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## Sex Differences in Sudden Cardiac Death

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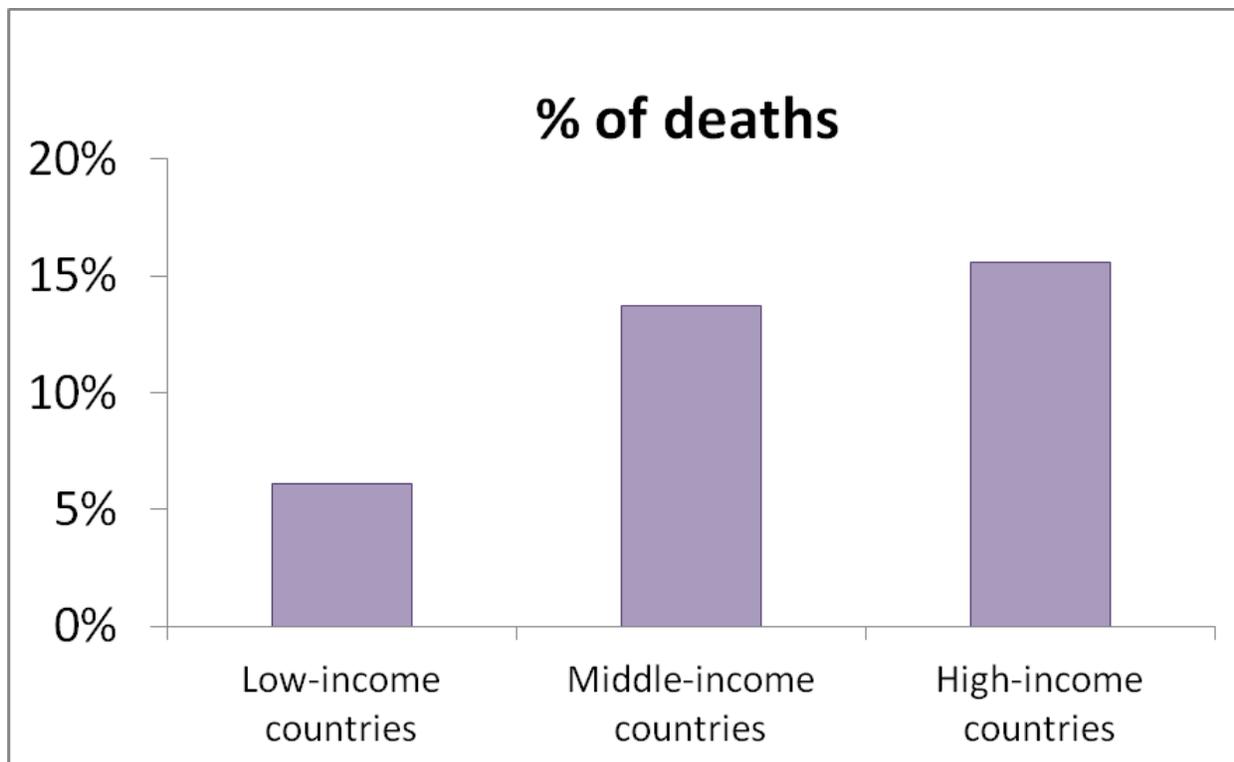
### 1. Introduction

