ESC HEART FAILURE
ESC Heart Failure 2020; **7**: 280–284
Published online 11 December 2019 in Wiley Online Library (wileyonlinelibrary.com) **DOI:** 10.1002/ehf2.12548

SHORT COMMUNICATION

Prognostic role of NYHA class in heart failure patients undergoing primary prevention ICD therapy

Sem Briongos-Figuero[1]*, Alvaro Estévez[1], M. Luisa Pérez[2], José B. Martínez-Ferrer[3], Enrique García[4], Xavier Viñolas[5], Ángel Arenal[6], Javier Alzueta[7] and Roberto Muñoz-Aguilera[1]

[1]*Hospital Universitario Infanta Leonor, Universidad Complutense de Madrid, Madrid, Spain;* [2]*Complejo Hospitalario Universitario A Coruña, A Coruña, Spain;* [3]*Hospital Universitario de Áraba, Álava, Spain;* [4]*Complejo Hospitalario Universitario de Vigo, Vigo, Spain;* [5]*Hospital Santa Creu i Sant Pau, Barcelona, Spain;* [6]*Hospital Universitario Gregorio Marañón, Madrid, Spain;* [7]*Hospital Virgen de la Victoria, Málaga, Spain*

Abstract

Aims Concerns about the prognostic value of NYHA functional class (FC) in heart failure (HF) patients carrying a prophylactic implantable cardioverter defibrillator (ICD) are still present. We aimed to compare whether mortality and arrhythmic risk were different, in a cohort of HF patients undergoing ICD-only implant, according to their FC.

Methods and results HF patients with left ventricle ejection fraction (LVEF) ≤35%, undergoing first prophylactic ICD-only implant were collected from a multicentre nationwide registry (2006–2015). Six hundred and twenty-one patients were identified (101 patients in NYHA I; 411 in NYHA II; 109 in NYHA III). After a mean follow-up of 4.4 years (±2.1), 126 patients died (20.3%). All-cause mortality risk was higher in symptomatic patients: 13.9% in NYHA I patients, 18.3% in NYHA II patients (HR: 1.8, 95% CI 1.1–3.2), and 32.9% in NYHA III patients (HR: 3.9, 95% CI 2.1–7.3). Seventy-eight out of all deaths were due to cardiovascular causes (12.6%). Cardiovascular mortality risk was also higher in symptomatic patients: 6.9% in NYHA I patients, 11% in NYHA II patients (HR: 2.2, 95% CI 1.1–4.9), and 23.9% in NYHA III (HR: 5.5, 95% CI 2.4–12.7). One hundred and seventeen patients received a first appropriate ICD therapy (19.4%). Arrhythmia free survival did not differ among study groups [20.8% in NYHA I patients, 18.7% in NYHA II (HR: 1.1, 95% CI 0.6–1.7) and 20.8% in NYHA III patients (HR: 1.3, 95% CI 0.7–2.5)]. NYHA class independently predicted cardiovascular mortality (NYHA III vs. NYHA I: HR, 4.7; 95% CI, 1.7–12.8, P = 0.002; NYHA II vs. NYHA I: HR, 2.1, 95% CI, 1.0–5.6, P = 0.05) but not all-cause death (NYHA III vs. NYHA I: HR: 1.8, 95% CI 0.8–3.9, P = 0.11; NYHA II vs. NYHA I: HR, 1.1, 95% CI 0.6–2.2, P = 0.71;). Atrial fibrillation, chronic kidney disease, and diabetes emerged as predictors of both all-cause death [(HR: 1.8, 95% CI 1.2–2.8, P = 0.005), (HR: 2.2, 95% CI 1.4–3.4, $P < 0.001$), (HR: 2.0, 95% CI 1.3–3.1, P = 0.001), respectively] and cardiovascular mortality [(HR: 1.8, 95% CI 1.1–3.1, P = 0.02), (HR: 3.1, 95% CI 1.8–5.4, $P < 0.001$), (HR: 1.7, 95% CI 1.1–3, P = 0.032), respectively].

Conclusions Mortality in HF patients undergoing prophylactic ICD implantation was higher in symptomatic patients. NYHA functional class along with other comorbidities might be helpful to identify a subgroup of ICD carriers with poorer prognosis and higher risk of cardiovascular death.

