Clin. Cardiol. 29, 237–242 (2006)

Reviews

Implantable Cardiac Arrhythmia Devices—Part II: Implantable Cardioverter Defibrillators and Implantable Loop Recorders

FRED KUSUMOTO, M.D., AND NORA GOLDSCHLAGER, M.D.*

Electrophysiology and Pacing Service, Division of Cardiology, Department of Medicine, Mayo Clinic, Jacksonville, Florida, and *Cardiology Division, Department of Medicine, San Francisco General Hospital, and Department of Medicine, University of California, San Francisco, California, USA

Part I of this paper appeared in May 2006 (Clin Cardiol 2006;29:189–194).

Summary: Implantable cardiac devices have become firmly entrenched as important therapeutic tools for a variety of cardiac conditions. The second part of this two-part review discusses the contemporary use and follow-up of implantable cardioverter defibrillators (ICD) and the implantable loop recorder. The ICD has become the standard therapy for protecting patients against sudden cardiac death. Two recent trials, the Multicenter Automatic Defibrillator Trial II (MADIT II) and the Sudden Cardiac Death Heart Failure Trial (SCD-HEFT), demonstrated that the ICD is associated with a significant survival benefit for patients with reduced ejection fraction (< 0.30–0.35), particularly if heart failure symptoms are present. The ICD has an important role in the management of other conditions associated with a high risk for sudden death, such as hypertrophic cardiomyopathy, long QT syndrome, and Brugada syndrome. The implantable loop recorder has become an important diagnostic tool for the patient with unexplained syncope.

Key words: pacemakers, defibrillators, cardiac resynchronization, loop recorder, syncope, implantable devices

Address for reprints:

Fred M. Kusumoto, M.D.
Electrophysiology and Pacing Service
Cardiology Division
Mayo Clinic
4500 San Pablo Ave.
Jacksonville, FL 32224, USA
e-mail: Kusumoto.fred@mayo.edu

Received: September 19, 2005
Accepted: February 16, 2006

Implantable Cardioverter Defibrillators

Indications

In general, implantable cardioverter defibrillators (ICD) are implanted in patients who have experienced cardiac arrest or an equivalent event such as syncope (secondary prevention), or to prevent a first episode in a patient at high risk for developing a potentially malignant ventricular arrhythmia (primary prevention).

Secondary prevention: Two large studies have evaluated the use of ICDs in patients who have experienced sudden cardiac death. In the Antiarrhythmics Versus Implantable Defibrillator (AVID) study, 1,016 patients were randomized to ICD implant or antiarrhythmic drug therapy.[1] The ICD was associated with a 31% decrease in mortality at 3 years. Similar results were found in the Canadian Implantable Defibrillator Study (CIDS).[2] In CIDS, 659 patients with cardiac arrest or syncope who had ventricular tachycardia (VT) induced at electrophysiologic testing were randomized to ICD therapy or amiodarone. At 3 years, the ICD was associated with a 20% decrease in mortality that approached statistical significance.

Several studies published from the AVID registry of 4,450 patients provide additional important information. First, 278 patients were identified as having transient or correctable causes for VT/ventricular fibrillation (VF) including myocardial ischemia or electrolyte disorders.[3] However, subsequent mortality was not different between patients with correctable causes and the rest of the registry patients. Second, the 334 patients with nonischemic cardiomyopathy had survival rates similar to those of the 2,268 patients with coronary artery disease.[4] In general, patients who have experienced sudden cardiac death should be evaluated for ICD implant, with specific consideration of patient wishes, life expectancy, and comorbid conditions.

Primary prevention: Patients with coronary artery disease (CAD), reduced left ventricular ejection fraction (EF), and nonsustained VT have a 20–30% incidence of cardiac arrest during the 5-year period after a myocardial infarction (MI).[5]

The Multicenter Automatic Defibrillator Trial (MADIT) randomized 196 patients with prior MI and EF < 0.35, nonsustained VT, and inducible ventricular arrhythmias at electrophysiologic testing to ICD implantation or medical therapy.[6] Implantation of an ICD was associated with a significant reduction in all-cause mortality (hazard ratio 0.46). In a similar patient population, the Multicenter Unsustained Tachycardia Trial (MUSTT) found that ICD implant was associated with a 60% decrease in mortality at 5 years.[7]

