JACC: CLINICAL ELECTROPHYSIOLOGY
VOL. 3, NO. 13, 2017

ISSN 2405-500X/$36.00
PUBLISHED BY ELSEVIER
http://dx.doi.org/10.1016/j.jacep.2017.06.012

Utility of Frailty Assessment for Elderly Patients Undergoing Cardiac Resynchronization Therapy

Maciej Kubala, MD,[a] Laurence Guédon-Moreau, MD,[b] Frédéric Anselme, MD, PhD,[c] Didier Klug, MD, PhD,[b] Geneviève Bertaina, MD,[a] Sarah Traullé, MD,[a] Otilia Buiciuc, MD,[a] Arnaud Savouré, MD,[c] Momar Diouf, PhD,[a] Jean-Sylvain Hermida, MD, PhD[a]

ABSTRACT

OBJECTIVES The aim of this study was to evaluate the impact of frailty in the elderly on response to cardiac resynchronization therapy (CRT).

BACKGROUND CRT has been shown to improve symptoms and outcome of patients with congestive heart failure (HF) and impaired left ventricular ejection fraction (LVEF). The impact of frailty on the results of CRT is unknown.

METHODS Frailty defined as <14 of 17 points using the ONCODAGE (Outil de dépistage gériatrique en oncologie) G8 score was assessed before device implantation in candidates for CRT who were >70 years of age. The primary endpoint was the response to CRT, defined as an improvement of >5% of the LVEF and the absence of hospitalization for HF or cardiovascular death at 9 months.

RESULTS Ninety-two of 151 included patients (61%) were frail, and 89 (59%) were responders. Frailty was more frequent in nonresponders: 45 of 62 (73%) versus 47 of 89 (53%) ($p = 0.014$) and was identified as an independent predictor of nonresponse to CRT ($R = 0.30$; 95% confidence interval: 0.02 to 0.59; $p = 0.039$). Frailty was associated with a higher cumulative probability of hospitalization for HF (log-rank $p = 0.032$) and of all-cause death (log-rank $p = 0.033$). A G8 score <10.25 correlated with hospitalization for HF or death at 9 months (area under the curve: 0.75; 95% confidence interval: 0.63 to 0.87; cutoff <10.25; 77% sensitivity, 63% specificity).

CONCLUSIONS Frailty is as an independent predictor of nonresponse to CRT. Frail patients implanted with CRT devices have a higher risk of hospitalization for HF and mortality. Routine comprehensive geriatric assessment at the time of screening for device therapy should be recommended to optimize management. (Frailty Score Assessment for Elderly Patients Undergoing Cardiac Resynchronization Therapy [FRAILTY]; NCT02369419)
(J Am Coll Cardiol EP 2017;3:1523–33) © 2017 by the American College of Cardiology Foundation.

Cardiac resynchronization therapy (CRT) has been shown to improve symptoms and outcome of patients with congestive heart failure (HF) and impaired left ventricular ejection fraction (LVEF) (1–3); however, ≈30% of patients with CRT implanted do not benefit from their device (4,5). Appropriate selection of patients should take into account the presence of factors that are associated with nonresponse. Several demographic, electrocardiographic, and echocardiographic characteristics have been identified that are associated with nonresponsiveness to CRT (6–9). Because the

From the [a]Centre Hospitalier Universitaire, Amiens, France; [b]Centre Hospitalier Régional Universitaire, Lille, France; and the [c]Centre Hospitalier Régional Universitaire, Rouen, France. This work was supported in part by Biotronik (for data processing). Dr. Kubala has received honoraria from LivaNova and Boston Scientific. Dr. Guédon-Moreau has received consulting fees from LivaNova, Medtronic, St. Jude Medical, Boston Scientific, and Biotronik. Dr. Anselme has received honoraria and consulting fees from LivaNova, Medtronic, St. Jude Medical, Boston Scientific, and Biotronik. Dr. Klug has received consulting fees from Livanova, Medtronic, St Jude Medical, Boston Scientific, and Biotronik. Dr. Hermida has received consulting fees from St. Jude Medical and LivaNova. All other authors have reported that they have no relationships relevant to the contents of this paper to disclose.
All authors attest they are in compliance with human studies committees and animal welfare regulations of the authors' institutions and Food and Drug Administration guidelines, including patient consent where appropriate. For more information, visit the *JACC: Clinical Electrophysiology* author instructions page.

Manuscript received March 1, 2017; revised manuscript received June 14, 2017, accepted June 30, 2017.

ABBREVIATIONS AND ACRONYMS

AF = atrial fibrillation

CI = confidence interval

CRT = cardiac resynchronization therapy

CRT-P = cardiac resynchronization therapy pacemaker

ECG = electrocardiogram

HF = heart failure

ICD = implantable cardioverter-defibrillator

LBBB = left bundle branch block

LV = left ventricular

LVEF = left ventricular ejection fraction

NYHA = New York Heart Association

prevalence of HF increases with age, and life expectancy is increasing, the proportion of elderly patients referred for CRT is growing (10,11). Clinical and echocardiographic benefits of CRT have been confirmed in the elderly (12,13); however, the advanced age population is heterogeneous, and frailty has been identified as a pivotal condition in predicting outcome (14,15).

Frailty is a complex condition that includes age-associated deficits in multiple organs with a functional impairment, adverse drug reactions, hospitalization, and heightened vulnerability to stressors (16). Frailty scores systematically evaluate geriatric conditions including physical activity, muscle weakness, slow walking speed, unintentional weight loss, exhaustion, and cognitive and behavioral impairment. Long-term survival in elderly patients hospitalized for HF depends on frailty and association of noncardiovascular comorbidities (17). Frailty has been identified as a risk factor for hospital admission for HF, and routine comprehensive geriatric assessment at the time of HF diagnosis has been recommended by several authors (14,18). The importance of frailty in patients with cardiovascular disease is systematically considered in the establishment of the optimal management strategy (14,19).

Given the complexity of CRT system implantation and the cost of devices and hospitalizations for HF, better estimation of indications for CRT in the elderly is needed. In this context, the prognostic relevance of frailty for hospital readmissions for HF and its effect on the results of CRT remain unclear. The goal of frailty assessment would be to identify frail patients whose management should be optimized before implantation or for whom intervention therapy is inappropriate and who should be treated with conventional medical therapy. The aim of this study was to assess the impact of frailty on the response to the CRT.

METHODS

STUDY POPULATION. This is a prospective multicenter study including patients hospitalized in cardiology units of the Amiens, Lille, and Rouen University hospitals between July 2011 and July 2015. The protocol was registered at ClinicalTrials.gov (NTC02369419). We included patients older than 70 years of age with New York Heart Association (NYHA) functional class II to IV, LVEF ≤35%, QRS duration >120 ms, and left bundle branch block (LBBB) in sinus rhythm or in atrial fibrillation (AF) on optimal medical therapy (20). Patients with a conventional pacemaker indication and >95% of ventricular pacing, LVEF ≤35%, and NYHA functional class II to IV were also included. Patients with a high degree of atrioventricular block and LVEF >35% who required de novo CRT with an expected high percentage of ventricular pacing were excluded. After receiving detailed written information, all patients provided informed consent for CRT device implantation and follow-up. The study was approved by the local research ethics committee.

