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Comparison of ventricular arrhythmia burden, therapeutic ınterventions, and survival, in patients <75 and patients ≥75 years of age treated with ımplantable cardioverter defibrillators

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Aim Implantable cardioverter defibrillators (ICD) reduce arrhythmic mortality in a wide range of patients with poor left ventricular (LV) function. However, whether ICD therapy is equally effective in younger and older patients remains uncertain. To address this question, we compared ICD-documented ventricular tachyarrhythmia burden in patients <75 years of age (Group 1) and ≥75 years of age (Group 2).

Methods Data were obtained from 208 consecutive ICD-treated patients: 159 Group 1 (mean age 59 ± 12), and 49 Group 2 (mean age 79±3). Demographic and clinical features including presenting arrhythmias, LV ejection fraction, and nature of heart disease were similar. Medications were comparable except that amiodarone use was more frequent in Group 2.

Results The numbers of combined ventricular tachycardia (VT) and ventricular fibrillation (VF) episodes per month were 0.4±2 and 0.3±2 for groups 1 and 2, respectively ($P = 0.7$). Individually, VT episodes per month were 0.4±2 and 0.3±2 ($P = 0.7$) and VF episodes per month were 0.003 ± 0.01 and 0.03 ± 0.2 ($P = 0.2$) for the two groups, respectively. The mean duration and average cycle length of arrhythmias were 3.1 ± 20.4 s and 275 ± 119 ms in Group 1, and 6 ± 45 s and 285 ± 114 ms in Group 2 (*P* values, 0.6 and 0.8). The mean time between the ICD implantation and the first episode of a device-treated arrhythmia was comparable in the two groups. Thirty-six patients died during follow-up; 22 (14%) Group 1 and 14 (29%) Group 2 ($P = 0.02$), almost exclusively on a non-sudden cardiac basis. Thus, despite higher ultimate mortality in older patients, both the nature and characteristics of spontaneous arrhythmia recurrence, and the time to first apparently beneficial therapy, were similar during follow-up in the two groups.

Conclusion In terms of reversing potentially life-threatening arrhythmias, the rationale for ICD therapy is comparable in older and younger individuals.

Introduction

Randomized clinical trials have clearly shown that implantable cardioverter defibrillators (ICDs) provide important survival benefits in a wide range of patients with structural heart disease and diminished left ventricular (LV) function.[1–6] Further, ICD treatment benefit is largely independent of the arrhythmic presentation. Mortality risk is reduced to almost the same degree whether the indication for ICD treatment is non-sustained or sustained ventricular tachyarrhythmias (NSVT, VT) or ventricular fibrillation (VF).[2–4] Nonetheless, uncertainty remains whether such findings are equally applicable in all age groups. Most importantly, as non-cardiac health issues become increasingly prevalent with advancing years, the relative ICD-related survival benefit may reasonably be expected to wane as age increases. If that were the case, then payors (whether government or private insurors) might be tempted to legislate against ICD use in older subsets of patients for cost containment reasons.

In an attempt to evaluate the potential impact of age on ICD benefit, we examined the nature and frequency of

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ICD-documented ventricular tachyarrhythmias, and the incidence of all-cause mortality, observed during follow-up in a single-centre consecutive series of both younger (<75 years) and more elderly (≥75 years) ICD-treated patients. We hypothesized that older individuals would manifest comparable or greater arrhythmia frequency and severity than would younger patients, and we anticipated that older patients would exhibit a similar frequency of potentially life-saving appropriate ICD therapies compared with younger patients. If true, these findings would favour offering ICD implantation as a treatment option in all patients with appropriate indications, irrespective of advanced age.

Methods

Patient population

The study population is derived from a consecutive series of 250 prospectively followed patients who received ICDs at Central Minnesota Heart Center, St Cloud, MN, USA. Among these individuals, the indication for implantation, and the frequency and nature of documented ventricular arrhythmias during a minimum 6 months follow-up could be evaluated in 208 individuals. Data review procedures were undertaken in accordance with institutional guidelines, and patient consent was obtained in conjunction with the device implantation procedure. The ethical committee approved this study, and patient identities were protected to provide anonymity.

