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# Reduction in Ventricular Tachyarrhythmias With Statins in the Multicenter Automatic Defibrillator Implantation Trial (MADIT)-II

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**OBJECTIVES** We evaluated whether statins have anti-arrhythmic effects by exploring the association of statin use with appropriate implantable cardioverter-defibrillator (ICD) therapy for ventricular tachycardia/ventricular fibrillation (VT/VF) in the Multicenter Automatic Defibrillator Implantation Trial (MADIT)-II.

**BACKGROUND** A few studies have suggested that lipid-lowering drugs may have anti-arrhythmic effects in patients with coronary artery disease.

**METHODS** Patients receiving an ICD (n = 654; U.S. centers only) in the MADIT-II study were categorized by the percentage of days each patient received statins during follow-up (90% to 100%, n = 386; 11% to 89%, n = 116; and 0% to 10%, n = 152). The Kaplan-Meier method with significance testing by the log-rank statistic and time-dependent proportional hazards regression analysis were used to evaluate the effect of statin use on the probability of ICD therapy for the combined end point VT/VF or cardiac death and for the end point VT/VF.

**RESULTS** The cumulative rate of ICD therapy for VT/VF or cardiac death, whichever occurred first, was significantly reduced in those with ≥90% statin usage compared to those with lower statin usage ($p = 0.01$). The time-dependent statin:no statin therapy hazard ratio was 0.65 ($p < 0.01$) for the end point of VT/VF or cardiac death and 0.72 ($p = 0.046$) for VT/VF after adjusting for relevant covariates.

**CONCLUSIONS** Statin use in patients with an ICD was associated with a reduction in the risk of cardiac death or VT/VF, whichever occurred first, and was associated with a reduction in VT/VF episodes. These findings suggest that statins have anti-arrhythmic properties. (J Am Coll Cardiol 2006;47:769–73) © 2006 by the American College of Cardiology Foundation

Sudden cardiac death (SCD) accounts for more than 50% of the deaths due to heart disease (1), with the vast majority from ventricular tachyarrhythmias. Statin-type hypolipidemic drugs have been shown to reduce mortality and cardiac death in patients with coronary artery disease (CAD) (2,3). These drugs also reduce the incidence of first acute major coronary events in subjects without overt CAD who have average levels of total cholesterol and low-density lipoprotein cholesterol (4). Recent data suggest that lipid-lowering drugs may have anti-arrhythmic effects (5,6).

The Multicenter Automatic Defibrillator Implantation Trial (MADIT)-II database includes information regarding ventricular arrhythmia (VA) occurrence obtained from ICD interrogation as well as detailed drug information during follow-up (7,8). The purpose of this study was to investigate whether statin use is associated with reduced VAs in patients receiving an ICD in the MADIT-II study.

## METHODS

**Study subjects.** The design, inclusion and exclusion criteria, and primary results of the MADIT-II study have been previously described (7,8). Briefly, 1,232 patients who were ≥21 years old, had a myocardial infarction one month or more before entry, and an ejection fraction ≤0.30 were randomized to ICD implant plus conventional medical therapy or conventional medical therapy alone in a 3:2 ratio.

Of 742 patients randomized to defibrillator therapy, 720 actually received an ICD. The study population consisted of 654 ICD-treated patients in whom detailed information of drug therapy for every day in the trial was available. Lipid-lowering therapy (drug and dose) was prescribed at the discretion of the treating physician. The statins used were atorvastatin, simvastatin, pravastatin, lovastatin, cerivastatin, and fluvastatin.

