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Review

Outcomes of elderly heart failure recipients of ICD and CRT

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Abstract

Implantable cardioverter defibrillator (ICD) therapy has been established as a highly effective method for primary and secondary prevention of sudden cardiac death in heart failure patients. In addition, cardiac resynchronization therapy (CRT) with and without defibrillator back-up improves symptoms, exercise capacity and prognosis in selected patients with advanced heart failure and intraventricular conduction delay. Unfortunately, mean patient age in ICD- and CRT-intervention trials was only 60 to 65 years with few patients being older than 75 years. None of these trials separately studied an elderly heart failure population. This review summarizes the available scientific evidence for the use of ICDs and CRT devices in elderly heart failure patients based on subgroup analyses of prospective randomized ICD- and CRT-intervention trials, and based on published cohort studies.

Keywords: Implantable defibrillator; Cardiac resynchronization; Elderly patients; Complications

Implantable cardioverter defibrillators (ICD) have become therapy of first choice in patients with structural heart disease and symptomatic ventricular tachycardia or ventricular fibrillation [1–3]. In addition, prophylactic ICD therapy has been shown to prolong survival in selected patients with ischemic or nonischemic cardiomyopathy and markedly reduced LV ejection fraction despite optimized medical heart failure therapy [4–10]. Finally, randomized controlled trials have demonstrated that cardiac resynchronization therapy (CRT) improves symptoms, exercise capacity and survival in selected patients with advanced heart failure and cardiac dysynchrony due to pronounced intraventricular conduction delay [11–14]. To date, however, it remains unclear, whether the favorable results of ICD and CRT therapy in these landmark studies are generalizable to elderly patients, because mean patient age in these trials was only about 60 to 65 years with only few patients being older than 75 years as summarized in Table 1.

1. ICDs for secondary prevention of sudden cardiac death

Three randomized controlled trials demonstrated a nearly 30% relative risk reduction in all-cause mortality for ICD therapy in patients who survived an episode of sustained ventricular tachycardia or ventricular fibrillation (Table 1): Antiarrhythmics Versus Implantable Defibrillators (AVID) [1], Canadian Implantable Defibrillator study (CIDS) [2], and Cardiac Arrest Study Hamburg (CASH) [3]. The AVID trial [1] was the largest ICD trial for secondary prevention of sudden death enrolling 1016 patients with a mean age of 65 years. AVID found a similar prognostic benefit in the ICD group in a prespecified subgroup analysis of patients aged <60 years versus patients aged 60 to 69 years versus patients aged ≥ 70 years (Fig. 1). The CIDS investigators [15] identified a subgroup of patients who were most likely to benefit from ICD therapy by using a simple risk score with at least 2 of the following 3 parameters: age ≥ 70 years, LV ejection fraction $\leq 35\%$, and NYHA class III or IV. Younger patients <70 years with better ejection fractions and lower NYHA classes were less likely to benefit from ICD therapy in CIDS [15]. In CASH [3], only 3% of 288 enrolled patients

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Table 1
Important prospective randomized ICD- and CRT-intervention trials

Study	Year	Mean age ± SD	Patients	LVEF, %	FU, months	Relative risk (95% CI)	NNT
ICDs for secondary prevention of sudden cardiac death							
AVID [1]	1997	65 ± 10	1016	35	18	0.66 (0.51–0.85)	9 for 3 years
CIDS [2]	2000	63 ± 10	659	34	35	0.85 (0.67–1.10)	
CASH [3]	2000	58 ± 11	288	45	57	0.82 (0.60–1.11)	
ICDs for primary prevention of sudden cardiac death							
MADIT [4]	1996	63 ± 9	196	26	27	0.46 (0.26–0.82)	4 for 5 years
CABG-patch (5)	1997	64 ± 9	900	27	32	1.07 (0.81–1.42)	
MUSTT [6]	1999	66.5 (meadian)	704	30	39	0.45 (0.32–0.63)	3 for 5 years
MADIT-II [7]	2002	64 ± 10	1232	23	20	0.69 (0.51–0.93)	11 for 3 years
DINAMIT [8]	2004	62 ± 11	674	28	30	1.08 (0.76–1.55)	
DEFINITE [9]	2004	58	458	21	29	0.65 (0.40–1.06)	
SCD-HeFT [10]	2005	60 (median)	2521	25	45	0.77 (0.62–0.96)	14 for 5 years
Cardiac resynchronization therapy							
COMPANION [11]	2004	65 ± 11	1520	22	17	0.64 (0.48–0.86)	14 for 1 year
CARE-HF [12]	2005	66	813	25	29	0.64 (0.48–0.85)	12 for 2 years

