Published in final edited form as:

Heart Fail Clin. 2010 January ; 6(1): 93–100. doi:10.1016/j.hfc.2009.08.005.

Targeting Device Therapy: Genomics of Sudden Death

J. Michael Frangiskakis, MD, PhD and Barry London, MD, PhD

Cardiovascular Institute, University of Pittsburgh, Pittsburgh, PA

Introduction

Sudden cardiac death (SCD), which is usually defined as death from cardiac causes within an hour of symptom onset, affects more than 3 million people annually worldwide.¹ In the United States, estimates of annual sudden deaths range from 200,000 to 450,000, but are typically cited as accounting for 300,000 annually.² With an estimated population of 300 million people in the United States, approximately 1/1,000 will die suddenly each year.

Clinical factors used to predict sudden death include a prior history of aborted sudden death, left ventricular dysfunction, and the diagnosis of inherited syndromes associated with arrhythmias such as hypertrophic cardiomyopathy, arrhythmogenic right ventricular cardiomyopathy, long QT syndrome, and Brugada syndrome.^{3–4} Diagnostic studies such as programmed electrical stimulation and T-wave alternans have proved disappointing, and the majority of SCD occurs in people without overt risk factors.⁵ Pharmacological therapy, with the exception of β -adrenergic blockade, does not prevent SCD.⁶ Implantable cardioverter defibrillators (ICDs) are effective therapy for those at risk for SCD, but their use is associated with complications during implantation, device and lead failure, inappropriate shocks, limitations to quality of life, and cost.⁷ In addition, when used as primary prevention for SCD in cardiomyopathy, as many as 10 ICDs must be placed to prevent one sudden death.

Our laboratory and others are searching for novel biomarkers to identify heart failure patients at highest risk for sudden death.⁸ In this chapter, we will discuss the development and use of genomic predictors to define the population at risk for sudden cardiac death.

Mechanisms of Sudden Death in Heart Failure

Prolonged action potential duration (APD) and downregulation of the repolarizing K^+ currents I_{to} and I_{K1} are present in tissue and cardiac myocytes isolated from patients and animal models with heart failure.^{9–12} This delayed repolarization, along with enhanced dispersion of repolarization, may contribute to arrhythmias and sudden death.^{13–15} Mechanisms leading to arrhythmias may include triggered activity, such as early afterdepolarizations (EADs, resulting from recovery from inactivation of inward calcium channels) and delayed afterdepolarizations (DADs, resulting from Ca^{2+} release from overloaded internal stores). In addition, reentry leading to the rotors and scroll waves that cause ventricular tachycardia and fibrillation may be enhanced by abnormalities in intercellular communication with slow conduction, anatomical abnormalities such as fibrosis and scars, and heterogeneities in ion channel distribution in the myopathic heart.^{16–19}

Corresponding Author Address: Barry London, M.D., Ph.D. Cardiovascular Institute, University of Pittsburgh Medical Center, Scaife S-572, 200 Lothrop Street, Pittsburgh, PA 15213-2582, (412) 647-1174 (phone), (412) 647-3913 (fax), londonb@upmc.edu.

Publisher's Disclaimer: This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting proof before it is published in its final citable form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

Changes in Ca^{2+} handling are also well documented in animal models and humans with heart failure, and may contribute to arrhythmias.^{18, 20–22} In most cases, sarcoplasmic reticulum calcium ATPase 2a (SERCA2a) is decreased, the ratio of SERCA2a to phospholamban (an inhibitor of SERCA2a) is decreased, and the Na-Ca exchanger is increased, leading to smaller but prolonged Ca^{2+} transients and decreased myocyte contractile function. As noted above, these changes may contribute to afterdepolarizations. In addition, abnormal Ca^{2+} handling appears to facilitate reentrant arrhythmias in both ischemic and nonischemic cardiomyopathies.²³ Beta adrenergic receptor downregulation and changes in protein phosphorylation further decrease contractile reserve in heart failure and may contribute to arrhythmias.^{24–26}

Implantable Cardioverter Defibrillators to Prevent Sudden Death

During the 1970's, ventricular tachycardia and fibrillation were identified as the primary cause of SCD in the context of coronary artery disease^{27, 28} and the benefits of external defibrillation were shown.^{29, 30} Because that the majority of SCD occurs out of the hospital and away from facilities with external defibrillators,³¹ investigators developed the implantable cardioverter defibrillator.³² ICDs were initially used in the 1980's with the primary indication being the treatment of malignant, refractory ventricular arrhythmias.³³ Randomized controlled trials subsequently showed that ICDs improved mortality in survivors of aborted SCD (secondary prevention), and in subjects with ischemic or non-ischemic cardiomyopathies (primary prevention).^{34–37}

