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Comparison of the Usefulness of Cardiac Resynchronization Therapy in Three Age-Groups (<65, 65-74 and ≥75 Years) (from the InSync/InSync ICD Italian Registry)

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Chronic heart failure is one of the most important geriatric syndromes, associated with disability, increased hospital admissions, and high mortality. The aim of this study was to evaluate the existence of age-related differences in clinical effectiveness and outcomes of cardiac resynchronization therapy (CRT), alone or in combination with an implantable cardioverter-defibrillator (CRT-D), in a large, real-world registry. A total of 1,787 patients admitted for CRT or CRT-D to the 117 centers participating in the InSync/InSync ICD Italian Registry from 1999 to 2005 were evaluated. Patients were divided into 3 age groups: <65 years (n = 571), 65 to 74 years (n = 740), and ≥75 years (n = 476). The left ventricular ejection fraction did not differ in the 3 groups (26 ± 8% vs 26 ± 7% vs 27 ± 8%, p = 0.123). Atrial fibrillation prevalence demonstrated an age-related increase. The use of recommended medical therapy for chronic heart failure decreased with age, as well as CRT-D implantation (p <0.001). The percentage of echocardiographic responders to CRT was similar in the 3 groups, and New York Heart Association class significantly improved independent of age. During the follow-up period (19 ± 13 months), all-cause mortality was higher in patients aged ≥75 years than in those aged <65 years (p = 0.005). In the whole population, mortality was associated with the nonresponder condition, the presence of atrial fibrillation and the lack of prescription of recommended medical therapy. In conclusion, CRT improved left ventricular performance and functional capacity independent of age. The proportion of the responder condition to CRT was the same in all groups. Pharmacologic undertreatment is an important issue in a "real-world" geriatric population. **(Am J Cardiol 2011;107:1510–1516)**

Despite the relevant increase in the prevalence and in the incidence of chronic heart failure (CHF) in older individuals, the mean age of patients enrolled in clinical trials of cardiac resynchronization therapy (CRT) is <70 years.[1–4] Thus, at present, there is no trial-derived specific information on the impact of CRT in subjects of advanced age. Observational data, obtained from clinical registries, may provide a useful insight into "real-world" CRT. Consequently, through analysis of the InSync/InSync ICD Italian Registry, a large database involving 117 Italian centers, we aimed to evaluate the existence of age-related differences in clinical and instrumental effectiveness (the primary end point) and long-term mortality (the secondary end point) during CRT, alone or in combination with an implantable cardioverter-defibrillator (CRT-D).

Methods

From 1999 to 2005, all 1,787 patients successfully implanted with biventricular pacing devices for CRT or CRT-D (Medtronic Inc., Minneapolis, Minnesota) were prospectively included in the InSync/InSync ICD Italian Registry. The registry enrolled patients with advanced symptomatic CHF, left ventricular ejection fraction (LVEF) ≤35%, and wide QRS complexe (≥130 ms).[5] According to protocol, CRT or CRT-D should have been added to optimal medical therapy as recommended by the current guidelines for the diagnosis and treatment of CHF.[6] The protocol of the InSync/InSync ICD Italian Registry, which complies with the Declaration of Helsinki, had been previously approved by the ethics committees of each participating center. At the time of enrollment, all patients gave their written informed consent to participate to the study. For each patient, demographic, history, and clinical variables were collected at baseline, before device implantation. The

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Table 1
Clinical and instrumental characteristics of the InSync/InSync ICD Italian Registry population

