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Intermediate-term mortality and incidence of ICD therapy in octogenarians after cardiac resynchronization therapy

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Abstract

Background Clinical outcomes of cardiac resynchronization therapy (CRT) in patients over the age of 80 have not been well described. **Methods** We retrospectively identified 96 consecutive patients ≥ 80 years old who underwent an initial implant or an upgrade to CRT, with or without defibrillator (CRT-D *vs*. CRT-P), at our institution between January 2003 and July 2008. The control cohort consisted of 177 randomly selected patients < 80 years old undergoing CRT implant during the same time period. The primary efficacy endpoint was all-cause mortality at 36 months, assessed by Kaplan-Meier time to first event curves. **Results** In the octogenarian cohort, mean age at CRT implant was 83.1 ± 2.9 years *vs*. 60.1 ± 8.8 years among controls ($P < 0.001$). Across both groups, 70% were male, mean left ventricular ejection fraction (LVEF) was 24.8% ± 14.1% and QRS duration was 154 ± 24.8 ms, without significant differences between groups. Octogenarians were more likely to have ischemic cardiomyopathy (74% *vs*. 37%, $P < 0.001$) and more likely to undergo upgrade to CRT instead of an initial implant (42% *vs*. 19%, $P < 0.001$). The rate of appropriate defibrillator shocks was lower among octogenarians (14% *vs*. 27%, $P = 0.02$) whereas the rate of inappropriate shocks was similar (3% *vs*. 6%, $P = 0.55$). At 36 months, there was no significant difference in the rate of all-cause mortality between octogenarians (11%) and controls (8%, $P = 0.381$). **Conclusion** Appropriately selected octogenarians who are candidates for CRT have similar intermediate-term mortality compared to younger patients receiving CRT.

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1 Introduction

Cardiac resynchronization therapy (CRT) improves symptoms, reduces heart failure (HF) hospitalization, and improves survival in patients with symptomatic HF, impaired left ventricular ejection fraction (LVEF) and prolonged QRS duration.[1–6] Although the prevalence of HF increases significantly with age from 2%–3% in the general population to 10%–20% among those aged greater than elderly patients have been underrepresented in the seminal trials assessing the safety and efficacy of CRT.[7] The median age of patients enrolled in the comparison of medical therapy, pacing and defibrillation in heart failure (COM-PANION),[3] cardiac resynchronization–heart failure (CARE-HF),[8] and cardiac resynchronization in chronic heart failure (MIRACLE)[1] trials was between 64 and 68 years old. Therefore, discordance exists between the burgeoning heart failure epidemic among elderly patients and the robustness of clinical evidence to support the use of CRT in this population. Although several studies have demonstrated comparable improvements in New York Heart Association (NYHA) class and parameters of left ventricular reverse remodeling, usually measured at 6–12 months post-implant, between elder and younger recipients of CRT,[9–13] data on longer-term clinical outcomes, including rates of all-cause mortality, are more discordant. Whereas some studies have suggested that survival in octogenarians after CRT is worse than that among younger recipients,[14] others have demonstrated comparable survival between age groups.[15]

Given the substantial costs associated with device implant and follow-up, defining evidence-based strategies for HF management among elderly patients is imperative. In order to better define outcomes of CRT in octogenarians, particularly with regard to all-cause mortality, we compared outcomes of consecutive octogenarians undergoing CRT at our institution to a control cohort of younger CRT recipients during the same time period.

2 Methods

2.1 Study population

Patients were retrospectively identified from a database of the Emory University Hospital (EUH) & Emory University Hospital Midtown (EUHM) cardiac electrophysiology labs from January 2003 to July 2008. The study cohort included all patients aged greater than or equal to 80 years old who underwent an initial implant or an upgrade to CRT, with or without an implantable cardioverter-defibrillator (ICD), (i.e., CRT-D or CRT-P). The control cohort consisted of 177 randomly selected patients < 80 years old undergoing CRT implantation during the same time period. The decision to refer for CRT and the decision to implant a concomitant ICD were made by the primary cardiologist in conjunction with the implanting electrophysiologist. Although criteria for CRT implantation evolved during the study period, decisions regarding CRT implantation were made primarily based on evidence of inter-ventricular conduction delay as evidenced by prolonged QRS duration, or high degree right ventricular pacing, in conjunction with impaired LVEF and symptoms of HF. In some instances, echocardiographic evidence of inter-ventricular dyssynchrony was also used for assessing CRT candidacy.