Ischemic heart disease continues to be the leading cause of death in most countries and a major health burden, with approximately 50% of deaths due to sudden cardiac death (SCD) [Zipes & Wellens, 1998; Wong et al. 2001; Mazeika 2001]. The increasing prevalence of diabetes will also impact on SCD incidence. Patients with either type 1 or type 2 diabetes have significantly higher mortality and morbidity following acute myocardial infarction (AMI) than do the rest of the population. Other conditions such as hypertension, hypertrophic cardiomyopathy, aortic stenosis and aging may also increase the risk of SCD. Sex differences in prevalence and clinical outcomes are recognised [Bailey et al. 2006; Wake et al. 2007], although many randomized clinical trials do not have adequate numbers of women to allow sex-specific analyses [Xhyheri & Bugiardini 2010; Melloni et al. 2010]. Ischemic heart disease is the primary cause of death for women at all ages, with annual mortality rates for women 35-55 years greater than breast cancer [Bell et al. 2000] and approximately 81% of deaths in low- and middle-income countries [Mosca et al. 2011]. The incidence of SCD differs according to geographical region depending on the prevalence of coronary or ischemic heart disease [Priori et al. 2001]. In the United States, during 1989 to 1998, there was markedly less of a decline in SCD rates among women than for men - women aged 35 to 44 years had a 21% increased SCD rate compared with a 2.8% decline for men of the same age group [Zheng et al. 2001]. During the same period, women were dying of a cardiac arrest before hospital arrival (52%) compared with 42% for men [Shaw et al. 2006]. Compared to males women are generally older when presenting with AMI [Canto et al. 2012] and with women's longer life expectancy, the estimates are expected to rise even further in future decades. Although risk factors for IHD and SCD are often assumed to be similar in women and men, there are also differences. For instance, SCD will occur before any other signs of coronary heart disease in women [de Vreede-Swagemakers et al. 1997; Kannel et al. 1998; Albert et al. 2003] whereas ventricular dysrhythmias following AMI,

contribute to increased risk in men but not women [Dahlberg, 1990; Kim et al. 2001]. There may also be differences in mechanisms for SCD between older and premenopausal or middle aged women. This chapter will review the sex differences in mechanism of SCD and possible treatment strategies.

## 2. Ischemic heart disease and sudden cardiac death

Cardiovascular disease (CVD) is the primary cause of death globally with 17.3 million deaths in 2008, representing approximately 50% of non-communicable disease deaths [World Health Report (WHO), 2012]. Of these deaths, approximately 7.3 million (42%) were due to ischemic heart disease (IHD). Figure 1 shows the proportion of IHD deaths according to income status (data adapted from WHO Report 2012). In middle- and high-income countries, IHD was the primary cause of deaths, whereas it was fourth highest in low-income countries. In the United States, coronary heart disease (CHD) resulted in 1 of every 6 deaths in 2008. According to the recent American Heart Association report [Roger et al. 2012], there is a coronary event approximately every 25 seconds, and approximately one death every minute. More women (64%) than men (50%) die suddenly of coronary heart disease without any previous symptoms of this disease, while people with previous AMI have sudden death rates 4 to 6 times that of the general population [Roger et al. 2012].



**Figure 1.** Ischemic heart disease deaths according to income status

The prevalence of SCD varies depending on the definition used between different studies. Another confounder is that many sudden deaths are not witnessed, and without cardiac monitoring at the time of death. Prevalence may vary from 13% when SCD is defined as death suddenly or unexpectedly within an hour of onset of symptoms, to 18.5% of all deaths when this period is extended to 24 hours after onset of symptoms [de Vreede-Swagemakers et al. 1997]. Most studies report that SCD results from a fatal cardiac arrhythmia, either degeneration of ventricular tachycardia (VT) into ventricular fibrillation (VF), leading to disorganized ventricular contraction or severe bradycardia or pulseless electrical activity [Lane et al. 2005]. Ventricular arrhythmias have been documented in 85% of patients with severe congestive heart failure [Singh et al. 1997]. Dilated nonischemic and hypertrophic cardiomyopathies contribute to the next largest number of SCDs, whereas other cardiac disorders, including congenital heart defects and genetically determined ion channel anomalies, contribute 5–10% of SCDs [Lane et al. 2005].