**Follow-up.** During the three-month follow-up visits, the dates of initiation and cessation of medications were recorded and ICD devices were interrogated. The average patient follow-up was 17 months. The distribution of the percent of statin use during follow-up (Fig. 1) was highly concentrated at both ends of the range. Thus, the cut points

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**Abbreviations and Acronyms**

CAD = coronary artery disease
CI = confidence interval
ICD = implantable cardioverter-defibrillator
MADIT = Multicenter Automatic Defibrillator Implantation Trial
SCD = sudden cardiac death
VA = ventricular arrhythmias
VF = ventricular fibrillation
VT = ventricular tachycardia

of ≥90% and ≤10% statin use were arbitrarily selected, and three groups of patients were identified: 1) patients who used statins for ≥90% of the time (n = 386); 2) patients who used statins 11% to 89% of the time (n = 116); and 3) patients who used statins ≤10% of the time (n = 152). As there were six statins used in this trial at varying dosages, no attempt was made to compare one statin and/or one dose to another.

**End points of the study.** The prespecified primary end point in this substudy was the first occurrence of cardiac death or appropriate ICD therapy (anti-tachycardia pacing or shock) for ventricular tachycardia (VT)/ventricular fibrillation (VF). The secondary end point was first appropriate ICD therapy for VT/VF, with censoring of death when it occurred. Tertiary end points included sudden and non-sudden cardiac death.

A core lab reviewed all stored electrocardiograms and determined the frequency of appropriate ICD therapy for treatment of VT or VF on the basis of the interrogation findings. Details of the ICD devices, their programming, and their interrogation were recently reported (9). An end point committee reviewed all mortality events, as recently reported (10).

**Statistical methods.** The effect of statins on the cumulative probabilities of the end points were determined by the Kaplan-Meier method, with significance testing by the log-rank statistic. Proportional hazards regression analysis was used to evaluate the effect of statin use (yes/no) on the probability of ICD therapy for the combined end point VT/VF or cardiac death and for the end point VT/VF (11).

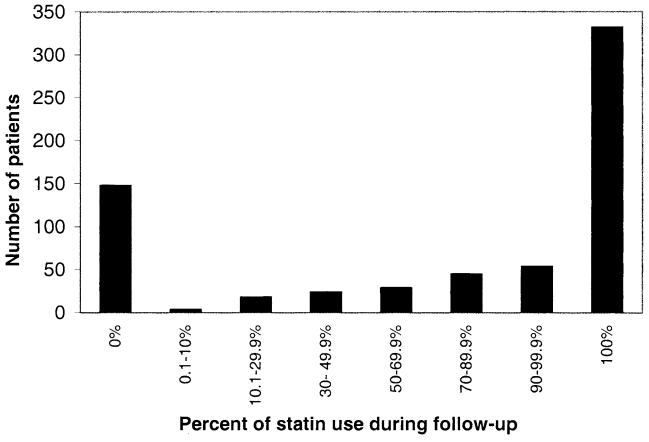


**Figure 1.** Frequency distribution of the percentage of days during follow-up on which the implantable cardioverter-defibrillator treated patients (n = 654) received statin drugs.