Patients were categorized according to their ages at the time of ICD implantation; i.e. Group 1, younger (<75 years) and Group 2, more elderly (≥75 years). Age 75 represented an apparent age 'barrier' for ICD candidacy based on patient groups in previous ICD trials like MADIT, MADIT II, SCD-HeFT, and COMPANION (see discussion below). In this regard, an age cut-off value of 75 was chosen to assess the efficay of ICD therapy in an elderly population.

Baseline clinical characteristics including age, gender, presenting arryhythmia and symptom, New York Heart Association (NYHA) class, LV ejection fraction, and drug treatment were also documented. Patients were seen at the clinic with a minimum follow-up interval of 3 months. Intervening clinical visits were performed if there was a clinical necessity.

The primary endpoint during the follow-up was ventricular tachyarrhythmia burden. In this regard, the number of ventricular tachyarrhythmia episodes, the frequency of antitachycardia pacing and/or defibrillation episodes, and the rhythm characteristics immediately after device therapies were evaluated by review of device interrogation data, including assessment of intracardiac electrograms. Secondary endpoints were all-cause mortality, the nature of detected ventricular tachyarrhythmias, and the number of appropriate ICD therapies.

Definitions

Arrhythmia burden: The total number of episodes and total duration of sustained ventricular tachyarrhythmia per patient presented on a per month basis.

Ventricular tachycardia Ventricular tachyarrhythmia with cycle length <400 ms but ≥320 ms.

Ventricular fibrillation: Ventricular tachyarrhythmia with cycle length <320 ms.

Non-sustained ventricular tachyarrhythmia: Ventricular tachyarrhythmias in either the VT or VF zone (aforementioned), but short enough in duration to remain untreated by the ICD based upon programme settings at the time of the event.

The definition of arrhythmias was based on device programming, since this was a clinically relevant definition in the eyes of the physicians caring for such patients.

Detection settings

Device detection settings (i.e. atrial/ventricular sensitivity, refractory durations, and blanking) were individually determined for each patient. Sensitivity settings were adjusted from time-to-time as need dictated, whereas the others were only rarely modified.

Statistical analysis

Comparison of arrhythmia burden was by Student's *t*-test, χ^2 test, and Fisher's exact test. Univariate analysis was performed to assess the effect of age on arrhythmia burden. All data are presented as mean ± SD or median. Kaplan–Meier actuarial method with log-rank statistics was used to calculate the episode free rate over time. A *P* value of <0.05 was considered statistically significant.

Results

Among the original 250 patients, the minimum duration of the follow-up (i.e. ≥6 months) required to calculate the arrhythmia burden was acheived in 208 individuals (mean age 63.9 ± 13.5 years, 3:1 male to female ratio). Among these 208 patients, 159 (76%) were in Group 1 (<75 years, mean age 59.3 ± 12.0 years) and 49 (24%) were in Group 2 (≥75 years, mean age 79.1±2.9 years) group. Mean age in Group 1 was 59±12 vs. Group 2: 79±3 years. The average follow-up durations were similar and were 33±3 months (median; 28 months) and 25±2 months (median; 21 months) in the two groups, respectively (T = 1.7, $P = 0.07$).

Demographic and clinical features including male/female ratios, presenting arrhythmias, LV ejection fraction, NYHA class, and nature of underlying heart disease were similar in the two groups (*Table 1*). Ischaemic cardiomyopathy was the most common underlying disease in both groups, but cardiomyopathy of ischaemic origin was more common in the older group—than in the younger patients ($P < 0.03$, *Table 1*). Use of medications did not differ, except for amiodarone which was more frequent in Group 2 patients (*Table 1*).

Primary endpoint: ventricular arrhythmia frequency and burden

The number of patients having at least one episode of ventricular arrhythmia was 46 (28.9%) in Group 1, and 8 (16.3%) in Group 2 ($P = 0.08$). The total number of VT, VF, and combined VT/VF episodes were 545, 63, and 608 in the younger group and 319, 5, and 324 in the older group, respectively ($P > 0.05$).

Total ventricular tachyarrhythmia burden (calculated as the number of VT and VF episodes per patient per month) based on the total patient population at risk was 0.3 ± 2.3 (median: 0) and 0.4 ± 1.9 (median: 0) for Group 1 and Group 2, respectively ($P = 0.74$). In terms of only those patients who had a tachyarrhythmic event, the arrhythmia burden calculated as the number of VT and VF episodes only per patient per month was 1.1 ± 4.1 (median: 0.09) and 2.2 ± 3.9 (median: 0.06) for the younger and older groups, respectively ($P = 0.45$).

