

# PATHOPHYSIOLOGY AND RISK STRATIFICATION OF SUDDEN CARDIAC DEATH IN ISCHEMIC HEART DISEASE

NABIL EL-SHERIF\*

Management of Sudden Cardiac Death (SCD) is undergoing a radical change in direction. It is becoming increasingly appreciated that besides depressed left ventricular systolic function and the conventional risk stratification tools, new markers for plaque vulnerability, enhanced thrombogenesis, specific genetic alterations of the autonomic nervous system, cardiac sarcolemmal and contractile proteins, and familial clustering may better segregate patients with atherosclerotic coronary artery disease who are at high risk for SCD from those who may suffer from nonfatal ischemic events. Better understanding of pathophysiological processes, such as post-myocardial infarction remodeling, the transition from compensated hypertrophy to heart failure, and the increased

cardiovascular risk of coronary artery disease in the presence of diabetes or even a pre-diabetic state will help to improve both risk stratification and management. The rapidly developing fields of microchips technology and proteomics may allow rapid and cost-effective mass screening of multiple risk factors for SCD. The ultimate goal is to identify novel methods for risk stratification, risk modification, and prevention of SCD that could be applied to the general public at large.

**Kew Word:** Sudden cardiac death, coronary artery disease, left ventricular dysfunction.

**PJC 2014; 25: 20-30**

## INTRODUCTION

SCD is a major public health problem both at the US and worldwide. It is estimated that each year in the US 400,000-460,000 persons die of unexpected SCD in Emergency Departments or before reaching a hospital. The current management of SCD is directed at a relatively small percentage of the total population at risk and primarily at those patients already known to be at increased risk by conventional criteria.

\* *State University of New York, Downstate Medical Center and New York harbor VA Healthcare System, Brooklyn, NY, USA*

*Supported in part by REAP and MERIT grants from the VA Central Office Research program, Washington, DC*

### **Address For Correspondence:**

*Nabil El-Sherif, MD*

*NY Harbor VA Healthcare System,*

*800 Poly Place, Brooklyn, NY 11209*

*Tel# 718-630-3740, Fax# 718-630-3740*

*e-mail: nelsherif@aol.com*

Pharmaceutical strategies to prevent SCD have been largely ineffective. Because device therapy [implantable cardioverter-defibrillator (ICD)] is designed to rescue patients once an event has already occurred, primary SCD prevention has become one of today's most critical public health challenges. Current conventional risk stratifiers for SCD have shown low positive predictive power either alone or in different combinations. As of 2005, the main criterion for primary ICD prophylaxis for SCD has been the presence of organic heart disease and depressed left ventricular ejection fraction (LVEF). Unfortunately, depressed LVEF may be a good marker for total cardiac mortality but is not specific for SCD resulting in a significant **redundancy** of this strategy. The cost to the health care system of sustaining this approach would be substantial. For the immediate future, attempts to optimize the selection process for primary ICD prophylaxis that

goes beyond depressed LVEF must continue.

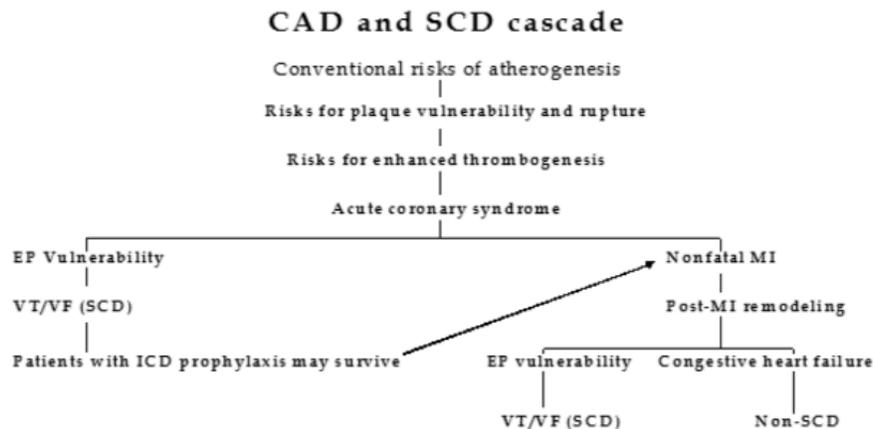
The present article will review the most recent pathophysiology and risk stratification of SCD in ischemic heart disease, and its management beyond the current single criterion of depressed LVEF.