The number needed-to-treat is shown only for trials with a significant reduction of all-cause mortality in the ICD group.
AVID = Antiarrhythmics Versus Implantable defibrillators.
CIDS = Canadian Implantable Defibrillator Study.
CASH = Cardiac Arrest Study Hamburg.
MADIT = Multicenter Automatic Defibrillator Implantation Trial.
CABG-Patch = Coronary Artery Bypass Graft Patch Trial.
MUSTT = Multicenter Unsustained Tachycardia Trial.
DINAMIT = Defibrillator In Acute Myocardial Infarction Trial.
DEFINITE = Defibrillators In Non-Ischemic Cardiomyopathy Treatment Evaluation.
SCD-HeFT = Sudden Cardiac Death in Heart Failure Trial.
COMPANION = Comparison of Medical Therapy, Pacing, and Defibrillation in Heart Failure.
CARE-HF = Cardiac Resynchronization in Heart Failure.

were ≥75 years old and no subgroup analysis was performed to evaluate a potential age-dependent benefit of ICD therapy [3].

Seven years after publication of AVID, CIDS and CASH, an age-specific metaanalysis of AVID, CIDS and CASH [16] was performed comparing the outcome of 1614 patients <75 years to 252 patients ≥75 years during 2.3 years mean follow-up. As a result, ICD therapy was found to significantly reduce all-cause mortality in patients <75 years (HR = 0.69, 95% CI: 0.56–0.85, $p < 0.0001$), but not in patients ≥75 years (HR 1.06, 95% CI: 0.69–1.64, $p = 0.79$) (Table 2). Elderly patients ≥75 years in AVID, CIDS and CASH suffered an excess of nonarrhythmic deaths and, therefore, did not derive the same prognostic benefit from ICD therapy that is seen in patients <75 years. It has to be kept in mind, however, that the data of this metaanalysis have limited statistical power with all inherent limitations of metaanalyses. In addition, the results of this AVID/CIDS/CASH-metaanalysis [16] are not consistent with the results of the prespecified subgroup analysis of AVID [1] (Fig. 1) and CIDS [15] as described above in detail. This discrepancy may, in part, be explained by different age cut-offs used in the metaanalysis [16] compared to subgroup analyses in AVID [1] and CIDS [15]. Therefore, ICD therapy for secondary prevention of sudden cardiac death should not be withheld in elderly patients based on age alone.

2. ICDs for primary prevention of sudden cardiac death

Similar to the secondary prevention trials described above, mean patient age in these prophylactic ICD trials was only about 60 to 65 years (Table 1). The two largest and most important primary prevention trials are the second Multicenter Automatic Defibrillator Implantation Trial (MADIT-II) [7] and the Sudden Cardiac Death in Heart Failure Trial (SCD-HeFT) [10].

MADIT-II [7] enrolled 1232 patients with a history of remote myocardial infarction and an ejection fraction ≤30% despite optimized medical heart failure therapy including β-blockers and ACE-Inhibitors. The main result of MADIT-II was a 31% relative risk reduction in all-cause mortality in the ICD group compared to conventional treatment after 20 months mean follow-up [7]. A retrospective subgroup analysis of the MADIT-II trial found that prophylactic ICD therapy was associated with a greater relative risk reduction for total mortality of 46% in 204 patients, who were ≥75 years old compared to 1028 patients <75 years at study enrollment ($p < 0.04$) [17]. These findings suggest that carefully selected elderly patients who have a reasonable life expectancy without additional severe comorbidities may be more likely to benefit from ICD therapy for primary prevention than elderly survivors of sustained ventricular tachyarrhythmias with more severe comorbidities [16] as described above in detail.