PRE-IMPLANTATION EXAMINATION. Before implantation, all patients underwent a clinical evaluation, an assessment of NYHA functional class, a 12-lead electrocardiogram (ECG), and a transthoracic echocardiogram. Ischemic heart disease was defined as 1 or more clinically documented (Q wave or enzyme-positive) prior myocardial infarctions or prior coronary artery bypass graft surgeries or percutaneous coronary interventions (balloon or stent angioplasty) (21).

LVEF was evaluated by 2-dimensional transthoracic echocardiography with the Simpson biplane method, magnetic resonance imaging, or angiographic or radionuclide methods. Associated aortic valvulopathy was defined as the presence of moderate (valvular area <1.5 cm^2) to severe (valvular area <1 cm^2) aortic stenosis or an aortic regurgitation of grade ≥2. All mitral regurgitation of grade ≥2 as evaluated using the proximal velocity surface area method was considered.

QRS duration was evaluated in lead II using the 12-lead ECG (25 mm/s) measurements (GE Marquette Mac 5000, GE Healthcare, Chicago, Illinois). In patients with permanently paced ventriculograms, the QRS duration was measured from the onset of the spike to the end of the QRS complex.

Typical LBBB was defined as QRS duration of ≥140 ms (men) or 130 ms (women), QS or rS in leads V_1 and V_2, and mid-QRS notching or slurring in ≥2 of leads V_1, V_2, V_5, V_6, I, and aVL (22). Atypical LBBB was defined as nonspecific intraventricular conduction delay and QRS widening >150 ms without typical features of LBBB or right bundle branch block (20,23).

PRE-IMPLANTATION FRAILTY ASSESSMENT. Frailty was assessed in all patients before CRT implantation by the attending cardiologist using the ONCODAGE (Outil de dépistage gériatrique en oncologie) G8 score, which includes 8 items on a scale of 1 to 17 (**Figure 1**) (24). The G8 score was chosen because it has been approved as one of the standard valuable screening methods of comprehensive geriatric assessment for predicting outcome (24,25). A score cutoff <14 points as identified in previous studies was required for a diagnosis of frailty (24–26).

Neuropsychological problems evaluated by G8 score including dementia and depression were examined as follows. The cognition was first assessed by the cognitive disorders examination evaluating spatial orientation with a 5-question scale giving 1 point to each correct answer (27). Cognition disorder was ruled out if the score was ≥4. In case of <4 points, a complete Mini-Mental State Examination was carried out with <10 points required for a diagnosis of severe cognition disorder and a score between 10 and 19 points for a diagnosis of moderate cognition disorder (28). The search for mood disorders was first made using the 4-question Mini-Geriatric Depression Scale, with 1 point given for each affirmative answer and a result <1 required to exclude mood disorder (29,30). If the score was ≥1, mood disorder was evaluated with the Center for Epidemiologic Studies Depression Scale (CES-D) questionnaire, which has a scale of 1 to 30 points (Online Figure 1) (31). A CES-D score >21 points was required for a diagnosis of severe mood disorder, with a score between 16 and 21 required for a diagnosis of moderate mood disorder (31).

Weight loss was defined as unintentional loss of at least 1 kg of weight during the past 3 months preceding the implantation attributed to decreased appetite or food intake. To avoid situations in which the weight loss could be attributed to increased use of a diuretic agent, patients with changes in dose of diuretic agents during the past 3 months were not enrolled. Anorexia, as defined by G8 score, was a moderate or severe decrease in food intake over the past 3 months due to loss of appetite or chewing or swallowing difficulties (25).

IMPLANTATION AND DEVICE PROGRAMMING. All enrolled patients underwent device implantation with standard transvenous techniques. Implantable cardioverter-defibrillator (ICD) therapy was chosen according to the American College of Cardiology/American Heart Association/Heart Rhythm Society 2008 Guidelines for Device-Based Therapy of Cardiac Rhythm Abnormalities (32). In the absence of a history of sustained ventricular tachycardia or ventricular fibrillation, the choice between a CRT defibrillator (CRT-D) and a CRT pacemaker (CRT-P) device was left to the discretion of the electrophysiologist. Very high-risk patients (defined by blood urea nitrogen 50 mg/dl or serum creatinine >2.5 mg/dl) with expected attenuation of the efficacy of an ICD were implanted with CRT-P devices (33). The right ventricular lead was positioned in the septum or, failing that, in the apex. The left ventricular (LV) lead was preferably placed in a posterolateral or lateral cardiac vein. Stimulation of basal LV segments was preferably programmed (34). The sensed atrioventricular delay was programmed at 100 ms with a 30-ms extension in patients in sinus rhythm. The VV delay was initially programmed at 0 ms. Pacing rate

FIGURE 1 The ONCODAGE (G8) Questionnaire, Including 8 Essential Items for Frailty Evaluation

Has food intake declined over the past 3 months owing to loss of appetite, digestive problems, chewing or swallowing difficulties	
Severe decrease	0
Moderate decrease	1
No decrease	2
Weight loss during the past 3 months	
> 3 kg	0
Patient doesn't know	1
1-3 kg	2
No weight loss	3
Mobility	
Bed or chair bound	0
Able to get out of bed/chair but does not go out	1
Goes out	2
Neuropsychological problems	
Severe dementia or depression	0
Mild dementia or depression	1
No psychological disorders	2
BMI (kg/m²)	
≤ 18.5	0
18.5 - < 21.0	1
21.0 - < 23.0	2
≥ 23.0	3
Takes more than three medications per day	
Yes	0
No	1
In comparison with other people of the same age, how does the patient consider his or her health status to be?	
Not as good	0
Does not know	0.5
As good	1
Better	2
Age (years)	
> 85	0
80 – 85	1
< 80	2

A cutoff value of <14 indicates frailty (25). BMI = body mass index; ONCODAGE = Outil de dépistage gériatrique en oncologie.

