ESC HEART FAILURE
ESC Heart Failure 2021; **8**: 2591–2596
Published online 1 May 2021 in Wiley Online Library (wileyonlinelibrary.com) **DOI:** 10.1002/ehf2.13340

SHORT COMMUNICATION

Wearable cardioverter-defibrillator: friend or foe in suspected myocarditis?

Florian Blaschke[1,3*†], Philipp Lacour[1,3†], Phi Long Dang[1], Abdul Shokor Parwani[1,3], Felix Hohendanner[1,7], Thula Walter[4], Karin Klingel[5], Uwe Kühl[1], Frank R. Heinzel[1,3], Mohammad Sherif[1,3], Leif-Hendrik Boldt[1,3], Burkert Pieske[1,6,7] and Carsten Tschöpe[1,2,3,7]

[1]*Department of Internal Medicine and Cardiology, Charité – Universitätsmedizin Berlin, Campus Virchow-Klinikum, Augustenburger Platz 1, Berlin, 13353, Germany;* [2]*BCRT – Berlin Institute of Health Center for Regenerative Therapies and Department of Cardiology (Virchow Klinikum), Charité – Universitätsmedizin Berlin and German Centre for Cardiovascular Research (DZHK) – Partner Site, Berlin, Germany;* [3]*DZHK (German Centre for Cardiovascular Research) – Partner Site, Berlin, Germany;* [4]*Department of Radiology, Charité – University Medicine Berlin, Berlin, Germany;* [5]*Department of Cardiopathology, Institute for Pathology and Neuropathology, University Hospital Tuebingen, Tuebingen, Germany;* [6]*Department of Internal Medicine and Cardiology, German Heart Center Berlin, Berlin, Germany; and* [7]*Berlin Institute of Health (BIH), Berlin, Germany*

Abstract

Aim Wearable cardioverter defibrillator (WCD, LifeVest, and Zoll) therapy has become a useful tool to bridge a temporarily increased risk for sudden cardiac death. However, despite extensive use, there is a lack of evidence whether patients with myocarditis and impaired LVEF may benefit from treatment with a WCD.

Methods and results We conducted a single-centre retrospective observational study analysing patients with a WCD prescribed between September 2015 and April 2020 at our institution. In total, 135 patients were provided with a WCD, amongst these 76 patients (mean age 48.9 ± 13.7 years; 84.2% male) for clinically suspected myocarditis. Based on the results of the endomyocardial biopsy and, where available cardiac magnetic resonance imaging, 39 patients (51.3%) were diagnosed with myocarditis and impaired LVEF and 37 patients (48.7%) with dilated cardiomyopathy (DCM) without evidence of cardiac inflammation. The main immunohistopathological myocarditis subtype was lymphocytic myocarditis in 36 (92.3%) patients, and four patients (10.3%) of this group had an acute myocarditis. Three patients had cardiac sarcoidosis (7.7%). Ventricular tachycardia occurred in seven myocarditis (in total 41 VTs; 85.4% non-sustained) and one DCM patients (in total one non-sustained ventricular tachycardia). Calculated necessary WCD wearing time until ventricular tachycardia occurrence is 86.41 days in myocarditis compared with 6.46 years in DCM patients.

Conclusions Our data suggest that myocarditis patients may benefit from WCD therapy. However, as our study is not powered for outcome, further randomized studies powered for the outcome morbidity and mortality are necessary.

Keywords Myocarditis; Arrhythmias; Wearable cardioverter defibrillator; Endomyocardial biopsy

Received: 26 June 2020; Revised: 22 December 2020; Accepted: 29 March 2021
**Correspondence to: Florian Blaschke, Department of Internal Medicine and Cardiology, Charité – Universitätsmedizin Berlin, Campus Virchow-Klinikum, Augustenburger Platz 1, 13353 Berlin, Germany. Phone: ++49-30-450-653635; Fax: ++49-30-450-7553635. Email: florian.blaschke@charite.de*
†These authors contributed equally to this work.

