Cardiologists’ Knowledge, Attitudes and Application of Risk towards
Implantable Cardioverter Defibrillators.

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Thesis submitted in requirement for the qualification of Doctor of Medicine
(M.D.)

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Abstract

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Dr Praveen P Sadarmin.

Patients with impaired left ventricular systolic function have an increased risk of sudden cardiac death. The implantable cardioverter defibrillator (ICD) is an effective therapy to treat life-threatening arrhythmias and randomized controlled trials have demonstrated statistically significant reductions in all-cause mortality in select patient groups. Despite this wealth of published data, the uptake of ICDs in high risk population remains low and the exact reasons not known.

My study focuses on the evidence for ICD therapy from the landmark RCTs that have influenced the current guidelines. Most trials have only published relative risk reduction or hazard ratios. The first part of this thesis analyzes data to reveal absolute risk reduction, the number needed to treat and the findings standardized for length of follow-up. There is considerable variation in the magnitude of benefit between different heart failure aetiologies and other patient characteristics highlighting the difficulty in generalising the results.

UK cardiologists’ knowledge of guidelines, estimates of 3-year mortality, management decisions, factors that influence decisions, influence of age, device cost, and overall attitudes to ICDs as a form of therapy was assessed with a questionnaire. There was lack of awareness of UK ICD guidelines amongst non-implanting cardiologists and even when guidelines were known they were often not applied, particularly in primary prevention setting. Most cardiologists are not aware of the magnitude of benefit an ICD offers and overestimate the effect in secondary prevention. In addition, there is also bias against elderly patients.

The final part of my thesis focuses on exploring barriers to primary prevention ICD uptake. The aim was to see what action was taken when all the data required for making a referral or assessment was available. Our study suggests more than half of potentially eligible patients do not receive ICD therapy. A low referral rate, lack of screening programmes and age bias seem to be the stumbling blocks for primary prevention ICD in the UK.
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- Last but not the least; I would like to thank my wife, Shruthi and my parents (Veena and Phaneendranath) for their constant encouragement and support.
Author’s declaration

I confirm that this thesis is a true reflection of research conducted by me and all material presented is original in nature except where other sources are credited.

No portion of this work referred to in this thesis has been submitted in support of an application for another degree, of this or any other university or institute of learning.

Copyright of this thesis rests with the author.

Dr. Praveen Sadarmin
My research work has been previously presented and or published as below:

**Presentations**

1. **Low Implant rate of primary prevention implantable cardioverter defibrillators in the UK: where does the buck stop?** Poster presentation at **EHRA Europace Conference**, Madrid, June 2011.

2. **An insight into Implanters’ practices of ICD implantation.** Moderated Poster presentation at the **British Cardiovascular Society Conference**, Manchester, June 2011.

3. **Where is the block to primary prevention ICDs?** Moderated Poster presentation at the **British Cardiovascular Society Conference**, Manchester, June 2010.

4. **A survey of UK Cardiologists’ understanding of and attitudes to guidelines, risk and the role of implantable cardioverter defibrillator.** Oral presentation at the **Heart Rhythm Congress (HRC)**, Birmingham, Oct 2009.


Publications


### Frequently Used Abbreviations

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<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
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<tbody>
<tr>
<td>ACC</td>
<td>American College of Cardiology</td>
</tr>
<tr>
<td>ACE-I</td>
<td>Angiotensin Converting Enzyme Inhibitors</td>
</tr>
<tr>
<td>AED</td>
<td>Automatic External Defibrillator</td>
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<td>AF</td>
<td>Atrial Fibrillation</td>
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<td>AHA</td>
<td>American Heart Association</td>
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<tr>
<td>AMIOVIRT</td>
<td>Amiodarone versus Implantable Cardioverter Defibrillator Randomised Trial</td>
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<td>ARR</td>
<td>Absolute Risk Reduction</td>
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<td>ARVC</td>
<td>Arrhythmogenic Right Ventricular Cardiomyopathy</td>
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<td>ATP</td>
<td>Anti tachycardia Pacing</td>
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<td>AVID</td>
<td>Antiarrhythmics versus Implantable Defibrillator Trial</td>
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<tr>
<td>B-blockers</td>
<td>Beta-blockers</td>
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<td>BMJ</td>
<td>British Medical Journal</td>
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<tr>
<td>BUN</td>
<td>Blood Urea Nitrogen</td>
</tr>
<tr>
<td>CABG</td>
<td>Coronary Artery Bypass Grafting</td>
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<td>CAD</td>
<td>Coronary Artery Disease</td>
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<td>CASH</td>
<td>Cardiac Arrest Study Hamburg Trial</td>
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<td>CAT</td>
<td>The Cardiomyopathy Trial</td>
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<tr>
<td>CCF</td>
<td>Congestive Cardiac Failure</td>
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<td>CHF</td>
<td>Congestive Heart Failure</td>
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<td>CI</td>
<td>Confidence Intervals</td>
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<td>Acronym</td>
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<tr>
<td>CIDS</td>
<td>Canadian Implantable Defibrillator Study</td>
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<td>CRT</td>
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<td>CRT-D</td>
<td>Cardiac Resynchronisation Therapy – Defibrillator</td>
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<td>CRT-P</td>
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<td>DCM</td>
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<td>Defibrillators in Non Ischaemic Cardiomyopathy Treatment Evaluation Trial</td>
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<td>DINAMIT</td>
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<td>ECG</td>
<td>Electrocardiogram</td>
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<tr>
<td>EHRA</td>
<td>European Heart Rhythm Association</td>
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<tr>
<td>EP</td>
<td>Electrophysiologist</td>
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<td>ESC</td>
<td>European Society of Cardiology</td>
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<td>FDA</td>
<td>Food and drug administration</td>
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<tr>
<td>FU</td>
<td>Follow-up</td>
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<td>HR</td>
<td>Hazards Ratio</td>
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<td>HRS</td>
<td>Heart Rhythm Society</td>
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<tr>
<td>ICD</td>
<td>Implantable Cardioverter Defibrillator</td>
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<td>IHD</td>
<td>Ischaemic Heart Disease</td>
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<tr>
<td>JAMA</td>
<td>Journal of American Medical Association</td>
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<tr>
<td>LQTS</td>
<td>Long QT Syndrome</td>
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<td>LV</td>
<td>Left Ventricle</td>
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<tr>
<td>LVEF</td>
<td>Left Ventricular Ejection Fraction</td>
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<td>Abbreviation</td>
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<tr>
<td>LVSD</td>
<td>Left Ventricular Systolic Dysfunction</td>
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<td>MADIT</td>
<td>Multicentre Automated Defibrillator Implantation Trial</td>
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<tr>
<td>Med</td>
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<tr>
<td>MI</td>
<td>Myocardial Infarction</td>
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<td>MUSTT</td>
<td>Multicentre UnSustained Tachycardia Trial</td>
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<tr>
<td>NEJM</td>
<td>New England Journal of Medicine</td>
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<tr>
<td>NICE</td>
<td>National Institute of Clinical Excellence</td>
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<tr>
<td>NNH</td>
<td>Number Needed to Harm</td>
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<td>NNT</td>
<td>Number Needed to Treat</td>
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<td>NSVT</td>
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<td>NYHA</td>
<td>New York Heart Association</td>
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<td>OOH</td>
<td>Out of hospital</td>
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<td>OR</td>
<td>Odds Ratio</td>
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<td>PCI</td>
<td>Percutaneous Intervention</td>
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<td>PVC</td>
<td>Premature Ventricular Complexes</td>
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<tr>
<td>QALY</td>
<td>Quality Adjusted Life Years</td>
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<td>QOL</td>
<td>Quality Of Life</td>
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<td>QRSd</td>
<td>QRS duration</td>
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<td>Randomized Control Trials</td>
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<td>RRR</td>
<td>Relative Risk Reduction</td>
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<td>SCD</td>
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<td>SCD-HeFT Trial</td>
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<td>SD</td>
<td>Standard Deviation</td>
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<td>VHR</td>
<td>Very High Risk</td>
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<td>VF</td>
<td>Ventricular Fibrillation</td>
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<td>Ventricular Tachycardia</td>
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<td>WPW</td>
<td>Wolf Parkinson White Syndrome</td>
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Chapter 1

Basics of Implantable Cardioverter Defibrillators
1.1 Sudden Cardiac Death

Sudden cardiac death (SCD) is sudden, individually unpredictable and accounts for the majority of deaths due to cardiac diseases.\(^1\) Typically, a cardiac arrest results from sustained ventricular tachycardia (VT) or ventricular fibrillation (VF) that progresses to death if effective resuscitative efforts are not started within minutes of the arrest.\(^2\) The overall survival rate of patients with cardiac arrest remains low and in particular, out-of-hospital cardiac arrest is estimated to be between 2-25% worldwide.\(^3\)\(^-\)\(^7\) Although more widespread use of automated external defibrillators could potentially lead to a reduction in SCD, it is unrealistic to expect a huge change in mortality because most cardiac arrests either are unwitnessed or occur in a location without ready access to a defibrillator.

Coronary artery disease (CAD) remains the predominant cause of SCD in more than 70% of patients in the western world.\(^1\) Patients at highest risk for SCD after myocardial infarction (MI) have substantial left ventricular systolic dysfunction (LVSD) or frequent premature ventricular complexes (PVC) or non-sustained ventricular tachycardia (NSVT), or both in addition to ventricular tachyarrhythmias.\(^8\) Therapies to prevent SCD were initially addressed by modifying the underlying disease substrate (CAD). Advances in drug treatment over the past few decades have led to improvements in the morbidity and mortality of heart disease in general. The use of selective Beta-blockers and angiotensin converting enzyme inhibitors (ACE-I) in particular has further reduced the incidence of CAD and SCD.\(^8\)
However, implantable cardioverter defibrillators (ICD) remains the single most effective therapy in the prevention of SCD and the management of tachyarrhythmias.\textsuperscript{9,10}

1.2 Defibrillator therapy

The treatment of ventricular tachyarrhythmias with device-based therapy had its beginnings in 1899, when two noted physiologists, Drs. Prevost and Battelli noted direct current shock could terminate VF in dogs.\textsuperscript{11} Decades later, further pioneering work in the field of defibrillation concluded that the passage of electrical current across the heart can both initiate and terminate VF.\textsuperscript{12,13} It was in 1947, Dr. Claude Beck (Cardio-thoracic surgeon) saved the first human life by successful use of cardiac defibrillation in a 14-year-old boy who developed VF during open heart surgery and went on to achieve a full recovery.\textsuperscript{14} These early accomplishments provided the foundation for the landmark work of Drs. Michael Mirowski and Morton Mower leading to successful development and human implantation.\textsuperscript{15}

Since then, remarkable technological and conceptual advances have taken place in the field of pacemakers and ICDs over the last 3 decades. They have evolved from a large machine on a trolley to a miniaturized device being implanted safely and effectively under the skin (Figure 1).
The concept of implantable defibrillators is the brain child of Dr Michael Mirowski and the engineering ability of Dr Morty Mower pioneered in the early 1980s. The Food and Drug Administration (FDA) approved the clinical use of the automatic implantable defibrillator (called the AID) and the first human implant took place on February 4th, 1980 at the Johns Hopkins Hospital. To meet criteria for the first pilot study, the patient had to have survived at least two episodes of cardiac arrest not associated with myocardial infarction and VF had to be documented at least once. The device was non-programmable, committed and had no telemetry.
capabilities. The first generation devices were designed only to recognise VF and treat it with high energy shock.\textsuperscript{15,16} The second generation devices had additional bradycardia pacing and minimal programmability while the third generation devices had anti-tachycardia pacing (ATP) and low energy shocking capabilities for treatment of VT, as well as defibrillation capability and more extensive programmability and telemetry.\textsuperscript{16} In addition to the development of smart generators, the development of stable, durable and biocompatible transvenous defibrillating leads transformed the implantation procedure from a 4-6 hour open chest procedure with a 3-5\% operative mortality to a far simpler procedure performed in the electrophysiology lab under conscious sedation. Finally, the devices continued to miniaturise from what began as an abdominal implant with leads stitched to the epicardium, to the current transvenous leads and pre-pectoral generators implanted either subcutaneously or submuscularly (Figure 2).
1.3 Indications for ICD therapy

A series of landmark studies\textsuperscript{17-25} have expanded the indications of ICD therapy over the last two decades and have targeted either patients who have already survived a potentially life-threatening arrhythmic event or are considered to be at high risk due to significant underlying structural heart disease. Patients in whom ICD implantation may be considered can generally be categorized into one of several broad groups:
(1) those who have been resuscitated from sudden cardiac arrest or have previously manifested potentially life threatening ventricular arrhythmias not related to a transient or correctable cause (secondary prevention);

(2) those with moderate to severe structural heart disease, including ischaemic, non ischaemic, and other cardiomyopathy at risk of SCD (primary prevention);

(3) those with inherited cardiac disorders, for whom the risk of arrhythmic death is considered high (a subset of primary prevention).  

It is a well-recognized paradox that the majority of SCD occur in those individuals with intermediate risk factors and those without known risk factors. Conversely, the highest-risk sub-groups, on which much attention is focused because of the magnitude of the risk of death actually constitute only a small proportion of the total number of sudden deaths annually. There were earlier concerns about the need for ICD therapy in those patients who had transient causes that put them at high risk, e.g. patients who had an acute MI and their blocked coronary arteries fixed either with coronary artery bypass grafting (CABG) or percutaneous coronary intervention (PCI). However, registry data shows that after adjustment for multiple variables, patients with transient or correctable causes such as new ischaemia or infarction, proarrhythmic drug reaction, electrolyte imbalance, or other causes, actually had worse survival than those considered to have primary VT or VF, thus highlighting the inherent challenges in identifying patients at low risk of recurrent arrhythmias and the limited long-term success in treating presumed transient
causes. Therefore a more satisfactory approach would be a dual strategy of tackling the revascularisation and treating the risk of ventricular arrhythmias on their own.

1.4 Clinical trials and evidence

Randomized control trials (RCT) of both primary prevention (MADIT, MUSTT, MADIT 2, SCD-HeFT) and secondary prevention therapy (AVID, CIDS and CASH and meta-analysis) have shown statistically significant mortality reduction in selected high-risk patients by treating life-threatening ventricular tachyarrhythmias.

1.5 Secondary prevention implantable cardioverter defibrillator therapy

Survivors of SCD due to arrhythmia carry a high risk of recurrence. Attempts to significantly reduce this risk with antiarrhythmic drugs have yielded disappointing results, except in the case of amiodarone. The recognition of the limitations of antiarrhythmic drugs for secondary prevention was paralleled by the development of smaller, transvenous ICD with tiered therapies, bradycardia pacing, and success rates of >95% in terminating VT and VF. 3 landmark RCTs (AVID, CIDS, CASH) and 1 meta-analysis have shown significant mortality reduction with ICD therapy.
1.5.1 AVID (Anti-arrhythmics Versus Implantable cardioverter Defibrillators) trial

The AVID study provided the first definitive evidence of the superiority of ICD therapy over antiarrhythmic drug therapy. This study randomized patients with resuscitated VF, sustained VT with syncope, or sustained VT with left ventricular ejection fraction (LVEF) ≤40% and evidence of hemodynamic compromise to receive either an ICD or antiarrhythmic therapy, predominantly amiodarone. There were a total of 1016 patients and 507 patients in the ICD arm. Mean age was 65 years and mean LVEF of 32%. 81% of patients had ischaemic cardiomyopathy and the mean follow-up was for 18 months. Overall mortality (relative risk reduction - RRR) in the ICD arm was reduced by 39% and 31% at 1 and 3 years respectively.

1.5.2 CIDS (Canadian Implantable Defibrillator Study) trial

This Canadian trial was the next to follow and recruited patients who had survived VF cardiac arrest, sustained VT with syncope, sustained VT without syncope and LVEF ≤35% and haemodynamic compromise, unmonitored syncope with inducible VT on electrophysiological studies (EPS). This trial was different from the other secondary prevention trials as it included patients with unmonitored syncope but inducible VT on EPS. There were a total of 659 patients with 328 in the ICD arm. Their mean age was 63 years and LVEF was 34%. 82% of the patients had ischaemic cardiomyopathy and the mean follow-up was for 35 months. The study reported a 20% RRR in all-cause mortality and a 33% reduction in arrhythmic mortality with ICD therapy compared with amiodarone.
1.5.3 CASH (Cardiac Arrest Study Hamburg) trial\textsuperscript{23}

This German study was published in the same year as CIDS and provided further evidence of the benefits of ICD therapy over anti-arrhythmic therapy. Cardiac arrest survivors secondary to documented ventricular arrhythmias were recruited in the trial. Out of the total 288 patients, 99 patients received an ICD. Mean age was 58 years and mean LVEF was 46%. 73% of patients had ischaemic cardiomyopathy and were followed-up for a period of 57 months. The outcome was reported as a 23% RRR in all-cause mortality in the ICD group compared to the anti-arrhythmic group (amiodarone/metoprolol).

1.5.4 Meta-analysis of Secondary Prevention trials\textsuperscript{21}

Meta-analysis of the above three secondary prevention trials further solidified the evidence for all-cause mortality reduction by ICD therapy over anti-arrhythmic therapy. These 3 RCTs form the basis for the provision of secondary prevention ICD therapy and are reflected in all the national and international guidelines. The combined total number of patients in the meta-analysis were 1866 with 934 patients in the ICD arm. Mean age was 63 years and majority of patients had ischaemic cardiomyopathy (81%) with a mean LVEF of 34%. There was a 28% reduction in the relative risk of death with the ICD, almost entirely due to a 50% reduction in arrhythmic death.
1.6 Primary prevention implantable cardioverter defibrillator therapy

Prevention is better than cure. This might be the common belief, but in the case of ICD therapy there was and still lacks complete acceptance for primary prevention. It is easy in many ways to decide on a secondary prevention ICD in a patient who has survived an arrhythmic event and proved he/she is at high risk for recurrent events. The same does not apply to primary prevention category and there has been endless debate about who benefits the most. The physician has to look at the SCD risk of the individual patient and decide whether an ICD therapy would lower this risk and balance this over the adverse effects from the therapy. As always, risk is not universal and varies substantially from one cardiac pathophysiology to another; e.g. the risk of SCD from ischaemic cardiomyopathy is greater than non ischaemic cardiomyopathy. The risk is even greater with severe LVSD but patients with the most severe symptoms of heart failure (New York Heart Association (NYHA) class IV) may not benefit from the defibrillator therapy to the same extent as their risk of dying from pump failure is much greater than an arrhythmic death. There is also a small but significant group of patients with inherited cardiac conditions who not only have a much higher risk of SCD than the general population but also an unpredictable course. These patients are excluded from my studies.
1.6.1 Primary Prevention in Ischaemic Cardiomyopathy

CAD contributes to more than two thirds of SCD. It is not unreasonable to conclude that therapies aimed at reducing the incidence of CAD have a direct effect on the risk of SCD. Davis et al. and Greene et al. estimate half of the deaths in the post-MI population are due to either VT or VF. Furthermore, the relationship between LVSD and deaths due to progressive heart failure and ventricular arrhythmias in patients who have had an MI is well established with the majority of studies concluding an LVEF of <40% serves as the threshold for identifying high-risk individuals. ICD is the single most effective and timely therapy for treating ventricular tachyarrhythmias and therefore a front runner in the management of ischaemic cardiomyopathy to prevent SCD. This formed the basis of all the major primary prevention trials that have evaluated the role of device therapy in the setting of primary prevention of SCD in post-MI patients with significant LVSD.

1.6.1.1 MADIT (Multicenter Automatic Defibrillator Implantation Trial) This was the first RCT to establish the superiority of ICD therapy over conventional medical therapy and published in 1996. This was a relatively small study recruiting 196 patients with a previous history of MI (>3 weeks), asymptomatic NSVT, LVEF ≤35%, NYHA class I-III and inducible VT on EPS. 95 patients were randomised to the ICD arm and 101 patients to conventional medical therapy. Mean age was 63 years and LVEF was 26%. After 27 months of follow-up, there was a 54% RRR of
mortality in the defibrillator group compared to the conventional group. There was no evidence of amiodarone, B-blockers or any other anti-arrhythmic therapy having a significant influence on the observed Hazards Ratio (HR).

1.6.1.2 MUSTT (Multicenter UnSustained Tachycardia Trial)\textsuperscript{19}
MUSTT continued with the theme of MADIT and hypothesised that electrophysiologically guided anti-arrhythmic therapy would reduce the risk of SCD among patients with CAD, LVSD (LVEF ≤40%), asymptomatic NSVT and inducible VT at EPS. It differs from the MADIT trial by recruiting patients immediately after their MI and not necessarily wait for 3 weeks. 704 patients were recruited in the study with 351 patients in the ICD arm. The mean age was 65 years and the mean LVEF was 28%. After 39 months of follow-up, 5 year Kaplan Meier curves show 24% RRR in all-cause mortality in addition to a 27% RRR in the arrhythmic mortality in the ICD arm suggesting a significant mortality benefit from ICD therapy.

1.6.1.3 MADIT 2 (Multicenter Automatic Defibrillator Implantation Trial 2)\textsuperscript{25}
MADIT 2 is the most important landmark trial in the history of defibrillator therapy. This study firmly established the role of ICD in primary prevention in addition to a change in guidelines. Prior to this study although many physicians accepted that there was a high risk of ventricular arrhythmias in patients with remote MI, they had to be risk-stratified with EPS to qualify for a primary prevention ICD. This trial changed the goal posts by broadening the eligibility criteria of selecting ischaemic cardiomyopathy patients i.e. anyone with a history of remote MI (>4 weeks) and
LVSD (LVEF ≤30%) eligible for primary prevention ICD without the need for invasive EPS. This was based on the rationale that there are uncertainties surrounding the long term predictive value of invasive EPS and the near ubiquitous findings of non-sustained arrhythmias in this ischaemic cardiomyopathy cohort.26

This study of 1232 patients compared overall mortality in ICD treated patients versus those treated with conventional medical therapy including B-blockers and ACE-I. It is notable that most patients in both arms were on optimal medical therapy including B-blockers (70% in both groups), ACE-I (68% ICD vs. 72% control) and statins (67% ICD vs. 64% controls). 742 patients were assigned to receive ICD therapy and 490 patients to medical therapy. Mean age was 64 years and mean LVEF was 23%. Overall mortality was reduced by 31% (RRR) in patients randomized to receive ICD during a mean follow-up of 20 months. The effect of ICD therapy on survival was similar in sub-group analysis stratified according to age, sex, LVEF, NYHA class and QRS duration.

Sub-group analysis
MADIT 2 has had the most sub-group analysis among all the ICD trials and probably any clinical trial to date.
Age

121 out of 204 elderly patients (≥75 years) in the MADIT 2 study underwent ICD implantation. Relative to the younger patients, those ≥75 years had a higher incidence of atrial fibrillation (AF), elevated blood urea nitrogen (BUN), widened QRS, and lower use of B-blockers and statins. There was a 44% RRR in mortality benefit among ICD patients in this group after a mean follow-up of 17.2 months. Comparatively, in the <75 years age group, RRR in mortality was 37% with ICD after 20.8 months.\textsuperscript{40}

Mortality and time from MI

In 1159 patients, mean time from most recent MI to enrollment was 81±78 months. Mortality rates (deaths per 100 person-years of follow-up) in both treatment groups were analyzed by time from MI divided into quartiles (<18, 18 to 59, 60 to 119, and ≥120 months). In conventional care patients, these rates increased as time from MI increased (7.8%, 8.4%, 11.6%, and 14%). Mortality rates in ICD patients were consistently lower in each quartile and showed minimal increase over time (7.2%, 4.9%, 8.2%, and 9%). Covariate-adjusted HR for risk of death associated with ICD therapy were 0.97 for recent MI (<18 months) and 0.55 for remote MI (≥18 months). The survival benefit associated with ICD resulted entirely from the observed reduction in the risk of arrhythmic death and appeared to be greatest for patients with more remote MI (>18 months) and remains substantial for up to 15 years after MI.\textsuperscript{41,42}
NYHA class and LVEF

Patients with higher NYHA class (II-III) and BUN >25 mg/dl had higher mortality (34%) and a higher risk of arrhythmic events (~35%) than patients in lower functional groups (16-20%). Further risk stratifying on the basis of different LVEF groups of (a) ≤20%, (b) 21-25% and (c) 26-29% did not differentiate the risk. The authors concluded that patients with more advanced heart failure have a higher risk of mortality and arrhythmic events than patients with less severe disease. However, there was no significant difference in the benefit from ICD therapy among the above sub-groups of MADIT 2 patients.43

Quality Of Life (QOL)

The benefits of ICD therapy solely measured as survival ignores the psychological aspect associated with the device. Quality adjusted life years (QALY) is a more robust measure of a person’s psychological wellbeing and widely used in clinical practice. Scores through Health Utilities Index Mark III (HUI) Questionnaire was used for assessment and showed no differences in QALYs for patients by treatment group or in overall QALYs loss by treatment group over 3 years. However, there exists a significant psychological impact of ICD treatment especially on patients who receive shock therapies. In the MADIT 2 sub-group analysis evaluating the impact of ICDs on health related QOL during first 3 years of ICD implantation, female patients demonstrated a trend towards greater survival benefit and overall QALYs.44 However, a recent patient data network meta-analysis has shown female patients benefit more from CRT (P/D) while men and
those <60 years benefit more from ICD. Adverse effects of ICD on health related QOL together with lower health related QOL among survivors may offset some of the survival benefit of ICD therapy over 3 years.