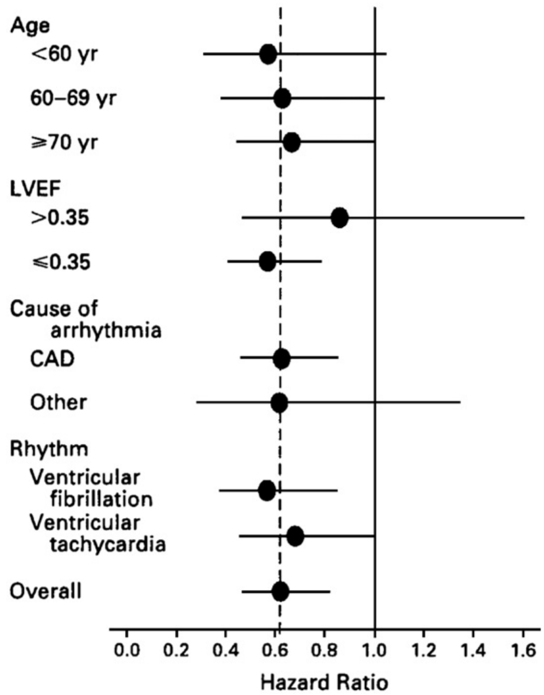

Fig. 1. Hazard ratios and 95% confidence intervals for all-cause mortality in prespecified subgroups in the AVID trial [1]. The hazard ration were not significantly different for any of these subgroups. Patients with a LVEF ≤35% tended to benefit more from ICD therapy compared to patients with a LVEF>35%. Elderly patients ≥70 years had a similar prognostic benefit in the ICD group compared to patients <60 years and compared to patients aged 60 to 69 years.

SCD-HeFT [10] was the largest and longest ICD intervention trial enrolling 2521 heart failure patients with median age of 60 years and a left ventricular ejection fraction ≤35% despite optimized medical therapy. Patients were randomized to receive amiodarone, placebo or an implantable defibrillator. In contrast to MADIT-II [7], which enrolled exclusively patients with ischemic cardiomyopathy, SCD-HeFT included 1211 patients (48%) with nonischemic cardiomyopathy. The main result of SCD-HeFT [10] was a significant absolute decrease in all-cause mortality of 7.2% after 5 years in the ICD group compared to the amidarone and placebo group, while amiodarone was associated with a similar risk of death compared to placebo. A prespecified subgroup analysis in SCD-HeFT [10] found a slightly higher survival benefit of ICD therapy versus placebo in 1098 patients <65 years (RR: 0.68; 95% CI: 0.50–0.93) compared to 578 patients ≥65 years (RR: 0.86; 95% CI: 0.62–1.18) (Table 2). To date, however, the clinical characteristics of these subgroups have not been published and no multivariate analysis adjusting for potential comorbidities in the elderly has been performed. Therefore, it is currently impossible to discern the true effect of age in SCD-HeFT. Importantly, prophylactic amiodarone therapy did not improve prognosis in SCD-HeFT patients ≥65 years (RR: 1.13; 95% CI: 0.83–1.52).

3. Cohort studies of elderly ICD recipients

Although more than 200,000 ICDs have already been implanted worldwide, only few cohort studies investigated the outcome of elderly ICD recipients. In 500 consecutive patients enrolled in our Marburg Defibrillator database [18], 40 patients (8%) were ≥75 years and 460 patients (92%) were <75 years at ICD implant. The 5-year sudden death rate was comparably low in patients <75 years compared to patients ≥75 years (Fig. 2A). In addition, the rate of appropriate ICD interventions for VT or VF was also comparable for elderly patients compared to younger patients, while total mortality was significantly higher in elderly patients (Fig. 2B and C). This increased mortality of elderly patients in our study was due to an increased rate of heart failure death. Importantly, elderly ICD recipients in our study [18] had a similar low complication rate as younger ICD recipients including all procedure-related, lead-related, and generator-related complications.

In contrast to our study, Duray et al. [19] found comparable overall survival rates in 375 recipients using an age cut-off of 70 years. Duray et al. [19] hypothesized that the low mortality rate in their elderly cohort might be due to a preselection of more healthy elderly patients with low comorbidities.

Panotopoulos et al. [20] used the same age cut-off as in our study for comparing the outcome of 74 patients ≥75 years to 695 patients <75 years at ICD implant. Similar to our cohort study, Panotopoulos et al. [20] found a significantly higher total mortality in elderly patients while the 4-year actuarial sudden death rate remained 0% in these

Table 2
Subgroup analyses for all-cause mortality stratified by age group in ICD- and CRT-intervention trials