Introduction

Over the last years, wearable cardioverter defibrillator (WCD, LifeVest, and Zoll) therapy has become a useful tool to bridge a temporarily increased risk for sudden cardiac death (SCD). According to the AHA/ACC/HRS guidelines, WCD therapy has a class IIb indication in patients who are at high risk for sudden death but do not meet other immediate indications for ICD therapy.[1] The first study suggesting efficacy of WCD therapy included patients with congestive heart failure in the WEAR-IT (wearable cardioverter defibrillator investigational trial) and patients post-MI or CABG at high risk for SCD in the BIRAOD (bridge to ICD in patients at risk of arrhythmic death) studies.[2] Currently, the largest group of patients with WCD therapy are patients with an LVEF ≤35% post-myocardial infarction or patients with newly diagnosed cardiomyopathy still undergoing optimal medical therapy within 90 days after diagnosis.

Despite extensive use, there is a lack of evidence whether patients with myocarditis (MC) and impaired LVEF may benefit from treatment with a WCD. Most WCD studies included only a small subgroup of patients (<10) with myocarditis.[3,4] The largest report on a subgroup of MC patients included 595 patients[5]; however, these data were retrieved from a registry maintained by the manufacturer of the WCD (Zoll, Pittsburgh, PA) with limited information regarding clinical work-up and outcome.

Myocarditis is a complex inflammatory disease of the myocardium, usually secondary to viral infection or immune dysregulating phenomena. The acute phase of viral MC is characterized by pathognomonic myocyte necrosis induced by virus replication. A subsequent activation of a cascade of humoral and cellular immunologic processes independent of myocardial genome presence may result in chronic post-infectious MC.[6] Ventricular arrhythmias were reported in patients with both acute and chronic stages of MC often independent of impaired LVEF.[7] This issue is particular relevant, as ventricular arrhythmias are a significant cause of death especially in young MC patients.[8]

Methods

We conducted a single-centre retrospective observational study analysing patients with a WCD prescribed between September 2015 and April 2020 at our institution. The study protocol was approved by the human ethics committee at our institution (ethic application number: EA1/356/16) and is in accordance with the 1975 Declaration of Helsinki. In total, 135 patients were provided with a WCD, amongst these 76 patients (mean age 48.9 ± 13.7 years; 84.2% male) for clinically suspected MC. The main criterion for WCD prescription was a severely impaired left ventricular ejection fraction (LVEF ≤35%) at baseline. Out of 76 patients with clinically suspected MC, seven patients were prescribed a WCD despite an LVEF >35%. The reasons for WCD prescription in these cases were non-sustained VTs (four patients) or sustained VTs (two patients) and severe borderline myocarditis (one patient). Baseline evaluation in all patients included transthoracic echocardiography, 12-lead electrocardiogram, and endomyocardial biopsy (EMB) as gold standard for the definite diagnosis of MC.[9,10] Coronary angiography was performed in all patients. In addition, baseline laboratory values with cardiac biomarkers (high-sensitive cardiac troponin and N-terminal pro-B-type natriuretic peptide) and inflammatory markers (leucocytes and C-reactive protein) were obtained in most cases. Cardiac magnetic resonance imaging (CMR) was performed in 56.6% of the cases and analysed based on the Lake–Louise criteria including native T1 and T2 mapping.[11] Follow-up data were collected both through outpatient clinic visits as well as during re-admission to the hospital. EMB-proved MC was defined by histological, immunological, and immunohistochemical criteria.[9]

Results

Based on the results of the EMB and, where available CMR, 39 patients (51.3%) were diagnosed with MC and impaired LVEF and 37 patients (48.7%) with dilated cardiomyopathy (DCM) without evidence of cardiac inflammation. Baseline characteristics of MC versus DCM patients are shown in *Table 1*. There were no significant differences in age, gender, medical history, clinical presentation, and echocardiographic parameters between the two groups. However, ST-segment elevations were significantly more common in the MC compared to the DCM group (P = 0.038). Elevations in troponin T were more common in MC compared with DCM patients without achieving statistical significance. Mean LVEF at baseline did not differ between MC (25.6% ± 11.7) and DCM patients (25.1% ± 8.72) and was severely impaired in 33 MC (84.5%) and 35 DCM (94.6%) patients. At the time of WCD prescription, 27 patients showed ventricular arrhythmia: non-sustained ventricular tachycardia in 11 MC and 13 DCM patients (P = 0.516) and sustained ventricular tachycardia in two MC and one DCM patients (P = 0.587).

