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VIA MEDICA
ORIGINAL ARTICLE
2011, Vol. 18, No. 5, pp. 503–514
10.5603/CJ.2011.0005
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ISSN 1897–5593

Use of implantable cardioverter-defibrillators for primary prevention in older patients: A systematic literature review and meta-analysis

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Abstract

Background: *Randomized clinical trials (RCTs) have demonstrated the efficacy of implantable cardioverter-defibrillators (ICDs) in reducing sudden cardiac death (SCD) in specific patient populations. However, patients ≥ 65 years were under-represented in these trials and the overall benefit of ICDs may be diminished in older patients due to competing risks for death. We evaluate the published data on ICD efficacy at reducing all-cause mortality in patients ≥ 65 years and in patients ≥ 75 years.*

Methods: *We searched MEDLINE to identify RCTs and observational studies of ICDs that provided age-based outcome data for primary prevention of SCD. The primary endpoint was mortality evaluated by a meta-analysis of the RCTs using a random-effects model. Secondary endpoints included operative mortality, long-term complications and quality of life.*

Results: *The enrollment of patients ≥ 65 years in RCTs was limited (range: 33% in DEFINITE to 56% in MUSTT). Combining data from four RCTs (n = 3,562) revealed that primary prevention ICD therapy is efficacious in reducing all-cause mortality in patients ≥ 65 years (HR 0.66; 95% CI 0.50–0.87; test of heterogeneity: $X^2 = 5.26$; $p = 0.15$). For patients ≥ 75 years, combining data from four RCTs (n = 579) revealed that primary prevention ICD therapy remains efficacious in reducing all-cause mortality (HR 0.73; 95% CI 0.51–0.974; $p = 0.03$). There appears to be no difference in ICD-related, operative, in-hospital, or long-term complications among older patients compared to younger patients, although it remains unclear if older patients have a better quality of life with an ICD than younger patients.*

Conclusions: *Although the overall evidence regarding ICD efficacy in patients ≥ 65 years is limited and divergent, and the evidence available for patients ≥ 75 years is even more sparse, our meta-analysis suggests that primary prevention ICDs may be beneficial in older patients. Our findings need to be validated by future studies, particularly ones examining ICD complications and quality of life.* (Cardiol J 2011; 18, 5: 503–514)

Key words: aging, defibrillation, sudden death

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Received: 07.11.2010 Accepted: 10.08.2011

Introduction

In the United States, sudden cardiac death (SCD) accounts for more than 350,000 deaths annually, disproportionately affecting those aged ≥ 65 years [1]. Currently, implantable cardioverter--defibrillators (ICDs) are the most effective treatment for patients at high risk of SCD. As a result, their use rose 20–30% annually throughout the 1990s [2]. However, individual randomized controlled trials (RCTs) of ICDs enrolled relatively few patients aged 65 years or older, and even fewer of these patients were aged 75 years or older [3–10]. Thus, the optimal use of ICDs in the older population remains uncertain.

Clinically, patients aged ≥ 65 years are distinctly different from their younger cohorts. Advanced age is often accompanied by greater susceptibility to complications and adverse effects of therapies, as well as more co-morbidities and multi-system diseases that increase the risk of non-SCD. Consequently, the risks of ICD implantation may be higher and the potential benefits of ICD therapy may be reduced in this patient population [11]. Given the limited evidence and the potential for disparate risks and benefits in this population, we conducted a systematic review of the published literature to evaluate the body of evidence addressing the use of ICDs in patients aged ≥ 65 years and performed the first formal meta-analysis of the primary prevention trials in the growing subpopulation of patients aged ≥ 75 years.

Methods

Data sources and study selection

We conducted a systematic search of MEDLINE, Cochrane Controlled Trials Register, clinicaltrials.gov, and fda.gov using the terms "defibrillator" or "clinical trial" (Fig. 1). Limiting our search to peer-reviewed studies performed in humans and published in English since 1 January, 1990, we identified 1,540 potentially relevant citations, of which 1,306 were excluded at the abstract screening stage. Studies of cardiac resynchronization therapy, studies that included ICD therapy in both treatment and control arms, and studies lacking estimates of ICD effect based on age were excluded (n = 1,306). Studies enrolling < 100 patients or lacking age subgroup analyses were also excluded (n = 195), leaving 39 studies for review. Of these, secondary prevention RCTs and substudies or meta-analyses of secondary prevention RCTs were excluded (n = 8). A review of the references cited in the remaining 31 studies did not identify any additional studies that met inclusion criteria.

Non-randomized prospective or retrospective case series investigating the effectiveness of ICDs based on age (n = 6) were found and included in the literature review, along with publications of primary prevention RCTs (n = 9) and their substudies (n = 10). However, only RCTs were included in the meta-analysis. Of the nine primary prevention RCTs, only five were selected for the meta-analysis. Of the four RCTs that were excluded, CAT and AMIOVIRT were excluded due to lack of estimates of ICD effect based on age, and DINAMIT and CABG-PATCH were excluded *a priori* due to their enrollment of markedly different patient populations than the RCTs that were included. Due to this significant heterogeneity, including DINAMIT and CABG-PATCH in the meta-analysis would not be valid. Additionally, COMPANION was not included in our meta-analysis because this trial was designed to evaluate cardiac resynchronization therapy, and not ICD therapy.

Data extraction and synthesis

Abstracts of identified studies were reviewed independently by two investigators (MHK, GDS). We abstracted data from each article on study design, treatment, patient and clinical characteristics, outcomes, subgroup findings, ICD complications, and quality of life (QoL). Discrepancies between reviewers were resolved through discussion. For the meta-analysis, the primary outcome of interest was all-cause mortality in patients ≥ 65 years old. Although not every study included in the meta-analysis provided the subgroup analysis for patients ≥ 65 years or for patients ≥ 75 years, we obtained these data for each RCT from the trials' principal investigators. Likewise, for the overall review, the primary endpoint was mortality. Secondary endpoints included operative mortality, long-term complications and QoL.

