Chapter 6

Left Ventricular Reverse Remodeling, Device-related Adverse Events and Long-Term Outcome after Cardiac Resynchronization Therapy in the Elderly

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Circ Cardiovasc Qual Outcomes. 2014 May;7(3):437-44

The incidence and prevalence of heart failure increases significantly with aging and older patients often present with more advanced heart failure as compared to younger patients.[1,2] Patients older than 75-80 years are often underrepresented in heart failure therapy trials, including the ones involving cardiac resynchronization therapy (CRT). The mean age of patients in the large CRT trials ranged between 62 and 67 years, whereas the mean age of patients included in large registries was higher with nearly one-third of patients being ≥75 years old.[3-7] Device-related adverse events, efficacy and long-term outcome after CRT implantation in the elderly are therefore unknown.[8] The present study aimed at evaluating 1) the effect of CRT on clinical and echocardiographic parameters in the elderly 2) the impact of age on LV reverse remodeling after CRT, 3) device-related adverse events after CRT and finally, 4) the long-term prognosis of elderly CRT recipients.

METHODS

Patient population

Patients included between June 2000 to July 2010 in an ongoing CRT registry from the Department of Cardiology of the Leiden University Medical Centre (Leiden, The Netherlands) were evaluated in the present analysis.9 Patients underwent CRT device implantation according to the presence of left ventricular ejection fraction (LVEF) ≤35%, a QRS duration ≥120 ms and New York Heart Association (NYHA) functional class II-IV heart failure symptoms despite optimal medical therapy.10 The etiology of heart failure was considered ischemic in the presence of significant coronary artery disease (>50% stenosis in ≥1 major epicardial coronary artery) on coronary angiography and/or a history of myocardial infarction or revascularization. Patients with decompensated heart failure prior to the implantation or recent myocardial infarction (<3 months) were excluded.

All patients underwent extensive clinical evaluation and transthoracic 2-dimensional (2D) echocardiography prior to and 6 months after CRT implantation. All patients were scheduled for regular visits to the outpatient clinic at 6 months of follow-up. To evaluate the association between age and CRT outcomes, patients were dichotomized in two groups: non-elderly (<75 years) and elderly (≥75 years) according to the age at CRT implantation.[11-13]

Patient data were prospectively collected in the departmental Cardiology Information System (EPD-Vision®, Leiden University Medical Center, Leiden, The Netherlands) and subsequently analyzed. For this retrospective analysis of clinically acquired data, the Institutional Review Board waived the need of patient written informed consent.

Clinical and echocardiographic evaluation

Clinical evaluation included quality-of-life score according to Minnesota living with Heart failure questionnaire (higher scores indicate worse quality of life), 6-minute walk-test, frailty score and NYHA functional class assessment. [14-16] At baseline, renal function was evaluated according to glomerular filtration rate (GFR) estimation according to the Cockcroft-Gault equation.[17]

Echocardiographic studies were performed with patients in the left lateral decubitus position,

using a commercially available ultrasound system (Vivid 7 and e9, General Electric Vingmed Ultrasound, Horten, Norway) equipped with 3.5 MHz and M5S transducers. Images were digitally stored for offline analysis in cine-loop format (EchoPac 112.0.1, GE-Vingmed, Horten, Norway). LV end-diastolic volume (LVEDV) and end-systolic volume (LVESV) were measured at the apical 2- and 4-chamber views, and (LVEF was calculated, using the Simpson's biplane rule.[18] In addition, LVEDV and LVESV were indexed for body surface area (BSA) and reported as LVEDVi and LVESVi, respectively. A reduction of ≥15% in LVESV at 6 months follow-up was considered a positive response to CRT. Death before 6-month follow-up or <15% reduction in LVESV at 6 months was considered non-response.[19]

Device implantation

A venogram of the coronary sinus was obtained with a balloon-guiding catheter. The LV lead was inserted into the coronary sinus through an 8-French guiding catheter and positioned in the venous system, preferably in a (postero-)lateral vein in a stable position without inducing phrenic stimulation. The right atrial and ventricular leads were positioned conventionally, and all leads were connected to a CRT device. Implanted systems were manufactured by Biotronik (Berlin, Germany), Boston Scientific (Natick, Massachusetts, formerly CPI, Guidant, St. Paul, Minnesota) and Medtronic (Minneapolis, Minnesota).