Keywords Prognosis; NYHA functional class; Implantable cardioverter defibrillator

Received: 27 May 2019; Revised: 6 September 2019; Accepted: 29 September 2019
**Correspondence to: Sem Briongos Figuero, Hospital Infanta Leonor, Cardiology Department, Madrid, Spain, Gran Vía del Este, Madrid, 28030. Tel: 0034686393592. Email: semdoc@hotmail.com*

Background

Primary prevention implantable cardioverter defibrillator (ICD) improves survival by reducing sudden cardiac death (SCD) in heart failure (HF) patients with impaired left ventricular ejection fraction (LVEF).[1,2] The New York Heart Association (NYHA) class subjectively estimates functional capacity of HF patients, and therefore, it has been widely used to select ICD candidates in randomized clinical trials.[3–6] Nevertheless, the European and the American practice guidelines show some disagreement, especially regarding the role of ICD therapy in patients with asymptomatic HF (NYHA Class I) and

reduced LVEF.[7–9] A pooled analysis of four randomized trials demonstrated that ICD-only therapy was effective in reducing mortality in NYHA Class II patients, but only a trend toward reducing mortality in the group of NYHA Class III patients was found.[10] Another recent study derived from MADIT II trial population, proved that prophylactic ICD improved survival in patients with previous myocardial infarction and LVEF $<30\%$, regardless of NYHA class.[11] There are few studies reporting the prognostic implication of NYHA class in a real-world setting.[12]

Aims

We aimed to compare survival and arrhythmic risk among different NYHA class subgroups of HF patients with reduced LVEF receiving a prophylactic ICD in a real-life cohort of contemporary patients.

Methods

The present study was developed within the UMBRELLA observational study (ClinicalTrials.gov/NCT01561144), which is a multicenter and voluntary registry promoted by Medtronic Iberica that includes patients with Medtronic ICDs and follows them by remote monitoring (CareLink®). The institutional review board of the participating centers approved patient inclusion and all patients provided informed consent.

All HF patients with LVEF $\leq 35\%$, undergoing their first prophylactic ICD-only implant were selected. People included in the registry after a replacement procedure were excluded to avoid retrospective data collection regarding outcomes. To achieve a homogeneous sample and to avoid the bias generated by improving LVEF, cardiac resynchronization therapy (CRT) carriers were excluded too.

The entire cohort was divided according to NYHA class at implant into three study groups: asymptomatic (NYHA I), mildly symptomatic patients (NYHA II), and severely symptomatic (NYHA III) patients. The prognostic role of NYHA class was studied with three different endpoints: (i) all-cause mortality; (ii) cardiovascular mortality defined as any death due to proximate cardiac cause (e.g. myocardial infarction, HF) or to non-coronary vascular causes such as cerebrovascular disease, pulmonary embolism, aortic dissection, or other vascular diseases; and (iii) arrhythmia free survival (as a surrogate marker of SCD) defined as survival free of first appropriate ICD therapy delivered in ventricular fibrillation (VF) detection zone or fast ventricular tachycardia zone when programmed within VF zone. Follow-up ran from ICD implant to data censored time-point (September 2017).

Baseline characteristics were collected from the mandatory baseline form at implant procedure. The UMBRELLA protocol required every centre to collect mortality data in specific sheets and to keep them updated at least annually. The principal investigator of each participating hospital classified every death following the definitions described before, according to medical records. Tachyarrhythmia detection and ICD settings were programmed at the discretion of local physicians. Data regarding the arrhythmic events and those related to ICD programming were collected by remote monitoring. Each arrhythmic event was reviewed in a blind manner by a committee of experts and was then classified according to the type of arrhythmia and the effectiveness of the delivered therapy.

Continuous variables were expressed as mean ± standard deviation (SD) and categorical data as numbers and percentages. Continuous variables were compared using the Student's *t*-test when normally distributed and the Mann–Whitney *U* test when not. Categorical variables were compared using χ^2, or the Fisher's exact test when the conditions required for the former test were not met. Time to first appearance of the study endpoints was described using Kaplan–Meier survival curves and significance was assessed by the log-rank test. A univariable Cox regression analysis was first performed to determine which parameters were significantly related to the study endpoints. After testing for proportional hazard assumptions, Cox models were fitted and hazard ratios (HRs) with 95% confidence intervals (CIs) were computed. Then a stepwise multivariable Cox proportional analysis was performed including those variables with clinical and biological plausibility that returned a *P* value <0.20 after univariable Cox regression analysis. Statistical analysis was performed from the binomial distribution using the Statistical Package for Social Sciences (version 20.0, SPSS, Inc., Chicago, IL, USA). A *P* value below 0.05 was considered significant for all tests.

