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Senescence and Arrhythmogenesis

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Introduction

Aging is associated with an increased incidence of cardiac arrhythmias that contributes significantly to the increased morbidity and mortality of old age.[1–3] The increased susceptibility to both ventricular and atrial arrhythmias in the senescent heart occurs despite the absence of apparent disease and is exaggerated in the presence of underlying comorbidities.[4,5] Cardiac dysrhythmias not only adversely affect the quality of life but also contribute to deterioration in myocardial function, increasing the susceptibility to heart failure, stroke, and sudden death.[5–7] With the rapid increase in the elderly population and the prevalence of cardiovascular diseases in the elderly, it is projected that the number of patients with cardiac arrhythmias and associated disability will more than double in 30 years, placing an enormous burden on health care resources.[8–10] Although progress is being made in understanding the pathogenesis of age-related cardiac diseases and therapies are being developed for these diseases, advanced age by itself poses significant dilemmas in therapy due to the lack of a full understanding of the molecular basis for the aging-associated increase in the susceptibility of the heart to arrhythmogenesis and the paucity of outcome studies in the very elderly.[6,11] This chapter summarizes the epidemiology, aging-associated changes in cardiac structure and function, basis for arrhythmogenesis, and evaluation and management of elderly patients with ventricular tachyarrhythmias causing sudden death.

Ventricular Arrhythmias and Sudden Cardiac Death

Unexpected death from cardiovascular causes, ranging from 300,000 to 350,000 deaths annually in the United States, is one of the most common modes of death in the elderly.[12] It accounts for 13% of all natural deaths and 50% of all deaths from cardiovascular causes.[4,13] Its incidence increases with advancing age in both those with structural heart disease, as well as those without recognizable risk factors for SCD.[4,14] In patients with coronary disease, sudden cardiac death (SCD) may occur as the first clinical event in 50% of the patients.[14] Despite advances in the management of cardiovascular diseases, the overall incidence of SCD in the general population (0.1–0.2% per year) has decreased only marginally and is expected to increase with the aging of the population and the increased prevalence of chronic heart disease.[15,16] Therefore, effective means to identify those at the highest risk of sudden death and development of strategies for the primary and secondary prevention of SCD in the elderly remain a priority.

Substrates for Sudden Cardiac Death in the Elderly

The substrate for SCD in the elderly varies depending on the underlying heart disease. The effect of aging alone on cardiac structure and function in

humans is difficult to study because of difficulties in separating the effect of aging from the effect of diseases associated with aging. The majority of sudden deaths in the elderly occur in the setting of coronary artery disease caused by ventricular arrhythmias, often triggered by acute ischemia.[12,14,17] Approximately 80% of patients who die suddenly from cardiac causes have underlying coronary artery disease and in 50% sudden death may be the first manifestation of their disease.[14] Active coronary lesions or acute changes in plaque morphology, such as plaque disruption or thrombus, may be present in more than 50% of the victims of sudden death.[18–20] The risk for ventricular arrhythmias increases after a myocardial infarction due to the presence of scar and the reduction in left ventricular systolic function. Other substrates for ventricular arrhythmias and sudden death in the elderly include ventricular hypertrophy, nonischemic cardiomyopathy, valvular diseases, or inflammatory or infiltrative diseases.[4,21–25] Only a small percentage of SCDs in the elderly occur due to a primary defect in ion channels responsible for sudden death in younger patients with inherited arrhythmia syndromes, such as the congenital long QT syndrome, short QT syndrome, Brugada syndrome, or catecholaminergic polymorphic ventricular tachycardia.[26–28] Familial clustering of cardiac events, however, does suggest a role of hereditary factors in the predisposition to sudden death,[29,30] which in the elderly appears to be due to genetic influences that increase the risk of a coronary event.[11,28,31–34] The presence of obesity, hypertension, and lipid abnormalities, and a history of smoking and diabetes increase the risk for sudden death.[35–37]

Mechanisms of Sudden Cardiac Death

Despite our understanding of risk factors and substrate for arrhythmogenesis, the exact mechanisms underlying initiation, propagation, maintenance, or prediction of timing for cardiac dysrhythmias causing SCD in the elderly are not fully understood. This is mainly due to the complex interactions between myocardial substrate and triggers that define the overall risk of susceptibility to arrhythmia.[38,39] Age-related changes in cardiac structure and function occur at macroscopic and microscopic levels in both the cellular and extracellular matrix.[1,40] This results in altered cellular excitability and cell-to cell coupling creating a proarrhythmic milieu that increases the predisposition to arrhythmogenesis due to abnormalities in impulse initiation and/or propagation. Failure of impulse initiation or conduction results in bradyarrhythmias, whereas enhanced impulse generation due to increased automaticity or triggered activity or slowed conduction resulting in reentry causes tachyarrhythmias.

Bradyarrhythmias, due to reduced normal automaticity and delayed conduction, are common in the very elderly, even in the absence of apparent heart diseases.[41,42] The intrinsic heart rate as measured following blockade of the parasympathetic and sympathetic nervous system and heart rate reserve decrease with aging.[43] This is related to aging-associated replacement of pacemaker cells within the sinoatrial node and atrioventricular conduction fibers with collagenous and elastic matrix[3] and impairment of signaling via cardiac G protein-coupled receptors, specifically β-adrenergic receptors contributing to diminished cardiac exercise reserve, spontaneous heart rate variability, and maximum heart rate achieved during stress resulting in a reduction in the aerobic work capacity in the elderly.[3,41,44] Myocyte hypertrophy and interstitial fibrosis also accompany aging, which alter cellular coupling and exaggerate directional differences in conduction (anisotropy); this increasing heterogeneity in conduction and refractoriness promotes the formation of zones of functional slowing or conduction block that stabilize reentry-enhancing susceptibility to arrhythmogenesis.[45,46] In addition, aging causes changes in expression, distribution, and/or functioning of ion channels, which alter action potential waveforms and propagation, further increasing vulnerability to dysrhythmias.[47–49] The action potential duration and repolarization are prolonged in the senescent heart,[50,51] in part due to the delay in the inactivation of the calcium current (I_{CaL})[52–54] and in part due to downregulation of potassium currents, including the transient outward (I_{to}) current, Ca^{2+}-activated potassium current, and ATP-sensitive potassium channel current that along with an increase in

the sodium–calcium exchanger increase the predisposition to Ca^{2+} overload-mediated triggered activity and reentrant arrhythmias.[51,54–59] Advanced age is also associated with a reduction of expression of the sarcoplasmic reticulum Ca^{2+}-ATPase (SERCA-2)[60,61] and posttranslational modifications causing phosphorylation-dependent changes in the function of SERCA-2, phospholamban, and other Ca^{2+} transport proteins, including the ryanodine receptor, the sarcoplasmic reticulum Ca^{2+} release channel.[62,63] The contribution of age-related changes in cardiac microstructure, including mitochondria[64] and other intracellular organelles, cytoskeleton, sarcolemma, intercellular gap junctions, cellular geometry, and interstitium on regulation of cardiac excitability or arrhythmogenesis is not well defined and warrants further studies.