### Coronary Artery Disease (CAD) and Sudden Cardiac Death (SCD) Cascade (Figure 1)

other susceptibility genes have been identified using genome-wide association studies or genome-wide linkage studies<sup>3</sup>.

On the other hand, there is a new understanding of the **cascade** that relates the distal events of atherosclerosis to the proximal event of SCD. New risk markers for SCD in CAD are likely to cluster under factors that may directly facilitate the development of acute coronary

**FIGURE 1:** ABBREVIATIONS: CAD, CORONARY ARTERY DISEASE; EP, ELECTROPHYSIOLOGICAL; ICD, IMPLANTABLE CARDIOVERTER DEFIBRILLATOR; MI, MYOCARDIAL INFARCTION; SCD, SUDDEN CARDIAC DEATH; VT/VF, VENTRICULAR TACHYCARDIA/VENTRICULAR FIBRILLATION



The majority of SCD occurs in patients with atherosclerotic CAD (65–85%)<sup>1</sup>. However, there is considerable evidence that traditional markers of CAD, such as hypertension, obesity, smoking, diabetes, and lipid abnormalities, are not specific enough to identify patients at high risk for SCD<sup>2</sup>. Patients with similar risk factors for CAD may suffer from SCD or nonfatal ischemic events. The reason for this difference is not clear. However, there is exciting evidence in recent years in genetic studies of CAD and MI that may in part explain this discrepancy. For example, one disease-causing gene for CAD and MI has been identified as MEF2A, which is located on chromosome 15q26.3 and encodes for a transcriptional factor with high level of expression in coronary endothelium<sup>3</sup>. Approximately 1% to 2% of CAD patients may carry an MEF2A mutation. Several

syndromes, specifically those factors that may facilitate transient triggering events, including plaque rupture, enhanced thrombogenesis, and coronary artery spasm<sup>4,5</sup>. There is significant data showing correlation between SCD and

- 1) markers of plaque vulnerability, such as heritable alterations of specific matrix metalloproteinases<sup>6</sup>;
- 2) markers of enhanced thrombogenesis, such as increased D-dimer, increased apo-B, and decreased apo-A1<sup>7</sup>; as well as polymorphism in platelet glycoprotein receptors<sup>8</sup>;
- 3) genetic variations that predispose to vasospasm, such as variations in the vascular endothelial nitric oxide synthetase (eNOS) system<sup>9,10</sup>; and

- 4) markers of inflammatory response, such as C-reactive protein (CRP)<sup>11</sup>.

Acute coronary syndrome can result either in early electrophysiological vulnerability leading to fatal ventricular tachyarrhythmia and SCD (unless the patient has a prior ICD) or in nonfatal myocardial infarction (MI). In patient who survive a nonfatal MI the heart undergoes a complex post-MI remodeling process that in the long run results in increased electrophysiological vulnerability, fatal ventricular tachyarrhythmia, and SCD or in progressive deterioration of ventricular systolic function, ischemic cardiomyopathy, congestive heart failure, and non-SCD.

#### **Diabetes, CAD, and Risk of SCD**

Cardiovascular disease is the leading cause of death in individuals with type 2 diabetes, which affects about 15 million Americans<sup>12</sup>. This is compatible with the “common soil” hypothesis, which postulates that both diabetes and cardiovascular disease have common genetic and environmental antecedents, i.e., “they spring from the same soil”<sup>13</sup>. There is evidence that diabetes is a significant risk factor for SCD but not for nonfatal MI<sup>14</sup>. The increased risk of death and mortality rates associated with diabetes are compounded by the fact that many diabetic individuals are unaware that they suffer from the metabolic syndrome. There is strong evidence that the elevated risk for cardiovascular disease starts to increase long before the onset of clinical diabetes, confirming the so-called “ticking clock” hypothesis<sup>15</sup>. The incidence of impaired glucose tolerance and diabetes may be as high as 39% and 31%, respectively, in patients admitted with acute MI<sup>16</sup>. Recent studies have documented increased inflammation, neovascularization, and intraplaque hemorrhage in human diabetic atherosclerosis<sup>17</sup>. Because of vulnerability of diabetic patients to plaque rupture and acute MI, a question of considerable importance is whether patients with CAD, diabetes or prediabetes, and relatively preserved LV systolic function (LVEF  $\geq$  35%) can

benefit from primary ICD prophylaxis.