QRS duration
In the medically treated arm, prolonged QRS duration (≥140 ms) was a significant independent predictor of SCD (HR 2.12). However, in the ICD-treated arm, prolonged QRS duration did not predict SCD or rapid VT/VF (HR 0.77). The difference in the prognostic effect of prolonged QRS duration in these two groups was significant (p<0.01). These results were not affected by varying the cycle length that defines rapid VT/VF (<260 ms) or the duration that defines QRS duration prolongation.

Race
Vorobiof et al. concluded ICD therapy in MADIT 2 was associated with a reduction in total mortality, cardiac death, and SCD in whites but not in blacks. Adjusting for relevant covariates, the ICD therapy/conventional therapy HR for total mortality were favorable in whites (0.75), but not in blacks (1.25). The HR for SCD was significantly lower in whites (0.29) compared to blacks (1.71).
Risk stratification

The selected risk score model comprised 5 clinical factors (NYHA functional class >II, age ≥70 years, BUN ≥26 mg/dl, QRS duration ≥120 ms, and AF). Crude mortality rates in the conventional group were 8% in no (zero) risk factors and 28% in patients with one or more risk factors respectively. In the very high risk (VHR) patients (defined by BUN ≥50 mg/dl and or serum creatinine ≥2.5 mg/dl) the crude annual mortality was 43%. Defibrillator therapy was associated with a 49% reduction in the risk of death among patients with ≥1 risk factors, whereas no ICD benefit was identified in patients with zero risk factors (HR 0.96) and in VHR patients (HR 1.00).48

1.6.1.4 DINAMIT (Defibrillator IN Acute Myocardial Infarction Trial)49

The highest risk of death due to CAD occurs around the time of an acute MI as a result of ventricular tachyarrhythmias or acute pump failure. The development of dedicated coronary care units since the 1960s, the accessibility to rapid external defibrillation and the rising use of cardiac medications (B-blockers and ACE-I) have led to gradual decline in the rates of post-MI mortality. With the exception of the MUSTT trial, most ICD studies excluded patients within 3 weeks of an acute MI. The DINAMIT study was designed to test the hypothesis that survivors of recent MI (6 to 40 days) with an LVEF of ≤35% and evidence of impaired cardiac autonomic modulation (manifested as depressed heart-rate variability or an elevated average 24 hour heart rate on Holter monitoring) would derive a survival benefit from ICD implantation. DINAMIT randomized 676 patients in total with 332
patients to the ICD arm. The mean age was 62 years and the mean LVEF was 28%. After 30 months of follow-up, there was no statistically significant difference in the overall mortality of both groups. There were more deaths in the ICD group compared to controls (62 vs. 58, HR – 1.08). There were 12 deaths in the ICD group due to arrhythmia compared to 29 deaths in the control group (HR – 0.42). In contrast, there were 50 deaths from non-arrhythmic causes in the ICD group compared to 29 in the control group (HR – 1.75). It was therefore concluded that patients surviving an acute MI (<6 weeks) do not benefit from early prophylactic ICD implantation and may indeed be harmful to provide this therapy to such patients.

1.6.1.5 SCD-HeFT (Sudden Cardiac Death in Heart Failure Trial)\textsuperscript{18}

This is the largest ICD study to date. This 3-armed study randomized 2521 patients with ischaemic or non ischaemic cardiomyopathy, LVEF ≤35%, and NYHA class II-III heart failure to conventional therapy, conventional therapy plus weight-adjusted amiodarone, or conventional therapy plus a single-zone, single-chamber ICD with backup pacing only. Mean age was 60 years and mean LVEF was 25%. 70% were in NYHA class II and 30% in class III heart failure. The cause of heart failure was ischaemic in 52% and non ischaemic in 48%. Over a mean follow-up of 45.5 months, survival was no different in the standard therapy groups with and without amiodarone but was 23% (RRR) lower in the group treated with ICD. These results were consistent regardless of the cause for heart failure. The 7% ARR in survival in SCD-HeFT at 5 years represents the longest demonstrated
benefit for primary prevention ICD. 25% had appropriate firing of their ICD for rapid
VT or VF over 5 years (7.1% annual rate for total shocks and 5.1% annual rate for
appropriate shocks). Amiodarone had no beneficial effect on survival, despite the
use of appropriate dosage and reasonable compliance rates over longer periods
than in other placebo controlled trials. ICD therapy had a significant benefit in
patients with NYHA class II but not in those with NYHA class III congestive cardiac
failure (CCF). In contrast, amiodarone therapy had no benefit in patients with
NYHA class II and decreased survival among patients in NYHA class III CCF, as
compared with those who received placebo.

1.6.2 Primary Prevention in Non ischaemic Cardiomyopathy

Although CAD accounts for >70% of cardiomyopathy cases, patients with non
ischaemic dilated cardiomyopathy (DCM) are also at increased risk of SCD by less
well-understood mechanisms. The main DCM trials are SCD-HeFT (included both
ischaemic and non ischaemic cardiomyopathy), DEFINITE, CAT and AMIOVIRT.

1.6.2.1 SCD-HeFT (Sudden Cardiac Death in Heart Failure Trial\textsuperscript{18}) – DCM

The cause of heart failure was ischaemic in 52% and non ischaemic in 48%. At 5
years follow-up, all-cause mortality in the non ischaemic group with ICD therapy
was significantly lower than the conventional group (HR 0.73) suggesting the
benefit of ICD therapy in this group of patients.
1.6.2.2  DEFINITE (DEFibrillators In Non Ischaemic cardiomyopathy Treatment Evaluation) trial\textsuperscript{22}

DEFINITE randomized 458 patients with non ischaemic DCM, LVEF ≤35%, ventricular arrhythmias (NSVT or PVC) detected on ambulatory electrocardiogram (ECG) monitoring and NYHA class I-III heart failure to receive either ICD or standard medical therapy. Throughout a mean follow-up of 29 months, there was a 35% RRR in all-cause mortality and a highly significant 80% reduction in risk of arrhythmic death. Patients with NYHA class 3 heart failure derived the largest survival benefit from ICD therapy suggesting the disease at this point may have increased electrical instability and mortality risk.

1.6.2.3  CAT (The CArdiomyopathy Trial)\textsuperscript{50}

Patients with recent onset of DCM (<9 months) and LVEF ≤30% were randomly assigned to implantation of an ICD or control. The trial was terminated early as the all-cause mortality rate at 1 year did not reach the expected 30% in the control group. 104 patients were enrolled in the trial of which 50 were assigned to ICD therapy and 54 to the control group. Mean follow-up was 22.8 months. No SCD occurred during the first 2 years of follow-up. After a mean follow-up of 5.5 years, 30 deaths had occurred (13 in the ICD group and 17 in the control group). Cumulative survival was not significantly different between the two groups (93% and 80% in the control group versus 92% and 86% in the ICD group after 2 and 4 years respectively). This trial did not provide evidence in favour of prophylactic ICD implantation in patients with DCM of recent onset and impaired LVEF.
1.6.2.4 Amiodarone Versus Implantable cardioverter defibrillator Randomized Trial in patients with non-ischaemic dilated cardiomyopathy and asymptomatic non-sustained ventricular tachycardia (AMIOVIRT trial) 51

The aim of this RCT was to compare total mortality with amiodarone vs. ICD in patients with DCM, LVEF ≤35% and NSVT. 103 patients were randomized to receive either amiodarone or an ICD. The study was stopped early and the percentage of patients surviving at 1 year were 90% vs. 96% and at 3 years were 88% vs. 87% in the amiodarone and ICD groups respectively. There was a trend with amiodarone (as compared to the ICD), towards improved arrhythmia-free survival (p<0.1) and lower costs during the first year of therapy ($8,879 vs. $22,039, p<0.1).

1.6.3 Primary Prevention of Sudden Death in Other Cardiac Diseases

A number of diseases other than ischaemic and non ischaemic DCM have been associated with an increased incidence of SCD. These include inherited ion channelopathies, such as long QT syndrome (LQTS), 52 Brugada syndrome, 53 and catecholaminergic polymorphic VT (CPVT). 54 In addition, other structural heart diseases, such as Arrhythmogenic right ventricular dysplasia (ARVC), 55 hypertrophic cardiomyopathy, 56 and other congenital heart diseases may be associated with increased risk of sudden death. The frequency of these conditions is not as high as that of ischaemic or non ischaemic DCM, which makes prospective RCTs difficult to perform. Non randomized observational studies
suggest sub-groups of high-risk patients may benefit from ICD therapy. In the absence of large-scale trials for most of these conditions, risk-stratification algorithms based on retrospective studies have been created in an attempt to help select appropriate high risk patients for ICD therapy. In addition, there are disease-specific markers, such as the length of the QTc interval in the inherited LQTS, the presence of persistent rather than intermittent right precordial ST elevation in Brugada syndrome, and the degree of left ventricular hypertrophy in patients with hypertrophic cardiomyopathy that appear to portend an increased risk of SCD and the use of ICD for the primary prevention of sudden death appropriate.

These are appropriately reflected in the recommendation of ICD therapy by issuing clinical practice guidelines by both national (National Institute of Clinical Excellence (NICE) in the United Kingdom) and international organizations (American College of Cardiology (ACC) / American Heart Association (AHA) / European Society of Cardiology (ESC) Guidelines in America and Europe).

1.7 National and international ICD Guidelines

National (NICE) and international guidelines (American Heart Association, European Society of Cardiology, etc) are published to guide physicians make decision regarding provision of ICD therapy.
1.7.1 UK NICE (2006) Guidelines

National Institute of Clinical Excellence (NICE) is the body responsible for framing the national guidelines in the United Kingdom for all evidence based therapies including ICDs. NICE aims to analyse the available data from all the clinical trials and issue practice guidelines based not only on clinical evidence but also by incorporating cost-benefit analysis. It also aims to provide universal care throughout the country and minimize regional variation.

1.7.1.1 Secondary Prevention NICE Guidelines

Secondary prevention of SCD is defined as the prevention of an additional life-threatening event in survivors of sudden cardiac event or in patients with recurrent unstable arrhythmias. ICD is recommended for patients who present with one of the following in the absence of a treatable cause:

- having survived a cardiac arrest due to either VT or VF
- spontaneous sustained VT causing syncope or significant haemodynamic compromise
- sustained VT without syncope or cardiac arrest, and who have an associated reduction in ejection fraction (LVEF ≤35%) and no worse than NYHA class III heart failure
1.7.1.2 Primary Prevention NICE Guidelines

Primary prevention of SCD is defined as prevention of a first life-threatening arrhythmic event. NICE recommends primary prevention ICD for patients who:

- have a history of previous MI (≥4 weeks) and:
  - either:
    - LVSD with LVEF ≤35% (no worse than NYHA class III heart failure) and NSVT on Holter monitoring and inducible VT on EPS
  - Or:
    - LVSD with LVEF ≤30% (no worse than NYHA class III heart failure) and QRS duration ≥120 ms
- a familial cardiac condition with a high risk of SCD, including long QT syndrome, hypertrophic cardiomyopathy, Brugada syndrome or ARVC, or have undergone surgical repair of congenital heart disease


1.7.2.1 Class I Indication: ICD therapy is indicated in patients:

- who are survivors of cardiac arrest due to VF or haemodynamically unstable sustained VT (A)
- with structural heart disease and spontaneous sustained VT, whether haemodynamically stable or unstable (B)
- with syncope of undetermined origin with clinically relevant, haemodynamically significant sustained VT or VF induced at EPS (B)
• with LVEF ≤35% due to prior MI who are at least 40 days post-MI and who are in NYHA functional class II or III (A)
• with non ischaemic DCM who have an LVEF ≤35% and who are in NYHA functional class II or III (B)
• with LVSD due to prior MI who are at least 40 days post-MI, have an LVEF ≤30% and are in NYHA functional class I (A)
• with NSVT due to prior MI, LVEF ≤40%, and inducible VF or sustained VT at EPS (B)

1.7.2.2 Class IIb: ICD therapy may be considered in patients with:
• non ischaemic DCM who have an LVEF ≤35% and who are in NYHA functional class I (C)
• LQTS and risk factors for SCD (B)
• syncope and advanced structural heart disease in whom thorough invasive and non-invasive investigations have failed to define a cause (C)
• a familial cardiomyopathy associated with SCD (C)
• Left Ventricular non-compaction (C)

1.7.2.3 Class III: ICD therapy is not indicated for patients:
• who do not have a reasonable expectation of survival with an acceptable functional status for at least 1 year, even if they satisfy ICD implantation criteria (C)
• with incessant VT or VF (C)
• with significant psychiatric illness that may be aggravated by device implantation or that may preclude systemic follow-up (C)

• with NYHA class IV symptoms and drug-refractory CCF who are not candidates for cardiac transplantation or implantation of a Cardiac Resynchronization Therapy (CRT) device that incorporates both pacing and defibrillation capabilities (C)

• with syncope of undetermined cause without inducible ventricular tachyarrhythmias and without structural heart disease (C)

• when VF or VT is amenable to surgical or catheter ablation (e.g. atrial arrhythmias associated with Wolf Parkinson White (WPW) syndrome, right ventricular or left ventricular outflow tract VT, idiopathic VT or fascicular VT in the absence of structural heart disease (C)

• with ventricular tachyarrhythmias due to a completely reversible disorder in the absence of structural heart disease (e.g. electrolyte imbalance, drugs or trauma) (B)

1.8 Application of clinical guidelines

Putting clinical guidelines into practice by applying it to individual patients is not straightforward. Published ICD trials have differing inclusion criteria, varying lengths of follow-up and not all have demonstrated a statistically-significant reduction in all-cause mortality uniformly. Some sub-groups have benefitted more than others. This has led to publication of a number of sub-group analyses from
some of the larger trials.\textsuperscript{40;42;43;47;48;62;63} To add to the confusion, the benefit gained from an ICD is not presented in a uniform format and can often be misleading. Frequently the results are presented as RRR or HR when absolute risk reduction (ARR) and number needed to treat (NNT) are considered the most appropriate forms of data presentation when explaining risks and benefits to patients and determining cost effectiveness.\textsuperscript{64-69}

Electrophysiologists and device specialists (e.g. cardiologists with a special interest in devices and surgeons) have been successfully implanting implantable devices for over three decades. The number of ICD implants have gradually increased over the years; however implant rates are low and well below the national target, with primary prevention ICD accounting only for a minority of procedures in the United Kingdom.\textsuperscript{70} The exact reasons for low implant rates remains unclear. This low implant rate is likely to be multifactorial including a lack of physician knowledge (particularly non-implanting cardiologists); failure to implement guidelines; failure to screen patients and collect relevant data such as LVEF; lack of financial resources or implanting cardiologists; age, gender or race bias or even patient refusal to accept the therapy.

The role of national guidelines (e.g. NICE in the United Kingdom) is to set standards of practice throughout the country and establish a uniform policy of ICD therapy guiding physicians to provide best evidence based care for all patients. Despite clear guidelines, implantation rates vary significantly both between and
within individual countries. The reasons for this variation are not fully understood and are likely to be multifactorial rather than cost alone. Differences in awareness of appropriate indications, availability of implanters and resources, financial constraints and physician attitudes and preference towards ICD implantation have all been proposed; yet in the United Kingdom (UK), none of these appear to correlate with variation in regional implant rates.

NICE updated the clinical guidelines for ICD therapy in June 2014 which has been discussed in chapter 8. This research work mainly relates to the 2006 NICE guidelines which were in practice at the time of conducting this research.

1.9 Harm associated with ICD therapy

No therapy or intervention is free of side effects and ICD is no exception. ICD complications can be subdivided into four broad categories: (a) device related, (b) lead related, (c) inappropriate shocks and (d) QOL related i.e. psychological problems secondary to device implantation.

1.9.1 Device related

Device related complications include bleeding, major haematoma requiring re-operation (0.7%\textsuperscript{73,74}), skin erosion, wound infection (0.6%\textsuperscript{73}), device infection requiring re-positioning or extraction (0.5-0.8%\textsuperscript{25,74-77}), device migration, pneumothorax (0.4-1.1%\textsuperscript{75-77}), death as a direct result of device implantation.
(0.42\(^{78}\) – 0.9\(^{79}\)), high defibrillation threshold (DFT) with an inability to defibrillate (1\(^{80}\) & 1.2\(^{81}\)), cardiac tamponade (0.2-0.6\(^{75-77}\)) and generator/hardware malfunction (1.4\(^{73}\); 6-7\(^{73;73}\)). Most of these complications occur at the time of the procedure or shortly after.

1.9.2  Lead related
Lead dislodgment requiring re-positioning (0.8\(^{76}\) and 1\(^{74}\)); lead failure requiring extraction or additional lead insertion (2.7\(^{76}\); lead fracture (6.6\(^{82}\)) and lead infections causing endocarditis are the major lead adverse outcomes. Leads are also subject to damage during implantation or after, fractures and malfunction (Sprint Fidelis and Riata leads).

1.9.3  Inappropriate shocks
Inappropriate shocks most often occur due to supraventricular tachycardia, self-terminating VT, and sensing artifacts (e.g. myopotentials or T wave over sensing). The rate of inappropriate shocks has been described to be between 12-25% in various studies.\(^{73;75;77;83;84}\)

1.9.4  QOL related (Psychological)
ICD is generally well accepted by the majority of patients;\(^{85}\) however a significant proportion of patients (25-33%) experience clinical levels of anxiety, depression and impaired QoL following ICD implantation.\(^{86-89}\) These difficulties may not only be attributed to the actual ICD shocks;\(^{89-91}\) but also to device-related concerns
including fear of shocks,\textsuperscript{92,93} ICD advisories (i.e. notification from ICD manufacturers that the hardware may potentially malfunction),\textsuperscript{94} and the psychological make-up of the patient, including lack of optimism\textsuperscript{95} and personality factors, such as the *distressed* (Type D) personality.\textsuperscript{88,89,96}

1.10 Low uptake of ICD therapy

RCTs have demonstrated statistically significant reductions in all-cause mortality in selected patient groups. Despite this wealth of published data as well as national and international guidelines, the uptake of ICDs in high risk population remains in the order of 15-20\% of eligible patients. ICD implantation rates for the United Kingdom is much lower than most of Western Europe and USA. The national target has been set at 100 new ICD implants per million population per year by NICE and it has been estimated 40 implants per million population will be for primary prevention. Although the implant rate of ICD in the UK has been gradually increasing (since 2005), it is not fast enough nor does it compare well to our European colleagues (72 vs. 141 new ICD implants per million population). A breakdown of implant rates for the UK countries is shown in Figure 3.\textsuperscript{97}
The new ICD implant rate for 2013/14 in England is 72 implants/million/year. Of some comfort is the significant increase in the CRT devices and the ‘high energy devices’ (i.e. ICD + Cardiac resynchronization therapy – defibrillator (CRT-D), both new and replacement devices) with an average of 155 implants/million/year. It is also estimated that there is an approximately 50-50 split between CRT-D and cardiac resynchronization therapy – Pacing (CRT-P) devices in the UK and is one of the lowest in the Europe (Figure 4).
Figure 4. Ratio of CRT-D to CRT-P implants in Europe.
The provision of ICD therapy when compared to the western European nations remains poor and reflects the United Kingdom in a poor light as an advanced and modern health care provider. USA remains top of the league table with annual implant rates greater than 434 per million population while Germany tops the European league with implant rates ~250 per million per year. Figure 5 shows the implant rates in Europe in comparison to UK.
Figure 5. New ICD implant rates across Europe.
1.11 Physician factors affecting ICD implantation

The question as to why there is such a low uptake of ICD therapy is not known, but many reasons have been postulated: lack of awareness of appropriate indications, lack of implanters and resources, the high up-front device costs and scepticism about the true benefits. The barriers to eligible patients receiving appropriate ICD implantation could lie with the following: (1) primary care (failure to identify cardiovascular disease in the community and refer to secondary care); (2) the general physician (failure to identify appropriate cardiovascular disease and refer to the general cardiologist) (3) the general cardiologist (failure to identify appropriate candidates, ignorance of referral guidelines or a failure to act in accordance due to scepticism and personal belief); (4) the implanting cardiologists (very few to provide the implanting service, or too high a threshold for offering therapy) or; (5) the patient (declining ICD therapy after weighing up the risks and benefits).

Physicians’ perception of individual risk and application of statistical data is not universal; is poorly understood and can play a key role for an eligible patient to receive the recommended therapy. It is important to consider the possibility of the physician withholding the offer of ICD therapy if he or she thinks a patient is unlikely to benefit. National and international guidelines significantly influence physicians and may reduce bias in treatment; however they are only guidelines and not binding. In addition to national and international guidelines, clinicians
(hospital specialists and general practitioners) also have local guidelines to adhere to. Many physicians might appreciate a treatment to be beneficial within certain patient groups (i.e. are aware of published guidelines for treatment), they may not be aware of the magnitude of risk reduction it confers, yet this may be integral to their decision to offer treatment and influence patient’s choice to accept it. Last but not the least, patients’ acceptance of the proposed therapy and mutual trust is at the heart of the doctor-patient relationship.
Chapter 2

Risk Perception

and

Implantable Cardioverter Defibrillators
2.1 Introduction

Life is not risk free\textsuperscript{99} and health (and health-related therapies) is no exception to this. As physicians we have a duty to understand and communicate this risk to our patients.\textsuperscript{99} Explaining the concept of risk entails not only critical thinking about the degree of risk but also how to approach and share that information with patients in a meaningful and constructive way. This is a two way process and involves active participation from both the physician and the patient. Risk assessment and perception has been previously shown to be subconscious, subjective, and personality-dependent and fails to follow any rational or methodical pattern.\textsuperscript{100}

From an individual’s perspective the understanding, interpretation and acceptance of risk varies significantly and is influenced by many external factors.

There is a cultural difference in risk perception between doctors and patients; and this is at the heart of the problem of risk communication. Why is risk communication difficult? Communicating risk entails confronting uncertainties that may be uncomfortable for both the physician and the patient and should not be an excuse to avoid risk communication. Good communication is likely to benefit patients (acceptance of risk), professionals (higher satisfaction) and healthcare systems (less patient discontent and therefore potentially less litigation). Although there is no universal rule for communication, research has shown that consultations in which doctors have been trained in the use of decision aids (e.g. booklets, tapes, videodiscs, interactive computer programs, and or paper based
charts) sharpened the focus of the consultation, changed the content according to patient needs, and resulted in greater perception of decisions actually being made. Often there exists more than one alternative treatment option and the ‘correct’ choice of treatment in such instances should largely be a matter of individual patient preference and physicians should not assume ‘they know best’. The opportunity for patients to take a more active role in the management of their illness by being better informed and included in decision making can result in a positive effect on their health and lead to enhanced patient and carer satisfaction.