### **3. Risk factors for sudden cardiac death**

To determine the risk factors for SCD many studies examine the same traditional factors associated with IHD, which include systolic blood pressure, dyslipidemia, smoking, obesity, heavy alcohol consumption, diabetes mellitus and age [Kannel et al. 1985; Jouven et al. 1999; Khot et al. 2003; Sandhu et al. 2012], summarised in Table 1. Subjects with inherited arrhythmogenic disorders such as long-QT syndrome and Brugada syndrome are also at increased risk for SCD. Similar risk factors for men and women were identified in the Framingham Study which compared 2873 women with 2336 men aged 30 to 62 years [Schatzkin et al. 1984; Kannel et al. 1998]. Similar to IHD, the presence of hypertension and diabetes increased the risk of SCD at all ages, whereas at all ages, sudden death risk ratios associated with diabetes were greater in women than men. Interestingly, the risk factors of hematocrit and vital capacity, predicted SCD in women but not men [Schatzkin et al. 1984]. Risk factors may also differ between premenopausal and older women. For instance, coronary heart disease (CHD) death in premenopausal women is due to plaque erosions with minimal coronary artery narrowing, whereas older women have high cholesterol levels and plaque rupture, with severe coronary artery narrowing [Canto et al. 2012].

As noted in Table 1, the risk factors for SCD are not consistently recorded and ventricular ectopy is one risk factor which is omitted since some of the deaths may have occurred in the absence of monitoring. Trials which have targeted only suppressing this ectopy to prevent SCD have not been successful and possibly hazardous [Akiyama et al. 1991]. Parental history of MI before age 60 years has also been identified as a risk factor for SCD, but only among women younger than age 60 years. The traditional factors for IHD also elevate the risk of SCD by 2- to 4-fold and include hypertension, diabetes and smoking [Albert et al. 2003]. Smoking was identified as a strong risk factor for SCD among young women (<60 years). Since it is a modifiable risk factor, Sandhu and colleagues (2012) recently reported a prospective study showing that smoking cessation significantly reduced and eliminated excess SCD risk [Sandhu et al. 2012].

	Age (yr)		M:F	High cholesterol		Prior CHD (%)		Hypertension		Diabetes		Smoking	
	M	F	%	M	F	without	with	M	F	M	F	M	F
Kannel et al. (1998)*		30-62	45:55			44M:63F	56M:37F						
35-64 yr				1.3	1.4			1.9	1.7	3.9	1.5	1	1.4
65-94 yr				1	1.4			2.2	1.7	4	1.3	0.9	1.2
Schatzkin et al. (1984)	30-62	30-62	45:55										
Without prior CHD								135±21	137±25				
With prior CHD								143±24	158±29				
Albert et al. (2003)	-	30-55	100F		1.33				3.17		4.9		
Parental history of MI		1.87 (<60)											
		1.36 (">60)											
Shaw et al. (2006)								↑	-	-	↑	↑	
Age threshold	≥45	≥55											
Family History of CHD	<55	<65											
Khot et al (2003)	59.9 (11.6)	66.1 (11.2)		34%	40%			38.4%	55.9%	15.3%	23.2%	29.5%	41.6%

M= males and F= females; \*Same cohort as Schatzkin et al. (1984)

**Table 1.** Relative risk for factors associated with Sudden Cardiac Death

In considering risk factors for IHD and SCD, one cannot overlook how endogenous levels of sex hormones may be contributing. Men and women show differences in ECG repolarization with QT prolongation in women, while male hearts from many species are hypertrophied relative to female hearts [Marsh et al. 1998]. In premenopausal women with normal ovulation, estrogen and other endogenous hormones provide cardioprotection and lower incidence of IHD compared to age-matched men. In contrast, during menopause, there is a fall in estrogen levels to approximately one-tenth that of premenopausal levels [Paoletti et al. 1997] and estrone, produced by peripheral conversion of androgens in the adipose tissue, is the main

estrogen. In the Women's Ischemia Syndrome Evaluation (WISE) Study premenopausal women that had a stress-induced disruption in ovulatory cycling with resulting low levels of estrogen had a 7.4-fold increased risk of obstructive coronary artery disease [Shaw et al. 2006]. Although there is increased focus on the lack of estrogen, the role of androgens should also be considered, given that they activate atherosclerotic-related genes in men but not women and activate androgen receptors in cardiac myocytes of both men and women, to produce hypertrophy [Marsh et al. 1999].