Device-related adverse events

To evaluate the safety of CRT implantation, device-related adverse events requiring invasive treatment or resulting in serious injury within 30 days after CRT implantation were registered. Pneumothorax, pericardial effusion, coronary sinus dissection or perforation, LV lead dislodgement, pocket hematoma requiring pocket exploration or prolonged hospitalization with and without change in anticoagulation regimen and device infection/device extraction were considered as device-related adverse events. Based on the timing of the event, device-related adverse events were compared between the two age groups; within 24h after the procedure (defined

as device-related in-hospital) and after 24h but within 30 days after the procedure (defined as device-related early adverse events). Device-related adverse events occurring 30 days after the procedure (lead fracture and replacement, pocket hematoma requiring pocket exploration, device infection and replacement) were defined as long-term device-related adverse events.[20,21]

Long-term outcome

Long-term follow-up was performed by medical chart review, outpatient clinical visits and telephone contact. The primary endpoint was all-cause mortality. The secondary endpoints included combination of all-cause mortality together with heart failure hospitalization or ventricular arrhythmias requiring appropriate ICD therapy (antitachycardia pacing and defibrillator shocks) and ventricular arrhythmic death.[22] Heart failure hospitalizations were adjudicated by the cardiologist responsible for the management of the patient during admission, while the appropriate ICD therapy was adjudicated by trained pacemaker technicians (and confirmed by a cardiologist) after device interrogation. Furthermore, the mode of death was compared between the two age groups. Death was categorized as cardiac, non-cardiac or unknown. Cardiac death included death due to progression of heart failure, sudden cardiac death, myocardial infarction, ventricular arrhythmias or other cardiac cause.[22]

Statistical analysis

Continuous variables with normal distribution are presented as mean and standard deviation, non-normally distributed data as median with interquartile range and dichotomous data as numbers and percentages. Student t–test was used to compare continuous variables and $\chi 2$ tests to compare categorical variables. Wilcoxon signed rank test was used for the comparison changes in nominal data at follow-up. Generalized estimating equations (GEE) was used to compare changes in clinical and echocardiographic parameters within and between the age groups at follow-up (interaction). Linear scale response was used for normally distributed data and ordinal logistic response for the nominal data.

Device-related in-hospital and device-related early adverse events were compared with the construction of Kaplan-Meier curves. To account for the effect of multiple device-related long-term adverse events, the long-term adverse events data were analyzed using the Frailty Model in R package.[23] The log-rank tests were utilized to compare the difference in Kaplan-Meier curves for the survival free from the primary and secondary endpoints between the age groups. The cumulative incidences of cardiac and non-cardiac death were calculated using competing risks analysis and the mode of death was compared by Cox regression analysis.[24] Furthermore, the predictors of the primary endpoint within the elderly group were evaluated with the

Cox proportional hazards model; all clinical and echocardiographic relevant predictors and the variables that showed a significant effect ($p<0.15$) at the univariable analysis were introduced in the multivariable model. In case of collinearity, only one of these variables was entered in the multivariable model. All statistical tests were 2-sided and for all tests, a p-value <0.05 was considered statistically significant. Windows IBM SPSS Statistics software (SPSS version 20.0, IBM SPSS statistics, Chicago, IL) and R version 2.14.1 (R development core team, Vienna, Austria) were used for data analyses.