In patients with severe left ventricular dysfunction, SCD rates generally range from 4–6% annually.^{38,39} Aggressive implementation of “standard of care” medical therapy including β -blockers and angiotensin converting enzyme inhibitors (ACEIs)/angiotensin receptor blockers (ARBs)/aldosterone inhibitors may decrease SCD rates^{40–42}, although the delay in mortality from pump failure might lead to an increase in the overall incidence of SCD. Antiarrhythmic medications other than β -blockers can cause sudden death (e.g. flecainide), or at best not alter mortality (e.g. amiodarone).^{6, 43} Current ACC/AHA/HRS guidelines recommend ICD placement for subjects with NYHA Class II or III heart failure and EF <35% due to a nonischemic cardiomyopathy or a prior MI at least 40 days previously, and for subjects who are NYHA Class I with an EF <30% from a prior MI at least 40 days previously.⁴⁴

It is estimated that only 1 in 11 people who receive an ICD for primary prevention in cardiomyopathy will experience a SCD event for which the ICD would deliver an appropriate shock.^{5, 7} There are complications associated with ICD implantation, including infection and bleeding at the time of placement, device and lead failure at later times, inappropriate shocks for atrial tachycardias, and limitations to type of employment, quality of life and leisure activities. In addition, the high cost of ICD therapy raises the questions regarding whether the health system can afford ICD therapy in everyone who currently has an indication for a device. As such, clinical tools beyond EF have been sought to predict the risk of SCD. Programmed electrical stimulation, signal averaged ECG, and T-wave alternans have proven disappointing in their ability to identify high-risk patient subsets.⁴⁵ The identification of genomic predictors of SCD risk could help to tailor ICD therapy to a highest risk subgroup of patients.

A Genetic Basis for Sudden Death following Myocardial Infarction

A number of studies support the presence of a significant heritable component to sudden cardiac death.⁸ In the Family History and Primary Cardiac Arrest study from Seattle, 235 out-of-hospital SCD subjects (with no known history of coronary artery disease, congenital heart disease, or other severe illnesses) were compared to matched controls to assess the importance of a family history of SCD and myocardial infarction (MI).⁴⁶ A history of SCD in a parent or a first degree relative was associated with a greater than 2-fold increased risk of cardiac arrest for age <65, independent of a family history of MI. In the Paris Prospective Study I, more than

7,700 subjects with known ischemic heart disease were prospectively followed for 5 years for SCD. After correcting for known risk factors and parental history of MI, subjects having a parent with a history of SCD had a 1.8-fold higher risk of SCD.⁴⁷ More recently, a retrospective case-control study showed that the incidence of SCD was 1.6-fold higher in relatives of subjects with SCD than in relatives of subjects with an MI but no SCD, and 2.2-fold higher in relatives of SCD than in relatives of controls.⁴⁸ In addition, a case-control study comparing ST elevation MI patients with or without primary VF showed a 2.7-fold higher incidence of familial sudden death in cases versus controls.⁴⁹

Thus, there is convincing evidence for a genetic component to the risk of SCD in the setting of acute MI. The genetic basis for this risk and its extension to sudden death in the setting of heart failure remain to be clarified.

Ion Channels and Inherited Arrhythmia Syndromes

During the last 15 years, the molecular determinants of a number of inherited arrhythmia syndromes associated with sudden cardiac death (long QT syndrome, short QT syndrome, Brugada syndrome, catecholaminergic polymorphic ventricular tachycardia) have been determined by positional cloning and the candidate gene approach (Table 1).^{50–52} The majority of mutations identified to date are in ion channels or ion-channel related genes. While it makes sense that ion channel genes should cause these syndromes, it is worth noting that investigators preferentially search for mutations in ion channel genes and other genetic causes may be underestimated.

Previously unidentified rare mutations in these ion channel genes are not responsible for a significant fraction of sudden cardiac death. In the Oregon Sudden Unexpected Death Study (Ore-SUDS), amino acid-altering variants of SCN5A did not contribute to the risk of sudden death in 67 SCD victims.⁵³ Similarly, no pathological mutations were identified in SCN5A or KvLQT1 in 59 Australian SCD victims.⁵⁴ In contrast, sequencing of SCN5A, KCNQ1, KCNH2, KCNE1, and KCNE2 in 113 SCD cases from the Nurses' Health Study and the Health Professional Follow-Up Study identified 5 rare SCN5A variants in 6 women, a frequency greater than in controls.⁵⁵ While similar studies have not been done for heart failure patients, rare ion channel mutations are unlikely to play a major role.

A number of relatively common single nucleotide polymorphisms (SNPs) that lead to amino acid changes have been identified in cardiac ion channel genes, along with many more in introns and non-coding regions that could affect RNA and protein expression (Table 2). If rare mutations in ion channel genes can cause sudden death in patients with structurally normal hearts, it seems logical to hypothesize that the SNPs that cause relatively minor changes in ion channel function or numbers could predispose individuals with structural heart disease and heart failure to arrhythmias and sudden death. In support of this hypothesis, the S1103Y polymorphism in the cardiac Na⁺ channel, which is relatively common only in African Americans (allele frequency ~7%) and causes subtle QT prolongation in vitro, is associated with unexplained arrhythmias, sudden death and sudden infant death syndrome.^{56–58} In addition, the SCN5A H558R polymorphism, which is common in Caucasians (allele frequency ~20%), has been shown to a) alter current expression in conjunction with an SCN5A splice variant in vitro, b) rescue Brugada syndrome mutations whether on the same or the other chromosome in vitro, and c) potentially explains some cases of incomplete penetrance.^{59–61} It remains to be proven whether any of these polymorphisms are associated with arrhythmia susceptibility and/or sudden death in heart failure patients.