Demographic data, baseline covariates and clinical history were obtained from review of medical records. Baseline QRS duration was measured during sinus rhythm for patients with native conduction and during pacing for patients with high burden right ventricular pacing as the indication for CRT. Certain baseline data were available for all octogenarian patients and controls whereas more detailed baseline data were only available for a subset of patients in both groups (41 out 96 octogenarians and 118 out of 177 controls). Patients for whom more detailed baseline data were not available were generally those implanted during the earlier years of the study cohort, such that electronic medical records were not available for review. Data on post-implant survival were obtained from review of medical records, routine device clinic follow-up and remote device monitoring. For patients whose vital status was not known, follow-up was censored at the date of last clinical contact.

Technical aspects of the CRT implant procedure, including positioning of the left ventricular lead, were performed at the discretion of the implanting physician. All left ventricular leads were implanted with a trans-venous approach via the coronary sinus. Device programming, including CRT parameters and ventricular tachyarrhythmia detection and therapy, was performed at the discretion of the implanting physician. Device follow-up, including in-office assessments and remote device monitoring, was performed through the EUH/EUHM arrhythmia center as clinically indicated. For patients presenting with ICD shocks, intracardiac electrogram adjudication for discrimination of appropriate from inappropriate therapies was performed through the arrhythmia center in conjunction with the implanting electrophysiologist, according to routine clinical protocol.

The protocol for this study was reviewed and approved by the Emory University Institutional Review Board.

2.2 Statistical analysis

The primary endpoint was all-cause mortality at 36 months after CRT. The time course of the primary endpoint, stratified by age ≥ or < 80 years at CRT implant, was estimated by Kaplan-Meier time to first event curves and tested with the log-rank test. Secondary endpoints included the frequency of appropriate and inappropriate ICD shocks during follow-up.

Continuous variables are presented as mean ± SD and categorical data are summarized as frequencies and percentages. Comparisons across groups were performed using the Student's *t*-test, Chi-square test or Fisher's exact test, as appropriate. For all comparisons, $P < 0.05$ was considered to be statistically significant. Analysis was performed using STATISTICA software (Statsoft, Inc., Tulsa, OK, USA).

3 Results

A total of 96 octogenarians underwent CRT implantation during the study period and were included as the study cohort. The control cohort included 177 patients < 80 years old undergoing CRT implant at our institution during the same time frame. Baseline characteristics available for all patients in both cohorts are presented in the top portion of Table 1 and more detailed baseline characteristics available for a subset of patients (41 out 96 octogenarians and 118 out of 177 controls) are presented in the bottom portion of Table 1. The mean age at CRT implant among octogenarians was 83 ± 2.9 years, compared to 60.1 ± 8.8 years in the control group ($P < 0.001$). The percentage of male patients was

Table 1.   Baseline characteristics.

	Cases (*n* = 96)	Controls (*n* = 177)	*P*
Age	83.1 ± 2.9	60.1 ± 8.8	< 0.001
Male	70 (73)	122 (69)	0.579
LVEF	23.2% ± 10.5%	25.9% ± 15.9%	0.161
QRS, ms	154.2 ± 22.6	154.0 ± 25.6	0.976
CAD	71 (74)	65 (37)	< 0.001
HTN	73 (76)	83 (47)	< 0.001
Initial implant (*vs.* upgrade)	56 (58)	143 (81)	< 0.001
CRT-D (*vs.* CRT-P)	86 (90)	159 (90)	0.834
	*Cases (*n* = 41)	*Controls (*n* = 118)	
New York Heart Association Class			
I	0	3 (3)	0.212
II	7 (17)	25 (21)	
III	34 (83)	85 (72)	
History of atrial fibrillation	17 (41)	27 (23)	0.027
History of MI	21 (51)	41 (35)	0.067
History of PCI	13 (32)	30 (25)	0.541
History of CABG	6 (15)	19 (16)	1.000
End stage renal disease	2 (5)	7 (6)	1.000
ICD implantation for secondary prevention	5 (12)	10 (8)	0.537
Medical therapy at time of CRT implant			
ACE-I/ARB	34 (83)	98 (83)	1.000
Beta blockers	34 (83)	99 (84)	1.000
Diuretics	35 (85)	99 (84)	1.000
Digoxin	10 (24)	41 (35)	0.249
Statins	22 (54)	70 (59)	0.583
Amiodarone	4 (10)	19 (16)	0.442
Aspirin	29 (71)	77 (65)	0.569
Warfarin	13 (32)	43 (36)	0.705