2.2 Risk Categories and their influence

Risk can be subjectively described using terms such as “likely”, “probable” and “possible” or using a more scientific and objective way (by using risk reduction, either relative or absolute). Subjective categories mean different things to different people and their use should be best avoided. RRR looks at the proportional difference in risk between one alternative and another and is most widely used because results seem more “impressive”. Therefore, it is more effective in persuading patients to agree to a proposed treatment when compared to other risk categories.
2.3 Pitfalls of data presentation

The initial phase of my research was focused on gathering the evidence (RRR, ARR and NNT for 1, 2 and 3 year follow-up) from the landmark RCTs that have influenced the national and international guidelines.\textsuperscript{17-25} There are many challenges when it comes to determining, defining, explaining and understanding risk. RCTs produce statistical data that is used to illustrate the effect on populations but it is not always clear how best to translate this to individuals. Trial data is presented in a variety of formats, most frequently RRR and less often ARR and NNT to save one life. Trials have different follow-up periods and a variety of inclusion and exclusion criteria and this makes comparison between trials difficult. There is evidence to suggest that ARR and NNT are the most informative and meaningful way of presenting statistical data and are required for cost-effectiveness calculations.\textsuperscript{105;106} Absolute risks (reductions and increases), such as from one to two in 1000, are transparent, while relative risks such as “twofold” provide incomplete and misleading risk information.\textsuperscript{107;108} Relative risks looks at the proportional difference in risk between one alternative and another, and do not tell us about the baseline risk - for example, twofold reduction holds true for both two to one reduction as well as from 100 to 50 but the baseline risk, for example 1000 patients will give a true meaning to this risk reduction. RRR is likely to magnify the benefits gained as the numerical figures are often large and conveys a false sense of greater benefit i.e. overestimate both benefits and harms depending on the way it is presented.\textsuperscript{64;65;108;109}
An analysis of articles published in the *Annals of Internal Medicine*, *British Medical Journal (BMJ)*, Journal of American Medical Association (JAMA), *Journal of the National Cancer Institute*, *Lancet*, and the *New England Journal of Medicine (NEJM)* from 2003 to 2004, showed that 68% (150/222) of publications failed to report the underlying absolute risks in the abstract. Among those, about half did report the absolute risks elsewhere in the article, but the other half did not. 110 Similarly, an analysis of 119 systematic reviews in *BMJ*, *JAMA*, and *Lancet* from 2004 to 2006 showed that every second article discussed only relative risks or odds ratios.111 The next widely committed mistake is ‘mismatched framing’- reporting benefits in big numbers (usually as relative reductions) and harm in small numbers (usually as absolute risk increases).108 One in three articles in the *BMJ*, *JAMA*, and *Lancet* from 2004 to 2006 used mismatched framing when both benefits and harm were reported.111

### 2.4 Better forms of representation

Employing a common and consistent denominator i.e. numerical representation (e.g. ‘out of 100’) has been proposed as a more accurate means of communicating risk to professionals and patients alike.67 NNT and number needed to harm (NNH) are key statistical tools, but it is ARR (from which NNT and NNH are derived) that is deemed to be the most appropriate form of data presentation when explaining risks and benefits.65 ARR is a more appropriate and less confusing means of
expressing risks and benefit from treatment and is felt to be more clinically-relevant. ARR also determines NNT which is required for calculating cost-effectiveness. The RRR, ARR and NNT need to be put into context against the total mortality in the untreated group to better understand the risks and benefit when subjecting patients to any procedure or therapy especially when there exists a harm from the proposed treatment. Although it is possible to find NNT data in some published ICD RCTs, there is no consistency between trials regarding the time period over which the NNT is derived, making comparison between trials challenging. Most trials have only published RRR and provide a figure for the trial duration (mean follow-up).

2.5 Informed consent

In clinical care, disclosure of risk developed from the obligation on doctors to obtain their patients’ consent before intervening medically. In the absence of an emergency, doctors who acted without their patients’ consent were initially accused of battery or intentional harm and later of negligence. The concept of obtaining consent from patients is not new and was first established as a judicial concept in a British case in 1767. Gradually the notion of consent evolved into informed consent, with the emphasis also being on information about risks rather than just benefits. The term “informed consent” was first introduced into the judicial lexicon in 1957 in the written opinion of an appellate judge in California. In British practice, Mazur highlighted the legal requirements for informed consent that
set the framework for both research and everyday practice.\textsuperscript{115} This continues to provide an important context for much of risk communication today.\textsuperscript{116} The “new medical conversation” outlined by Mazur builds on existing skills and traditional values in interactions between doctors and patients and addresses the patients’ need for information while maintaining other aspects, such as support.\textsuperscript{117} But with focus shifting towards greater autonomy for patients, the goal is changing to become one of informing patients, enabling them to make their own choices, regardless of whether this is believed to be right by the physician and may or may not reduce overall risk. The information offered should be simple, relevant, and responsive to the needs and values of individual patient, not assuming what is most important. There should be a two way exchange of opinions and values, as well as information, seeking to maximise trust and support. This may need to be done over a series of consultations rather than being a one-off event.\textsuperscript{118}

2.6 Risk as applicable to cardiology patients

Estimating individual patient’s mortality and morbidity is extremely difficult and highly variable. When asked about patients’ estimated mortality and morbidity from PCI, physicians (both interventionists and non-interventionists) differed substantially and both groups overestimated mortality and underestimated morbidity compared to computer calculation tools.\textsuperscript{119} Similarly, studies have shown significant discordance with patients’ and physicians’ expectation of survival and symptomatic benefit following PCI vs. CABG.\textsuperscript{120} Risk perception among patients is
relatively poor and even when formally educated, their retention of risk and benefit information is minimal by 30 days of follow-up. A further barrier to risk communication is that not all patients want to know about the nitty gritty of specific risks and want physicians to decide on their behalf. An interesting study highlights nearly half of patients undergoing CABG (after informed consent) did not want to know about the risk of death or stroke associated with the procedure. Most of those that do want to be informed of the risk of death are not concerned with specific probabilities.\textsuperscript{121}

2.7 Risk as applicable to potential implantable cardioverter defibrillator recipients

Patients with structural heart disease, in particular LVSD, have an annual mortality risk greater than the general population. A component of this risk of all-cause mortality is the risk of SCD. RCT have demonstrated statistically significant reduction in all-cause mortality in select patient groups with ICD and have been reflected in the national and international guidelines. Despite well-published data and guidelines, the uptake of ICD in high risk populations remains low. The question as to why this is the case is not known; but many reasons have been postulated, including lack of awareness of appropriate indications, lack of implanters and resources, the high up-front device costs, or scepticism about the magnitude of benefit. It is not clear if the cardiologists will withhold the option of ICD therapy if they judge that the patient will not derive a justifiable benefit. Studies
have shown that health care professionals often rate patients’ health status worse than the patients rate it themselves.\textsuperscript{122,123} There can sometimes be a conflict between the provider (physician) and the user (patient). To put it in other terms there appears to be a difference between what is deemed “acceptable risk” by the physician as compared to the patient. One of the ways to avoid this is by explaining the risks and benefits in an accurate and understandable format, involving the patient in decision making and agreeing to an acceptable course of action.

The concept of offering ICD to “high risk” groups is dependent on the belief that there is an acceptable threshold for the risk of SCD below which an ICD should not be offered. At what level does risk become “high”? How is the threshold of acceptable risk determined? Is it clinical, statistical, ethical, legal or financial? A simplistic approach would be the level at which the chance of harm from a therapy outweighs the chance of benefit. Fortunately, ICD implant procedure related mortality is extremely low (~0.5%). In a US registry of 161,470 patients, in-hospital mortality was 0.42%.\textsuperscript{78} Healthcare economists may produce a level of acceptable risk based on QALYs or life years gained, setting the bar at a level where the cost of saving one life year is less than or equal to $50,000. This financial threshold may have little relationship to a physician’s perception of “clinically acceptable risk” at an individual level, which in turn may be very different from a patient’s threshold. How a patient determines acceptable risk is likely to be influenced by their age, background, co-morbidities, understanding and personality, amongst many other
social, cultural and individual factors. Personal experience plays a role, which may go some way to explain the high uptake of secondary ICD compared to the low implant rates for primary prevention ICD.

Do we know anything about physician or patient risk perception and its influence on ICD acceptance or refusal? A small Swedish study\textsuperscript{124} of 31 heart failure patients referred for ICD implantation reported that none were informed of the alternative choice of medical therapy or the survival benefits that an ICD offered. No patient had any knowledge of their expected survival time from their medical condition with or without the ICD. Despite the lack of well-informed consent, all 31 patients expressed no regrets about having an ICD implanted. ICD treatment does have potential harm, with an incidence of implant-related complications and a long-term risk of inappropriate shock therapies, infection, device or lead failure and a need for generator replacement. Shock therapies, whether appropriate or inappropriate may contribute to deterioration in QOL scores;\textsuperscript{125} but there is some comforting evidence that this may be overcome with counselling and cognitive behavioural therapy.\textsuperscript{126}

\subsection*{2.8 Communication of risk and its impact on ICD patients}

Patients with structural heart disease, in particular impaired LVSD, have an annual mortality greater than that of the general population due to an increased risk of SCD. Communication of this risk from the physician to the patient is an essential
component of health management (and physician responsibility) and is integral to the informed consent process. Defibrillators are commonly accepted therapy for both primary and secondary prevention. As device therapies are associated with complications like inappropriate shocks, infections and implant related complications, it is vital that patients are completely aware of the risks in addition to the benefits offered by ICD. This is entirely dependent on good communication and a robust informed consent process. This is essential not only from a medico-legal perspective but also to preserve the trust between the physician and the patient. Consent process is not universal and there are no specific guidelines educating physicians on how risks and benefits are expressed as part of the consent process for ICD implantation. A large (non-ICD) study examined 1057 consultations with 59 primary care physicians and 65 general and orthopedic surgeons in community based private offices. Information related to the nature of the decision was discussed in 71% of consultations, patient preferences in 21%, alternative treatments in 11.3%, the risks and benefits of the recommended procedure and its alternatives in 5.8%, the patient’s role in decision making in 5.9%, uncertainties associated with the decision in 4.1%, and patient understanding in 1.5%. Similarly, ICD studies have highlighted that communication (and consent process) is far from adequate. Despite pre-implantation education, patient comprehension of the risks and benefits of ICD therapy is poor and patient’s expectations of ICD therapy may be inappropriate. They did not have any knowledge of their expected survival time from their medical condition with or without the ICD. Despite the lack of well-informed consent, >90%
of patients were very satisfied regarding their decision and had no regrets. It is not hard to imagine that these are not isolated occurrences. There is however general guidance about consenting patients issued by the General Medical Council (in the United Kingdom) available since 2008 which sets out the principles on which good clinical decisions should be based. \textsuperscript{129}

On the other end of the spectrum is ICD de-activation and end-of-life discussion which is never easy for the patient (or relatives) nor the implanting physician. Though there are guidelines, there is also differing opinion among physicians caring for these patients. It is interesting to note that in a physician survey, the majority of general physicians (95\%) and geriatricians (95\%) believed information about deactivation should be given during the time of the consent process. \textsuperscript{130} In striking contrast, only about half (56\%) of the electrophysiologists agreed that deactivation information should be provided during procedure consent. \textsuperscript{130} Consensus statements from both Heart Rhythm Society (HRS) and European Heart Rhythm Association (EHRA) in 2010 recommend communications regarding ICD deactivation should begin prior to ICD implantation and continue over time and reflect changes in patient’s health status. \textsuperscript{131;132}
Chapter 3

Analysis of Primary and Secondary Prevention

Implantable Cardioverter Defibrillator

Clinical Trials
3.1 Introduction

RCTs and meta-analysis have demonstrated ICDs reduce total mortality in select high-risk patients by treating life-threatening ventricular tachyarrhythmias\textsuperscript{17-25} and has led to national and international guidelines for the provision of ICD therapy in both primary and secondary prevention.\textsuperscript{60,61} Published ICD trials have differing inclusion criteria, varying lengths of follow-up and not all have demonstrated a statistically-significant reduction in all-cause mortality across all sub-groups and has been reflected in the sub-group analysis from some of the larger trials.\textsuperscript{40;42;43;47;48;62;63} Another important confounding issue is the way in which the results are presented in these clinical trials. The results are presented either as RRR, Odds Ratio (OR) or HR and seem more impressive when compared to ARR. ARR and NNT are the better forms of presenting data when explaining risks and benefits to patients as well as determining cost effectiveness but are not readily published in these clinical trials.\textsuperscript{66} There could be some cardiologists who might be skeptical about the true benefits offered by ICD as data on ARR and NNT is lacking, and this could be one of the many reasons for low implant levels.
3.2 Hypotheses and Aims of the study

ICD implantation rates in the United Kingdom are low and the reasons for such a low implant are not known. Awareness of the benefits (and harm) offered by the ICD is a key aspect in convincing the cardiologists to offer this effective therapy to eligible patients. If the cardiologists are not aware of the magnitude of benefits (and harm) and if this information is not readily available or in a standardized fashion, it could potentially lead to low implant rates. We therefore designed a project to look at the evidence in detail and express the results in the most appropriate form of data presentation (ARR and NNT) standardized for the length of follow-up.

The aim of this study was to establish one, two and three year ARR and NNT data from published ICD RCTs, to better understand risk / benefit analysis and comparison between different patient groups. This would ultimately lead to better physician understanding as well as aid better informed patient consent process.

3.3 Methodology: Clinical trial selection and Kaplan Meier curve analysis

The RCT included in the analysis were identified through the Medline database and from citations in national (NICE) and international guidelines. Landmark trials that compared ICD therapy with medical therapy or no therapy were included, if the publication contained annual survival data in the form of percentage all-cause
mortality or Kaplan Meier graphs of total mortality. Sub-group analysis of RCTs with annual survival data or Kaplan Meier survival graphs were also included. Annual mortality rates for the ICD and medically-treated patient groups in each trial were taken from the text and ARR and NNT calculated for one, two and three years follow-up. Annual percentage survival data was available from the publication text in MADIT 2, DEFINITE, AVID and CIDS main studies; and sub-studies from MADIT 2 (LVEF, NYHA, Age, Race and Risk score) and AVID (LVEF). The number of patients at risk was also identifiable in all primary and secondary prevention RCTs except AMIOVIRT and MADIT 2 sub-study (Time from MI). Estimation of survival was obtained from Kaplan Meier graphs for 8 trials (MADIT, MUSTT, SCD-HeFT, DEFINITE, CAT, AMIOVERT, CASH and Meta-analysis) and 5 sub-studies (MADIT 2, SCD-HeFT, DEFINITE, CIDS and Meta-analysis).

3.3.1 Data derived from Kaplan Meier Graphs

In publications, where the percentage of survival (or mortality) was not available in the text, the annual mortality was estimated from Kaplan Meier graphs using the method similar to that described by Salukhe et al.\textsuperscript{133} They described life-years gained from ICD implantation from the RCTs (MADIT, MUSTT, MADIT 2, AVID, CIDS, CASH, ICD vs. Medical therapy by Wever et al.\textsuperscript{134} and ICD vs. Amiodarone by Schlapfer et al.\textsuperscript{135} – non-randomised trial). As trial populations, clinical status and prognosis varied widely between studies, the benefit gained was expressed at different time points up to 3 years. Calibrated enlargement of the Kaplan Meier
curves was performed and the area between the curves taken to represent the life years gained. This method was validated and they found the number of life years gained grows approximately with the square of follow up duration for the 3 year period after ICD implantation. A squared relationship implies that at 1 year, one can only see approximately $1/9^{th}$ of the benefit that one would be able to see at 3 years. Terminating a trial at 1 year instead of 3 years would artificially increase the NNT by 7-fold.

3.3.2 Kaplan Meier curves analysis and validation

Calibrated enlargement of the Kaplan Meier curves were performed for analysis and the estimated survival measured at one, two and three years by five blinded observers. The procedure was validated by performing error for inter and intra observer variability from 5 publications in which the annual survival data was also available. 3 years was a compromise between the advantages of portraying meaningful data over longer periods of time and the disadvantages of a relatively small number of patients included in long term follow-up. Error of the mean for inter-observer variability was 0.82±0.38 and intra-observer variability was 1.14±0.54. Intra-observer co-efficient of variability was 2.1% (2.4% reported by Salukhe et al.). Obtaining additional unpublished statistical data is not easy and Salukhe et al. report that they approached the trial investigators for the mortality / survival information and were not successful. Given that the trials we were analyzing were similar (six out of eight trials were the same), we did not think it would be fruitful to pursue this approach. The number of patients at risk at each
annual measurement was used to calculate the 95% confidence intervals in those trials with the published data.  

3.4 Results: Primary prevention clinical trials and their selection criteria

Eight primary prevention RCTs (MADIT, MUSTT, MADIT2, SCD-HeFT, DEFINITE, AMIOVIRT, CAT and DINAMIT) were included in our study for data analysis. Three of the primary prevention RCTs (DEFINITE, SCD-HeFT and MADIT 2) also had sub-group analysis available in their publication. Trial data, including inclusion criteria, patient characteristics and outcomes for these trials are shown in Table 1.
Table 1. Inclusion criteria, patient characteristics and outcomes of primary prevention ICD trials.

<table>
<thead>
<tr>
<th>Trial</th>
<th>MADIT</th>
<th>MUSTT</th>
<th>MADIT2</th>
<th>DINAMIT</th>
<th>SCD-HeFT</th>
<th>DEFINIT</th>
<th>AMIOVIRT</th>
<th>CAT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aetio</td>
<td>IHD</td>
<td>IHD</td>
<td>IHD</td>
<td>IHD</td>
<td>IHD or</td>
<td>DCM</td>
<td>DCM</td>
<td>DCM (&lt;9 mths)</td>
</tr>
<tr>
<td>LVEF</td>
<td>≤35%</td>
<td>≤40%</td>
<td>≤30%</td>
<td>≤35%</td>
<td>≤35%</td>
<td>≤35%</td>
<td>≤35%</td>
<td>≤30%</td>
</tr>
<tr>
<td>Additional Req</td>
<td>nsVT &amp; +ve EPS</td>
<td>nsVT &amp; +ve EPS</td>
<td>6-40 days, cardiac autonomic dysfn</td>
<td>NYHA II or III</td>
<td>PVCs or nsVT</td>
<td>NSVT</td>
<td>NYHA II or III</td>
<td></td>
</tr>
<tr>
<td>No. of pts (ICD, Med)</td>
<td>95, 101</td>
<td>351, 353</td>
<td>742, 490</td>
<td>332, 344</td>
<td>829, 1692</td>
<td>229, 229</td>
<td>51, 52</td>
<td>50, 54</td>
</tr>
<tr>
<td>Ave age in yrs (ICD, Med)</td>
<td>62±9, 64±9</td>
<td>66±6, 65±7</td>
<td>64±10, 65±10</td>
<td>61.5±11, 62.1±11</td>
<td>60.5±9 (all pts)</td>
<td>58.3 (all pts)</td>
<td>58±11, 60±12</td>
<td>52±12, 52±10</td>
</tr>
<tr>
<td>Mean LVEF% (ICD, Med)</td>
<td>27±7, 25±7</td>
<td>27.5±8, 28.5±7</td>
<td>23±5, 23±6</td>
<td>28±5, 28±5</td>
<td>25, 25</td>
<td>21 (all pts)</td>
<td>22±10, 23±8</td>
<td>24±6, 25±8</td>
</tr>
<tr>
<td>Mean FU (mths)</td>
<td>27</td>
<td>39</td>
<td>20</td>
<td>30±13</td>
<td>45.5</td>
<td>29±14.4</td>
<td>20.1±12.6</td>
<td>22.7±5, 22.9±4</td>
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<tr>
<td>Med Group 3 yr mortality</td>
<td>42%</td>
<td>35.4%</td>
<td>31%</td>
<td>17.5%</td>
<td>22%</td>
<td>19.4%</td>
<td>20%</td>
<td>18%</td>
</tr>
<tr>
<td>Outcome as reported</td>
<td>HR: 0.46 (0.26-0.82)</td>
<td>RR:0.40 (0.27-0.59)</td>
<td>P=0.009</td>
<td>HR: 0.69 (0.51-0.93)</td>
<td>P=0.016</td>
<td>HR: 1.08 (0.76-1.55)</td>
<td>P=0.66</td>
<td>HR: 0.77 (0.62-1.06)</td>
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<td></td>
<td>HR: 0.65 (0.4-1.06)</td>
<td>P=0.08</td>
<td>HR: 0.65</td>
<td>No diff</td>
<td>P = 0.6</td>
<td>No diff</td>
<td>P = 0.554</td>
<td></td>
</tr>
</tbody>
</table>
FU = follow-up; pts = patients; Diff = difference; Med = medical; Aetio = aetiology; Ave = average; Yr = year; Req = Requirements

Data from the SCD-HeFT trial sub-groups (aetiology) were used in preference to the overall combined statistics as the trial was powered for post-hoc aetiology sub-study analysis. The ICD recipients in SCD-HeFT were compared to the placebo group and the amiodarone group were excluded. DINAMIT study included patients after an MI within 6-40 days and was a negative trial. Clinical guidelines have excluded this trial and it is now clearly established that providing an ICD in this early period after MI is not only not beneficial but detrimental. Therefore, we have excluded this trial data and results from further analysis.

3.5 Results from Primary prevention trial analysis

The 3-year mortality benefit for primary prevention trials varied significantly between heart failure aetiologies (i.e. ischaemic cardiomyopathy and non ischaemic DCM). The total mortality in the medically-treated groups in all the trials was significantly higher when compared to ICD therapy in the ischaemic cardiomyopathy patients. These high risk patients with ischaemic heart disease (IHD) enrolled in MADIT and MUSTT (although they have high mortality), had the most to gain over 3 years in terms of ARR and NNT (ARR 24.6% and 19% with a NNT of 4 and 5 respectively) from an ICD; particularly those in MADIT group
where Holter monitoring and provocative EPS was used to further risk stratify these already high risk patients. In the MADIT2 trial, where patient selection was solely based on LVEF (with no requirement for provocative EPS) and ischaemic cardiomyopathy as in the previous MADIT and MUSTT trials, the 3-year RRR was 29% with the ARR 9% (NNT 11). Patients enrolled in the SCD-HeFT trial (which included both IHD and non IHD DCM), IHD arm had a 3-year RRR of 20% and an ARR of 5.6% (NNT 18) whereas patients in the same trial with non ischaemic DCM had a 3-year RRR of 25.3% and ARR of 4% (NNT 25). Of those trials that exclusively enlisted DCM patients, the DEFINITE trial showed a 3-year RRR of 32% and ARR of 6.2% (NNT 16), whereas the CAT and AMIOVIRT trials showed a 2% absolute risk increase in mortality in the ICD group. Total mortality in trial patients with DCM was less than those with IHD and as a consequence resulted in smaller ARR and failure for all trials (DEFINITE, p=0.08; CAT, negative trial, and AMIOVIRT, negative trial and SCD-HeFT – DCM, p=0.06) to show statistically-significant reductions in mortality with the use of an ICD.

Results from the main trial analysis with respect to mortality from medically treated patients in comparison to ICD therapy; benefit gained from ICD therapy in terms of ARR, RRR and NNT at 1, 2 and 3 years follow-up have been summarized in Table 2.
Table 2. Mortality, ARR with 95% CI, RRR and NNT at 1, 2 and 3 year follow-up from primary prevention trials.

<table>
<thead>
<tr>
<th>Trial</th>
<th>FU</th>
<th>Med (%)</th>
<th>ICD (%)</th>
<th>RRR (%)</th>
<th>ARR &amp; CI (%)</th>
<th>NNT</th>
</tr>
</thead>
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<tr>
<td></td>
<td>Year 2</td>
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<td>62.3</td>
<td>20.8±16</td>
<td>5</td>
</tr>
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<td></td>
<td>Year 3</td>
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<td>58.6</td>
<td>24.6±22.4</td>
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<td>MUSTT</td>
<td>Year 1</td>
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<td>Year 2</td>
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<tr>
<td></td>
<td>Year 3</td>
<td>35.4</td>
<td>16.4</td>
<td>53.7</td>
<td>19±8.6</td>
<td>5</td>
</tr>
<tr>
<td>MADIT2</td>
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<td>10</td>
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<td>1±4</td>
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<tr>
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<td>Year 2</td>
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<td>6±7.5</td>
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<td></td>
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<td>11</td>
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<tr>
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<td>1±3.9</td>
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<tr>
<td></td>
<td>Year 2</td>
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<td>15.2</td>
<td>16.5</td>
<td>3±5.4</td>
<td>33</td>
</tr>
<tr>
<td></td>
<td>Year 3</td>
<td>28</td>
<td>22.4</td>
<td>20</td>
<td>5.6±7.7</td>
<td>18</td>
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<td>Year 2</td>
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<td>7.4</td>
<td>30.2</td>
<td>3.2±4.1</td>
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<tr>
<td></td>
<td>Year 3</td>
<td>15.8</td>
<td>11.8</td>
<td>25.3</td>
<td>4±5.9</td>
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<tr>
<td>DEFINITE</td>
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<td>58.1</td>
<td>3.6±3.8</td>
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<td>Year 2</td>
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</tr>
<tr>
<td></td>
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<td>-2</td>
<td>-</td>
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<td>AMIOVIRT</td>
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<td>-</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Year 2</td>
<td>7</td>
<td>11</td>
<td>-4</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Year 3</td>
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<td>22</td>
<td>-2</td>
<td>-</td>
<td></td>
</tr>
</tbody>
</table>
Med = Medical mortality; ICD = ICD mortality; FU = follow-up; CI = confidence interval

3.6 Results: Primary prevention sub-group analysis

3.6.1 NYHA status sub-group analysis

NYHA status sub-group analysis was available from the MADIT2, SCD-HeFT and DEFINITE trials. In MADIT2 patients, the ARR was greatest in those with NYHA class III symptoms (13% at 3 years, NNT 8). Patients with NYHA class III symptoms in the DEFINITE trial also had the greatest ARR (18.2% at 3 years, NNT 5). Sub-group analysis of the SCD-HeFT trial, which combined IHD and non-IHD patients, showed the greatest benefit in NYHA class II patients (ARR 9.2% at 3 years, NNT 11) and no benefit in the NYHA class III group. Results are summarized in Table 3.
Table 3. Primary prevention sub-studies: NYHA status.