Other Genetic Polymorphisms and Sudden Cardiac Death

β -adrenergic receptor polymorphisms have been associated with differences in heart failure progression and altered pharmacogenetic responses to β -adrenergic blockade.^{62, 63} Of note, homozygotes for the glutamine allele of the β 2-AR Q27E polymorphism had an ~1.6 fold increased risk of sudden death in both the Cardiovascular Health Study and the Cardiac Arrest Blood Study.⁶⁴ Similarly, we recently reported an ~1.7-fold increased appropriate shock frequency for glutamine homozygotes in patients with heart failure and ICDs enrolled in the Genetic Risk Assessment of Defibrillator Events (GRADE) study.⁶⁵

Genome-wide association studies (GWAS) have been used to identify genes associated with QTc prolongation on the surface electrocardiogram, an intermediate phenotype expected to correlate with sudden death. Multiple studies have identified several SNPs in the nitric oxide synthase 1 adaptor protein (NOS1AP) responsible for 3–5 ms of QTc prolongation per allele.^{66, 67} SNPs in the same region of NOS1AP were associated with an ~1.3 fold per allele increased risk of sudden cardiac death in subjects in the Atherosclerosis Risk In Communities Study and the Cardiovascular Health Study.⁶⁸ It remains to be seen whether similar findings are true in heart failure populations.

We do not currently know all of the genes that are associated with arrhythmias and sudden death. Genes associated with inflammation, redox state, and omega-3 fatty acid metabolism are other potential candidates.^{69, 70} GWAS studies will identify additional genes associated with QTc prolongation that are candidate genes for sudden death, and may be used to directly identify sudden death genes in the future.

Using Genomics to Target Device Therapy

The identification of genetic predictors of sudden death in heart failure is in its earliest stages. Mutations in ion channels have been shown to cause inherited forms of sudden death; there is, however, little evidence that mutations or rare SNPs in those genes are important causes of the common forms of sudden death.⁸ Other common variants in ion channels and related genes are associated with sudden death in the setting of acute MI and/or heart failure. Unfortunately, the mechanisms of sudden death in heart failure differ from those in the setting of acute MI. It is likely that multiple genetic variants will interact to control risk, and that different variants will be relevant for different underlying disease states. In addition, potential interactions with race, gender, environment, and other cardiovascular risk factors may further complicate the analysis.

Ultimately, we hope to identify a handful of SNPs that modulate the risk of sudden death in heart failure and develop an algorithm to predict risk based on genotype. This will require prospective testing in large heart failure cohorts, most likely using appropriate ICD shocks as a surrogate for sudden cardiac death. Of note, however, appropriate ICD shock rates significantly exceeds the rates of sudden death.⁷¹

A significant question is whether genetic testing can or should be used to restrict ICD placement. If successful, genetic predictors would be used in conjunction with other clinical predictors of sudden death risk. Currently, the beneficial effects of ICDs in preventing sudden death in heart failure patients are counteracted by the relatively low likelihood of sudden death, the morbidity associated with device placement, ongoing complications from the device, effects on quality of life, and cost. As a result, many physicians are reluctant to strongly advise ICD placement in heart failure patients and only a fraction of patients with indications for ICDs accept the therapy. Better predictors of sudden death risk could identify a group of patients with the highest risk who would benefit most from ICD placement, and might identify patients with less severe left ventricular dysfunction at sufficient risk to warrant ICD placement. In

addition, delineation of a group of patients at low risk for sudden death could shift the focus on that cohort from devices to optimal medical management.