RESULTS

Baseline clinical and echocardiographic characteristics

Baseline clinical and echocardiographic characteristics of the overall population are listed in Tables 1 and 2. A total of 798 patients (mean age of 67±11 years) were included, of which 208 (26%) were elderly (age ≥75 years). Elderly patients were more likely to have an ischemic etiology of cardiomyopathy (69% versus 57%, $p=0.002$) and higher prevalence of atrial fibrillation (26% versus 15%, $p=0.001$; Table 1). The prevalence of diabetes was lower among elderly patients as compared to non-elderly patients (11% versus 24%, $p<0.001$) and a worse renal function was observed among elderly patients as compared to their counterparts (GFR of 51±18 versus 76±34 mL/min/1.73 m^2, $p<0.001$;Table 1). Additionally, at the time of implantation, functional capacity of non-elderly patients was superior to elderly patients (according to NYHA functional class, 6-minute walk-test, frailty score and quality-of-life score). With the exception of the higher percentage of anticoagulant use in the elderly patients, the use of medications was equally distributed in both age groups. Furthermore, LV volumes were larger in non-elderly patients whereas LVEF was comparable between the two groups.

Follow-up clinical and echocardiographic characteristics

In the overall population, a significant improvement in functional and echocardiographic parameters was observed at 6-month follow-up as compared to baseline. NYHA functional class decreased from 3 [IQR: 3-3] to 2 [IQR: 2-2] (Z-score: -19.927, Wilcoxon $p<0.001$), while quality of life score decreased from 34±19 to 23±18 ($p<0.001$), and 6-minute walked distance increased from 300±118 to 373±122 m ($p<0.001$). Furthermore, LVEDVi decreased from 112±40 to 100±38 ml/m^2, ($p<0.001$), LVESVi decreased from 84±36 to 70±33 ml/m^2 ($p<0.001$) while LVEF increased from 26±8 to 32±9 % ($p<0.001$).

Table 1. Baseline characteristics of the study population and comparing non-elderly patients with elderly patients.

	Age <75 years (n=590)	Age ≥75 years (n=208)	p-value
Age, years	63±10	78±3	<**0.001**
Ischemic etiology, n(%)	336(57)	144(69)	**0.002**
Male gender, n(%)	454(77)	164(79)	0.574
QRS duration, ms	155±33	160±30	0.072
Atrial fibrillation, n(%)	86(15)	51(26)	**0.001**
Diabetes, n(%)	142(24)	23(11)	<**0.001**
GFR, mL/min/1.73 m²	76±34	51±18	<**0.001**
Frailty score ≥3 points, n(%)*	41(8)	33(17)	**0.001**
β-blockers, n(%)	424(72)	136(65)	0.079
ACE-I/ ARB-II, n(%)	529(90)	182(88)	0.390
Diuretics, n(%)	508(86)	183(88)	0.494
Calcium-antagonists, n(%)	35(6)	13(6)	0.868
Digoxin, n(%)	98(17)	39(19)	0.482
Oral anticoagulant or anti-platelet agent, n(%)	515(87)	196(94)	**0.006**
Statins, n(%)	345(59)	115(55)	0.424
Amiodarone, n(%)	111(19)	44(21)	0.463

Values are mean±SD or n. Bold p-values are statistically significant. ACE-I/ARB-II = Angiotensin-Converting Enzyme Inhibitor/Angiotensin-Receptor Blockers II; GFR = Glomerular Filtration Rate estimated according Cockcroft-Gault equation; * Percentage is valid for the population were frailty could be assessed; in 96 patients (14%) the assessment of the frailty was not possible.

Table 2. Baseline, follow-up and the evaluation of change in clinical and echocardiographic variables in non-elderly and elderly patients undergoing CRT implantation.

	Age <75 years (n=590)		Age ≥75 years (n=208)		Interaction p-value
Variable	**Baseline**	**Follow-up**	**Baseline**	**Follow-up**	
NYHA functional class, [IQR]	3 [3-3]	2 [2-2]*	3 [3-3]	2 [2-3]*	0.311
Quality-of-life score	35±19	23±18*	32±17	23±17*	**0.019**
6-min walked distance, m	314±117	388±120	257±112	327±114	0.687
LVEDVi, ml/m²	114±42	102±40*	105±35	93± 33*	0.406
LVESVi, ml/m²	86±37	71±35*	79±30	64±28*	0.939
LVEF, %	26±8	32±10*	27±8	33±9*	0.662