Study	Age group, years	Patients	HR or RR (95% CI)
ICDs for secondary prevention			
AVID/CIDS/CASH-Metanalysis [16]	<75	1614	0.69 (0.56–0.85)
	≥75	252	1.06 (0.69–1.64)
ICDs for primary prevention			
MUSTT [6]	<70	461	0.52 (0.33–0.77)
	≥70	243	0.43 (0.27–0.80)
MADIT-II [7]	<60	370	0.46 (0.23–0.93)
	60–69	426	0.77 (0.47–1.25)
	≥70	436	0.65 (0.42–0.98)
DEFINITE [9]	<65	301	0.70 (0.35–1.40)
	≥65	157	0.63 (0.32–1,23)
SCD-HeFT [10]	<65	1098	0.68 (0.50–0.93)
	≥65	578	0.86 (0.62–1.18)
Cardiac resynchronization therapy			
COMPANION [11]	≤65	272	0.58 (0.36–0.94)
	>65	323	0.69 (0.48–1.00)
CARE-HF [12]	<66,4	406	0.55 (0.40–0.75)
	≥66,4	407	0.68 (0.52–0.89)

HR = hazard ratio; RR = relative risk; CI = confidence interval.

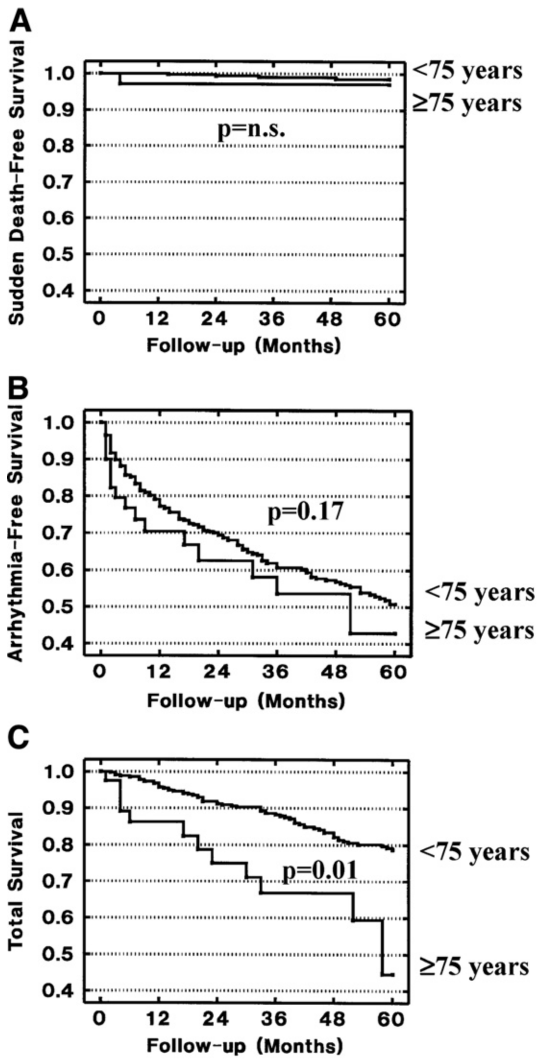

Fig. 2. Kaplan-Meier estimates for sudden cardiac death (A), arrhythmic events defined as appropriate ICD interventions for VT or VF (B), and all-cause mortality (C) in 500 ICD recipients stratified for patients aged 75 years or older versus patients aged <75 years at ICD implantation [18].

patients. In addition, perioperative mortality within 30 days of ICD implant was low in patients ≥75 years (1.4%) as well as in patients <75 years (0.7%) [20].

More recently, Noseworthy and colleagues [21] examined ICD related complications and survival in 29 octogenarians compared to 183 patients aged 70 to 79 years at the time of ICD implant. Noseworthy et al. [21] found no significant differences in the complication rate between both age groups with a perioperative mortality of 0% in both age groups.

Ermiz and colleagues [22] reported a cohort study including 202 ICD recipients using an age cut-off of 75 years. Similar to the results our study [18] and to the results of Panotopulos et al. [20], elderly ICD>75 years recipients were found to have a similar low sudden death rate and a similar incidence of appropriate ICD shocks, but a higher total mortality during follow-up compared to younger ICD recipients. This was due to a higher nonarrhythmic mortality in the elderly subgroup.

4. Cardiac resynchronization therapy in elderly patients

Approximately one quarter of heart failure patients exhibit more or less pronounced cardiac dysynchrony, which can be easily visualized by echocardiography. Cardiac dysynchrony is most often the consequence of an increased QRS width due to left bundle branch block, which can be reversed using biventricular or left ventricular stimulation. To date, multiple clinical trials demonstrated significant improvements in clinical heart failure symptoms and quality of life, as well as measures of left ventricular function and exercise capacity in appropriately selected heart failure patients with cardiac dysynchrony due to intraventricular conduction delay [11–14]. This symptomatic benefit of CRT appears to be independent of patients' age [23]. In addition, two well-designed, randomized studies showed a mortality benefit for CRT recipients with advanced heart failure.