References

1. Josephson M, Wellens HJ. Implantable defibrillators and sudden cardiac death. *Circulation* 2004;109(22):2685–2691. [PubMed: 15184292]
2. Smith TW, Cain ME. Sudden cardiac death: epidemiologic and financial worldwide perspective. *J Interv Card Electrophysiol* 2006;17(3):199–203. [PubMed: 17333367]
3. Prystowsky EN. Prevention of sudden cardiac death. *Clin Cardiol* 2005;28(11 Suppl 1):I12–18. [PubMed: 16450808]
4. Priori SG, Napolitano C. Genetics of cardiac arrhythmias and sudden cardiac death. *Ann N Y Acad Sci* 2004;1015:96–110. [PubMed: 15201152]
5. Huikuri HV, Castellanos A, Myerburg RJ. Sudden death due to cardiac arrhythmias. *N Engl J Med* 2001;345(20):1473–1482. [PubMed: 11794197]
6. 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(6):406–412. [PubMed: 2473403]
7. Tung R, Zimetbaum P, Josephson ME. A critical appraisal of implantable cardioverter-defibrillator therapy for the prevention of sudden cardiac death. *J Am Coll Cardiol* 2008;52(14):1111–1121. [PubMed: 18804736]
8. Spooner PM. Sudden cardiac death: The larger problem... The larger genome. *J Cardiovasc Electrophysiol* 2009;20(5):585–596. [PubMed: 19207788]
9. Beuckelmann DJ, Nabauer M, Erdmann E. Alterations of K⁺ currents in isolated human ventricular myocytes from patients with terminal heart failure. *Circ Res* 1993;73(2):379–385. [PubMed: 8330380]
10. Kaab S, Nuss HB, Chiamvimonvat N, O'Rourke B, Pak PH, Kass DA, Marban E, Tomaselli GF. Ionic mechanism of action potential prolongation in ventricular myocytes from dogs with pacing-induced heart failure. *Circ Res* 1996;78(2):262–273. [PubMed: 8575070]
11. Nabauer M, Beuckelmann DJ, Erdmann E. Characteristics of transient outward current in human ventricular myocytes from patients with terminal heart failure. *Circ Res* 1993;73(2):386–394. [PubMed: 8330381]
12. Vermeulen JT, McGuire MA, Opthof T, Coronel R, de Bakker JM, Kloppe C, Janse MJ. Triggered activity and automaticity in ventricular trabeculae of failing human and rabbit hearts. *Cardiovasc Res* 1994;28(10):1547–1554. [PubMed: 8001044]
13. Baker LC, London B, Choi BR, Koren G, Salama G. Enhanced dispersion of repolarization and refractoriness in transgenic mouse hearts promotes reentrant ventricular tachycardia. *Circ Res* 2000;86(4):396–407. [PubMed: 10700444]
14. El-Sherif N, Chinushi M, Caref EB, Restivo M. Electrophysiological mechanism of the characteristic electrocardiographic morphology of torsade de pointes tachyarrhythmias in the long-QT syndrome: detailed analysis of ventricular tridimensional activation patterns. *Circulation* 1997;96(12):4392–4399. [PubMed: 9416909]
15. Frazier DW, Wolf PD, Wharton JM, Tang AS, Smith WM, Ideker RE. Stimulus-induced critical point. Mechanism for electrical initiation of reentry in normal canine myocardium. *J Clin Invest* 1989;83(3):1039–1052. [PubMed: 2921316]
16. Cabo C, Boyden PA. Heterogeneous gap junction remodeling stabilizes reentrant circuits in the epicardial border zone of the healing canine infarct: a computational study. *Am J Physiol Heart Circ Physiol* 2006;291(6):H2606–2616. [PubMed: 16936009]
17. Brahmajothi MV, Morales MJ, Reimer KA, Strauss HC. Regional localization of ERG, the channel protein responsible for the rapid component of the delayed rectifier, K⁺ current in the ferret heart. *Circ Res* 1997;81(1):128–135. [PubMed: 9201036]
18. London B, Baker LC, Lee JS, Shusterman V, Choi BR, Kubota T, McTiernan CF, Feldman AM, Salama G. Calcium-dependent arrhythmias in transgenic mice with heart failure. *Am J Physiol Heart Circ Physiol* 2003;284(2):H431–441. [PubMed: 12388316]

