Subcutaneous and transvenous implantable cardioverter defibrillators:

Developing an individualised approach to assessment and treatment

by

David G Wilson

Thesis for the degree of Doctor of Medicine

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SUBCUTANEOUS AND TRANSVENOUS IMPLANTABLE CARDIOVERTER DEFIBRILLATORS:
DEVELOPING AN INDIVIDUALISED APPROACH TO ASSESSMENT AND TREATMENT

By David Graham Wilson

In recent years the subcutaneous implantable cardioverter-defibrillator (S-ICD) has emerged as a novel technology which offers an alternative choice to the traditional transvenous implantable cardioverter-defibrillator (TV-ICD) in treatment and prevention of sudden cardiac death. Early experience with the S-ICD however has highlighted that its capacity to accurately sense the cardiac signal can be challenged, in particular with regard to the risk of varying amplitude of signals and risk of T wave oversensing. S-ICD sensing is therefore an important weakness of this technology which this thesis addresses.

Initially only a relatively small group of patients were thought to be suitable for S-ICD, in particular patients with difficult venous anatomy or young patients. Therefore I explored how the important ECG parameters in S-ICD sensing, the R wave, the T wave and the R:T ratio, vary when measured from a right compared to a left parasternal lead position in a population of patients with complex congenital heart disease and normal controls. I go on to explore how the R wave, T wave and R:T ratio in the same patient population vary with posture and discuss how this relates to potentially clinically important in relation to S-ICD sensing. As the sensed S-ICD signal resembles the signal measured with a standard 12 lead ECG, I go on to evaluate what are the ECG predictors of T-wave oversensing are. Lastly, I explore how application of mathematical vector transformation techniques can help reconstruct an 8 lead ECG from 2 S-ICD vectors, and from then create a 12-lead ECG, and I discuss how this technique may potentially help solve some sensing problems related to the S-ICD.

Within this thesis, I demonstrate that much could be done at an individual level (optimise lead position, identify patients at risk of T wave oversensing and using vector transformation to reduce
the likelihood of inappropriate therapy) in order to maximise the potential benefit (and reduce the unwanted consequences) of S-ICDs. This thesis has advanced the understanding of how to improve therapy to treat SCD by reducing the unwanted events of S-ICD therapy by developing a concept of a tailored assessment of patient’s suitability for ICD therapy.
Table of Contents

Table of Contents ........................................................................................................i
DECLARATION OF AUTHORSHIP ........................................................................ forearm.ix
List of peer reviewed publications ...........................................................................x
List of Tables .............................................................................................................xiv
List of Figures ........................................................................................................... xv
List of Accompanying Materials ............................................................................. xix
Acknowledgements ..................................................................................................xxi
Definitions and Abbreviations ................................................................................xxiii

Chapter 1: Introduction .......................................................................................... 1

1.1 Personalised medicine ......................................................................................... 1
1.2 The global burden of cardiovascular disease ...................................................... 2
  1.2.1 Mortality associated with CVD ..................................................................... 2
  1.2.2 Implantable cardioverter-defibrillators to treat and prevent sudden cardiac death ............................................................................................................. 3
  1.2.3 The S-ICD .................................................................................................... 3
1.3 Research problem defined .................................................................................. 4
  1.3.1 Early signal of sensing difficulties associated with the S-ICD .................... 4
  1.3.2 Motivation to carry out research .................................................................. 5
  1.3.3 Difficulties evaluating S-ICD sensing without access to the commercially available S-ICD sensing algorithm ................................................................. 6
  1.3.4 Novel contribution ....................................................................................... 6

Chapter 2: Background and general methods ..................................................... 9

2.1 Overview of the history of ICDs ......................................................................... 9
2.2 ICD trials ............................................................................................................ 11
  2.2.1 Danish trial ................................................................................................ 15
2.3 Impact on policy and practice ........................................................................... 18
  2.3.1 United Kingdom guidelines ....................................................................... 18
2.3.2 The National Institute for Health and Care (clinical) Excellence guidelines for the implantation of ICDs .......................................................... 18

2.3.3 Secondary prevention of sudden cardiac death .................................. 18

2.3.4 Primary prevention of sudden cardiac death .................................... 19

2.3.5 European Society of Cardiology guidelines for the implantation of ICDs ........................................................................................................ 20

2.4 Effectiveness of ICDs ........................................................................... 21

2.5 Limitations of the ICD ........................................................................ 21

2.5.1 Lead and generator failure ............................................................... 24

2.6 Evolution of the S-ICD ...................................................................... 25

2.6.1 Defibrillation energy requirements .................................................. 26

2.7 Shock efficacy and safety ..................................................................... 27

2.7.1 Preclinical ....................................................................................... 27

2.7.2 Clinical .......................................................................................... 27

2.8 S-ICD screening .................................................................................. 29

2.9 Sensing with the subcutaneous implantable cardioverter ..................... 30

2.10 Overview of S-ICD sensing algorithms .............................................. 31

2.11 Rhythm discrimination in S-ICD ........................................................ 35

2.11.1 The Insight™ algorithm ............................................................... 35

2.11.2 Static morphology analysis ........................................................... 35

2.11.3 Dynamic morphology analysis ..................................................... 35

2.11.4 QRS width analysis ..................................................................... 35

2.12 Calculation of heart rate ..................................................................... 36

2.12.1 The importance of accurate heart rate detection ......................... 36

2.12.2 Five shocks two mechanisms ...................................................... 36

2.12.3 How does sensing influence tachycardia therapy? ...................... 42

2.12.4 Previous experience analysing sensing vectors ............................ 43

2.13 Clinical experience with S-ICD ........................................................ 44

2.14 Comparison of S-ICD and TV-ICDs .................................................. 44

2.15 S-ICDs in patients with complex anatomy ......................................... 46
Chapter 3: Evaluating the use of right parasternal versus left parasternal ECG parameters using surface electrodes as surrogates for sensed ECG signal from subcutaneous implantable cardioverter defibrillator in adult congenital heart disease patients and normal controls ........................................... 53