Ventricular arrhythmias are common in the elderly, being present in more than 70% of persons over the age of 60 years. The incidence, prevalence, and complexity of ventricular arrhythmias and their prognostic significance increase with advancing age[35] and the presence of heart disease.[4,65–67] In the absence of heart disease, asymptomatic premature ventricular complexes (PVC) observed at rest do not carry an adverse prognosis, but when elicited during exercise[68] or the postexercise recovery period[69] are associated with an increased risk of cardiovascular death. In those with structural heart disease, PVCs do indicate an increased mortality risk, especially if ventricular function is reduced.[35,70–76] The mechanisms underlying ventricular arrhythmias vary depending on the underlying substrate. During the acute phase of myocardial infarction or with acute ischemia, ventricular fibrillation may result from functional reentry, whereas in patients with healed myocardial infarction, a reentry circuit can form around scarred tissue causing ventricular tachycardia that can then degenerate into fibrillation, even in the absence of active ischemia. In the periinfarction period, the senescent heart is more vulnerable to arrhythmogenesis, with a greater likelihood of in-hospital cardiac arrest in those 75 years and older compared to younger patients.[77] Although ventricular tachyarrhythmias occurring within 48 h of the acute coronary syndrome is associated with an increase in hospital mortality, long-term mortality is not affected unless significant ventricular dysfunction persists.[78] The incidence of scar-related reentrant ventricular arrhythmias, however, increases following myocardial infarction, increasing exponentially as the left ventricular ejection fraction falls below 30%.[12,17]

The exact electrophysiological basis for SCD in the elderly is difficult to determine and results from multiple factors depending on the underlying cardiac substrate with which dynamic transient factors (such as ischemia, hypoxia, catecholamine, pH and electrolyte changes, stretch, or inflammation) interact to precipitate arrhythmias.[12] In addition, an arrhythmia may be initiated by one mechanism, perpetuated by another, and then degenerate into a different mechanism. At the time of cardiac arrest, ventricular fibrillation is, however, the most commonly recorded rhythm observed in 75–80% of patients compared to advanced atrioventricular block or asystole documented in 15–20% of the cases.[79,80] The true incidence of bradyarrhythmias causing sudden death in the elderly is not known because by the time the first rhythm is recorded, an arrhythmia beginning as ventricular tachyarrhythmia may degenerate into or appear as asystole.

Evaluation of Elderly Patients at Risk for Sudden Cardiac Death

Several risk stratification protocols have been developed for the identification of patients at risk for ventricular arrhythmias who may benefit from interventions to reduce the risk of sudden death. These include noninvasive tests, such as a standard 12 lead electrocardiogram (ECG), exercise tests or parameters to determine the severity of left ventricular systolic dysfunction, the presence of late potentials on signal-average electrocardiography (SAECG), the severity of ventricular arrhythmias determined by ambulatory cardiac monitoring, the detection of repolarization instability by measurement of QT interval, QT dispersion, and microvolt T-wave alternans, and autonomic balance by heart rate variability or baroreflex sensitivity, or invasive tests to determine inducibility of sustained ventricular arrhythmias by programmed electrical stimulation.[4]

A standard 12-lead ECG allows identification of underlying structural disease, such as conduction system abnormalities with heart block, bundle-branch block, intraventricular conduction delay, ventricular hypertrophy, or prior infarction, as well as primary electrical disorders, such as the long QT syndrome, short QT syndrome, Brugada syndrome, or arrhythmogenic right ventricular cardiomyopathy. A prolonged QRS duration >120 msec in patients with a severely depressed ventricular function or a prolonged QTc interval in the elderly predict a higher risk of SCD.[2,81] The absence of a slowly conducting zone, the electrophysiological substrate for reentrant ventricular arrhythmias that is otherwise detected as late potentials on SAECG, may be useful with its high negative predictive value to exclude a wide-complex tachycardia as a cause of unexplained syncope in the elderly patient with coronary artery disease.[82,83] An exercise ECG may also provide useful diagnostic and prognostic information in the evaluation of patients with known or suspected coronary artery disease, cardiomyopathies, or frequent premature ventricular complexes. The appearance of exercise-induced complex ventricular ectopy or ventricular tachycardia in the elderly may predict an increased risk of mortality compared to patients with simple ectopy observed at rest only.[68,69,84] T-wave alternans detected as microvolt fluctuation in the amplitude or morphology of the T-wave during exercise testing or atrial pacing is also a useful tool for identifying high-risk patients after myocardial infarction or with cardiomyopathy and carries a high negative predictive accuracy.[85,86]

Assessment of left ventricular systolic function and other structural and functional information about myocardial dimensions, wall thickness, and valvular and congenital heart disorders with imaging techniques, such as echocardiogram, is an essential part of risk stratification of patients with ventricular arrhythmias at risk for SCD.[87] Cardiac magnetic resonance imaging (MRI) or computed tomography (CT) scan is helpful in patients with suspected arrhythmogenic right ventricular cardiomyopathy.[88] Myocardial perfusion single-photon emission computed tomography (SPECT) using exercise or pharmacological agents is useful for the detection of ischemia in those suspected of having ventricular arrhythmias triggered by ischemia.[89] Coronary angiography is useful in the assessment of obstructive coronary artery disease in patients with ventricular arrhythmias or aborted sudden death,

The utility of electrophysiology (EP) testing with intracardiac recording and electrical stimulation in the elderly varies with the type and severity of heart disease.[90–92] It is useful for the assessment of arrhythmia and risk stratification for SCD in elderly patients with ischemic heart disease and left ventricular dysfunction or syncope, but plays only a minor role in the evaluation of patients with dilated cardiomyopathy (DCM) or inherited arrhythmia syndromes, such as the long or short QT syndrome.[90–94] Its utility in patients with Brugada syndrome or hypertrophic cardiomyopathy is controversial.[95–97] In patients with coronary artery disease, nonsustained ventricular tachycardia, and left ventricular ejection fraction (EF) less than 40%, the inducibility of sustained ventricular tachycardia identifies patients at high risk for ventricular arrhythmias and predicts a worse prognosis.[98] However, in those with severe ventricular dysfunction (EF <30%), noninducibility of ventricular tachycardia with program electrical stimulation does not indicate a good prognosis[99] and is not helpful in risk stratification.

Management of Elderly Patients at Risk for Sudden Cardiac Death

Antiarrhythmic Drugs

The essential goals of antiarrhythmic therapy in the elderly are acute termination of an ongoing arrhythmia and/or prevention of the recurrence of arrhythmia. Although antiarrhythmic agents, except for the β-blockers, have not been shown to reduce mortality in randomized trials,[100–103] they continue to play an important role for symptom relief by suppression of recurrences of arrhythmia in elderly patients. However, these agents should be used with caution as they can also cause arrhythmia in susceptible individuals.[104] Selection of an effective yet safe medication in the elderly is challenging due to variability in the pathophysiological substrate, mechanisms of arrhythmia, clinical presentation, and prognostic implications

of the arrhythmia.[105] In addition, the presence of comorbidities, concomitant drug use, and variability in drug disposition, and/or responses due to aging-associated physiological changes that alter the pharmacokinetics and pharmacodynamics of a drug, require careful adjustment of drug regimens and frequent monitoring for efficacy and side effects.[106] The empiric use of antiarrhythmic drugs regardless of the prognostic significance of an arrhythmia or choosing antiarrhythmic drugs by trial and error is not acceptable due to deleterious effects, including the risk of proarrhythmia,[107,108] which may be increased in the elderly due to impaired renal clearance and the potential for drug interactions.[106] There is no evidence that suppression of asymptomatic nonsustained ventricular tachycardia prolongs life, and the only indication to treat these arrhythmias is for symptom control due to frequent recurrences of rapid tachycardia compromising hemodynamics. These could be managed with antiarrhythmic therapy, preferably with β-blockers, sotalol, or amiodarone, or with catheter ablation. In the presence of structural heart disease or myocardial ischemia, class I antiarrhythmic agents should be avoided as clinical trials, such as the Cardiac Arrhythmia Suppression Trial, have demonstrated increased mortality or incessant arrhythmias in patients treated with antiarrhythmic agents compared to placebo.[107] Patients with atrial fibrillation treated with a class I antiarrhythmic agent may become symptomatic with a rapid 1:1 atrioventricular response as the atrial rhythm becomes more organized and if used these agents should be given with drugs that slows atrioventricular node conduction. In addition, use of class I antiarrhythmic agents in patients with a pacemaker or implantable cardioverter defribillator (ICD) may result in an increase in pacing threshold or defibrillation energy requirement[109,110] necessitating reprogramming of pacing or ICD systems.