<table>
<thead>
<tr>
<th>Trial</th>
<th>FU</th>
<th>Med (%)</th>
<th>ICD (%)</th>
<th>RRR (%)</th>
<th>ARR &amp; CI (%)</th>
<th>NNT</th>
</tr>
</thead>
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<td>MADIT2 NYHA I</td>
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<td>Year 2</td>
<td>16</td>
<td>11</td>
<td>31.3</td>
<td>5±10.2</td>
<td>20</td>
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<tr>
<td></td>
<td>Year 3</td>
<td>25</td>
<td>18</td>
<td>28</td>
<td>7±18.3</td>
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<td>MADIT2 NYHA II</td>
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<td>44.4</td>
<td>4±6.1</td>
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<tr>
<td></td>
<td>Year 2</td>
<td>18</td>
<td>12</td>
<td>33.3</td>
<td>6±11.6</td>
<td>17</td>
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<td></td>
<td>Year 3</td>
<td>23</td>
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<td>30.4</td>
<td>7±22.2</td>
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<td>0</td>
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<td>Year 2</td>
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<td>9±18.2</td>
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<td></td>
<td>Year 2</td>
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<tr>
<td></td>
<td>Year 3</td>
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<td>31.6</td>
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<td>Year 2</td>
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<td>13.8</td>
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<td>Year 3</td>
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<td>45.5</td>
<td>18.2±37.6</td>
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</table>

Med = Medical mortality; ICD = ICD mortality; FU = follow-up; CI = confidence interval.
3.6.2 Other sub-group analysis from MADIT 2

Further sub-group analysis was only available from the MADIT2 trial. The greatest benefit at 3 years was seen in patient groups of more than 18 months from their last MI (ARR 9.4%, NNT 11), LVEF <21% (ARR 12%, NNT 8), age ≥75 years (ARR 13%, NNT 8), a risk score of 2 (ARR 29%, NNT 3) and of Caucasian origin (ARR 7%, NNT 14). Results are summarized in Table 4.
Table 4. MADIT2 sub-group analysis.

<table>
<thead>
<tr>
<th>Trial</th>
<th>FU</th>
<th>Med (%)</th>
<th>ICD (%)</th>
<th>RRR (%)</th>
<th>ARR &amp; CI (%)</th>
<th>NNT</th>
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<tr>
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<td>31.3</td>
<td>5±11.1</td>
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<td>38.7</td>
<td>12±24.5</td>
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<td>7</td>
<td>36.4</td>
<td>4±7.7</td>
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<td>15</td>
<td>28.6</td>
<td>6±13.9</td>
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<td>6±7</td>
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<td>18</td>
<td>33.3</td>
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<tr>
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<td>37.5</td>
<td>4.8</td>
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<tr>
<td>Year 2</td>
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<td>31.3</td>
<td>7</td>
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<td>9.1</td>
<td>1±14.9</td>
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<tr>
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<td>15</td>
<td>21.1</td>
<td>4±27.5</td>
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<td></td>
</tr>
<tr>
<td>Year 3</td>
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<td></td>
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<td>-5</td>
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<td><strong>White race</strong></td>
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<td>Year 1</td>
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<td>1±4.4</td>
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<tr>
<td>Year 2</td>
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<td>16</td>
<td>23.8</td>
<td>5±8</td>
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</tr>
<tr>
<td>Year 3</td>
<td>29</td>
<td>22</td>
<td>24.1</td>
<td>7±14.3</td>
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3.6.3 MADIT 2 Risk Score (sub-study)

Goldenberg et al.\textsuperscript{48} tried to design a simple risk stratification score to better define the high risk patients and their all-cause mortality in the MADIT 2 trial. The risk score model comprised of 5 clinical factors – NYHA class >II, BUN ≥26 mg/dl, QRS duration ≥120 ms, age >70 years and AF contributing 1 point each. Patients were categorised into 5 groups with scores 0, 1, 2, 3 and very high risk (VHR) group (broadly subdivided into 3 groups – no risk, ≥1 and VHR). The VHR risk group was defined as patients having BUN ≥50 mg/dl and or serum Creatinine ≥2.5 mg/dl. Patients with NYHA class IV heart failure; who had undergone coronary revascularisation within the preceding 3 months; had MI in the last 4 weeks; advanced cerebrovascular disease; significant renal impairment (BUN ≥70 mg/dl or serum creatinine ≥3 mg/dl) or had any other non-cardiac condition that was associated with a high likelihood of death during the trial period were excluded.

Patients with no risk factors did not benefit from ICD therapy while patients with 1-2 risk factors benefitted the most. Patients with more risk factors (≥3) and VHR category patients did not benefit from ICD therapy as well and evidence shows it is
detrimental to provide ICD therapy to these patients. The results are summarized in Table 5.

Table 5. MADIT2 risk score (sub-study).

<table>
<thead>
<tr>
<th>Trial</th>
<th>FU</th>
<th>Med (%)</th>
<th>ICD (%)</th>
<th>RRR (%)</th>
<th>ARR &amp; CI (%)</th>
<th>NNT</th>
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<td>0</td>
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</tr>
<tr>
<td></td>
<td>Year 2</td>
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<td>9</td>
<td>-1</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Year 3</td>
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<td>10</td>
<td>0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Score ≥1</td>
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<td>8</td>
<td>33.3</td>
<td>4±5.27</td>
<td>20</td>
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<tr>
<td></td>
<td>Year 2</td>
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<td>44.4</td>
<td>12±9.92</td>
<td>8</td>
</tr>
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<td>Year 3</td>
<td>33.4</td>
<td>14.4</td>
<td>56.9</td>
<td>19±16</td>
<td>5</td>
</tr>
<tr>
<td>Score 2</td>
<td>Year 1</td>
<td>10</td>
<td>9</td>
<td>10</td>
<td>1±8.4</td>
<td>100</td>
</tr>
<tr>
<td></td>
<td>Year 2</td>
<td>27</td>
<td>15</td>
<td>44.4</td>
<td>12±16.3</td>
<td>8</td>
</tr>
<tr>
<td></td>
<td>Year 3</td>
<td>49</td>
<td>20</td>
<td>59.2</td>
<td>29±33.8</td>
<td>3</td>
</tr>
<tr>
<td>Score ≥3</td>
<td>Year 1</td>
<td>17</td>
<td>16</td>
<td>5.9</td>
<td>1±14.4</td>
<td>100</td>
</tr>
<tr>
<td></td>
<td>Year 2</td>
<td>38</td>
<td>27</td>
<td>28.9</td>
<td>11±31</td>
<td>9</td>
</tr>
<tr>
<td></td>
<td>Year 3</td>
<td>38</td>
<td>47</td>
<td>-9</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Very High Risk</td>
<td>Year 1</td>
<td>27</td>
<td>27</td>
<td>0</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Year 2</td>
<td>54</td>
<td>49</td>
<td>9.3</td>
<td>5±63.6</td>
<td>20</td>
</tr>
<tr>
<td></td>
<td>Year 3</td>
<td>53.2</td>
<td>68.4</td>
<td>-15.2</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Med = Medical mortality; ICD = ICD mortality; FU = follow-up; CI = confidence interval; Risk factors include NYHA class >II, age >70 years, BUN (blood urea nitrogen) >26 mg/dl, QRS duration ≥120 ms, and atrial fibrillation. Very high risk = BUN >50 mg/dl and or serum creatinine >2.5 mg/dl.

3.6.4 Summary of 3-year ARR and NNT of all Primary prevention trials

The results of the 3-year medical and ICD mortality, RRR, ARR and NNT of all the primary prevention clinical trials including sub-group analyses are summarized in the Figure 6 in a flow chart representation.

Figure 6. Flow chart representation of 3-year mortality, RRR, ARR and NNT of all primary prevention trials including sub-groups.
3.7 Results: Secondary prevention clinical trials and their selection criteria

Three secondary prevention RCTs (AVID, CIDS, CASH) and one secondary prevention meta-analysis were included in the study for data analysis. Two of the secondary prevention (AVID and CIDS) RCTs and the secondary prevention meta-analysis also had published sub-group analysis available. Annual percentage survival data was available from the publication text in AVID and CIDS and in AVID-LVEF sub-study. The number of patients at risk was also identifiable in all 3 RCTs and meta-analysis and 2 sub-studies (AVID and meta-analysis). Trial data, including inclusion criteria and patient characteristics for secondary prevention are shown in Table 6.
Table 6. Inclusion criteria, patient characteristics and outcomes of secondary prevention ICD trials.

<table>
<thead>
<tr>
<th>Trial</th>
<th>AVID</th>
<th>CIDS</th>
<th>CASH</th>
<th>Meta-analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Inclusion criteria</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>VF; sustained VT with syncope; VT with LVEF ≤40% &amp; haemodynamic compromise</td>
<td>VF; sustained VT with syncope; VT with LVEF ≤35% &amp; haemodynamic compromise; unmonitored syncope with inducible VT at EPS</td>
<td>CA survivors</td>
<td>Criteria from all 3 trials</td>
</tr>
<tr>
<td>No. of pts</td>
<td>ICD</td>
<td>Med</td>
<td>ICD</td>
<td>Med</td>
</tr>
<tr>
<td>-----------</td>
<td>-----</td>
<td>-----</td>
<td>-----</td>
<td>-----</td>
</tr>
<tr>
<td></td>
<td>507</td>
<td>509</td>
<td>328</td>
<td>331</td>
</tr>
<tr>
<td>Age in yrs</td>
<td>65±11</td>
<td>65±10</td>
<td>63.3±9.2</td>
<td>63.8±9.9</td>
</tr>
<tr>
<td>LVEF (%)</td>
<td>32±13</td>
<td>31±13</td>
<td>34.3±14.5</td>
<td>33.3±14.1</td>
</tr>
<tr>
<td>VF or CA as index arrhythmia</td>
<td>44.6%</td>
<td>45%</td>
<td>45.1%</td>
<td>50.1%</td>
</tr>
<tr>
<td>IHD</td>
<td>81%</td>
<td>81%</td>
<td>82.9%</td>
<td>82.2%</td>
</tr>
<tr>
<td>Mean FU (months)</td>
<td>18±12.2</td>
<td></td>
<td>35</td>
<td></td>
</tr>
<tr>
<td>3 yr mortality in Med group</td>
<td>35.9%</td>
<td></td>
<td>27.3%</td>
<td></td>
</tr>
<tr>
<td>Outcome as reported</td>
<td>ARR - 8.2%</td>
<td></td>
<td>RRR: 19.7% (-7.7 - 40%)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>RRR - 39±20%, 27±21% &amp; 31±21% at 1, 2 &amp; 3 years</td>
<td>P = 0.142</td>
<td>P = 0.081</td>
<td></td>
</tr>
</tbody>
</table>
3.8 Results from secondary prevention trial analysis

The three secondary prevention trials contained a mix of patients with IHD and non-IHD as well as different presenting arrhythmias. The mortality benefit from ICD therapy (ARR) at 3 years ranged from 3.7% to 11.3% with the meta-analysis revealing an overall ARR of 8% (NNT 13). Results from published RCTs and the meta-analysis are summarised in Table 7.
Table 7. Mortality, risk reduction with ARR and NNT at 1, 2 and 3 year follow-up from secondary prevention trials.

<table>
<thead>
<tr>
<th>Trial</th>
<th>FU</th>
<th>Med (%)</th>
<th>ICD (%)</th>
<th>RRR (%)</th>
<th>ARR &amp; CI (%)</th>
<th>NNT</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Year 1</td>
<td>17.7</td>
<td>10.7</td>
<td>39.5</td>
<td>7±5.3</td>
<td>14</td>
</tr>
<tr>
<td>AVID</td>
<td>Year 2</td>
<td>25.3</td>
<td>18.4</td>
<td>27.3</td>
<td>6.9±8.8</td>
<td>14</td>
</tr>
<tr>
<td></td>
<td>Year 3</td>
<td>35.9</td>
<td>24.6</td>
<td>31.5</td>
<td>11.3±17.5</td>
<td>9</td>
</tr>
<tr>
<td></td>
<td>Year 1</td>
<td>15</td>
<td>8</td>
<td>46.7</td>
<td>7±7.8</td>
<td>14</td>
</tr>
<tr>
<td>CASH</td>
<td>Year 2</td>
<td>25</td>
<td>17</td>
<td>32</td>
<td>8±10.8</td>
<td>13</td>
</tr>
<tr>
<td></td>
<td>Year 3</td>
<td>39</td>
<td>31.3</td>
<td>19.7</td>
<td>7.7±14.2</td>
<td>13</td>
</tr>
<tr>
<td></td>
<td>Year 1</td>
<td>11.1</td>
<td>9.4</td>
<td>15.4</td>
<td>1.7±4.9</td>
<td>58</td>
</tr>
<tr>
<td>CIDS</td>
<td>Year 2</td>
<td>20.9</td>
<td>14.7</td>
<td>29.7</td>
<td>6.2±7.3</td>
<td>16</td>
</tr>
<tr>
<td></td>
<td>Year 3</td>
<td>27.3</td>
<td>23.3</td>
<td>13.7</td>
<td>3.7±9.3</td>
<td>27</td>
</tr>
<tr>
<td></td>
<td>Year 1</td>
<td>15</td>
<td>10</td>
<td>33.3</td>
<td>5±3.4</td>
<td>20</td>
</tr>
<tr>
<td>Meta-analysis</td>
<td>Year 2</td>
<td>24</td>
<td>16</td>
<td>33.3</td>
<td>8±5.2</td>
<td>13</td>
</tr>
<tr>
<td></td>
<td>Year 3</td>
<td>32</td>
<td>24</td>
<td>25</td>
<td>8±7.7</td>
<td>13</td>
</tr>
</tbody>
</table>

Med = Medical mortality; ICD = ICD mortality; FU = follow-up; CI = confidence interval
3.9 Results: Secondary prevention sub-group analysis

Analysis of LVEF sub category in the meta-analysis showed the greatest mortality benefit of ICD therapy at 3 years in those patients with LVEF ≤35% (ARR 11.3% and NNT 9) when compared to those with LVEF >35% (ARR 2.2% and NNT 45). In the CIDs trial, sub-group analysis was carried out on a group of ‘high risk’ patients. They were defined as patients having 2 or more of the risk factors: age >70 years, LVEF ≤35% and NYHA heart failure class III or IV symptoms. They had a significant reduction in mortality with ICD therapy with an ARR of 16.8% (NNT 6) at 3 years. The results of the sub-group analysis are summarized in Table 8.
Table 8. Secondary prevention trial sub-group analysis.

<table>
<thead>
<tr>
<th>Trial</th>
<th>FU</th>
<th>Med (%)</th>
<th>ICD (%)</th>
<th>ARR &amp; CI (%)</th>
<th>NNT</th>
<th>RRR (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>AVID LVEF &lt;20%</td>
<td>Year 1</td>
<td>27</td>
<td>17.6</td>
<td>9.4±17.8</td>
<td>11</td>
<td>34.8</td>
</tr>
<tr>
<td></td>
<td>Year 2</td>
<td>36.2</td>
<td>28.4</td>
<td>7.8±28.8</td>
<td>13</td>
<td>21.5</td>
</tr>
<tr>
<td></td>
<td>Year 3</td>
<td>No Data</td>
<td>No Data</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>AVID LVEF 20-34%</td>
<td>Year 1</td>
<td>20.2</td>
<td>10.8</td>
<td>9.4±8.3</td>
<td>11</td>
<td>46.5</td>
</tr>
<tr>
<td></td>
<td>Year 2</td>
<td>28.2</td>
<td>17.5</td>
<td>10.7±13.6</td>
<td>9</td>
<td>37.9</td>
</tr>
<tr>
<td></td>
<td>Year 3</td>
<td>No Data</td>
<td>No Data</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>AVID LVEF &gt;34%</td>
<td>Year 1</td>
<td>10.7</td>
<td>8.5</td>
<td>2.2±7.1</td>
<td>7</td>
<td>20.6</td>
</tr>
<tr>
<td></td>
<td>Year 2</td>
<td>17.3</td>
<td>16.6</td>
<td>0.7±12.4</td>
<td>143</td>
<td>4</td>
</tr>
<tr>
<td></td>
<td>Year 3</td>
<td>No Data</td>
<td>No Data</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Meta-analysis LVEF ≤35%</td>
<td>Year 1</td>
<td>18.8</td>
<td>11</td>
<td>7.8±4.7</td>
<td>13</td>
<td>41.5</td>
</tr>
<tr>
<td></td>
<td>Year 2</td>
<td>26</td>
<td>18.2</td>
<td>7.8±7.1</td>
<td>13</td>
<td>30</td>
</tr>
<tr>
<td></td>
<td>Year 3</td>
<td>39.2</td>
<td>27.8</td>
<td>11.4±10.8</td>
<td>9</td>
<td>29.1</td>
</tr>
<tr>
<td>Meta-analysis LVEF &gt;35%</td>
<td>Year 1</td>
<td>7</td>
<td>7</td>
<td>0</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Year 2</td>
<td>14</td>
<td>12.4</td>
<td>1.6±7.1</td>
<td>63</td>
<td>11.4</td>
</tr>
<tr>
<td></td>
<td>Year 3</td>
<td>19.6</td>
<td>17.4</td>
<td>2.2±10.4</td>
<td>45</td>
<td>11.2</td>
</tr>
<tr>
<td>CIDS high risk</td>
<td>Year 1</td>
<td>29.2</td>
<td>15.6</td>
<td>13.6</td>
<td>7</td>
<td>46.6</td>
</tr>
<tr>
<td></td>
<td>Year 2</td>
<td>47.2</td>
<td>27.6</td>
<td>19.6</td>
<td>5</td>
<td>41.5</td>
</tr>
<tr>
<td></td>
<td>Year 3</td>
<td>55.2</td>
<td>38.4</td>
<td>16.8</td>
<td>6</td>
<td>30.4</td>
</tr>
</tbody>
</table>

Med = Medical mortality; ICD = ICD mortality; FU = follow-up; CI = confidence interval; High risk = ≥2 risk factors (age >70 years, LVEF ≤35% and NYHA class III or IV).
3.9.1 Summary of 3-year ARR and NNT of all Secondary prevention trials

The results of the 3-year medical and ICD mortality, RRR, ARR and NNT of all the secondary prevention clinical trials including sub-group analyses are summarized in the Figure 7 in a flow chart representation.
Figure 7. Flow chart representation of 3-year mortality, RRR, ARR and NNT of all secondary prevention trials.
3.10 Results: Benefit of ICD therapy over time

ICD therapy is unique from other therapies (particularly drug therapy) in that the benefit may not be upfront. Salukhe et al.\textsuperscript{133} their life-years paper believe that the benefit seen at one year could be as low as \(\sim 1/9\)th of the benefit seen at 3 years. As previously shown, in ischaemic heart disease patients, benefit of ICD is seen with more remote MI and not in the immediate post MI period. Indeed there is a significant harm in implanting ICDs in the immediate post-MI period as shown by the DINAMIT trial and guidelines advice against this practice for at least 4 weeks post infarction. ICD therapy is also associated with immediate complications (usually procedure related at the time of implant) while the benefits may not be immediately measurable (applies to both primary and secondary prevention). The conventional way of comparing therapy vs. no therapy does not hold good with ICD and may even tilt the balance towards no therapy in primary prevention patients. We hypothesized that the benefit would improve over time and ICDs remain a highly effective therapy in both primary and secondary prevention.
3.10.1 Primary prevention ARR over time

In the primary prevention trials, the mortality benefit (ARR) increases with the length of follow-up. In negative trials (CAT and AMIOVERT), there was less harm with increasing follow-up (Figure 8).

Figure 8. Primary prevention ARR at 1, 2 and 3 years.
3.10.2 Secondary prevention ARR over time

Of the secondary prevention trials, only AVID trial showed a large increase in benefit between 2 and 3 years follow-up. As this is by far the largest trial, it heavily influences the outcome of secondary prevention meta-analysis and offsets the reduction of benefit in CIDS group seen with longer follow-up (see Figure 9).

Figure 9. Secondary Prevention ARR at 1, 2 and 3 years.
3.11 Results: Correlation with total mortality in medically treated patients

In primary prevention trials, there was a correlation between medical group total mortality and ARR in the ICD group but did not reach statistical significance (p=0.9). Patients with the highest mortality have the greatest benefit in ARR with an ICD. Sub-group analysis however revealed patient groups with very high total mortality and no benefit from ICD therapy. Comparison of mortality between medically treated and ICD groups at 3 years in both primary prevention trials (Figure 10) and secondary prevention trials (Figure 11) are shown below.
Figure 10. Comparison of medical mortality with ARR gained at 3 years in primary prevention trials.
Figure 11. Comparison of medical mortality with ARR gained at 3 years in secondary prevention trials.
3.12 Results: Number of patients at risk and confidence intervals

The number of ‘patients at risk’ used for ARR calculations at 3 years are displayed in Figure (12). Only 14% of MADIT2 and 10% of AVID patients were eligible for 3 year follow-up. The relatively short follow-up times in AVID heavily influenced the secondary prevention meta-analysis. Only CASH, MUSTT, SCD-HeFT and CAT trials had more than half of patients enrolled who were eligible for 3 year mortality assessment.

Figure 12. Number of patients at risk at 1, 2 and 3 years follow-up.
As a consequence, the relatively small patient numbers and magnitudes of ARR resulted in confidence intervals of 3 year ARR being greater than the ARR itself (other than for the secondary prevention meta-analysis, MADIT, MUSTT, the SCD-HeFT NYHA class II and MADIT2 ‘risk score of 2’ sub-groups). The results of the 3 year ARR and 95% Confidence Interval (CI) are presented in Figure 13.

Figure 13. 3 year ARR and 95% CI for primary and secondary prevention trials.

Circle represents primary prevention trials and square represents secondary prevention trials.
3.13 Summary and clinical implications

3.13.1 Data from Kaplan Meier curves

In our study we present 3 year data including ARR, NNT and RRR for all the published ICD RCTs and sub-studies that contribute to national and international guidelines (whether in their original format or as part of a meta-analysis), allowing comparison between primary and secondary prevention, aetiology of heart disease and other patient characteristics like NYHA status, LVEF, age, time from MI and risk scores. Where the 1, 2 and 3 year numerical data was not available in the manuscript, \(^{19-22,24,25,51}\) this was calculated from the published Kaplan-Meier curves. We report ARR and NNT from published trials comparing ICD to medical therapy and the findings are standardized for length of follow-up. There is considerable variation in the magnitude of benefit between different heart failure aetiologies (ischaemic cardiomyopathy and non-ischaemic DCM) and other patient characteristics. One of our principal findings is that patient groups with the highest mortality (e.g. those who meet MADIT or MUSTT trial entry criteria) have the most to gain from a primary prevention ICD with a small NNT signifying huge benefits in patients pre-selected based on their risk factors. Patients with DCM have a larger NNT and comparatively lesser benefit than patients with IHD. Within the SCD-HeFT trial, although the 3-year RRR was greater for DCM, the ARR was greater and the NNT smaller for those with IHD, offering ischaemic patients more “bang for their buck”. A comparison between primary and secondary prevention study data also shows that the ARR greater and NNT smaller in the majority of primary
prevention trials (MADIT, MUSTT and MADIT2) than the secondary prevention meta-analysis, a fact that may surprise many physicians and patients. This may be integral to a physician’s belief and is likely to directly influence which patients are referred for ICD implantation and in turn overall ICD implant rates in the United Kingdom.

3.13.2 Cost effectiveness

There is evidence to suggest ARR and NNT are the most informative and meaningful way of presenting statistical data and are required for cost-effective calculations. Cost-effectiveness, as measured by QALYs, is determined by the NNT to save one life in addition to the cost of the treatment over a lifetime. Relatively expensive treatments such as the ICD therefore need to be effective in a greater proportion of patients (a smaller NNT) than less expensive interventions; ideally in a patient group with high risk of SCD but an otherwise low mortality from other causes to maximise the benefits of an ICD over a long period of time. Primary prevention ICDs are more cost-effective than secondary prevention ICDs at 3 year follow-up, particularly for those patients fulfilling the MADIT and MUSTT criteria (NNT of 4 and 5 compared to NNT of 9 in AVID). Overall, both primary and secondary prevention ICD therapy are cost effective and has been successfully incorporated in both national (NICE) and international guidelines (ACC/AHA and ESC).
The relatively small number of patients who have had follow-up periods of 2 or more years results in wide confidence intervals and thus reduces the validity of risk reduction statistics over a longer time period, despite the fact that the ARR figures are larger. As the typical lifespan of an ICD is 5-7 years, follow-up data over longer time periods are required for cost-benefit analysis to account for the expensive “up-front” costs.\textsuperscript{136-138} This highlights the difficulty in formulating robust cost-effectiveness analysis. Some authors have proposed ‘life years saved’ as the most appropriate way to assess cost-effectiveness of ICD therapy and that the benefits from an ICD increase exponentially over time.\textsuperscript{133} In our study the use of 3-year risk reduction figures are therefore a compromise between the advantages of portraying meaningful data for patient consent and cost-effectiveness analysis, and the disadvantages of a relatively small number of patients included in long-term follow-up.