**Table 1.** Baseline Clinical Characteristics of Patients by Use of Statins During Follow-up*

| Variable | ≤10% Statin Use (n = 152) | 11%–89% Statin Use (n = 116) | ≥90% Statin Use (n = 386) | p Value |
|---|---|---|---|---|
| Age ≥65 yrs | 68 | 48 | 50 | <0.01 |
| Men | 82 | 81 | 85 | 0.47 |
| Non-Hispanic whites | 82 | 84 | 89 | 0.12 |
| Past treatment for hypertension | 55 | 57 | 51 | 0.43 |
| Past treatment for ventricular arrhythmias | 10 | 14 | 10 | 0.57 |
| Current or former cigarette smoker | 78 | 80 | 81 | 0.63 |
| Diabetes mellitus | 30 | 41 | 33 | 0.14 |
| NYHA functional class II–IV† | 72 | 66 | 62 | 0.10 |
| Blood urea nitrogen >25 mg/dl | 40 | 36 | 24 | <0.01 |
| Coronary angioplasty | 38 | 42 | 50 | 0.03 |
| Coronary artery bypass graft | 54 | 59 | 61 | 0.28 |
| Interval of >18 months between most recent MI and enrollment | 73 | 74 | 79 | 0.37 |
| Heart rate ≥80 beats/min | 35 | 37 | 27 | 0.07 |
| Dual chamber ICD | 45 | 38 | 50 | 0.06 |
| Cardiac findings at enrollment | | | | |
| Atrial fibrillation | 11 | 13 | 7 | 0.12 |
| QRS interval >0.12 s | 43 | 43 | 38 | 0.45 |
| Left bundle branch block | 19 | 21 | 18 | 0.68 |
| Right bundle branch block | 9 | 10 | 9 | 0.94 |
| Ejection fraction <0.25 | 54 | 57 | 45 | 0.04 |
| Medications at enrollment | | | | |
| Beta-blockers | 50 | 68 | 67 | <0.01 |
| Calcium antagonists | 13 | 10 | 13 | 0.72 |
| Digitalis | 66 | 64 | 58 | 0.14 |
| ACE inhibitors | 78 | 75 | 78 | 0.82 |
| Amiodarone | 7 | 9 | 6 | 0.41 |
| Class I anti-arrhythmics | 3 | 3 | 2 | 0.67 |
| Diuretics | 82 | 77 | 71 | 0.03 |

Values are expressed as percentages. The p values are for a comparison of the three groups by a chi-square test or a Fisher's exact test. *Statin use (≤10%, 11% to 89%, ≥90%) reflects the percentage of days the patients received statins during follow-up. See Methods for further details. †New York Heart Association (NYHA) functional class recorded in the 3-month period before enrollment.

ACE = angiotensin-converting enzyme; ICD = implantable cardioverter-defibrillator.

Subsequently, a time-dependent proportional hazards analysis was used to evaluate the effect of statin use on these end points in a more precise manner. Statin use was treated as a time-dependent covariate, an approach that takes into account each day a patient was on or off a statin during the study, with the onset or offset of statin use on the day of change. The baseline variables that had differences between the three statin use groups (Table 1), using a p value <0.10, and variables that were thought to be of clinical relevance, were evaluated in the proportional hazards stepwise selection model. Only covariates with a p value <0.05 in the

proportional-hazards model were included in the final model. All tests of statistical significance were two-sided. SAS version 9.1.3 (SAS Institute, Cary, North Carolina) was used in the data analyses.

## RESULTS

**Baseline characteristics.** Of the 720 patients in the ICD arm, 67% were taking lipid-lowering drugs (statins in 96%) at baseline, and of the 490 patients in the conventional therapy arm, 65% were taking lipid-lowering drugs (statins in 96%) at baseline. The baseline characteristics of the patients grouped by statin use (≤10%, 11% to 89%, ≥90% of the follow-up time in the trial) are presented in Table 1. The group receiving statins for ≥90% of the follow-up time were younger and had lower blood urea nitrogen, less diuretic use, more coronary angioplasty, higher ejection fraction and greater beta-blocker use compared with the group receiving statins ≤10% of the follow-up time ($p < 0.05$).

**Statin effects on VT/VF.** The cumulative probabilities of time to appropriate therapy for the combined end point VT/VF or cardiac death and for just VT/VF by statin usage are presented in Figures 2A and 2B, respectively. When comparing the ≥90% statin versus the ≤10% statin use groups, there was a lower cumulative probability of VT/VF or cardiac death ($p < 0.01$) and of VT/VF ($p = 0.06$). Statin use was associated with a significant reduction in SCD ($p < 0.01$), but no meaningful reduction in non-sudden cardiac death ($p = 0.21$) in the ≥ 90% statin group compared with the ≤10% statin group (Figs. 3A and 3B).