3.1 Abstract ............................................................................................................. 53
3.1.1 Aim ................................................................................................................. 53
3.1.2 Methods ......................................................................................................... 53
3.1.3 Results .......................................................................................................... 53
3.1.4 Conclusion .................................................................................................... 54

3.2 Introduction ...................................................................................................... 55

3.3 Methods .......................................................................................................... 56
3.3.1 Use of surface ECG data ............................................................................... 56
3.3.2 Statistical methods ......................................................................................... 57
3.3.3 Explanation of statistical methods used ......................................................... 58

3.4 Results .............................................................................................................. 60
3.4.1 Subgroup analysis ......................................................................................... 64
3.4.2 Explanation of how to interpret sub-group summary boxes ....................... 64

3.5 Discussion ....................................................................................................... 67
3.5.1 Limitations ................................................................................................... 68

3.6 Conclusion ....................................................................................................... 69

Chapter 4: Evaluating the impact of postural change on ECG parameters using surface electrodes as surrogates for sensed ECG signal from subcutaneous
implantable cardioverter defibrillator in adult congenital heart disease patients and normal controls

4.1 Abstract ........................................................................................................ 71
   4.1.1 Introduction............................................................................................. 71
   4.1.2 Methods .................................................................................................. 71
   4.1.3 Results .................................................................................................... 71
   4.1.4 Conclusion ............................................................................................... 72

4.2 Introduction .................................................................................................... 73

4.3 Methods .......................................................................................................... 73
   4.3.1 Statistical methods ................................................................................ 75
   4.3.2 Explanation of statistical methods used .................................................. 76

4.4 Results ............................................................................................................ 78
   4.4.1 Ranking position .................................................................................... 79
   4.4.2 Magnitude of postural variation ............................................................. 80
   4.4.3 Subgroup analysis .................................................................................. 83
   4.4.4 Explanation of matrix comparison boxes ............................................. 83

4.5 Discussion ....................................................................................................... 85
   4.5.1 Effect of postural change on signal variation in S-ICD......................... 85
   4.5.2 Limitations .............................................................................................. 86

4.6 Conclusion ...................................................................................................... 86

Chapter 5: ECG predictors of T wave oversensing in S-ICD recipients ............... 87

5.1 Abstract ......................................................................................................... 87
   5.1.1 Introduction ............................................................................................. 87
   5.1.2 Methods .................................................................................................. 87
   5.1.3 Results .................................................................................................... 87
   5.1.4 Conclusion ............................................................................................... 87

5.2 Introduction .................................................................................................... 89

5.3 Methods .......................................................................................................... 89
   5.3.1 Statistical analysis ................................................................................ 90
   5.3.2 Explanation of statistical analyses ......................................................... 90
Chapter 5: Results

5.4 Results ................................................................................................................................. 91
5.4.1 Clinical and electrocardiographic predictors of T-wave oversensing ......................... 95
5.4.2 Predictive accuracy for determining T-wave oversensing ............................................ 95

5.5 Discussion ............................................................................................................................ 95
5.5.1 Dynamic nature of electrocardiogram ........................................................................... 97
5.5.2 Limitations ....................................................................................................................... 98

5.6 Conclusion ........................................................................................................................... 98

Chapter 6: Reconstruction of an 8–lead ECG from two S-ICD vectors ..................... 101

6.1 Abstract ............................................................................................................................... 101
6.1.1 Background ..................................................................................................................... 101
6.1.2 Methods .......................................................................................................................... 101
6.1.3 Results ............................................................................................................................ 101
6.1.4 Conclusions .................................................................................................................... 101

6.2 Introduction ......................................................................................................................... 102

6.3 Materials and methods ...................................................................................................... 103
6.3.1 Study population ............................................................................................................ 103
6.3.2 Study procedure ............................................................................................................. 103
6.3.3 Randomisation .............................................................................................................. 104
6.3.4 Selection of representative beat for analysis ................................................................. 106
6.3.5 Generation a signal averaged beat ............................................................................... 106
6.3.6 Generation of coefficients, conversion matrix and derived ECGs .............................. 106
6.3.7 Application of matrix to validation dataset ................................................................. 107
6.3.8 Statistical analysis ....................................................................................................... 107
6.3.9 Explanation of statistical analyses ............................................................................... 108

6.4 Results ................................................................................................................................ 108
6.4.1 Transformation coefficients ......................................................................................... 110
6.4.2 Reconstructed signal .................................................................................................... 110
6.4.3 Validation group ............................................................................................................ 111

6.5 Discussion and Conclusion ............................................................................................... 113
6.5.1 Feasibility and accuracy of S-ICD derived 12-lead ECGs .......................................... 113
Chapter 7: Discussion and conclusion ..............................................117