The risk factors for IHD common in postmenopausal women, include obesity, hypertension, and dyslipidemia. Menopausal women also have a greater loss in physical functioning compared to men [Poehlman 2002], which aggravates weight gain, insulin resistance, and hypertension [Shaw et al. 2006]. Loss of ovarian estrogen during menopause is also associated with redistribution of abdominal fat, further increasing the risk of IHD [Lamon-Fava et al. 1996]. The role of hormone replacement therapy (HRT) for postmenopausal women has been controversial. This is due to conflicting results from observational trials performed prior to 2002 which showed a reduction in risk of cardiovascular disease, osteoporosis, and colon cancer whereas large randomized clinical trials such as the Women's Health Initiative showed no cardiovascular benefit from hormone replacement therapy [Schierbeck et al. 2012]. The timing of initiating hormone therapy has been suggested as a possible explanation for these conflicting results. The observational studies started hormone therapy shortly after menopause, whereas the large randomised studies, which showed no or negative cardiovascular effects, initiated hormone therapy 5 to 20 years after menopause. The recent prospective, multicentre, HRT study, the Danish Osteoporosis Prevention Study (DOPS) was initiated to evaluate HRT as primary prevention for osteoporotic fractures [Schierbeck et al. 2012]. Healthy, recently postmenopausal women (within 7 months) aged 45-58 were recruited to the study and were randomly allocated to receive HRT or no treatment (control). Treatment ceased after 11 years although participants were followed for death, cardiovascular disease, and cancer for a further 5 years (total 16 years). Following 10 years randomised treatment, women receiving HRT early after menopause had significantly reduced risk of mortality, heart failure, or myocardial infarction, without any increase in risk of cancer, venous thromboembolism, or stroke.

#### **4. Mechanism of sudden cardiac death**

Sustained VT and VF are responsible for at least two thirds of sudden cardiac deaths [Huikuri et al. 2001] with sex-differences in arrhythmic SCD reported [Orencia et al. (1993); Kannel et al. (1998); Zheng et al. (2001); Abildstrom et al. (2002); Adabag et al. (2008); Verheugt et al. (2008)]. Pre-existing coronary heart disease significantly contributes to SCD in men [Lane et al. 2005] whereas women are 66% less likely to be diagnosed with coronary heart disease before SCD [Albert et al. 1996; Chiuve et al. (2011)]. Several studies have investigated whether sex disparities in the risk factors for SCD may contribute to these differences. Atherogenic risk factors were found to be predictive in men but not women. Similarly, asymptomatic ventricular dysrhythmias are an independent risk for death in men but have not been shown to be a risk for women [Dahlberg, 1990]. Patients with congestive heart failure due to cardiomyopathy or ischemic heart

disease have the highest rate of SCD, although the contributing factors remain poorly defined. Recent studies have suggested that genetic or environmental factors may predispose to fatal ventricular arrhythmia, particularly in women. However, mutations or rare variants in the cardiac sodium channel SCN5A were found in <2% cases screened and further studies are required [Albert et al. 2008]. Stress cardiomyopathy, also known as takotsubo cardiomyopathy, transient apical ballooning or broken heart syndrome is found predominantly in postmenopausal women [Nef et al. 2010]. Emotional or physical stress trigger symptom onset, which is similar to those in AMI, including sudden onset of chest pain associated with ST-segment elevation, and moderate increases in creatine kinase and troponin levels. Prognosis for stress cardiomyopathy is favorable, although fatal complications may occur, including cardiogenic shock, malignant arrhythmias and left ventricular free wall rupture.

Cardiac remodelling following either ischemia or AMI initially develops to compensate for failing cardiac function with evidence of hypertrophy, cardiomyocyte apoptosis, inflammation and fibrosis. Initially these changes are beneficial but ultimately transition to deteriorating cardiac function and lead to heart failure [Abel et al. 2008]. Although left ventricular (LV) dysfunction significantly increases the risk of SCD [Anand et al. 2006; Stecker et al. 2006], other risk factors need to be considered since women are 50% less likely to exhibit severe LV dysfunction, with structurally normal hearts identified at autopsy [Chugh et al. 2003]. Alternative mechanisms of SCD therefore need to be considered, given that women with coronary heart disease have significantly lower risk for SCD.