*Data only available for 41 out of 96 cases and 118 out of 177 controls. Data are presented as mean ± SD or *n* (%). ACE-I/ARB: angiotensin converting enzyme-inhibitor/angiotensin receptor blocker; CABG: coronary artery bypass grafting; CAD: coronary artery disease; CRT-D: cardiac resynchronization therapy-defibrillator; CRT-P: cardiac resynchronization therapy-pacemaker; HTN: hypertension; ICD: implantable cardioverter defibrillator; LVEF: left ventricle ejection fraction; MI: myocardial infarction; PCI: percutaneous coronary intervention.

similar in both groups (73% *vs*. 69%, *P* = NS) whereas baseline comorbidities including the presence of coronary artery disease (CAD) (74% *vs*. 37%) and hypertension (76% *vs*. 47%) were significantly more common among octogenarians (*P* < 0.001 for both comparisons).

Baseline LVEF (23.2% ± 10.5% *vs*. 25.9% ± 15.9%) and QRS duration (154.2 ± 22.6 ms *vs*. 154.0 ± 25.6 ms) were similar between groups. Octogenarians were more likely to undergo upgrade to CRT from pre-existing devices (42% *vs*. 19%, *P* < 0.001) and 90% of patients in both groups were implanted with ICDs, without significant difference between octogenarians and controls.

Data on procedural and clinical outcomes are presented in Table 2. Acute procedural success was excellent in both groups with 99% of patients implanted successfully with LV leads without any major peri-procedural adverse events in either group. One patient in each group developed a significant pocket hematoma requiring intervention during the index hospitalization. During a mean follow-up of 4.27 ± 2.88 years, the frequency of patients receiving at least one ICD shock was lower among octogenarians (17%) than controls (33%, *P* = 0.011). Similarly, the frequency of patients receiving at least one appropriate ICD shock was also lower among octogenarians (14% *vs*. 27%, *P* = 0.024) whereas the frequency of inappropriate shocks was similar between groups (octogenarians 3% *vs*. controls 6%, *P* = N.S.).

The cumulative rate of all-cause mortality at 36 months estimated by Kaplan-Meier product limit estimates is presented in the Figure. There was no significant difference in the time-dependent cumulative rate of all-cause mortality between octogenarians (15%) and controls (10%) at three years (*P* = 0.232).

4   Discussion

Despite the growing HF epidemic among elderly patients, there is a relative paucity of data-driven strategies for HF management in this population. Our data from a large single-center retrospective study suggest that among appropriately selected patients, survival among octogenarians following CRT implant is comparable to that among younger patients.

Table 2.   Procedural outcomes.

	Cases (n = 96)	Controls (n = 177)	*P*
Acute LV lead implant success	95 (99)	175 (99)	0.542
Hematoma	1 (1)	1 (0.5)	1.000
Shocks			
All shocks	16 (17)	58 (33)	0.011
Appropriate	13 (14)	48 (27)	0.024
Inappropriate	3 (3)	11 (6)	0.550

Data are presented as mean ± SD or *n* (%). LV: left ventricle.
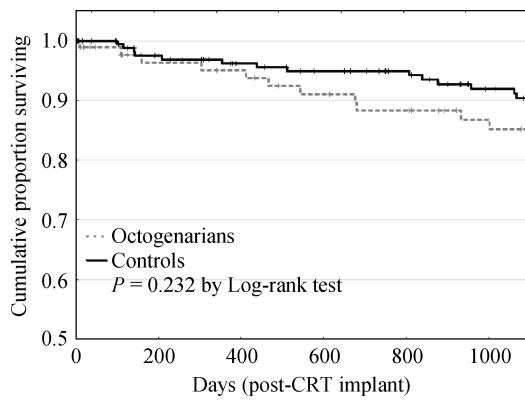
Octogenarians	96	67	55
Controls	177	139	115

Figure 1. **Kaplan-Meier event-free survival curves for all-cause mortality following CRT implantation.** There was no significant difference in survival at three years between octogenarians (85%) and younger controls (90%, *P* = 0.232). CRT: cardiac resynchronization therapy.