#### **The Autonomic System and Enhanced Susceptibility to SCD**

Autonomic neural influences, especially increased adrenergic and decreased cholinergic activity, can modulate the susceptibility to SCD following MI. Resting heart rate has been shown to be an independent risk factor for SCD in middle-aged men<sup>18</sup>. There are data showing the heritability of heart rate variation<sup>19</sup>. Adrenergic agonists are known to trigger ventricular arrhythmias, and their circulating levels have similar diurnal patterns as SCD events<sup>20</sup>. Genetic polymorphism of  $\beta$ -adrenergic receptors have been associated with increased susceptibility to SCD in ischemic heart disease<sup>21</sup>. The association between plasma nonesterified fatty acids and SCD may be related to increased adrenergic tone or the effect on ion channel and transporters<sup>22</sup>. Further, mental stress was found to be associated with lateralization of mid brain activity resulting in imbalanced activity in right and left cardiac sympathetic nerves and increased dispersion of repolarization, predisposing to arrhythmia<sup>23</sup>. Recently a third type of  $\beta$ -adrenergic receptors,  $\beta$ -3 adrenergic receptors were found in the human heart<sup>24</sup>. In both failing and post-MI myocardium,  $\beta$ -3 adrenergic receptors stimulation may have protective effects against  $\beta$ -1 and  $\beta$ -2 catecholaminergic stimulation<sup>25</sup>. This makes  $\beta$ -3 adrenergic receptors a very attractive target for pharmacologic therapy of cardiac arrhythmias related to cardiac sympathetic nerve stimulation.

#### **Cardiac Gene Mutations and Enhanced Susceptibility to SCD**

There is compelling evidence that a genetic mechanism may increase a patient susceptibility to SCD following MI. Subtle genetic variations such as single nucleotide polymorphisms can influence the phenotypic expression of low penetrance ion channel mutations and increased the propensity to VA and SCD<sup>26</sup>. One clue of the

role that genetic factors may play in SCD has been evidence of “family clustering” of SCD victims. Population studies have reported that familial clustering of SCD events is an important independent factor in multifactorial analyses of SCD risk. This may be related to shared environmental or genetically transmittable abnormalities. Evidence favoring a focus on genetic factors was presented in epidemiologic studies that suggested not only that familial risks for SCD appear substantial, but that they are statistically distinct and separable from familial risks of MI<sup>27-30</sup>. In one study parental history of SCD increased the relative risk of SCD to 1.8 after adjustment for conventional CAD risk factors, but it did not elevate the risk for deaths coded as non-sudden. In a small subset in which there was a history of both maternal and paternal SCD events, the relative risk for SCD in offspring was up to 9.4<sup>28</sup>.

Further, the role of modifier genes (gene-gene interaction) is beginning to be appreciated.

Modifier genes are genes that are not involved in the genesis of the disease but modify the severity of the phenotypic expression. The final phenotype is the result of interactions among causal genes, modifier genes, and environmental factors. Identification of modifier genes will complement the results of studies of causative genes and could enhance genetic-based diagnosis, risk stratification, and implementation of preventive and therapeutic measures of SCD<sup>31</sup>.