The number of VT episodes per patient per month calculated from all patients at risk was 0.3 ± 2.2 (median: 0) and 0.4 ± 1.9 (median: 0) ($P = 0.68$) and the number of VT episodes per patient per month calculated from patients

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Table 1 Baseline data of the two patient groups.

	Younger (<75 years old)	More Elderly (≥75 years old)	Statistics
Number of Patients	159	49	
Gender			
M	121 (76%)	36 (74%)	$p = 0.71$
F	38 (24%)	13 (26%)	
Presenting Arrhythmia			
NSVT	35 (22%)	7 (14%)	$p = 0.15$
VT	82 (52%)	33 (68%)	
VF	42 (26%)	9 (18%)	
Left Ventricle EF (%)	37 ± 2	35 ± 1	$p = 0.5$
Presenting Symptoms			
Cardiac arrest	48 (30%)	11 (22%)	$p = 0.34$
Syncope	38 (24%)	18 (37%)	
Presyncope	16 (10%)	4 (8%)	
Other	57 (36%)	16 (33%)	
NYHA Class (Mean)	2.5	2.7	$p = 0.4$
Heart Disease			
Ischaemic	107 (67%)	41 (84%)	$p = 0.03$
Non-Ischaemic	52 (33%)	8 (16%)	
Medications			
ACE Inhibitors	94 (59%)	25 (62%)	$p = 0.32$
Beta Blockers	104 (65%)	28 (65%)	$p = 0.29$
Calcium Antagonists	13 (8%)	5 (13%)	$p = 0.66$
Amiodarone	4 (26%)	20 (32%)	$p = 0.05$
Other	39 (24%)	18 (37%)	$p = 0.1$

M = male, F = female, NSVT = non-sustained ventricular tachycardia, VT = ventricular tachycardia, VF = ventricular fibrillation, EF = ejection fraction, NYHA = New York Heart Association, ACE = angiotensin converting enzyme.

having an episode was 1.0 ± 4.0 (median: 0.04) and 2.2 ± 3.9 (median: 0.04) ($P = 0.42$) for Group 1 and Group 2, respectively. Similarly, the number of VF episodes per patient per month calculated from all patients at risk were 0.03 ± 0.02 (median: 0) and 0.003 ± 0.001 (median: 0) ($P = 0.18$) for Group 1 and Group 2, respectively. The number of VF episodes per patient per month calculated from patients having an episode were 0.1 ± 0.4 (Group 1) (median: 0) and 0.01 ± 0.02 (Group 2) (median: 0) ($P = 0.2$).

Secondary endpoints

Arrhythmia characteristics

The mean duration of detected ventricular arrhythmias per patient per month calculated from all patients were 5.9 ± 45.3 s in Group 1 (median: 0) and 3.1 ± 20.4 s in Group 2 (median: 0) ($P = 0.56$). Similarly, the mean duration of the arrhythmias per patient per month calculated from patients having an episode were 20.1 ± 82.7 s (median: 1.01) in the younger group and 16.1 ± 45.9 s (median: 0.43) in the older group ($P = 0.84$).

The average cycle length of episodes per patient from all patients having an episode was 285.1 ± 113.6 ms (median: 320.5) and 274.6 ± 119.3 ms (median: 310) in the younger and older groups, respectively ($P = 0.82$).

ICD therapy delivery

Total number of antitachycardia pacing (ATP) episodes was 319 and 529 in the younger and older groups, respectively ($P > 0.05$). Number of episodes accelerating to a faster rhythm requiring a shock after ATP was 10 and 22 for the two groups again ($P > 0.05$). The mean time between the ICD implantation and the first episode of a device treated arrhythmia was comparable in two groups (*Figure 1*). For patients having a first and a second episode of device treated arrhythmia, the mean time between these two episodes was also similar in the younger and more elderly patient groups (*Figure 2*).

Mortality

At the last follow-up, 86.2% of younger patients and 71.4% of older patients remained alive. In brief, there were 36 deaths: 22 patients (13.8%) in the younger group and 14 patients (28.6%) in the older group ($P = 0.02$). Although precise characterization of the cause of death (i.e. 'sudden cardiac', 'non- sudden cardiac', or 'non-cardiac') cannot be stated with certainty, review of availble records indicated that most deaths in both groups were 'non-sudden cardiac' in nature due to progression of LV dysfunction. There were no sudden cardiac deaths documented in either group, but there were two deaths in the older group attributed to non-cardiac causes.