Overall, class I or III antiarrhythmic drugs should not be used as primary therapy in the management of ventricular arrhythmias or the prevention of SCD in the elderly. Its use as a hybrid treatment with ICD implantation, however, can be considered for symptom control and improvement in quality of life by suppression of recurrences of arrhythmia and frequency of ICD discharges.[111,112] Amiodarone, a complex drug with multiple electrophysiological effects, is useful for the termination and suppression of ventricular arrhythmias, especially when used with β-blockers. However, the long-term survival benefit from amiodarone alone was not shown in most of the randomized, placebo-controlled studies, demonstrating no significant benefit over standard of care in high-risk patients with heart failure or coronary artery disease.[113–115] Similarly, use of sotalol, despite its effectiveness in suppressing ventricular arrhythmias, has not been shown to improve survival.[116] Use of amiodarone (with a β-blocker) or sotalol is recommended in patients who do not meet the criteria for ICD implantation, or in those who have an ICD with the therapeutic goal of reducing the recurrence of ventricular arrhythmias and the frequency of ICD shocks.[111,112]

Drugs that are relatively safe and have been shown to be effective in improving survival in high-risk elderly patients include β-blockers, angiotensin converting enzyme inhibitors, angiotensin receptor antagonists, and statins; these do not possess classic antiarrhythmic properties and should be considered in high-risk patients after myocardial infarction or with heart failure.[117,118] The combination of β-blockers and amiodarone appears to be more effective in reducing overall mortality and sudden death than amiodarone alone.[119,120]

Implantable Cardioverter Devices

Patients who had cardiac arrest due to ventricular fibrillation or sustained ventricular tachycardia in the absence of a removable cause or those with persistent severe left ventricular dysfunction (EF <35%) due to nonischemic or ischemic cardiomyopathy 40 days after acute myocardial infarction are at increased risk of SCD and should be considered for ICD implantation.[4,121,122] Randomized, prospective trials comparing antiarrhythmic drug therapy to ICD have demonstrated the efficacy of ICDs in primary and secondary prevention of sudden death in those at high risk of SCD or in those resuscitated after cardiac arrest.[100–102,123–125] However, none of these trials has focused specifically on the efficacy of ICD in the elderly. The survival benefit of ICD in those 65 years or older appears to be similar to those <65 years of

age,[126–128] with the benefit of ICD therapy apparently greater in those in whom an ICD is implanted for primary prophylaxis of SCD than in those for secondary prevention after a life-threatening arrhythmic event or in those with advanced heart failure and a higher risk of nonarrhythmic cardiac or noncardiac death.[129,130] Because of the limited availability of data, the efficacy of ICD therapy in the older elderly with limited life expectancy is not clear, as only a very small number of elderly above 80 years of age have been included in these trials; these trials may also suffer from selection bias for the use of more expensive devices in "healthier" elderly patients with a lower risk of noncardiac or cardiac death.[131] Pooled analysis of the secondary prevention trials does indicate that the very elderly may derive less benefit from an ICD than younger patients, due to an increased number of nonarrhythmic cardiac and noncardiac deaths.[132] Similarly, cohort studies reporting an equivalent survival benefit in the elderly and younger patients may not reflect the true benefit of ICD therapy in the overall elderly population as selection bias may be present, with use of more expensive device implantation considered in only "healthier elderly" free of serious comorbidities with a better functional capacity.[131,133–135] In the absence of symptomatic arrhythmias in those with preserved ventricular function (EF >40%), the risk for SCD is relatively low, and at this time ICD therapy is not indicated.[4] In addition, in the very elderly patient who has multiple comorbidities with a limited life expectancy from nonarrhythmic causes, ICD may not prolong survival and could have an adverse impact on quality of life, and therefore should be avoided. Patients with ICD with compromised ventricular function who require pacing may have exacerbation of heart failure when paced from the right ventricular (RV) apex.[136] In these patients RV pacing should be minimized by selecting a low minimum rate, programming a long AV interval, selecting an ICD with algorithms utilizing automatic mode selection that favors atrial over ventricular pacing, or using ICDs with biventricular pacing capabilities.[137]

Radiofrequency Ablation

Ablation therapy should be considered in the elderly as adjunctive therapy for recurrent ventricular tachycardia in those with recurrent ICD shocks not manageable by reprogramming of ICD or antiarrhythmic therapy or who do not wish long-term drug therapy.[4,138–141] Ablation as primary therapy is indicated only in those who are otherwise at low risk for SCD and have symptomatic predominantly monomorphic ventricular arrhythmias that are drug resistant, or in patients who are drug intolerant or do not wish long-term drug therapy.[4,142] Ablation of the tachycardia circuit involving the bundle branches in bundle branch ventricular tachycardia may be curative, but these patients typically have severe ventricular dysfunction with an underlying substrate that increases the risk for other arrhythmias and therefore may need ICD. Ventricular arrhythmias arising from the right and less commonly the left ventricular outflow tract are usually seen in healthy young individuals, but may present in the elderly. They are associated with a good prognosis[143] and often respond to treatment with β-blockers and calcium channel blockers or class IC antiarrhythmic drugs. In those who remain symptomatic or do not respond to drug therapy, catheter ablation should be considered.[4]

Other Interventions

Ablation of the tachycardia circuit using surgery to resect or modify the arrhythmia substrate is an alternative therapy that may be suitable for patients in whom catheter ablation is unsuccessful and who are otherwise fit to undergo cardiac surgery. Coronary revascularization with percutaneous coronary intervention or bypass surgery reduces myocardial ischemia and SCD during long-term follow-up,[144] but controlled trials evaluating the effect of myocardial revascularization on ventricular arrhythmias in the elderly have not been conducted. If ventricular arrhythmias are triggered by acute ischemia, coronary revascularization helps reduce the frequency and complexity of the arrhythmias. However, sustained monomorphic ventricular tachycardia in patients with scarred myocardium from a previous infarction is not affected by revascularization[145]; neither is the risk of recurrent cardiac arrest in patients with markedly reduced ventricular function eliminated with revascularization even if the original

arrhythmia appeared to result from transient ischemia.[146]

With the continuing rise in medical costs and the rapid increase in the elderly population and in the prevalence of cardiovascular diseases and associated disability, urgency exists to better integrate our efforts in basic science and clinical practice to enhance our understanding of arrhythmogenesis and its effect on outcomes in the elderly, so as to advance both therapeutic and preventive strategies to improve health and longevity of elderly patients.