7.1 Summary of original findings......................................................117

7.1.1 Assessment of a patient’s suitability for an S-ICD and implications on S-ICD implantation.................................................................117
The impact of parasternal lead position and posture on sensing with the S-ICD. 117
7.1.2 Assessment and follow-up of patients with S-ICDs .....................118
7.1.3 Follow up of S-ICDs.................................................................118
Reconstructing an 8-lead ECG from 2-independent S-ICD vectors .........118

7.2 Contemporary challenges to defibrillator therapy and how findings from this thesis may influence these ......................................................119

7.2.1 Current challenges to S-ICD sensing..........................................119
7.2.2 Novel solutions........................................................................120
7.2.3 Difficulties of calculating heart rates ........................................120
7.2.4 Overview of QRS detectors: ....................................................121

7.3 S-ICD sensing in the future .........................................................123

7.3.1 Automated screening ..............................................................123
7.3.2 Floating bipole away from the heart to provide optimal sensing and reducing the risk of inappropriate sensing .................................124
7.3.3 Integrating the signals from more than 1 vector to achieve the best sensing vector.................................................................124
7.3.4 Combining transvenous, epicardial or leadless pacemakers with the S-ICD ...........................................................................124

7.4 The future role of S-ICD in an ACHD population ..........................126

7.4.1 Vector transformation..............................................................126
7.4.2 Identification of patients at risk of T-wave oversensing prior to inappropriate therapy ..........................................................129
7.4.3 Does device therapy for prevention of sudden cardiac death need to be tailored to the individual? .......................... 130

7.5 Final conclusion............................................................................................................ 130

Appendices.......................................................................................................................... 131
Appendix A............................................................................................................................. 131
Appendix B............................................................................................................................. 137
Bibliography .......................................................................................................................... 139
DECLARATION OF AUTHORSHIP

I, DAVID WILSON.......................................................................................... [please print name]

declare that this thesis and the work presented in it are my own and has been generated by me as the result of my own original research.

Subcutaneous and transvenous implantable cardioverter defibrillators: Developing an individualised approach to assessment and treatment

I confirm that:

I confirm that:
1. This work was done wholly or mainly while in candidature for a research degree at this University;

2. Where any part of this thesis has previously been submitted for a degree or any other qualification at this University or any other institution, this has been clearly stated;

3. Where I have consulted the published work of others, this is always clearly attributed;

4. Where I have quoted from the work of others, the source is always given. With the exception of such quotations, this thesis is entirely my own work;

5. I have acknowledged all main sources of help;

6. Where the thesis is based on work done by myself jointly with others, I have made clear exactly what was done by others and what I have contributed myself;

7. Parts of this work have been published as: [please list references below]

Signed: ..........................................................................................................................

Date: .............................................................................................................................
List of peer reviewed publications

1. Chapter 3
   Left and right parasternal sensing for the S-ICD in adult congenital heart disease patients and normal controls
   Wilson D, Zeb M, Veltman G, Dimitrov D, Morgan J.

2. Chapter 5
   ECG predictors of T wave oversensing in S-ICD recipients.

3. Chapter 6
   Reconstruction of an 8-lead surface ECG from two subcutaneous ICD vectors.
   Wilson DG, Cronbach PL, Panfilo D, Greenhut SE, Stegemann BP, Morgan JM
   Int J Cardiol. 2017 Jan 27

4. Chapter 6
   Electrode positions, transformation coordinates for ECG reconstruction from S-ICD vectors.
   Wilson DG, Cronbach PL, Panfilo D, Greenhut SE, Stegemann BP, Morgan JM
   Data Brief. 2017 Feb 22;11:611-616

Presented abstracts

Oral presentation

   Wilson DG, Cronbach PL, Panfilo D, Greenhut SE, Stegemann B, Morgan JM
   Heart Rhythm Congress, Birmingham 2015

Poster Presentation

1. Reconstruction of 12 – lead ECG from TWO S-ICD vectors: generation and validation of transformation coefficients
   Cronbach PL, Wilson DG, Panfilo D, Greenhut SE, Stegemann B, Morgan JM.
   American Heart Association, Miami November 2015
   Circulation 2015;132:A13578
2. ECG predictors of T-wave oversensing in subcutaneous implantable cardioverters.

Wilson DG, Leventigiannis G, Barr C, Morgan JM

Heart Rhythm Congress 2015
List of Tables

Table 1 Summary of secondary prevention ICD trials adapted from Santini et al. Heart 2007 49
Table 2 An overview of the important primary prevention ICD trials .......................... 14
Table 3 Treatment options with ICD or CRT for people with heart failure who have left ventricular .......................... 19
Table 4 Summary of ICD implantation guidelines for the secondary prevention of sudden cardiac................................................................. 20
Table 5 Summary of ICD implantation guidelines for the primary prevention of sudden cardiac20
Table 6 Summary of early complications related to transvenous-ICD implantation. .............. 22
Table 7 Summary of late complications related to the ICD............................................. 23
Table 8 Interventions that have been shown to reduce the incidence of inappropriate shock or T wave oversensing ................................................................. 36
Table 9 A comparison of transvenous-ICDs and subcutaneous-ICDs. .............................. 45
Table 10 Risk factors for SCD in complex ACHD .......................................................... 48
Table 11 Mean amplitude of the R wave and T wave in millivolts and the R:T ratio................. 61
Table 12 Mean amplitude of the R wave and T wave in millivolts and the R:T ratio............ 79
Table 13 Posture ranking for the ACHD and control group ......................................... 80
Table 14 Summary of the number of episodes of oversensed signal .................................. 92
Table 15 Summary of baseline characteristics of patients who experienced T wave oversensing. Yrs, years, PP, primary prevention of sudden cardiac death, SP, secondary prevention of sudden cardiac death, ST, sinus tachycardia, A Flutter, atrial flutter, SR, sinus rhythm. ................................................................. 92
Table 16 Baseline clinical characteristics ........................................................................ 93
Table 17 Baseline ECG characteristics ........................................................................... 94
Table 18 Results of univariate and multivariate analysis ................................................ 95
Table 19 Summary of participants assigned to training and validation datasets ................................108