Time-dependent statin use, using a time delay of zero days, was associated with a hazard ratio of 0.65 (95% confidence interval [CI] 0.49 to 0.87; $p < 0.01$) for the combined end point cardiac death (n = 42) or appropriate

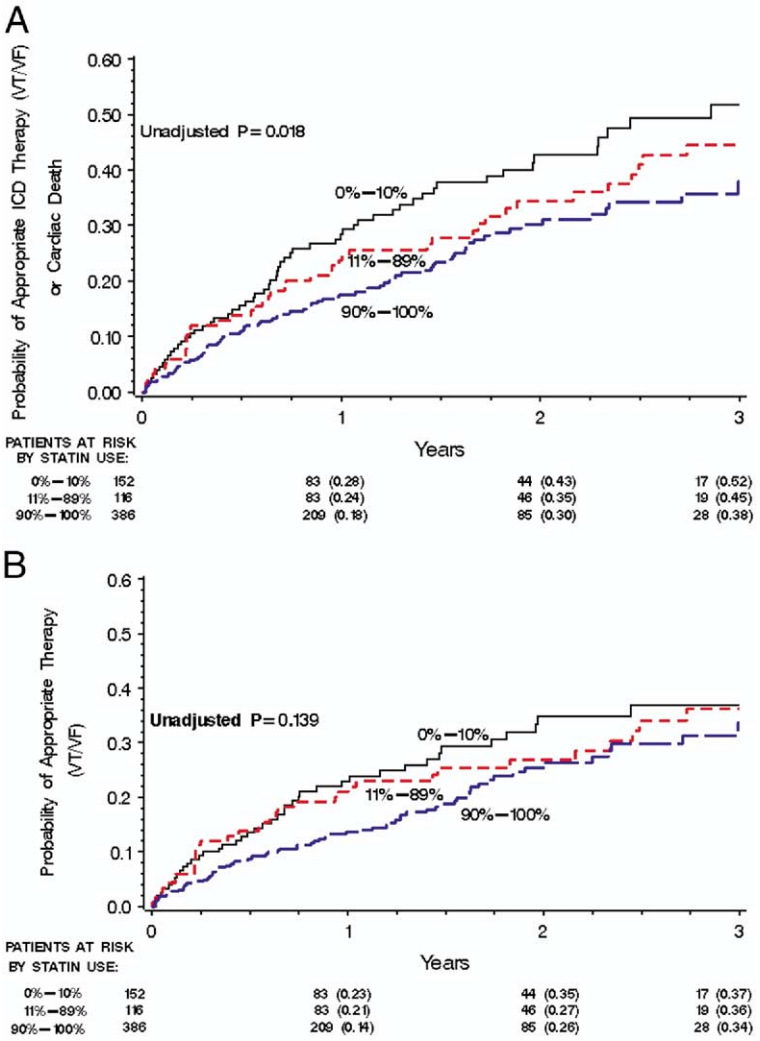


**Figure 2.** **(A)** Cumulative probability of appropriate implantable cardioverter-defibrillator (ICD) therapy for cardiac death or ventricular tachycardia/ventricular fibrillation (VT/VF) by percentage of days that statin therapy was used (≥90%, 11% to 89%, and ≤10%) during follow-up. Numbers below each graph are the number of patients at risk in the time period; the p value assesses differences among the three curves. **(B)** Cumulative probability of appropriate ICD therapy for VT/VF by percentage of days that statin therapy was used (≥90%, 11% to 89%, and ≤10%) during follow-up. Numbers below each graph are the number of patients at risk in the time period; the p value assesses differences among the three curves.