19. Petkova-Kirova PS, Gursoy E, Mehdi H, McTiernan CF, London B, Salama G. Electrical remodeling of cardiac myocytes from mice with heart failure due to the overexpression of tumor necrosis factor- α . *Am J Physiol Heart Circ Physiol* 2006;290(5):H2098–2107. [PubMed: 16339842]
20. Bers DM, Despa S, Bossuyt J. Regulation of Ca^{2+} and Na^{+} in normal and failing cardiac myocytes. *Ann N Y Acad Sci* 2006;1080:165–177. [PubMed: 17132783]
21. Beuckelmann DJ, Nabauer M, Erdmann E. Intracellular calcium handling in isolated ventricular myocytes from patients with terminal heart failure. *Circulation* 1992;85(3):1046–1055. [PubMed: 1311223]
22. O'Rourke B, Kass DA, Tomaselli GF, Kaab S, Tunin R, Marban E. Mechanisms of altered excitation-contraction coupling in canine tachycardia-induced heart failure, I: experimental studies. *Circ Res* 1999;84(5):562–570. [PubMed: 10082478]
23. Pu J, Robinson RB, Boyden PA. Abnormalities in Ca^{2+} handling in myocytes that survive in the infarcted heart are not just due to alterations in repolarization. *J Mol Cell Cardiol* 2000;32(8):1509–1523. [PubMed: 10900177]
24. Bristow MR, Hershberger RE, Port JD, Gilbert EM, Sandoval A, Rasmussen R, Cates AE, Feldman AM. Beta-adrenergic pathways in nonfailing and failing human ventricular myocardium. *Circulation* 1990;82(2 Suppl):I12–25. [PubMed: 2164894]
25. Anderson ME. Multiple downstream proarrhythmic targets for calmodulin kinase II: moving beyond an ion channel-centric focus. *Cardiovasc Res* 2007;73(4):657–666. [PubMed: 17254559]
26. Houser SR. When does spontaneous sarcoplasmic reticulum Ca^{2+} release cause a triggered arrhythmia? Cellular versus tissue requirements. *Circ Res* 2000;87(9):725–727. [PubMed: 11055973]
27. Schaffer WA, Cobb LA. Recurrent ventricular fibrillation and modes of death in survivors of out-of-hospital ventricular fibrillation. *N Engl J Med* 1975;293(6):259–262. [PubMed: 1138178]
28. Ritchie JL, Hamilton GW, Trobaugh GB, Weaver WD, Williams DL, Cobb LA. Myocardial imaging and radionuclide angiography in survivors of sudden cardiac death due to ventricular fibrillation: preliminary report. *Am J Cardiol* 1977;39(6):852–857. [PubMed: 871111]
29. Campbell NP, Webb SW, Adgey AA, Pantridge JF. Transthoracic ventricular defibrillation in adults. *Br Med J* 1977;2(6099):1379–1381. [PubMed: 589223]
30. Adgey AA, Campbell NP, Webb SW, Kennedy AL, Pantridge JF. Transthoracic ventricular defibrillation in the adult. *Med Instrum* 1978;12(1):17–19. [PubMed: 634183]
31. Olshansky B, Wood F, Hellkamp AS, Poole JE, Anderson J, Johnson GW, Boineau R, Domanski MJ, Mark DB, Lee KL, Bardy GH. Where patients with mild to moderate heart failure die: results from the Sudden Cardiac Death in Heart Failure Trial (SCD-HeFT). *Am Heart J* 2007;153(6):1089–1094. [PubMed: 17540216]
32. Filippi A, Sessa E Jr, Mazzaglia G, Pecchioli S Jr, Capocchi R Jr, Caprari F, Scivales A, Cricelli C. Out of hospital sudden cardiac death in Italy: a population-based case-control study. *J Cardiovasc Med (Hagerstown)* 2008;9(6):595–600. [PubMed: 18475128]
33. Mirowski M, Mower MM, Reid PR. The automatic implantable defibrillator. *Am Heart J* 1980;100(6 Pt 2):1089–1092. [PubMed: 7192485]
34. The Antiarrhythmics versus Implantable Defibrillators (AVID) Investigators. A comparison of antiarrhythmic-drug therapy with implantable defibrillators in patients resuscitated from near-fatal ventricular arrhythmias. *N Engl J Med* 1997;337(22):1576–1583. [PubMed: 9411221]
35. Bardy GH, 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, Fraulo ES, Fishbein DP, Luceri RM, Ip JH. Amiodarone or an implantable cardioverter-defibrillator for congestive heart failure. *N Engl J Med* 2005;352(3):225–237. [PubMed: 15659722]
36. 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(26):1933–1940. [PubMed: 8960472]
37. 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(12):877–883. [PubMed: 11907286]