The COMPANION trial [13] used CRT with and without prophylactic ICD back-up in 1520 patients with advanced heart failure and bundle branch block in addition to optimized medical therapy (Table 1). As a result, CRT significantly decreased the combined risk of death from any cause or hospitalization due to worsened heart failure compared to patients who received optimal medical therapy without CRT. In addition, COMPANION [13] found a significant reduction in total mortality in heart failure recipients of CRT-ICDs (Fig. 3). A subgroup analysis in COMPANION demonstrated a similar benefit of CRT for patients below and above the age of 65 years (Table 2).

The Cardiac Resynchronization-Heart Failure (CARE-HF) [14] study randomized 813 patients with NYHA class 3 or 4 heart failure and cardiac dysynchrony to optimized medical therapy with and without additional CRT. In contrast to COMPANION, exclusively CRT pacemakers without ICD back-up were used in CARE-HF. As a result, CRT improved symptoms and quality of life and reduced total mortality (Table 1). A subgroup analysis in CARE-HF

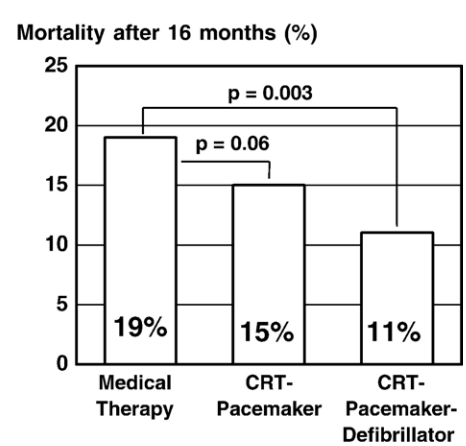

Fig. 3. All-cause mortality as secondary endpoint in COMPANION [13].

demonstrated a similar benefit for patients below and above the age of 66.4 years (Table 2). Unfortunately, subgroup analyses for more advanced age groups have not been published for both, COMPANION [13] and CARE-HF [14]. Therefore, it remains to be determined, whether the favorable prognostic results of CRT are applicable to patients aged >75 years or to octogenarians. Based on the results of many clinical studies and on the experience of all physicians, who take care of CRT recipients, there is no doubt, that CRT does improve quality of life and exercise capacity dramatically in the majority of elderly patients including octogenarians with advanced heart failure and cardiac desynchronization due to left bundle branch block [23]. Several open questions concerning CRT, however, need to be clarified by future studies: Do patients with atrial fibrillation, which is common in elderly patients, benefit from CRT? What is the role of CRT in less advanced heart failure NYHA class 2? Is CRT helpful in patients with cardiac desynchronization and predominantly diastolic dysfunction? What is the long-term complication rate of CRT and what can be done to minimize this complication rate? Finally, comorbidities present in elderly patients as well as the individual patient's preference should influence the device choice of a CRT pacemaker primarily to improve quality versus a CRT defibrillator to improve quality of life and to prolong life.

5. Complications of ICD- and CRT-therapy

In 500 consecutive patients enrolled in the Marburg Defibrillator database [18], the long-term overall complication rate associated with ICDs was similar in patients ≥75 years compared to younger patients (25% versus 23%, p=n.s.). All patients received pectoral nonthoracotomy ICD lead systems with the exception of one patient who had an artificial tricuspid valve. During 4-year mean follow-up, 118 of 500 patients (24%) experienced at least one complication including implant procedure-related complications in 49 patients (10%), ICD generator-related complications in 32 patients (6%), and lead-related complications in 65 patients (13%). The most frequent complication during follow-up were inappropriate shocks for atrial fibrillation with rapid ventricular response, atrial tachycardia, nonsustained ventricular tachycardia or artefact oversensing in 62 patients (12%). Serious complications included one perioperative death due to heart failure in 1 patient (0.2%), two ICD system infections necessitating device removal (0.5%) and two perioperative cerebrovascular strokes (0.5%). This complication rate, which is not at all negligible, as well as the considerable costs of ICD therapy is reminders for careful patient selection, particularly in an elderly heart failure patient cohort with a limited life expectancy due to an increased rate of nonarrhythmic death during short-term follow-up.