Table 20 Transformation coefficients for all 8-leads .................................................................110

Table 21 Pearson correlation coefficients and RMSE for all leads ...........................................111

Table 22 Pearson correlation coefficients (r) for all patients and leads ....................................112

Table 23 Comparison of published ECG detection algorithms. .....................................................123
List of Figures

Figure 1 Results of Pubmed search for ‘Personalised medicine’ ..................................................1

Figure 2 Illustration of the S-ICD with the anatomical location of the sensing components. ........4

Figure 3 The original defibrillator ..................................................................................................11

Figure 4 Left ventricular dysfunction without ischaemic heart disease: impact of primary ....16

Figure 5 Time-to-event curves for death from any cause (A), cardiovascular death (B), and sudden
cardiac death(C) from the DANISH trial..........................................................17

Figure 6 Five year failure-free survival of ICD leads from 3 manufactures. ..............................25

Figure 7 S-ICD experimental configurations .............................................................................28

Figure 8 Pre-implant screening tool...........................................................................................29

Figure 9 Surface ECG, IEGM and S-ICD electrograms. ..............................................................30

Figure 10 Illustration of the use of a variable threshold detection profile to avoid the unnecessary
detection of the T wave after having detected the preceding QRS complex..32

Figure 11 Novel sensing algorithm to reduce T wave oversensing............................................34

Figure 12 Stored S-ICD ECG from the alternate vector taken from treated episode in November
2013........................................................................................................................................40

Figure 13 Subcutaneous ECG from the secondary vector taken from treated episode in October
2013........................................................................................................................................41

Figure 14 Illustration of the sensing electrodes used in the recording of the right parasternal and
left parasternal lead position. .................................................................................................57

Figure 15 Estimated linear regression line showing the intercept $a$ and the slope $b$, .............59

Figure 16 Three-dimensional charts of the R and T wave amplitudes and R:T ratio magnitudes in
the right and left parasternal sensing positions in the ACHD group. .......................62

Figure 17 Three-dimensional charts of the R and T wave amplitudes and R:T ratio magnitudes in
the right and left parasternal sensing positions in the control group.................63
Figure 18 The panel is a representation of the results recorded in the R wave in the primary vector in all 6 postures. .................................................................................................. 64

Figure 19 Subgroup analysis of impact of parasternal lead position on amplitude of the R wave, T wave and the R:T ratio. ........................................................................................................ 66

Figure 20 Illustration of the sensing electrodes used in the recording of the electrode lead positions utilising the Prime ECG™ system. ................................................................. 75

Figure 21 Estimated linear regression line showing the intercept \( a \) and the slope \( b \), ................. 77

Figure 22 Three dimensional charts depicting the postural variation in amplitude of the R and T wave in millivolts (mV) and R:T ratio magnitude in all three vectors for the ACHD group. ................................................................................................................... 81

Figure 23 Three dimensional charts depicting the postural variation in amplitude of the R and T wave in millivolts (mV) and R:T ratio magnitude in all three vectors for the ACHD group. ................................................................................................................... 82

Figure 24 Explanation of matrix comparison boxes .................................................................. 83

Figure 25 Subgroup analysis of impact of postural change on amplitude of the R wave, T wave and ....................................................................................................................................... 84

Figure 26 Montage of selection of four patients (1-4) who experienced T wave oversensing... 94

Figure 27 Illustration of the Mason-Likar 12-lead electrode arrangement.......................... 104

Figure 28 Representation of how the transformation was created with the training dataset and used with the validation dataset................................................................. 105

Figure 29 Flow chart for selection of participants................................................................. 109

Figure 30 A scatter plot comparing the amplitude of the measured and derived signal for all leads. .................................................................................................................. 111

Figure 31 Sample reconstructed electrograms ................................................................. 113

Figure 32 An example of wavelet based QRS identification............................................... 122

Figure 33 Right hand triangle formed from the three sensing vectors ......................... 127

Figure 34 Transforming vectors to reduce the amplitude of the T wave......................... 128
List of Accompanying Materials

1. Appendix A – Primary prevention ICD programming from University Hospital of Southampton NHS Foundation Trust and The Bristol Heart Institute
2. Appendix B – Details of therapy delivered for heart rates > 200bpm and for rates <200bpm
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# Definitions and Abbreviations