References

1. Lakatta EG, Sollott SJ. Perspectives on mammalian cardiovascular aging: Humans to molecules. *Comp Biochem Physiol A Mol Integr Physiol* 2002; 132:699–721.
2. Chugh SS, Jui J, Gunson K, Stecker EC, John BT, Thompson B, Ilias N, Vickers C, Dogra V, Daya M, Kron J, Zheng ZJ, Mensah G, McAnulty J. Current burden of sudden cardiac death: Multiple source surveillance versus retrospective death certificate-based review in a large U.S. community. *J Am Coll Cardiol* 2004;44:1268–1275.
3. Lakatta EG. Cardiovascular regulatory mechanisms in advanced age. *Physiol Rev* 1993;73:413–467.
4. Zipes DP, Camm AJ, Borggrefe M, Buxton AE, Chaitman B, Fromer M, Gregoratos G, Klein G, Moss AJ, Myerburg RJ, Priori SG, Quinones MA, Roden DM, Silka MJ, Tracy C. ACC/AHA/ESC 2006 guidelines for management of patients with ventricular arrhythmias and the prevention of sudden cardiac death: A report of the American College of Cardiology/American Heart Association Task Force and the European Society of Cardiology Committee for Practice Guidelines (Writing Committee to Develop Guidelines for Management of Patients with Ventricular Arrhythmias and the Prevention of Sudden Cardiac Death). *J Am Coll Cardiol* 2006;48:e247–e346.
5. Fuster V, Ryden LE, Cannom DS, Crijns HJ, Curtis AB, Ellenbogen KA, Halperin JL, Le Heuzey J-Y, Kay GN, Lowe JE, Olsson SB, Prystowsky EN, Tamargo JL, Wann S, Smith SC Jr, Jacobs AK, Adams CD, Anderson JL, Antman EM, Hunt SA, Nishimura R, Ornato JP, Page RL, Riegel B, Priori SG, Blanc J-J, Budaj A, Camm AJ, Dean V, Deckers JW, Despres C, Dickstein K, Lekakis J, McGregor K, Metra M, Morais J, Osterspey A, Zamorano JL. ACC/AHA/ESC 2006 guidelines for the management of patients with atrial fibrillation-executive summary: A report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines and the European Society of Cardiology Committee for Practice Guidelines (Writing Committee to Revise the 2001 Guidelines for the Management of Patients with Atrial Fibrillation). *Circulation* 2006;114:700–752.
6. Aronow WS. Heart disease and aging. *Med Clin North Am* 2006;90:849–862.
7. Thom T, Haase N, Rosamond W, Howard VJ, Rumsfeld J, Manolio T, Zheng Z-J, Flegal K, O'Donnell C, Kittner S, Lloyd-Jones D, Goff DC Jr, Hong Y, Members of the Statistics Committee and Stroke Statistics Subcommittee, Adams R, Friday G, Furie K, Gorelick P, Kissela B, Marler J, Meigs J, Roger V, Sidney S, Sorlie P, Steinberger J, Wasserthiel-Smoller S, Wilson M, Wolf P. Heart Disease and Stroke Statistics—2006 Update: A Report from the American Heart Association Statistics Committee and Stroke Statistics Subcommittee. *Circulation* 2006;113:e85–151.
8. Go AS, Hylek EM, Phillips KA, Chang Y, Henault LE, Selby JV, Singer DE. Prevalence of diagnosed atrial fibrillation in adults: National implications for rhythm management and stroke prevention: The Anticoagulation and Risk Factors in Atrial Fibrillation (ATRIA) Study. *JAMA* 2001;285:2370–2375.
9. Jahangir A, Shen WK. Pacing in elderly patients. *Am Heart J* 2003;146:750–753.
10. Miyasaka Y, Barnes ME, Gersh BJ, Cha SS, Bailey KR, Abhayaratna WP, Seward JB, Tsang TSM. Secular trends in incidence of atrial fibrillation in Olmsted County, Minnesota, 1980 to 2000, and implications on the projections for future prevalence. *Circulation* 2006;114:119–125.
11. Myerburg RJ. Scientific gaps in the prediction and prevention of sudden cardiac death. *J Cardiovasc Electrophysiol* 2002;13:709–723.
12. Myerburg RJ, Castellanos A. Emerging paradigms of the epidemiology and demographics of sudden cardiac arrest. *Heart Rhythm* 2006;3:235–239.
13. Gillum RF. Geographic variation in sudden coronary death. *Am Heart J* 1990;119:380–389.
14. Myerburg RJ. Sudden cardiac death: Exploring the limits of our knowledge. *J Cardiovasc Electrophysiol* 2001;12:369–381.
15. Braunwald E. Shattuck lecture cardiovascular medicine at the turn of the millennium: Triumphs, concerns, and opportunities. *N Engl J Med* 1997; 337:1360–1369.
16. Schatzkin A, Cupples LA, Heeren T, *et al.* Sudden death in the Framingham Heart Study.

Differences in incidence and risk factors by sex and coronary disease status. *Am J Epidemiol* 1984;120:888–899.
17. Huikuri HV, Castellanos A, Myerburg RJ. Medical progress: Sudden death due to cardiac arrhythmias. *N Engl J Med* 2001;345:1473–1482.
18. Theroux P, Fuster V. Acute coronary syndromes: Unstable angina and non-Q-wave myocardial infarction. *Circulation* 1998;97:1195–1206.
19. Naghavi M, Falk E, Hecht HS, Jamieson MJ, Kaul S, Berman D, Fayad Z, Budoff MJ, Rumberger J, Naqvi TZ, Shaw LJ, Faergeman O, Cohn J, Bahr R, Koenig W, Demirovic J, Arking D, Herrera VL, Badimon J, Goldstein JA, Rudy Y, Airaksinen J, Schwartz RS, Riley WA, Mendes RA, Douglas P, Shah PK; SHAPE Task Force. From vulnerable plaque to vulnerable patient—Part III: Executive summary of the Screening for Heart Attack Prevention and Education (SHAPE) Task Force report. *Am J Cardiol* 2006;17:2H–15H.
20. Farb A, Tang AL, Burke AP, Sessums L, Liang Y, Virmani R. Sudden coronary death: Frequency of active coronary lesions, inactive coronary lesions, and myocardial infarction. *Circulation* 1995;92: 1701–1709.
21. Hulot JS, Jouven X, Empana JP, Frank R, Fontaine G. Natural history and risk stratification of arrhythmogenic right ventricular dysplasia/cardiomyopathy. *Circulation* 2004;110:1879–1884.
22. Klein GJ, Krahn AD, Skanes AC, Yee R, Gula LJ. Primary prophylaxis of sudden death in hypertrophic cardiomyopathy, arrhythmogenic right ventricular cardiomyopathy, and dilated cardiomyopathy. *J Cardiovasc Electrophysiol* 2005;16: S28–34.
23. Maron BJ, McKenna WJ, Danielson GK, Kappenberger LJ, Kuhn HJ, Seidman CE, Shah PM, Spencer I, William H., Spirito P. American College of Cardiology/European Society of Cardiology Clinical Expert Consensus Document on Hypertrophic Cardiomyopathy: A report of the American College of Cardiology Foundation Task Force on Clinical Expert Consensus Documents and the European Society of Cardiology Committee for Practice Guidelines. *J Am Coll Cardiol* 2003;42: 1687–1713.
24. Maron BJ, Estes NA III, Maron MS, Almquist AK, Link MS, Udelson JE. Primary prevention of sudden death as a novel treatment strategy in hypertrophic cardiomyopathy. *Circulation* 2003; 107:2872–2875.
25. More D, O'Brien K, Shaw J. Arrhythmogenic right ventricular dysplasia in the elderly. *Pacing Clin Electrophysiol* 2002;25:1266–1269.
26. Locati EH, Zareba W, Moss AJ, Schwartz PJ, Vincent GM, Lehmann MH, Towbin JA, Priori SG, Napolitano C, Robinson JL, Andrews M, Timothy K, Hall WJ. Age- and sex-related differences in clinical manifestations in patients with congenital long-QT syndrome: Findings from the international LQTS registry. *Circulation* 1998;97:2237–2244.
27. Bjerregaard P, Jahangir A, Gussak I. Targeted therapy for short QT syndrome. *Expert Opin Ther Targets* 2006;10:393–400.
28. Spooner PM, Albert C, Benjamin EJ, Boineau R, Elston RC, George AL Jr, Jouven X, Kuller LH, MacCluer JW, Marban E, Muller JE, Schwartz PJ, Siscovick DS, Tracy RP, Zareba W, Zipes DP. Sudden cardiac death, genes, and arrhythmogenesis: Consideration of new population and mechanistic approaches from a National Heart, Lung, and Blood Institute workshop, part I. *Circulation* 2001;103:2361–2364.
29. Friedlander Y, Siscovick DS, Weinmann S, Austin MA, Psaty BM, Lemaitre RN, Arbogast P, Raghunathan TE, Cobb LA. Family history as a risk factor for primary cardiac arrest. *Circulation* 1998; 97:155–160.
30. Jouven X, Desnos M, Guerot C, Ducimetiere P. Predicting sudden death in the population. The Paris prospective study I. *Circulation* 1999;99: 1978–1983.
31. Boerwinkle E, Ellsworth DL, Hallman DM, Biddinger A. Genetic analysis of atherosclerosis: A research paradigm for the common chronic diseases. *Human Mol Genet* 1996;5:1405–1410.
32. Faber BCG, Cleutjens KB, Niessen RL, Aarts PL, Boon W, Greenberg AS, Kitslaar PJ, Tordoir JH, Daemen MJ. Identification of genes potentially involved in rupture of human atherosclerotic plaques. *Circ Res* 2001;89:547–554.
33. Topol EJ, McCarthy J, Gabriel S, Moliterno DJ, Rogers WJ, Newby LK, Freedman M, Metivier J, Cannata R, O'Donnell CJ, Kottke-Marchant K, Murugesan G, Plow EF, Stenina O, Daley GQ. Single nucleotide polymorphisms in multiple novel thrombospondin genes may be associated with familial premature myocardial infarction. *Circulation* 2001;104:2641–2644.
34. Splawski I, Timothy KW, Tateyama M, Clancy CE, Malhotra A, Beggs AH, Cappuccio FP, Sagnella GA, Kass RS, Keating MT. Variant of SCN5A sodium channel implicated in risk of cardiac arrhythmia. *Science* 2002;297:1333–1336.
35. Kannel WB, Cupples LA, D'Agostino RB. Sudden death risk in overt coronary heart disease: The Framingham Study. *Am Heart J* 1987;113:799–804.