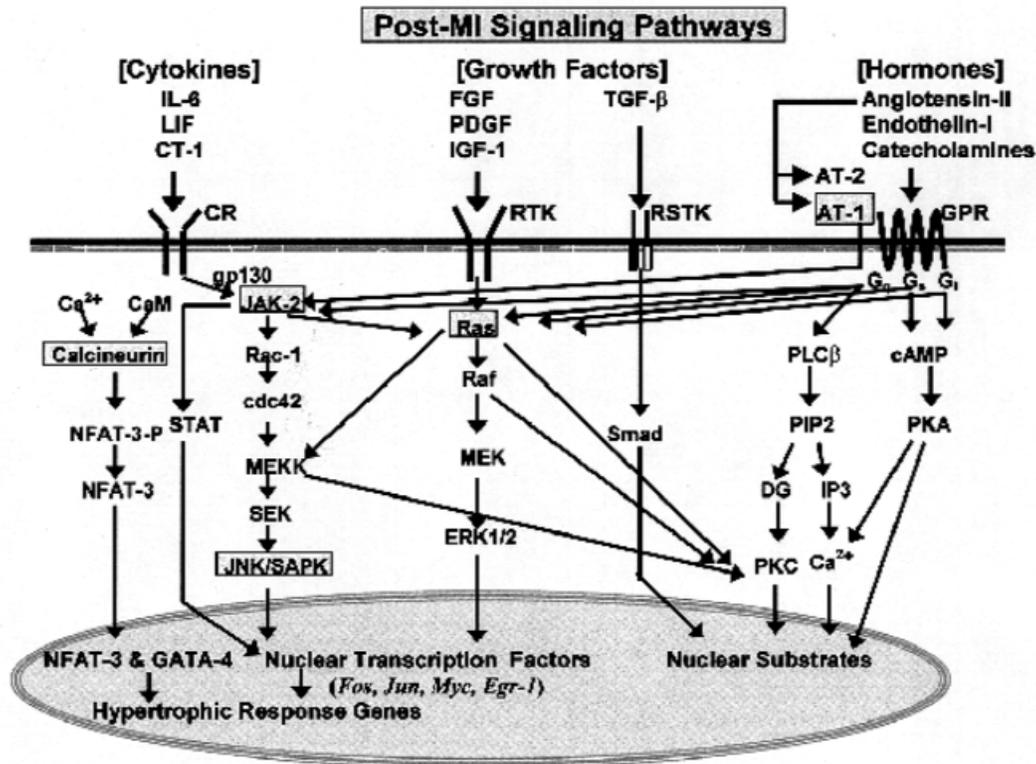
### **Post-MI remodeling and SCD**

Patients who suffer from a nonfatal MI as well as those who survive SCD in the setting of acute MI later undergo post-MI remodeling. Ventricular remodeling is the process by which ventricular size, shape and function are regulated by mechanical, neurohormonal, and genetic factors<sup>32-34</sup>. Remodeling may be physiological and adaptive during normal growth or pathological due to MI, cardiomyopathy, hypertension, or valvular heart disease. Post-MI remodeling is a complex time-

dependent process that involves structural, biochemical, neurohormonal and electrophysiologic alterations. The acute loss of myocardium results in an abrupt increase in loading conditions that induces a unique pattern of remodeling involving the infarcted border zone and remote noninfarcted myocardium<sup>35</sup>. Post-MI remodeling is associated with time-dependent dilatation, distortion of ventricular shape, and hypertrophy of the noninfarcted myocardium. Following a variable period of compensatory hypertrophy, deterioration of contractile function may develop resulting in congestive heart failure.

In recent years the understanding of the signal transduction pathways for cardiac remodeling in the post-MI heart<sup>36,37</sup> has provided opportunities for novel therapeutic interventions. Figure 2 illustrates a proposed scheme for post-MI signaling pathways<sup>31</sup>. Many of these pathways were shown to be activated either in response to ischemia/reperfusion stimuli or to a stretch stimulus using different experimental models and sometimes non-cardiac cell systems. However, cell membrane receptors and intracellular signaling proteins are highly conserved between mammalian species and the triggering events for cellular hypertrophy in humans are likely to resemble closely those in the various animal models used. The diagram shows that a cascade of successive transduction steps allows signal enhancement and diversification at branching points and thus permits combinatorial interactions between multiple pathways. Although multiple signaling pathways may act in synergistic, antagonistic, or permissive way some key pathways may play a dominant role. There is a plethora of experimental and clinical evidence showing that the renin-angiotensin system (RAS) and the B-adrenergic system play major roles in post-MI remodeling<sup>34</sup>. This explains the beneficial role that ACE inhibitors, AT-1 receptor antagonists, and beta-blockers in the post-MI period. More recently, other signaling pathways, for example, the calcineurin pathway<sup>38</sup> and the Janus kinase/signal transducer and activator of transcription (JAK-

**FIGURE 2:** POST-MI SIGNALING PATHWAYS. (MODIFIED FROM HEFTI MA, HARDER BA, EPPENBERGER HM, SCHAUB MC: SIGNALING PATHWAYS IN CARDIAC MYOCYTE HYPERTROPHY. J MOL CELL CARDIOL 1007;29:2873-2892, WITH PERMISSION OF ELSEVIER).



STAT)<sup>39</sup> signaling pathway were also found to play a significant role in post-MI remodeling. Pharmaceutical agents that can block these pathways may provide new therapeutic modalities in the post-MI period.

### Post-MI remodeling and electrophysiological vulnerability

A key electrophysiological alteration in post-MI remodeled heart is down regulation of K<sup>+</sup> gene expression and K<sup>+</sup> currents resulting in spatially heterogeneous prolongation of action potential duration and increased dispersion of refractoriness<sup>40</sup>. For many years the observation was made that cardiac hypertrophy from whatever cause is consistently associated with down regulation of K<sup>+</sup> channel genes and K<sup>+</sup> currents. However, recent studies have shown that, in the

post-MI heart, this down regulation occurs early and may be dissociated from the slower time course of post-MI remodeled hypertrophy<sup>40</sup>. It is therefore not surprising that the post-MI heart is more sensitive to hypokalemia and the proarrhythmic effects of drugs that depress K<sup>+</sup> currents, especially I<sub>kr</sub> blockers. Some pharmacological interventions that have been shown to reduce the incidence of SCD in post-MI patients, like magnesium<sup>41</sup> and spironolactone<sup>42</sup> may act by countering the effects of low K<sup>+</sup>.