TABLE 1 Baseline Characteristics

	All Patients (N = 151)	Frail (n = 92)	Nonfrail (n = 59)	Effect Size
Age, yrs	78.3 ± 5.2	79.4 ± 5.6	76.6 ± 3.9	0.52
Male	116 (77)	71 (77)	45 (76)	0.02
Ischemic cardiomyopathy	80 (53)	49 (53)	31 (52)	0.02
LVEF, %	27.3 ± 6.8	27.2 ± 7.2	27.4 ± 6.2	0.03
NYHA functional class	2.8 ± 0.5	2.9 ± 0.4	2.6 ± 0.5	0.68
II	37 (24)	13 (14)	24 (41)	0.66
III	108 (71)	73 (79)	35 (59)	0.45
IV	6 (4)	6 (6)	0	0.32
Persistent/permanent AF	61 (40)	39 (42)	22 (37)	0.10
History of cardiac surgery	37 (24)	20 (22)	17 (29)	0.16
CABG	16 (11)	8 (9)	8 (14)	0.16
Valvular surgery	16 (11)	9 (10)	7 (12)	0.06
CABG and valvular surgery	5 (3)	3 (3)	2 (3)	0.00
BMI, kg/m^2	26.6 ± 4.6	26.1 ± 5.1	27.1 ± 3.5	0.22
Hypertension	108 (71)	67 (73)	41 (69)	0.18
Diabetes mellitus	52 (34)	35 (38)	17 (29)	0.19
Glomerular filtration rate, ml/min*	55.5 ± 25.3	52.7 ± 21.5	60.0 ± 30.2	0.29
BNP, ng/l	713 ± 668	774 ± 642	620 ± 694	0.23
Echocardiographic characteristics				
LVEDD, mm	63 ± 8	63 ± 8	64 ± 8	0.12
Moderate aortic stenosis or regurgitation	25 (17)	17 (18)	8 (14)	0.11
Mitral regurgitation	34 (22)	25 (27)	9 (15)	0.29
ECG characteristics				
QRS duration, ms	178 ± 27	180 ± 28	176 ± 27	0.14
LBBB	74 (49)	40 (43)	34 (58)	0.30
Atypical LBBB	24 (16)	18 (20)	6 (10)	0.27
Paced QRS	53 (35)	34 (37)	19 (32)	0.10
Pharmacotherapy				
Beta-blockers	128 (85)	75 (81)	53 (90)	0.25
ACE inhibitor	106 (70)	60 (65)	46 (78)	0.29
ARB	22 (15)	12 (13)	10 (17)	0.11
Loop diuretic	133 (88)	81 (88)	52 (88)	0.00
Aldosterone antagonist	62 (41)	41 (45)	21 (36)	0.18
Statin	103 (68)	59 (64)	44 (75)	0.24
Oral anticoagulant	83 (55)	50 (54)	33 (56)	0.04

Values are mean ± SD or n (%). *Glomerular filtration rate was estimated using the MDRD (Modification of Diet in Renal Disease) method.

ACE = angiotensin-converting enzyme; AF = atrial fibrillation; ARB = angiotensin II receptor blocker; BMI = body mass index; BNP = brain natriuretic peptide; CABG = coronary artery bypass graft; ECG = electrocardiogram; LBBB = left bundle branch block; LVEDD = left ventricular end-diastolic diameter; LVEF = left ventricular ejection fraction; NYHA = New York Heart Association.

was programmed at 50/min in patients in sinus rhythm and at 70/min in patients in AF using a rate-adaptive mode. Anteroposterior and left anterior oblique 45° chest radiographs were systematically performed before discharge.

FOLLOW-UP. Clinical ECG evaluation and device testing were performed at 3- and 9-month visits and echocardiographic evaluation at 9 months. All adverse events were documented: cardiovascular (sudden cardiac death or death of HF) or non-cardiovascular deaths, with the causes specified. In case of nonimprovement of clinical and hemodynamic status (based on NYHA functional class and clinical examination) at the 3-month visit or a hospitalization for HF, atrioventricular and VV delays were adjusted according to the optimal aortic ejection volume obtained by Doppler evaluation (35).

DEFINITION OF RESPONSE TO CRT. We chose a combined endpoint based on echocardiographic improvement of LVEF of >5% and the absence of major clinical events in relation to heart disease, including cardiovascular death or hospitalization for HF. The diagnosis of HF was based on symptoms and responsiveness to intravenous decongestive therapy observed by experienced cardiologists unaware of the study protocol.

PRIMARY AND SECONDARY ENDPOINTS. The primary endpoint was the impact of frailty as assessed by G8 score on the response to CRT in patients older than 70 years of age implanted with biventricular devices. The secondary endpoints were the effects of frailty on deaths of any cause, hospitalizations, and the rate of redo procedures after CRT device implantation.

STATISTICAL ANALYSIS. For all statistical analysis, we used the SPSS software package version 9.0 (SPSS Inc., Chicago, Illinois). Discrete variables were reported as percentages and continuous variables as mean ± SD. Standardized differences were estimated using Cohen's effect size, with values of 0.2, 0.5, and 0.8 considered low, medium, and high, respectively.

Differences between groups were tested with the chi-square test or Fisher exact test. For continuous variables, Student *t* test or Mann-Whitney *U* test were used. A 2-sided $p < 0.05$ was considered statistically significant. The absolute change in LVEF between baseline and 9-month follow-up was evaluated by paired-sample *t* test.

Event-free survival was compared by the Kaplan-Meier method and log-rank statistic. To evaluate potential predictors of nonresponsiveness to CRT, only variables with $p < 0.04$ on univariate analysis were included in the multivariate logistic regression model giving odds ratios and 95% confidence intervals (CIs). A generalized linear mixed model was used to exclude a multicenter effect. Given a 30% expected rate of nonresponders to CRT and the unknown proportion of frail patients as evaluated by G8 score in this population, the number of subjects needed to obtain a significantly powered result was estimated at 150 using nonparametric tests (4,5). The α and β risks were set at 5% and 20%, respectively. Receiver-operating characteristic analysis was performed to

determine the optimal cutoff value of the G8 score associated with hospitalizations for HF and mortality (36,37).

RESULTS

A total of 155 of the 161 initially recruited patients (96%) underwent successful CRT device implantation. Four patients were lost to follow-up; therefore, 151 patients were included in the analysis. The baseline characteristics of all included patients are shown in Table 1.

PREVALENCE OF FRAILTY BEFORE RESYNCHRONIZATION THERAPY. Ninety-two (61%) of 151 patients in whom a CRT device was implanted had a G8 score <14 and were identified as frail. No significant difference was found between frail and nonfrail subjects according to device implantation data except for the proportion of implanted CRT-D compared to CRT-P devices, which was higher in nonfrail patients (46 of 59 [78%] vs. 47 of 92 [51%]; p = 0.001) (Table 2).

RESPONSE TO CRT. After 9 months of follow-up, 89 of 151 patients (59%) were responders. Mean increase in LVEF was 9.8 ± 10.5%. Eleven patients (7%) were hospitalized for HF, and 10 (6.5%) died of cardiovascular causes. Frailty was associated with nonresponse to CRT (45 of 62 [73%] vs. 47 of 89 [53%]; p = 0.014) (Table 3). Changes in NYHA functional class, LVEF, LV end-diastolic diameter, and QRS duration at 9-month follow-up in frail and nonfrail patients are shown in Table 4 and illustrated in Figure 2.