Statistical methods

To be included in the meta-analysis, all studies had to be randomized clinical trials with an appropriate control analyzed by the intention-to-treat principle. Using an empirical Bayes random-effects estimator, we combined trial-level data on older patients from the major RCTs of primary prevention ICDs, which represent populations for which ICDs are recommended [12]. When no heterogeneity is present, this

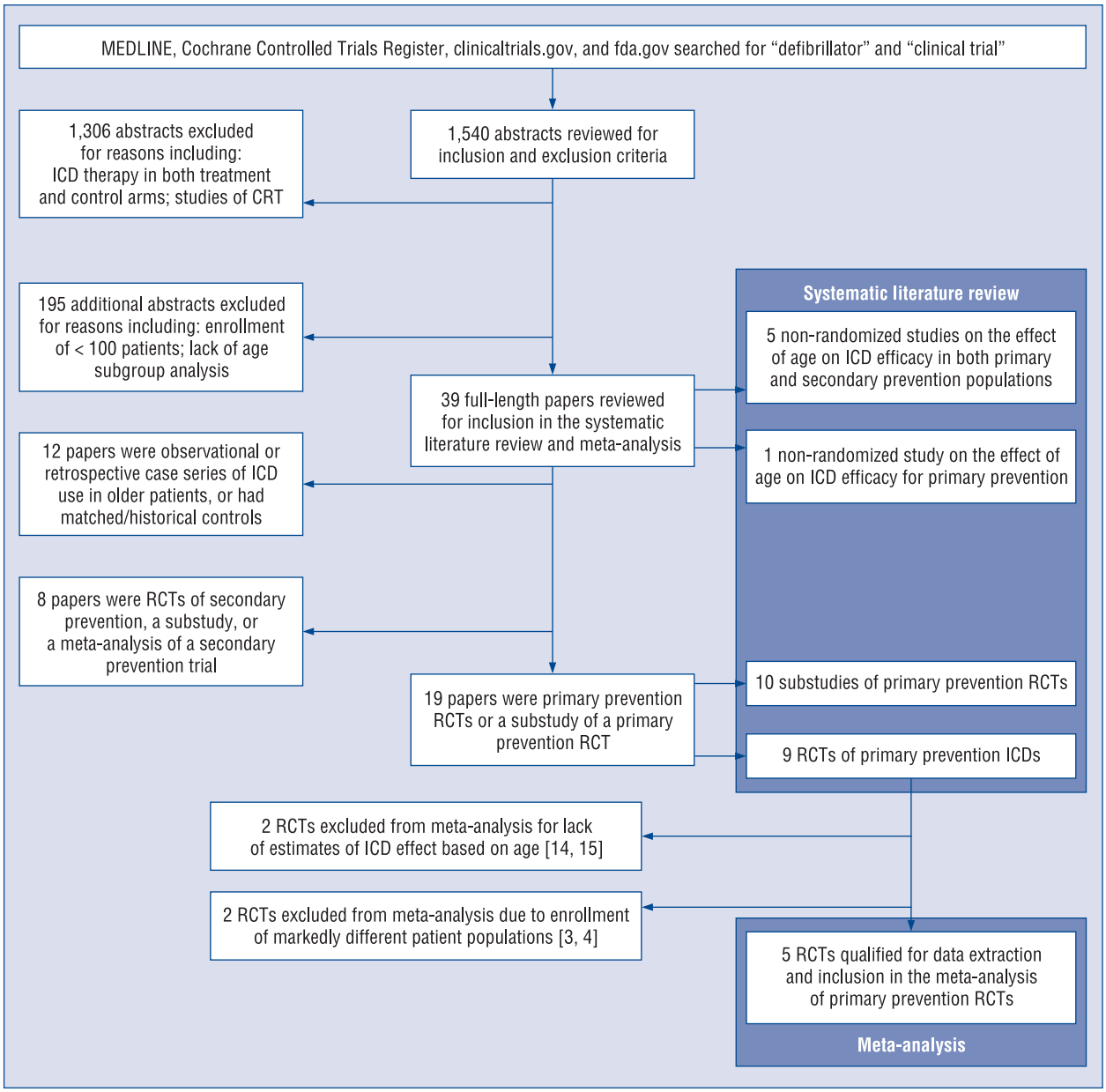

Figure 1. QUOROM flowchart; CRT — cardiac resynchronization therapy; ICD — implantable cardioverter-defibrillator; RCT — randomized clinical trials.

estimator reduces to a fixed effects estimator. The estimates were computed using Comprehensive Meta-Analysis Software™ (BIOSTAT, Englewood, NJ, USA). Statistical heterogeneity was measured using the χ^2 test. Statistical tests were two-tailed, and statistical significance was declared at $p < 0.05$. We did not combine data on older patients from the major RCTs of secondary prevention ICDs as this has been done previously [13].

Results

ICDs for primary prevention of SCD in patients aged 65 years and older

Table 1 presents data on the mean age of patients enrolled in the nine RCTs of primary prevention ICDs [3–9, 14, 15]. The number of patients ≥ 65 years ranged from 55% in the Multicenter Unsustained Tachycardia Trial (MUSTT) to 34% in the

Table 1. Randomized controlled trials of implantable cardioverter-defibrillator (ICD) therapy in primary prevention of sudden cardiac death.

Trial (year)	Treatment group	Patients	Mean age (years)	Patients ≥ 65 y/o (%)	Hazard ratio for effect of ICD therapy on all-cause mortality (95% CI)
MADIT-I (1996) [5]	Total	196	63 ± 9*	53.5	0.46 (0.26–0.82)
	ICD	95	62 ± 9	53.5	
	Control	101	64 ± 9	53.5	
CABG-PATCH (1997) [4]	Total	900	64 ± 9*	49.89	1.07 (0.81–1.42)
	ICD	446	64 ± 9	50.0	
	Control	454	63 ± 9	50.0	
MUSTT (1999) [7]	Total	704	66.5*†	55.97	0.45 (0.32–0.63)
	ICD	161	65.4 (8.52)‡	56.9	
	Control	543	64.9 (9.65)‡	54.1	
CAT (2002) [14]	Total	104	52 ± 11	NR	0.83 (0.45–1.52)
	ICD	50	52 ± 12	NR	
	Control	54	52 ± 10	NR	
MADIT-II (2002) [6]	Total	1,232	64 ± 10*	48.0	0.69 (0.51–0.93)
	ICD	742	64 ± 10	44.2	
	Control	490	65 ± 10	51.4	
AMIOVIRT (2003) [15]	Total	103	NR	NR	NR
	ICD	51	58 ± 11	NR	
	Control	52	60 ± 12	NR	
DINAMIT (2004) [3]	Total	674	62 ± 11*	NR	1.08 (0.76–1.55, p = 0.66)
	ICD	332	61.5 ± 10.9	NR	
	Control	342	62.1 ± 10.6	NR	
DEFINITE (2004) [8]	Total	458	58.3	34.28	0.65 (0.40–1.06, p = 0.08)
	ICD	229	58.4	35.4	
	Control	229	58.1	33.2	
SCD-HeFT (2005) [9]	Total	2,521	60*†	34.49	0.77 (0.62–0.96, p = 0.007)§
	ICD	829	60.1†	35.5	
	Control (amiodarone)	845	60.4†	33.5	
	Control (placebo)	847	59.7†		