The renin-angiotensin-aldosterone system (RAAS) plays a significant role in ischemic heart disease and AMI and blockade of this system has emerged as an important therapeutic intervention. Elevated plasma aldosterone levels are an independent risk factor for mortality during AMI [Beygui et al. 2006; Palmer et al. 2008] and are predictive of cardiovascular events in acute coronary syndrome in the presence or absence of AMI [Tomaschitz et al. 2010]. Aldosterone exerts its actions by interacting with its receptor, the mineralocorticoid receptor (MR) or “aldosterone” receptor. Both aldosterone and the physiological glucocorticoids (cortisol (humans)/corticosterone (rodents), which are at 100-fold higher circulating levels bind to the MR. Selective activation of MR in target tissues is achieved by co-expression of the enzyme 11 $\beta$ -hydroxysteroid dehydrogenase type 2 (11 $\beta$ -HSD2). In contrast with vascular and renal tissues, 11 $\beta$ HSD2 is not expressed in cardiomyocytes [Sheppard & Autelitano 2002], and therefore endogenous glucocorticoids normally do not mimic aldosterone, but act as MR antagonists [Gomez et al 1990; Sato & Funder, 1996; Young & Funder, 1996]. Redox regulation has been shown to modulate glucocorticoid hormone action *in vivo* [Makino et al. 1999] and expression of oestrogen receptors [Tamir et al. 2002]. For every molecule of cortisol converted to cortisone, one molecule of the pyridine nucleotide NAD is reduced to NADH. Since NADH has been shown to activate corepressors for other transcription factors in various systems [Zhang et al. 2002; Fjeld et al. 2003], and changes in redox state may determine cardiomyocyte MR activation by glucocorticoids [Mihailidou et al. 2009].

Elevated aldosterone levels promote electrical remodelling through activation of MR or “aldosterone” receptors, thus potentially increasing the incidence of sudden cardiac death. In experimental studies, aldosterone has a direct effect on cardiomyocyte calcium [Ouvrard-

Pascaud et al. 2005] and sodium [Mihailidou et al. 2000] as well as producing hypokalemia and hypomagnesemia [Mihailidou et al. 2002]. These electrolyte imbalances have been translated clinically with the Framingham Heart Study showing that low serum concentrations of potassium and magnesium were linked to increased risk of SCD. A decrease in potassium of 0.48 mEq/litre or magnesium of 0.16 mEq/litre level was associated with a 27% (C.I. 6% - 51%) and a 20% (C.I. 3% - 41%) greater odds of complex or frequent ventricular premature contractions [Tsuji et al. 1994].

Possible other targets include the gap junction connexins and identifying whether they are regulated differently between males and females. Connexins allow rapid and coordinated electrical excitation and facilitate intercellular exchange of small molecules. Experimental studies have shown that normal gap junction expression and phosphorylation in the heart is essential for organized myocellular electrical activity [Stauffer et al. 2011]. Interestingly female hearts have higher levels of cardiac connexin 43 (Cx43) [Tribulova et al. 2005] and lower lethal arrhythmia susceptibility [Knezl et al. 2008]. Further studies are required to confirm whether abnormalities in cardiac Cx43 expression and phosphorylation are the primary trigger of arrhythmogenesis, since this occurs prior to other structural remodelling changes [Stauffer et al. 2011].

Recent studies have explored the role of microRNAs (miRNAs) in many biological and pathological processes and the role of circulating miRNAs as sensitive biomarkers with aberrant expression of miRNA directly reflecting disease state. Ai and colleagues (2010), recently found upregulated cardiac miR-1 in an animal model of AMI, with similar increases in plasma in patients with AMI. These increased miR-1 levels correlated with abnormal QRS widening in AMI [Ai et al. 2010]. Over-expression of miR-1 has been shown to induce and aggravate arrhythmogenesis. The mechanism proposed is by impairing cardiac conduction by post-transcriptional repression of KCNJ2 that encodes the inward rectifier K<sup>+</sup> channel subunit Kir2.1 and GJA1 which encode connexin 43 gap junction channels [Yang et al. 2007].