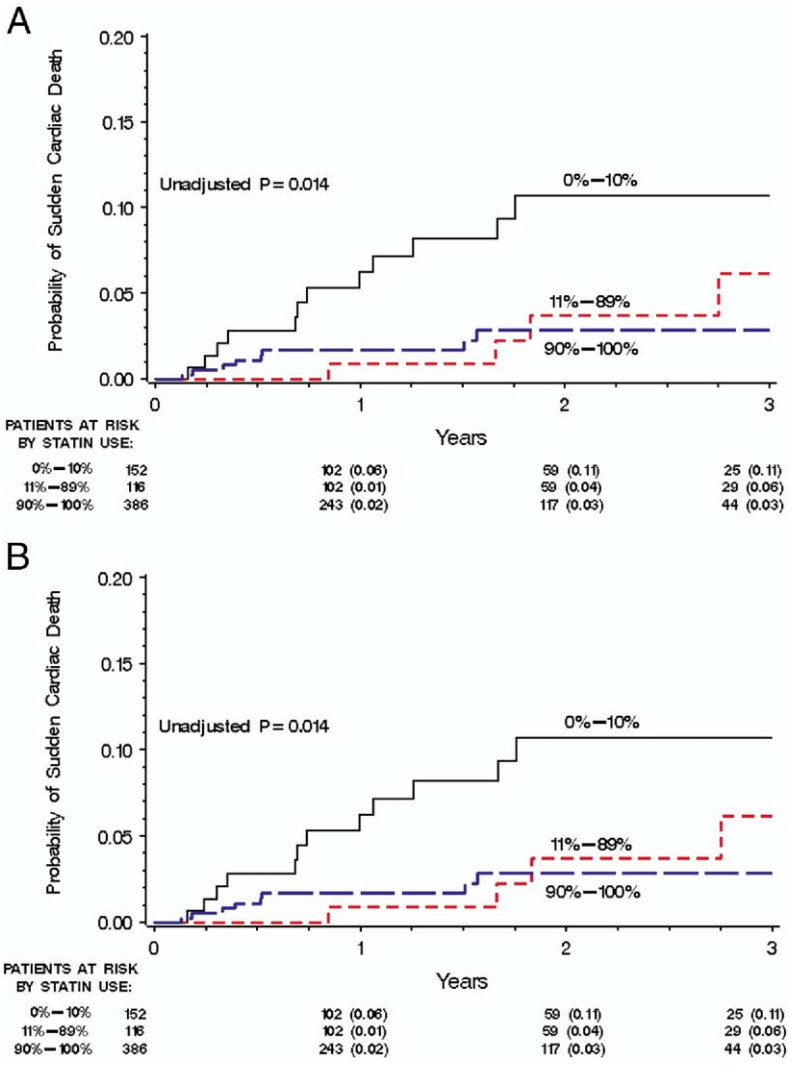


**Figure 3.** **(A)** Cumulative probability of death classified as sudden cardiac, by percentage of days that statin therapy was used (≥90%, 11% to 89%, and ≤10%) during follow-up. Numbers below each graph are the number of patients at risk in the time period; the p value assesses differences among the three curves. **(B)** Cumulative probability of death classified as non-sudden cardiac, by percentage of days that statin therapy was used (≥90%, 11% to 89%, and ≤10%) during follow-up. Numbers below each graph are the number of patients at risk in the time period; the p value assesses differences among the three curves.

VT/VF therapy (n = 153), whichever comes first, and 0.72 (95% CI 0.52 to 0.99; p = 0.046) for the single end point appropriate VT/VF therapy, after adjusting for relevant covariates, which were beta-blocker use, blood urea nitrogen >25 mg/dl, and New York Heart Association functional class ≥2 (Table 2). These hazard ratios translate into risk reductions of 35% for cardiac death or VT/VF and 28% for VT/VF, respectively.

Time-dependent statin use, using a time delay of four weeks, was associated with adjusted hazard ratios of 0.77 (95% CI 0.58 to 1.04; p = 0.08) and 0.79 (95% CI 0.57 to 1.11; p = 0.17) for the two specified end points, respectively.

## DISCUSSION

The principal finding of this analysis is that statin use was associated with fewer VT/VF episodes. There was a 28% reduction in the risk of a first VT/VF episode with statin use.