### SCD and systolic dysfunction

Although the exact mechanisms involved in the strong correlation between decreased left ventricular (LV) systolic function and increased incidence of SCD are not clearly defined, it is now recognized that one way to combat SCD following MI is to try to halt or improve the deterioration in

LV function. The mechanism(s) for the transition from compensated to decompensated heart failure is under intensive investigation and it is clear that multiple factors are involved<sup>43</sup>. The role of continuous loss of cardiomyocytes to apoptosis in the noninfarcted myocardium; the negative consequences of remodeling of the interstitial matrix; the downregulation of the beta-adrenergic receptor-G protein-adenylyl cyclase pathway; the downregulation of the L-type calcium current, and the alterations in calcium regulated excitation-contraction coupling are some of the major mechanisms involved. Recent years have seen significant advances in the treatment of ventricular systolic dysfunction and heart failure. The therapeutic armamentarium includes not only pharmacological agents, but also electrical and surgical devices. Besides the cornerstone drugs for heart failure like digoxin, diuretics, ACE inhibitors, and beta-blockers, newer agents like the aldosterone receptor antagonist spironolactone, the endothelin antagonist bosentan, the vasopeptidase inhibitor omapatrilat, and the brain natriuretic peptide (BNP) nesiritide have been investigated in multicenter trials with varying results<sup>44</sup>. BNP level was shown to be a strong predictor of SCD in patients with chronic heart failure<sup>45</sup>. On the other hand, electrical devices like biventricular pacing in selected groups of patients can improve LVEF and mortality<sup>46</sup>. Further, surgical procedures like passive external support have been shown in experimental studies to reverse remodeling with reduced systolic wall stress and improved adrenergic signaling<sup>47</sup>. The success of the LV assist devices<sup>48</sup> has shown that even in an advanced stage of heart failure, the remodeling process could be reversed with significant improvement of ventricular function. Finally, clinical research has demonstrated that gene transfer is a potential therapeutic option to restore diseased cardiomyocytes and rescue the failing heart<sup>49</sup>.

### **Risk Stratification of SCD in the Post-MI Period (table 1)**

In 2005, the Centers for Medicare and Medicaid Services (CMS) approved primary

implantable cardiac cardioverter defibrillator (ICD) for patients in the post-MI period who have LVEF of 35% and New York Heart Association (NYHA) class II or III heart failure<sup>50</sup>. These criteria were based on data from MADIT II<sup>51</sup> and SCD-HeFT<sup>52</sup>. Implantation is approved only after 40 days or more have elapsed from the time of MI, on the basis of data from DINAMIT<sup>53</sup>. One area of uncertainty of these criteria is the unreliability of LVEF measurements as well as evolution of LVEF over time and the way in which this influences risk<sup>54</sup>. There is general consensus that there is a need for more robust risk stratification of SCD beyond LVEF.

All completed SCD primary ICD prophylaxis trials addressed patients with one or more conventional risk factors for SCD (Table 2)<sup>31</sup>. The electrophysiological surrogates for SCD, including measures of myocardial conduction disorders, dispersion of repolarization, and autonomic imbalance, are based on sound scientific evidence. However, the majority of conventional electrophysiological risk stratifiers of SCD have a relatively low positive predictive value that would preclude their wide application as guidelines for ICD implantation in patients known to be at risk for SCD. This is not to mention the impracticality of their use for risk stratification in the general asymptomatic public. It is not therefore surprising that the current main criteria for SCD primary ICD prophylaxis are measures of ventricular dysfunction, i.e., LVEF and NYHA class. There is general consensus that these criteria may have strong predictive value for total cardiac mortality but are not specific enough for arrhythmic mortality. This explains the continued effort to identify additional risk factors with independent or additive predictive power for arrhythmic death. These may include the use of newer techniques of nuclear magnetic resonance with contrast material to define anatomy of the infarct<sup>55</sup> as well as possible future use of genetic risk profiling.