The main immunohistopathological MC subtype was lymphocytic MC in 36 (92.3%) patients, and four patients (10.3%) of this group had an acute MC (clinical onset of symptoms <30 days). Three patients had cardiac sarcoidosis (7.7%). Myocardial specimens were analysed for the presence of viral genomes of enteroviruses, adenoviruses, cytomegalovirus, Epstein–Barr virus (EBV), human herpesvirus 6 (HHV6), parvovirus B19 (B19V), and Coxsackie B virus. Testing of blood samples ruled out systemic virus infections. As it is well known that herpes viruses and B19V are wildly distributed even in healthy hearts or other cardiac pathologies, we found a viral genome presence of HHV6, EBV, or B19V with low copy numbers in 66% of the MC and 64.9% of the DCM patients.[12,13] In the absence of viral genome, MC patients were treated with immunosuppressive therapy, either prednisolone alone, prednisolone and azathioprine, or a combination of prednisolone, azathioprine, and cyclosporine.[13] All patients were treated with optimized guideline-directed heart failure therapy. Pharmacological antiarrhythmic treatment at discharge consisted of beta-blocker (93.4% of all patients) and amiodarone (7.9% of all patients). Patients with MC were more likely to be treated with beta-blockers compared with DCM patients (100% vs. 86.5%, P = 0.02). There was no significant difference in the use of amiodarone between the two groups. Late gadolinium enhancement (LGE) at CMR was found in 44.2% (n = 19) of all CMR scans.

Table 1 Characteristics of the patient population

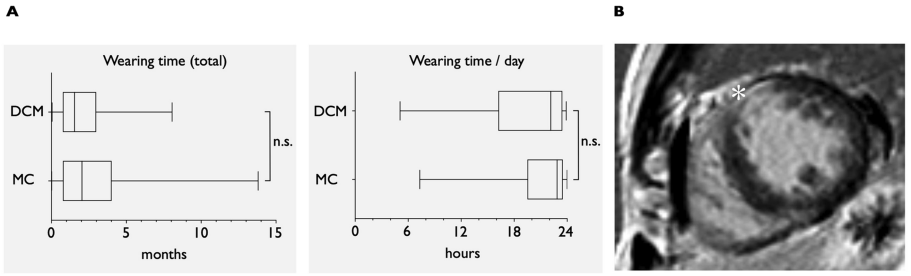
Baseline characteristics of the study population	Myocarditis (n = 39)	Dilated cardiomyopathy (n = 37)	P value
Demographics			
Age (years)	47.5 ± 14.7	50.5 ± 12.6	0.326
Male gender	34	30	0.466
Medical history			
CAD	2	3	0.600
Diabetes mellitus	4	4	0.937
Hypertension	16	11	0.304
Hyperlipoproteinaemia	8	6	0.629
Clinical presentation			
Pericardial chest pain	5	6	0.929
Fever	3	2	0.688
HR (b.p.m.)	82.5 ± 17.5	81.3 ± 21.9	0.539
Medication			
ACE inhibitor	21	13	0.101
ARB	10	8	0.680
Beta-blocker	39	32	0.018
Loop diuretics	35	26	0.052
Digitalis	3	2	0.688
ARNI	8	15	0.057
MRAs	21	17	0.491
Amiodarone	5	1	0.102
Ivabradine	5	4	0.786
ECG			
PQ (ms)	161.1 ± 26.9	168.6 ± 27.5	0.291
QRS (ms)	117.1 ± 27.2	119.1 ± 34.6	0.708
QTc (ms)	461.8 ± 34.3	454.6 ± 55.8	0.492
ST segment elevation	4	0	0.038
ST segment depression	0	0	-
T wave inversion	13	12	0.741
Baseline laboratory values			
Troponin T (ng/L)	193.4 ± 485.5	39.1 ± 35.0	0.375
CK (U/L)	121.6 ± 98.5	159.0 ± 132.1	0.195
CK MB (U/L)	20.5 ± 7.6	19.9 ± 8.2	0.824
NT-proBNP (ng/L)	4040.5 ± 4629.9	3896.5 ± 4921.5	0.398
CRP (mg/L)	20.4 ± 37.8	12.7 ± 16.9	0.723
Leukozyten (per nL)	8.8 ± 2.8	8.5 ± 2.7	0.589
Echocardiographic parameters			
LVEF (%)	25.6 ± 11.7	25.1 ± 8.2	0.623
LVEDD (mm)	61.8 ± 9.1	63.1 ± 7.7	0.501
LVESD (mm)	54.9 ± 7.4	49.7 ± 4.8	0.137
Pericardial effusion	6	7	0.639