3.13.3 ARR and sub-studies

The wide ranges of ARR in the MADIT2 trial LVEF sub-group analysis and the ‘risk score’ data suggest that certain patient groups have much to gain whereas in others there may be no benefit at all. Caution must be exercised however when using sub-group data to influence decision making, particularly when not proposed in the original trial design.\textsuperscript{139} A typical example of this is the MADIT2 sub-study of black versus white ethnicity as it reveals an ARR at 3 years of 7% in white patients but increased mortality of 5% in black patients. However there were only 154 out of 1073 white patients and 10 out of 102 black patients who were followed up for this
length of time, resulting in very wide confidence intervals.\textsuperscript{47} Similarly, elderly patients (>75 years) appear to benefit more than younger patients but with a significant caveat that these patients are higher risk and have more than twice the younger group mortality. Patients with more remote MI (>18 months) appear to have twice the benefit seen in patients with less remote MI. Patients in NYHA class I heart failure seem to benefit less at 1 year (MADIT 2). Patients in NYHA class II seem to benefit the most in all trials while there was no benefit of NYHA class III patients at year 1 but significant benefit at year 2 and 3 (except SCD-HeFT). In the risk sub-study (MADIT 2), patients with no risk and ‘very high risk’ patients seem to have minimal or no overall benefits from ICD therapy while patients with 1-2 risk factors have the most to gain from an ICD.

3.13.4 Magnitude of benefit

Clinical guidelines are based on patient groups in whom statistically significant reduction in total mortality with the use of an ICD has been demonstrated in RCT or meta-analysis. A huge amount of importance is placed on statistically – significant reduction in total mortality which is heavily influenced by the number of patients enrolled and thus the power of the study to test a pre-specified value. Yet it may come as a huge surprise to many that none of the major RCTs involving DCM patients (SCD-HeFT – DCM, DEFINITE, CAT and AMIOVIRT) showed statistically significant reduction in all cause mortality ($p<0.05$) despite showing significant reduction in ARR and RRR. It is yet to be determined what magnitude of ARR is deemed to be clinically or ethically significant by patients, physicians and
healthcare providers, even though this will inevitably drive choice and decision making. The 5.6% ARR seen in the SCD-HeFT study may be regarded as small by some, yet meaningful and enough to act upon by most and has become incorporated in national guidelines to varying degrees.\textsuperscript{60;61} It has also been suggested that a NNT of 50 per year (which equates to 17 over a 3 year period) is “clinically significant” and only patients whose baseline risk of arrhythmic death is greater than 3% per year (9% over 3 years) will achieve this magnitude of benefit and justify the ICD implant.\textsuperscript{112} Only patients with IHD who satisfy MADIT, MADIT2 and MUSTT trial criteria and DEFINITE from non-ischaemic DCM meet this requirement in the setting of primary prevention, whereas those with criteria based on the AVID and CASH trials, satisfy it for secondary prevention.

The magnitude of benefit obtained in the primary prevention trials for high risk ICD patients i.e. MADIT (ARR 25%, RRR 59% and NNT 4 at 3 years) and MUSTT (ARR 19%, RRR 54% and NNT 5 at 3 years) is much higher than the less selective MADIT 2 trial (ARR 9%, RRR 29% and NNT 11 at 3 years). The magnitude of benefit widens further in the non-ischaemic DCM group with CAT and AMIOVIRT patients deriving no benefit and DEFINITE patients having an ARR 6%, RRR 32% and NNT 16 at 3 years. In the single trial consisting of both IHD and non-ischaemic DCM patients (SCD-HeFT), IHD patients derive more benefit (IHD - ARR 5.6%, RRR 20%, NNT 18 vs. ARR 4%, RRR 25%, NNT 25 in non-ischaemic DCM).
Similarly, in the secondary prevention trials the magnitude of benefit varies between the high risk group (cardiac arrest survivors, sustained VT with syncope or haemodynamic compromise and VT in association with impaired LV function) compared to the addition of less high risk group (unmonitored syncope with inducible VT at EPS) in the CIDS trial. Magnitude of benefit at 3 years in AVID and CIDS trial are - (ARR 11.3%, RRR 31.5%, NNT 9 vs. ARR 3.7%, RRR 13.7%, NNT 27).

3.13.5 Application to real world

One of the recurring themes from my study is that all primary and secondary patients do not derive the same benefit. There exists a difference in the magnitude of benefit between ischaemic heart disease patients and non-ischaemic DCM patients. However, there is little doubt that ICD therapy is effective in both primary (ischaemic and non-ischaemic DCM) and secondary prevention. There exists further difference in the magnitude of benefit derived among sub-groups and various risk factors but this has to be recognized with the limitations associated with sub-group analysis. The results of this study will be useful not only in appreciating the positive benefits of ICD therapy in much greater detail but also to understand the limitation (or lesser benefit) in some sub-groups. We believe this information can help aid an honest and frank discussion among physicians and patients when faced with real and complex issues.
The second recurring theme is the magnitude of benefit that increases over time. As we have shown benefit is less pronounced in year 1 compared to year 3 in general. Our results echo other studies mentioned earlier of the impact of time on the overall benefit especially in primary prevention patients. Primary prevention ICD therapy is unique among therapies in that the harms and cost is front loaded while benefits are felt in the longer term. It is generally believed that ICD therapy benefits are maintained up to 15 years post-implantation.

The data presented in this study is derived from published RCTs and I have made an attempt to unify the results obtained from different clinical trials under a single platform i.e. present data in ARR and NNT standardized for the length of follow-up. It is not possible to derive a single reference unit as the clinical trials are different with different entry criteria and characteristics, but with the information obtained from my study there is a much realistic hope to match the ‘real world’ patient to either one of these main studies or indeed match them to the sub-study accepting the limitations of such results. I hope physicians and indeed patients will be much clearer about the potential benefits expressed in ARR, RRR and NNT at different time points (i.e. 1, 2 and 3 years). This may help them make important decisions regarding providing and accepting ICD therapy.
There is concern in many quarters of medical profession that individuals enrolled in RCTs may not represent “real world” patients, who are often older and have more co-morbidities and may potentially benefit less from the ICD therapy.\textsuperscript{39} Reassuringly, registry data indicate that patients with IHD appear to derive the same amount of benefit in the real world as those enrolled in clinical trials.\textsuperscript{105} ARR should be the preferred statistic for use in informed consent and I hope the results of this study may help facilitate better communication between physicians, patients and healthcare providers, and individualize the risks and benefits according to the patient characteristics.
Chapter 4

Questionnaire Survey of Cardiologist’s knowledge, attitude to and guideline application of Implantable Cardioverter Defibrillators
4.1 Introduction

Primary prevention trials (MADIT, MUSTT, MADIT 2, SCD-HeFT) and secondary prevention trials (AVID, CIDS and CASH) have demonstrated statistically-significant mortality benefit from ICD in the prevention of SCD. This has been reflected in the clinical practice guidelines issued by the NICE in the United Kingdom (NICE Guidelines\textsuperscript{60}) and international organisations (ACC/AHA/ESC Guidelines\textsuperscript{61}). Despite clear guidelines, implantation rates remain low and vary significantly both between and within individual countries.\textsuperscript{140} Previous studies have tried to reason the causes for this variation and were not able to come up with clear answers. Differences in awareness of appropriate indications, availability of implanters and resources, financial constraints and physician attitudes and preference towards ICD implantation have all been proposed, yet they were not able to show any significant correlating factors in the UK.\textsuperscript{71,140}

4.2 Hypotheses and Aims of the study

No direct physician studies have been performed to understand the reasons for the low implant rate. We therefore designed a physician questionnaire and hypothesized that there is likely to be less awareness of guidelines and knowledge of benefits offered by ICD therapy as well as biases, misconceptions and skepticism about this valuable therapy. This knowledge about the knowledge of cardiologists is vital to remove the barriers for ICD implantation.
This study was designed to assess a national sample of UK cardiologists’ knowledge of ICD guidelines, attitudes towards device therapy and management preferences in both primary and secondary prevention settings.

### 4.3 Methodology: Design of Questionnaire and rationale

The survey included both Consultant and trainee electrophysiologists. The questionnaire was predominately sent electronically with only a handful of responders requesting paper copies. No incentive was offered to do the survey and response to the questionnaire was completely voluntary. We requested the responders to refrain from referring to the guidelines and give their best educated guess if they were not sure. Physician surveys have a typically low response rate,\textsuperscript{141-143} and therefore we targeted the national audience through the global email system of the British Cardiovascular Society, Heart Rhythm UK and the Arrhythmia Alliance in addition to sending the questionnaire locally throughout the region. This was a detailed questionnaire (see Appendix - Questionnaire, page No. 191) and recorded responder details including age; trainee or consultant; clinical role (ICD implanter or non-implanter) and whether they worked in an implanting or non-implanting institution; together with current practice (screening programs and implant rates).
Questions were then sub-divided into the following categories:

- Knowledge of current UK NICE guidelines (as published in 2006) and international guidelines;
- estimates of three-year mortality rates in medically-treated and ICD-treated patients from published RCTs;
- management decisions based on clinical vignettes describing patients with the typical inclusion criteria of published trials;
- the minimum magnitude of ARR the responder felt was required to justify ICD implant in different case scenarios;
- factors that influence decisions to provide for ICD therapy;
- specific questions on patient’s age and device cost;
- Overall attitude to ICD as a form of therapy.

Prior to distribution, the questionnaire was trialed by 5 in-house cardiologists (2 trainees and 3 consultants) to assess clarity and understanding.

Complete understanding of UK guidelines was defined as correctly recalling the two primary prevention categories and three secondary prevention categories publicized in the NICE Guidelines for primary and secondary prevention ICD implantation. Responses had to include the correct LV ejection fraction, haemodynamic compromise and cardiac arrest criteria for secondary prevention in the absence of a reversible cause and the correct LV ejection fraction, etiology of heart disease, role of Holter monitoring, ventricular programmed stimulation and QRS duration for primary prevention. UK guidelines do not address primary
prevention in non ischaemic cardiomyopathy. Knowledge of ICD indications in familial cardiomyopathies and congenital heart disease was not assessed.

All variables are expressed as mean ± standard deviation (SD). Comparison between groups were performed with either an unpaired Student’s t-test or where a normal distribution could not be assumed, the Mann-Whitney U-test. Categorical variables expressed as numbers and percentages were compared with chi-square test. A p value <0.05 was considered statistically significant.

4.4 Results from the Questionnaire survey

4.4.1 Demographics
A total of 60 completed questionnaires were received (17% response rate). There were 23 implanter and 37 non-implanter. Of them 42 were consultants and 18 trainees. 80% of the responders said they worked in an implanting institution. Only 4 responders (7%) had a screening program for potential primary prevention patients, 3 of whom worked in implanting institutions. Responder details are summarized in Table 9.
Table 9. Details of questionnaire responders.

<table>
<thead>
<tr>
<th></th>
<th>All responders</th>
<th>Implanters</th>
<th>Non-implanters</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of responders</td>
<td>60</td>
<td>23 (38%)</td>
<td>37 (62%)</td>
</tr>
<tr>
<td>Consultant grade</td>
<td>42 (70%)</td>
<td>19 (83%)</td>
<td>23 (62%)</td>
</tr>
<tr>
<td>Trainee</td>
<td>18 (30%)</td>
<td>4 (17%)</td>
<td>14 (38%)</td>
</tr>
<tr>
<td>Working in implanting centre</td>
<td>48 (80%)</td>
<td>22 (96%)</td>
<td>26 (70%)</td>
</tr>
<tr>
<td>Age 30-39 years</td>
<td>29 (48%)</td>
<td>12 (52%)</td>
<td>17 (46%)</td>
</tr>
<tr>
<td>Age 40-49 years</td>
<td>23 (38%)</td>
<td>9 (39%)</td>
<td>14 (38%)</td>
</tr>
<tr>
<td>Age 50-59 years</td>
<td>6 (10%)</td>
<td>2 (9%)</td>
<td>4 (11%)</td>
</tr>
<tr>
<td>Age 60+ years</td>
<td>2 (3%)</td>
<td>0</td>
<td>2 (5%)</td>
</tr>
</tbody>
</table>

4.4.2 Awareness of guidelines

Complete awareness of primary and secondary prevention indications were present in 27/60 responses (45%). Responders were more familiar with secondary prevention guidelines in comparison to primary prevention (81% vs. 65%). Implanters had a greater awareness of primary and secondary prevention guidelines when compared to non-implanters (19/23 (83%) vs. 16/37 (43%) for primary prevention, p<0.001 and 18/23 (78%) vs. 16/37 (43%) for secondary prevention, p<0.005 respectively). The greatest knowledge gap was in the understanding of the MADIT criteria (IHD, LVEF≤35%, NSVT and a positive EPS).
There was no significant knowledge difference among Consultants and trainees.

Findings are summarized in Figure 14.

Figure 14. Awareness of NICE (UK) Guidelines.
4.4.3 Three-year mortality estimates for medically-treated and ICD recipients

Scenario 1: Mean estimates of 3-year survival in a typical MADIT2 patient were 65 +/- 15% (range 20-97%) for medically-treated patients vs. 75 +/- 14% (range 30-90%) for ICD recipients. The 3-year ARR was estimated to be 10.5 +/- 7% (range 0-35%). Implanters estimated greater survival in both the medically-treated and ICD-treated patients than non-implanters, but there was no significant difference in the estimated 3-year ARR (9% for implanters vs. 11% for non-implanters, p = 0.34). 23/60 (38%) of ARR estimates were within 2% either side of the trial result (Figure 15).
Figure 15. Estimates of 3 year survival in a typical MADIT 2 patient.

Patients receiving medical treatment are in blue bars and ICD in red bars. The difference in each responder’s black and red bar represents their estimate of 3-year ARR. The actual trial results are superimposed as horizontal lines. Rx = treatment.
Scenario 2: Mean estimates of 3-year survival in a typical SCD-HeFT patient with IHD were 69±17% (range 20-95%) for medically-treated vs. 75±15.5% (range 25-96%) for ICD recipients. The 3-year ARR was estimated to be 5±7% (range 0-40%). Implanters estimated greater survival in both the medically-treated and ICD-treated patients than non-implanters, but there was no difference in the estimated 3-year ARR (4% for implanters vs. 6% for non-implanters, p = 0.24). 19/60 (32%) of ARR estimates were within 2% either side of the trial result.

Scenario 3: Mean estimates of 3-year survival in a typical SCD-HeFT patient with non ischaemic DCM were 70±16% (range 20-97%) for medically-treated vs. 77.5±15% (range 20-98%) for ICD recipients. The 3-year ARR was estimated to be 7±6% (range 0-25%). Implanters estimated greater survival in both the medically-treated and ICD-treated patients than non-implanters, but there was no difference in the estimated 3-year ARR (5% for implanters vs. 7% for non-implanters, p = 0.17). 26/60 (43%) of ARR estimates were within 2% either side of the trial result.

Scenario 4: Mean estimates of 3-year survival in a typical AVID patient with ischaemic cardiomyopathy and haemodynamically-compromising VT were 51±22% (range 5-85%) for medically-treated vs. 70.5±17% (range 25-95%) for ICD recipients. The 3-year ARR was estimated to be 19±13% (range 4-60%). Implanters estimated greater survival in both the medically-treated and ICD-treated patients than non-implanters. Implanters estimated a significantly lower 3-year
ARR than non-implanters (15% for implanters vs. 22% for non-implanters, p < 0.05). 20/60 (33%) of ARR estimates were within 2% either side of the trial result.

Scenario 5: Mean estimates of 3-year survival in an AVID,\textsuperscript{17} CIDS\textsuperscript{20} or CASH\textsuperscript{23} trial patient with DCM resuscitated from a VF arrest were 58±20% (range 5-95%) for medically-treated vs. 74±16% (range 20-97%) for ICD recipients. The ARR was estimated to be 16.5±12% (range 0-60%). Implanters estimated greater survival in the medically-treated group patients than non-implanters, however difference in estimated 3-year ARR did not reach statistical significance (13% for implanters vs. 19% for non-implanters, p = 0.07). 18/60 (30%) of ARR estimates were within 2% either side of the secondary prevention meta-analysis result.

The findings of the estimates of the estimated 3 year survival in ICD and medical therapy groups for Scenarios 4 and 5 falling within the remit of the secondary prevention trials are plotted as a bar diagram and the results of the meta-analysis represented as horizontal bars for reference and shown in Figure 16.

Figure 16. Estimates of 3-year survival in a typical secondary prevention patient.

Patients receiving medical treatment are in blue bars and ICD in red bars. The difference in each responder’s black and red bar represents their estimate of 3-year ARR. The results from the meta-analysis of secondary prevention trials are superimposed as horizontal lines. Rx = treatment.
Table 10 summarizes the ARR estimated by responders and the actual figures derived from the trial results. The mean estimate was similar to the actual ARR for primary prevention trials (with non-implanters slightly overestimating the benefits of an ICD). The mean estimate of ARR for secondary prevention patients was much greater than that demonstrated in the trials, particularly from non-implanters.

Table 10. Estimated vs. actual ARR from published trials

<table>
<thead>
<tr>
<th>Scenario</th>
<th>Trial</th>
<th>3-year ARR</th>
<th>Estimate of ARR (mean +/- SD)</th>
<th>Imp estimate of ARR (mean)</th>
<th>Non-imp estimate of ARR (mean)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>MADIT2</td>
<td>9%</td>
<td>10.5±7.3%</td>
<td>9.3%</td>
<td>11.2%</td>
</tr>
<tr>
<td>2</td>
<td>SCD-HeFT (IHD)</td>
<td>5.6%</td>
<td>5.4±6.9%</td>
<td>4.0%</td>
<td>6.2%</td>
</tr>
<tr>
<td>3</td>
<td>SCD-HeFT (DCM)</td>
<td>4%</td>
<td>6.6±6.4%</td>
<td>5.0%</td>
<td>7.4%</td>
</tr>
<tr>
<td>4</td>
<td>AVID</td>
<td>11.3%</td>
<td>19.4±13.2%</td>
<td>14.7%</td>
<td>22.2%</td>
</tr>
<tr>
<td>5</td>
<td>SP meta-analysis</td>
<td>8%</td>
<td>16.5±11.7%</td>
<td>12.8%</td>
<td>18.6%</td>
</tr>
</tbody>
</table>

Imp = implanters; Non-imp = non-implanters; SP = secondary prevention.
4.4.4 Minimum ARR justifying an ICD implant

The mean 3-year ARR justifying an ICD implant in four different case scenarios are shown in Table 11. Whether the responder was an implanter or non-implanter or whether the cardiologist was younger or older than 40 years of age did not affect the result. All responders required a significantly higher ARR for an 80 year old female than a 56 year old male, irrespective of primary prevention (21% vs. 9%, p<0.0000001) or secondary prevention (18% vs. 9%, p<0.0005) indication.

Table 11. Estimate of minimum 3-year ARR justifying an ICD implant.

<table>
<thead>
<tr>
<th>Scenario</th>
<th>Estimated minimum ARR (mean+/SD)</th>
<th>Actual ARR from published trial data</th>
</tr>
</thead>
<tbody>
<tr>
<td>56 year old male with MADIT2 criteria</td>
<td>9.4±8.0%</td>
<td>9%</td>
</tr>
<tr>
<td>80 year old female with MADIT2 criteria</td>
<td>21.4±18.1%</td>
<td>9% (13% in ≥75 yrs)*</td>
</tr>
<tr>
<td>56 year old male with IHD and VF arrest</td>
<td>8.8±8.0%</td>
<td>8%</td>
</tr>
<tr>
<td>80 year old female with IHD and compromising VT</td>
<td>17.8±16.1%</td>
<td>4-11.3% (8%**)</td>
</tr>
</tbody>
</table>

* indicates MADIT 2 sub-study; ** indicates secondary prevention meta-analysis.
This can be further broken down into implanters’ and non-implanters’ expectation compared to the trial data and is represented in Figure 17.

Figure 17. Expected minimum 3-year ARR to justify an ICD.

![Expected ARR over 3 yrs to justify an ICD implant](image)

SP = secondary prevention; yr = year; Imp = Implanters; Non-Imp = Non-Implanters
4.4.5 Management decisions based on clinical vignettes

**Clinical vignette 1:** for a patient with IHD, LVEF 33% and NSVT on Holter monitoring, 16/23 (70%) implanters vs. 13/37 (35%) non-implanters would recommend a VT stimulation study (EPS); 4/23 (17%) implanters vs. 10/37 (27%) non-implanters would recommend an ICD; 2/37 (5%) non-implanters would prescribe Amiodarone and the remainder would take no action. UK NICE guidelines recommend EPS in this setting to assess eligibility for an ICD in accordance with the MADIT trial. Knowledge of this guideline was associated with correct management decision among responders (p = 0.0007).

**Clinical vignette 2:** for a patient with IHD, LVEF <30% and a narrow QRS, 16/23 (70%) implanters vs. 10/37 (27%) non-implanters would perform Holter monitoring; 2/23 (9%) implanters vs. 4/37 (11%) non-implanters would recommend an ICD and the remainder would take no further action. UK NICE guidelines require a QRS of ≥120ms before MADIT2 patients are eligible for an ICD. If screening with Holter monitoring reveals NSVT, the patient may then be assessed with an EPS in accordance with the MADIT criteria. Knowledge of this guideline was associated with correct management decision among responders (p = 0.0336).
Clinical vignette 3: for a patient with IHD, NYHA class 1-2, LVEF <30% and a broad QRS, 18/23 (78%) implanters vs. 11/37 (30%) non-implanters would recommend an ICD; 2/23 (9%) implanters vs. 9/37 (24%) non-implanters would perform a Holter monitor; 3/37 (8%) non-implanters would prescribe amiodarone and the remainder would take no further action. NICE guidelines recommend an ICD in this situation. Knowledge of this guideline was associated with correct management decision among responders (p = 0.001).

Clinical vignette 4: for a patient with non ischaemic DCM, NYHA class 2 and LVEF ≤35%, 13/23 (57%) implanters vs. 18/37 (49%) non-implanters would take no further action; 4/23 (17%) implanters vs. 12/37 (32%) non-implanters would perform Holter monitoring; 1 (4%) implanters and 1 (3%) non-implanter would recommend an ICD and the remainder would take no further action. UK NICE guidelines do not address primary prevention ICD for non ischaemic DCM. International guidelines recommend an ICD in this situation.

Clinical vignette 5: for a 60 year old patient with previous MI and LVEF 45% who survived an out of hospital (OOH) cardiac arrest with no reversible cause, every responder would recommend an ICD.
Clinical vignette 6: for a 81 year old patient with previous IHD and LVEF 35% who survives an OOH VF arrest, 20/23 (87%) implanters vs. 20/37 (54%) of non-implanters would recommend an ICD. NICE guidelines recommend ICD in this situation. Also, the guidelines do not specify an upper age limit but require a reasonable quality of life with a life expectancy of at least 12 months.

Clinical vignette 7: for a 75 year old patient of non ischaemic DCM and LVEF 25% with sustained VT which was not severely compromising, 19/23 (83%) implanters vs. 30/37 (81%) non-implanters would recommend an ICD and 1/23 (4%) implanters vs. 5/37 (14%) non-implanters would prescribe Amiodarone. UK guidelines recommend an ICD in this situation.

Clinical vignette 8: for a 67 year old patient with IHD and LVEF of 29% who had sustained VT which was compromising, 23/23 (100%) implanters vs. 33/37 (89%) non-implanters would recommend an ICD. UK guidelines recommend an ICD in this situation.

Clinical vignette 9: for a 64 year old patient with remote MI and LVEF of 50% who had well-tolerated, sustained VT, 4/23 (17%) implanters vs. 13/37 (35%) non-implanters would prescribe Amiodarone; 3/23 (13%) implanters vs. 5/37 (14%) non-implanters would recommend an ICD and the remainder would continue standard drug therapy including beta blockers. UK guidelines do not recommend
an ICD in this situation with LVEF >35% and the VT not haemodynamically compromising.