Several recently published trials have provided additional information on the use of ICDs in patients with reduced EF due to CAD. In MADIT II, 1,232 patients with CAD and severely reduced EF (< 0.30) without documented nonsustained VT were randomized to receive an ICD or medical therapy alone.[8] After mean follow-up of 20 months, the mortality rate was 19.8% in the patients who did not receive an ICD and 14.2% in the ICD group (p = 0.016). In the Sudden Cardiac Death Heart Failure Trial (SCD-HEFT), patients with reduced EF (< 0.35) due to ischemic or nonischemic cardiomyopathy and New York Heart Association (NYHA) class II or III heart failure were randomized to receive placebo, amiodarone, or an ICD.[9] Over 2,500 patients were enrolled, and after 3.8 year follow-up a 23% reduction in all-cause mortality was observed in patients receiving ICD compared with placebo. No differences in survival were detected between patients receiving amiodaone or placebo. However, in the Defibrillator in Acute Myocardial Infarction Trial (DINAMIT), 674 patients with MI within the preceding 6 to 40 days with an EF < 0.35 and abnormal heart rate variability indices by Holter monitoring were followed for 2.5 years, with no significant difference in survival in patients who did (7.5%) and did not (6.9%) receive and ICD.[10]

At the present time, the data support consideration for ICD implantation in patients with CAD, severely reduced EF (< 0.30–0.35), and class III or higher heart failure (Fig. 1). However, application of trial data to individual patient care is not always straightforward. First, even with careful measurements, EF estimates from standard echocardiography varied from −18 to 8% from EF obtained from magnetic resonance imaging.[11] Ejection fraction varies with loading conditions and temporally from acute ischemic events. The DINAMIT data appear to stress the importance of waiting > 40 days after an MI before using EF to evaluate risk. Similarly, in a subgroup analysis of the MADIT II data, ICD therapy did not confer a survival benefit in patients enrolled within 18 months of an acute MI.[12] However, in an analysis of the Valsartan in Acute Myocardial Infarction Trial (VALIANT), the risk for sudden death was highest during the first 30 days after MI, 1.4% per month and decreased to 0.14% per month after 2 years.[13] In addition, EF provided the greatest discriminatory effect for identifying risk of sudden cardiac death during the first 6 months after MI. The complexity of data from randomized trials underscores the importance of careful physician and patient discussion before ICD implantation.