Persistent or permanent AF (p = 0.028; R = 0.34; 95% CI: 0.04 to 0.64) and frailty (p = 0.014; R = 0.30; 95% CI: 0.02 to 0.59) were identified as independent predictors of nonresponse to CRT in multivariate analysis. Percentage of biventricular pacing was similar in patients with persistent/permanent AF and those in sinus rhythm (95 ± 7% vs. 96 ± 12%; p = 0.570) and in frail versus nonfrail patients (95 ± 11% vs. 95 ± 8%; p = 0.686).

HOSPITALIZATIONS, REDO PROCEDURES, AND ICD THERAPIES. Rates of hospitalizations, reinterventions, and ICD therapy are shown in Table 5. There were 35 hospitalizations related to cardiovascular disease, which included 11 (31%) for HF, 17 (48%) for a heart rhythm disorder, and 2 (6%) for acute coronary syndrome. Five other hospitalizations were caused by 1 atrioventricular node ablation, 1 pocket hematoma, 1 healing delay, 1 regressive inflammatory syndrome, and 1 atypical chest pain.

TABLE 2 CRT Device Implantation Data

	All Patients (N = 151)	Frail (n = 92)	Nonfrail (n = 59)	Effect Size
ICD	93 (62)	47 (51)	46 (78)	0.58
Primary prevention	70/93 (75)	37/47 (79)	33/46 (72)	0.16
Upgrade to CRT device	64 (42)	42 (46)	22 (37)	0.18
Septal right ventricular lead position	101 (67)	61 (66)	40 (68)	0.04
Left ventricular lead position				
Posterolateral basal	88 (58)	55 (60)	33 (56)	0.08
Posterolateral apical	18 (12)	11 (12)	7 (12)	0.00
Anterolateral basal	43 (29)	25 (27)	18 (30)	0.07
Anterolateral apical	2 (1)	1 (1)	1 (2)	0.09
Multipolar left ventricular lead	34 (22)	18 (20)	16 (27)	0.17
First targeted vein success	112 (74)	69 (75)	43 (73)	0.05
Fluoroscopy, min	21 ± 18	23 ± 19	17 ± 14	0.11

Values are n (%) or n/N (%).
CRT = cardiac resynchronization therapy; ICD = implantable cardioverter-defibrillator.

Cumulative survival without hospitalization for HF was better in nonfrail patients (98% vs. 89%; log-rank p = 0.032) (Figure 3). The 14 reinterventions included 10 LV lead repositionings, 1 additional LV lead implantation, 1 LV lead exchange, 1 device extraction for pocket infection, and 1 drainage of pocket hematoma.

CARDIOVASCULAR, NONCARDIOVASCULAR, AND OVERALL MORTALITY. Fifteen of 151 patients (10%) died during the follow-up. Ten cardiovascular deaths were caused by HF. The causes of the 5 noncardiovascular deaths were colon cancer (1), esophageal cancer (1), pneumonia (1), septic shock (1), and unexplained death without preceding cardiovascular symptoms (1).

Frailty was associated with a higher cumulative probability of all-cause death (96% vs. 86%; p = 0.033). Cumulative survival curves for all-cause death, cardiovascular death, and noncardiovascular death in frail and nonfrail patients are illustrated in Figures 3 and 4.

A G8 score <10.25 correctly predicted hospitalization for HF or death (area under the curve: 0.75; 95% CI: 0.63 to 0.87; cutoff <10.25; 77% sensitivity, 63% specificity) (Figure 5).

DISCUSSION

MAJOR FINDINGS. This study establishes a strong relation between frailty and worse outcome in the population of elderly patients with HF treated with CRT. The major findings are as follows: 1) frailty, as defined by G8 score <14, is an independent predictor

TABLE 3 Comparison Between Responders and Nonresponders to CRT

	All Patients (N = 151)	Responders (n = 89)	Nonresponders (n = 62)	p Value
Age, yrs	78.3 ± 5.2	78.5 ± 5.5	78.0 ± 4.7	0.570
Male	116 (77)	66 (74)	50 (81)	0.353
Ischemic cardiomyopathy	80 (53)	50 (56)	30 (48)	0.345
LVEF, %	27.3 ± 6.8	27.8 ± 7.2	26.6 ± 6.2	0.303
NYHA class at implantation	2.8 ± 0.5	2.7 ± 0.5	2.9 ± 0.4	0.007
Persistent/permanent AF	61 (40)	28 (31)	33 (53)	0.009
History of cardiac surgery	37 (24)	22 (25)	15 (24)	0.941
CABG	16 (11)	9 (10)	7 (11)	0.817
Valvular surgery	16 (11)	9 (10)	7 (11)	0.817
CABG + valvular surgery	5 (3)	4 (4)	1 (2)	0.649
Hypertension	108 (71)	65 (73)	43 (69)	0.622
Diabetes mellitus	52 (34)	29 (33)	23 (37)	0.566
Glomerular filtration rate (ml/min)	55.5 ± 25.3	58.1 ± 27.9	51.8 ± 22.7	0.141
BNP, ng/l	713 ± 668	622 ± 635	860 ± 699	0.045
Echocardiographic characteristics				
LVEDD, mm	63 ± 8	62 ± 8	65 ± 9	0.141
Moderate aortic stenosis or regurgitation	25 (17)	14 (16)	11 (18)	0.790
Mitral regurgitation	34 (22)	14 (16)	20 (32)	0.019
ECG characteristics				
QRS duration, ms	178 ± 27	178 ± 28	178 ± 27	0.973
LBBB	74 (49)	45 (51)	29 (47)	0.647
Atypical LBBB	24 (16)	10 (11)	14 (23)	0.061
Paced QRS	53 (35)	34 (38)	19 (31)	0.338
Implantation data				
ICD	93 (62)	57 (64)	36 (58)	0.457
Septal RV lead position	101 (77)	59 (66)	42 (68)	0.852
Posterolateral basal LV lead position	88 (58)	51 (57)	37 (60)	0.771
Posterolateral apical LV lead position	18 (12)	11 (12)	7 (11)	0.842
Anterolateral basal LV lead position	43 (29)	25 (28)	18 (29)	0.900
Anterolateral apical LV lead position	2 (1)	2 (2)	0 (0)	0.513
First targeted vein success	112 (74)	68 (76)	44 (71)	0.427
G8 score <14	92 (61)	47 (53)	45 (73)	0.014
Anorexia	51 (34)	19 (21)	32 (52)	<0.001
Weight loss >1 kg	78 (52)	41 (46)	37 (60)	0.100
BMI, kg/m^2	26.6 ± 4.6	26.2 ± 4.4	27.1 ± 4.8	0.240
Limited mobility*	27 (18)	11 (12)	16 (26)	0.034
Dementia	28 (19)	12 (13)	16 (26)	0.055
Depression	15 (10)	9 (10)	6 (10)	0.930
Dementia or depression	40 (26)	18 (20)	22 (35)	0.037
Worse self-reported health	54 (36)	31 (35)	23 (37)	0.775

Values are mean ± SD or n (%). *Bed- or chair-bound status (Figure 1).
ICD = implantable cardioverter-defibrillator; LV = left ventricular; RV = right ventricular; other abbreviations as in Table 1.