38. Sweeney MO, Hellkamp AS, Ellenbogen KA, Lamas GA. Reduced ejection fraction, sudden cardiac death, and heart failure death in the mode selection trial (MOST): implications for device selection in elderly patients with sinus node disease. *J Cardiovasc Electrophysiol* 2008;19(11):1160–1166. [PubMed: 18554201]
39. Mozaffarian D, Anker SD, Anand I, Linker DT, Sullivan MD, Cleland JG, Carson PE, Maggioni AP, Mann DL, Pitt B, Poole-Wilson PA, Levy WC. Prediction of mode of death in heart failure: the Seattle Heart Failure Model. *Circulation* 2007;116(4):392–398. [PubMed: 17620506]
40. Jessup M, Abraham WT, Casey DE, Feldman AM, Francis GS, Ganiats TG, Konstam MA, Mancini DM, Rahko PS, Silver MA, Stevenson LW, Yancy CW. Focused Update: ACCF/AHA Guidelines for the Diagnosis and Management of Heart Failure in Adults. A Report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. *Circulation*. 2009
41. Nessler J, Nessler B, Kitlinski M, Libionka A, Kubinyi A, Konduracka E, Piwowarska W. Sudden cardiac death risk factors in patients with heart failure treated with carvedilol. *Kardiologia Pol* 2007;65(12):1417–1422. discussion 1423–1414. [PubMed: 18181053]
42. Anand K, Mooss AN, Mohiuddin SM. Aldosterone inhibition reduces the risk of sudden cardiac death in patients with heart failure. *J Renin Angiotensin Aldosterone Syst* 2006;7(1):15–19. [PubMed: 17083069]
43. Singh SN, Fletcher RD, Fisher SG, Singh BN, Lewis HD, Deedwania PC, Massie BM, Colling C, Lazzeri D. Amiodarone in patients with congestive heart failure and asymptomatic ventricular arrhythmia. Survival Trial of Antiarrhythmic Therapy in Congestive Heart Failure. *N Engl J Med* 1995;333(2):77–82. [PubMed: 7539890]
44. Epstein AE, DiMarco JP, Ellenbogen KA, Estes NA 3rd, Freedman RA, Gettes LS, Gillinov AM, Gregoratos G, Hammill SC, Hayes DL, Hlatky MA, Newby LK, Page RL, Schoenfeld MH, Silka MJ, Stevenson LW, Sweeney MO, Smith SC Jr, Jacobs AK, Adams CD, Anderson JL, Buller CE, Creager MA, Ettinger SM, Faxon DP, Halperin JL, Hiratzka LF, Hunt SA, Krumholz HM, Kushner FG, Lytle BW, Nishimura RA, Ornato JP, Riegel B, Tarkington LG, Yancy CW. ACC/AHA/HRS 2008 Guidelines for Device-Based Therapy of Cardiac Rhythm Abnormalities: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Writing Committee to Revise the ACC/AHA/NASPE 2002 Guideline Update for Implantation of Cardiac Pacemakers and Antiarrhythmia Devices) developed in collaboration with the American Association for Thoracic Surgery and Society of Thoracic Surgeons. *J Am Coll Cardiol* 2008;51(21):e1–62. [PubMed: 18498951]
45. Rosenbaum DS. T-wave alternans in the sudden cardiac death in heart failure trial population: signal or noise? *Circulation* 2008;118(20):2015–2018. [PubMed: 19001031]
46. 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(2):155–160. [PubMed: 9445167]
47. Jouven X, Desnos M, Guerot C, Ducimetiere P. Predicting sudden death in the population: the Paris Prospective Study I. *Circulation* 1999;99(15):1978–1983. [PubMed: 10209001]
48. Kaikkonen KS, Kortelainen ML, Linna E, Huikuri HV. Family history and the risk of sudden cardiac death as a manifestation of an acute coronary event. *Circulation* 2006;114(14):1462–1467. [PubMed: 17000909]
49. Dekker LR, Bezzina CR, Henriques JP, Tanck MW, Koch KT, Alings MW, Arnold AE, de Boer MJ, Gorgels AP, Michels HR, Verkerk A, Verheugt FW, Zijlstra F, Wilde AA. Familial sudden death is an important risk factor for primary ventricular fibrillation: a case-control study in acute myocardial infarction patients. *Circulation* 2006;114(11):1140–1145. [PubMed: 16940195]
50. Katz G, Arad M, Eldar M. Catecholaminergic polymorphic ventricular tachycardia from bedside to bench and beyond. *Curr Probl Cardiol* 2009;34(1):9–43. [PubMed: 19068246]
51. Zareba W, Cygankiewicz I. Long QT syndrome and short QT syndrome. *Prog Cardiovasc Dis* 2008;51(3):264–278. [PubMed: 19026859]
52. Schulze-Bahr E. Susceptibility genes & modifiers for cardiac arrhythmias. *Prog Biophys Mol Biol* 2008;98(2–3):289–300. [PubMed: 19351519]