TABLE 1: RISK STRATIFICATION OF SCD

<b>Electrophysiological Surrogates</b>	<b>Functional, Biochemical, and Genetic Surrogates</b>
<b>Measures of conduction disorder:</b> SAECG, % of scar tissue in CMR	<b>Functional Markers:</b> -LVEF**
<b>Measures of Dispersion of Repolarization:</b> QT dispersion, TWA	-NYHA Class
<b>Measures of Autonomic Nervous System:</b> a) <i>Direct:</i> sympathetic nerve activity, 1231-MIBG scan b) <i>ECG-based:</i> HRV, Baroreceptor Sensitivity, HR Turbulence, QT dynamicity	<b>Biochemical Markers:</b> -C-reactive protein -Homocysteine level -Serum matrix metalloproteinase -BNP, etc
<b>Measures of altered calcium kinetics ???</b>	<b>Genetic Markers ???</b>

Abbreviations: BNP, Beta natriuretic peptide; CMR, Cardiac magnetic resonance; HR, heart rate; HRV, heart rate variability; LVEF, left ventricular ejection fraction; NYHA, New York Heart Association; SAECG, signal averaged electrocardiogram; SCD, sudden cardiac death; TWA, microvolt T-wave alternans

\*\* Currently, LVEF  $\leq$  35% is the main criterion for primary ICD prophylaxis

## CONCLUSIONS

The immediate future goals for risk stratification and management of SCD post-MI could be summarized as follows: 1. Identification of novel clinical, biochemical, and genetic markers for SCD and assessment of the functional consequences of sequence variants identified in human genetic studies as well as relevant environmental-genetic interactions. 2. Determination of the heritability of genetic risk factors for SCD as well as the factors involved in ethnic-specific differences in risk of SCD. 3. Identification of a battery of a relatively limited number of incrementally cumulative low-intermediate risk variants and development of a “signature” combination of clinical, biochemical, and genetic markers of SCD. However, we should not be surprised that the positive predictive value of some of the new risk factors, similar to conventional risk factors, will be relatively low, especially if these are applied to large populations who are at low risk. In fact, the true value of risk stratification of SCD in the future may be to identify low-risk populations who do not warrant prophylactic intervention with therapy that demonstrated efficacy, e.g. the ICD. 4.

Identification of novel pharmacological and non-pharmacological approaches for risk modification and prevention of SCD. One example is the interest in clinical prevention of SCD by n-3 polyunsaturated fatty acids. Although this relatively new diet-heart hypothesis that underlies this therapeutic modality is yet to catch the attention of the clinical community at large, several experimental and clinical evidence point to the validity of this approach<sup>56</sup>. 5. Wider collaboration among different academic and industrial institutions by sharing research results as well as resources such as clinical data, blood and other tissues from Biorepository centers. The ultimate goal is not only to change the current direction of management strategy of SCD away from increased ICD utilization, but primarily to identify novel methods for risk stratification, risk modification, and prevention of SCD that could be applied to the general public at large.