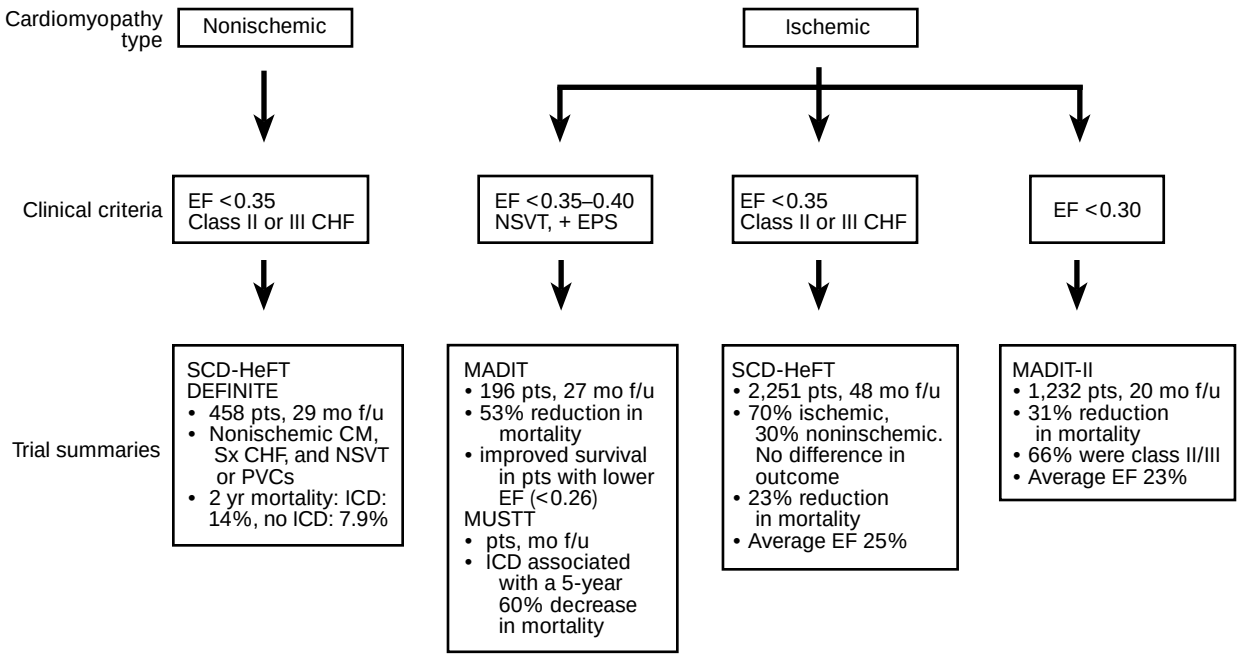

FIG. 1 Summary of trial data from primary prevention studies for patients with cardiomyopathy based on ejection fraction and other clinical characteristics. MADIT = Multicenter Automatic Defibrillator Implantation Trial, MUSTT = Multicenter Unsustained Tachycardia Trial, SCD-HeFT = Sudden Cardiac Death in Heart Failure Trial, DEFINITE = Defibrillators in Non-Ischemic Cardiomyopathy Treatment Evaluation trial, pts = patients, yr = year, mo = month, EF = ejection fraction, EPS = electrophysiologic testing, f/u = follow-up, CHF = congestive heart failure, NSVT = nonsustained ventricular tachycardia, PVC = premature ventricular contraction, ICD = implantable cardioverter defibrillator, CM = cardiomyopathy.

Although clinically effective, the cost implications of ICD therapy for primary prevention must be addressed.[14, 15] In the United States, there are approximately three million persons with advanced left ventricular dysfunction or other risk factors for sudden cardiac death; with an average ICD cost of $20,000 to $25,000, the potential cost to the United States healthcare system is 60–75 billion dollars, with an annual cost of 8 billion dollars. Since the likelihood of appropriate use of ICD therapy in primary prevention studies is approximately 20% over 5 years, development of further risk stratification tools will become important to determine optimal use of the ICD in clinical practice.[9]

Several specific patient groups at high risk for sudden death should also be considered for primary prevention with ICD therapy (nonischemic cardiomyopathy, hypertrophic cardiomyopathy, long QT syndrome, Brugada syndrome, and congenital heart disease). The use of the ICD in these patient groups is summarized in Table I and below. The clinician should also be aware of other conditions associated with sudden cardiac death, such as arrhythmogenic right ventricular cardiomyopathy and the short QT syndrome, that are not covered in this review.

Three small- to moderate-sized prospective randomized trials have specifically evaluated the use of ICDs in patients with nonischemic cardiomyopathy. In the Amiodarone Versus Implantable Cardioverter Defibrillator Randomized Trial in Patients with Nonischemic Cardiomyopathy and Asymptomatic Nonsustained Ventricular Tachycardia (AMIOVIRT), 103 patients with nonischemic cardiomyopathy (EF < 0.35) and asymptomatic VT were randomized to amiodarone or ICD therapy.[16] The study was stopped prematurely after 3 years when interim analysis revealed no significant differences in the survival curves between the two groups (amiodarone 87% vs. ICD 88%). In the Cardiomyopathy Arrhythmia Trial (CAT), 104 patients with angiographically proven symptomatic nonischemic cardiomyopathy (NYHA II or III, EF < 0.30) were randomized to receive an ICD or medical therapy alone.[17] At a 1-year interim analysis, the overall mortality for the entire patient group was 5.6%. Since this was significantly less than the expected 30% mortality rate, the tri-

TABLE I Use of implantable cardioverter defibrillators (ICD)

Condition	Indications	Clinical scenarios in which ICD implant should be considered
Coronary artery disease	• Aborted sudden cardiac death[1,2] • Sustained ventricular arrhythmias • EF< 0.30 more than 6 weeks after myocardial infarction[8,10] • EF< 0.40, nonsustained ventricular tachycardia, and inducible at EPS[7]	
Dilated cardiomyopathy	• Aborted sudden cardiac death • Sustained ventricular arrhythmias • Ejection fraction < 0.35 associated with NYHA II or III symptoms, particularly if ventricular arrhythmias are present[9, 18]	• Syncope
Hypertrophic cardiomyopathy	• Aborted sudden cardiac death • Sustained ventricular arrhythmias	• Syncope[20] • Significant family history of SCD[20] • Nonsustained ventricular tachycardia on continuous 24° electrocardiographic monitoring[20] • Septal thickness > 3 cm[20]
Long QT syndrome	• Aborted sudden cardiac death • Continued symptoms despite Rx	• High-risk genotypes (LQT 3) or significant family history of SCD[21] • Drug intolerance or noncompliance
Brugada syndrome	• Aborted sudden cardiac death • Sustained ventricular arrhythmias	• Syncope and classic associated ECG findings (RBBB pattern and ST-segment elevation in V_1) [22, 23] • Significant family history of SCD
Repaired congenital heart disease	• Aborted sudden cardiac death • Sustained ventricular arrhythmias	• Syncope associated with repaired tetralogy of Fallot, transposition of the great vessels, coarctation of the aorta, particularly if inducible at EPS [24, 25]