53. Stecker EC, Sono M, Wallace E, Gunson K, Jui J, Chugh SS. Allelic variants of SCN5A and risk of sudden cardiac arrest in patients with coronary artery disease. *Heart Rhythm* 2006;3(6):697–700. [PubMed: 16731473]
54. Doolan A, Langlois N, Chiu C, Ingles J, Lind J, Semsarian C. Postmortem molecular analysis of KCNQ1 and SCN5A genes in sudden unexplained death in young Australians. *Int J Cardiol* 2008;127(1):138–141. [PubMed: 17544529]
55. Albert CM, Nam EG, Rimm EB, Jin HW, Hajjar RJ, Hunter DJ, MacRae CA, Ellinor PT. Cardiac sodium channel gene variants and sudden cardiac death in women. *Circulation* 2008;117(1):16–23. [PubMed: 18071069]
56. Splawski I, Timothy KW, Tateyama M, Clancy CE, Malhotra A, Beggs AH, Cappuccino FP, Sagnella GA, Kass RS, Keating MT. Variant of SCN5A sodium channel implicated in risk of cardiac arrhythmia. *Science* 2002;297(5585):1333–1336. [PubMed: 12193783]
57. Burke A, Creighton W, Mont E, Li L, Hogan S, Kutys R, Fowler D, Virmani R. Role of SCN5A Y1102 polymorphism in sudden cardiac death in blacks. *Circulation* 2005;112(6):798–802. [PubMed: 16061744]
58. Plant LD, Bowers PN, Liu Q, Morgan T, Zhang T, State MW, Chen W, Kittles RA, Goldstein SA. A common cardiac sodium channel variant associated with sudden infant death in African Americans, SCN5A S1103Y. *J Clin Invest* 2006;116(2):430–435. [PubMed: 16453024]
59. Viswanathan PC, Benson DW, Balser JR. A common SCN5A polymorphism modulates the biophysical effects of an SCN5A mutation. *J Clin Invest* 2003;111(3):341–346. [PubMed: 12569159]
60. Makielski JC, Ye B, Valdivia CR, Pagel MD, Pu J, Tester DJ, Ackerman MJ. A ubiquitous splice variant and a common polymorphism affect heterologous expression of recombinant human SCN5A heart sodium channels. *Circ Res* 2003;93(9):821–828. [PubMed: 14500339]
61. Poelzing S, Forleo C, Samodell M, Dudash L, Sorrentino S, Anaclerio M, Troccoli R, Iacoviello M, Romito R, Guida P, Chahine M, Pitzalis M, Deschenes I. SCN5A polymorphism restores trafficking of a Brugada syndrome mutation on a separate gene. *Circulation* 2006;114(5):368–376. [PubMed: 16864729]
62. Dorn GW, Liggett SB. Mechanisms of Pharmacogenomic Effects of Genetic Variation of the Cardiac Adrenergic Network in Heart Failure. *Mol Pharmacol*. 2009
63. McNamara DM, MacGowan GA, London B. Clinical importance of beta-adrenoceptor polymorphisms in cardiovascular disease. *Am J Pharmacogenomics* 2002;2(2):73–78. [PubMed: 12083943]
64. Sotoodehnia N, Siscovick DS, Vatta M, Psaty BM, Tracy RP, Towbin JA, Lemaitre RN, Rea TD, Durda JP, Chang JM, Lumley TS, Kuller LH, Burke GL, Heckbert SR. Beta2-adrenergic receptor genetic variants and risk of sudden cardiac death. *Circulation* 2006;113(15):1842–1848. [PubMed: 16618831]
65. Refaat M, Frangiskakis JM, Grimley S, Gutmann R, Bloom HL, Dudley SC Jr, Ellinor PT, Shalaby A, Weiss R, McNamara DM, London B. The β 2-adrenergic receptor Gln27 polymorphism is associated with increased ventricular arrhythmias in patients with severe heart failure. *Heart Rhythm* 2009;6:S456.
66. Arking DE, Pfeufer A, Post W, Kao WH, Newton-Cheh C, Ikeda M, West K, Kashuk C, Akyol M, Perz S, Jalilzadeh S, Illig T, Gieger C, Guo CY, Larson MG, Wichmann HE, Marban E, O'Donnell CJ, Hirschhorn JN, Kaab S, Spooner PM, Meitinger T, Chakravarti A. A common genetic variant in the NOS1 regulator NOS1AP modulates cardiac repolarization. *Nat Genet* 2006;38(6):644–651. [PubMed: 16648850]
67. Aarnoudse AJ, Newton-Cheh C, de Bakker PI, Straus SM, Kors JA, Hofman A, Uitterlinden AG, Witteman JC, Stricker BH. Common NOS1AP variants are associated with a prolonged QTc interval in the Rotterdam Study. *Circulation* 2007;116(1):10–16. [PubMed: 17576865]
68. Kao WH, Arking DE, Post W, Rea TD, Sotoodehnia N, Prineas RJ, Bishe B, Doan BQ, Boerwinkle E, Psaty BM, Tomaselli GF, Coresh J, Siscovick DS, Marban E, Spooner PM, Burke GL, Chakravarti A. Genetic variations in nitric oxide synthase 1 adaptor protein are associated with sudden cardiac death in US white community-based populations. *Circulation* 2009;119(7):940–951. [PubMed: 19204306]

69. Hernesniemi JA, Karhunen PJ, Rontu R, Ilveskoski E, Kajander O, Goebeler S, Viiri LE, Pessi T, Hurme M, Lehtimäki T. Interleukin-18 promoter polymorphism associates with the occurrence of sudden cardiac death among Caucasian males: the Helsinki Sudden Death Study. *Atherosclerosis* 2008;196(2):643–649. [PubMed: 17765248]
70. London B, Albert C, Anderson ME, Giles WR, Van Wagoner DR, Balk E, Billman GE, Chung M, Lands W, Leaf A, McNulty J, Martens JR, Costello RB, Lathrop DA. Omega-3 fatty acids and cardiac arrhythmias: prior studies and recommendations for future research: a report from the National Heart, Lung, and Blood Institute and Office Of Dietary Supplements Omega-3 Fatty Acids and their Role in Cardiac Arrhythmogenesis Workshop. *Circulation* 2007;116(10):e320–335. [PubMed: 17768297]
71. Ellenbogen KA, Levine JH, Berger RD, Daubert JP, Winters SL, Greenstein E, Shalaby A, Schaechter A, Subacius H, Kadish A. Are implantable cardioverter defibrillator shocks a surrogate for sudden cardiac death in patients with nonischemic cardiomyopathy? *Circulation* 2006;113(6):776–782. [PubMed: 16461817]
72. Ruan Y, Liu N, Priori SG. Sodium channel mutations and arrhythmias. *Nat Rev Cardiol* 2009;6(5):337–348. [PubMed: 19377496]
73. Kaab S, Schulze-Bahr E. Susceptibility genes and modifiers for cardiac arrhythmias. *Cardiovasc Res* 2005;67(3):397–413. [PubMed: 15949790]
74. Small KM, Wagoner LE, Levin AM, Kardia SL, Liggett SB. Synergistic polymorphisms of beta1- and alpha2C-adrenergic receptors and the risk of congestive heart failure. *N Engl J Med* 2002;347(15):1135–1142. [PubMed: 12374873]