<table>
<thead>
<tr>
<th>Abbreviation</th>
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</tr>
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<tbody>
<tr>
<td>ACEi</td>
<td>angiotensin converting enzyme</td>
</tr>
<tr>
<td>ACHD</td>
<td>Adult congenital heart disease</td>
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<tr>
<td>AICD</td>
<td>Automated implantable cardioverter-defibrillator</td>
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<tr>
<td>BSM</td>
<td>Body surface mapping</td>
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<tr>
<td>CABG</td>
<td>Coronary artery bypass graft</td>
</tr>
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<td>CABG-PATCH</td>
<td>Coronary artery bypass Patch trial</td>
</tr>
<tr>
<td>CCU</td>
<td>Coronary care unit</td>
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<tr>
<td>CKD</td>
<td>Chronic kidney disease</td>
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<tr>
<td>DER</td>
<td>defibrillation energy requirements</td>
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<tr>
<td>DINAMIT</td>
<td>Defibrillator in acute myocardial infarction trial</td>
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<td>ECG</td>
<td>Electrocardiogram</td>
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<td>EF</td>
<td>Ejection fraction</td>
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<td>EFFORTLESS</td>
<td>Evaluation of factors impacting clinical outcome and cost effectiveness of the S-ICD – International S-ICD registry</td>
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<tr>
<td>ICD</td>
<td>Implantable cardioverter-defibrillator</td>
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<tr>
<td>HIV</td>
<td>Human immunodeficiency virus</td>
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<tr>
<td>HCM</td>
<td>Hypertrophic cardiomyopathy</td>
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<td>MADIT II</td>
<td>Multicenter Automatic Defibrillator Implantation Trial II</td>
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<td>MADIT-RIT</td>
<td>Multicenter Automatic Defibrillator Implantation reduction in inappropriate therapy trial</td>
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<tr>
<td>NOAC</td>
<td>Novel oral anticoagulant</td>
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<tr>
<td>NNT</td>
<td>Number needed to treat</td>
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<tr>
<td>Abbreviation</td>
<td>Definition</td>
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<tr>
<td>NICM</td>
<td>Non-ischaemic cardiomyopathy</td>
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<td>OR</td>
<td>Odds ratio</td>
</tr>
<tr>
<td>PCI</td>
<td>Percutaneous coronary intervention</td>
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<tr>
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<td>Pulmonary embolism</td>
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<tr>
<td>PEA</td>
<td>Pulseless electrical activity</td>
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<tr>
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<td>Peripheral vascular disease</td>
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<tr>
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<td>Post-traumatic stress disorder</td>
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<td>QOL</td>
<td>Quality of life</td>
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<tr>
<td>S-ICD</td>
<td>Subcutaneous implantable cardioverter-defibrillator</td>
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<tr>
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<tr>
<td>SVT</td>
<td>Supraventricular tachycardia</td>
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<tr>
<td>VF</td>
<td>Ventricular fibrillation</td>
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Chapter 1: Introduction

1.1 Personalised medicine

The completion of the human genome project in 2003 has resulted in a greater understanding of molecular medicine and has led to a burgeoning interest in personalised medicine as evidenced by the increase in the publications of scientific and medical journals on the subject. (Figure 1) Personalised medicine can be defined in the following way 2:

1. The use of combined knowledge (genetics, or otherwise) about a person to predict treatment response and thereby improve that person’s health
2. The use of combined knowledge (genetics, or otherwise) about a person to predict disease prognosis or treatment response and thereby improve that person’s health
3. The use of combined knowledge (genetics, or otherwise) about a person to predict disease susceptibility, disease prognosis or treatment response and thereby improve that person’s health

![Results of Pubmed search for 'Personalised medicine' by year](image)

Figure 1 Results of Pubmed search for ‘Personalised medicine’

Schleigden et al. sought to quantitatively refine and render the definition of personalised medicine more precise:
Personalised medicine seeks to improve stratification and timing of health care by utilizing biological information and biomarkers on the level of molecular disease pathways, genetics, proteomics as well as metabolomics.

The terms personalised medicine is used interchangeably with precision medicine or individualised medicine (imedicine) and occasionally the term P4 is used (personalized, predictive, preventive, and participatory). For the purpose of this thesis, the term personalised medicine will be used hereafter.

Medical practitioners have always sought to treat the patient as an individual, and thus one might argue that personalised medicine has existed for hundreds of years. However, practitioners have been bound in their ability to treat each individual in a unique way by their limited understanding of disease process and relatively narrow array of therapeutic options. Increasingly though, thanks largely to progress in the understanding of the genetics underpinning diseases and pharmacotherapy, medical specialities have embraced personalised medicine.

Such is the promise of personalised medicine that NHS England have recently published a ‘Personal Medicine Strategy’ in which ‘emergent approaches in areas such as diagnostic tests, functional genomic technologies, molecular pathway, data analytics and real time monitoring of conditions to better manage patients’ health and to target therapies to achieve the best outcomes in the management of a patient’s disease or predisposition to disease’.

Thus the vision for the future of the NHS requires the implementation of targeted and personalised interventions in order to improve outcomes.

1.2 The global burden of cardiovascular disease

Cardiovascular disease (CVD) is a leading cause of global mortality, accounting for approximately 30% of deaths worldwide. In high income countries, cardiovascular disease (excluding cerebrovascular disease) accounts for more deaths that all pulmonary and gastrointestinal malignancies combined and in low and middle incomes countries, cardiovascular disease causes more deaths than HIV/AIDS, malaria and TB combined.