Abbreviations: EPS = electrophysiologic testing, SCD = sudden cardiac death, LQT 3 = long QT syndrome type 3 associated with Na^+ channel defects, EF = ejection fraction, NYHA = New York Heart Association, Rx = drug treatment.

al was stopped before complete enrollment. Most recently, in the Defibrillators in Nonischemic Cardiomyopathy Treatment Evaluation (DEFINITE) trial, 458 patients with nonischemic cardiomyopathy (EF < 0.35) and spontaneous ventricular ectopy (> 10 premature ventricular contractions (PVCs)/h or nonsustained VT) were randomized to receive an ICD or standard medical therapy.[18] After 2-year follow-up, the mortality rate was not significantly different between the two groups (medical therapy 33 deaths vs. ICD 23 deaths; p = 0.06). However, the arrhythmic death rate was significantly higher in the group receiving medical therapy alone (medical therapy 13.8% vs. ICD 8.1%). In the much larger SCD-HeFT trial, approximately 50% of patients had nonischemic cardiomyopathy and the survival benefit for ICD therapy was similar for both ischemic and nonischemic cardiomyopathy.[9] To summarize, ICD implantation should de considered in patients with reduced EF (< 0.35) due to nonischemic cardiomyopathy and heart failure symptoms.

Patients with hypertrophic cardiomyopathy have an estimated annual mortality rate of 1% as shown in community-based studies and are at increased risk for sudden cardiac death depending on the presence or absence of risk factors.[19] No randomized trials of ICD use in patients with hypertrophic cardiomyopathy are currently available. In a multicenter retrospective evaluation of ICD use in patients with hypertrophic cardiomyopathy at high risk for sudden cardiac death, appropriate ICD use was observed at a rate of 11% per year for secondary prevention (cardiac arrest or spontaneous and sustained VT) and in 5% per year for primary prevention in a high-risk cohort.[20] Risk factors for future arrhythmic events include syncope, particularly in young patients or patients with recurrent or exertional syncope; family history of sudden cardiac death, particularly in a first-degree relative; absolute thickening of the ventricular septum ≥ 30 mm; spontaneous nonsustained or sustained VT; and an abnormal hemodynamic response to exercise (≤ 20 mmHg rise in blood pressure during exercise or after recovery).

The use of ICDs in patients with "primary electrical" disease has not been well studied. The long QT syndrome is a heterogeneous group of genetically determined disorders associated with QT interval prolongation (QTc > 0.44 s in men and > 0.46 s in women) due to defects associated with changes in potassium or sodium permeability. Beta blockers are first-line therapy, and an ICD is usually considered in patients with continued symptoms despite beta-blocker therapy.[21] Brugada syndrome also appears to be a genetic disease associated with abnormal sodium-channel function and has a characteristic electrocardiogram with terminal positive forces and ST-segment elevation in lead V_1.[22] The use of ICDs in this population has not been formally studied with randomized controlled trials. However, these patients once identified appear to be at high risk for ventricular arrhythmias and often have ICDs implanted. In the Defibrillators vs. Beta Blockers in Unexpected Death in Thailand (DEBUT) trial, 86 patients who survived cardiac arrest or had a Brugada type electrocardiogram were randomized to beta blockers or prophylactic ICD implant.[23] After 3-year follow-up, there were four deaths that all occurred in the beta-blocker arm. There were seven patients in the ICD arm who had appropriately treated VF.