TABLE 4 Changes in NYHA Functional Class, Mean LVEF, Mean LVEDD, and QRS Width Between Baseline and Follow-Up Values in Frail and Nonfrail Patients

	Frail (n = 92)	Nonfrail (n = 59)	p Value
Δ NYHA functional class	−0.8 ± 0.7	−0.7 ± 0.5	0.236
Δ LVEF, %	8.4 ± 10.3	12.0 ± 10.6	0.043
Δ LVEDD, mm	−1.5 ± 6.8	−3.8 ± 6.5	0.055
Δ QRS duration, ms	−31 ± 27	−24 ± 27	0.089

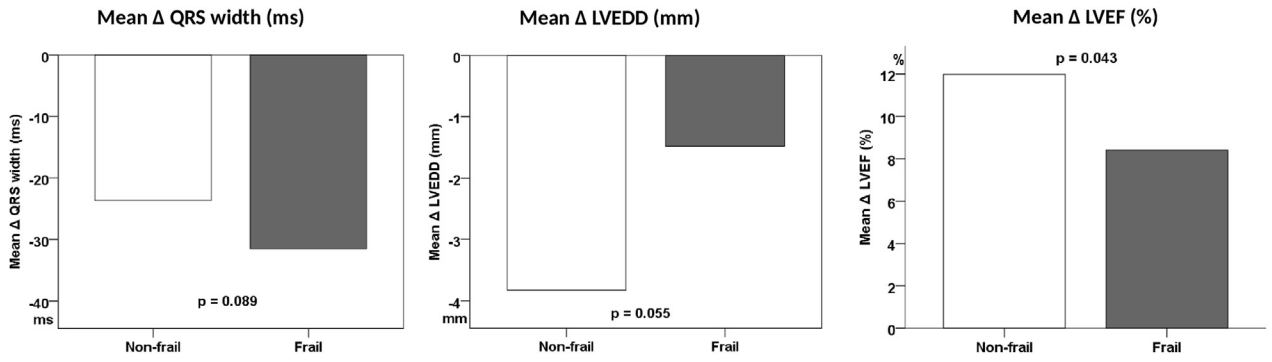
Values are mean ± SD.
Abbreviations as in Table 1.

of nonresponse to CRT in patients >70 years of age in whom a CRT device has been implanted for conventional indications; and 2) frail patients have an increased risk of hospitalization for HF and an increased risk of all-cause death.

FRAILTY AND RESPONSE TO CRT. For years, research on predictors of long-term results of CRT has been based on the assessment of conventional clinical, electrocardiographic, and echocardiographic parameters. Elderly patients with decreased LVEF are at high risk for HF and are most in need of treatment; however, the benefit for an individual patient with decreased physiological reserve and comorbidities remains difficult to evaluate. A detailed evaluation of frailty, routinely performed in geriatric units, can be applied to patients affected with HF in addition to conventional examination. Frailty scoring systems have demonstrated the potential to provide a valuable assessment of mortality and preoperative risks in previous studies (37,38). Several authors have reported the association of frailty with the risk of more frequent and longer hospitalizations in the general population (39,40). The same trend to decompensate at a lower threshold has been demonstrated in patients with HF (18,41). Furthermore, frailty syndrome has been reported as common in candidates for CRT (42), which was confirmed in our study. The G8 score, validated in previous geriatric series, appeared in our study to be a valuable tool to identify frailty in a similar proportion of elderly patients with HF as described previously (36,37). The proportion of nonresponders to the CRT was similar to previous series concerning the elderly (13). The cutoff value of <14 identified patients less likely to benefit from their device. Frailty has been identified as a predictor of HF in patients with nonischemic cardiomyopathy undergoing CRT (43). Our study confirmed an increased risk of hospitalization for HF in frail patients with severe impairment of LV systolic function, expanding these results to the population with all-cause cardiomyopathies.

Separate evaluation of all geriatric conditions included in the G8 score showed that some were associated with nonresponse to CRT; however, the total score, representing a more complete and objective assessment, was identified as an

FIGURE 2 Changes in Mean QRS Width, Mean LVEDD, and Mean LVEF Between Baseline and Follow-Up Values in Frail and Nonfrail Patients



LVEDD = left ventricular end-diastolic diameter; LVEF = left ventricular ejection fraction.

independent predictor of nonresponse to CRT. Interestingly, despite a similar shortening of QRS width, frail patients had a significantly lower increase in LVEF.

The G8 test can be easily accomplished in 10 min and included in clinical practice. The score can be integrated in the discussion with the patient and taken into account while choosing the optimal therapy. Frailty has been described as a reversible condition (44). Hence, in mildly frail patients (G8 score >10.5 to 14), we believe that implantation of CRT device should be discussed individually for each patient. An etiological evaluation of decreased physiological status to rule out all underlying neoplastic processes should be systematic. Then a specific therapy to limit the progression of frailty, including measures to improve physical activity and nutritional and cognitive impairment, along with CRT, could be proposed.

This study also showed that the patients with persistent or permanent AF were less likely to respond to CRT therapy. Previous results of biventricular pacing in patients with chronic AF reported in observational studies were controversial (45-47). Patients in our series were older than in trials that showed a benefit of CRT in AF (79 years of age vs. 68 years of age in the study by Kiès et al.) (47).

MORTALITY AND HOSPITALIZATIONS FOR HF. In this study, frail patients had a higher risk of mortality and hospitalization for HF. The total and cardiovascular mortality in our study (10% and 6.5%, respectively) was in line with the results of other series. Cardiovascular mortality of 7% was reported in the MADIT-CRT (Multicenter Automatic Defibrillator Implantation Trial-Cardiac Resynchronization Therapy) trial in younger patients (65 years of age vs. 79 years of age) and with a longer follow-up (28 months vs. 9 months) than in our series (21).