1.2.1 Mortality associated with CVD

Approximately 40-50% of cardiovascular deaths are sudden cardiac deaths (SCD) and about 80% of these are caused by ventricular tachyarrhythmia. SCD is an unexpected death due to cardiac causes that occurs in a short time period (generally within one hour of symptom onset) in a person with known or unknown cardiac disease.
In the UK, it is estimated that 60,000 out of hospital cardiac arrests occur each year. An out of hospital cardiac arrest can be defined as a sudden disturbance of the cardiac rhythm caused by ventricular fibrillation or ventricular tachycardia that can occur either in the context of an acute myocardial infarction or of a structural or electrical abnormality of the heart and will usually result in SCD unless promptly treated by cardiopulmonary resuscitation and cardiac defibrillation.

Approximately 1 person every day aged <35 years suffers a cardiac death in the UK. Survival rates following an out of hospital cardiac arrest in the UK remain poor ranging from 2% to 12%. Despite using the best appropriate medical treatment, arrhythmia recurrence rates in survivors of cardiac arrests are still 40-50% at five years.

1.2.2 Implantable cardioverter-defibrillators to treat and prevent sudden cardiac death

To combat this, implantable cardioverter-defibrillators (ICD) have been developed and are implanted in those considered to have an elevated risk of SCD. ICD technology is over 30 years old and have traditionally consisted of an active can (battery and computing power) and transvenous leads which are implanted into the right ventricle in order to sense the cardiac signal. If a pathological ventricular arrhythmia is sensed the ICD will attempt to abort the rhythm by delivering overdrive pacing or by delivering a high voltage shock. Unfortunately, the presence of a transvenous lead with the heart can be problematic not only in terms of implanting the lead and the potential trauma the can result (pneumothorax and cardiac tamponade secondary to localised perforation of the heart due to the ICD lead), but the lead can serve both as a conduit for infection descending from the pocket and as a nidus for infection seeding on the intra-cardiac lead. Given these limitations a novel technology has emerged that offers an alternative solution to treating a preventing sudden cardiac death, the subcutaneous ICD (S-ICD).

1.2.3 The S-ICD

The S-ICD consists of an active can (battery and computing power) and single defibrillation electrode which is tunnelled subcutaneously across from the left axilla to an area left of the xiphisternum and upwards, to be left in a left parasternal position. The can is buried in a pocket between the serratus anterior and the trapezius muscle. Thus the lead forms a large ‘L’ shape on the torso, see Figure 2.
Figure 2 Illustration of the S-ICD with the anatomical location of the sensing components. The sensing vector can be selected from the proximal electrode B-CAN (primary), the distal electrode A-CAN (secondary), or the distal to proximal electrode A-B (alternate). Image reused with permission from Wolters Kluwer Health, Inc. (Rowley CP, Gold MR Subcutaneous Implantable Cardioverter Defibrillator 2012; Circ Arrhythm Electrophysiol. 5:587-593).

1.3 Research problem defined

1.3.1 Early signal of sensing difficulties associated with the S-ICD

In 2009 the S-ICD received Conformité Européene (CE) mark approval and in the autumn of 2012, the U.S. Food and Drug Administration (FDA) granted Boston Scientific Corporation regulatory approval for its S-ICD System. From the outset of clinical experience with the S-ICD it became apparent that the ability of the S-ICD to accurately sense the cardiac signal all the time may be challenged.
In 2012 a Dutch group reported on their initial experience with the S-ICD implanted in 118 patients in four centres and followed up over 18 months. The rate of inappropriate shocks was 13%, much higher than conventional TV-ICDs, and were mainly due to T wave oversensing. However, authors did comment that a lot of these sensing problems were resolved by a software update and changing the sensing vector. The following year, a report summarised the United Kingdom experience in S-ICD and reported an inappropriate shock rate that remained above what many clinicians would consider acceptable, occurring in 15% in 111 patients. T-wave oversensing was the most common cause of inappropriate shock delivery.

The same year, a landmark Investigation Device Exemption (IDE) study was published and this led to the FDA approval being granted for the S-ICD. This study was prospective, nonrandomized, multicentre trial included adult patients with a standard indication for an ICD with an aim of evaluating the safety and efficacy of the S-ICD. In total, 330 patients were recruited (314 devices implanted) in 33 sites in United States, New Zealand, the Netherlands and the United Kingdom. The rate of inappropriate shock remained high at 13.1% and inappropriate sensing of the cardiac signal was the most common cause, occurring in 7% of the 314 patients.

1.3.2 Motivation to carry out research

It is in this context that the motivation for carrying out this research must be viewed. The S-ICD is a novel technology that appeared to offer a useful alternative to the transvenous-ICD. However with approximately one in eight persons implanted with an S-ICD receiving an inappropriate shock caused mainly by T wave oversensing, this technology, in particular the sensing component appeared to be somewhat flawed.

This thesis investigates the sensing difficulties related to the S-ICD. In order to understand more about the sensing characteristics that may be important or relevant to the S-ICD, a number of studies were carried out. The first two studies evaluated how varying posture and the location of where the sensed ECG signal recorded from cutaneous electrodes recorded over where a S-ICD sensing electrode would lie, would impact on— the R wave, the T wave and the R:T ratio. These parameters are considered to be the most important components of the ECG signal for S-ICD sensing. These studies were carried out using participants with complex congenital heart disease as these patients were originally considered to be ideal recipients of S-ICDs due to their difficult venous anatomy, young age and relative high risk of endocardial lead complications with TV-ICDs. The population of patients consisted of 3 groups, Transposition of the Great Arteries, single ventricle physiology and Tetralogy of Fallot. These groups were compared to a control group of participants with structurally normal hearts. It must be noted that since this study was performed,
implanting physicians have become more accustomed to the S-ICD and the population into whom the device is implanted has broadened to include patients with LV systolic dysfunction.