NR — not reported; *values not reported in original trial publications, but obtained from reference [45]; †median; ‡mean (standard deviation); §97.5% confidence interval (CI)

Defibrillators in Non-Ischemic Cardiomyopathy Treatment Evaluation (DEFINITE) trial [16]. Defibrillator in Acute Myocardial Infarction Trial (DINAMIT) data was not available. Five RCTs provided data on primary prevention ICDs in patients ≥ 65 years (Table 2) [1, 6, 8, 9, 17, 18]. Of these trials, MUSTT enrolled the highest percentage of patients > 65 years (55.97%) and the oldest patient population (mean age 66 years) [7]. A MUSTT substudy explored the effect of age on ICD benefit by examining 243 patients aged ≥ 70 years and showed that the benefit from ICD therapy was similar in older and younger patients [17].

The Multicenter Automatic Defibrillator Implantation Trial-II (MADIT-II) randomized patients with a prior myocardial infarction and left ventricular ejection fraction (LVEF) ≤ 30% to ICD therapy or conventional medical therapy. Of this population, 1,028 patients were < 75 years of age, and 204 patients were ≥ 75 years of age. Hazard ratios (HR) for the three predefined age subsets were 0.46 for age < 60 years; 0.77 for age 60–69 years; and 0.65 for age ≥ 70 years [6]. Subsequently, two substudies from MADIT-II addressed the effect of age on ICD efficacy (Table 2) [1, 18]. Patients aged ≥ 75 years in MADIT-II had a HR of 0.56 compared with conventional therapy (95% CI 0.29–1.08; p = 0.08) [18]. The second substudy re-examined the prespecified age subgroups (< 65, 65–74, and ≥ 75 years of age) to assess ICD benefit with respect to age [1]. In patients aged ≥ 75 years, there was a 68% reduction in the risk of SCD with ICD therapy and

Table 2. Effect of age on implantable cardioverter-defibrillator (ICD) efficacy in substudies and subgroup analyses from randomized clinical trials of ICD therapy for the primary prevention of sudden cardiac death (SCD).

Author (year)	Parent trial	Age subgroups (years)	Patients	Hazard ratio for effect of ICD therapy on all-cause mortality (95% CI)
Moss (1996) [5]	MADIT-I	None	196	For patients ≥ 65: 0.38 (0.17–0.86)*
Bigger (1997) [4]	CABG-PATCH	None	900	No significant difference in HR for ICD group compared to control therapy in subgroup analysis stratified by age. However, for patients ≥ 65: 1.216 (0.858–1.724)*
Moss (2002) [6]	MADIT-II	< 60	370	0.46 (0.23–0.93)†
		60–69	426	0.77 (0.47–1.25)†
		≥ 70	436	0.65 (0.42–0.98)†
Peterson (2003) [17]§	MUSTT	< 70	461	0.52 (0.33–0.77)†
		≥ 70	243	0.43 (0.27–0.80)†
Greenberg (2004) [48]	MADIT-II	None	1,232	0.33 (0.20–0.53, p < 0.0001). No significant difference in reduction of SCD by ICD in subgroup analysis stratified by age
Kadish (2004) [8]	DEFINITE	< 65	301	0.70 (0.35–1.40)†
		≥ 65	157	0.63 (0.32–1.23)†
Hohnloser (2004) [3]	DINAMIT	< 60	275	HR < 1.0, 95% CI crosses 1.0‡
		≥ 60	399	For patients ≥ 65: 1.23 (0.82–1.84)*
Bardy (2005) [9]	SCD-HeFT	< 65	1,098	0.68 (0.50–0.93)
		≥ 65	578	0.86 (0.62–1.18)
Huang (2007) [18]	MADIT-II	< 75	1,028	0.63 (0.45–0.88, p = 0.01)
		≥ 75	204	0.56 (0.29–1.08, p = 0.08)§
Goldenberg (2007) [1]	MADIT-II	< 65	574	0.79 (0.48–1.29)
		65–74	455	0.63 (0.41–0.95)
		≥ 75	204	0.70 (0.41–1.20)§

NA — not applicable; *hazard ratios (HR) and confidence intervals (CI) not published, but obtained from personal communication with trial investigators; †HR and CI not reported in original trial publications, but obtained from reference [45]; ‡exact point estimates have not been published; §these published point estimates for the 204 patients in MADIT-II ≥ 75 years of age are different because each was derived using a different statistical model

this finding was similar in patients aged 65–74 years. The greatest benefit of ICD therapy for all-cause mortality was seen in the group aged 65–74 years, who experienced a 37% reduction (p = 0.03), while younger patients experienced a 21% reduction (p = 0.35), and older patients a 30% reduction (p = 0.20). However, these results also need to be interpreted cautiously given the known limitations of subgroup analyses [19].

The DEFINITE trial comprised exclusively patients with non-ischemic cardiomyopathy and thus enrolled a younger patient population, with a mean age of 58 years. DEFINITE suggested that patients aged ≥ 65 years derived similar benefit from ICD therapy as did their younger counterparts [8].

An age-related subgroup analysis of the Sudden Cardiac Death in Heart Failure Trial (SCD-HeFT) showed greater benefit in ICD recipients < 65 years [9]. The largest of the primary prevention trials, SCD-HeFT enrolled 2,521 patients with NYHA class II–III congestive heart failure and an LVEF ≥ 35% and randomized patients to placebo, amiodarone, or a single-lead ICD [9]. Compared to placebo, ICD therapy resulted in a 23% reduction in risk of death. For the group aged ≥ 65 years, ICD implantation compared to placebo carried a favorable HR of 0.86, but the 97.5% CI crossed unity (0.62–1.18), reflecting the smaller sample size of the older age group (n = 578) compared to their younger counterparts (n = 1,098; HR 0.68; 97.5% CI 0.50–0.93).