Values are mean±SD or median and [IQR]. Bold p-values are statistically significant. IQR= interquartile range; LVEDVi= Left Ventricular End-Diastolic Volume index; LVESVi= Left Ventricular End-Systolic Volume index; LVEF= Left Ventricular Ejection Fraction; NYHA= New York Heart Association. * p<0.001, baseline vs. follow-up

A comparable magnitude of improvement in clinical and echocardiographic characteristics was observed in elderly and non-elderly patients at 6-month follow-up (see interaction p-value in Table 2). Of interest, the incidence of response to CRT (defined as reduction of ≥15% in LVESV) was not significantly different between both age groups (53% in the non-elderly vs. 58% in the elderly, p=0.202)

Device-related adverse events

Table 3 summarizes the incidence of device-related in-hospital and device-related early adverse events in elderly versus non-elderly patients. There were no differences between elderly and non-elderly patients and only a trend toward a slightly higher incidence of pneumothorax and pocket hematoma was observed among elderly patients. During a median of 38.6 months, elderly patients were exposed to similar risk of the device-related long-term adverse events: lead fractures/replacements (Frailty Model HR 0.56 CI: 0.31-1.01, p=0.055) and device infections/extraction as compared to non-elderly patients (Frailty Model HR 1.86 CI: 0.82- 4.21, p=0.140). Moreover, the Frailty Model demonstrated a significant higher risk of pocket hematomas among elderly patients (Frailty Model HR 6.23 CI: 1.07-36.33, p=0.042). However, the total number of device-related long-term adverse events was similar between the two groups (Frailty Model HR 0.90 CI: 0.58-1.38, p=0.620).

Table 3. Device related in-hospital and early adverse events after CRT implantation in the total patient population and compared in elderly and non-elderly patients.

		Total N=798 n(%)	Age <75 years n(%)	Age ≥75 years n(%)	p-value*
0-24h	**In-hospital adverse events**	23 (2.9)	16 (2.7)	7 (3.4)	0.552
	Pneumothorax	6 (0.8)	3 (0.5)	3 (1.4)	0.158
	Pocket hematoma	4 (0.5)	2 (0.3)	2 (1.0)	0.250
	Sinus coronarius dissection, lead perforation or pericardial effusion	2 (0.3)	1 (0.2)	1 (0.5)	0.563
	LV lead dislodgement	11 (1.4)	10 (1.7)	1 (0.5)	0.218
24h-30d	**Early adverse events**	20 (2.5)	15 (2.5)	5 (2.4)	0.984
	Pocket hematoma	2 (1)	1 (0.2)	1 (0.5)	0.418
	LV lead dislodgement	14 (1.8)	11 (1.9)	3 (1.4)	0.748
	Device infections/Explantation	4 (0.5)	3 (0.5)	1 (0.5)	0.995

*Based on log rank test comparison

Long-term outcome

During long-term follow-up (median 38.6 months, interquartile range 22.5 to 61.8 months), a total of 274 patients (34%) died of which 84 (40%) were elderly patients

and 190 (32%) were non-elderly patients. The cumulative incidence of the primary endpoint was significantly higher in elderly patients (log rank p=0.013). Of note, survival difference was statistically significant only after 4 years follow-up with a survival rate of 72% in the non-elderly [95%-CI: 68%-76%] versus 60% in the elderly [95%-CI: 52%-68%], log rank p=0.013 (Figure 1).