Results

We analysed 621 patients (2006–2015) undergoing their first prophylactic ICD implant (61.1 ± 11.4 years; 87.3% male). The distribution of study groups was as follows: 101 patients were in NYHA I; 411 patients were in NYHA II; and the remaining 109 cases were in NYHA III. More symptomatic patients were older, had higher prevalence of atrial fibrillation (AF) and chronic kidney disease (CKD), and they also had lower LVEF (*Table 1*).

After a mean follow-up of 4.4 years (±2.1), 126 patients died (event rate: 20.3%). All-cause mortality was higher in patients with NYHA Class II and III compared to asymptomatic patients (*Figure 1*A). All-cause death rates were 13.9% in NYHA I patients, 18.3% in NYHA II patients (HR: 1.8, 95% CI

Table 1 Baseline characteristics

	Overall (n = 621)	NYHA I (n = 101)	NYHA II (n = 411)	NYHA III (n = 109)	P value
Age (years), mean ± SD	61.1 ± 11.4	57.6 ± 13.5	61.7 ± 10.7	61.8 ± 11.4	0.004
Female gender, *n* (%)	79 (12.7)	9 (8.9)	49 (11.9)	21 (19.3)	0.056
Diabetes, *n* (%)	220 (36.2)	29 (29.6)	149 (36.8)	42 (40.4)	0.259
Hypertension, *n* (%)	366 (59.7)	53 (53)	247 (60.8)	66 (62.3)	0.305
Smoker, *n* (%)	284 (50.5)	40 (48.2)	196 (51.4)	48 (49)	0.818
Hypercholesterolemia, *n* (%)	343 (57.7)	49 (51.6)	238 (60.6)	56 (54.4)	0.200
Stroke, *n* (%)	35 (6.4)	8 (8.8)	18 (4.9)	9 (10.1)	0.113
COPD, *n* (%)	79 (12.7)	10 (9.9)	49 (11.9)	20 (18.3)	0.259
Chronic kidney disease*, *n* (%)	101 (16.8)	9 (9.3)	68 (17)	24 (23.3)	0.030
Ischemic aetiology, *n* (%)	439 (70.7)	72 (71.3)	295 (71.8)	72 (66.1)	0.501
Atrial fibrillation, *n* (%)	168 (27.5)	19 (19)	114 (28.1)	35 (33.3)	0.064
LBBB, *n* (%)	91 (14.7)	17 (16.8)	61 (14.8)	13 (11.9)	0.594
Previous HF admission, *n* (%)	594 (95.8)	75 (74.3)	411 (100)	109 (100)	0.001
QRS duration (ms), mean ± SD	109.8 ± 25.3	111.4 ± 26.4	109.3 ± 24.2	110.8 ± 28.2	0.625
LVEF (%), mean ± SD	26.6 ± 5.4	27.5 ± 4.8	27.1 ± 5.3	24.9 ± 5.7	0.003
Betablockers, *n* (%)	572 (92.1)	91 (90.1)	381 (92.7)	100 (91.7)	0.777
ACEi/ARB, *n* (%)	539 (86.8)	86 (85.1)	358 (87,1)	95 (87.1)	0.916
Aldosterone antagonists, *n* (%)	374 (60.2)	50 (49.3)	247 (60.1)	77 (70.9)	0.024

ACEi, angiotensin-converting enzyme inhibitors; ARB, angiotensin II receptor blockers; COPD, chronic obstructive pulmonary disease; HF, heart failure; LBBB, left bundle branch block; LVEF, left ventricular ejection fraction; ms, milliseconds; SD, standard deviation.
*Glomerular filtration rate ($<$ 60 ml/min/1.73 m^2).