36. Alpert MA. Obesity cardiomyopathy: Pathophysiology and evolution of the clinical syndrome. *Am J Med Sci* 2001;321:225–236.
37. Luscher TF, Creager MA, Beckman JA, Cosentino F. Diabetes and vascular disease: Pathophysiology, clinical consequences, and medical therapy: Part II. *Circulation* 2003;108:1655–1661.
38. Myerburg RJ, Kessler KM, Castellanos A. Sudden cardiac death: Epidemiology, transient risk, and intervention assessment. *Ann Intern Med* 1993; 119:1187–1197.
39. Adamson P, Barr RC, Callans DJ, Chen PS, Lathrop DA, Makielski JC, Nerbonne JM, Nuss HB, Olgin JE, Przywara DA, Rosen MR, Rozanski GJ, Spach MS, Yamada KA. The perplexing complexity of cardiac arrhythmias: Beyond electrical remodeling. *Heart Rhythm* 2005;2:650–659.
40. Juhaszova M, Rabuel C, Zorov DB, Lakatta EG, Sollott SJ. Protection in the aged heart: Preventing the heart-break of old age? *Cardiovasc Res* 2005; 66:233–244.
41. Gregoratos G, Abrams J, Epstein AE, Freedman RA, Hayes DL, Hlatky MA, Kerber RE, Naccarelli GV, Schoenfeld MH, Silka MJ, Winters SL. 2. ACC/AHA/NASPE 2002 guideline update for implantation of cardiac pacemakers and antiarrhythmia devices: A report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (ACC/AHA/NASPE Committee on Pacemaker Implantation). Available at www.acc.org/clinical/guidelines/pacemaker/pacemaker.pdf, 2002.
42. Vlietstra RE, Jahangir A, Shen WK. Choice of pacemakers in patients aged 75 years and older: Ventricular pacing mode vs. dual-chamber pacing mode. *Am J Geriatr Cardiol* 2005;14:35–38.
43. Jose A. Effect of combined sympathetic and parasympathetic blockade on heart rate and cardiac function in man. *Am J Cardiol* 1966;18: 476–478.
44. Fleg JL, O'Connor F, Gerstenblith G, Becker LC, Clulow J, Schulman SP, Lakatta EG. Impact of age on the cardiovascular response to dynamic upright exercise in healthy men and women. *J Appl Physiol* 1995;78:890–900.
45. Koura T, Hara M, Takeuchi S, Ota K, Okada Y, Miyoshi S,Watanabe A, Shiraiwa K, Mitamura H, Kodama I, Ogawa S. Anisotropic conduction properties in canine atria analyzed by high-resolution optical mapping: Preferential direction of conduction block changes from longitudinal to transverse with increasing age. *Circulation* 2002; 105:2092–2098.
46. de Bakker JM, van Rijen HM. Continuous and discontinuous propagation in heart muscle. *J Cardiovasc Electrophysiol* 2006;17:567–573.
47. Schram G, Pourrier M, Melnyk P, Nattel S. Differential distribution of cardiac ion channel expression as a basis for regional specialization in electrical function. *Circ Res* 2002;90:939–950.
48. Nerbonne JM, Kass RS. Physiology and molecular biology of ion channels contributing to ventricular repolarization. In: Gussak I, Antzelevitch C, Hammill SC, Shen WK, Bjerregaard P, Eds. *Cardiac Repolarization: Bridging Basic and Clinical Science (Contemporary Cardiology)*. Totowa, NJ: Humana Press, 2003:25–62.
49. Kléber AG, Rudy Y. Basic mechanisms of cardiac impulse propagation and associated arrhythmias. *Physiol Rev* 2004;84:431–488.
50. Josephson IR, Guia A, Stern MD, Lakatta EG. Alterations in properties of L-type Ca channels in aging rat heart. *J Mol Cell Cardiol* 2002;34:297–308.
51. Jahangir A, Cabrera Aguilera CC, Oberlin AS, Ashfaque N, Alexei A, Terzic A. Molecular basis for the increased vulnerability of the aging heart to injury. *Eur Heart J* 2006;27:875.
52. Janczewski AM, Spurgeon HA, Lakatta EG. Action potential prolongation in cardiac myocytes of old rats is an adaptation to sustain youthful intracellular Ca2+ regulation. *J Mol Cell Cardiol* 2002;34: 641–648.
53. Walker KE, Lakatta EG, Houser SR. Alterations in properties of L-type Ca channels in aging rat heart. *J Mol Cell Cardiol* 2002;34:297–308.
54. Walker KE, Lakatta EG, Houser SR. Age associated changes in membrane currents in rat ventricular myocytes. *Cardiovasc Res* 1993;27: 1968–1977.
55. Jahangir A, Terzic A. KATP channel therapeutics at the bedside. *J Mol Cell Cardiol* 2005;39:99–112.
56. Toro L, Marijic J, Nishimaru K, Tanaka Y, Song M, Stefani E. Aging, ion channel expression, and vascular function. *Vasc Pharmacol* 2002;38:73–80.
57. Zhou YY, Lakatta EG, Xiao RP. Age-associated alterations in calcium current and its modulation in cardiac myocytes. *Drugs Aging* 1998;13:159–171.
58. Xiao R-P, Tomhave ED, Wang D-J, Ji X, Boluyt MO, Cheng H, Lakatta EG, Koch WJ. Age-associated reductions in cardiac beta 1- and beta 2-adrenergic responses without changes in inhibitory G proteins or receptor kinases. *J Clin Invest* 1998; 101:1273–1282.
59. Xiao R-P, Zhu W, Zheng M, Cao C, Zhang Y, Lakatta EG, Han Q. Subtype-specific [alpha]1- and