Values are given as n, or mean ± SD.
ACE, angiotensin converting enzyme; ARB, angiotensin receptor blocker; ARNI, angiotensin receptor neprilysin inhibitor; CAD, coronary artery disease; CRP, C-reactive protein; HR, heart rate; LVEDD, left ventricular enddiastolic diameter; LVEF, left ventricular ejection fraction; LVESD, left ventricular endsystolic diameter; MRAs, mineralocorticoid receptor antagonist; NT-proBNP, N-terminal pro B-type natriuretic peptide; SD, standard deviation.

Mean WCD wearing time was 90.8 ± 95.3 days (daily use 20.5 ± 4.7 h) in the MC and 63.7 ± 55.7 days (daily use 19.2 ± 5.8 h) in the DCM group (P = 0.326 and 0.289, respectively) (*Figure 1A*). Ventricular tachycardia occurred in seven MC (in total 41 VTs; 85.4% non-sustained) and one DCM patients (in total one non-sustained VT) (*Figure 1C*). Calculated necessary WCD wearing time until VT occurrence is 86.4 days in MC compared with 6.5 years in DCM patients. Noteworthy, no malignant ventricular arrhythmic events occurred in patients in the absence of LGE in CMR scan. One MC patient received two appropriate shocks after a WCD wearing time of 27 days. The patient was admitted to the hospital, and a cardiac resynchronization device with a defibrillator function (CRT-D) was implanted. Ventricular arrhythmic episodes in MC patients showed no significant association with either the histopathological type of MC, detection of viral DNA in the heart, with QRS duration >120 ms at baseline ECG, or LVEF. In addition, immunosuppressive drug therapy in MC patients had no effect on the onset of ventricular tachycardias (P = 0.83). In relation to the entire study population, antiarrhythmic drug therapy at discharge had no statistically relevant influence on the incidence of ventricular tachycardias (P = 0.43). During WCD therapy, mean LVEF improved to 38.8% ± 12.8 in MC and 32.4% ± 10.1 in the DCM group (P = 0.034). Ventricular function improved in MC patients regardless of whether patients received immunosuppressive