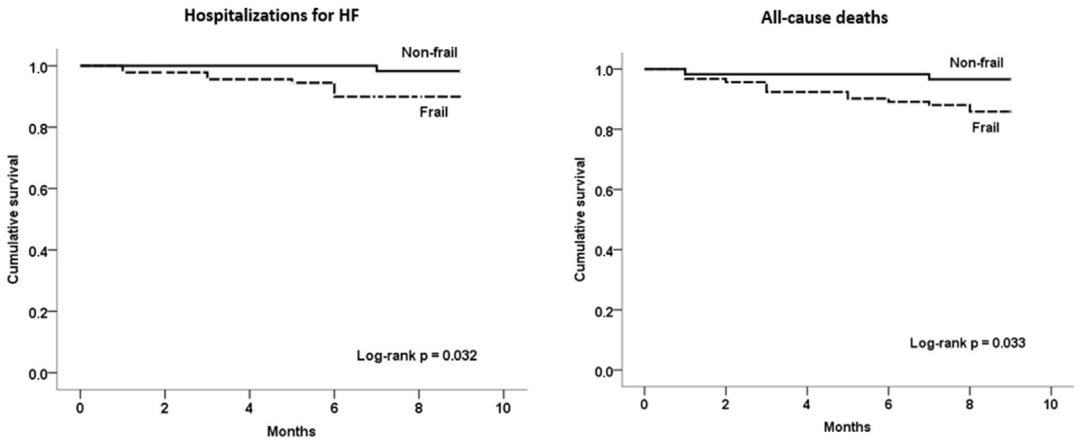
The presence of frailty in patients with HF has been described as an additional risk factor for mortality (17). Our study confirmed this finding in the population with severe LV systolic dysfunction. A G8 score with a cutoff value of <10.25 identified patients with a significantly higher risk of hospitalization for HF or death. The impact of frailty on mortality in patients undergoing CRT should be taken into account during initial screening for device therapy. We believe that a conventional drug treatment should be preferred in candidates with a G8 score <10.25.

TABLE 5 Comparison of Hospitalization and Reintervention Rates and ICD Therapies Between Frail and Nonfrail Patients

	All Patients (N = 151)	Frail (n = 92)	Nonfrail (n = 59)	p Value
Hospitalization for cardiovascular disease	35 (23)	20 (22)	15 (25)	0.601
Heart failure	11 (7)	10 (11)	1 (2)	0.051
Heart rhythm disorder	17 (11)	8 (9)	9 (15)	0.213
Hospitalization for device dysfunction	10 (7)	5 (5)	5 (8)	0.464
Left ventricular lead dislodgement	10 (7)	3 (3)	7 (12)	0.048
Reintervention	14 (9)	6 (7)	8 (14)	0.161
ICD therapy	7/93 (7)	4/47 (8)	3/46 (6)	1.000

Values are n (%) or n/N (%).
ICD = implantable cardioverter-defibrillator.

FIGURE 3 Kaplan-Meier Plots for Hospitalizations for HF and Mortality



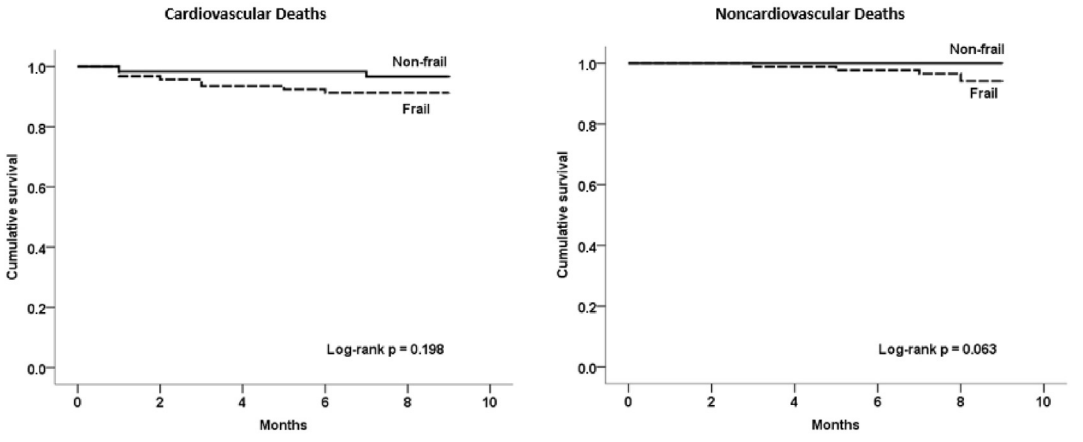
(Left) Cumulative survival without hospitalization for HF according to the presence of frailty was 98% in nonfrail patients versus 89% in frail patients (p = 0.032). **(Right)** Cumulative survival for all-cause deaths was 96% in nonfrail patients versus 86% in frail patients (p = 0.033). HF = heart failure.

The higher rate of hospitalization for HF results in increased health service care. In our study, a frailty assessment identified patients at higher risk of rehospitalization for HF. In this context, the G8 score can be useful to identify patients likely to be hospitalized and needing an optimized therapy.

Moreover, frailty is associated with increased vulnerability to stressors, including hospitalizations or surgery (48). This study also demonstrates that in patients undergoing less invasive interventions than cardiac surgery, frailty is also associated with higher risk of mortality. CRT device implantation in frail patients, if indicated, should involve pre-operative and post-operative surveillance optimization.

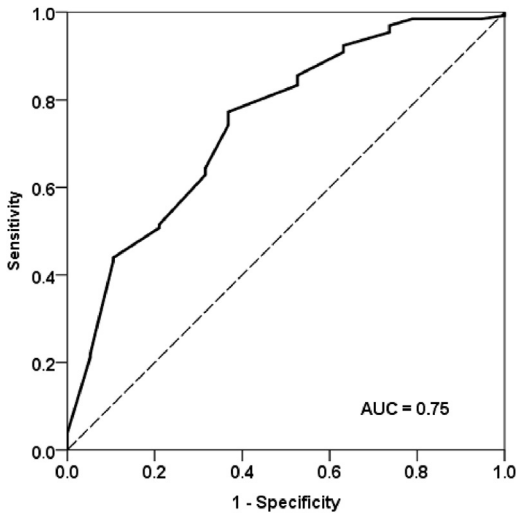
Frailty appears to be one of the missing parameters not captured by conventional evaluation before

FIGURE 4 Kaplan-Meier Plots for Cardiovascular and Noncardiovascular Mortality in Frail Versus Nonfrail Patients



(Left) Cumulative survival without cardiovascular death according to the presence of frailty: 96% in nonfrail patients versus 91% in frail patients (p = 0.198). **(Right)** Cumulative survival without noncardiovascular death according to the presence of frailty: 100% in nonfrail patients versus 94% in frail patients (p = 0.063).

FIGURE 5 Receiver-Operating Characteristic Curve of G8 Score to Predict Hospitalization for HF or Death



Area under the curve (AUC): 0.75; 95% confidence interval: 0.63 to 0.87; cutoff <10.25; 77% sensitivity, 63% specificity. HF = heart failure.

cardiac resynchronization. The influence of frailty both on results of biventricular pacing and on outcome shows the limits of device therapy. All cardiovascular deaths in our study were caused by HF, and there were no sudden deaths. The recently published DANISH (Danish Study to Assess the Efficacy of ICDs in Patients With Nonischemic Systolic Heart Failure on Mortality) study has suggested a possible lack of benefit of ICD therapy with regard to death of any cause in nonischemic cardiomyopathy among older patients (>68 years of age) (49). In this context, frailty assessment appears to be an appropriate tool to improve selection of elderly candidates for CRT. Further studies are needed to demonstrate whether frailty scores could be helpful to identify a subgroup of patients less likely to benefit from ICD therapy.