The final high-risk group considered here are patients with congenital heart disease. In a retrospective analysis of a large database of 3,589 patients with surgically repaired congenital heart disease, unexpected sudden cardiac death was more common in patients with aortic stenosis, coarctation of the aorta, corrected transposition of the great arteries, or tetralogy of Fallot.[24] The risk of sudden cardiac death increased incrementally 20 years after surgery for aortic stenosis, coarctation of the aorta, and tetralogy of Fallot. In another retrospective study of adult patients with repaired tetralogy of Fallot, sudden cardiac death was more common in those with wide QRS complexes (> 180 ms) and moderate to severe left ventricular systolic dysfunction (EF < 0.40).[25]

Follow-Up

Implantable cardioverter-defibrillators should be interrogated every 3 to 6 months and after delivery of any shock therapy. During device interrogation, pacing thresholds can be ascertained and electrograms evaluated for the presence of noise that might suggest lead malfunction due to fracture or insulation break. Lead resistances should be directly measured; high resistances suggest the possibility of a conductor wire fracture, while low impedances suggest an insulation break. Event counters should be evaluated to determine whether the patient is having brief episodes of ventricular arrhythmias that have not required ICD therapy.

In earlier generations of ICDs, patients had the ICD function tested directly by induction of VF in the electrophysiology laboratory (defibrillation threshold testing); for current ICDs implanted in the pectoral region defibrillation, testing may not be routinely required if low (< 20 joules) thresholds were documented at implant or if intervening clinical events have not occurred.[26] However, given the grave consequences of ICD failure, decisions on the frequency of defibrillation threshold testing should be carefully considered for individual patients.

Finally, several highly publicized ICD recalls or software problems have involved several manufacturers. Medtronic ICDs implanted between April 2001 and December 2003 can potentially develop sudden battery depletion within hours or days that can result in loss of device function with an estimated rate of 0.2–1.5%.[27] Certain Guidant (Guidant Corp., Indianapolis, Ind., USA) ICDs may develop deterioration of the wire insulator within the lead connector block that can result in loss of device function with an estimated rate of failure between 0.2–0.6% over the lifetime of the device.[28] Since 1990, the Food and Drug Administration has issued nearly 30 safety alerts and recalls affecting nearly 337,000 ICDs.[29] When counseling patients, clinicians must consider the device failure rate, age of the device, and the risk and accompanying consequences of infection (approximately 1%) after device replacement. These problems underscore the importance for physicians and their professional organizations to take an active role in monitoring device reliability and safety.

Implantable Loop Recorders

Indications

Several randomized trials have evaluated the use of implantable loop recorders (ILRs) for the evaluation of patients with syncope.[30–32] Syncope is a common problem that may be the first manifestation of a life-threatening arrhythmia. Cardiac causes of syncope have a much worse prognosis than noncardiac causes, but diagnostic tests such as echocardiography, tilt table testing, Holter monitoring, and electrophysiologic testing are costly and have low diagnostic yield, particularly in patients without a history of cardiac disease. In the Randomized Assessment of Syncope Trial (RAST), 60 patients with unexplained syncope were randomized to "conventional" cardiac evaluation (external loop recorder, echocardiography, Holter monitoring, electrophysiologic testing) or prolonged monitoring using an ILR. Prolonged monitoring (months to even years) was more likely to result in a diagnosis than conventional testing (55 vs. 19%, $p = 0.0014$).[30] Episodes of transient symptomatic bradycardia were the most common findings. In the International Study of Syncope of Uncertain Etiology (ISSUE) study, ILRs were implanted and tilt table testing was performed in 111 patients.[31] The patients were analyzed in two groups: 29 patients with tilt-positive and 82 patients with tilt-negative results. Syncope recurred in 34% of patients in both groups, and the most frequent cause was prolonged sinus pauses. The ILR should be considered in selected patients with unexplained syncope.

Conclusion

Implantable cardiac devices are now standard therapies as well as diagnostic modalities for multiple cardiac problems. Pacemakers are used for the treatment of symptomatic bradycardia and in patients with symptomatic heart failure, left ventricular dysfunction, and wide QRS complexes. The use of ICDs for the treatment of patients who are at increased risk for ventricular arrhythmias and sudden death is now well established. Implantable loop recorders have become an important part of the diagnostic evaluation of patients with syncope. With the rapid development of different types of cardiac devices, it is important to understand the potential uses of these devices and issues in the management of patients in whom they are implanted.