This study adds to the findings from several other studies. De Sutter et al. (5) examined 78 patients with coronary disease and life-threatening VA treated with ICD therapy. Patients who received lipid-lowering therapy had fewer VA episodes compared with those who did not (6 of 27 or 22%, vs. 29 of 51 or 57%, p < 0.05). Mitchell et al. (6) examined VA recurrence rates in patients who had CAD and near-fatal VA and received an ICD. There was a 40% reduction in the risk of VA recurrence in the group that received lipid-lowering therapy (n = 83; 79% statins) compared with the group that did not (n = 279) (reduction in hazard 0.40, 95% CI 0.15 to 0.58), after adjusting for baseline inequities. Chiu et al. (12) studied 281 patients who had CAD and underwent ICD implantation and observed a reduction in first ICD therapy for VA (adjusted hazard ratio 0.60, p = 0.01) among patients who used statin therapy (n = 154) compared with those who did not (n = 127).

**Table 2.** Effect of Statin Therapy on Cardiac Death and ICD Therapy for Ventricular Tachyarrhythmias

| | Cardiac Death or ICD Therapy for VT/VF Hazard Ratio† (95% CI) | ICD Therapy for VT/VF Hazard Ratio† (95% CI) |
|---|---|---|
| Statin* | 0.65 (0.49, 0.87) | 0.72 (0.52, 0.99) |
| p Value | 0.004 | 0.046 |

*Time-dependent statin use, using a time-delay of zero days (see Methods). The variables evaluated in the proportional hazards regression stepwise selection model were age ≥65 yrs, congestive heart failure New York Heart Association (NYHA) function class ≥2, blood urea nitrogen (BUN) >25 mg/dl, coronary angioplasty, heart rate ≥80 beats/min, dual chamber implantable cardioverter-defibrillator (ICD), ejection fraction (EF) <0.25, beta-blocker use, diuretic use, coronary artery bypass graft, atrial fibrillation, and QRS duration >0.12 s. †This hazard ratio is adjusted for BUN >25 mg/dl, congestive heart failure NYHA functional class ≥2, and beta-blocker use, the only three variables that made a significant contribution to the combined end point model. There were eight missing observations in this model due to missing information about BUN in one patient and NYHA functional class in seven patients. Analyses are based on 153 ventricular tachycardia/ventricular fibrillation (VT/VF) events and 42 cardiac death events not preceded by VT/VF events.

Statins have also been reported to improve regulation of coronary arterial tone and nitric oxide-mediated endothelial function, inhibit cell proliferation, stabilize atherosclerotic plaques, have anti-inflammatory properties, and provide anti-oxidant effects. The mechanism by which statins reduce VAs may relate indirectly to one or more of these effects. For example, the anti-oxidant and anti–cell-proliferative effects of statins may play a role in plaque stabilization and thus contribute to an anti-arrhythmic effect by reducing ischemia-related ventricular tachyarrhythmias. Of interest, statin therapy has been associated with improved survival in heart failure patients independent of its effect on cholesterol levels (13).

Dietary polyunsaturated fatty acids have been reported to favorably alter the structure of the phospholipid part of the cardiac cell membrane and provide immediate anti-arrhythmic effects in lab experiments (14–16). We speculate that statins may similarly alter the lipid portions of the membrane through which the transmembrane segments of ion channels penetrate, thereby affecting ion-channel conductances. Statins may also have some membrane-stabilizing properties. The exact mechanism by which statins may reduce arrhythmias is unknown.

Several lines of evidence from our study favor the hypothesis that statins have anti-arrhythmic properties. First, a dose-response effect was present. Second, the time-dependent analysis revealed a greater decrease in VA in patients taking statin therapy compared with those not taking a statin, using a time delay of zero days rather than four weeks. This suggests an immediate effect of these drugs rather than a delayed effect related to a slowing of the rate of progression of atherosclerosis. Third, the findings have biologic plausibility related to potential lipid-altering effects in the cardiac cell membrane.