[beta]-adrenoceptor signaling in the heart. *Trends Pharmacol Sci China* 2006;27:330–337.
60. Lompre AM, Lambert F, Lakatta EG, Schwartz K. Expression of sarcoplasmic reticulum Ca2.-ATPase and calsequestrin genes in rat heart during ontogenic development and aging. *Circ Res* 1991; 69:1380–1388.
61. Taffet GE, Tate CA. ATPase content is lower in cardiac sarcoplasmic reticulum isolated from old rats. *Am J Physiol* 1993;264:H1609–H1614.
62. Koban MU, Moorman AF, Holtz J, Yacoub MH, Boheler KR. Expressional analysis of the cardiac Na-Ca exchanger in rat development and senescence. *Cardiovasc Res* 1998;37:405–423.
63. Xu A, Narayanan N. Effects of aging on sarcoplasmic reticulum Ca2.-cycling proteins and their phosphorylation in rat myocardium. *Am J Physiol* 1998;275:H2087–H2094.
64. Jahangir A, Ozcan C, Holmuhamedov EL, Terzic A. Increased calcium vulnerability of senescent cardiac mitochondria: Protective role for a mitochondrial potassium channel opener. *Mech Ageing Dev* 2001;122:1073–1086.
65. Fleg JL, Kennedy HL. Cardiac arrhythmias in a healthy elderly population: Detection by 24-hour ambulatory electrocardiography. *Chest* 1982;81: 302–307.
66. Kennedy HL, Whitlock JA, Sprague MK, Kennedy LJ, Buckingham TA, Goldberg RJ. Long-term follow-up of asymptomatic healthy subjects with frequent and complex ventricular ectopy. *N Engl J Med* 1985;312:193–197.
67. Hinkle LEJ, Carver ST, Stevens M. The frequency of asymptomatic disturbances of cardiac rhythm and conduction in middle-aged men. *Am J Cardiol* 1969;24:629–650.
68. Jouven X, Zureik M, Desnos M, Courbon D, Ducimetiere P. Long-term outcome in asymptomatic men with exercise-induced premature ventricular depolarizations. *N Engl J Med* 2000;343: 826–833.
69. Frolkis JP, Pothier CE, Blackstone EH, Lauer MS. Frequent ventricular ectopy after exercise as a predictor of death. *N Engl J Med* 2003;348:781–790.
70. Messerli FH, Ventura HO, Elizardi DJ, Dunn FG, Frohlich ED. Hypertension and sudden death: Increased ventricular ectopic activity in left ventricular hypertrophy. *Am J Med* 1984;77:18–22.
71. Bigger JT Jr, Fleiss JL, Kleiger R, *et al.* The relationships among ventricular arrhythmias, left ventricular dysfunction, and mortality in the 2 years after myocardial infarction. *Circulation* 1984;69:250–258.
72. Huikuri HV, Makikallio TH, Raatikainen MJP, Perkiomaki J, Castellanos A, Myerburg RJ. Prediction of sudden cardiac death: Appraisal of the studies and methods assessing the risk of sudden arrhythmic death. *Circulation* 2003;108: 110–115.
73. Stevenson WG, Stevenson LW, Middlekauff HR, Saxon LA. Sudden death prevention in patients with advanced ventricular dysfunction. *Circulation* 1993;88:2953–2961.
74. Aronow WS, Ahn C, Mercando AD, Epstein S, Kronzon I. Prevalence and association of ventricular tachycardia and complex ventricular arrhythmias with new coronary events in older men and women with and without cardiovascular disease. *J Gerontol Ser A Biol Sci Med Sci* 2002;57:M178–M180.
75. Volpi A, Cavalli A, Turato R, Barlera S, Santoro E, Negri E. Incidence and short-term prognosis of late sustained ventricular tachycardia after myocardial infarction: Results of the Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto Miocardico (GISSI-3) Data Base. *Am Heart J* 2001;142:87–92.
76. Trusty JM, Beinborn DS, Jahangir A. Dysrhythmias and the athlete. *AACN Clin Issues* 2004;15: 432–448.
77. Ornato JP, Peberdy MA, Tadler SC, Strobos NC. Factors associated with the occurrence of cardiac arrest during hospitalization for acute myocardial infarction in the second national registry of myocardial infarction in the US. *Resuscitation* 2001; 48:117–123.
78. Behar S, Goldbourt U, Reicher-Reiss H, Kaplinsky E, The Principal Investigators of the SPRINT Study. Prognosis of acute myocardial infarction complicated by primary ventricular fibrillation. *Am J Cardiol* 1990;66:1208–1211.
79. Luu M, Stevenson WG, Stevenson LW, Baron K, Walden J. Diverse mechanisms of unexpected cardiac arrest in advanced heart failure. *Circulation* 1989;80:1675–1680.
80. Bayes de Luna A, Coumel P, Leclercq JF. Ambulatory sudden cardiac death: Mechanisms of production of fatal arrhythmia on the basis of data from 157 cases. *Am Heart J* 1989;117:151–159.
81. Schouten EG, Dekker JM, Meppelink P, Kok FJ, Vandenbroucke JP, Pool J. QT interval prolongation predicts cardiovascular mortality in an apparently healthy population. *Circulation* 1991;84: 1516–1523.
82. Steinberg JS, Berbari EJ. The signal-averaged electrocardiogram: Update on clinical applications. *J Cardiovasc Electrophysiol* 1996;7:972–988.