The third study was designed to evaluate the hypothesis that as the sensed S-ICD signal resembles the cardiac signal measured with a standard 12 lead ECG, it should be possible to identify ECG characteristics that are more prevalent in patients who have received an inappropriate shock due to T wave oversensing. In order to test this, I conducted a logistic regression analysis to identify ECG predictors of T wave oversensing.

In my final study, I tested the hypothesis of whether it is feasible to apply techniques used in reconstructing 12 lead ECGs from reduced lead sets and generate reconstructed 8-lead ECG from 2 S-ICD vectors. An 8-lead ECG contains all the necessary information to create a 12-lead ECG (augmented leads are generated from the measured leads I and II). This study has particular relevance for clinical practice and I discuss how this technique may potentially help solve some sensing problems related to the S-ICD.

1.3.3 Difficulties evaluating S-ICD sensing without access to the commercially available S-ICD sensing algorithm

This thesis was carried out in part as a results of a research grant from Medtronic Inc. who do not have a commercially available S-ICD at present. However, their market competitors, Boston Scientific purchased the original company who developed the S-ICD (Cameron Health) and therefore I was never given privileged access to the S-ICD sensing algorithm in order to perform my data analysis and studies. My understanding of how the commercially available S-ICD functions from a sensing perspective is derived from information available in the public domain, mainly in scientific journals and medical conferences. I have not knowledge or understanding of what signal processing and filtering of the recorded signal is performed by the S-ICD, both of which are important in cardiac signal sensing performance. It is important for the reader to understand this whilst reviewing this thesis.

1.3.4 Novel contribution

This thesis has generated a number of novel contributions in understanding issues surrounding S-ICD sensing.

Firstly, I have demonstrated that sensing the cardiac signal from electrodes located over where a right parasternal S-ICD may lie may potentially offer some useful beneficial sensing characteristics
compared to a left parasternal sensing location in particular with patients with structurally normal hearts.

Secondly, I have demonstrated that varying posture can have a significant impact on the sensed ECG signal when it is measured from skin electrodes located over where a conventional S-ICD may lie. In particular, the left lateral, the right lateral and the prone postures accounted for the greatest extremes (maximal and minimal R wave, T wave amplitude and R:T ratio). Again, this effect appeared to be more important in those with structurally normal hearts rather than those with complex congenital heart disease.

The statistical methods employed to analyse the data for these paired studies are novel and were purposely written by a statistician (Dr Borislav Dimitrov, Associate Professor of Medical Statistics). The data were particularly challenging to analyse given the large number of variables (4 subgroups, 3 vectors and 6 postures) and therefore a bespoke statistical analysis was required. The graphical presentation of the data are also novel, namely the summary boxes. This method of presenting the data succinctly summarise the data from over 400 pages of statistical results.

Thirdly I have demonstrated that in a retrospective analysis of the resting 12 lead ECGs recorded at the time of the patient’s S-ICD implant that it is possible to identify ECG predictors of inappropriate shock due to T wave oversensing. However, given the small numbers of patients who went on to receive inappropriate shocks due to T wave oversensing, these results must be viewed as exploratory and hypothesis generating.

Lastly, the concept of generating an 8-lead ECG from 2 S-ICD vectors is entirely novel and has the potential for application in future generators of S-ICD. The results from this study are again exploratory and would need to be replicated in a larger dataset including patients with structurally normal hearts, congenital heart disease and arrhythmias and also exploring whether increasing the number of recording electrodes on the S-ICD would improve the results of the transformation.
Chapter 2: Background and general methods

2.1 Overview of the history of ICDs

The importance and scale of problem posed by SCD became apparent in the 1960s. The advent of electrocardiographic monitoring resulted in the observation that ventricular arrhythmias occurring in patients with acute myocardial infarction in a hospital setting was directly associated with a high mortality. Coronary care units (CCU) were therefore developed. These were specialist wards in which patients admitted with myocardial infarction were clustered. CCUs were staffed with personnel who were in constant attendance, observing patients for the onset of lethal arrhythmias so that they could treat them with the necessary drugs, cardiopulmonary resuscitation and electrical defibrillation. Patients with acute myocardial infarction treated on coronary care ward had significantly improved survival compared to those who were treated elsewhere. There continued to be however a high incidence of sudden cardiac death occurring predominately in the community.

Epidemiological studies in men and women in the 1970s and 1990s suggested that 88% to 91% of deaths that occur within 1 hour of symptom onset are arrhythmic in nature. Pharmacological treatments were proving to be relatively ineffective in preventing SCD. A more robust approach was required.

Dr Michael Mirowski, is credited for developing the first implantable cardioverter defibrillator (ICD). Mirowski was born in Poland in 1924 but escaped to Russia to avoid the invading Germans in 1939. At the age of 15, Mirowski first considered how a defibrillator could be developed, remarkable considering, cardiopulmonary resuscitation and even pacemakers had yet to be developed. He went to medical school in Lyon, France and subsequently moved to Baltimore, USA to work as a cardiologist. It was only after his mentor, Professor Harold Heller died following several episodes of ventricular tachycardia that he focused on developing away to tackle the problem of treating ventricular arrhythmias more seriously. Mirowski had the vision of applying external defibrillator technology that had been successful used in the coronary care units to pacemaker technology and so be implanted in humans. This idea was met with considerable criticism.