Furthermore, the prevalence of total and appropriate ICD shocks among octogenarians implanted with CRT-defibrillators was lower than that among younger counterparts with CRT-D devices, whereas the prevalence of inappropriate shocks was similar between groups.

Our data add to a limited body of literature reporting outcomes of CRT in elderly patients. In a retrospective, single-center series from the Mayo Clinic, survival over five years following CRT among 90 octogenarians was significantly worse than younger patients, although the difference in survival was no longer significant after adjusting for baseline covariates.[13] An important difference between our data and the series from the Mayo Clinic is that in our cohort, the frequency of concomitant defibrillator therapy was identical in octogenarians and younger controls (90% in both groups received CRT-D) whereas in the Mayo series, octogenarians were significantly less likely to receive CRT-D *vs*. CRT-P (78.9% CRT-D in octogenarians *vs*. 92% CRT-D in younger controls, *P* < 0.001). The difference in all-cause mortality between octogenarians and younger controls in our study and the series from Mayo Clinic may be explained by the difference in prevalence of concomitant ICD therapy noted in the Mayo series. The impact of ICDs on CRT outcome in different age subgroups was also highlighted in a subgroup analysis from the multicenter automatic defibrillator implantation trial with cardiac resynchronization therapy (MADIT-CRT) trial,[5] in which randomization to CRT with defibrillator was associated with a significant reduction in risk of HF or death (*vs*. defibrillator therapy alone) among patients ≥ 75 years old, whereas the benefit of CRT-D *vs*. ICD was attenuated in patients

younger than 60.[14] However, it is important to note that in the smaller subgroup of octogenarians from MADIT-CRT, randomization to CRT-D *vs*. ICD was not associated with a significantly improved outcome, further highlighting the disparity of data on outcomes specifically among patients over the age of 80. Lastly, in a recently published ICD registry from Israel, recipients of CRT-D aged > 75 years had similar rates of survival and appropriate ICD shocks compared to younger patients. Conversely, in ICD recipients without CRT, patients older than 75 years old had significantly worse survival.[15] These studies highlight the complex interactions noted between age and concomitant ICD therapy in assessing CRT outcomes among elderly patients.

The majority of CRT recipients in our study received concomitant ICD therapy and our results should be interpreted in this context. Relatively few octogenarians underwent CRT-P implantation precluding statistical analysis in this subgroup. However, previous studies have assessed outcomes among larger groups of octogenarians implanted with CRT-P devices. In two single center studies, crude mortality rates during a mean follow-up of 20 months[10] and 60 months[13] were significantly higher among octogenarians compared to younger counterparts. In both of these studies, octogenarians were significantly less likely to be implanted with defibrillators than the younger control cohorts. Although prior studies of ICD therapy have suggested that elderly patients likely benefit from primary prevention ICD therapy,[16,17] in our study octogenarians were less likely to receive appropriate ICD therapy than younger patients. Also, in prior studies, no significant difference has been noted in incidence of appropriate device therapies between older and younger CRT-D recipients.[13,15] Therefore, the observation in retrospective studies that elderly CRT-D recipients seem to fair better compared to younger controls than elderly CRT-P recipients is probably not related to the protective effects of ICD therapy *per se*. Rather, this observation is likely a reflection of the fact that elderly patients who are felt to have sufficiently good life expectancy to merit ICD implantation likely have better overall survival than elderly patients with symptomatic HF who may be felt to benefit from CRT but may not necessarily be felt to have sufficiently good life expectancy to merit concomitant ICD therapy. In this regard, our data reflect the immense importance of patient selection in determining which elderly patients are most likely to benefit from cardiac resynchronization, and CRT-D in particular.

4.1 Limitations

Several important limitations of our study should be noted. Most importantly, our data is retrospective and the

decision to refer for CRT was not randomized but rather made at the discretion of the treating physicians. This clearly introduces a selection bias and limits the ability to extrapolate these findings to the general population of elderly patients with HF who might be CRT candidates. Furthermore, although prior studies have demonstrated comparable improvements in HF symptoms and quality of life among elderly patients undergoing CRT compared to younger counterparts, we do not have data on quality of life metrics which would also be particularly important considerations in making the decision to refer elderly patients for device implant.