83. Cook JR, Flack JE, Gregory CA, Deaton DW, Rousou JA, Engelman RM, The CABG Patch Trial. Influence of the preoperative signal-averaged electrocardiogram on left ventricular function after coronary artery bypass graft surgery in patients with left ventricular dysfunction. *Am J Cardiol* 1998;82:285–289.
84. Podrid PJ, Graboys TB. Exercise stress testing in the management of cardiac rhythm disorders. *Med Clin North Am* 1984;68:1139–1152.
85. Bloomfield DM, Bigger JT, Steinman RC, Namerow PB, Parides MK, Curtis AB, Kaufman ES, Davidenko JM, Shinn TS, Fontaine JM. Microvolt T-wave alternans and the risk of death or sustained ventricular arrhythmias in patients with left ventricular dysfunction. *J Am Coll Cardiol* 2006;47:456–463.
86. Chow T, Kereiakes DJ, Bartone C, Booth T, Schloss EJ, Waller T, Chung ES, Menon S, Nallamothu BK, Chan PS. Prognostic utility of microvolt T-wave alternans in risk stratification of patients with ischemic cardiomyopathy. *J Am Coll Cardiol* 2006; 47:1820–1827.
87. Cheitlin MD, Armstrong WF, Aurigemma GP, Beller GA, Bierman FZ, Davis JL, Douglas PS, Faxon DP, Gillam LD, Kimball TR. ACC/AHA/ASE 2003 guideline update for the clinical application of echocardiography: Summary article: A report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (ACC/AHA/ASE Committee to Update the 1997 Guidelines for the Clinical Application of Echocardiography). *J Am Coll Cardiol* 2003;42:954–970.
88. Kies P, Bootsma M, Bax J, Schalij MJ, van der Wall EE. Arrhythmogenic right ventricular dysplasia/cardiomyopathy: Screening, diagnosis, and treatment. *Heart Rhythm* 2006;3:225–234.
89. Klocke FJ, Baird MG, Lorell BH, Bateman TM, Messer JV, Berman DS, O'Gara PT, Carabello BA. ACC/AHA/ASNC Guidelines for the Clinical Use of Cardiac Radionuclide Imaging—Executive Summary: A Report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (ACC/AHA/ASNC Committee to Revise the 1995 Guidelines for the Clinical Use of Cardiac Radionuclide Imaging). *J Am Coll Cardiol* 2003;42:1318–1333.
90. Wilber DJ, Garan H, Finkelstein D, Kelly E, Newell J, McGovern B, Ruskin JN. Out-of-hospital cardiac arrest. Use of electrophysiologic testing in the prediction of long-term outcome. *N Engl J Med* 1988;318:19–24.
91. Bachinsky WB, Linzer M, Weld L, Estes I, Mark NA. Usefulness of clinical characteristics in predicting the outcome of electrophysiologic studies in unexplained syncope. *Am J Cardiol* 1992;69: 1044–1049.
92. Chen LY, Jahangir A, Decker WW, Smars PA, Wieling W, Hodge DO, Gersh BJ, Hammill SC, Shen WK. Score indices for predicting electrophysiologic outcomes in patients with unexplained syncope. *J Interv Card Electrophysiol* 2005;14:99–105.
93. Brignole M, Alboni P, Benditt DG, Bergfeldt L, Blanc J-J, Thomsen PEB, Gert van Dijk J, Fitzpatrick A, Hohnloser S, Janousek, *et al*. Guidelines on management (diagnosis and treatment) of syncope-update 2004. Executive Summary. *Eur Heart J* 2004;25:2054–2072.
94. Priori SG, Schwartz PJ, Napolitano C, Bloise R, Ronchetti E, Grillo M, Vicentini A, Spazzolini C, Nastoli J, Bottelli G, Folli R, Cappelletti D. Risk stratification in the long-QT syndrome. *N Engl J Med* 2003;348:1866–1874.
95. Priori SG, Napolitano C, Gasparini M, Pappone C, Della Bella P, Giordano U, Bloise R, Giustetto C, De Nardis R, Grillo M, Ronchetti E, Faggiano G, Nastoli J. Natural history of Brugada syndrome: Insights for risk stratification and management. *Circulation* 2002;105:1342–1347.
96. Brugada J, Brugada R, Brugada P. Determinants of sudden cardiac death in individuals with the electrocardiographic pattern of Brugada syndrome and no previous cardiac arrest. *Circulation* 2003; 108:3092–3096.
97. Nienaber CA, Hiller S, Spielmann RP, Geiger M, Kuck KH. Syncope in hypertrophic cardiomyopathy: Multivariate analysis of prognostic determinants. *J Am Coll Cardiol* 1990;15:948–955.
98. Schmitt C, Barthel P, Ndrepepa G, Schreieck J, Plewan A, Schomig A, Schmidt G. Value of programmed ventricular stimulation for prophylactic internal cardioverter-defibrillator implantation in postinfarction patients preselected by noninvasive risk stratifiers. *J Am Coll Cardiol* 2001;37: 1901–1907.
99. Buxton AE, Lee KL, Hafley GE, Wyse DG, Fisher JD, Lehmann MH, Pires LA, Gold MR, Packer DL, Josephson ME, Prystowsky EN, Talajic MR. Relation of ejection fraction and inducible ventricular tachycardia to mode of death in patients with coronary artery disease: An analysis of patients enrolled in the multicenter unsustained tachycardia trial. *Circulation* 2002;106:2466–2472.
100. Buxton AE, Lee KL, Fisher JD, Josephson ME, Prystowsky EU, Hafley G. A randomized study of