The relationship of frailty with HF remains challenging given the similar outcome of both entities. Association of frailty with HF resulting in exacerbation creates a vicious circle that leads to higher mortality and increased risk of hospitalization. This bidirectional relationship has not been fully understood, and in our opinion, both subclinical HF and pre-frailty should be targeted earlier.

STUDY LIMITATIONS. The G8 score used previously in oncogeriatric evaluations has lower specificity than other scores to detect cognitive disorders, although the G8 score is easier to use in clinical practice and is of higher value to evaluate nutrition impairment. In this study, the impact of biventricular pacing on reversibility of frailty in patients who responded positively to CRT was not studied.

CONCLUSIONS

Frailty is as an independent predictor of nonresponse to CRT in the elderly. Frail patients have a higher risk of hospitalization for HF and mortality. Routine comprehensive geriatric assessment at the time of screening for device therapy should be recommended to optimize management. A G8 score cutoff value of 10.25 can be proposed for better selection of candidates for CRT. Further evaluation and better understanding of the bidirectional effects of frailty and HF is needed.

ADDRESS FOR CORRESPONDENCE: Dr. Maciej Kubala, Service de Rythmologie et Stimulation Cardiaque, Centre Hospitalier Universitaire, Avenue Laennec, 80054 Amiens, France. E-mail: Kubala.Maciej@chu-amiens.fr.

PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE: Frailty assessment in the elderly before CRT for conventional indications identifies a subgroup of frail patients less likely to benefit from their devices. Frail patients identified using the G8 score have a higher risk of hospitalization for HF and mortality.

TRANSLATIONAL OUTLOOK: The G8 score cutoff value of 10.25 can be used for better selection of candidates for CRT. In mildly frail patients with G8 score >10.5 to 14, specific measures to improve reversible reduced mobility and nutritional and cognitive impairment can be proposed along with CRT. The easily evaluable G8 test can be included in routine practice in addition to conventional clinical evaluation at the time of screening for device therapy.

REFERENCES

1. Cazeau S, Leclercq C, Lavergne T, et al., for the Multisite Stimulation in Cardiomyopathies (MUSTIC) Study Investigators. Effects of multisite biventricular pacing in patients with heart failure and intraventricular conduction delay. N Engl J Med 2001;344:873–80.

2. Linde C, Leclercq C, Rex S, et al. Long-term benefits of biventricular pacing in congestive heart failure: results from the MUltisite STimulation in cardiomyopathy (MUSTIC) study. J Am Coll Cardiol 2002;40:111–8.

3. Cleland JG, Daubert JC, Erdmann E, et al., for the Cardiac Resynchronization-Heart Failure (CARE-HF) Study Investigators. The effect of cardiac resynchronization on morbidity and mortality in heart failure. N Engl J Med 2005;352:1539–49.

4. van Bommel RJ, Bax JJ, Abraham WT, et al. Characteristics of heart failure patients associated with good and poor response to cardiac resynchronization therapy: a PROSPECT (Predictors of Response to CRT) sub-analysis. Eur Heart J 2009;30:2470–7.

5. Bleeker GB, Bax JJ, Fung JW, et al. Clinical versus echocardiographic parameters to assess response to cardiac resynchronization therapy. Am J Cardiol 2006;97:260–3.

6. Gold MR, Thébault C, Linde C, et al. Effect of QRS duration and morphology on cardiac resynchronization therapy outcomes in mild heart failure: results from the Resynchronization Reverses Remodeling in Systolic Left Ventricular Dysfunction (REVERSE) study. Circulation 2012;126:822–9.

7. Bordachar P, Lafitte S, Reuter S, et al. Echocardiographic parameters of ventricular dyssynchrony validation in patients with heart failure using sequential biventricular pacing. J Am Coll Cardiol 2004;44:2157–65.

8. Yu CM, Abraham WT, Bax J, et al., on behalf of the PROSPECT Investigators. Predictors of response to cardiac resynchronization therapy (PROSPECT): study design. Am Heart J 2005;149:600–5.

9. Beshai JF, Grimm RA, Nagueh SF, et al., for the RethinQ Study Investigators. Cardiac-resynchronization therapy in heart failure with narrow QRS complexes. N Engl J Med 2007;357:2461–71.

10. Roger VL, Go AS, Lloyd-Jones DM, et al., on behalf of the American Heart Association Statistics Committee and Stroke Statistics Subcommittee. Heart disease and stroke statistics–2012 update: a report from the American Heart Association [published correction appears in Circulation 2012;125:e1002]. Circulation 2012;125:e2–220.

11. Hancock HC, Close H, Mason JM, et al. High prevalence of undetected heart failure in long-term care residents: findings from the Heart Failure in Care Homes (HFinCH) study. Eur J Heart Fail 2013;15:158–65.

12. 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;15:203–10.

13. Delnoy PP, Ottervanger JP, Luttikhuis HO, et al. Clinical response of cardiac resynchronization therapy in the elderly. Am Heart J 2008;155:746–51.

14. Afilalo J, Karunananthan S, Eisenberg MJ, Alexander KP, Bergman H. Role of frailty in patients with cardiovascular disease. Am J Cardiol 2009;103:1616–21.

15. Chaudhry SI, Wang Y, Gill TM, Krumholz HM. Geriatric conditions and subsequent mortality in older patients with heart failure. J Am Coll Cardiol 2010;55:309–16.

16. Fried LP, Tangen CM, Walston J, et al., Cardiovascular Health Study Collaborative Research Group. Frailty in older adults: evidence for a phenotype. J Gerontol A Biol Sci Med Sci 2001;56:M146–56.

17. Cacciatore F, Abete P, Mazzella F, et al. Frailty predicts long-term mortality in elderly subjects with chronic heart failure. Eur J Clin Invest 2005;35:723–30.

18. Chaudhry SI, McAvay G, Chen S, et al. Risk factors for hospital admission among older persons with newly diagnosed heart failure: findings from the Cardiovascular Health Study. J Am Coll Cardiol 2013;61:635–42.

19. Singh M, Stewart R, White H. Importance of frailty in patients with cardiovascular disease. Eur Heart J 2014;35:1726–31.

20. Brignole M, Auricchio A, Baron-Esquivias G, et al. 2013 ESC guidelines on cardiac pacing and cardiac resynchronization therapy: the Task Force on cardiac pacing and resynchronization therapy of the European Society of Cardiology (ESC): developed in collaboration with the European Heart Rhythm Association (EHRA). Eur Heart J 2013;34:2281–329.