1.1–3.2), and 32.9% in NYHA III patients (HR: 3.9, 95% CI 2.1–7.3) Seventy-eight out of 126 deaths were related to cardiovascular causes (overall event rate: 12.6%). Symptomatic patients also showed a higher risk of cardiovascular death compared to NYHA I patients (*Figure 1*B). Cardiovascular mortality rates were 6.9% in NYHA I patients, 11% in NYHA II patients (HR: 2.2, 95% CI 1.1–4.9), and 23.9% in NYHA III (HR: 5.5, 95% CI 2.4–12.7) Multivariable regression model for both mortality endpoints included NYHA class, age, gender, hypertension, diabetes, stroke, previous HF, AF, CKD, chronic obstructive pulmonary disease (COPD), LVEF, and betablocker therapy as covariates. After multivariable analysis, worse NYHA class independently predicted cardiovascular mortality (NYHA III vs. NYHA I: HR, 4.7; 95% CI, 1.7–12.8, P = 0.002; NYHA II vs. NYHA I: HR, 2.1, 95% CI, 1.0–5.6, P = 0.05) but not all-cause death (NYHA III vs. NYHA I: HR: 1.8, 95% CI 0.8–3.9, P = 0.11; NYHA II vs. NYHA I: HR, 1.1, 95% CI 0.6–2.2, P = 0.71;). Independent predictors for all-cause mortality were age (HR: 1.0, 95% CI 1.0–1.1, P = 0.008), diabetes (HR: 2.0, 95% CI 1.3–3.1, P = 0.001), AF (HR: 1.8, 95% CI 1.2–2.8, P = 0.005), CKD (HR: 2.2, 95% CI 1.4–3.4, $P < 0.001$), and COPD (HR: 1.9, 95% CI 1.2–3.1, P = 0.008). Moreover, AF (HR: 1.8, 95% CI 1.1–3.1, P = 0.02), CKD (HR: 3.1, 95% CI 1.8–5.4, $P < 0.001$), and diabetes (HR: 1.7, 95% CI 1.1–3, P = 0.032) were also predictors for cardiovascular mortality.

A single-chamber ICD was implanted in nearly two-thirds of the entire cohort (n = 411; 66.2%). The ICD settings of the whole population and study groups are depicted in *Table 2*. A delayed detection time (30 of 40 intervals) was only programmed in 34.8% of patients, what is probably related to the 9-year period of data collection in which scientific evidence was continuously evolving. No differences regarding ICD programming were found among study groups, except for a trend toward longer detection time in

Figure 1 Cumulative incidence for (A) all-cause mortality, (B) cardiovascular mortality and (C) first appropriate implantable cardioverter defibrillator therapy within ventricular fibrillation zone according to NYHA functional class. P values correspond to log-rank test.