## REFERENCES

1. American Heart Association 2001 Heart and Stroke Statistical Update. Dallas, TX: American Heart Association, 2001.

2. Braunwald E: Shattuck Lecture. Cardiovascular medicine at the turn of the millennium: Triumphs, concerns and opportunities. *N Engl J Med* 1997;377:1360-1369.
3. Wang Q. Advances in the genetic basis of coronary artery disease. *Curr Atherosclerosis Rep* 2005;7(3):235-241.
4. Spooner PM, Albert C, Benjamin EL, et al. 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.
5. Spooner PM, Albert C, Benjamin EL, et al. Sudden cardiac death, genes, and arrhythmogenesis: Consideration of new population and mechanistic approaches from a National Heart, Lung, and Blood Institute Workshop, part II. *Circulation* 2001;103:2447-2452.
6. Gnasso A, Motti C, Irace C. Genetic variation in human stromelysin gene promoter and common carotid geometry in healthy male subjects. *Arterioscler Thromb Vasc Biol* 2000;20:1600-1605.
7. Moss AJ, Goldstein RE, Marder VJ, et al. Thrombogenic factors and recurrent coronary events. *Circulation* 1999;99:2517-2522.
8. Weiss EJ, Bray PF, Tayback M, et al. A polymorphism of a platelet glycoprotein receptor as an inherited risk factor for coronary thrombosis. *N Engl J Med* 1996;334:1090-1094.
9. Nakayama M, Yasue H, Yoshimura M, et al. T786→C mutation in the 5'-flanking region of the endothelial nitric oxide synthase gene is associated with coronary spasm. *Circulation* 1999;99:2864-2870.
10. Wang XL, Sim AS, Wang MX, Murrell GA, Trudinger B, Wang J. Genotype dependent and cigarette specific effects on endothelial nitric oxide synthase gene expression and enzyme activity. *FEBS Lett* 2000;471:45-50.
11. Albert CM, Ma J, Rifai N, Stampfer MJ, Ridker PM. Prospective study of C-reactive protein, homocysteine, and plasma lipid levels as predictors of sudden cardiac death. *Circulation* 2002;105:2595-2599.
12. American Diabetes Association: diabetes facts and figures, 2000. Available from <http://www.diabetes.org>.
13. Stern MP. Diabetes and cardiovascular disease, the "common soil" hypothesis. *Diabetes* 1995;44:396-374.
14. Balkau B, Jouven X, Ducimetiere P, Eschwege E. Diabetes as a risk of factor for sudden death. *Lancet* 1999;354:1968-1969.
15. Hu FB, Stampfer MJ, Haffner SM, Soloman CG, Willett WC, Manson JE. Elevated risk of cardiovascular disease prior to clinical diagnosis of type 2 diabetes. *Diabetes Care* 2002;25:1129-1134.
16. Haffner SM. Glucose-intolerance testing in acute myocardial infarction. *Lancet* 2002;359:2127-2128.
17. Moreno PR, Fuster V. New aspects in the pathogenesis of diabetic atherothrombosis. *J Am Coll Cardiol* 2004;44:2293-3000.

18. Jouven X, Zureik M, Desnos M, Guerot C, Ducimetiere P. Resting heart rate as a predictive risk factor for sudden death in middle aged men. *Cardiovasc Res* 2001;50:373-378.
19. Singh JP, Larson MG, O'Donnell CJ, Tsuji H, Evans JC, Levy D. Heritability of heart rate variability: The Framingham Heart Study. *Circulation* 1999;99:2251-2254.
20. Muller JE. Circadian variation and triggering of acute coronary events. *Am Heart J* 1999;137(Pt 2):51-58.
21. Jaillon P, Simon T. Genetic polymorphism of beta-adrenergic receptors and mortality in ischemic heart disease. *Therapie* 2007;62:1-7.
22. Jouven X, Charles MA, Desnos M, Ducimetiere P. Circulating nonesterified fatty acid level as a predictive risk factor for sudden cardiac death in the population. *Circulation* 2001;104:756-761.
23. Critchley HD, Taggart P, Sutton PM, et al. Mental stress and sudden cardiac death: asymmetric midbrain activity as a linking mechanism. *Brain* 2005;128:75-85.
24. Gauthier C, Tavernier G, Charpentier F, Langin D, Le Marec H. Functional beta3-adrenergic receptors in the human heart. *J Clin Invest* 1996;98:556-562.
25. Vadim VF, Ilya TL. Is beta3-adrenergic receptors a new target for treatment of post-infarct ventricular tachyarrhythmias and prevention of sudden cardiac death. *Heart Rhythm* 2008;5:298-299.
26. Rubart M, Zipes DP. Genes and cardiac repolarization: the challenge ahead. *Circulation* 2005;112:1242-1244.
27. Friedlander Y, Siscovick DS, Weinmann S, et al. Family history as a risk factor for primary cardiac arrest. *Circulation* 1998;97:155-160.
28. Jouven X, Desnos M, Guerot C, Ducimetiere P. Predicting sudden death in the population: The Paris Prospective Study I. *Circulation* 1999;99:1978-1983.
29. Friedlander Y, Siscovick DS, Arbogast P, et al. Sudden cardiac death and myocardial infarction in first degree relatives as predictors of primary cardiac arrest. *Atherosclerosis* 2002;162:211-216.
30. Lukas RCD, Connie RB, Jose PSH, et al. Familial sudden death is an important risk factor for primary ventricular fibrillation. A case-control study in acute myocardial infarction patients. *Circulation* 2006;114:1140-1145.
31. El-Sherif N, Turitto G. Risk stratification and management of sudden cardiac death: A new paradigm. *J Cardiovasc Electrophysiol* 2003; 14:1-7.
32. Pfeffer JM, Pfeffer MA, Fletcher PJ, Braunwald E. Progressive ventricular remodeling in rat with myocardial infarction. *Am J Physiol*, 1991; 260: H1406-H1414.
33. Swynghedauw B. Molecular mechanisms of myocardial remodeling. *Physiol reviews* 1999; 79: 215-262.
34. Hefti MA, Harder BA, Eppenberger HM, Schaub MC. Signaling pathways in cardiac myocyte hypertrophy. *J Mol Cell Cardiol* 1997; 29: 2873-2892.