Combining data from MADIT-I, MADIT-II, DEFINITE, and SCD-HeFT, we found ICDs to be efficacious in reducing all-cause mortality in patients ≥ 65 years (HR 0.66; 95% CI 0.50–0.87; test

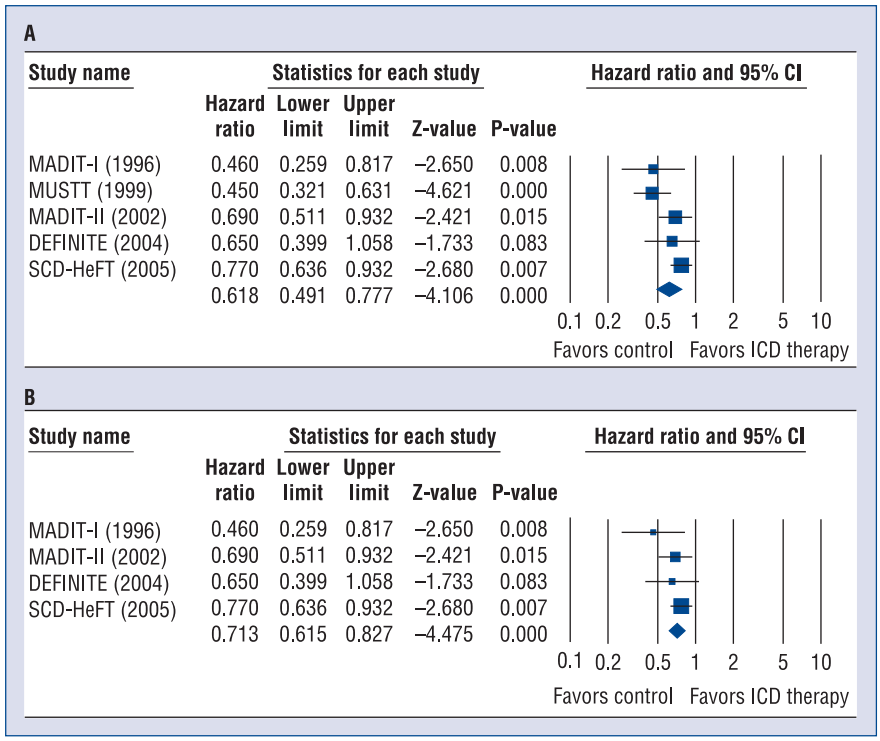

Figure 2. Hazard ratios for all-cause mortality in patients ≥ 65 years with MUSTT (**A**) and without MUSTT (**B**).

Table 3. Randomized controlled trials of implantable cardioverter-defibrillator (ICD) therapy in primary prevention of sudden cardiac death.

Trial (year)	Patients	Patients ≥ 75 y/o (n)	Patients ≥ 75 y/o (%)	Hazard ratio for effect of ICD therapy on all-cause mortality (95% CI)
MADIT-I (1996) [5]	196	18	9.18	No deaths in ICD treatment arm
MUSTT (1999) [7]	704	96	13.6	1.00 (0.58–1.75)
MADIT-II (2002) [6]	1,232	204	16.6	0.71 (0.42–1.19)
DEFINITE (2004) [8]	458	43	9.4	0.29 (0.09–0.97)
SCD-HeFT (2005) [9]	2,521	236	9.4	0.65 (0.39–1.05)

of heterogeneity: $X^2 = 5.26$; $p = 0.15$). When we included the MUSTT trial, ICD therapy was still efficacious in reducing all-cause mortality (HR 0.60; 95% CI 0.45–0.78); however, there was a trend toward significant heterogeneity among the trials ($X^2 = 8.01$; $p = 0.09$) (Figs. 2A, B). This increased heterogeneity may reflect the fact that, unlike the other trials included, ICD therapy was not randomized in MUSTT.

ICDs for primary prevention of SCD in patients aged 75 years and older

The number of patients ≥ 75 years ranged from 17% in MADIT-II to 9% in MADIT-I, DEFINITE, and SCD-HeFT alike (Table 3) [5, 6, 8, 9]. Four RCTs provided data on primary prevention ICDs in patients ≥ 75 years (Table 3) [6–9]. There were no deaths among the 18 patients aged ≥ 75 years randomized to the ICD treatment arm of MADIT-I, and as such a HR was not calculable [5]. Combining data from MUSTT, MADIT-II, DEFINITE, and SCD-HeFT, we found that ICDs remained efficacious in reducing all-cause mortality in patients ≥ 75 years (HR 0.73; 95% CI 0.51–0.974; $p = 0.03$) (Fig. 3).

Non-randomized studies of ICDs in older patients

Numerous non-randomized studies have attempted to examine the efficacy of ICD implantation in older patients (Table 4) [20–24]. One study

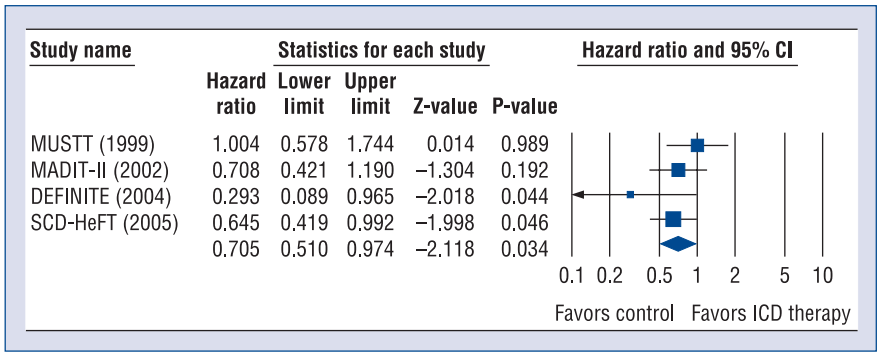

Figure 3. Hazard ratios for all-cause mortality in patients ≥ 75 years.

examined patients who received ICDs for primary prevention indications. Others included both secondary and primary prevention indications. A few studies included patients who had received an ICD for either secondary or primary prevention indications [20–24]. Two of these studies found ICDs to be of similar effectiveness in older and younger patients [20, 22], and three studies found that younger patients derived more benefit than older patients [21, 23, 24]. These studies were limited by small sample sizes, non-randomized design, and lack of appropriate adjustment for different sources of bias.