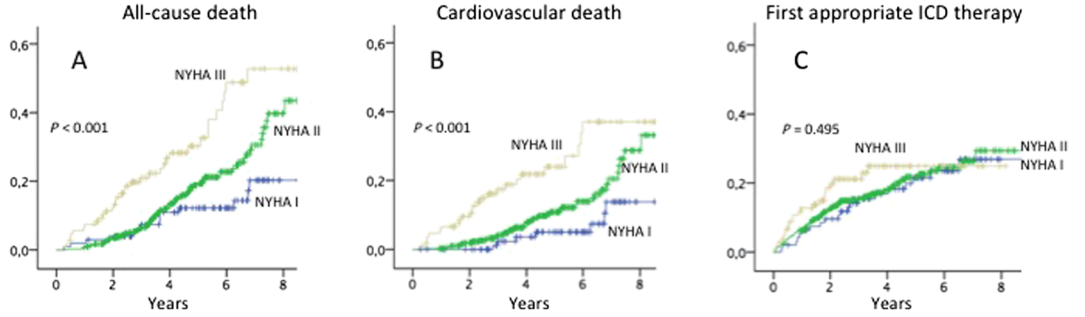

Table 2 ICD type and programming

	Overall (n = 621)	NYHA I (n = 101)	NYHA II (n = 411)	NYHA III (n = 109)	P value
Single chamber ICD, n (%)	210 (66.2)	58 (57.4)	280 (68.1)	73 (67)	0.123
VF detection zone cut-off, mean ± SD	304.7 ± 17.9	307.1 ± 16.8	303.7 ± 18.1	306,7 ± 17.8	0.111
ATP*, n (%)	585 (96.7)	94 (96.9)	390 (97.3)	101 (94.4)	0.335
NID, n (%)	387 (65.1)	71(75.5)	253 (63.9)	62 (60.2)	0.054
• <30 of 40					
• >30 of 40	207 (34.9)	23 (24.5)	143 (36.1)	41 (39.8)	
FVT programmed**, n (%)	174 (29.4)	20 (21.3)	109 (27.5)	45 (43.7)	0.342
FVT detection zone cut-off (ms), mean ± SD	267.4 ± 26.2	269.5 ± 22.8	269 ± 28.1	262.6 ± 21.9	0.113
VT zone programmed, n (%)	311 (52.4)	40 (42.6)	217 (54.8)	54 (52.4)	0.257
VT detection zone cut-off (ms), mean ± SD	356.7 ± 20.7	357.9 ± 17.8	355.7 ± 19.3	359.1 ± 27.6	0.127

ATP, anti-tachycardia pacing; ICD, implantable cardioverter defibrillator; FVT, fast ventricular tachycardia; ms, milliseconds; NID, number of interval detection; SD, standard deviation; VF, ventricular fibrillation; VT, ventricular tachycardia.
*Before charging.
**Within VF detection zone.

more symptomatic patients. One hundred and seventeen patients received a first appropriate ICD therapy (19.4%). The majority of the arrhythmic episodes were due to sustained monomorphic ventricular tachycardia (VT) (n = 84, 71.8%), whereas sustained polymorphic VT/VF accounted for the rest episodes (n = 33, 28.2%). The mean tachycardia cycle length of these episodes was 258 ± 37.3 ms. Arrhythmia free survival was not different among study groups [20.8% in NYHA I patients, 18.7% in NYHA II (HR: 1.1, 95% CI 0.6–1.7) and 20.8% in NYHA III patients (HR: 1.3, 95% CI 0.7–2.5); *Figure 1*C]. Multivariable regression analysis for first appropriate ICD therapy included diabetes, COPD, AF, LVEF, VF detection zone cut-off, and number of interval detection within VF zone as covariates. After adjustment, AF was the only variable independently related to an increased risk of first appropriate ICD therapy (HR: 1.8, 95 % CI 1.2–2.6, P = 0.003).

Conclusions

Our study was performed including ischemic and non-ischemic daily clinical patients and it focused the analysis on the prognosis that NYHA class has in a HF cohort of prophylactic ICD-only patients. Previous reports dealing with this topic have excluded asymptomatic patients[10] and patients with non-ischemic HF.[11] Furthermore, previous observational studies did not report the ICD settings, and therefore, no programming parameter was considered in the analysis of the study endpoints. The main limitation of our study is the observational nature and the potential for study population bias, especially after exclusion of CRT carriers. Moreover the lack of a control group composed of patients without ICD, may limit the study conclusions.

In HF patients with reduced LVEF undergoing a prophylactic ICD-only implant, a worse NYHA class was independently related to an increased risk of death from cardiovascular origin. Furthermore, the risk of life threatening ventricular arrhythmia requiring ICD interventions was not different across all ranges of NYHA FC. Nevertheless, we cannot dismiss that an increased risk of death in more symptomatic patients might hamper the possibility of suffering an arrhythmic event. Increasing comorbidities such as a poorer NYHA class, AF, diabetes, or CKD might help physicians to identify a subgroup of ICD carriers with worse prognosis and higher mortality.

Acknowledgment

To the Spanish SCOOP team.

Conflict of interest

None declared.

Funding

No funding was received for this study.

References

1. Stavrakis S, Asad Z, Reynolds D. Implantable cardioverter defibrillators for primary prevention of mortality in patients with nonischemic cardiomyopathy: a meta-analysis of randomized controlled trials. *J Cardiovasc Electrophysiol* 2017**28**: 659–665.
2. Theuns DAMJ, Smith T, Hunink MGM, Bardy GH, Jordaens L. Effectiveness of prophylactic implantation of cardioverter-defibrillators without cardiac resynchronization therapy in patients with ischaemic or non-ischaemic heart disease: a systematic review and meta-analysis. *Europace England* 2010; **12**: 1564–1570.