21. Moss AJ, Hall WJ, Cannom DS, et al., for the MADIT-CRT Trial Investigators. Cardiac-resynchronization therapy for the prevention of heart-failure events. N Engl J Med 2009;361:1329–38.

22. Strauss DG, Selvester RH, Wagner GS. Defining left bundle branch block in the era of cardiac resynchronization therapy. Am J Cardiol 2011;107:927–34.

23. Zareba W, Klein H, Cygankiewicz I, et al., on behalf of the MADIT-CRT Investigators. Effectiveness of cardiac resynchronization therapy by QRS morphology in the Multicenter Automatic Defibrillator Implantation Trial-Cardiac Resynchronization Therapy (MADIT-CRT). Circulation 2011;123:1061–72.

24. Hamaker ME, Jonker JM, de Rooij SE, Vos AG, Smorenburg CH, van Munster BC. Frailty screening methods for predicting outcome of a comprehensive geriatric assessment in elderly patients with cancer: a systematic review. Lancet Oncol 2012;13:e437–44.

25. Velghe A, Petrovic M, De Buyser S, Demuynck R, Noens L. Validation of the G8 screening tool in older patients with aggressive haematological malignancies. Eur J Oncol Nurs 2014;18:645–8.

26. Kenis C, Decoster L, Van Puyvelde K, et al. Performance of two geriatric screening tools in older patients with cancer. J Clin Oncol 2014;32:19–26.

27. Belmin J, Pariel-Madjlessi S, Surun P, et al. The cognitive disorders examination (Codex) is a reliable 3-minute test for detection of dementia in the elderly (validation study on 323 subjects). Presse Med 2007;36:1183–90.

28. Folstein MF, Folstein SE, McHugh PR. "Mini-mental state": a practical method for grading the cognitive state of patients for the clinician. J Psychiatr Res 1975;12:189–98.

29. Yesavage JA, Sheikh JI. Geriatric Depression Scale (GDS): recent evidence and development of a shorter version. Clin Gerontol 1986;5:165–73.

30. Yesavage JA. Geriatric Depression Scale. Psychopharmacol Bull 1988;24:709–11.

31. Radloff LS. The CES-D scale: a self-report depression scale for research in the general population. Appl Psychol Meas 1977;1:385–401.

32. Epstein AE, DiMarco JP, Ellenbogen KA, et al. ACC/AHA/HRS 2008 guidelines for device-based therapy of cardiac rhythm abnormalities: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Writing Committee to Revise the ACC/AHA/NASPE 2002 Guideline Update for Implantation of Cardiac Pacemakers and Antiarrhythmia Devices) developed in collaboration with the American Association for Thoracic Surgery and Society of Thoracic Surgeons [published corrections appear in J Am Coll Cardiol 2009;53:1473 and J Am Coll Cardiol 2009;53:147]. J Am Coll Cardiol 2008;51:e1–62.

33. Goldenberg I, Vyas AK, Hall WJ, et al. Risk stratification for primary implantation of a cardioverter-defibrillator in patients with ischemic left ventricular dysfunction. J Am Coll Cardiol 2008;51:288–96.

34. Kydd AC, Khan FZ, Watson WD, Pugh PJ, Virdee MS, Dutka DP. Prognostic benefit of optimum left ventricular lead position in cardiac resynchronization therapy: follow-up of the TARGET Study Cohort (Targeted Left Ventricular Lead Placement to guide Cardiac Resynchronization Therapy). J Am Coll Cardiol HF 2014;2:205–12.

35. Vidal B, Sitges M, Marigliano A, et al. Optimizing the programation of cardiac resynchronization therapy devices in patients with heart failure and left bundle branch block. Am J Cardiol 2007;100:1002–6.

36. McNallan SM, Chamberlain AM, Gerber Y, et al. Measuring frailty in heart failure: a community perspective. Am Heart J 2013;166:768–74.

37. Sündermann SH, Dademasch A, Seifert B, et al. Frailty is a predictor of short- and mid-term mortality after elective cardiac surgery independently of age. Interact Cardiovasc Thorac Surg 2014;18:580–5.

38. Stortecky S, Schoenenberger AW, Moser A, et al. Evaluation of multidimensional geriatric assessment as a predictor of mortality and

cardiovascular events after transcatheter aortic valve implantation. J Am Coll Cardiol Intv 2012;5:489–96.

39. Fried LP, Ferrucci L, Darer J, Williamson JD, Anderson G. Untangling the concepts of disability, frailty, and comorbidity: implications for improved targeting and care. J Gerontol A Biol Sci Med Sci 2004;59:255–63.

40. Volpato S, Onder G, Cavalieri M, et al. Characteristics of nondisabled older patients developing new disability associated with medical illnesses and hospitalization. J Gen Intern Med 2007;22:668–74.

41. Lupón J, González B, Santaeugenia S, et al. Prognostic implication of frailty and depressive symptoms in an outpatient population with heart failure. Rev Esp Cardiol 2008;61:835–42.

42. Mlynarska A, Mlynarski R, Biernat J, Sosnowski M, Golba KS. Frailty syndrome in heart failure patients who are receiving cardiac resynchronization. Pacing Clin Electrophysiol 2016;39:370–4.

43. Dominguez-Rodriguez A, Abreu-Gonzalez P, Jimenez-Sosa A, et al. The impact of frailty in older patients with non-ischaemic cardiomyopathy after implantation of cardiac resynchronization therapy defibrillator. Europace 2015;17:598–602.

44. Lang PO, Michel JP, Zekry D. Frailty syndrome: a transitional state in a dynamic process. Gerontology 2009;55:539–49.

45. Molhoek SG, Bax JJ, Bleeker GB, et al. Comparison of response to cardiac resynchronization therapy in patients with sinus rhythm versus chronic atrial fibrillation. Am J Cardiol 2004;94:1506–9.

46. Delnoy PP, Ottervanger JP, Luttikhuis HO, et al. Comparison of usefulness of cardiac resynchronization therapy in patients with atrial fibrillation and heart failure versus patients with sinus rhythm and heart failure. Am J Cardiol 2007;99:1252–7.

47. Kiès P, Leclercq C, Bleeker GB, et al. Cardiac resynchronisation therapy in chronic atrial fibrillation: impact on left atrial size and reversal to sinus rhythm. Heart 2006;92:490–4.

48. Bergman H, Ferrucci L, Guralnik J, et al. Frailty: an emerging research and clinical paradigm: issues and controversies. J Gerontol A Biol Sci Med Sci 2007;62:731–7.

49. Køber L, Thune JJ, Nielsen JC, et al., for the DANISH Investigators. Defibrillator implantation in patients with nonischemic systolic heart failure. N Engl J Med 2016;375:1221–30.

KEY WORDS cardiac resynchronization therapy, elderly, frailty, heart failure

APPENDIX For a supplemental figure, please see the online version of this paper.