Discussion

This study evaluated whether advancing age alone adversely impacts the potential therapeutic benefits of implantable cardioverter-defibrillator ICD therapy. Four principal observations were made. First, although ventricular tachyarrhythmia burden tended to be higher in older patients (79 ± 3 years, Group 2), there was no statistically significant difference compared with younger individuals (59 ± 12 years, Group 1). Second, the nature of ICD-detected tachyarrhythmic events, as characterized by both the cycle length of the arrhythmias and the duration of the

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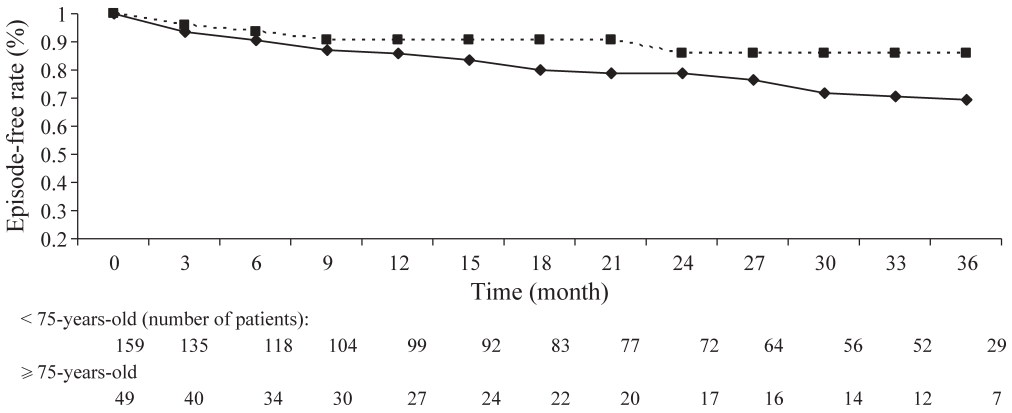


Figure 1 Graph depicting the analysis for the time to the first VT or VF episode following ICD implantation based on the age of patients at implant. The ordinate depicts the proportion of spontaneous 'arrhythmia recurrence-free' patients. The solid line reflects younger patients, whereas the dotted line depicts more elderly patients.

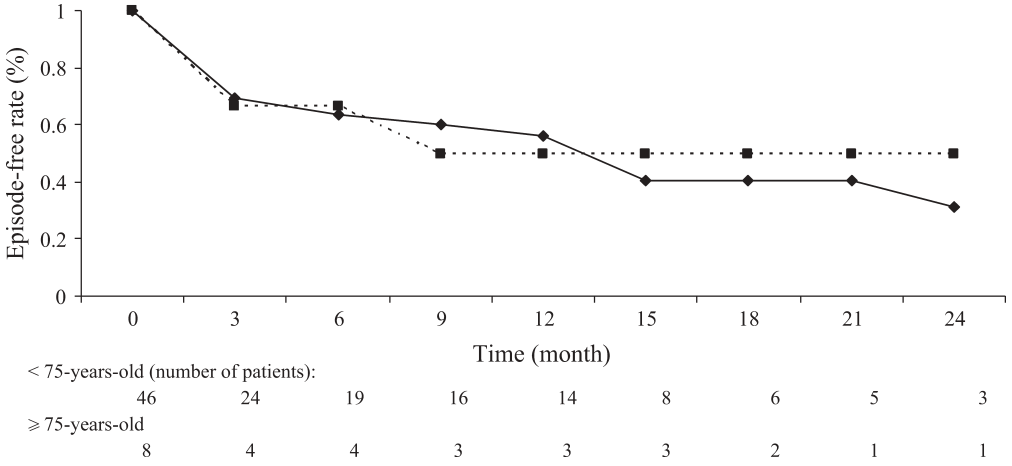


Figure 2 Graph illustrating the analysis for the time from the first to the second VT or VF episode based on the age of patients at implant. The layout is the same as for *Figure 1*.

episodes, was similar in the two groups. Third, the number of ICD treatment interventions was comparable in both patient groups. Finally, although not surprisingly, all-cause mortality rate tended to be higher in the older group, the latter primarily reflected the relative impact of non-arrhythmic heart failure deaths in the two populations.