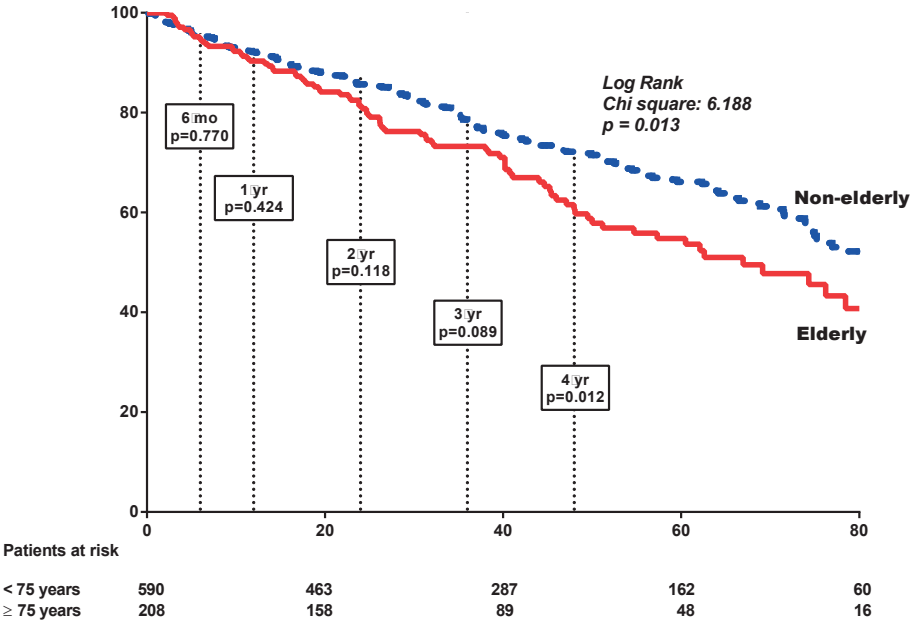

Figure 1. Kaplan-Meier curve of the overall survival (primary endpoint) in non-elderly (<75 years) and elderly patients (≥75 years) after CRT.

Regarding the cause of death (Table 4), 61 patients (22%) died from a non-cardiac cause and 176 patients (64%) from a cardiac cause (mainly progression of heart failure, 79%). In 34 patients (12%) the mode of death was unknown. A higher rate of non-cardiac cause of death was observed among elderly patients (Table 4). Moreover, as depicted in Figure 2, the cumulative incidence of non-cardiac death between the two groups was significantly different which suggests that non-cardiac mortality is the determinant of the survival difference between elderly and non-elderly patients (Figure 1, log rank p<0.001).

Regarding the secondary endpoints, similar event rates for the combination of all-cause mortality or heart failure hospitalizations were observed between the age groups (survival free from events 45% [95%-CI: 40%-51%] in the elderly versus 53% [95%-CI: 50%-56%] in the non-elderly, log rank p=0.099). Furthermore, the cumula-

tive incidence rates of ventricular arrhythmias requiring appropriate ICD therapy and ventricular arrhythmic death were comparable between the two groups (survival free from events 47% [95%-CI: 31%-63%] in the elderly versus 42% [95%-CI: 22%-62%] in the non-elderly, log-rank p=0.792)

Table 4. Causes of death in non-elderly and elderly patients after CRT implantation

	Age < 75 years (n= 590)	**Age ≥ 75 years (n= 208)**	**p-value***
All-cause, n (%)	190 (32)	84 (40)	**0.013**
Cardiac, n (%)	125 (66)	51 (61)	0.164
Decompensated heart failure, n (%)	101 (53)	38 (45)	**0.027**
Sudden cardiac death, n (%)	14 (7)	7 (8)	0.740
Myocardial infarction, n (%)	4 (2)	1 (1)	0.648
Ventricular arrhythmia, n (%)	1 (1)	2 (2)	0.057
Other cardiac, n (%)	5 (3)	3 (4)	0.734
Non-cardiac, n (%)	37 (19)	24 (29)	< **0.001**
Cancer, n (%)	13 (7)	6 (7)	0.626
Unknown, n (%)	28 (15)	9 (11)	0.256

*Based on log rank test comparison. Bold p-values are statistically significant.