Only one study was limited to patients with a primary prevention indication for an ICD [25]. This study prospectively enrolled 965 patients, with or without an ICD, and with either ischemic or non-ischemic cardiomyopathy. Using a landmark analysis and multivariable Cox proportional hazards models that included propensity scores for ICD implantation, this study showed that ICD use was associated with lower all-cause mortality, even among older patients and those with co-morbid conditions [25].

In-hospital complications in patients aged 65 and older

Of all patients receiving an ICD, about 30% experience one or more complications post-implantation, 10% of which are directly related to the implantation procedure [26]. The inherent risks of ICD implantation must therefore be considered when evaluating their potential use in older patients [27]. Although sparse, current evidence suggests that ICD operative mortality may be independent of age. In one case series of consecutive patients referred to a single institution for ICD implantation, mortality was similar in patients aged ≥ 70 years *vs* < 70 years [28].

Complications related to ICD implantation include atrial or ventricular lead dislodgement or fracture, device migration or malfunction, pneumothorax, damage to arteries and nerves, air embolism, vein thrombosis, cardiac perforation and resultant pericardial effusion with or without tamponade, pocket hematoma, pocket or systemic infection, and arrhythmias related to lead manipulation [29]. A study of Medicare Provider Analysis and Review (MedPAR) files from fiscal year 2003 analyzed 31,000 Medicare beneficiaries receiving ICDs as an isolated procedure in 2002–2003. It found that the rate of one or more in-hospital complications related to ICD implantation was 10.8% [30]. In this study, the age distribution was similar among patients who experienced complications compared to those who did not. Another retrospective database analysis of prospectively collected data from a single center stratified patients into two groups: patients aged 70–79 years and ≥ 80 years [20]. Except for age, the two groups were similar demographically, and had similar actuarial survival rates and complication rates ($p = 0.16$). A third retrospective case series of 450 patients who underwent ICD implantation at a single center found that perioperative mortality by age group was not significantly different among age groups [11].

More recently, a study of Medicare beneficiaries who received an ICD between 2002 and 2005 examined patient and implanting physician factors associated with the outcomes of ICD implantation [31]. The mean age of the 8,581 patients who had an ICD implanted during the study period was 75 years. Age was not found to be an independent risk factor for increased complications [31].

Long-term ICD complications in patients aged 65 and older

Little is known about the long-term complications of ICD therapy in the general population, and as such, even less can be extrapolated to older patients. Based on data from 500 consecutive patients

Table 4. Non-randomized studies of the effect of age on implantable cardioverter-defibrillator (ICD) efficacy.

Author (year)	Inclusion criteria	Study type	Groups	Patients	Mean age (years ± SD)	Primary endpoint	Findings
Primary prevention							
Chan (2009) [25]	965 consecutive patients enrolled from seven outpatient cardiology clinics at two centers from March 2001 to June 2005	Prospective cohort in which 494 patients received an ICD	Total < 65 65–74 ≥ 75	965 383 313 269	67.3*	Long-term mortality	Comparable absolute and relative mortality risk reductions with ICD use among older patients despite higher annual mortality rates HR 0.74 (95% CI 0.43–1.28, p = 0.43) HR 0.76 (95% CI 0.45–1.29, p = 0.43) HR 0.59 (95% CI 0.39–0.90, p = 0.43)
Primary and secondary prevention							
Noseworthy (2004) [20]	Patients aged > 70 selected from database of 637 patients who underwent ICD implantation at single center from December 1985 to March 2002	Prospective case series	Total 70–79 ≥ 80	637 183 29	63 ± 13 73.6 ± 2.9 83.3 ± 2.3	Actuarial survival	No difference in actuarial survival between 70–79 years age group and ≥ 80 years group (p = NS)
Duray (2005) [22]	375 consecutive ICD recipients with structural heart disease at single center	Retrospective case series	Total < 70 ≥ 70	375 273 102	63.6 ± 10.0 59.7 ± 8.9 74.0 ± 3.1	Time to death from any cause	No significant difference in average time to death among the two groups (28.4 ± 16.7 *vs* 30.4 ± 22.1 months, p = NS)
Koplan (2006) [21]	Consecutive patients ≥ 80 years of age at ICD implantation from July 1995 to September 2003 and consecutive nonelderly patients aged 60–70 years who underwent ICD implantation over same time period	Retrospective case series	Total 60–70 ≥ 80	348 241 107	NR 65 ± 3 82 ± 2	Median survival	Median survival was 4.2 years after implantation in the older group *vs* seven years in the younger group (p < 0.01)
Ermis (2007) [24]	250 consecutive patients who underwent ICD implantation at single center	Prospective case series	Total < 75 ≥ 75	208 159 49	NR 59 ± 12 79 ± 3	Ventricular tachy-arrhythmia burden	Total ventricular tachyarrhythmia burden (calculated as the number of VT and VF episodes per patient per month) based on 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)
Grimm (2007) [23]	500 consecutive patients from the Marburg Defibrillator database who underwent ICD implantation at single center from January 1994 to February 2006	Retrospective case series; indications for ICD implantation were not reported	Total < 75 ≥ 75	500 460 40	58 ± 14 56 ± 14 77 ± 4	Overall mortality	Five-year overall mortality rate was higher in patients age ≥ 75 than in patients < 75 years (55% *vs* 21%, p = 0.001)

NR — not reported; NS — non-significant; *median age; VT — ventricular tachycardia; VF — ventricular fibrillation

enrolled in the Marburg Defibrillator Database, rates of inappropriate shocks over a 48 month period were similar for patients aged ≥ 75 years compared to patients aged < 75 years (3% *vs* 13%; p = 0.29) [23]. Rates of generator-related complications and total mortality were higher among the older subgroup compared to the younger subgroup (33% *vs* 20%; p = 0.01). However, the number of older patients was very small, making the true long-term complication rate uncertain.

In the aforementioned study on patient and implanting physician factors associated with outcomes of ICD therapy in Medicare beneficiaries, the one-year mortality rate declined from 16.4% in 2002 to 13.2% in 2005 (p < 0.001) [31]. Older age was found to be independently associated with an increased risk of one-year mortality. Additional risk factors for increased mortality included history of myocardial infarction, congestive heart failure, chronic lung disease, dementia, diabetes, metastatic cancer, peripheral vascular disease, renal disease, and admission from the emergency room, many of which are more often found in older patients with significant co-morbid illnesses.