Variable	Age Group (years)			p Value
	<65 (n = 571)	65–74 (n = 740)	≥75 (n = 476)	
Age (years)	57 ± 7	70 ± 3	78 ± 3	—
Men	481 (84%)	603 (81%)	362 (76%)*†	0.003
Chronic obstructive pulmonary disease	26 (5%)	55 (7%)*	27 (6%)	0.088
Diabetes mellitus	47 (8%)	64 (9%)	30 (6%)	0.312
Hypertension	73 (13%)	133 (18%)*	97 (20%)*	0.003
Renal failure	18 (3%)	58 (8%)*	21 (4%)†	0.001
≥3 co-morbidities	24 (4%)	68 (9%)*	34 (7%)*	0.002
Coronary artery disease	223 (39%)	367 (50%)*	240 (50%)*	<0.001
LV end-diastolic diameter (mm)	70 ± 10	69 ± 9	68 ± 9*	0.015
LV end-systolic diameter (mm)	60 ± 12	58 ± 10	57 ± 11*	0.016
LV end-diastolic volume (ml)	242 ± 94	221 ± 91	209 ± 104*	0.050
LV end-systolic volume (ml)	168 ± 81	154 ± 85	133 ± 63*	0.025
LVEF (%)	26 ± 8	26 ± 7	27 ± 8	0.123
QRS length (ms)	167 ± 33	165 ± 31	162 ± 32	0.136
New York Heart Association class	2.9 ± 0.6	3.0 ± 0.6	3.0 ± 0.6*	0.063
Hospitalizations (n)	1.6 ± 1.4	1.6 ± 1.5	1.7 ± 1.4	0.256
Permanent AF	61 (11%)	131 (18%)*	101 (21%)*	<0.001
Atrioventricular node ablation	28 (5%)	67 (9%)*	32 (7%)	0.014
Angiotensin-converting enzyme inhibitors/angiotensin receptor blockers	450 (79%)	525 (71%)*	335 (70%)*	0.001
β blockers	341 (60%)	331 (45%)*	176 (37%)*†	<0.001
Digoxin	244 (43%)	316 (43%)	216 (45%)	0.604
Diuretics	494 (87%)	658 (89%)	419 (88%)	0.415
Nitrates	96 (17%)	169 (23%)*	126 (26%)*	0.001
Class III antiarrhythmic drugs	193 (34%)	278 (38%)	164 (34%)	0.312

Data are expressed as mean ± SD or as number (percentage).
LV = left ventricular.
* p <0.05 vs <65 years.
† p <0.05 vs 65 to 74 years.

presence of chronic obstructive pulmonary disease, diabetes, hypertension, and renal failure was ascertained according to current guidelines.[7–10] The stage of CHF was assessed according to New York Heart Association functional classification.[11] Moreover, the number of hospitalizations due to CHF in the preceding 12 months was reported in the database. According to the design of the present study, we introduced only 2 variables to the original data set, the first associated with the presence of >2 co-morbid conditions in the same subject and the second for the age stratification of the population, which was consequently divided into 3 groups: <65, 65 to 74, and ≥75 years.

The echocardiographic evaluation of a patient was performed as previously reported.[12] At all centers, all examinations of a subject were always made by the same physician, who had a specific competence in assessing the effects of CRT. Interventricular mechanical delay (the time interval between the onset of anterograde blood flow in the right and in the left ventricular outflow tracts) was used as the indicator of interventricular dyssynchrony.[13] Optimization of CRT was recommended through echocardiography-guided programming of atrioventricular delay.[12]

All patients underwent standard clinical visits at 1, 3, and 6 months and every 6 months thereafter; the study charts were always compiled by the physicians operating at the electrophysiology center. By protocol, a complete clinical and instrumental reassessment was performed at least 6 and 12 months after the implantation of the device. At 17 and 33 months, entire evaluations were available for 836 (47%) and 296 (17%) subjects of the original cohort. Patients showing reductions of left ventricular end-systolic volume >10% at the 6-month follow-up visit were defined as responders to CRT.[12,14] For the purposes of this study, we reported only the results of the 6- and 12-month clinical and instrumental evaluations of patients. However, mortality data are related to the entire length of follow-up.

Statistical analysis was performed using SPSS for Windows version 18.0 (SPSS Inc., Chicago, Illinois). All analyses were carried out in the statistical laboratory of Medtronic Italy (Milan, Italy) on proposal of the chief investigators of the study. Continuous variables are expressed as mean ± SD. Categorical variables are expressed as percentages. Comparisons between groups of patients were performed using analysis of variance or chi-square tests for continuous or categorical variables, respectively. Changes in clinical and instrumental parameters during follow-up were evaluated using analysis of variance for repeated measures. Post hoc tests were applied to assess the existence of significant differences between each point of the follow-up and the baseline value.