**Study limitations.** This was an observational study and statin therapy was not randomized. The higher statin-use subjects may have been less sick than the lower statin-use subjects, and there may have been incomplete statistical adjustment for observed imbalances. In addition, there may be imbalance in other relevant variables that were not measured.

**Conclusions.** In the MADIT-II study, statins were associated with a reduced risk of cardiac death or VT/VF and with reduced VT/VF episodes. These findings suggest that statins have anti-arrhythmic properties.

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## REFERENCES

1. Centers for Disease Control and Prevention. State specific mortality from sudden cardiac death—United States, 1999. MMWR 2002;51:123–6.
2. Scandinavian Simvastatin Survival Study Group. Randomised trial of cholesterol lowering in 4444 patients with coronary disease: the Scandinavian Simvastatin Survival Study (4S). Lancet 1994;344:1383–9.
3. LIPID Study Group. Prevention of cardiovascular events and death with pravastatin in patients with coronary heart disease and a broad range of initial cholesterol levels. N Engl J Med 1998;339:1349–57.
4. Downs J, Clearfield M, Weis S, Whitney E, et al. Primary prevention of acute coronary events with lovastatin in men and women with average cholesterol levels: results of AFCAPS/TexCAPS. JAMA 1998;279:1615–22.
5. De Sutter J, Tavernier R, De Buyzere M, Jordaens L, et al. Lipid lowering drugs and recurrences of life-threatening ventricular arrhythmias in high-risk patients. J Am Coll Cardiol 2000;36:766–72.
6. Mitchell LB, Powell JL, Gillis AM, Kehl V, et al. Are lipid-lowering drugs also antiarrhythmic drugs? An analysis of the Antiarrhythmics Versus Implantable Defibrillators (AVID) trial. J Am Coll Cardiol 2003;42:81–7.
7. Moss AJ, Cannom DS, Daubert JP, Hall WJ, et al. Multicenter Automatic Defibrillator Implantation Trial II (MADIT II): design and clinical protocol. Ann Noninvasive Electrocardiol 1999;4:83–91.
8. Moss AJ, Zareba W, Hall WJ, Klein H, et al. Prophylactic implantation of a defibrillator in patients with myocardial infarction and reduced ejection fraction. N Engl J Med 2002;346:877–83.
9. Moss AJ, Greenberg H, Case RB, Zareba W, et al. Defibrillator long-term clinical course of patients after termination of ventricular tachyarrhythmia by an implanted defibrillator. Circulation 2004;110:3760–5.
10. Greenberg H, Case RB, Moss AJ, Brown MW, et al. Analysis of mortality events in the Multicenter Automatic Defibrillator Implantation Trial (MADIT-II). J Am Coll Cardiol 2004;43:1459–65.
11. Cox D. Regression and life-tables. J R Stat Soc B 1972;34:187–220.
12. Chiu JH, Abdelhadi RH, Chung MK, Gurm HS, et al. Effect of statin therapy on risk of ventricular arrhythmia among patients with coronary artery disease and an implantable cardioverter-defibrillator. Am J Cardiol 2005;95:490–1.
13. Horwich TB, MacLellan WR, Fonarow GC. Statin therapy is associated with improved survival in ischemic and non-ischemic heart failure. J Am Coll Cardiol 2004;43:642–8.
14. Lamers J, Hartog J, Verdouw P, Hulsmann W. Dietary fatty acids and myocardial infarction. Basic Res Cardiol 1987;82 Suppl 1:209–21.
15. Kang J, Leaf A. Prevention of fatal cardiac arrhythmias by polyunsaturated fatty acids. Am J Clin Nutr 2001;71 Suppl 1:202S–7S.
16. Pound E, Kang J, Leaf A. Partitioning of polyunsaturated fatty acids, which prevent cardiac arrhythmias, into phospholipids cell membranes. J Lipid Res 2001;42:346–51.