Effect of age on quality of life in ICD patients

Equally important to understanding the morbidity and mortality risks associated with ICD implantation are the QoL implications of ICDs in older patients. Three of the large RCTs have systematically examined the impact of ICD therapy on QoL — MADIT-II, CABG-PATCH, and most recently, SCD-HeFT [32–36]. However, short follow-up and methodological issues have limited the value of these substudies. Furthermore, it remains unclear how ICDs affect QoL in patients who receive primary prevention ICDs [36]. The largest QoL study in ICD recipients for primary prevention of SCD was performed in the SCD-HeFT population; however, the effect of age on QoL was not examined.

The only study that examined the relationship between age and QoL in the setting of a RCT was a MADIT-II substudy that included 1,089 patients and measured Health Utility Index-3 scores at three, 12, 24, and 36 months following enrollment [35]. Mean patient age in this substudy was approximately 65 years. Patients in the control group maintained a steady health-related quality of life (HRQOL), while ICD patients showed a gradually diminishing HRQOL. The declining average HRQOL in the control group was only due to mortality, but in the ICD group it was due to both mortality and decreasing HRQOL values for survivors. The difference in quality adjusted life years (QALY) between the two groups was not statistically significant. Within this study, key subgroup analyses were performed and for patients ≥ 65 years there was no significant decrease in QALYs while alive.

The relationship between age and QoL has been examined in several non-randomized studies [18, 35, 37, 38]. These studies were limited by small sample size, non-randomized study design, and lack of adjustment for potential confounders. Nonetheless, in general, these studies showed that although older patients with ICDs had decreased physical functioning, more co-morbid illness, and worse symptoms that negatively impact QoL, younger patients with ICDs tended to experience increased psychological distress, anxiety, and depression, which negatively impact QoL.

Discussion

With the aging of the US population, expanding indications for ICD implantation, and growing evidence favoring device-based therapy over antiarrhythmic drugs, data on the utilization and efficacy of ICDs in older patients is becoming increasingly important.

Despite the growing body of evidence from numerous large RCTs demonstrating that ICDs improve survival rates in various subsets of patients, the mean age of the patients enrolled in the RCTs of primary prevention ICDs was < 65 years and no RCT has prospectively focused on evaluating the outcomes and efficacy of these devices in patients aged ≥ 65 years, much less in those patients aged ≥ 75 years. In fact, some trials have purposely excluded patients over 80 years of age [3, 4, 39]. Still, conclusions about the impact of ICDs for the primary prevention of SCD in older patients are often extrapolated from such studies performed in these younger patient subgroups with mean ages much less than 65 years. In light of the established guidelines, an RCT specifically addressing ICD therapy in the older population is unlikely to be performed. Our meta-analysis and systematic literature review highlights the considerable under-representation of older patients in the available RCTs. Additionally, the validity of the non-randomized, retrospective studies is unclear, since they did not adjust for inherent selection biases and their study populations consisted of patients who had already been referred for, or had already received, ICD therapy.

Given the limited number of older patients enrolled in the primary prevention RCTs of ICD therapy, we combined data from four major RCTs

of primary prevention ICDs (MADIT-I, MADIT-II, DEFINITE, and SCD-HeFT). We chose these trials to minimize heterogeneity because all of them randomized patients to ICD *vs* a control arm, and the patients enrolled were similar. The results of our meta-analysis are concordant with a recent qualitative overview that concluded that the relative benefit of ICD therapy is somewhat higher in older than in younger patients in MADIT-II, MUSTT, and DEFINITE; somewhat lower in older than in younger patients in SCD-HeFT; and equivocal, but tending toward harm, in the older group compared to the younger group in DINAMIT [40]. A few studies have examined the effect of age at implantation on outcomes after ICD implantation. Most trials only provide follow-up data ranging from 3–6 years, so longer-term outcomes remain largely unknown [36]. Likewise, very little is known about the physical, emotional, and social adjustments associated with ICD implantation and the impact of age on these factors. As such, concerns are frequently raised about the effect of advanced age on the outcomes, cost–effectiveness, and QoL of such patients who receive ICDs. Based on our review of the literature, there appears to be no difference in operative, in-hospital, or long-term complications among older patients compared to younger patients [11, 18, 20, 23, 28].

One of the goals of our paper was to highlight the fact that there is extremely little QoL data on the use of ICDs in older patients — a subpopulation in which QoL is often a critical factor in clinical decision making. At this time, it remains unclear if older patients actually have a better QoL with an ICD than younger patients [35, 37, 41–44].

Two qualitative reviews have addressed the use of ICDs in older patients [1, 45]. Each review describes RCTs of ICD therapy for both secondary and primary prevention and includes descriptions of a few non-randomized cohort studies of ICD therapy in older patients. In contrast, our systematic literature review provides the first and only formal meta-analysis of data on patients ≥ 65 years and ≥ 75 years from the major RCTs on primary prevention ICDs. Additionally, our review examines in more detail both perioperative and long-term complications in older patients, and considers the effect of age on QoL in patients with ICDs.

In contrast to our findings, a recently published meta-analysis by Santangeli et al. [46] examined the effectiveness of ICDs for the primary prevention of SCD in older patients using data from MADIT-II, DEFINITE, and SCD-HeFT and found only a minimal and statistically non-significant survival benefit in older patients (HR 0.81; 95% CI 0.62–1.05; $p = 0.11$). However, the analysis by Santangeli et al. [46] defined older patients as those ≥ 60 years of age, combined data from one study for patients ≥ 60 years old with data from other studies for patients ≥ 65 years old, and did not include data from the MADIT-I and MUSTT trials of primary prevention, citing the unavailability of this data.

While RCTs will provide the strongest data on ICDs in patients ≥ 65 years, data on ICD benefit in older patients can be gleaned from registries of patients in the general population. One such registry is the American College of Cardiology-National Cardiovascular Data Registry (ACC-NCDR)-operated National ICD Registry. Since Medicare patients account for 70% of all patients entered into the National ICD Registry, this registry provides a unique opportunity to address key questions relevant to clinical practice that remain unanswered by the numerous, large RCTs [47]. Long-term outcomes data will be evaluated by combining the ICD Registry with the Medicare Claims Database and potentially with the National Death Index and as such, the National ICD Registry will more accurately reflect the costs and outcomes of ICDs implanted in older patients seen in general clinical practice compared to the highly selected, younger patient populations with fewer co-morbidities typically enrolled in RCTs [38]. Although this data will be useful, one limitation of this type of data source is the lack of a control group, because everyone enrolled in the registry will have received an ICD.