In patients with severe LV dysfunction, clinical trials have consistently demonstrated an ICD mortality benefit whether or not the ICD indication was a resuscitated sudden death, a sustained life-threatening ventricular tachyarrhythmia, non-sustained VT, or even severe LV systolic dysfunction in the absence of documented arrhythmia.[2,3,4,7,8] However, for the most part, the average age of the clinical trials' study populations has tended to be relatively 'young'. By way of example, the AVID,[4] MUSTT,[2] and DEFINITE[5] populations, each of which assessed patients having documented ventricular arrhythmias leading to ICD therapy, averaged 65, 66, and 58 years of age, respectively. In MADIT,[3] trial the control group was 64 ± 9 years and the ICD group was 62 ± 9 years, again suggesting that many patients were >70 years, but not likely very many >75 years. In MADIT II[7] trial the populations were 64 ± 10 for the ICD group and 65 ± 10 for the conventional treatment arm. In SCD-HeFT[9] the mean age was lower than MADIT or MADIT 2 being about 60 years in all groups, but the interquartile range was $\sim$10 years in all three cases. Thus, many patients were close to 70 years, but not very many were >75 years. In COMPANION[10] the median age for ICD patients was 66, for pacemaker was 67, and for OPT (optimum medical therapy) was 68. The range was not provided but it is likely that many patients were <70 years of age. Consequently, whether the observations from these important studies can be reliably extended to older populations is currently unclear.

Our findings, showing comparable arrhythmia burden and ICD treatment frequency in younger patients and patients averaging 79 years of age, support the view that both groups stand to benefit comparably from ICD implantation. In this regard, Trappe and colleagues[11] similarly examined the effect of age on ICD treatment efficacy, and found that older individuals received treatment benefit with no greater risk than did younger individuals. However, the oldest patients included in the cohort studied by Trappe et al were 78 years, and their 'older group' incorporated the age range 65–78 years; these individuals may no longer be considered as representative of an 'elderly' population as is the 79 ± 3 years of the Group 2 patients in our study.

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In another cohort, Sajadieh *et al.*[12] studied the predictive significance of ventricular ectopy in middle-aged and elderly subjects. Despite the lack of a comparison between two groups and of an ICD-based monitoring utility, they concluded that healthy middle-aged and elderly subjects both had an increased risk when they demonstrated frequent ventricular ectopy.

Noseworthy *et al.*[13] reported a favourable ICD experience in an older patient population more comparable with ours. They compared findings in 29 ICD-treated individuals $\geq$80 years of age (mean 83 years) with a cohort of 183 individuals aged 70–79 years (mean 74 years). Actuarial survival at 1 year was 93 and 91% in the younger and older group, respectively. With follow-up to $\sim$1.5 years, survival statistics remained similar in the two groups.

Based on the limited available published literature, it appears that advanced age-alone (at least into the first half of the octogenarian decade) should not preclude offering ICD therapy. Our findings extend this argument, by demonstrating that older ICD-treated patients not only exhibit an arrhythmia frequency and ICD-treatment rate comparable with patients 10 years their junior, but they also exhibit a relatively high crude survival rate, albeit somewhat lower than the younger ICD-treated individuals. In essence then, during the time frame examined by our report, as well as that of Noseworthy *et al.*, non-cardiac and non-arrhythmic causes of death did not appear to diminish substantially the value of ICD treatment for preventing premature deaths.

Limitations

Two important limitations impact interpretation of our findings. First, this study examined follow-up in patients already referred for ICD therapy. Thus, the population, while uniformly exhibiting severe heart disease, may have undergone a pre-referral selection process. Thus, it is possible that only the 'healthier' of the older population may have been referred to receive ICDs, and other less well patients may not have been considered for such therapy. Absent, a randomized prospective trial enrolling all candidate patients with appropriate indications, it is not possible to protect against bias introduced by the pre-referral selection process. Second, the follow-up duration in this report was limited. Thus, the inevitable ultimate impact of older age on mortality could not be definitively assessed.

Conclusion

Given the potential economic impact of broadly applied ICD therapy, the importance of assessing whether the elderly patient will benefit as much as do younger individuals has become of increasing importance. In this context, our findings indicate that among surviving ICD-treated patients, the frequency of life-threatening arrhythmia and the requirement for ICD intervention is comparable in both older ($\geq$75 years) and younger ($<$75 years) age groups. Consequently, within the constraints associated with the limitations noted earlier, our findings provide further evidence that ICD therapy is both warranted and effective in the more elderly patient population (at least into the eighth decade).