All-cause mortality was studied using Kaplan-Meier curves and Cox regression analysis in univariate models. All significant clinical predictors were further introduced in a Cox multivariate regression model. In case of colinearity,

Table 2
Changes in left ventricular geometry and performance at the 6- and the 12-month follow-up evaluations

Variable	Study Phase			p Value*	p Value†
	Baseline	6 Months	12 Months		
LV end-diastolic diameter (mm)					
<65 years	70 ± 10	67 ± 12‡	66 ± 12‡	<0.001	
65–74 years	69 ± 9	66 ± 10‡	66 ± 11‡	<0.001	0.131
≥75 years	68 ± 9	64 ± 10‡	64 ± 10‡	<0.001	
LV end-systolic diameter (mm)					
<65 years	60 ± 12	54 ± 13‡	54 ± 13‡	<0.001	
65–74 years	58 ± 10	54 ± 12‡	53 ± 13‡	<0.001	0.251
≥75 years	57 ± 11	52 ± 12‡	51 ± 13‡	<0.001	
LV end-diastolic volume (ml)					
<65 years	242 ± 94	192 ± 91	191 ± 89§	<0.001	
65–74 years	221 ± 91	181 ± 74§	180 ± 74§	<0.001	0.197
≥75 years	209 ± 104	158 ± 64	158 ± 65	0.008	
LV end-systolic volume (ml)					
<65 years	168 ± 81	126 ± 77§	125 ± 76§	<0.001	
65–74 years	154 ± 85	121 ± 61‡	120 ± 63§	<0.001	0.365
≥75 years	133 ± 63	102 ± 60	100 ± 60	<0.001	
LVEF (%)					
<65 years	26 ± 8	34 ± 10‡	34 ± 11‡	<0.001	
65–74 years	26 ± 7	33 ± 11‡	34 ± 11‡	<0.001	0.830
≥75 years	27 ± 8	36 ± 11‡	37 ± 12‡	<0.001	
Interventricular mechanical delay (ms)					
<65 years	38 ± 44	22 ± 29‡	22 ± 26‡	<0.001	
65–74 years	44 ± 28	18 ± 25‡	20 ± 26‡	<0.001	0.841
≥75 years	39 ± 34	14 ± 25‡	13 ± 23‡	<0.001	

Data are expressed as mean ± SD.
LV = left ventricular.
* The p value for the whole trend in each age-group.
† The p value exploring the interaction between each parameter trend and age groups (p values >0.05 indicate behaviors not different by age group during the follow-up).
‡ p ≤0.001 vs baseline.
§ p <0.05 vs baseline.

only the variable that was more tightly associated with mortality was used. The results are reported also as hazard ratios with their related 95% confidence intervals. Assessing the influence of age on survival, the reference level (hazard ratio 1) was attributed to the group aged <65 years. For all analyses, a 2-tailed p value <0.05 was considered to indicate statistical significance.

Results

From 1999 to 2005, as previously mentioned, 1,787 consecutive subjects were enrolled in the InSync/InSync ICD Italian Registry. The oldest patients represented 27% (n = 476) of the entire cohort; the percentage of women significantly increased with age (Table 1). Coronary artery disease, hypertension, and the coexistence of ≥3 co-morbid conditions were most represented in the 2 oldest groups. Baseline left ventricular diameters and volumes significantly decreased in an age-related fashion, while interventricular mechanical delay did not differ at all (Table 1). The prevalence of atrial fibrillation (AF) was significantly higher in patients aged ≥65 years. The use of angiotensin-converting enzyme inhibitors and angiotensin receptor blockers and of β blockers significantly decreased with age (Table 1). CRT-D was progressively less often adopted with advancing age (<65 years, 48%; 65 to 74 years, 43%; ≥75 years, 29%; p <0.001).

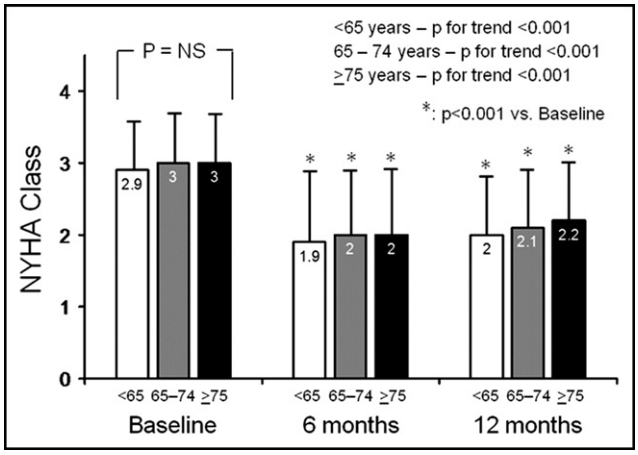

Figure 1. CRT-induced changes in New York Heart Association (NYHA) class between baseline and the 12-month evaluation, by age group.

CRT produced significant and similar left ventricular reverse remodeling in the 3 age groups (Table 2), which showed the same prevalence of responders (<65 years, 58%; 65 to 74 years, 60%; ≥75 years, 62%; p = 0.419).