4.4.6 Relationship between knowledge of guidelines and correct management decision.

The proportion of correct decisions in secondary prevention vignettes was higher than in primary prevention vignettes. When comparing the management decision to the knowledge of the specific part of NICE guidelines relevant to the clinical vignette, there was a correlation between guideline knowledge and correct decision for primary prevention indications, but not for secondary prevention indications.

Table 12 summarizes the decision making in clinical vignettes and also the relationship between knowledge of guidelines and the subsequent correct management of the patient.
Table 12. Guideline knowledge and management decision in clinical vignettes.

<table>
<thead>
<tr>
<th>Vignette Number</th>
<th>Awareness of NG &amp; correct MD</th>
<th>Awareness of NG &amp; incorrect MD</th>
<th>Not aware of NG &amp; correct MD</th>
<th>Not aware of NG &amp; incorrect MD</th>
<th>Association between NG awareness &amp; correct MD</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 (PP)</td>
<td>23/60 (38%)</td>
<td>11/60 (18%)</td>
<td>6/60 (10%)</td>
<td>21/60 (35%)</td>
<td>p = 0.0007</td>
</tr>
<tr>
<td>2 (PP)</td>
<td>20/60 (33%)</td>
<td>16/60 (27%)</td>
<td>6/60 (10%)</td>
<td>17/60 (28%)</td>
<td>p = 0.0336</td>
</tr>
<tr>
<td>3 (PP)</td>
<td>27/60 (45%)</td>
<td>17/60 (28%)</td>
<td>2/60 (3%)</td>
<td>14/60 (23%)</td>
<td>p = 0.0010</td>
</tr>
<tr>
<td>4 (PP)</td>
<td>Not addressed by UK NICE guidelines</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>5 (SP)</td>
<td>58/60 (97%)</td>
<td>0</td>
<td>2/60 (3%)</td>
<td>0</td>
<td>p = 1.000</td>
</tr>
<tr>
<td>6 (SP)</td>
<td>39/60 (65%)</td>
<td>16/60 (27%)</td>
<td>1/60 (2%)</td>
<td>1/60 (2%)</td>
<td>p = 0.5113</td>
</tr>
<tr>
<td>7 (SP)</td>
<td>38/60 (63%)</td>
<td>6/60 (10%)</td>
<td>11/60 (18%)</td>
<td>4/60 (7%)</td>
<td>p = 0.257</td>
</tr>
<tr>
<td>8 (SP)</td>
<td>44/60 (73%)</td>
<td>0</td>
<td>12/60 (20%)</td>
<td>1/60 (2%)</td>
<td>p = 0.2281</td>
</tr>
<tr>
<td>9 (SP)</td>
<td>40/60 (67%)</td>
<td>4/60 (7%)</td>
<td>11/60 (18%)</td>
<td>4/60 (7%)</td>
<td>p = 0.1837</td>
</tr>
</tbody>
</table>
PP = primary prevention; SP = secondary prevention; NG = NICE (UK) guidelines; MD = management decision.

4.4.7 Factors that influence physicians’ ICD recommendations

When ranking factors that could potentially influence whether or not an ICD was recommended, the median responder score was 5/5 (very important) for patient wishes, in accordance with UK NICE guidelines and in accordance with published RCT data. The physician’s belief that the ICD offered a prognostic benefit scored 4/5 (important). The patient’s age and potential complications scored 3/5 (a moderate influence). The financial costs and potential medico-legal issues scored 2/5 (minor importance).

4.4.8 Influence of age on ICD prescription

When asked specific questions regarding patient age, 13/23 (57%) implanters vs. 18/37 (50%) non-implanters said that they had no age limit for primary prevention ICD i.e. nearly half of the responders believed that there should be an age cut-off or in other words these responders would not provide ICD therapy to elderly patients (no universal definition) even if they satisfied all the other criteria for ICD therapy. Of those that did, the median age limit was 80 years. For secondary prevention, 19/23 (93%) implanters vs. 13/36 (36%) non-implanters had no age limit. Of those that did, the median age limit was 85 years. Age was an independent and statistically significant variable influencing ICD prescription
among both implanter and non-implanter. When asked specifically regarding provision of ICD therapy for a 80 year old patient compared to a 56 year old patient, age was a significant consideration among both implanter (p=0.0062) and non-implanter (p=0.0008).

The chances of getting a secondary prevention ICD for a 81 year old cardiac arrest survivor halves (56%) on seeing a non-implanter compared to a 90% chance of being offered one if seen by an implanter (p=0.34). The magnitude of estimated ARR to justify both primary and secondary prevention ICD in a 80 year patient is more than twice compared to a 56 year old patient (p=0.0003). This is shown in Table 13.

Table 13. Estimate of ARR over 3 years to justify primary and secondary prevention ICD based on age.

<table>
<thead>
<tr>
<th>ARR over 3 yrs to justify an ICD</th>
<th>Imp</th>
<th>Non-Imp</th>
<th>RCT data</th>
</tr>
</thead>
<tbody>
<tr>
<td>MADIT 2 56 yr male</td>
<td>8.09±6.21%</td>
<td>10.16±8.81%</td>
<td>9±11.9%</td>
</tr>
<tr>
<td>MADIT 2 80 yr female</td>
<td>20±16.14%</td>
<td>23.55±18.97%</td>
<td>9±11.9%</td>
</tr>
<tr>
<td>SP ICD 56 yr male</td>
<td>7.4±4.96%</td>
<td>9.58±9.32%</td>
<td>8±7.7%</td>
</tr>
<tr>
<td>SP ICD 80 year female</td>
<td>15.5±15.31%</td>
<td>19.79±16.6%</td>
<td>8±7.7%</td>
</tr>
</tbody>
</table>

SP = secondary prevention; Imp = implanter; Non-Imp = non-implanter
Responder’s estimate of ICD related complications

ICD therapy is not risk free and is often front loaded with complications, mainly procedure related. In addition, one can expect hardware issues and inappropriate shocks; and not to forget the psychological issues which can be significant in a small proportion of patients. This has already been alluded to in the introduction chapter. Responders’ estimates of complication rates are compared to published literature and summarized in Table 14.

Table 14. Responders’ estimate of complication rates during lifetime of an ICD.

<table>
<thead>
<tr>
<th>Complication</th>
<th>All responders median (range)</th>
<th>Imp median (range)</th>
<th>Non-Imp median (range)</th>
<th>Trial / Registry data</th>
</tr>
</thead>
<tbody>
<tr>
<td>Inappropriate shocks</td>
<td>13.5% (0-50)</td>
<td>15% (3-50)</td>
<td>10% (0-30)</td>
<td>12 -25% (^75)</td>
</tr>
<tr>
<td>Hardware failure</td>
<td>5% (0.5-30)</td>
<td>5% (0.5-15)</td>
<td>5% (1-25)</td>
<td>1.4 -7% (^73)</td>
</tr>
<tr>
<td>Infection</td>
<td>2% (0.5-10)</td>
<td>2% (1-5)</td>
<td>3% (0.5-10)</td>
<td>1% (^75)</td>
</tr>
<tr>
<td>Psychological harm</td>
<td>17.5% (1-100)</td>
<td>10% (2-100)</td>
<td>20% (1-100)</td>
<td>13 -38% (^145)</td>
</tr>
</tbody>
</table>

Imp = implanters; Non-imp = Non-implanters.
4.4.10 Overall opinion on ICD therapy

Responders overall opinion on ICD therapy is summarized in Table 15. All responders felt that ICDs were underutilized. Secondary prevention ICDs were believed to be much more cost-effective than primary prevention ICD. There was no significant difference in implanters and non-implanters’ opinion.

Table 15. Responders’ overall opinion on ICDs.

<table>
<thead>
<tr>
<th>Opinion</th>
<th>All responders median (range)</th>
<th>Imp median (range)</th>
<th>Non-Imp median (range)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pts who satisfy UK PP guidelines should be offered an ICD</td>
<td>5 (2-5)</td>
<td>4 (2-5)</td>
<td>5 (3-5)</td>
</tr>
<tr>
<td>Pts who are outside of UK PP guidelines but satisfy published RCT criteria and international guidelines should be offered an ICD</td>
<td>4 (1-5)</td>
<td>4 (2-5)</td>
<td>4 (1-5)</td>
</tr>
<tr>
<td>Pts who satisfy UK SP guidelines should undergo ICD implant</td>
<td>5 (4-5)</td>
<td>5 (4-5)</td>
<td>5 (4-5)</td>
</tr>
<tr>
<td>PP ICDs are cost-effective</td>
<td>4 (1-5)</td>
<td>3 (2-5)</td>
<td>4 (1-5)</td>
</tr>
<tr>
<td>SP ICDs are cost-effective</td>
<td>4 (2-5)</td>
<td>4 (3-5)</td>
<td>5 (2-5)</td>
</tr>
<tr>
<td>ICDs are underutilised in the UK</td>
<td>5 (1-5)</td>
<td>4.5 (3-5)</td>
<td>5 (1-5)</td>
</tr>
</tbody>
</table>
PP = primary prevention; SP = secondary prevention; Imp = Implanters; non-imp = Non-implanters; scale of 1-5 with 1 being strongly disagree and 5 being strongly agree; Pts = patients.

4.5 Limitations of the study

Selection bias amongst responders may have resulted in a sample that does not accurately reflect UK cardiology practice. It is possible that those who chose to respond have a greater interest in the treatment of SCD and may have been more guideline-aware and in favour of device therapy. Responders may have disobeyed instructions and taken time to look up guidelines before completing questions, leading to an overestimate of awareness. The low incidence of complete guideline awareness makes this unlikely.

The questions asked in this questionnaire mostly reflect the everyday patients we all see in our clinical practice and may potentially differ from the clinical trial patients as they have a much stricter inclusion and exclusion criteria. The responses were compared against the clinical trial findings and it is possible that the real world patients are a much higher risk cohort and may derive less benefit from ICD compared to the trial patients. However, registry data have shown similar benefit to clinical trials with ‘real world’ patients.105
Clinical vignettes were used to assess attitude and responses in relation to national guidelines. Although this method has been well validated, the response to a written scenario and the approach taken when confronted with an individual patient in the real world may not always be the same.

4.6 Summary and clinical implications

My survey looks at the knowledge, attitudes and application of risk to SCD and the impact of ICD on SCD. This study is the first detailed survey to assess the knowledge of implanting and non-implanting cardiologists, and application of ICD guidelines and their attitude to the use of ICD for the prevention of SCD. The key findings are a lack of complete awareness of current guidelines, particularly for primary prevention, and a failure of non-implanters to follow guidelines that is linked to poor knowledge. Overall, responders accurately assessed the survival benefit in primary prevention patients but overestimated the benefits to secondary prevention patients. There was however a wide range of perceived 3-year ARR with only a minority having estimates within 2% either side of published trial data. There was significant impact of patient’s age on decision making to refer for an ICD implant and magnitude of benefit to justify implantation, particularly amongst non-implanters.
4.6.1 Knowledge of guidelines

UK NICE ICD guidelines were published in 2006 and unlike North American and European guidelines, they address only primary prevention ICD in IHD and restrict the application of MADIT2 criteria to patients who have a wide QRS duration $\geq 120$ms. As would be expected, implanting cardiologists had a greater awareness of guidelines than non-implanting cardiologists, however even implanters sometime have incorrect recall. Non-implanters had poor knowledge of primary prevention guidelines, particularly when dealing with a higher degree of complexity such as those required for the original MADIT trial. The majority of UK cardiologists do not implant defibrillators but they are a key stage in the identification of potentially eligible patients and initiate the referral process. Thus a lack of guideline knowledge may be a critical barrier to ICD provision. Similar findings are echoed by a New Zealand questionnaire survey from rural and urban physicians which found rural physicians were less aware of local and international guidelines and identified fewer indications for ICD implantation.\textsuperscript{148} Although use of complex criteria identifies patients at highest risk and the most to gain (MADIT patients have the smallest NNT to save a life of any ICD trial), such criteria are only applicable to a small proportion of potential ICD recipients and are not easily recalled by cardiologists.

In primary prevention case scenarios, the majority (57-78\%) of implanters’ management decisions were in accordance with UK guidelines and recommendations; however this is lower than might be expected. The technical
ability to implant a device does not necessarily mean there is also full awareness of guidelines and a guarantee of their correct application. Only a minority (27-49%) of non-implanters took the correct course of action in primary prevention scenarios, but the knowledge of guidelines were associated with the correct management decision. In secondary prevention case scenarios, guideline knowledge and appropriate management was significantly better. Even when guideline knowledge was not correctly recalled, most physicians would still appropriately refer the patient for an ICD. In secondary prevention there is a simple choice (ICD or no ICD), with no requirement for the correct etiology of heart disease, QRS duration measurement, Holter monitoring or invasive EPS. The greater adherence to secondary prevention guidelines in the case scenarios may reflect the dramatic and highly-emotive nature of the presentation of failed cardiac arrest.

4.6.2 Prescribing national guidelines for physicians

The reasons why physicians don’t follow guidelines are complex.\textsuperscript{149} As our study shows, lack of awareness, although significant, is not the only factor. Guideline knowledge does not necessarily mean that the guideline-recommended management action was followed, particularly in primary prevention where 27-28% of responders who were aware of guidelines chose an approach that was not the guideline-recommended option. Although previous studies indicate physicians believe prescriptive guidelines can improve the quality of patient care, there remains fear that they are externally imposed and are a tool for containing costs.\textsuperscript{150,151} There may also be concerns that results from research trials cannot be
applied to individuals, particularly those with co-morbidities. Although guidelines are essentially consensus documents they are based on evidence obtained from RCTs. There will occasionally be scenarios where clinical opinion would recommend an ICD even though the patient is outside of the guideline recommendations, particularly in high-risk patient groups who have not been studied in RCTs. Healthcare purchasers use published guidelines for reimbursement purposes. Failure to discuss the role of ICD implant to patients who fall within guidelines may also expose clinicians to the risk of medical litigation. Thus, even if guidelines may not be universally accepted by all clinicians, there is a need to recognise their role and justify why they are not being adhered to when that is the case.

UK cardiologists appear to believe secondary prevention ICD offers greater risk reduction than primary prevention therapy. Published data varies significantly between trials; however the highest risk primary prevention patients (e.g. MADIT and MUSTT criteria) have a greater 3-year ARR than secondary prevention patients from AVID. This belief may go some way to explain why the majority of ICD implants in the UK are for secondary prevention, even though the number of eligible primary prevention patients is much greater. In the survey of New Zealand physicians and cardiologists, one third felt that real life benefits from an ICD were greater than that demonstrated in the AVID trial, whereas 19% felt that real life benefits in primary prevention were greater than published trials and 9% felt they were less.
### 4.6.3 Age impact and bias

In case scenarios with the patient’s age in their sixties, the minimum ARR over 3 years that cardiologists felt justified an ICD implant was comparable to the benefit achieved in published trials. Cardiologists demanded a much greater ARR to justify ICD implantation in an 80 year old patient, more than what was demonstrated in trials and more than they estimated was achievable. A significant proportion of responders in this survey would not offer an ICD to an octogenarian. The mean age of patients included in published trials is early sixties which is not dissimilar to the “real world” registries where the mean age is their late sixties. In the MADIT2 trial, the ARR achieved in patients over the age of 75 was greater than that achieved in the under-75s, although the total mortality was higher in the elderly. This bias against ICD use in old age appears to be consistent between countries and regions and is unlikely to be the reason for variation in implant rate although certainly a cause for low implant rate.

### 4.6.4 Impact of various factors on ICD provision

Cardiologists included in this survey felt very strongly that the guidelines should dictate clinical practice and that ICD therapy was underutilised. They indicated that costs did not influence their clinical decision making. A potential solution to greater appropriate utilisation of ICD may appear to be better education, particularly of non-implanters. However, in the treatment of hypertension, it has been reported that both education and incentives fail to increase adherence to guidelines and the only solution is to remove barriers and reduce the effort required to deliver
An automated, computerized screening service to identify and refer patients could facilitate this step as we have shown that only 7% of responders had such a screening program. In this regard, a screening algorithm may help to overcome some of the challenges of recalling complex primary prevention selection criteria although it would not overcome age bias and individual clinicians’ unwillingness to follow guidelines. Another reason as to why there is a lower primary prevention ICD implantation rates in the UK compared to USA or Europe is the requirement of an ischaemic aetiology for primary prevention. UK guidelines restrict the use of primary prevention ICD to ischaemic cardiomyopathy with MADIT and MADIT 2 wide QRS criteria. The role of primary prevention ICD in non-ischaemic cardiomyopathy is at the discretion of individual clinicians and locally-negotiated agreements with purchasers (General Practitioners and or Clinical Commissioning Groups) and may be more prevalent when combined with cardiac resynchronization pacing.

Our study found lack of awareness of UK NICE guidelines amongst non-implanting cardiologists. Even when guidelines are known they are often not applied, particularly in the primary prevention setting. Most cardiologists are not aware of the magnitude of benefit an ICD offers and overestimate the effect in secondary prevention. Also, there is a bias against elderly patients. Cardiologists do not indicate that the device costs and fear of potential complications influence their decision making.
Chapter 5

An Insight into Implanters’ practices

on

Implantable Cardioverter Defibrillator implantation
5.1 Introduction

ICD is the single most effective therapy in the prevention of SCD and the management of ventricular tachyarrhythmias. Electrophysiologists and non-electrophysiologists (e.g. cardiologists with a special interest in devices and surgeons) have been successfully implanting these devices for over three decades. A well informed patient consent is an essential part of this process. There are no formal guidelines and no previous studies looking at this.

5.2 Hypotheses and Aims of the study

We hypothesized that implanters would be aware of national guidelines as would be expected of them but the consent process may not be adequate or uniform. Implanters may not completely discuss all the benefits (and risk) offered by the ICD. They may not discuss these evidence based benefits in terms of universal denominator (ARR and NNT) and may underestimate mortality and morbidity. We designed a questionnaire survey to test our hypotheses.

The aims of this study were to assess the knowledge of national guidelines and to get an insight into implanters’ practices prior to an ICD implantation. This information would be very helpful to understand the informed consent process better.
5.3 Implanter Questionnaire and rationale

5.3.1 The Questionnaire

A detailed questionnaire was designed to look at the knowledge, attitudes, application of guidelines, factors influencing ICD prescription and implantation. A sub-section of this questionnaire (see Appendix – Questionnaire, page No. 208) for implanters focusing on patient consent aids, pros and cons of an ICD, risks and benefits terminology, complications of an ICD, and style and language of consent was assessed. Personal information including age, grade, specialty and hospital setting for ICD implantation were also collected.

5.3.2 Sample selection

The survey included both Consultant and trainee electrophysiologists (implanters). Trainee electrophysiologists had successfully completed general and specialty cardiology training and were mostly undertaking clinical fellowship in Electrophysiology i.e. they were about to become consultants in about 6-12 months time. The questionnaire was predominately sent electronically. As mentioned before, no incentive was offered to do the survey and response to the questionnaire was completely voluntary. As physician surveys have a typically low response rate, we targeted the national audience through the global email system of the British Cardiovascular Society, Heart Rhythm UK and the Arrhythmia Alliance in addition to sending the questionnaire locally throughout the region. Prior to distribution, the questionnaire was trialed by five cardiologists (two trainees and
three ICD implanters) to assess clarity and understanding. Complete understanding of UK guidelines was defined as correctly recalling the two primary prevention categories and three secondary prevention categories publicized in the NICE Guidelines for primary and secondary prevention ICD implantation.

5.3.3 UK NICE guidelines

UK NICE ICD guidelines were published in 2006 and unlike the North American and European guidelines, only address primary prevention ICD in ischaemic cardiomyopathy patients with LVSD (LVEF ≤35%) and restrict the application of MADIT2 criteria to patients who have a wide QRS complex (≥120ms). For patients who have a narrow QRS duration (<120 ms), additional screening with Holter monitoring is needed for evidence of NSVT and if positive, the need for inducible VT on further EPS testing. For secondary prevention ICD, patients would have to survive a cardiac arrest either due to VT or VF, sustained VT causing syncope or haemodynamic compromise, or sustained VT without syncope or haemodynamic compromise but with an LVEF ≤35%.
5.4 Results of the Implanters’ Questionnaire survey

We received a total of 23 implanter responses. Majority of implanters were Consultants (83%), aged between 40-49 years (39%) and worked in a hospital that implanted ICD (96%). One responder was not working in an implanting centre and is very likely to be employed by the district general hospital (non-implanting centre) who would attend the implanting (tertiary) centre for device implantation. This is a common practice in the United Kingdom where an implanter cardiologist would be employed by the district general hospital but the procedure would be carried out at the local tertiary (implanting) centre. The results of the responder characteristics are summarized in Figure 18.

Figure 18. Implanter questionnaire responder demographics.
5.4.1 Awareness of NICE guidelines

19/23 (83%) of implanters were completely aware of primary prevention UK NICE guidelines. The knowledge gap in primary prevention was in the understanding of MADIT criteria (IHD, LVEF ≤35%, NSVT and a positive EPS). Of those that did not, 4/23 (27%) were consultant cardiologists. 18/23 (78%) were fully aware of secondary prevention NICE guidelines. The knowledge gap in secondary prevention was the ICD indication for ‘sustained VT causing syncope or haemodynamic compromise’ – 3/23 (13%) and ‘sustained VT without haemodynamic compromise and LVEF≤35%’ – 5/23 (22%). There was no significant difference in knowledge between consultants and trainees (p=1.00).

5.4.2 Consent Aids

Majority of Implanters (87%) use information leaflets in addition to routine discussion as part of the consent process to inform patients about ICDs. Most Implanters (83%) would ask their specialist ICD nurse to review the patient and all the responders would personally speak to the patient in whom they are implanting. The findings are summarized in Table 16.
Table 16. Various consent aids used in patient consent process.

<table>
<thead>
<tr>
<th>Consent Aids</th>
<th>n = 23</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Paper literature (information leaflets)</td>
<td>20</td>
<td>87</td>
</tr>
<tr>
<td>Video</td>
<td>7</td>
<td>30</td>
</tr>
<tr>
<td>Electronic resources (e.g. web page)</td>
<td>2</td>
<td>9</td>
</tr>
<tr>
<td>Discussion with allied professional (e.g. ICD nurse)</td>
<td>19</td>
<td>83</td>
</tr>
<tr>
<td>Discussion with the implanting doctor</td>
<td>23</td>
<td>100</td>
</tr>
</tbody>
</table>

5.4.3 Pros and cons of an ICD therapy used during consent process

In response to ‘pros and cons’ of an ICD that will be routinely discussed at the time of consent for ICD: most Implanters (96%) would explain to the patient the risk of SCD and how an ICD can prevent this. They appropriately inform the patient of the potential ICD complications, appropriate and inappropriate therapies including the consequences of inappropriate shocks, infections or lead failures. They also fulfill the legal requirement of informing the patient of driving restrictions following appropriate shock therapy. The results are summarized in Table 17.
Table 17. Implanters’ use of ‘pros and cons’ while consenting for an ICD.

<table>
<thead>
<tr>
<th>Pros and cons of ICD</th>
<th>n = 23</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Risk of SCD and the impact of ICD</td>
<td>22</td>
<td>96</td>
</tr>
<tr>
<td>Total mortality and the impact of ICD</td>
<td>14</td>
<td>61</td>
</tr>
<tr>
<td>Mode of eventual death and the impact of ICD</td>
<td>12</td>
<td>52</td>
</tr>
<tr>
<td>Risk and consequences of inappropriate shocks</td>
<td>22</td>
<td>96</td>
</tr>
<tr>
<td>ICD complications (e.g. Infection or lead fracture)</td>
<td>21</td>
<td>91</td>
</tr>
<tr>
<td>Appropriate shock therapy and driving</td>
<td>22</td>
<td>96</td>
</tr>
<tr>
<td>Voluntary end-of-life ICD deactivation</td>
<td>6</td>
<td>26</td>
</tr>
</tbody>
</table>

5.4.4 Risks and benefits terminology used during consent process

There are different ways of informing the patients about risks and benefits offered by an ICD. We asked responders to select from the list those terminologies they commonly used in their clinical practice. Majority of the responders (61%) use phrases such as ‘small risk’ or ‘moderate risk’ while consenting patients. Very few responders use the actual ARR percentages (22%) or the NNT (26%). Results are summarized in Table 18.
Table 18. Use of risks and benefits terminology during consent process.

