [9]	2004	65 ± 11	1520	Reduction of all-cause mortality or hospitalization
CARE-HF [6]	2005	67 (60–73)	813	Reduction of mortality or hospitalization Improvement in NYHA functional class, quality of life and ejection fraction
MIRACLE [10]		63.9 ± 10.7	453	Improvement in NYHA functional class, 6-minute walk test, quality of life and ejection fraction
MIRACLE-ICD [11]	2003	66.6 ± 11.3	369	Improvement in NYHA functional class and quality of life

and hospitalization due to worsened heart failure in the two arms receiving CRT compared to the arm receiving pharmacological therapy alone. On a subgroup analysis the primary end point did not vary with age, with similar benefit of CRT for patients below and above the age of 65 years [12].

Another landmark CRT trial, the CARE-HF study also included many elderly patients. That trial randomly assigned 813 patients (mean age 67) with NYHA class III or IV HF to optimized medical therapy alone or plus CRT. At a mean follow-up of 29 months, CRT significantly improved the symptoms and the quality of life and reduced the total mortality [6]. Again, a subgroup analysis demonstrated a similar benefit for patients below and above the age of 66.4 years.

A recently published subgroup analysis by age of the MIRACLE and MIRACLE-ICD trials showed that elderly patients who receive CRT have comparable improvement in NYHA class and LVEF as younger patients [13].

Equivalent benefits of CRT were also noted in observational studies comparing elderly with younger patients [14,15]. Bleeker et al. [14] showed after a relatively short follow-up of 6-months a similar clinical and echocardiographic (improvement in the LV ejection fraction and extent of LV reverse remodeling) responses in patients ≥ 70 years of age (mean age 76) compared to patients < 70 years of age (mean age 59). Moreover, survival at 1-year after implantation was comparable in both groups [14]. More recently, Delnoy et al. [15] also demonstrated a similar clinical and echocardiographic benefit of CRT in patients aged > 75 years in comparison to younger patients.

Unfortunately, elderly heart failure patients > 75 years, octogenarians or patients with more severe comorbidities have been largely underrepresented or excluded in CRT trials.

Recently, the efficacy of CRT in octogenarians has been evaluated in the Insync/Insync ICD Italian registry. In that study, which included 1181 patients (85 of whom were ≥ 80 years old) CRT demonstrated similar efficacy in patients aged ≥ 80 years and in those under 80, in terms of clinical and functional parameters, reverse remodeling and even cardiac mortality [3].

In conclusion, based on the results of all these clinical studies, there seems to be no reasonable doubt that the full age range of patients with advanced HF and appropriate indication can benefit from CRT. Therefore, in elderly patients without major comorbidities, the data support the use of CRT devices for standard indication according to published guidelines.

1.2. Complications of CRT in the elderly

Overall, transvenous biventricular pacemaker implantation is a safe, well-tolerated, procedure with a high rate of successful implantation in the first attempt [16].

Cohort studies have demonstrated low perioperative mortality rates for CRT in geriatric patients, including octogenarians [3]. In fact, in the Insync/Insync ICD Italian registry, no major complication occurred during the implant procedure, and device-related complications observed during the follow-up were relatively rare. LV leads dislodged occurred in 4.4% of patients aged < 80 years and in 2.4% aged ≥ 80 years (P = NS) and 1.8% pocket erosions were reported in the < 80 years group [3].

In the subgroup analysis by age of the MIRACLE and MIRACLE-ICD trials, there was no evidence of increased adverse events after CRT implantation in the elderly [13]. However, this study suffers the limitations of a post-hoc analysis. In fact, to date, no prospective, randomized trial has specifically addressed the safety of CRT in the elderly.

1.3. Impact of comorbidities

Comorbidities such as atrial fibrillation, peripheral vascular disease, diabetes, pulmonary disease, depression, anemia and renal dysfunction complicate HF care and are prevalent in one form or another for the majority of elderly patients scheduled for CRT [17].

The question of whether older patients with multiple comorbidities will benefit in terms of survival and quality of life from implantation of costly devices is important. However, despite the fact that elderly patients scheduled for CRT in “the real world” clinical practice usually present several co-morbidities, this type of patients has clearly been underrepresented in prospective CRT trials.