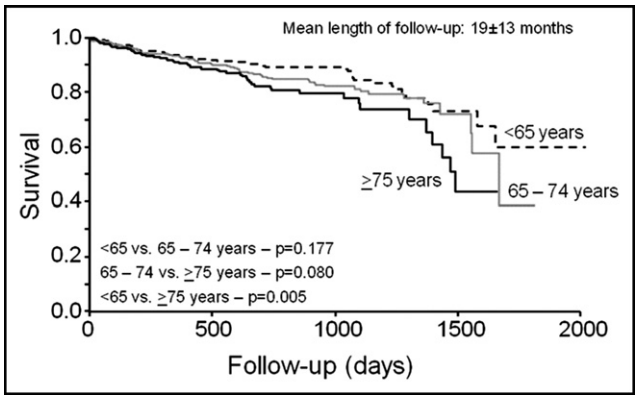

Figure 2. Kaplan-Meier analysis of overall survival in the InSync population by age group. Only the comparison between the trends observed in patients aged ≥75 and <65 years showed a statistically significant difference.

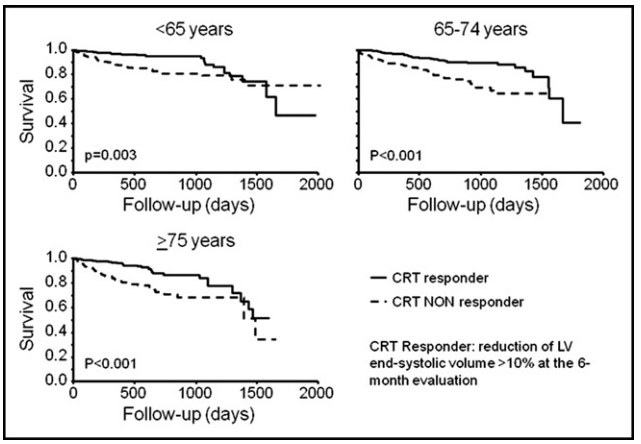

Figure 3. Kaplan-Meier analysis of overall survival in each age group, by CRT responder condition. The favorable effects on prognosis of the condition are evident also in the oldest patients. LV = left ventricular.

Table 3
Results of univariate Cox regression analyses exploring the association between clinical and instrumental variables and all-cause follow-up mortality in the entire InSync/InSync ICD Italian Registry population

Variable	HR	95% CI	p Value
Age group (years)			
<65	1		
65–74	0.99	0.76–1.31	0.976
≥75	1.47	1.10–1.98	0.010
Men vs women	1.67	1.12–2.49	0.012
Chronic obstructive pulmonary disease (+ vs −)	1.53	0.90–2.60	0.113
Diabetes mellitus (+ vs −)	0.93	0.55–1.57	0.775
Hypertension (+ vs −)	1.14	0.80–1.62	0.483
Renal failure (+ vs −)	1.94	1.24–3.05	0.004
≥3 co-morbidities (+ vs −)	1.75	1.13–2.73	0.013
Coronary artery disease (+ vs −)	1.34	1.02–1.76	0.033
LV end-diastolic diameter (mm)	1.01	0.99–1.02	0.592
LV end-systolic diameter (mm)	1.01	0.98–1.02	0.887
LVEF (%)	0.98	0.96–0.99	0.025
QRS length (ms)	1.00	0.99–1.01	0.605
New York Heart Association class	1.07	0.84–1.36	0.596
Permanent atrial fibrillation (+ vs −)	1.62	1.18–2.22	0.003
Atrioventricular node ablation (+ vs −)	0.96	0.57–1.63	0.890
Angiotensin-converting enzyme inhibitors/angiotensin receptor blockers (+ vs −)	0.64	0.48–0.85	0.002
β blockers (+ vs −)	0.46	0.35–0.62	<0.001
CRT responder (+ vs −)	0.40	0.30–0.52	<0.001
CRT-D (+ vs −)	0.94	0.70–1.25	0.664

CI = confidence interval; HR = hazard ratio; LV = left ventricular.

CRT significantly improved functional capacity independent of age (Figure 1).

After 12 months, the proportion of patients with ≥1 readmission for CHF was not statistically different among the 3 groups (<65 years, 10%; 65 to 74 years, 12%; ≥75 years, 13%; p = 0.509).