<table>
<thead>
<tr>
<th>Risks and benefits terminology</th>
<th>n = 23</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>ARR expressed in percentages</td>
<td>5</td>
<td>22</td>
</tr>
<tr>
<td>RRR expressed in percentages</td>
<td>5</td>
<td>22</td>
</tr>
<tr>
<td>ARR expressed as a fraction (e.g. 1/10)</td>
<td>4</td>
<td>17</td>
</tr>
<tr>
<td>RRR expressed as a fraction (e.g. 1/3)</td>
<td>1</td>
<td>4</td>
</tr>
<tr>
<td>ARR expressed as a ratio (e.g. 1 in 10)</td>
<td>6</td>
<td>26</td>
</tr>
<tr>
<td>RRR expressed as a ratio (e.g. 1 in 3)</td>
<td>2</td>
<td>9</td>
</tr>
<tr>
<td>Phrases such as ‘small risk’ / ‘moderate risk’</td>
<td>14</td>
<td>61</td>
</tr>
<tr>
<td>Life prolongation (e.g. lets you live longer by an average of 3 months)</td>
<td>7</td>
<td>30</td>
</tr>
<tr>
<td>NNT (e.g. saves the life of 1 in 11 people who have the device implanted)</td>
<td>6</td>
<td>26</td>
</tr>
</tbody>
</table>

5.4.5 Implanters’ estimation of ICD complications

In our final section, we asked responders to estimate the percentage of different complications associated with the ICD therapy. The results are summarized in Table 19.
Table 19. Implanters’ estimate of ICD complications in comparison to published data.

<table>
<thead>
<tr>
<th>Estimate of ICD complications</th>
<th>Mean %</th>
<th>Published data %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Death as a complication of device implant</td>
<td>0.37±0.48</td>
<td>0.42(^{18}) &amp; 0.9(^{19})</td>
</tr>
<tr>
<td>Lead dislodgement requiring lead repositioning</td>
<td>3.5±2.08</td>
<td>0.8(^{76}) &amp; 1(^{74})</td>
</tr>
<tr>
<td>Lead failure requiring extraction or additional lead insertion</td>
<td>5.4±7.28</td>
<td>2.7 @ 45 days(^{76})</td>
</tr>
<tr>
<td>High DFTs with inability to defibrillate</td>
<td>2.34±2.25</td>
<td>1(^{80}) &amp; 1.2(^{81})</td>
</tr>
<tr>
<td>Major haematoma requiring reoperation</td>
<td>2.72±3.07</td>
<td>0.7(^{73:74})</td>
</tr>
<tr>
<td>Infection requiring device removal/extraction</td>
<td>2.27±2.4</td>
<td>0.5-0.8(^{25:74:77})</td>
</tr>
<tr>
<td>Cardiac tamponade</td>
<td>0.7±1.07</td>
<td>0.2-0.6(^{75:77})</td>
</tr>
<tr>
<td>Pneumothorax</td>
<td>1.68±1.17</td>
<td>0.4-1.1(^{75:77})</td>
</tr>
<tr>
<td>Inappropriate shocks</td>
<td>14.8±10.92</td>
<td>12-25(^{73:75:77:83:84})</td>
</tr>
<tr>
<td>Generator/hardware failure</td>
<td>6.9±5.6</td>
<td>1.4,(^{73}) 6-7(^{73:75})</td>
</tr>
<tr>
<td>Psychological problems associated with the device</td>
<td>22.6±26.68</td>
<td>25-33(^{85:89})</td>
</tr>
<tr>
<td>Failure of the device to treat life threatening arrhythmia</td>
<td>1.57±2.2</td>
<td>1.79(^{77})</td>
</tr>
</tbody>
</table>
5.5 **Summary and clinical implications**

5.5.1 **Role of the implanter**

As expected a high proportion (83%) of implanters were fully aware of primary prevention NICE guidelines. However, a sizeable number (17%) of implanters were not aware of the MADIT criteria of NICE guidelines. Similarly, only 78% of implanters were fully aware of secondary prevention NICE guidelines and the gap in knowledge was ‘sustained VT causing haemodynamic compromise or syncope’ – 13% and ‘sustained VT without syncope or haemodynamic compromise with LVEF ≤35%’ – 22%. It is not possible to conclude that they were not aware of the guidelines with 100% certainty as they may have chosen not to document this in our survey. If it is indeed true it highlights a need for further education or further simplification of the guidelines as is the case with international guidelines. It is not a surprise that there was no difference in the knowledge of guideline awareness among trainees and consultants as the trainees had mostly finished their general cardiology training and were likely within 6-12 months of finishing their EP training.

It is comforting to know that all implanters would personally discuss the procedure with their patients prior to ICD implantation, even though if it had been discussed earlier by another doctor. Providing additional information on ICD through ICD leaflets and discussion with an allied professional (ICD specialist nurse) is widespread. Our survey reflects the fact ICD patients being in their 70’s, routine use of
electronic media and internet is not widespread. It is likely to change over the years as internet use spreads to this age group as well.

Consent process is not universal and our survey reflects this. Very well (>90%) done aspects include discussion regarding risks and benefits from ICD for the prevention of SCD, consequences of appropriate and inappropriate shocks, ICD complications and shocks and driving implications. Not so well (50-60%) discussed subjects include the total mortality with and without the ICD and the influence of ICD on the mode of eventual death. However, most implanters (3 out of 4) fail to discuss end-of-life scenario and role of ICD deactivation in those situations. Previous studies have shown that physicians are willing and in fact most will discuss ICD deactivation in appropriate patients at that time.\textsuperscript{130} In one study, most physicians believe informed consent for ICD implantation should also include information about deactivation and endorsed the need for expert guidance in this area.\textsuperscript{130}

There is total lack of consensus among implanters regarding the way data (e.g. ARR, RRR, NNT, life prolongation, simplistic terms like mild, moderate, severe risk, risk expressed as percentage, fraction or ratio) is presented and discussed with the patient. Most implanters (61%) use phrases such as ‘small risk’ and ‘moderate risk’ while explaining risks and benefits gained from ICD. However, it is the ARR and NNT that are considered the most appropriate forms of data presentation when explaining risks and benefits to patients and determining cost
Less than 1 in 4 responders use ARR and NNT to inform the risks and benefits according to our survey. These findings are significant as there will be some patients who would want to know the specific details while some who will take the physician recommended approach. It is therefore important to be aware of the data in much greater detail and tailor it according to the needs of the individual patient.

5.5.2 Implanters’ perspective of ICD complications

Estimation of complications (both mortality and morbidity) is never accurate. Although there are no ICD studies, previous studies of CABG and PCI have shown that cardiologists over-estimate mortality and under-estimate morbidity. Our results show implanters under-estimate mortality and over-estimate morbidity (e.g. lead failure requiring extraction or additional lead insertion, infection leading to device removal, high DFTs with inability to defibrillate and the incidence of pneumothorax) when compared to trial or published data. This is not a straightforward like with like comparison as the incidence of complication varies substantially among different publications, e.g. lead dislodgement requiring lead repositioning varies from 0.8% to as high as 5% and is therefore often not possible to generalize.

Although the medical benefits of the ICD seem unequivocal, ICD implantation may result in adverse psychosocial outcome for particular sub-groups of patients, with at least 1 in 3 patients (30%) manifesting clinically significant levels of anxiety and
depressive symptoms.\textsuperscript{91,145} It is not easy to estimate the prevalence of this problem as it a subjective analysis. A systematic review estimated an incidence of 11-28% of patients with depressive disorder and 11-26% with anxiety disorder using validated diagnostic interviews. However, there was wide variation with self-reported questionnaires and time of assessment (8-63% with anxiety and 5-41% for depression).\textsuperscript{154} Research has shown ICD-related fears and concerns (in particular the fear of ICD firing), is universal and has been identified as a major determinant of psychological distress, impaired QoL, and the extent to which patients experience the ICD implantation as positive.\textsuperscript{90,91,119,155} Clinically significant anxiety related to having an ICD implantation may influence the risk of arrhythmic events, as stress and anxiety are established precipitants of arrhythmias.\textsuperscript{156} On a positive note, although ICD implantation has been shown to impact adversely on QoL,\textsuperscript{90,155} research has also shown QoL to improve to pre-implant levels at 1-year follow-up with appropriate counselling.\textsuperscript{91} Our survey responders estimated 23±27% psychological related adverse events in keeping with published data.
Chapter 6

Where is the block for Primary Prevention

Implantable Cardioverter Defibrillator?
6.1 Introduction

RCTs have shown mortality benefit from primary prevention ICD in patients at high risk of SCD.\textsuperscript{18;19;22;24;25} Indications for primary prevention ICD implantation in the United Kingdom were published in January 2006 by NICE and eligible patients must have a history of previous MI (>4 weeks) and either; (a) LVEF ≤35%, no worse than class NYHA class III heart failure, NSVT on Holter monitoring and inducible VT on EPS testing or (b) LVEF ≤30%, no worse than NYHA class III heart failure and have a QRS duration ≥120 milliseconds. Despite these well publicized guidelines, implant rates are lower than national targets (UK NICE target is 100 new ICD implants per million population per year, including an estimated 40 primary prevention ICDs\textsuperscript{97;157}). Primary prevention ICD only accounts for a minority of implants in the United Kingdom.\textsuperscript{70;97;158}

The reason for low implant rates are likely to be multifactorial including lack of physician knowledge (particularly non-implanting cardiologists), failure to implement guidelines, failure to screen patients and collect relevant data such as LVEF, lack of financial resources or implanting cardiologists; age, gender or race bias or even patient’s refusal to accept the therapy.
6.2 Hypotheses and Aims of the study

We hypothesize that there is lack of referral from the general cardiologist to the implanter cardiologist as we have shown in the previous study that there is lack of guideline knowledge especially among non-implanters and existence of age bias. We therefore designed a study to look at the progression of patients in the referral pathway.

This study aims to investigate whether there is a failure to refer patients with appropriate documentation of heart failure aetiology, LVEF and QRS duration from general physician to the general cardiologist and from the general cardiologist to the electrophysiologist (implanter) when all the data is available to make a decision regarding provision of ICD therapy.

6.3 Study inclusion criteria

A search was performed on the Oxford Radcliffe Hospitals electronic database that included echocardiography, heart failure and BCIS (British Cardiovascular Intervention Society) databases for patients with an Oxfordshire postcode who had documentation of LVEF recorded in the calendar year 2007. The study period was chosen so that all LVEF assessments took place at least 12 months after the publication of the 2006 UK NICE guidelines and the medical notes were assessed after at least 18 months following the echocardiography, so that sufficient time had
been allowed for the echocardiography to be reviewed and acted upon. Patients younger than 18 years were excluded from the study. The patients for this study were selected on the basis of their echocardiography i.e. patients who had an echocardiogram in the first instance. The prevalent pool of patients with previous MI and severe LV impairment who were admitted to hospital and did not have an echocardiogram as well as those patients who may have been seen by the cardiologist but not referred for echocardiography, and in addition those patients managed by the general practitioner in the community who were not referred to the cardiologist is not known.

Database search criteria was LVEF ≤35%. In addition, the descriptive terms 'severely impaired' or 'poor LVEF' were taken to indicate LVEF ≤30% and the term 'moderate to severely impaired' was taken to indicate LVEF between 30-35%. Our study was done before the British Society of Echocardiography guidelines (2012)\(^{159}\) which encourage LV (EF) function to be reported as a percentage based on Simpson's biplane method. However, it is very common to find echo reports with descriptive terms like mild (45-54%), moderate (36-44%) and severe (≤35%) dysfunction in addition to other descriptive terms like mild-moderate and moderate-severe impairment. There is no official guideline recommendation for these descriptive terms and we chose the above values based on local practice. For patients thus identified, medical case notes were assessed for age, aetiology of heart disease, time from MI, NYHA heart failure status, 12 lead ECG for QRS duration, evidence of NSVT, confirmation of echocardiography results, Holter
monitoring, and EPS if available. Documentation of consultation with general medical physicians, general (non-implanter) cardiologists and implanter cardiologists were noted and outcomes recorded.

Patients deemed eligible for an ICD were those with a history of previous MI (>4 weeks) and LVEF ≤30%, no worse than NYHA class III and have a QRS duration ≥120 ms i.e. MADIT2 wide QRS criteria. Patients deemed eligible for screening investigations with Holter monitoring and if positive for NSVT, to undergo EPS, were those with a history of previous MI (>4 weeks) and LVEF ≤35%, and no worse than class NYHA class III i.e. MADIT criteria. Patients with severe co-morbidities (e.g. cancer, advanced renal disease, advanced COPD, etc.) that indicated a potential life expectancy of <12 months were excluded. Patients were subsequently grouped into those who were aged ≤80 years and those who were >80 years.

6.4 Results

A total of 326 patients with impaired LVEF ≤35% were identified from 3554 echocardiography assessments, BCIS database and 1104 heart failure patients. There was an overlap of patients in the databases. Mean age was 72±12 years and the study group comprised predominantly of men (71% vs. 29%).
Patients were excluded from subsequent analysis for the following reasons: 15/326 (5%) patients had incorrect documentation of LVEF in the database which was found out on medical notes assessment; 1/326 (0.3%) had missing aetiology and we were unable to trace their medical notes; 27/326 (8%) patients had improvement in their LVEF on subsequent echocardiography measurements and were therefore excluded from the study; 22/326 (7%) patients died either during the index hospital admission or within 4 weeks of echo being performed; 35/326 (11%) patients had one or more significant co-morbidities, thus contraindicating the implantation of a primary prevention ICD; 38/326 (12%) had non ischaemic DCM and were not eligible for primary prevention ICD according to UK NICE guidelines; 41/326 (13%) patients had already received a secondary prevention ICD for a previous ventricular tachyarrhythmia (VT or VF).

This left a group of 135 patients with eligible criteria for implantation or screening as documented in their medical records. 41 patients without any exclusion criteria were >80 years and 94 patients were aged ≤80 years and had no contraindication and had all the required data documented in their medical records making them eligible for implantation of an ICD or referral for further EPS. 72/135 (53.3%) had LVEF ≤30% and wide QRS duration (≥120 ms) satisfying NICE primary prevention criteria without any further investigations needed. Of these, 35/72 (48.6%) had been referred to the implanter and 28/35 (80%) did receive primary prevention ICD therapy. Only 2/35 (5.7%) patients refused ICD therapy when offered. 31/72 (43%) patients seen by the general cardiologist were not referred for ICD implantation.
63/135 (46.6%) patients satisfied the MADIT criteria requiring further screening with Holter monitoring for evidence of NSVT ± EPS. Only 12/63 (19%) patients were referred to the implanter and 8/12 (66.7%) patients had appropriate therapy. Only 1/12 (8.3%) patients refused ICD therapy.

The block for the provision of primary prevention ICD therapy in patients with ischaemic cardiomyopathy with poor LV function (LVEF ≤30% and broad QRS duration ≥120 ms) satisfying NICE criteria without any further investigations were the general physician in 6/72 (8.3%) patients, general cardiologists in 31/72 (43%) patients and the electrophysiologist in 5/35 (6.9%) patients.

Similarly, the block for patients with ischaemic cardiomyopathy, poor LV function (LVEF ≤35%) and requiring further screening with Holter monitoring ± EPS were the general physician in 2/63 (3.1%) patients, the general cardiologist in 45/63 (71.4%) patients and the electrophysiologist in 3/12 (25%) patients.

Findings of the study are summarized in Figure 19.
Figure 19. Flow chart showing criteria for primary prevention ICD implantation and referral pathway.
6.4.1 Patients aged ≤80 years seen by Cardiology

There were a total of 94 patients ≤80 years, of whom 2 patients were seen by the general physician only. Of the remaining 92 patients who were reviewed by the general cardiologist, 48/92 (52%) had MADIT2 wide QRS (UK NICE) criteria making them eligible for ICD implant with no further testing. 42/92 (46%) were referred to the implanting cardiologist for further assessment. There was no evidence in the medical records of discussion about SCD prevention and the role of an ICD in those that had not been referred onwards. Of the 42 patients referred to implanting cardiologist, 35/42 (83%) received an ICD; 4/42 (10%) patients were not offered ICD or further appropriate screening; 1/42 (2%) patient had negative EPS and 2/42 (5%) patients declined ICD therapy after consultation. Only 1/52 patients seen by the general cardiologist but not referred to the implanting cardiologist had Holter monitoring to screen for NSVT. Findings are summarized in Figure 20.
Figure 20. Flow chart showing onward referral and eventual decision for patients ≤80 years of age with MADIT and MADIT 2 wide QRS criteria.

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General Cardiology / Imaging / Heart Failure / Coronary intervention

LVEF $< 30\%$, wide QRS = 48
LVEF $< 30\%$, narrow QRS or LVEF 31-35% = 44

Total eligible for PP ICD = 92

EP

LVEF $< 30\%$, wide QRS = 30
LVEF $< 30\%$, narrow QRS or LVEF 30-34% = 12

Total pts referred to EP = 42

35 pts ICD implanted
4 pts not offered ICD / screening
1 pt had Negative EP study & hence no ICD
2 pts declined ICD
6.4.2 Patients aged >80 years seen by cardiology

There were a total of 41 patients aged >80 years satisfying UK NICE primary prevention ICD criteria. Of these 6/41 (14.63%) were seen only by the general physician and not referred to cardiology. There were 35 elderly patients (>80 years of age) seen by the general cardiologist and only 5/35 (14.28%) patients were further referred to implanting cardiologist. Upon review by the electrophysiologist, 1 patient declined ICD therapy and none of the other four patients, who had LVEF ≤30% and wide QRS duration were offered ICD therapy by the implanting cardiologist. Therefore, in this group of elderly patients (age >80 years) with no obvious contraindication and achieving all the criteria set by the National and International guidelines, none had primary prevention ICD implanted. Of the remaining patients, only 1 patient had Holter monitoring to look for evidence of NSVT and the rest were not appropriately investigated. The findings are summarized in Figure 21.
6.4.3 Gender Bias

Majority of patients in the study group were men (95 out of 135 – 70%). There was a trend towards gender bias with 29 out of 95 (31%) of eligible or potentially eligible male patients receiving an ICD compared with 6 of 40 (15%) of female patients; however, this did not reach statistical significance (p=0.08).
6.5 Limitations

This was a retrospective study and has the typical limitations of such a study including data collection, documentation and selection bias. Our database is likely to be an underestimate as there could be a huge subset of patients with low LVEF undiagnosed both in the medical wards and the community. Our patients were identified from different databases and the assumption is that they were either seen or discussed with the general cardiologist. Assessment of LV function is not always objective and echo reports frequently quote impaired LV systolic function subjectively (i.e. mild, moderate or severe and also in between grades e.g. moderate-severely impaired). Holter monitoring may have been organized outside the hospital by the general practitioner and it is possible that the GP may have taken the appropriate action of not referring back to the cardiologist. Finally, there may have been a small number of patients who may have translocated outside our catchment area.

6.6 Summary and clinical implications

6.6.1 Potentially eligible patients

This study focuses on exploring barriers to primary prevention ICD implantation in patients with known ischaemic cardiomyopathy patients. As stated earlier, the implant rate for ICD in the United Kingdom is one of the lowest in the industrialized nations. The UK national target is 100 new ICD implants per million population.\textsuperscript{97}
Furthermore, the majority of ICD implants are for secondary prevention, yet primary prevention patients are the largest potentially-eligible group. NICE estimate 40 implants/million/year as primary prevention implants. The UK 2013/14 National Heart Rhythm device survey published in December 2014 recorded an average new ICD implant rate of 72 per million population per year. The implant rates for Oxfordshire have gradually gone up from 57 to 72 per million population in 2007 to 2012 but still lower than the recommended national target levels. It has been estimated from studies looking at acute admissions to UK coronary care units that there should be at least 40 primary prevention ICD implants per million population, a figure that is likely to be an underestimate as it does not include patients with long standing, stable ischaemic cardiomyopathy.

Extrapolating my study results, if the patients with MADIT 2 wide QRS criteria had been referred to the implanting physician, all remaining 37/72 (51.3%) patients would have received the primary prevention ICD therapy unless the patient declined ICD or was not offered ICD in the first place by the electrophysiologist. Therefore, all 72/72 (100%) should have been offered ICD therapy in an ideal world. Similarly, of those patients satisfying the MADIT criteria, 48/63 (76.1%) patients would be eligible for further screening. Extrapolating the outcomes from electrophysiologist review, there would have been an additional 8 (16.7%) patients with positive EPS and subsequent ICD implantation; 20 (41.7%) patients offered ICD outside NICE indications; 4 (8.3%) of patients with negative EPS and no need for ICD; and 4 (8.3%) patients declining ICD.
6.6.2 Lack of referral to the implanting physician

Our study was designed to identify the blocks for primary prevention ICD therapy. The aim was to see what action was taken when all the data required for making a referral for primary prevention ICD was available in the medical records. Particular attention was paid to how far along the referral path patients progressed and where the barriers were. We identified 135 patients with ischaemic cardiomyopathy and a LVEF ≤35%. Of the 72 patients who had wide QRS duration (≥120 ms) and no co-morbidities, satisfying national guidelines (NICE) for a primary prevention ICD, 8% had not seen a cardiologist and 43% who had, were not referred to an implanting physician for consideration of an ICD. Of the 47% (63/135) who were eligible for screening with Holter monitoring and EPS, 97% had seen a cardiologist and yet only 19.6% were referred on to an implanting physician for further assessment.

6.6.3 Inappropriate management

In a healthcare where a large proportion of heart failure patients are still managed by general physicians, even in a tertiary centre, it is perhaps not surprising that specialist therapies are underutilised. In our study, 6% of patients were not seen by a cardiologist. This is likely to be a vast underestimate as we do not know of those patients that did not have an echocardiogram in the first place! What is more concerning is that general cardiologists’ frequently failed to refer these patients for further assessment and ICD implantation. This may be due to lack of knowledge
and awareness of UK guidelines whereas European and North American guidelines select patients primarily based on LVEF alone. The UK guidelines are limited to patients with IHD aetiology plus either ECG criteria of a wide QRS complex (≥120 ms) or assessment with Holter monitoring and if appropriate, EPS. This added complexity may prevent recall of indications for ICD implantation. It is notable that general cardiologists referred a larger proportion of MADIT2 wide QRS duration patients for ICD and only a minority of MADIT patients for Holter monitoring and EPS, suggesting less knowledge/awareness of the MADIT component of the guidelines which has been already been demonstrated in our survey (Chapter 4). Alternatively, cardiologists may mistakenly believe MADIT2 wide QRS patients are at higher risk and have more to gain, whereas in reality, the NNT to prevent one death in the original MADIT trial was smaller than MADIT2 (4 vs. 11).\textsuperscript{24,25}

6.6.4 Regional differences and attitude towards ICD

Wide differences in implantation rates exist throughout the world. Variation exists among different advanced health care economies and significant regional variations exist which is hard to explain solely based on a country’s wealth. In the United Kingdom, these regional differences are also seen with some centres implanting twice the national recommended target and other centres implanting less than half of what is recommended.\textsuperscript{97} A study in the United States was unable to explain the regional differences in ICD implantation other than hospitals with higher implant rates appeared to be better at adopting guidelines across the range
of cardiac services.\textsuperscript{157} To overcome the deficit in the UK there either needs to be improved education and guideline awareness amongst UK cardiologists or a simplification of the guidelines, broadening the criteria and bringing them in line with Europe and North America. In a survey of New Zealand cardiologists' and general physicians' knowledge and use of ICD, 62\% replied that they were familiar with international guidelines.\textsuperscript{148} Only half thought primary prevention ICD use was cost-effective. A minority of surveyed doctors thought referral streams were a barrier, with most thinking cost, followed by lack of expertise and local guidelines were responsible. In our study, it is therefore possible that some patients were not referred by the general cardiologists to the implanting physician due to a prejudice or bias against device therapy including financial costs in addition to a lack of guideline awareness.

6.6.5 Primary prevention in sub-groups

Even in USA, the country with the highest ICD implantation rates, there is underutilisation, particularly in women and ethnic minorities.\textsuperscript{161} In our study, we found twice the number of women not receiving ICD therapy compared to men. As with most clinical trials, more than three quarter of patients were men in our study. Many reasons may exist for this disparity, including the higher prevalence of CAD in men, but one that is difficult to ignore is the fact that more men were referred for echocardiography in the first instance. There was also an age bias found in our study with no patient >80 years of age receiving a primary prevention ICD. This elderly group made up 30\% of all patients identified with eligible criteria and
represents a more “real world” population when compared to the primary prevention trials, where 50% of patients enrolled were under the age of 60.\textsuperscript{18,19,22,24,25,162} A greater proportion of the elderly were referred to the general cardiologist than those under the age of 80, however the general cardiologist only referred 14% of the over-80s to the implanting physician and none of them were offered an ICD. In an analysis of 25,000 ICD or CRT-D implants performed in the USA between 2004-2005, 16% were in patients aged 80 or more.\textsuperscript{163} It would therefore appear that practice in the UK is more biased against the elderly with most patients filtered out by the general cardiologist. A recent meta-analysis of primary prevention trials has concluded that patients <60 years of age have a significant mortality benefit from primary prevention ICD, while in those over 60 the difference does not reach statistical significance.\textsuperscript{164} This is in contrary to the results from the MADIT2 sub-study where the mortality benefit gained was greater in the >75 year old patients but with the caveat that these patients had a much higher overall mortality (Table 4). The role of primary prevention ICD in the elderly is yet to be widely accepted and is more likely to be judged on an individual basis.