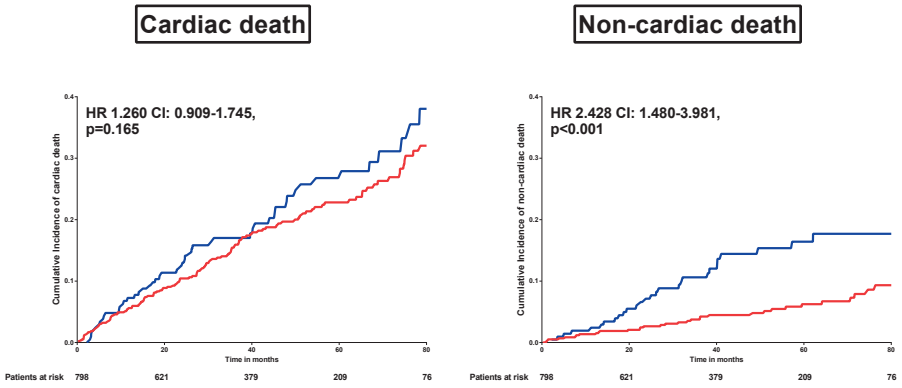

Figure 2. Cumulative incidence of mortality specified in cardiac and non-cardiac death within the non-elderly (< 75 years) and elderly patients (≥75 years) after CRT implantation.

Predictors of the primary endpoint in the elderly

Univariable analysis performed in the elderly population indicated that NYHA functional class, quality-of-life score, 6-minute walked distance, GFR, LVESVi and LVEF were significantly related to all-cause mortality (primary endpoint). These variables together with other clinical and echocardiographic relevant characteristics (age, ischemic etiology, atrial fibrillation and diabetes mellitus) were included in the multivariable model (Table 5). The multivariate analysis showed that presence of diabetes, impaired renal function (lower GFR values) and reduced 6-min walked distance at baseline were independently associated with the primary endpoint among elderly CRT recipients (Table 5).

Table 5. Cox regression survival analysis for the primary end point in the elderly (age ≥75 years) patients with heart failure after CRT implantation

	Univariable Model			Multivariable Model		
	HR	**CI 95%**	**p-value**	**HR**	**CI 95%**	**p-value**
Age (per year)	1.022	0.950-1.100	0.491	0.949	0.863-1.047	0.295
Male gender	1.340	0.754-2.383	0.319	1.234	0.639-2.472	0.540
Ischemic etiology	1.709	1.031-2.832	**0.038**	1.734	0.865-3.370	0.096
QRS duration (per ms)	1.000	0.993-1.008	0.965			
NYHA functional class II (reference)			**0.030**			
NYHA functional class III	1.550	0.795-3.025	0.199			
NYHA functional class IV	3.349	1.349-8.313	**0.009**			
Atrial fibrillation	1.472	0.912-2.378	0.114	1.543	0.868-3.106	0.166
Diabetes	1.810	0.999-3.279	0.050	2.322	0.979-4.178	**0.019**
Quality-of-life score (per point)	1.024	1.010-1.037	**0.001**			
6-min walked distance (per meter)	0.995	0.993-0.998	<**0.001**	0.996	0.993-0.998	**0.001**
GFR (per ml/min/1.73m²)	0.976	0.962-0.989	**0.001**	0.975	0.959-0.995	**0.006**
β-blockers use	0.828	0.535-1.282	0.398			
Oral anticoagulants use	0.532	0.231-1.226	0.139			
LVEDVi (per ml/m²)	1.005	0.998-1.011	0.156			
LVESVi (per ml/m²)	1.009	1.002-1.016	**0.015**	1.000	0.990-1.010	0.994
LVEF (per %)	0.942	0.913-0.971	<**0.001**			
Frailty score ≥ 3 points, n(%)	1.520	0.859-2.691	0.150			

Bold p-values are statistically significant. GFR = Glomerular Filtration Rate estimated according Cockcroft-Gault equation; LVEDVi= Left Ventricular End-Diastolic Volume index; LVESVi= Left Ventricular End-Systolic Volume index; LVEF= Left Ventricular Ejection Fraction; NYHA= New York Heart Association

DISCUSSION

The present evaluation shows that elderly patients benefit from CRT similarly to non-elderly patients, with comparable improvements in clinical symptoms and LV function and similar rates of in-hospital and early device-related adverse events. However, elderly patients had significantly higher 4-year mortality rate, specifically with higher rate of non-cardiac mortality. Diabetes, reduced 6-minute walk distance and impaired renal function were independently associated with all-cause mortality among elderly patients.