Implantation-related complications in CRT recipients are similar to the above described complications for ICD recipients with the exception of an additional risk of dissection or perforation of the coronary sinus with subsequent cardiac tamponade during placement of the left ventricular pacing lead. Life-threatening cardiac tamponade during CS lead placement was observed in 0.5% of CRT pacemaker patients and in 0.3% of CRT defibrillator patients in COMPANION [13]. Furthermore, intravenous contrast agents to visualize coronary sinus anatomy during CRT pacemaker implantation may cause acute renal failure in elderly patients.

6. Quality of life and ethical end of life issues

Most studies examining quality of life before and after ICD implantation have shown unchanged or improved quality of life scores after implant [23–28]. Factors associated with poor quality of life in ICD recipients include adverse events and/or multiple painful ICD shocks, preexisting anxiety disorders, and a severely diminished health status with significant comorbidities prior to ICD implant. Although only few prospective studies examined quality of life in ICD and CRT recipients, advanced age by itself has not been found to be an independent predictor of poor quality of life after implant [24,25]. Elderly patients with multiple comorbidities, however, have clearly been underrepresented in prospective ICD and CRT trials as summarized in Tables 1 and 2. Therefore, the relative benefits and risks of ICD and/or CRT therapy must be weighed and discussed with each individual elderly patient.

During the process of dying in a patient with end-stage heart failure or any other untreatable end-stage disease deactivation of an ICD should be performed in order to avoid multiple painful ICD shocks caused by a terminal arrhythmia storm [27]. ICD deactivation has been performed in 12 out of 742 heart failure patients (1.6%) during 20 months mean follow-up in the MADIT II trial [7]. In the absence of clinical trials, however, there is frequently no discussion of end of life issues between clinicians and ICD recipients or their family members. Goldstein et al. [28] performed interviews with family members of deceased ICD recipients and found, that clinicians failed to discuss the possibility of deactivating ICDs during the process of dying in 73% of cases!

7. Cost effectiveness

Sanders et al. [29] analyzed 6 randomized primary prevention ICD trials and found that cost-effectiveness of the ICD compared to control therapy ranged from $34,000 to $70,200 per quality-adjusted life-year. Similar cost-ranges per quality-adjusted life-year have been published for secondary prevention with ICD and for CRT trials [30,31] dependent upon the modeling framework to calculate the cost-benefit ratio. Similar to the quality of life issues discussed above, cost-effectiveness of ICD therapy has not been evaluated in large cohorts of elderly heart failure recipients of ICD and/or CRT. Whether the cost-benefit ratio of patient populations with a mean age of 60 to 65 years as summarized in Table 1 can be extrapolated to elderly patient cohorts with more comorbidities remains to be determined in the future.

8. Conclusions

ICDs have clearly been demonstrated to improve survival in heart failure patients at high risk for sudden death in well-designed prospective randomized trials and the ICD has emerged as therapy of first choice for both primary and secondary prevention of sudden cardiac death. In addition, CRT devices with and without defibrillator back-up have been shown to improve symptoms, exercise capacity and prognosis in heart failure patients with pronounced intraventricular conduction delay. Subgroup analyses of these trials have demonstrated a similar benefit of for elderly and younger patients using age cut-offs of 60, 65, or 70 years. Unfortunately, elderly heart failure patients >75 years, octogenarians or patients with more severe comorbidities have been largely underrepresented or excluded in ICD- and CRT-intervention trials. Therefore, it is currently not possible to draw any firm conclusions with regard to the risk benefit ratio in this elderly population. Available data from many randomized trials as well as from cohort studies support the conclusion that ICD or CRT therapy should not be withheld by age alone. In addition, cohort studies demonstrated a low perioperative mortality <1% using modern ICDs with nonthoracotomy lead systems in selected elderly heart failure patients above the age of 75 years. Thus, in elderly patients without major comorbidities, the data support the use of ICDs and CRT devices for standard indication according to published guidelines. In elderly patients with more severe comorbidities, the relative risks and benefits of ICD or CRT devices must be weighed and discussed with each individual patient in order to reach a collaborative decision between patient and physician. This discussion should include ethical end-of-life issues like the possibility of ICD inactivation during the process of dying once end-stage heart failure has occurred. For individual elderly heart failure patients with cardiac desynchronization due to left bundle branch block and severe comorbidities, implantation of a CRT device without ICD back-up might be a good choice to improve quality of life.

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