## 5. Treatment strategies

Primary prevention of SCD continues to be a public health challenge since most deaths are among people who were not identified as high risk prior to the event. Implantable cardioverter-defibrillator (ICD) therapy is the current recommended treatment strategy for high risk patients with severe left ventricular dysfunction (Sudden Cardiac Death in Heart Failure Trial (SCDHeFT), [Bardy et al. 2005]. Subgroup analysis in SCDHeFT as well as in another primary prevention trial, the Defibrillators in Nonischemic Cardiomyopathy Treatment Evaluation (DEFINITE) [Kadish et al. 2004] suggested that women may receive less benefit from ICD therapy than men. Interestingly in both these large trials, only 24%-30% of participants and since women have a lower incidence of VF compared to men [Kim et al. 2001; Wigginton et al. 2002] and therefore may not have been adequately powered to determine the influence of gender on outcome for ICD therapy.

ICDs treat (but do not prevent) the ventricular arrhythmias and therefore increased morbidity remains. ICD therapy is rarely considered where LV function is preserved, except in specific

conditions with increased SCD risk such as hypertrophic obstructive cardiomyopathy, long QT and Brugada syndromes, and idiopathic VF [DiMarco 2003]. A community-based study conducted by Stecker and colleagues (2006) showed that only 30% of patients that died from SCD previously had sufficiently decreased LV systolic function to meet the criteria for ICD implantation. Patients with normal LV systolic function were generally younger, predominantly female and less likely to have an established diagnosis of coronary heart disease. Since ICDs treat the arrhythmia but not prevent the underlying cause, there is a need to find new treatment strategies that target the cellular mechanisms involved. Standard antiarrhythmic medication has not reduced (and in some cases, has increased), the incidence of SCD [Lane et al. 2005]. Suitable adjunct treatment in the primary and secondary prevention of SCD includes beta blockers and non-anti-arrhythmic agents, i.e., those that do not directly target the electrophysiological action in cardiac muscle or specialized conduction system, such as angiotensin converting enzyme inhibitors (ACEI), angiotensin receptor-blockers, lipid-lowering agents, aldosterone or MR antagonists, thrombolytic and antithrombotic agents [Lane et al. 2005].

It is worth considering the role of aldosterone or MR blockade for both primary prevention of SCD for those at high-risk and as an adjunct therapy based on the important findings from the large randomized clinical studies, the Randomized ALdactone Evaluation Study (RALES) [Pitt et al. 1999] and the Eplerenone Post-Acute Myocardial Infarction Heart Failure Efficacy and Survival Study (EPHESUS) [Pitt et al. 2003], which showed a significant reduction in SCD. The first of these trials, RALES, was a double blind study in patients who had severe heart failure with left ventricular systolic dysfunction and were receiving standard therapy including ACE inhibitor treatment, a loop diuretic, and digoxin. Patients were randomly assigned to receive low dose MR antagonist, spironolactone or placebo added to their standard treatment. The trial was discontinued early due to an interim analysis showing the addition of spironolactone resulted in a 30% reduction in mortality and reducing SCD by 29%. In the next study, EPHESUS [Pitt et al. 2003] was designed to determine whether selective MR blockade with eplerenone could be tolerated by patients with acute myocardial infarction (AMI) complicated by heart failure due to systolic left ventricular dysfunction. Addition of the selective MR antagonist, eplerenone, substantially increased survival (15% reduction in mortality) and decreased hospitalization, and had a 21% reduction in SCD.

## 6. Conclusion

Since women do not present with severe left ventricular dysfunction and diagnosed CHD before SCD, they will not receive the current recommended treatment. Prospective studies are required that have the same proportion of women to men with ischemic heart disease to identify the sex-specific risk factors and pathophysiology of ischemic heart disease in women which leads to an adverse cardiovascular outcome [Malenka et al. 2002]. Further investigations are required to examine whether women will show the same benefit to adjunct treatment with angiotensin-converting enzyme (ACE) inhibitors, angiotensin receptor-blocking agents, lipid-lowering agents, mineralocorticoid receptor antagonists, thrombolytic and antithrombotic agents.

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