References

1. AVID Investigators: A comparison of antiarrhythmic-drug therapy with implantable defibrillators in patients resuscitated from near-fatal ventricular arrhythmias. The Antiarrhythmics versus Implantable Defibrillators (AVID) Investigators. *N Engl J Med* 1997;337:1576–1583
2. Connolly SJ, Gent M, Roberts RS, Dorian P, Roy D, Sheldon RS, Mitchell LB, Green MS, Klein GJ, O'Brien B: Canadian Implantable Defibrillator study (CIDS): A randomized trial of the implantable cardioverter defibrillator. *Circulation* 2000;101:1297–1301
3. Wyse GD, Friedman PL, Brodsky MA, Beckman KJ, Carlson MD, Curtis AB, Hallstrom AP, Raitt MA, Wilkoff BL, Greene HL, for the AVID Investigators: Life-threatening ventricular arrhythmias due to transient or correctable causes: High risk for death in follow-up. *J Am Coll Cardiol* 2001; 38:1718–1724
4. Ehlert FA, Cannom DS, Renfroe EG: Comparison of dilated cardiomyopathy and coronary artery disease in patients with life-threatening ventricular arrhythmias: Differences in presentation and outcome in the AVID registry. *Am Heart J* 2001;142:816–822
5. Buxton AE, Lee KL, DiCarlo L, Gold MR, Greer GS, Prystowsky EN, O'Toole MF, Tang A, Fisher JD, Coromilas J, Talajic M, Hafley G, for the Multicenter Unsustained Tachycardia Trial Investigators: Electrophysiology testing to identify patients with coronary artery disease who are at risk for sudden death. *N Engl J Med* 2000;342:1937–1945
6. Moss AJ, Hall WJ, Cannom DS, Daubert JP, Higgins SL, Klein H, Levine JH, Saksena S, Waldo AL, Wilber D, Brown MW, Heo M: Improved survival with an implanted defibrillator in patients with coronary disease at high risk for ventricular arrhythmia. Multicenter Automatic Defibrillator Implantation Trial Investigators. *N Engl J Med* 1996;335:1933–1940
7. Buxton AE, Lee KL, Fisher JD, Josephson ME, Prystowsky EN, Hafley G, for the Multicenter Unsustained Tachycardia Trial Investigators: A randomized study of the prevention of sudden death in patients with coronary artery disease. *N Engl J Med* 1999;341:182–190
8. Moss AJ, Zareba W, Hall WJ, Klein H, Wilber DJ, Cannom DS, Daibert JP, Higgins SL, Brown MW, Andrews ML, for 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;346:877–893
9. Bardy G, Lee KL, Mark DB, Poole JE, Packer DL, Boineau R, Domanski M, Troutman C, Anderson J, Johnson G, McNulty SE, Clapp-Channing N, Davidson-Ray LD, Faulo ES, Fishbein DP, Luceri RM, Ip JH, for the 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. Hohnloser SH, Kuck KH, Dorian P, Roberts RS, Hampton JR, Hatala R, Fain E, Gent M, Connolly SJ, for the DINAMIT Investigators: Prophylactic use of an implantable cardioverter defibrillator after acute myocardial infarction. *N Engl J Med* 2004;351:2481–2488
11. Malm S, Frigstad S, Sagberg E, Larssson H, Skjaerpe T: Accuracy and reproducibile measurement of left ventricular volume and ejection fraction by contrast echocardiography: A comparison with magnetic resonance imaging. *J Am Coll Cardiol* 2004;44:1030–1035
12. Wilber D, Zareba W, Hall W, Brown MW, Lin AC, Andrews ML, Burke M, Moss AJ: Time dependence of mortality risk and defibrillator benefit after myocardial infarction. *Circulation* 2004;109:1082–1084
13. Solomon SD, Zelenkofske S, McMurray JVJ, Finn PV, Velazquez E, Ertl G, Haranyi A, Rouleau JL, Maggioni A, Kober L, White H, Van de Werf F, Pieper K, Califf RM, Pfeffer MA, for the Valsartant in Acute Myocardial Infarction Trial (VALIANT) Investigators: Sudden death in patients with myocardial infarcion and left ventricular dysfunction, heart failure, or both. *N Engl J Med* 352:2581–2588
14. Sanders GD, Hlatky MA, Every NR: Potential cost-effectiveness of the implantable cardioverter defibrillator or amiodarone after myocardial infarction. *Ann Intern Med* 2001;135:870–883
15. Hlatky MA: Evidence-based use of cardiac procedures and devices. *N Engl J Med* 2004;350:2126–2128
16. Strickberger SA, Hummel JD, Bartlett TG, Frumin HI, Schuger CD, Beau SL, Bitar C, Morady F, for the AMIOVIRT Investigators: 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
17. Bansch D, Antz M, Boczor S, Volkmer Tebbenjohanns J, Seidl K, Block M, Gietzen F, Berger J, Kuck KH: Primary prevention of sudden cardiac death in idiopathic dilated cardiomyopathy: The Cardiomyopathy Trial (CAT). *Circulation* 2002;105:1453–1458
18. Kadish A, Dyer A, Daubert JP, Quigg R, Estes NA, Anderson KP, Calkins H, Hoch D, Goldberger J, Shalaby A, Sanders WE, Schaechter A, Levine JH, for the 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
19. Kofflard MJ, Ten Cate FJ, van der Lee C, van Domburg RT: Hypertrophic cardiomyopathy in a large community-based population. Clinical outcome and identification of risk factors for sudden cardiac death and deterioration. *J Am Coll Cardiol* 2003;41:987–993
20. Maron BJ, Shen W-K, Link MS, Epstein AE, Almquist AK, Daubert JP, Bardy GH, Favale S, Rea RF, Boriani G, Estes NA, Spirito P: Efficacy of im-