Renal dysfunction is a common comorbidity in HF and is individually associated with poorer outcomes [18]. However, it has been demonstrated that renal impairment does not prevent the positive response to CRT, even in elderly patients [19]. Actually, previous studies have indicated that CRT can be a renal-protective strategy in HF and that the improvement in renal function can be another mechanism to explain the beneficial effects of CRT [20–22].

Diabetes and chronic HF commonly coexist [23]. In addition, diabetes is a powerful independent predictor of morbidity and mortality among patients with HF [24]. Regarding the impact of diabetes on CRT effectiveness, previous studies have demonstrated that this frequent comorbidity is not a predictor of poor response [19,25]. In fact, diabetic HF patients treated with CRT seem to have a very favorable functional and survival outcome, which is comparable to non-diabetic patients [26].

The prevalence of atrial fibrillation (AF) in patients with HF varies with severity, ranging from 5% in patients with NYHA functional class I to 40% in patients with NYHA class IV and markedly increases with age [27].

A recent meta-analysis of prospective cohort studies comparing CRT in patients with AF and sinus rhythm, concluded that patients with AF show significant improvement after CRT with similar or slightly greater improvements in left ventricular ejection fraction than patients in sinus rhythm [28].

All the available data indicate that even elderly patients with comorbidities, but with a good life expectancy, could benefit from CRT. Nevertheless, comorbidities should certainly be considered when determining whether an elderly patient will benefit from a HF device or not and could also influence the decision of which device to implant—a CRT-P primarily to improve quality of life or a CRT-D to improve quality of life and to prolong survival? In selected elderly patients with severe HF symptoms and frequent hospitalizations, but severe comorbidities, CRT without ICD back-up may be a good choice to improve quality of life, irrespective of impact on mortality.

1.4. CRT plus ICD versus CRT alone

Once an indication for CRT has been confirmed the choice of the most appropriate device (CRT-P or CRT-D) needs to be made. In

clinical practice, most patients who are candidates to CRT also meet criteria for ICD implantation. In fact, combination devices account for more than 80% of CRT implants [29].

Biventricular pacing alone without an ICD backup decreases mortality [6]. However, in the COMPANION trial, CRT plus ICD showed a trend toward lower all-cause mortality compared to CRT alone [12]. Moreover, the mortality benefit in COMPANION began immediately in the CRT plus ICD group compared to eight months with CRT alone [9]. A similar delayed benefit was seen with CRT alone in CARE-HF [6]. Of note, a recent meta-analysis of randomized controlled trials confirmed that CRT predominantly reduces mortality due to worsening HF, not affecting sudden cardiac death [30]. These results suggest that ICD prevents sudden death from the beginning, while the mortality benefit of CRT requires time for reverse ventricular remodeling.

Importantly, in elderly patients which frequently have several comorbidities, the choice of the HF device has to consider not only the potential benefit of the therapy and, the life expectancy but also the cost-effectiveness related to the device. A benefit-risk evaluation should always be conducted and the choice between a CRT or CRT plus ICD must be discussed for each individual elderly patient.

2. Conclusion

Available data from randomized trials as well as from cohort studies support the conclusion that CRT is effective in the full age range of patients with advanced HF. Thus, in elderly patients without major comorbidities, data support the use of CRT-P and CRT-D devices for standard indication according to published guidelines. For patients whose functional status and life expectancy are limited predominantly by chronic noncardiac conditions, the relative risks and benefits of CRT-P or CRT-D devices must be weighted and discussed for each patient.

Cost-effectiveness of CRT has not been evaluated in large cohorts of elderly HF patients. Whether the cost-benefit ratio of younger patient populations can be extrapolated to elderly patient cohorts with more comorbidities remains to be determined in the future.

Large, multicenter, randomized trials on CRT in the elderly are warranted to confirm the net benefit of this therapy in this increasing population.

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The authors of this manuscript have certified that they comply with the Principles of Ethical Publishing in the International Journal of Cardiology [31].

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