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References

1. Gregoratos G, Abrams J, Epstein AE, Freedman RA, Hayes DL, Hlatky MA *et al.* ACC/AHA/NASPE 2002 Guideline update for ımplantation of cardiac pacemakers and antiarrhythmia devices—summary article: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (ACC/AHA/NASPE Committee to Update the 1998 Pacemaker Guidelines). *J Am Coll Cardiol* 2002;**40**:1703–19.
2. Buxton AE, Lee KL, DiCarlo L, Echt DS, Fisher JD, Greer GS *et al.* The Multicenter UnSustained Tachycardia Trial (MUSTT) Investigators. A randomized study of the prevention of sudden death in patients with coronary artery disease. *N Engl J Med* 1999;**341**:1882–90.
3. Moss AJ, Hall WJ, Cannom DS, Daubert JP, Higgins SL, Klein H *et al.* and the MADIT Investigators. Improved survival with an implanted defibrillator in patients with coronary disease at high risk for ventricular arrhythmia. *N Engl J Med* 1996;**335**:1933–40.
4. The Antiarrhythmic Versus Implantable Defibrillators (AVID) Investigators. A comparison of antiarrhythmic drug therapy with implantable defibrillators in patients resuscitated from near-fatal ventricular arrhythmias. *New Engl J Med* 1997;**337**:1576–83.
5. Kadish A, Dyer A, Daubert JP, Quigg R, Estes MNA, Anderson KP *et al.* for the Defibrillators in Non-Ischemic Cardiomyopathy Treatment Evaluation (DEFINITE) Investigators. Prophylactic defibrillator implantation in patients with nonischemic dilated cardiomyopathy. *New Engl J Med* 2004;**350**:2151–8.
6. Evonich RF, Maheshwari A, Gardiner JC, Khasnis A, Kantipudi S, Ip JH *et al.* Implantable cardioverter defibrillator therapy in patients with ischemic or non-ischemic cardiomyopathy and non-sustained ventricular tachycardia. *J Intervent Cardiac Electrophysiol* 2004;**11**:59–65.
7. Moss AJ, Zareba W, Hall WJ and the Multicenter Automatic Defibrillator Implantation Trial II Investigators. Prophylactic implantation of a defibrillator in patients with myocardial infarction and reduced ejection fraction. *N Engl J Med* 2002;**346**:877–83.
8. Ermis C, Zhu AX, VanHeel L, Lemke MJ, Sakaguchi S, Lurie KG *et al.* Comparison of ventricular arrhythmia frequency in patients with ischemic cardiomyopathy versus nonischemic cardiomyopathy treated with implantable cardioverter defibrillators. *Am J Cardiol* 2005; **96**:233–8.
9. Bardy GH, Lee KL, Mark DB *et al.* for SCD-HeFT investigators. Amiodarone or ımplantable cardioverter defibrillator for heart congestive failure. *N Engl J Med* 2005;**352**:225–37.
10. Bristow MR, Saxon LA, Boehmer J *et al.* for the Comparison of Medical Therapy, Pacing and Defibrillation in Heart Failure (COMPANION) investigators. Cardiac-resynchronization therapy with or without an implantable defibrillator in advanced chronic heart failure. *N Engl J Med* 2004;**350**:2140–50.
11. Trappe HJ, Pfitzner P, Achtelik M, Fieguth HG. Age dependent efficacy of implantable cardioverter-defibrillator treatment: observations in 450 patients over an 11 year period. *Heart* 1997;**78**:364–70.
12. Sajadieh A, Nielsen OW, Rasmussen V, Hein HO, Frederiksen BS, Davanlou M, Hansen JF. Ventricular arrhythmias and risk of death and acute myocardial infarction in apparently healthy subjects of age $\geq$55 years. *Am J Cardiol* 2006;**1**:97:1351–7.
13. Noseworthy PA, Lashevsky I, Dorian P, Greene M, Cvitkovic S, Newman D. Feasibility of implantable cardioverter defibrillator use in elderly patients: a case series of octogenarians. *Pacing Clin Electrophysiol*. 2004;**27**:373–8.

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