Impact of age on LV reverse remodeling after CRT

CRT induces favorable LV reverse remodeling and improvement in LV systolic function. These favorable effects have been shown independent of age. For example, the Multicenter InSync ICD Randomized Clinical Evaluation (MIRACLE) and MIRACLE-ICD trials showed that patients randomized to CRT-ON group had important reductions in LV end-diastolic diameters across all age groups.[25] Similarly, the sub-analysis of the InSync/InSync ICD Italian Registry demonstrated significant reductions in LV volumes at 6 and 12 months follow-up independent of age.[12] In line with these observations, sub-analysis of the Multicenter Automatic Defibrillator Implantation Trial with Cardiac Resynchronization Therapy (MADIT-CRT) comparing the magnitude of LVESV change at 12-month follow-up between patients <60 years, 60-74 years and ≥75 years reported no significant differences between age groups.[13] The present results provide more evidence on the beneficial effects of CRT on LV structure and function and would support the appropriateness of implanting CRT in old patients with heart failure.

Device-related adverse events

Despite the technical challenges associated with CRT implantation, the overall perioperative complications rates have significantly decreased over the last decades (from 28% in earlier trials to 4% in recent trials).[10] The relationship between age and CRT implantation related adverse events remains controversial. Data from the InSync registry, MADIT-CRT, MIRACLE and MIRACLE-ICD trial subanalyses demonstrated that the incidence of device-related adverse events was not influenced by age.[12,13,25] However, a recent study including 26,887 recipients of ICD or CRT devices has shown a significant higher frequency of acute device-related adverse event among elderly patients, females and black race/ethnicity.[26] Similarly to the results of the InSync, MADIT-CRT, MIRACLE and MIRACLE-ICD studies, the present evaluation showed that the rates of early adverse events were not different between young and elderly patients. Regarding the long-term CRT-related complications the data

are scarce. This evaluation is especially in the elderly patients important considering potential impact of device-related adverse events on the quality of life.[27] In the present study, we observed only a significant difference in the proportion of pocket hematomas after device-related interventions between the two groups which probably could be explained by the higher percentage of anticoagulant therapy among elderly patients. However, the Frailty Model analysis showed for total number of all device-related long-term adverse events that the safety of CRT in the elderly is similar to the non-elderly.

Long-term prognosis after CRT

Subgroup analyses of the COMPANION, MIRACLE and MIRACLE ICD trials reported no significant difference in survival between elderly and non-elderly patients.[25,28] The results were probably limited by the relative short-term follow-up (up to 12 months). Remarkably, the MADIT-CRT trial, evaluating CRT efficacy versus ICD in mild or non-symptomatic heart failure patients, reported significant reduction in heart failure hospitalization or mortality rates only among patients older than 60 years.[13] In the present study, which reflects a real-world evaluation of CRT patients, we demonstrated that the survival difference between elderly and non-elderly patients became significant after 4 years of follow-up. This difference was mainly due to an increase rate of non-cardiac death among elderly patients. An age-related increase in non-cardiac mortality was also reported in the InSync ICD Italian Registry.[12] Additionally, we evaluated two important endpoints for the elderly population. First, our study showed an equal proportional incidence of heart failure hospitalizations combined with all-cause mortality between the age groups suggesting a comparable impact of CRT on clinical symptoms and quality of life. Second, we observed a comparable incidence rate of ventricular arrhythmias requiring appropriate ICD therapy together with ventricular arrhythmic death. This suggests that elderly patients do benefit equally to non-elderly patients from CRT-D.

Limitations

Several limitations of the current study should be mentioned. First, the study design was retrospective and reported the experience of a single center. Therefore, these findings should be confirmed in larger prospective multicenter studies. Second, atrial fibrillation was more often present in elderly patients. Finally, the majority of the study population (95%) received a CRT-D system and a comparison with a CRT-P system could not be performed.

CONCLUSION

CRT efficacy and device-related adverse events in elderly patients were comparable to non-elderly patients. However, after 4 years of follow-up, elderly patients showed worse survival and the cause of death was mainly non-cardiac. Diabetes, impaired renal function and reduced 6-minute walk distance were independently associated with all-cause mortality of elderly patients.

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