At the end of the follow-up period (mean 19 ± 13 months), all-cause mortality was 10% (n = 60), 12% (n = 86), and 14% (n = 65) in patients aged <65, 65 to 74, and ≥75 years, respectively. Kaplan-Meier analysis revealed a lower survival rate in the oldest group compared to the youngest group (Figure 2). Among patients with known causes of mortality (n = 177/211 [84%]), no age-related differences in sudden (<65 years, 2.3%; 65 to 74 years, 2.3%; ≥75 years, 2.1%; p = 0.870) and nonsudden cardiac death (<65 years, 5.3%; 65 to 74 years, 4.7%; ≥75 years, 5.9%; p = 0.378) were observed, while the proportion of noncardiac death was highest in the oldest group (<65 years, 1.1%; 65 to 74 years, 3.0%; ≥75 years, 3.4%; p = 0.006). The complete results of univariate survival analysis are listed in Table 3. The responder condition to CRT was associated with longer survival in the whole series of patients and in each age group when independently studied (survival hazard ratio for nonresponder vs responder condition: <65 years, 0.46, p = 0.003; 65 to 74 years, 0.34, p <0.001; ≥75 years, 0.38, p <0.001; Figure 3). The use of CRT-D was not associated with a significant reduction in mortality.

Table 4
Clinical predictors of all-cause mortality during follow-up: results of multivariate Cox regression analysis

Variable	HR	95% CI	p
Age groups (years)			
<65	1		
65–74	1.17	0.80–1.69	0.420
≥75	1.57	1.06–2.35	0.026
Men vs women	1.38	0.90–2.12	0.144
Renal failure (+ vs −)	1.29	0.75–2.22	0.349
Coronary artery disease (+ vs −)	1.18	0.87–1.60	0.281
LVEF (%)	0.96	0.94–0.98	<0.001
Permanent AF (+ vs −)	1.63	1.16–2.30	0.005
Angiotensin-converting enzyme inhibitors/angiotensin receptor blockers (+ vs −)	0.72	0.52–0.98	0.038
β blockers (+ vs −)	0.49	0.35–0.67	<0.001
CRT responder (+ vs −)	0.37	0.27–0.51	<0.001

Abbreviations as in Table 3.

Cox multivariate regression analysis showed that age ≥75 years and the presence of AF were independent predictors of a worse prognosis, while a higher LVEF and the use of angiotensin-converting enzyme inhibitors or angio-

tensin receptor blockers and of β blockers were correlated with improved survival. Finally, the condition of responder to CRT was associated with a 63% reduction in the risk for death (Table 4). Separate multivariate survival analysis models developed for each age group pointed out that the protective role of β-blocker use and the worse prognosis associated with AF were evident only in patients aged ≥65 years.

Device implantation complications were observed in 190 patients (11%). The most frequent event was the dislodgment of 1 of the leads (n = 126 [7.1%]). Pocket infection with or without skin erosion was observed in 44 patients (2.5%). The only other complication, the stimulation of the phrenic nerve, was present in the 28 remaining patients (1.6%). No age-related trend was noticed in the incidence of adverse events (<65 years, 10%; 65 to 74 years, 11%; ≥75 years, 10%; p = 0.596).

Discussion

Our study shows that the use of CRT in the elderly is a common practice in the real world: patients aged ≥75 years accounted for >1/4 of all implanted patients, and no age-related differences in the efficacy of the treatment were observed. Moreover, the database of the InSync/InSync ICD Italian Registry was made up of one of the largest group of elderly subjects ever studied, a segment of population usually excluded in clinical trials.[2,3,15] The recent demonstration, in the Framingham Offspring Cohort, that lower cardiac performance is associated with accelerated brain aging[16] and that CRT improved neurocognitive measures of attention, information processing, and quality of life[17] further strengthens the geriatric meaning of our results. To define CRT responders, we adopted a cut-off value of 10% for the reduction of left ventricular end-systolic volume, as obtained by Yu et al[14] in a younger population. We found that this criterion was able to identify a proportion of responders similar to those of other studies (pooled prevalence of echocardiographic responders in 15 large studies: 56.9%[18]) and to predict favorable clinical outcomes independent of age. Furthermore, a previous analysis of the InSync/InSync ICD Italian Registry revealed that an ischemic cause of CHF was the only clinical determinant of the nonresponder condition.[12]