the prevention of sudden death in patients with coronary artery disease. *N Engl J Med* 1999;341: 1882–1890.
101. 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. *N Engl J Med* 1996;335:1933–1940.
102. Moss AJ, Zareba W, Hall WJ, Klein H, Wilber DJ, Cannom DS, Daubert JP, Higgins SL, Brown MW, Andrews ML. Prophylactic implantation of a defibrillator in patients with myocardial infarction and reduced ejection fraction. *N Engl J Med* 2002; 346:877–883.
103. Connolly SJ, Hallstrom AP, Cappato R, Schron EB, Kuck KH, Zipes DP, Greene HL, Boczor S, Domanski M, Follmann, *et al.* Meta-analysis of the implantable cardioverter defibrillator secondary prevention trials. AVID, CASH and CIDS studies. Antiarrhythmics vs implantable defibrillator study. Cardiac Arrest Study Hamburg. Canadian Implantable Defibrillator Study. *Eur Heart J* 2000; 21:2071–2078.
104. Roden DM. Drug-induced prolongation of the QT interval. *N Engl J Med* 2004;350:1013–1022.
105. Jahangir A, Terzic A, Shen WK. Antiarrhythmic drugs and future direction In: Gussak I, Antzelevitch C, Hammill SC, Shen WK, Bjerregaard P, Eds. *Cardiac Repolarization: Bridging Basic and Clinical Science (Contemporary Cardiology)*. Totowa, NJ: Humana Press, 2003:387–404.
106. Williams BR. Cardiovascular drug therapy in the elderly: Theoretical and practical considerations. *Drugs Aging* 2003;20:445–463.
107. The Cardiac Arrhythmia Suppression Trial (CAST) Investigators. Preliminary report effect of encainide and flecainide on mortality in a randomized trial of arrhythmia suppression after myocardial infarction. *N Engl J Med* 1989;321: 406–412.
108. Waldo AL, Camm AJ, deRuyter H, Friedman PL, MacNeil DJ, Pauls JF, Pitt B, Pratt CM, Schwartz PJ, Veltri EP. Effect of d-sotalol on mortality in patients with left ventricular dysfunction after recent and remote myocardial infarction. *Lancet* 1996;348:7–12.
109. Hellestrand KJ, Burnett PJ, Milne JR, *et al.* Effect of the antiarrhythmic agent flecainide acetate on acute and chronic pacing thresholds. *Pacing Clin Electrophysiol* 1983;6:892–899.
110. Echt DS, Black JN, Barbey JT, Coxe DR, Cato E. Evaluation of antiarrhythmic drugs on defibrillation energy requirements in dogs. Sodium channel block and action potential prolongation. *Circulation* 1989;79:1106–1117.
111. Connolly SJ, Dorian P, Roberts RS, Gent M, Bailin S, Fain ES, Thorpe K, Champagne J, Talajic M, Coutu B, Gronefeld GC, Hohnloser SH. Comparison of [beta]-blockers, amiodarone plus [beta]-blockers, or sotalol for prevention of shocks from implantable cardioverter defibrillators—The OPTIC study: A randomized trial. *JAMA* 2006;295:165–171.
112. Pacifico A, Hohnloser SH, Williams JH, Tao B, Saksena S, Henry PD, Prystowsky EN. Prevention of implantable-defibrillator shocks by treatment with sotalol. *N Engl J Med* 1999;340:1855–1862.
113. Connolly SJ. Meta-analysis of antiarrhythmic drug trials. *Am J Cardiol* 1999;84:90R-93R.
114. Farre J, Romero J, Rubio JM, Ayala R, Castro-Dorticos J. Amiodarone and "primary" prevention of sudden death: Critical review of a decade of clinical trials. *Am J Cardiol* 1999;83:55D-63D.
115. Steinberg JS, Martins J, Sadanandan S, Goldner B, Menchavez E, Domanski M, Russo A, Tullo N, Hallstrom A. Antiarrhythmic drug use in the implantable defibrillator arm of the antiarrhythmics versus implantable defibrillators (AVID) study. *Am Heart J* 2001;142:520–529.
116. Kuhlkamp V, Mewis C, Mermi J, Bosch RF, Seipel L. Suppression of sustained ventricular tachyarrhythmias: A comparison of d,l-sotalol with no antiarrhythmic drug treatment. *J Am Coll Cardiol* 1999;33:46–52.
117. Alberte C, Zipes DP. Use of nonantiarrhythmic drugs for prevention of sudden cardiac death. *J Cardiovasc Electrophysiol* 2003;14:S87–S95.
118. Woods KL, Ketley D, Lowy A, Agusti A, Hagn C, Kala R, Karatzas NB, Leizorowicz A, Reikvam A, Schilling J, Seabra-Gomes R, Vasiliauskas D, Wilhelmsen L. Beta-blockers and antithrombotic treatment for secondary prevention after acute myocardial infarction. Towards an understanding of factors influencing clinical practice. *Eur Heart J* 1998;19:74–79.
119. Cairns JA, Connolly SJ, Roberts R, Gent M. Randomised trial of outcome after myocardial infarction in patients with frequent or repetitive ventricular premature depolarisations: CAMIAT. *Lancet* 1997;349:675–682.
120. Julian D, Camm A, Frangin G, Janse M, Munoz A, Schwartz P, Simon P. Randomised trial of effect of amiodarone on mortality in patients with left-ventricular dysfunction after recent myocardial infarction: EMIAT. *Lancet* 1997;349:667–674.
121. Wilber DJ, Zareba W, Hall WJ, 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.
122. Hohnloser SH, Kuck KH, Dorian P, Roberts RS, Hampton JR, Hatala R, Fain E, Gent M, Connolly SJ. Prophylactic use of an implantable cardioverter-defibrillator after acute myocardial infarction. *N Engl J Med* 2004;351:2481–2488.
123. 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 against amiodarone. *Circulation* 2000;101:1297–1302.
124. Lee KL, Hafley G, Fisher JD, Gold MR, Prystowsky EN, Talajic M, Josephson ME, Packer DL, Buxton AE, for the Multicenter Unsustained Tachycardia Trial Investigators. Effect of implantable defibrillators on arrhythmic events and mortality in the Multicenter Unsustained Tachycardia Trial. *Circulation* 2002;106:233–238.
125. Kuck K-H, Cappato R, Siebels J, Ruppel R. Randomized comparison of antiarrhythmic drug therapy with implantable defibrillators in patients resuscitated from cardiac arrest: The Cardiac Arrest Study Hamburg (CASH). *Circulation* 2000; 102:748–754.
126. Trappe H-J, Pfitzner P, Achtelik M, Fieguth H-G. Age dependent efficacy of implantable cardioverter-defibrillator treatment: Observations in 450 patients over an 11 year period. *Heart* 1997; 78:364–370.
127. Duray G, Richter S, Manegold J, Israel CW, Granefeld G, Hohnloser SH. Efficacy and safety of ICD therapy in a population of elderly patients treated with optimal background medication. *J Interv Cardiac Electrophysiol* 2005;14:169–173.
128. Daubert J, Sesselberg H, Huang D. Implantable cardioverter-defibrillators for primary prevention: How do the data pertain to the aged? *Am J Geriatr Cardiol* 2006;15:88–92.
129. Bardy GH, Lee KL, Mark DB, *et al.* Amiodarone or an implantable cardioverter-defibrillator for congestive heart failure. *N Engl J Med* 2005;352: 225–237.
130. Cleland JGF, Daubert J-C, Erdmann E, Freemantle N, Gras D, Kappenberger L, Tavazzi L. The effect of cardiac resynchronization on morbidity and mortality in heart failure. *N Engl J Med* 2005;352: 1539–1549.
131. Jahangir A, Shen WK, Neubauer SA, Ballard DJ, Hammill SC, Hodge DO, Lohse CM, Gersh BJ, Hayes DL. Relation between mode of pacing and long-term survival in the very elderly. *J Am Coll Cardiol* 1999;33:1208–1216.
132. Krahn AD, Connolly SJ, Roberts RS, Gent M. Diminishing proportional risk of sudden death with advancing age: Implications for prevention of sudden death. *Am Heart J* 2004;147:837–840.
133. Geelen P, Lorga Filho A, Primo J, Wellens F, Brugada P. Experience with implantable cardioverter defibrillator therapy in elderly patients. *Eur Heart J* 1997;18:1339–1342.
134. Panotopoulos PT, Axtell K, Anderson AJ, Sra J, Blanck Z, Deshpande S, Biehl M, Keelan ET, Jazayeri MR, Akhtar M, Dhala A. Efficacy of the implantable cardioverter-defibrillator in the elderly. *J Am Coll Cardiol* 1997;29:556–560.
135. Saksena S, Mathew P, Giorgberidze I, Krol RB, Kaushik R. Implantable defibrillator therapy for the elderly. *Am J Geriatr Cardiol* 1998;7:11–13.
136. Wilkoff BL, *et al.* Dual-chamber pacing or ventricular backup pacing in patients with an implantable defibrillator: The Dual Chamber and VVI Implantable Defibrillator (DAVID) Trial. *JAMA* 2002;288:3115–3123.
137. Kocovic DZ. Cardiac resynchronization therapy and other new approaches for the treatment of heart failure in the elderly. *Am J Geriatr Cardiol* 2006;15:108–113.
138. Silva RM, Mont L, Nava S, Rojel U, Matas M, Brugada J. Radiofrequency catheter ablation for arrhythmic storm in patients with an implantable cardioverter defibrillator. *Pacing Clin Electrophysiol* 2004;27:971–975.
139. Scheinman MM. NASPE survey on catheter ablation. *Pacing Clin Electrophysiol* 1995;18:1474–1478.
140. Tchou P, Jazayeri M, Denker S, Dongas J, Caceres J, Akhtar M. Transcatheter electrical ablation of right bundle branch. A method of treating macroreentrant ventricular tachycardia attributed to bundle branch reentry. *Circulation* 1988;78:246–257.
141. Stevenson WG, Khan H, Sager P, Saxon LA, Middlekauff HR, Natterson PD, Wiener I. Identification of reentry circuit sites during catheter mapping and radiofrequency ablation of ventricular tachycardia late after myocardial infarction. *Circulation* 1993;88:1647–1670.
142. Gurevitz OT, Glikson M, Asirvatham S, Kester TA, Grice SK, Munger TM, Rea RF, Shen WK, Jahangir A, Packer DL, Hammill SC, Friedman PA. Use of advanced mapping systems to guide ablation in complex cases: Experience with noncontact mapping and electroanatomic mapping systems. *Pacing Clin Electrophysiol* 2005;28:316–323.
143. Joshi S, Wilber DJ. Ablation of idiopathic right ventricular outflow tract tachycardia: Current

perspectives *J Cardiovasc Electrophysiol* 2005;16: S52–S58.
144. Kelly P, Ruskin JN, Vlahakes GJ, Buckley MJJ, Freeman CS, Garan H. Surgical coronary revascularization in survivors of prehospital cardiac arrest: Its effect on inducible ventricular arrhythmias and long-term survival. *J Am Coll Cardiol* 1990;15:267–273.
145. Brugada J, Aguinaga L, Mont L, Betriu A, Mulet J, Sanz G. Coronary artery revascularization in patients with sustained ventricular arrhythmias in the chronic phase of a myocardial infarction: Effects on the electrophysiologic substrate and outcome. *J Am Coll Cardiol* 2001;37:529–533.
146. Natale A, Sra J, Axtell K, Maglio C, Dhala A, Blanck Z, Deshpande S, Jazayeri M, Akhtar M. Ventricular fibrillation and polymorphic ventricular tachycardia with critical coronary artery stenosis: Does bypass surgery suffice? *J Cardiovasc Electrophysiol* 1994;5:988–994.