3. Moss AJ, Zareba W, Hall WJ, Klein H, Wilber DJ, Cannom DS, Daubert JP, Higgins SL, Brown MW, Andrews ML. Prophylactic implantation of a defibrillator in patients with myocardial infarction and reduced ejection fraction. *N Engl J Med* 2002; **346**: 877–883.
4. Bardy GH, Lee KL, Mark DB, Poole JE, Packer DL, Boineau R, Domanski M, Troutman C, Anderson J, Johnson G, McNulty SE, Clapp-Channing N, Davidson-Ray LD, Fraulo ES, Fishbein DP, Luceri RM, Ip JH. Amiodarone or an implantable cardioverter-defibrillator for congestive heart failure. *N Engl J Med* 2005; **352**: 225–237.
5. Buxton AE, Lee KL, Fisher JD, Josephson ME, Prystowsky EN, Hafley G. A randomized study of the prevention of sudden death in patients with coronary artery disease. Multicenter Unsustained Tachycardia Trial Investigators. *N Engl J Med* 1999; **341**: 1882–1890.
6. Moss AJ, Hall WJ, Cannom DS, Daubert JP, Higgins SL, Klein H, Levine JH, Saksena S, Waldo AL, Wilber D, Brown MW, Heo M. Improved survival with an implanted defibrillator in patients with coronary disease at high risk for ventricular arrhythmia. Multicenter Automatic Defibrillator Implantation Trial Investigators. *N Engl J Med* 1996; **335**: 1933–1940.
7. Priori SG, Blomstrom-Lundqvist C, Mazzanti A, Blom N, Borggrefe M, Camm J, Elliott PM, Fitzsimons D, Hatala R, Hindricks G, Kirchhof P, Kjeldsen K, Kuck K-H, Hernandez-Madrid A, Nikolaou N, Norekval TM, Spaulding C, Van Veldhuisen DJ. 2015 ESC guidelines for the management of patients with ventricular arrhythmias and the prevention of sudden cardiac death: the task force for the management of patients with ventricular arrhythmias and the prevention of sudden cardiac death of the Europe. *Eur Heart J* 2015; **36**: 2793–2867.
8. Al-Khatib SM, Stevenson WG, Ackerman MJ, Bryant WJ, Callans DJ, Curtis AB, Deal BJ, Dickfeld T, Field ME, Fonarow GC, Gillis AM, Granger CB, Hammill SC, Hlatky MA, Joglar JA, Kay GN, Matlock DD, Myerburg RJ, Page RL. 2017 AHA/ACC/HRS guideline for management of patients with ventricular arrhythmias and the prevention of sudden cardiac death: a report of the American college of cardiology/american heart association task force on clinical practice guidelines and the HEA. *Hear Rhythm* 2018; **15**: e73–e189.
9. Ponikowski P, Voors AA, Anker SD, Bueno H, Cleland JGF, Coats AJS, Falk V, Gonzalez-Juanatey JR, Harjola V-P, Jankowska EA, Jessup M, Linde C, Nihoyannopoulos P, Parissis JT, Pieske B, Riley JP, Rosano GMC, Ruilope LM, Ruschitzka F, Rutten FH, van der Meer P. 2016 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure: the task force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC). Developed with the special contribution. *Eur J Heart Fail* 2016; **18**: 891–975.
10. Friedman DJ, Al-Khatib SM, Zeitler EP, Han J, Bardy GH, Poole JE, Bigger JT, Buxton AE, Moss AJ, Lee KL, Steinman R, Dorian P, Cappato R, Kadish AH, Kudenchuk PJ, Mark DB, Inoue LYT, Sanders GD. New York Heart Association class and the survival benefit from primary prevention implantable cardioverter defibrillators: a pooled analysis of 4 randomized controlled trials. *Am Heart J* 2017; **191**: 21–29.
11. Biton Y, Rosero S, Moss A, Zareba W, Kutyifa V, Baman J, Barsheshet A, McNitt S, Polonsky B, Goldenberg I. Long-term survival with implantable cardioverter-defibrillator in different symptomatic functional classes of heart failure. *Am J Cardiol* 2018; **121**: 615–620.
12. Providência R, Boveda S, Defaye P, Segal O, Algalarrondo V, Sadoul N, Lambiase P, Piot O, Klug D, Perier M-C, Bouzeman A, Barra S, Bories M-C, Gras D, Fauchier L, Bordachar P, Babuty D, Deharo J-C, Leclercq C, Marijon E, DAI-PP Investigators. Outcome of primary prevention implantable cardioverter defibrillator therapy according to New York Heart Association functional classification. *Am J Cardiol* 2016; **118**: 1225–1232.