plantable cardioverter defibrillators for the prevention of sudden death in patients with hypertrophic cardiomyopathy. *N Engl J Med* 2000;342:365–373
21. Zareba W, Moss AJ, Daubert JP, Hall WJ, Robinson JL, Andrews M: Implantable cardioverter defibrillator in high-risk long QT patients. *J Cardiovasc Electrophysiol* 2003;14:337–341
22. Brugada P, Brugada R, Brugada J: The Brugada syndrome. *Curr Cardiol Rev* 2000;2:507–514
23. Nademanee K, Veerakul G, Mower M, Likittanasombat K, Krittayapong R, Bhuripanyo K, Sitthisook S, Chaothawee L, Lai MY, Anzen SP: Defibrillator vs. Beta Blockers for unexpected death in Thailand (DEBUT): A randomized clinical trial. *Circulation* 2003;107:221–226
24. Silka MJ, Hardy BG, Menashe VD, Morris CD: A population-based prospective evaluation of risk of sudden cardiac death after operation for common congenital heart defects. *J Am Coll Cardiol* 1998;32:245–251
25. Ghai A, Silversides C, Harris L, Webb GD, Siu SC, Therrien J: Left ventricular dysfunction is a risk factor for sudden cardiac death in adults late after repair of tetralogy of Fallot. *J Am Coll Cardiol* 2002;40:1675–1680
26. Glikson M, Luria D, Friedman PA, Trusty JM, Benderly M, Hammill SC, Stanton MS: Are routine arrhythmia inductions necessary in patients with pectoral implantable cardioverter defibrillators? *J Cardiovasc Electrophysiol* 2000;11:127–135
27. US Food and Drug Administration Website: Medtronic issues notification regarding certain implantable defibrillator models. Available at http://www.fda.gov/oc/po/firmrecalls/medtronic20_05.html. Accessed September 16, 2005
28. US Food and Drug Administration Website: FDA statement on Guidant Corporations worldwide physician communications. Available at http://www.fda.gov/opacom/Enforce.html. Accessed September 16, 2005
29. Maisel WH: Safety issues involving medical devices. *J Am Med Assoc* 2005;294:955–958
30. Krahn AD, Klein GJ, Yee R, Skanes AC: Randomized Assessment of Syncope Trial. *Circulation* 2001:46–51
31. Moya A, Brignole M, Menozzi C, Garcia-Civera R, Tognarini S, Mont L, Botto G, Giada F, Cornacchia D, for the International Study on Syncope of Uncertain Etiology (ISSUE) Investigators: Mechanism of syncope in patients with isolated syncope and in patients with tilt-positive syncope. *Circulation* 2001;104:1261–1267
32. Menozzi C, Brignole M, Garcia-Civera R, Moya A, Botto G, Tercedor L, Migliorini R, Navarro X, for the International Study on Syncope of Uncertain Etiology (ISSUE) Investigators: Mechanism of syncope in patients with heart disease and negative electrophysiologic test. *Circulation* 2002;105:2741–2745