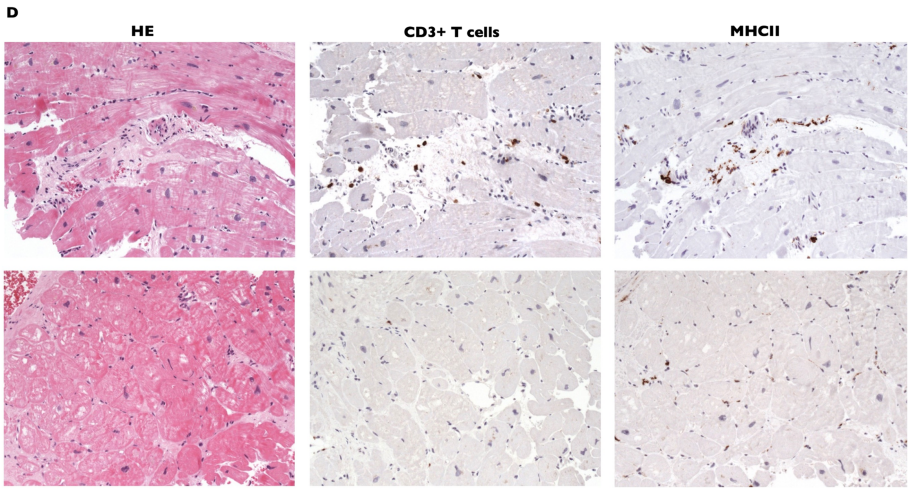
DOI: 10.1002/ehf2.13340

Figure 1 (A) Box-and-whisker plot for total WCD wearing time and wearing time per day. Vertical lines within boxes denote median values. The whiskers and each half of the box represent 25% of the data. (B) Short-axis cardiac magnetic resonance (late gadolinium enhancement) of a patient with chronic lymphocytic myocarditis shows circumscript transmural scar tissue and focal thinning of the midventricular anteroseptal left ventricular and right ventricular wall (*). (C) Ventricular arrhythmia events during WCD use. (D) Histopathology and immunopathology of chronic lymphocytic myocarditis before and after immunosuppressive therapy. Left column: haematoxylin-eosin (HE); middle column: staining with anti-CD3 antibody (pan T lymphocyte marker); right column: staining with MHCII (major histocompatibility complex class II) antibody.



C

Cardio-myopathy	Patients with VT (n)	Total episodes of VT (n)	Sustained VT (n)	Non-sustained VT (n)	VT duration (seconds)	VT frequency (bpm)	Morpho-logy	Maximal number of morpho-logies per patient	Therapy (shocks)
DCM	1	1	0	1	Min: 14 Max: 14	Min: 187 Max: 187	Mono: 1 Poly: 0	1	0
MC	7	41	6 in 3 patients	35	Min: 1 Max: 80	Min: 130 Max: 260	Mono: 25 Poly: 16	2	2 in 1 patient
P value	0.03	0.03	0.09	0.10	-	-	-	-	-



therapy (P = 0.52). *Figure 1D* shows the histopathology and immunopathology of a patient with chronic lymphocytic MC before and after immunosuppressive therapy. At the end of WCD therapy, 16 patients were implanted with an ICD (six MC and 10 DCM patients), and 10 with a CRT-D (six MC and four DCM patients).

In our study population, no device implantation-associated adverse events (hematoma, pneumothorax, and pocket infection) occurred. During a mean follow-up of 31.6 ± 19.3 month, no adverse events related to the generator (pocket infection and pocket erosion) or leads (lead dislodgement, pacing threshold increase or sensitivity decrease, and endoplastitis) were documented.

Study limitations

The main limitation of this single-centre retrospective observational study is the relatively small number of patients. Thus, the incidence of sustained VTs and hard end points such as WCD shock delivery was low.

Conclusions

The indications for ICD implantations in patients with myocarditis are the same as those for patients with non-ischaemic DCM.[14] Of note, results from the DANISH Study suggest that many patients with non-ischaemic DCM do not benefit from ICD implantation.[15] However, as illustrated by our single-centre observational study, ventricular arrhythmias (sustained and non-sustained) are significantly more common in patients with MC than in patients with DCM. As immunosuppression and heart failure medication may resolve inflammation and achieve left ventricular reverse remodelling in patients with active myocardial inflammation, WCD therapy enables a watchful waiting strategy. However, long-term data on the mortality or morbidity of patients with a history of myocarditis are missing. CMR scans are useful in MC patients to detect replacement fibrosis and thus to identify patients at potentially increased arrhythmic risk.

In conclusion, our data suggest that MC patients may benefit from WCD therapy. However, our data are not powered for outcomes, and further randomized controlled trials powered for the outcome morbidity and mortality are needed.

Acknowledgement

Open access funding enabled and organized by Projekt DEAL.

Conflict of interest

All the authors have no disclosure related to this study.

Funding

No funding for this study.