TABLE 1

INHERITED ARRHYTHMIA GENES

LOCUS	GENE	PROTEIN	CURRENT	CHROMOSOME
<u>LONG QT SYNDROME</u> ⁵¹				
LQT1	<i>KCNQ1</i>	KvLQT1	↓ I _{Ks}	11p15.5
LQT2	<i>KCNH2</i>	HERG	↓ I _{Kr}	7q35-36
LQT3	<i>SCN5A</i>	SCN5A, Na _v 1.5	↑ I _{Na}	3p21
LQT4	<i>ANK2</i>	Ankyrin-B	↑ I _{Na} (?)	4q25-27
LQT5	<i>KCNE1</i>	MinK	↓ I _{Ks}	21q21-22
LQT6	<i>KCNE2</i>	MiRP1	↓ I _{Kr} (?)	21q21-22
LQT7 Andersen	<i>KCNJ2</i>	IRK1, K _{ir} 2.1	↓ I _{K1}	17q23.1
LQT8 Timothy	<i>CACNA1C</i>	Ca _v 1.2	↑ I _{Ca}	12p13.3
LQT9	<i>CAV3</i>	Caveolin-3	↑ I _{Na} (?)	3p25.3
LQT10	<i>SCN4B</i>	SCN4B	↑ I _{Na}	11q23.3
LQT11	<i>AKAP9</i>	Yotiao	↓ I _{Ks}	7q21-22
<u>SHORT QT SYNDROME</u> ⁵¹				
SQT1	<i>KCNH2</i>	HERG	↑ I _{Kr}	7q35-36
SQT2	<i>KCNQ1</i>	KvLQT1	↑ I _{Ks}	11p15.5
SQT3	<i>KCNJ2</i>	IRK1, K _{ir} 2.1	↑ I _{K1}	17q23.1
<u>BRUGADA SYNDROME</u> ⁷²				
BRUG1	<i>SCN5A</i>	SCN5A, Na _v 1.5	↓ I _{Na}	3p21
BRUG2	<i>GPD1-L</i>	GPD1-L	↓ I _{Na}	3p24
BRUG3	<i>CACNA1C</i>	Ca _v 1.2	↓ I _{Ca}	12p13.3
BRUG4	<i>CACNB2B</i>	Ca _v 2b	↓ I _{Ca}	10p12
BRUG5	<i>SCN1B</i>	SCN1B	↓ I _{Na}	19q13
<u>CATECHOLAMINERGIC POLYMORPHIC VENTRICULAR TACHYCARDIA</u> ⁵⁰				
CPVT1	<i>RYR2</i>	Ryanodine Receptor	↑ Ca _i	1q42.1
CPVT2	<i>CASQ2</i>	Calsequestrin	↑ Ca _i	1p13.3

TABLE 2
POLYMORPHISMS THAT MAY AFFECT SUDDEN DEATH

GENE	PROTEIN	CHROMOSOME	VARIANT (Freq)	MECHANISMS
<u>ION CHANNELS & RELATED GENES</u> ^{8, 73}				
<i>KCNQ1</i>	KvLQT1	11p15.5	P448R (0.07 A) G640S (0.10 A)	ΔI_{Ks}
<i>KCNH2</i>	HERG	7q35-36	K897T (0.20 C)	ΔI_{Kr}
<i>KCNE1</i>	MinK	21q21-22	G38S (0.35 C) D85N (0.02 A)	ΔI_{Ks}
<i>KCNE2</i>	MiRP1	21q21-22	T8A (0.01)	ΔI_K
<i>SCN5A</i>	SCN5A	3p21	H558R (0.20 C) (0.27 AA) S1103Y (0.07 AA)	Δ Expression Δ Trafficking ΔI_{Na} Kinetics
<i>CASQ2</i>	Calsequestrin	1p13.3	T66A (0.28 C) V76M (0.03 C)	Δ Ca Binding
<i>NOS1AP</i>	NOS1AP	1q23	Various	$\uparrow$ APD
<u>ADRENERGIC RECEPTORS</u> ^{63, 74}				
<i>ADRB1</i>	$\beta 1$ -AR	10q25.3	S49G (0.30 C) R389G (0.15 C)	Δ Responsiveness Δ Downregulation
<i>ADRB2</i>	$\beta 2$ -AR	5q31-32	G16R (0.40 C) Q27E (0.45 C) T164I (0.05 C)	Δ Responsiveness Δ Downregulation
<i>ADRA2C</i>	$\alpha 2C$ -AR	4p16	Del 322-325 (.04 C, .41 AA)	Δ Responsiveness Synergy to $\beta 1$ -R389G

A, Asian; C, Caucasian; AA, African American; APD, action potential duration; Del, deletion.