35. Sutton MG, St J, Sharpe N: Left ventricular remodeling after myocardial infarction. Pathophysiology and Therapy. *Circulation* 2000; 101: 2981-2988.
36. Qin D, Zang ZH, Caref EB, Boutjdir M, Jain P, El-Sherif N. Cellular and ionic basis of arrhythmias in post infarction remodeled ventricular myocardium. *Circ Res* 1996; 79: 461-473.
37. Gidh-Jain M, Huang B, Jain P, El-Sherif N. Differential expression of voltage-gated K<sup>+</sup> channel genes in left ventricular remodeled myocardium after experimental myocardial infarction. *Circ Res*. 1996; 79: 669-675.
38. Deng L, Huang B, Qin D, Ganguly K, El-Sherif N. Calcineurin inhibition ameliorates structural, contractile, and electrophysiological consequences of post-infarction remodeling. *J Cardiovasc Electrophysiol* 2001;12:1055-1061.
39. El-Adawi H, Deng L, Tramontano A, et al. The functional role of the JAK-STAT pathway in post infarction remodeling. *Cardiovasc Res* 2003;58:126-135.
40. Huang B, Qin D, El-Sherif N: Early down-regulation of K<sup>+</sup> channel genes and currents in the post infarction heart. *J Cardiovasc Electrophysiol* 2000; 11: 1252-1261.
41. Gyamlani G, Parikh G, Kulkani AG, Benefits of magnesium in acute myocardial infarction. Timing is crucial. *Am Heart J* 2000;139:e2.
42. Pitt B, Zannad F, remme WJ, et al. The effect of spironolactone on morbidity and mortality in patients with severe heart failure. *New Engl J Med* 1999;341:709-717.
43. Lorell BH (1997): Transition from hypertrophy to failure. *Circulation* 1997;96:2824.
44. Carson P. Current reviews of heart failure trials. *Cardiology* 2001;7:27-32.
45. Berger R, Huelsmon M, Strecker K, et al.  $\beta$ -type natriuretic peptide predicts sudden death in patients with chronic heart failure. *Circulation* 2002;105:2392-2397.
46. Bradley DJ, Bradely EA, Baughman KL, et al. Cardiac resynchronization and death from progressive heart failure: A meta-analysis of randomized controlled trials *JAMA* 2003;289:730-740.
47. Saavedra WF, Tunin RS, Paolocci N, et al: Reverse remodeling and enhanced adrenergic reserve from passive external support in experimental dilated heart failure. *J Am Coll Cardiol* 2002; 39: 2069-2076.
48. Frazier OH, Benedict CR, Radovancevic B, et al: Improved left ventricular function after chronic left ventricular unloading. *Ann Thorac Surg* 1996; 62: 675-682.
49. Hajjar RT, del Monte F, Matsui T, Rosenweig A. prospects for gene therapy of heart failure. *Circ Res* 2000;86:616-621.
50. McClellan MB, Tunis SR. Medicare coverage of ICDs. *N Engl J Med* 2005;352:222-224.
51. Moss AJ, Zareba W, Hall WJ, et al. prophylactic implantation of a defibrillator in patients with myocardial infarction and reduced ejection fraction. *N Engl J Med*

- 2002;346:877-83.
52. Brady GH, Lee KL, Mark DB, et al. Amiodarone or an implantable cardioverter-defibrillator for congestive heart failure. *New Engl J Med* 2005;352:225-237.
53. Honloser SH, Kuck KH, Dorian P, et al. Prophylactic use of implantable cardioverter-defibrillator after myocardial infarction. *New engl J med* 2004;352:2481-2488.
54. Myerburg RJ. Implantable cardioverter-defibrillators after myocardial infarction. *New Engl J Med*. 2008; 395:2245-2253.
55. Yan AT, Shayne AJ, Brown KA, et al. Characterization of the peri-infarct zone by contrast-enhanced cardiac magnetic resonance imaging is a powerful predictor of post-myocardial infarction mortality. *Circulation* 2006;114:32-39.
56. Leon H, Shibata MC, Sivakumaran S, Dorgan M, Chatterly T, Tsuyuki RT. Effect of fish oil on arrhythmias and mortality: Systematic review. *BMJ* 2008;23:337-a2931-99.