In the presence of overt CHF, age and gender may significantly influence medical behavior. In an outpatient population with LVEF ≤35%, the Registry to Improve the Use of Evidence-Based Heart Failure Therapies in the Outpatient Setting (IMPROVE-HF) showed that older subjects, particularly older women, were significantly less likely to receive guideline-recommended CHF therapies.[19] The results of the American Heart Association's Get With the Guidelines–Heart Failure (GWTG-HF) program, extending the observation to devices, further supported this evidence, demonstrating also that women had a lower probability than men to receive CRT[20] and implantable cardioverter-defibrillators.[21] In our study, angiotensin-converting enzyme inhibitors or angiotensin receptor blockers and β blockers were significantly underused, particularly at advanced age. These findings were confirmed by recent observations obtained in a tertiary center of care, which demonstrated the reduced use of β blockers in CRT patients, with a resulting increase of mortality and need for heart transplantation.[22] Possible explanations of the underuse of drug therapy in the elderly may involve factors related to patients (e.g., frailty, co-morbidities, poor tolerance) or to physicians (e.g., fear of side effects, lack of awareness of guidelines prescriptions).[23] In our study, probably because of the improved clinical status and the certainty that bradycardia could have not developed, the 12-month use of β blockers increased in the 2 oldest segments of population (<65 years, 60% vs 62%, p = 0.396; 65 to 74 years, 45% vs 53%, p = 0.001; ≥75 years, 37% vs 50%, p <0.001).

Results from the Candesartan in Heart Failure—Assessment of Reduction in Mortality and Morbidity (CHARM) program,[24] then confirmed by a meta-analysis of 7 randomized trials and 9 observational studies,[25] proved that the presence of AF determined an increased risk for morbidity and mortality in patients with symptomatic heart failure regardless of baseline LVEF. Moreover, as shown by the Euro Heart Survey on AF, when CHF and AF coexist, the underprescription of guidelines-recommended medical therapy can be further potentiated.[26] Also in our patients, permanent AF was associated with increased mortality. In this regard, Kamath et al[27] demonstrated the importance of an effective biventricular capture to ensure clinical response from CRT in subjects with permanent AF. In this situation, there is no atrioventricular synchrony, and effective CRT is difficult to establish. Atrioventricular junction ablation allows a steady ventricular capture with a favorable impact on prognosis.[28] In our study, in patients with permanent AF, the execution of atrioventricular junction ablation significantly decreased with age (<65 years, 46%; 65 to 74 years, 51%; ≥75 years, 32%; p = 0.011). Thus, the risk for a suboptimal proportion of paced beats in 2/3 of the oldest patients with AF needs to be considered.

One of the most intriguing aspects of our study is the lack of statistical significance between CRT-D and survival during follow-up. Our findings seem to be in contrast to those of the Comparison of Medical Therapy, Pacing, and Defibrillation in Heart Failure (COMPANION) trial, in which only CRT-D, and not CRT, proved to have a significant effect on mortality.[15] Our results can be interpreted through the following assumptions: (1) the increase in mortality in patients with advanced forms of CHF is due to a progressively higher incidence of the refractory nonarrhythmic forms of disease[29]; (2) likewise, in elderly patients with heart failure, it is possible to observe a similar shift in mortality causes independent of the LVEF and New York Heart Association class. In this regard, in the 6,252 subjects enrolled in the Amiodarone Trialists Meta-Analysis, Krahn et al[30] observed that the sudden cardiac death/overall mortality ratio reduced from 0.50 to 0.26 from age <50 years to age >80 years. Confirming this hypothesis, in the InSync population, we observed a significant age-related increase only for noncardiac mortality causes. However, we cannot rule out that if our length of follow-up had been longer or the data set dimensions adequately powered, the influence of CRT-D on survival would have been significant.

Our data are derived from a registry, so we cannot exclude the presence of some selection bias. In particular, concerning our elderly patients, the prevalence of co-mor-

bidities and the number of hospitalizations for CHF in the 12 months preceding the study are low, not dissimilar from what is observed at younger ages. These findings are consistent with the possibility that our oldest subjects were "significantly healthier" than their counterparts who were not proposed for CRT. However, the end point of our study, aiming to assess the existence of age-related differences in the clinical and instrumental response to CRT, should have not been influenced by this limitation. The analyzed data were derived from a multicenter registry. So, despite the existence of a well-defined protocol and the several meetings that were held among the researchers, we cannot rule out that data collection was not fully homogenous in the different laboratories involved in the study. Regarding echocardiographic evaluation, it was impossible to blind the operator to the phase of the follow-up in which the patient was examined. Also in this case, the high degree of intracenter and intercenter consistency of the results should exclude the existence of a significant bias.

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