Our study has some limitations. As with any literature search of databases like PubMed, publication bias cannot be excluded and our inclusion of only published, peer-reviewed studies contributes to selection bias. Similarly, our decision to meta-analyze only RCTs may not reflect patients in general clinical practice because trial populations are often highly-selected patient subgroups. Finally, the lack of patient-level data precluded more detailed analyses such as examination of the extremely small subgroup of octogenarians who received primary prevention ICDs.

Conclusions

In contrast to a previously published age-specific meta-analysis demonstrating a lack of ICD efficacy for the secondary prevention of SCD in patients ≥ 75 years, our meta-analysis of ICD use for primary prevention of SCD suggests that ICDs may be beneficial for older patients, including those patients ≥ 75 years.

Given that the current data supporting the efficacy of ICD therapy in older patients is sparse and inconclusive, implanting an ICD in an older patient should be a decision made between the patient and the physician, which takes into account each individual's overall health status, co-morbidities, physical and mental functioning, and personal preferences. The use of ICDs in older patients should not be withheld based on age alone.

Acknowledgements

Special thanks to Gust Bardy, MD; Alfred E. Buxton, MD; Paul Dorian, MD; Jackson W. Hall, PhD; Alan Kadish, MD; Kerry Lee, PhD; Arthur J. Moss, MD; and Kevin Thorpe, PhD, who provided data for this analysis.

Conflict of interest: Dr. Kong serves on an advisory board for Medtronic and Biotronik, receives research funding from Biotronik (< $10K) and was also supported by the Ruth L. Kirschstein--National Service Research Award (Kirschstein--NRSA) National Institutes of Health (NIH) [grant number 5-T32-DK-007731-15]. The contents of this work are solely the responsibility of the authors and do not necessarily represent the official views of the NIH; Dr. Al-Khatib receives research funding (> $10K) and speaking fees (< $10K) from Medtronic Inc., and research funding and speaking fees from Biotronik (both < $10K); Dr. Sanders is co-investigator on a Medtronic Inc. research grant (> $10K); Dr. Peterson receives research funding from St. Jude Medical (<$10K).

Sponsor's role: Research supported by grant #U18HS016964 from the Agency for Healthcare Research and Quality (AHRQ). Content is solely the responsibility of the authors and does not necessarily represent the official views of the AHRQ. The sponsor had no role in the design, methods, subject recruitment, data collections, analysis or preparation of the paper.

References

1. Goldenberg I, Moss AJ. Treatment of arrhythmias and use of implantable cardioverter-defibrillators to improve survival in elderly patients with cardiac disease. Clin Geriatr Med, 2007; 23: 205–219.
2. Al-Khatib SM, Sanders GD, Mark DB et al. Implantable cardioverter defibrillators and cardiac resynchronization therapy in patients with left ventricular dysfunction: Randomized trial evidence through 2004. Am Heart J, 2005; 149: 1020–1034.
3. Hohnloser SH, Kuck KH, Dorian P et al.; DINAMIT Investigators. Prophylactic use of an implantable cardioverter-defibrillator after acute myocardial infarction. N Engl J Med, 2004; 351: 2481–2488.
4. Bigger JT Jr. Prophylactic use of implanted cardiac defibrillators in patients at high risk for ventricular arrhythmias after coronary-artery bypass graft surgery. Coronary Artery Bypass Graft (CABG) Patch Trial Investigators. N Engl J Med, 1997; 337: 1569–1575.
5. Moss AJ, Hall WJ, Cannom DS et al. 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.
6. Moss AJ, Zareba W, Hall WJ et al.; 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: 877–883.
7. Buxton AE, Lee KL, Fisher JD et al. 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.
8. Kadish A, Dyer A, Daubert JP et al.; Defibrillators in Non-Ischemic Cardiomyopathy Treatment Evaluation (DEFINITE) Investigators. Prophylactic defibrillator implantation in patients with nonischemic dilated cardiomyopathy. N Engl J Med, 2004; 350: 2151–2158.
9. Bardy GH, Lee KL, Mark DB et al.; Sudden Cardiac Death in Heart Failure Trial (SCD-HeFT) Investigators. Amiodarone or an implantable cardioverter-defibrillator for congestive heart failure. N Engl J Med, 2005; 352: 225–237.
10. Bristow MR, Saxon LA, Boehmer J et al. Cardiac-resynchronization therapy with or without an implantable defibrillator in advanced chronic heart failure. N Engl J Med, 2004; 350: 2140–2150.
11. Trappe HJ, Pfitzner P, Achtelik M et al. Age dependent efficacy of implantable cardioverter-defibrillator treatment: Observations in 450 patients over an 11 year period. Heart, 1997; 78: 364–370.
12. Hedges LV, Olkin I. Statistical methods for meta-analysis. Academic Press, Orlando 1985.
13. Healey JS, Hallstrom AP, Kuck KH et al. Role of the implantable defibrillator among elderly patients with a history of life--threatening ventricular arrhythmias. Eur Heart J, 2007; 28: 1746–1749.
14. Bansch D, Antz M, Boczor S et al. Primary prevention of sudden cardiac death in idiopathic dilated cardiomyopathy: The Cardiomyopathy Trial (CAT). Circulation, 2002; 105: 1453–1458.
15. Strickberger SA, Hummel JD, Bartlett TG et al. Amiodarone versus implantable cardioverter-defibrillator: Randomized trial in patients with nonischemic dilated cardiomyopathy and asymptomatic nonsustained ventricular tachycardia: AMIOVIRT. J Am Coll Cardiol, 2003; 41: 1707–1712.
16. Sanders GD, Inoue L, Samsa G et al. Use of Bayesian techniques in randomized clinical trials: A CMS case study. Evidence Report/Technology Assessment. Agency for Healthcare Research and Quality, Rockville, MD, 2009.
17. Peterson M. Do elderly benefit from defibrillator as primary prevention in coronary artery disease and left ventricular dysfunction? Pacing Clin Electrophysiol, 2003; 26: part II.
18. Huang DT, Sesselberg HW, McNitt S et al. Improved survival associated with prophylactic implantable defibrillators in elderly patients with prior myocardial infarction and depressed ventricular function: A MADIT-II Substudy. J Cardiovasc Electrophysiol, 2007; 18: 833–838.
19. Peto R. Why do we need systematic overviews of randomized trials? Stat Med, 1987; 6: 233–244.