References

1. 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: Executive Summary: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines and the Heart Rhythm Society. *Circulation* 2018; **138**: e210–e271.
2. Feldman AM, Klein H, Tchou P, Murali S, Hall WJ, Mancini D, Boehmer J, Harvey M, Heilman MS, Szymkiewicz SJ, Moss AJ, investigators W, coordinators, investigators B and coordinators. Use of a wearable defibrillator in terminating tachyarrhythmias in patients at high risk for sudden death: results of the WEARIT/BIROAD. *Pacing Clin Electrophysiol* 2004; **27**: 4–9.
3. Erath JW, Vamos M, Sirat AS, Hohnloser SH. The wearable cardioverter-defibrillator in a real-world clinical setting: experience in 102 consecutive patients. *Clin Res Cardiol* 2017; **106**: 300–306.
4. Duncker D, Konig T, Hohmann S, Bauersachs J, Veltmann C. Avoiding untimely implantable cardioverter/defibrillator implantation by intensified heart failure therapy optimization supported by the wearable cardioverter/defibrillator—the PROLONG study. *J Am Heart Assoc* 2017; **6**.
5. Wassnig NK, Gunther M, Quick S, Pfluecke C, Rottstadt F, Szymkiewicz SJ, Ringquist S, Strasser RH, Speiser U. Experience with the wearable cardioverter-defibrillator in patients at high risk for sudden cardiac death. *Circulation* 2016; **134**: 635–643.
6. Heymans S, Eriksson U, Lehtonen J, Cooper LT Jr. The quest for new approaches in myocarditis and inflammatory cardiomyopathy. *J Am Coll Cardiol* 2016; **68**: 2348–2364.
7. Peretto G, Sala S, Rizzo S, De Luca G, Campochiaro C, Sartorelli S, Benedetti G, Palmisano A, Esposito A, Tresoldi M, Thiene G, Basso C, Della Bella P. Arrhythmias in myocarditis: state of the art. *Heart Rhythm* 2019; **16**: 793–801.
8. Vio R, Zorzi A, Corrado D. Myocarditis in the athlete: arrhythmogenic substrates, clinical manifestations, management, and eligibility decisions. *J Cardiovasc Transl Res* 2020; **13**: 284–295.
9. Caforio AL, Pankuweit S, Arbustini E, Basso C, Gimeno-Blanes J, Felix SB, Fu M, Helio T, Heymans S, Jahns R, Klingel K, Linhart A, Maisch B, McKenna W, Mogensen J, Pinto YM, Ristic A, Schultheiss HP, Seggewiss H, Tavazzi L, Thiene G, Yilmaz A, Charron P, Elliott PM, European Society of Cardiology Working Group on M and Pericardial D. Current state of knowledge on aetiology, diagnosis, management, and therapy of myocarditis: a position statement of the European Society of Cardiology Working Group on Myocardial and Pericardial Diseases. *Eur Heart J* 2013; **34**: 2636–2648 2648a-2648d.
10. Katzmann JL, Schlattmann P, Rigopoulos AG, Noutsias E, Bigalke B, Pauschinger M, Tschope C, Sedding D, Schulze PC, Noutsias M. Meta-analysis on the immunohistological detection of inflammatory cardiomyopathy in endomyocardial biopsies. *Heart Fail Rev* 2020; **25**: 277–294.
11. Ferreira VM, Schulz-Menger J, Holmvang G, Kramer CM, Carbone I, Sechtem U, Kindermann I, Gutberlet M, Cooper LT, Liu P, Friedrich MG. Cardiovascular magnetic resonance in nonischemic myocardial inflammation: expert recommendations. *J Am Coll Cardiol* 2018; **72**: 3158–3176.
12. Van Linthout S, Tschope C. Viral myocarditis: a prime example for endomyocardial biopsy-guided diagnosis and therapy. *Curr Opin Cardiol* 2018; **33**: 325–333.
13. Tschope C, Cooper LT, Torre-Amione G, Van Linthout S. Management of myocarditis-related cardiomyopathy in adults. *Circ Res* 2019; **124**: 1568–1583.
14. 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 KH, Hernandez-Madrid A, Nikolaou N, Norekval TM, Spaulding C, Van Veldhuisen DJ, Group ESCSD. 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 European Society of Cardiology (ESC). Endorsed by: Association for European Paediatric and Congenital Cardiology (AEPC). *Eur Heart J* 2015; **36**: 2793–2867.

15. Kober L, Thune JJ, Nielsen JC, Haarbo J, Videbaek L, Korup E, Jensen G, Hildebrandt P, Steffensen FH, Bruun NE, Eiskjaer H, Brandes A, Thogersen AM, Gustafsson F, Egstrup K, Videbaek R, Hassager C, Svendsen JH, Hofsten DE, Torp-Pedersen C, Pehrson S, Investigators D. Defibrillator implantation in patients with nonischemic systolic heart failure. *N Engl J Med* 2016; **375**: 1221–1230.