4.2 Conclusion

In a single-center retrospective cohort, appropriately selected octogenarians undergoing CRT implantation, predominantly with concomitant ICD therapy, experienced similar rates of all-cause mortality during intermediate term follow-up (3 years) compared to younger CRT recipients. Although we are unable to comment on functional capacity and LVEF trends after CRT, our findings support the idea that with regard to overall survival, appropriate candidates for CRT should be offered this therapy even if they are of advanced age.

Acknowledgements

References

1   Abraham WT, Fisher WG, Smith AL, *et al*. Cardiac resynchronization in chronic heart failure. *N Engl J Med* 2002; 346: 1845–1853.

2   Young JB, Abraham WT, Smith AL, *et al*. Combined cardiac resynchronization and implantable cardioversion defibrillation in advanced chronic heart failure: the MIRACLE ICD Trial. *JAMA* 2003; 289: 2685–2694.

3   Bristow MR, Saxon LA, Boehmer J, *et al*. Cardiac-resynchronization therapy with or without an implantable defibrillator in advanced chronic heart failure. *N Engl J Med* 2004; 350: 2140–2150.

4   Linde C1, Abraham WT, Gold MR, *et al*. Randomized trial of cardiac resynchronization in mildly symptomatic heart failure patients and in asymptomatic patients with left ventricular dysfunction and previous heart failure symptoms. *J Am Coll Cardiol* 2008; 52: 1834–1843.

5   Moss AJ1, Hall WJ, Cannom DS, *et al*. Cardiac-resynchronization therapy for the prevention of heart-failure events. *N Engl J Med* 2009; 361: 1329–1338.

6   Tang AS1, Wells GA, Talajic M, *et al*. Cardiac-resynchronization therapy for mild-to-moderate heart failure. *N Engl J Med* 2010; 363: 2385–2395.

7   Lloyd-Jones DM, Wang TJ, Leip EP, *et al*. Lifetime risk for development of atrial fibrillation: the Framingham Heart Study. *Circulation* 2004; 110: 1042–1046.

8   Cleland JG, Daubert JC, Erdmann E, *et al*. The effect of cardiac resynchronization on morbidity and mortality in heart failure. *N Engl J Med* 2005; 352: 1539–1549.

9   Kron J, Aranda JM Jr, Miles WM, *et al*. Benefit of cardiac resynchronization in elderly patients: results from the Multicenter InSync Randomized Clinical Evaluation (MIRACLE) and Multicenter InSync ICD Randomized Clinical Evaluation (MIRACLE-ICD) trials. *J Interv Card Electrophysiol* 2009; 25: 91–96.

10   Verbrugge FH, Dupont M, De Vusser P, *et al*., Response to cardiac resynchronization therapy in elderly patients (>/=70 years) and octogenarians. *Eur J Heart Fail* 2013; 15: 203–210.

11   Delnoy PP1, Ottervanger JP, Luttikhuis HO, *et al*. Clinical response of cardiac resynchronization therapy in the elderly. *Am Heart J* 2008; 155: 746–751.

12   Brambatti M, Guerra F, Matassini MV, *et al*. Cardiac resynchronization therapy improves ejection fraction and cardiac remodelling regardless of patients' age. *Europace* 2013; 15: 704–710.

13   Killu AM1, Wu JH, Friedman PA, *et al*. Outcomes of cardiac resynchronization therapy in the elderly. *Pacing Clin Electrophysiol* 2013; 36: 664–672.

14   Penn J1, Goldenberg I, Moss AJ, *et al*. Improved outcome with preventive cardiac resynchronization therapy in the elderly: a MADIT-CRT substudy. *J Cardiovasc Electrophysiol* 2011; 22: 892–897.

15   Suleiman M, Goldenberg I, Haim M, *et al*. Clinical characteristics and outcomes of elderly patients treated with an implantable cardioverter-defibrillator or cardiac resynchronization therapy in a real-world setting: data from the Israeli ICD Registry. *Heart Rhythm* 2014; 11: 435–441.

16   Chan PS, Nallamothu BK, Spertus JA, *et al*. Impact of age and medical comorbidity on the effectiveness of implantable cardioverter-defibrillators for primary prevention. *Circ Cardiovasc Qual Outcomes* 2009; 2: 16–24.

17   Yung D, Birnie D, Dorian P, *et al*., Survival after implantable cardioverter-defibrillator implantation in the elderly. *Circulation* 2013; 127: 2383–2392.