20. Noseworthy PA, Lashevsky I, Dorian P et al. Feasibility of implantable cardioverter defibrillator use in elderly patients: A case series of octogenarians. Pacing Clin Electrophysiol, 2004; 27: 373–378.
21. Koplan BA, Epstein LM, Albert CM et al. Survival in octogenarians receiving implantable defibrillators. Am Heart J, 2006; 152: 714–719.
22. Duray G, Richter S, Manegold J et al. Efficacy and safety of ICD therapy in a population of elderly patients treated with optimal background medication. J Interv Card Electrophysiol, 2005; 14: 169–173.
23. Grimm W, Stula A, Sharkova J et al. Outcomes of elderly recipients of implantable cardioverter defibrillators. Pacing Clin Electrophysiol, 2007; 30 (suppl. 1): S134–S138.
24. Ermis C, Zhu AX, Vanheel L et al. Comparison of ventricular arrhythmia burden, therapeutic interventions, and survival, in patients < 75 and patients > or = 75 years of age treated with implantable cardioverter defibrillators. Europace, 2007; 9: 270–274.
25. Chan PS, Nallamothu BK, Spertus JA et al. Impact of age and medical comorbidity on the effectiveness of implantable cardioverter-defibrillators for primary prevention. Cardiovascular Quality and Outcomes. Circulation, 2009; 2: 16–24.
26. Alter P, Waldhans S, Plachta E et al. Complications of implantable cardioverter defibrillator therapy in 440 consecutive patients. Pacing Clin Electrophysiol, 2005; 28: 926–932.
27. Buxton AE. Implantable cardioverter-defibrillators should be used routinely in the elderly. Am J Geriatr Cardiol, 2006; 15: 361–364 (quiz 365–366).
28. Quan KJ, Lee JH, Costantini O et al. Favorable results of implantable cardioverter-defibrillator implantation in patients older than 70 years. Ann Thorac Surg, 1997; 64: 1713–1717.
29. Bailey SM, Wilkoff BL. Complications of pacemakers and defibrillators in the elderly. Am J Geriatr Cardiol, 2006;15: 102–107.
30. Reynolds MR, Cohen DJ, Kugelmass AD et al. The frequency and incremental cost of major complications among medicare beneficiaries receiving implantable cardioverter-defibrillators. J Am Coll Cardiol, 2006; 47: 2493–2497.
31. Al-Khatib SM, Greiner MA, Peterson ED et al. Patient and implanting physician factors associated with mortality and complications after implantable cardioverter-defibrillator implantation, 2002–2005. Circ Arrhythmia Electrophysiol, 2008; 1: 240––249.
32. Schron EB, Exner DV, Yao Q et al. Quality of life in the antiarrhythmics *versus* implantable defibrillators trial: Impact of therapy and influence of adverse symptoms and defibrillator shocks. Circulation, 2002; 105: 589–594.
33. Irvine J, Dorian P, Baker B et al. Quality of life in the Canadian Implantable Defibrillator Study (CIDS). Am Heart J, 2002; 144: 282–289.
34. Namerow PB, Firth BR, Heywood GM et al. Quality-of-life six months after CABG surgery in patients randomized to ICD *versus* no ICD therapy: Findings from the CABG Patch Trial. Pacing Clin Electrophysiol, 1999; 28: 81–88.
35. Noyes K, Corona E, Zwanziger J et al. Health-related quality of life consequences of implantable cardioverter defibrillators: Results from MADIT II. Med Care, 2007; 45: 377–385.
36. Mark DB, Anstrom KJ, Sun JL et al. Quality of life with defibrillator therapy or amiodarone in heart failure. N Engl J Med, 2008; 359: 999–1008.
37. Hamilton GA, Carroll DL. The effects of age on quality of life in implantable cardioverter defibrillator recipients. J Clin Nurs, 2004; 13: 194–200.
38. Nichol G, Stiell IG, Hebert P et al. What is the quality of life for survivors of cardiac arrest? A prospective study. Acad Emerg Med, 1999; 6: 95–102.
39. Wenger NK. Enrollment and maintenance of elderly patients in cardiovascular clinical trials. Am J Geriatr Cardiol, 2006; 15: 352–356.
40. Daubert JP, Sesselberg HW, Huang DT. Implantable cardioverter-defibrillators for primary prevention: How do the data pertain to the aged? Am J Geriatr Cardiol, 2006; 15: 88–92.
41. Craney JM, Mandle CL, Munro BH et al. Implantable cardioverter defibrillators: Physical and psychosocial outcomes. Am J Crit Care, 1997; 6: 445–451.
42. Friedmann E, Thomas SA, Inguito P et al. Quality of life and psychological status of patients with implantable cardioverter defibrillators. J Interv Card Electrophysiol, 2006; 17: 65–72.
43. Sossong A. Living with an implantable cardioverter defibrillator: Patient outcomes and the nurse's role. J Cardiovasc Nurs, 2007; 22: 99–104.
44. Thomas SA, Friedmann E, Kao CW et al. Quality of life and psychological status of patients with implantable cardioverter defibrillators. Am J Crit Care, 2006; 15: 389–398.
45. Grimm W. Outcomes of elderly heart failure recipients of ICD and CRT. Int J Cardiol, 2008; 125: 154–160.
46. Santangeli P, Di Biase L, Dello Russo A et al. Meta-analysis: Age and effectiveness of prophylactic implantable cardioverter--defibrillators. Ann Intern Med, 2010; 153: 592–599.
47. Hammill SC, Stevenson LW, Kadish AH et al. Review of the registry's first year, data collected, and future plans. Heart Rhythm, 2007; 4: 1260–1263.
48. Greenberg H, Case RB, Moss AJ et al.; MADIT-II Investigators. Analysis of mortality events in the Multicenter Automatic Defibrillator Implantation Trial (MADIT-II). J Am Coll Cardiol. 2004; 43: 1459–1465.