Of all the patients ≤80 years referred to the implanting cardiologist, only 1 out of 29 (3.4%) MADIT 2 wide QRS duration patient declined an ICD and 1 out of 11 (9%) MADIT patients declined further screening tests. In a previous study from the United States, patient refusal was the cause for eligible patients not receiving ICD in 7% of cases, whereas non-referral was the dominant reason, accounting for 33-38% patients.\textsuperscript{165} Another study shows only 4.4% of eligible patients received ICD
therapy for the prevention of SCD. Common reasons for under-referral included non-availability of EP cardiologists (34%), poor quality of life of patients (25.7%), patients not being on optimal therapy (25.7%) and low awareness (22.8%). All these studies suggest patients will almost always accept device therapy when offered, appreciating that the potential benefits of an ICD outweigh the harm except in a handful of cases. Patients are generally more optimistic about the benefits of therapy than their physicians as shown in cardiac surgery patients. A similar phenomenon may apply for ICD therapy and account for cardiologists’ failure to refer, assuming patients are unlikely to benefit.

My study suggests that in a tertiary care ICD implanting centre, more than half of potentially eligible primary prevention ICD patients do not receive the guideline recommended therapy. The majority of these patients were managed by a General Cardiologist and or the General Physician who do not assess these patients further (when indicated) nor refer them to the implanting physician for ICD therapy when appropriate. In conclusion, a low referral rate from the general cardiologist and the general physician, lack of screening programmes and age bias seem to be the stumbling blocks for primary prevention ICD in a tertiary referral centre in the United Kingdom.
Chapter 7

Conclusion
My studies address a common theme of low implant rate for the provision of ICD therapy in the United Kingdom.

I present here, the ARR and NNT from landmark ICD clinical trials that have influenced national and international guidelines. These findings are standardized for the length of follow-up and show considerable variation in the magnitude of benefit between different heart failure aetiologies and other patient characteristics. The relatively small number of patients who have follow-up periods of 2 or more years result in wide confidence intervals and highlights the difficulty in generalizing the results. As ARR is the preferred statistic for use in informed consent, the results of this study may help facilitate communication between physicians, patients and healthcare providers, to better understand the risk and benefits as applicable to individual patients.

The questionnaire survey of UK cardiologists show that in the setting of secondary prevention of SCD, most patients will be appropriately referred for an ICD regardless of guideline knowledge; unless they are over 80 years of age and present to a non-implanter. In a primary prevention setting there is a much stronger relationship with guideline knowledge, which unfortunately is poor, especially amongst non-implanters. Underutilization of primary prevention ICD appears to be the result of lack of knowledge, complex guideline criteria, failure to follow guidelines even if fully aware, belief that secondary prevention ICD offer greater benefit and general bias against ICD use in the elderly.
The majority of implanters in the present survey are aware of UK ICD guidelines, although complete knowledge is not universal. The patient consent process varies between operators and is not uniform, however written consent aids and support from nurse specialists is widespread. Discussion about end-of-life care is not undertaken as comprehensively as they ought to be. Risk and benefit is rarely explained using ARR, RRR or NNT, and implanters' estimate of complication rates is broadly in accordance with published literature.

When the relevant data is available in medical records, the principal barrier to a primary prevention ICD is the failure of general cardiologist to refer patients to the implanting cardiologist. Patients who already have all the criteria (IHD, LVEF ≤30% and wide QRS) are more likely to be referred than those who require additional screening with Holter monitoring and EPS. There is an age bias against the elderly with no patients aged >80 years in this study offered an ICD. When offered, almost all patients accept the ICD therapy. Better education of general cardiologists may help raise UK implant rates up to national target levels.

The United Kingdom continues to have a low implant rate in the western world. Numerous factors have been cited and discussed in detail. Better education, increased awareness and additional resources should be directed in overcoming these barriers. This will help towards achieving national targets and will have a direct impact on improving patient care.
Chapter 8

Update of UK (NICE) Guidelines

and

Future Research
8.1 Update of NICE (UK) Guidelines

Eight years after their last review (NICE technology appraisal guidance 95 in 2006\textsuperscript{60} and NICE technology appraisal guidance 120 in 2007\textsuperscript{167}), NICE updated the ICD guidelines in June 2014 (NICE technology appraisal guidance 314\textsuperscript{72} to combine ICD and CRT guidance and to include CRT trial data published since 2007.

Implantable Cardioverter Defibrillators are recommended as options for:

1. treating patients with a previous serious ventricular arrhythmia, i.e. people who, without a treatable cause:
   - have survived a cardiac arrest caused by either VT or VF or
   - have spontaneous sustained VT causing syncope or significant haemodynamic compromise or
   - have sustained VT without syncope or cardiac arrest, and also have an associated reduction in LVEF of ≤35% but their symptoms are no worse than class III of NYHA heart failure

2. treating patients who:
   - have a familial cardiac condition with a high risk of SCD, such as long QT syndrome, hypertrophic cardiomyopathy, Brugada syndrome or ARVC or
   - have undergone surgical repair of congenital heart disease
ICD, CRT with CRT-D or CRT-P are recommended as treatment options for patients with heart failure who have left ventricular dysfunction with a LVEF ≤35% as specified in the table 20.

Table 20. Treatment options with ICD or CRT for patients with heart failure who have left ventricular dysfunction with an LVEF ≤35% (according to NYHA class, QRS duration and presence of LBBB).

<table>
<thead>
<tr>
<th>QRS duration</th>
<th>NYHA Class</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>II</td>
</tr>
<tr>
<td>&lt;120 ms</td>
<td>ICD if there is a high risk of SCD</td>
</tr>
<tr>
<td>120-149 ms without LBBB</td>
<td>ICD</td>
</tr>
<tr>
<td>120-149 ms with LBBB</td>
<td>ICD</td>
</tr>
<tr>
<td>≥150 ms with or without LBBB</td>
<td>CRT-D</td>
</tr>
</tbody>
</table>
This is a significant shift in the provision for ICD prescription in the United Kingdom. The distinction between ischaemic and non ischaemic DCM aetiologies is being done away with and any patient with significantly impaired LVEF is being considered for the device therapy.

8.2 Overlap of ICD and CRT-D therapy

Patients with significant LVSD have higher morbidity and mortality than the general population. The two major causes of death are due to tachyarrhythmias (SCD) and terminal heart failure. There is no benefit of ICD therapy in severe heart failure (NYHA class IV) patients and is therefore contraindicated. Biventricular pacing (CRT) has been established as standard therapy for patients with moderate-severe heart failure with severe LVSD (LVEF ≤35%) and significant intra-ventricular conduction delay (QRS ≥120 ms). Many of the indications for primary prevention ICD and CRT therapy overlap and these are appropriately reflected in the national (NICE72) and international guidelines. In simple terms, patients with severe LVSD (LVEF≤35%) will become eligible for high energy device (ICD or CRT-D) based on their QRS duration and morphology.

CRT therapy in patients with impaired LVSD (LVEF ≤35%), significant heart failure (NYHA class 3 and 4) and significant intra-ventricular conduction delay (wide QRS) has shown to improve symptoms, lower rates of hospitalization for heart failure, improve exercise capacity, improve overall quality of life and improve survival
(CARE-HF, COMPANION, MIRACLE and MUSTIC trials). CRT-P improves heart failure symptoms and prognosis but these patients are also at high risk of SCD. Combining biventricular pacing with defibrillator (CRT-D) has the dual advantage of an ICD (to prevent SCD and treat tachyarrhythmias) and biventricular pacing (to improve heart failure symptoms and QOL).

COMPANION and CARE-HF trials have shown significant reduction in mortality and morbidity in patients with moderate to severe HF (NYHA class III and IV) and in sinus rhythm. In COMPANION, there was a 36% reduction in all cause mortality with CRT-D (but not CRT-P) and 36% reduction in all cause mortality with CRT-P in CARE-HF. MADIT-CRT (41% risk reduction) and RAFT (25% risk reduction) have expanded the indication for CRT therapy in patients with less severe heart failure (NYHA class II). CRT-D trials (CONTAK-CD, MIRACLE ICD, MIRACLE ICD II, RAFT, RethinQ and Rhythm ICD) have further cemented the role of CRT-D in these patients.

Data from Medicare ICD Registry, REVERSE study, MADIT-CRT and RAFT all support effectiveness of CRT therapy in patients with LBBB morphology only. Meta-analysis by Sipahi et al. showed significant reduction in all cause mortality or hospitalization in patients with QRS duration ≥150 ms only. Based on all these data, guidelines (both NICE and ESC) make the distinction based not only on QRS duration but also the morphology of QRS complex (LBBB vs. non-LBBB morphology). (Table 20).
Although the uptake of ICD remains very low in the United Kingdom (Figure 3), CRT therapy and particularly CRT-D has shown steady improvement in uptake and there were an average of 155 implants/million/population in 2013-14. However, this figure is still relatively on the lower end of the spectrum when compared to our European colleagues (Figure 4), highlighting the problem of under-provision of these high energy devices (both ICD and CRT-D) to the UK population. Therefore, it is a welcome sign that NICE have updated the guidelines in June 2014 and have removed the complex MADIT criteria barrier and issued guidelines combining ICD and CRT therapy as there is a significant overlap of patients qualifying for both ICD and CRT (Table20). I hope this will eventually lead to improved uptake of device therapy (both ICD and CRT-D) in appropriate patients in this country.

8.3 Future research

ICD therapy although well established remains an evolving therapy. As goal posts are moved (e.g. NICE update in 2014), more patients will become eligible for device therapy. As stated before, one of the reasons for low implant in the UK could be the limitation of ICD provision to patients with IHD and complex MADIT criteria which has been finally updated and are similar to international guidelines. Therefore, this predominant reason for low implant rates may not be relevant in the future years. As the benefit gained from different heart failure aetiologies are different and as the uptake of ICD in the non ischaemic group increases in the UK,
it can potentially provide an opportunity for researchers to analyze the magnitude of benefit gained and compare it with trial / international data.

The current national target for primary prevention in the UK is 100 implants per million population and there is hope that the uptake of ICD therapy will gradually increase over time. It will be naïve to think uptake of ICD therapy in the United Kingdom (especially primary prevention) will sky rocket in the next couple of years as there has been a relaxation in the rules. As we have shown, the reasons for not implanting (and not referring) are complex, even when physicians are aware of guidelines. The risk of litigation and potential medico-legal action (for not providing ICD therapy) was not a strong factor in our survey and I believe that the way forward should be increasing awareness and education (both benefits and harm caused by ICD) among physicians, health care providers and finally patients. This will lead to enhanced satisfaction amongst care providers and care receivers.
Chapter 9

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The Implantable Cardioverter Defibrillator

Physician Questionnaire
Implantable Cardioverter Defibrillator

Physician Questionnaire

Dr Praveen P Sadarmin

(Research Fellow)

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(Consultant Cardiologist & Electrophysiologist)

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About this Questionnaire:

- This questionnaire is designed to gain understanding of physician’s knowledge of risk reduction with ICDs.
- It will begin by asking you a little about yourself and your clinical practice.
- It will then ask about your knowledge and understanding of current indications for ICDs.
- It will ask you how much benefit you would expect different patient groups to receive from an ICD.
- It will then investigate the reasoning behind the decision to refer or not refer, implant or not implant ICDs in different case scenarios, and how that decision is reached.
- In completing this questionnaire you will help support a research project looking at physicians’ knowledge and attitudes to the risk of sudden death and the role of an ICD and how this affects referral and implant practice in the UK.
- The first part is for all cardiologists including implanters and non-implanters. There is an additional small section for implanters.

Completing the questionnaire will take approximately 10-15 minutes.
Your responses will be treated with confidence and at all times data will be presented in such a way that your identity cannot be connected with specific published data.

Tick boxes to fill in answers.

**Participant information**

Age group:  <30   30-39   40-49   50-59   60+

Grade:       ☐ Trainee
             ☐ Staff grade/Assoc specialist
             ☐ Consultant

Specialty:    ☐ Physician (non-cardiologist)
             ☐ Cardiologist (not an ICD implanter)
             ☐ Cardiologist (ICD implanter)

Do you work in a hospital where ICD implants take place?  Yes / No
CURRENT ICD INDICATIONS, GUIDELINES AND TRIAL DATA:

Please write down your understanding of the indications for a primary prevention ICD according to current NICE guidelines. Primary prevention refers to patients who have not previously suffered sustained VT or a cardiac arrest.

Please write down your understanding of the indications for a secondary prevention ICD according to current NICE guidelines. Secondary prevention refers to patients who have previously suffered sustained VT or a cardiac arrest.

Please write down your understanding of the current indications for ICDs according to published guidelines or trial data, outside those issued by NICE. Please include the name of the trial or organisation if possible.
RISKS AND BENEFITS OF ICDs

Please estimate the mortality rates for total all-cause mortality over 3 years that an ICD could offer to the following patients by writing down what you would expect their survival rates to be with and without an ICD. Even if you have no idea, please give your best “educated guess”.

65 year old with ischaemic heart disease, previous MI 2 years earlier, NYHA class 2, LVEF 28%, QRS duration 130 ms, no documented VT, no syncope.

- 3 year survival with medical treatment □ %
- 3 year survival with ICD implant □ %

50 year old with ischaemic heart disease, previous MI 2 years earlier, NYHA class 3, LVEF 34%, QRS duration 110 ms, no non-sustained VT on Holter monitor, no syncope.

- 3 year survival with medical treatment □ %
- 3 year survival with ICD implant □ %

51 year old with non ischaemic, dilated cardiomyopathy, NYHA class 2, LVEF 26%, QRS duration 110 ms, no non-sustained VT on Holter monitor, no syncope.
• 3 year survival with medical treatment ☐ %
• 3 year survival with ICD implant ☐ %

65 year old with ischaemic heart disease, previous MI 3 years earlier, NYHA class 1, LVEF 36%, resuscitated from severely compromising sustained VT.

• 3 year survival with medical treatment ☐ %
• 3 year survival with ICD implant ☐ %

59 year old with non ischaemic, dilated cardiomyopathy, NYHA class 2, LVEF 46%, successfully resuscitated from out-of-hospital VF arrest.

• 3 year survival with medical treatment ☐ %
• 3 year survival with ICD implant ☐ %

REFERRAL AND DECISION MAKING

Please estimate what proportion of patients under your care who receive ICDs do so for (total should = 100%)

• Primary prevention ☐ %
• Secondary Prevention ☐ %
PRIMARY PREVENTION

In your practice is there a formal screening program to identify potential primary prevention ICD recipients?  Yes / No

What proportion of patients under your care with known stable ischaemic heart disease & LVEF <35% undergo regular Holter monitoring to look for ventricular arrhythmias?

☐ %

In patients with stable ischaemic heart disease, LVEF <35% and QRS <120 ms, if non-sustained VT (≥3 beats) is seen on a Holter or other form of telemetry and they are NYHA class 1-3, what would be your usual course of action?

☐ Continue monitoring and only treat if sustained VT/syncope

☐ Start Amiodarone therapy

☐ Refer for/perform a VT stimulation study

☐ Refer for/perform an ICD implant

☐ Other

When you see a patient with stable ischaemic heart disease, NYHA class 1-3, LV ejection fraction <30%, QRS duration 110 ms, no syncope or palpitations, on β-blockers and ACE-I, which of the following is your usual course of action?
When you see a patient with stable ischaemic heart disease, NYHA class 1-3, LV ejection fraction <30%, QRS duration >120 ms, no syncope or palpitations, on B-blockers and ACE-I, which of the following is your usual course of action?

☐ Ongoing standard follow-up
☐ Holter monitor to look for ventricular arrhythmias
☐ Prophylactic Amiodarone therapy
☐ Refer for/perform a VT stimulation
☐ Refer for/perform an ICD implant
☐ Other

When you see a patient for with stable non ischaemic dilated cardiomyopathy, NYHA class 2-3, LV ejection fraction <35%, no syncope or palpitations, on B-blockers and ACE-I, which of the following is your usual course of action?
☐ Ongoing standard follow-up
☐ Holter monitor to look for ventricular arrhythmias
☐ Prophylactic Amiodarone therapy
☐ Refer for/perform VT stimulation
☐ Refer for/perform an ICD implant
☐ Other

In a 56 year old male, remote MI, LVEF 29%, NYHA class 2, QRS duration 130 ms, what is the minimum magnitude of all-cause mortality benefit (absolute % risk reduction) over a 3 year period you would consider appropriate to justify referral and implant of an ICD?

At least ☐ % over 3 years

In an 80 year old diabetic female with remote MI, LVEF 24%, NYHA 3, QRS duration 140 ms, what is the minimum magnitude of all-cause mortality benefit (absolute % risk reduction) over a 3 year period you would consider appropriate to justify referral and implant of an ICD?

At least ☐ % over 3 years
When considering referral for/implant of a primary prevention ICD, please indicate how important the following factors are in reaching your decision using the scale of 1-5

1. no importance
2. slight influence
3. moderate influence
4. strong influence
5. very strong influence and of overriding importance

The patient’s indication must satisfy NICE guidelines

The patient’s indications must fall within published RCT criteria

The patient’s age

Your **personal belief** that the ICD will offer a benefit of significant magnitude to justify its implant

The patient’s desire to have or refuse an ICD

The financial cost of an ICD

The potential complications and harm of an ICD

The potential medicolegal consequences of not implanting despite NICE indications

The potential medicolegal consequences of implanting an ICD that is outside of NICE indications
Secondary prevention

In your practice, please estimate what proportion of patients who present with haemodynamically-compromising VT and LVEF<40% or an out-of-hospital cardiac arrest, not due to acute ST elevation MI or other reversible cause, are referred to a subspecialist for/are recommended by you to receive an ICD?

☐ %

If a 60 year old male with previous CABG, LVEF 45%, NYHA class 1 survives an out-of hospital VF arrest which is not due to an acute coronary event or reversible cause, what is your usual course of action?

☐ Discharge on B-blocker therapy
☐ Discharge on B-blocker and amiodarone therapy
☐ Refer for / implant an ICD
☐ Other

If an 81 year old male with previous remote MI, LVEF 35%, NYHA class 2 survives an out-of hospital VF arrest which is not due to an acute coronary event or reversible cause, what is your usual course of action?

☐ Discharge on B-blocker therapy
☐ Discharge on B-blocker and amiodarone therapy
If a 75 year old male with dilated cardiomyopathy, LVEF 25%, NYHA class 2 has an urgent DC cardioversion for VT (180 bpm, causing palpitations and breathlessness but otherwise haemodynamically-tolerated) which is not due to a reversible cause, what is your usual course of action?

☐ Discharge on B-blocker therapy
☐ Discharge on B-blocker and amiodarone therapy
☐ Refer for / implant an ICD
☐ Other

If a 67 year old male with previous CABG, LVEF 29%, NYHA class 2 has an urgent DC cardioversion for haemodynamically-compromising VT which is not due to an acute coronary event or reversible cause, what is your usual course of action?

☐ Discharge on B-blocker therapy
☐ Discharge on B-blocker and amiodarone therapy
☐ Refer for / implant an ICD
☐ Other
If a 64 year old male with previous remote inferior MI, LVEF 50%, NYHA class 1 has an urgent DC cardioversion for VT (causing palpitations but otherwise haemodynamically-tolerated) which is not due to a reversible cause, what is your usual course of action?

☐ Discharge on B-blocker therapy
☐ Discharge on B-blocker and amiodarone therapy
☐ Refer for / implant an ICD
☐ Other

In a 56 year old male, remote MI, LVEF 32%, NYHA class 2, presenting with successful resuscitation from a VF cardiac arrest, what is the minimum magnitude of total mortality benefit (absolute % risk reduction) sustained over a 3 year period you would consider appropriate to justify referral and implant of an ICD?

at least ☐% over 3 years

In an 80 year old diabetic female with syncope and haemodynamically-compromising VT, remote MI, LVEF 28%, NYHA 3, what is the minimum magnitude of total mortality benefit (absolute % risk reduction) sustained over a 3 year period you would consider appropriate to justify referral and implant of an ICD?

at least ☐% over 3 years
When considering referral for a secondary prevention ICD, please indicate how important the following factors are in reaching your decision using the scale of 1-5

1. no importance
2. slight influence
3. moderate influence
4. strong influence
5. very strong influence and of overriding importance

The patient’s indication must satisfy NICE guidelines

The patient’s indications must fall within published RCT criteria

The presenting arrhythmia (cardiac arrest due to VF or haemodynamic compromise due to VT?)

The patient’s age

Your personal belief that the ICD will offer a benefit of significant magnitude to justify its implant

The patient’s desire to have or refuse an ICD

The financial cost of an ICD

The potential complications and harm of an ICD

The potential medicolegal consequences of not implanting despite satisfying NICE indications

The potential medicolegal consequences of implanting an ICD that is outside of NICE indications
Is there an age limit above which you feel a primary prevention ICD should not be offered?

☐ Yes (please write upper age limit) ☐

☐ No

Is there an age limit above which you feel a secondary prevention ICD should not be offered?

☐ Yes (please write upper age limit) ☐

☐ No

What do you think is the average cost of an ICD and lead system (hardware only, excluding hospital implant and follow-up cost)?

Single chamber £

Dual chamber £

What proportion of ICD recipients do you think suffer the following complications?

Inappropriate shocks for atrial fibrillation or sinus tachycardia ☐%

Hardware failure (e.g. lead fracture) ☐%

Device infection requiring removal ☐%
Psychological problems associated with the device itself □%
Failure of the device to recognize and treat a life-threatening ventricular arrhythmia □%

Overall view of ICDs, their use and indications

In your opinion, how strongly do you feel about the use of ICDs?

Use a scale of 1-5, with
1. strongly disagree
2. mildly disagree
3. ambivalent, neither agree nor disagree
4. mildly agree
5. Strongly agree

Patients who satisfy NICE guidelines for a primary prevention ICD should undergo ICD implant □
Patients who satisfy published RCT data but are outside of NICE guidelines for primary prevention ICD should undergo ICD implant □
Patients who satisfy NICE guidelines for secondary prevention ICDs should undergo ICD implant □
Primary prevention ICDs implanted under NICE guidelines are a cost-effective treatment □
Secondary prevention ICDs implanted under NICE guidelines are a cost effective treatment.
ICDs are under-utilized in the UK.

*Non-implanters can stop here and return the questionnaire. Implanters, please continue on…*
SECTION FOR IMPLANTERS

Prior to ICD implant, which of the following consent aids are **routinely** used in your practice?

- Paper literature (information leaflets)
- Video
- Electronic resource (e.g. web page)
- Discussion with allied professional (e.g. ICD nurse)
- Discussion with implanting doctor

When personally discussing the pros and cons of an ICD, which of the following subjects do you routinely raise? *Tick all that apply*

- The risk of sudden cardiac death and the impact of the ICD on this
- Total mortality (i.e. death from other causes such as pump failure, non-cardiac) and the effect of the ICD on this
- Mode of eventual death and the effect of the ICD on this
- The risk and consequences of inappropriate shocks
- ICD complications such as infection or lead fracture
- Appropriate shock therapy leads to 6 months off driving
- The possibility of voluntary end-of-life ICD deactivation (e.g. with end-stage CHF or cancer)
When quoting risks and benefits of an ICD to patients, what terminology would you usually use? *Tick all that apply*

- Absolute risk reduction expressed in percentages
- Relative risk reduction expressed in percentages
- Absolute risk reduction expressed as a fraction (e.g. 1/10)
- Relative risk reduction expressed as a fraction (e.g. 1/3)
- Absolute risk reduction expressed as ratios (e.g. 1 in 10)
- Relative risk reduction expressed as a ratio (e.g. 1 in 3)
- Phrases such as "small risk", “moderate risk"
- Life prolongation
  (e.g. lets you live longer by an average of 3 months)
- Numbers needed to treat (e.g. saves the life of 1 in 11 people who have the device implanted)
How often do you estimate the following ICD complications occur? (% of device implants)

- Death as a complication of device implant
- Lead dislodgement requiring lead repositioning
- Lead failure requiring extraction/additional lead insertion
- High DFTs with inability to defibrillate at time of implant
- Major haematoma requiring reoperation
- Infection requiring device removal/extraction
- Cardiac tamponade
- Pneumothorax
- Inappropriate shocks
- Generator failure

Thank you for your time and effort!
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