Mirowski first described a device capable of sensing and appropriately treating ventricular fibrillation (the most lethal ventricular arrhythmia) forty-six years ago in 1970. A sensor placed in the right ventricle of a dog sensed ventricular fibrillation and a 30-50 wattsecond (SIC joule) shock was delivered between a cutaneous electrode and the intra-cardiac electrode (
It was hypothesised that this technology could be refined and introduced into man in order to provide protection from sudden cardiac death.

Three years later an article was published on the efficacy of low energy intraventricular catheter defibrillation in human patients in ventricular fibrillation at the time of coronary artery bypass grafting.\(^{33}\) One electrode was introduced to the right ventricle via an atriotomy and the second electrode, a saline-soaked sponge was placed on the superior vena cava. Eight of the 11 patients were successfully defibrillated in this manner. This study laid the scene for the technological development that would result in the development of a totally automated version.

In 1976 the first implant of an automated implantable cardioverter defibrillator (AICD) was made in a dog\(^ {34}\) and the first implant in a human was made in February 1980. Outcomes from three patients suffering from recurrent malignant arrhythmias (arrhythmia likely to be lethal unless treated appropriately) underwent AICD implantation were published shortly afterwards.\(^ {35}\) Seven episodes of ventricular tachycardia and flutter/fibrillation were documented in the following weeks and six were automatically reverted to normal sinus rhythm by the device. One episode was treated with conventional external defibrillation before the implantable device could recharge.

These early iterations of the ICD (Figure 3) were rudimentary compared to contemporary transvenous ICD (TV-ICD) technology.\(^ {36}\) Implantation of the device required a thoracotomy or a sub-xiphoid approach. The potential implantees were all cardiac arrest survivors, and needed to have survived two episodes of cardiac arrest due to VA outside the context of a myocardial infarction. These must have been resistant to conventional and investigational pharmacotherapy. The response to sensed ventricular fibrillation or ventricular tachycardia at rates above a pre-specified threshold was to deliver a 25 joule pulse. The device could re-charge 3 times. Battery longevity was estimated at 3 year of monitoring or ability to deliver 100 shocks. One year mortality in those implanted with these devices was 22.9%, half that than in an equivalent population without the device (52% one-year mortality).\(^ {36}\)
The original defibrillator

The implantable defibrillator with apex and superior vena cava electrodes appears at the bottom left of the image and the fibrillator at the bottom right. This was used to induce ventricular fibrillation in animal studies. The defibrillator analyser in the upper half of the photograph. The arrow points toward the electromagnetic transducer. Reused with permission from Wolters Kluwer Health, Inc. (Circulation 1978 Mirowski Defibrillation in dogs 34).

2.2 ICD trials

The early clinical trials involving ICDs compared ICD therapy to medical drug treatment for the prevention of death in survivors of ventricular fibrillation or ventricular tachycardia where no reversible cause was found, in other words, for secondary prevention of SCD 37-40 Table 1 provides an overview of the secondary prevention ICD trials. These trials consistently found that the ICD reduced the risk of SCD death due to a 50% reduction in malignant ventricular arrhythmias. 41
Subsequently, a series of clinical trials tested the hypothesis that ICD may prevent death in patients at elevated risk of ventricular arrhythmias, primary prevention trials. Elevated risk of ventricular arrhythmia can be defined variously as reduced left ventricular ejection fraction, evidence of non-sustained ventricular tachycardia, positive electrophysiology stimulation test, depressed heart rate variability, elevated 24-hour heart rate on holter monitoring or abnormalities on signal averaged ECG). \(^{42-48}\) Five of these seven trials demonstrated the superiority of ICD therapy of medical therapy in improving survival in this primary prevention population. \(^{44,46-48}\) The majority of these trials evaluated patients with established coronary artery disease, though Kadish and Bardy demonstrated the superiority of ICD over medical therapy in non-ischaemic cardiomyopathy, \(^{42,46}\) however the recently published Danish trial challenges this viewpoint, and will be discussed in more detail below.

Table 2 provides an overview of the important primary prevention ICD trials. \(^{49}\) MADIT II was the largest of these trials and established reduced ejection fraction (<30%) as the principal predictor of SCD. \(^{48}\) Not all the trials demonstrated a mortality benefit from the ICD. Two trials CABG-PATCH and DINAMIT had negative results. \(^{43,45}\) The CABG-PATCH trial evaluated the effect on survival of a prophylactic ICD on patients at the time of coronary bypass grafting (CABG). No evidence of improved survival in the ICD group was found, a finding that is explained by the positive remodelling that occurred post CABG and the limited role of a tool used to risk stratify patients which has not been found to be useful in identifying high risk patients, the signal averaged ECG. The DINAMIT trial was an open label comparison of ICD therapy versus no ICD therapy in the early (day 6 to day 40) post myocardial infarction stage. The results demonstrated a reduction in the rate of death due to arrhythmia, this was offset by an increase in the rate of non-arrhythmic death, which were reportedly cardiovascular in nature.

The effectiveness of ICDs without cardiac resynchronisation therapy in patients with ischaemic and non-ischaemic cardiomyopathy was evaluated in a systematic review and meta-analysis and ICDs were found to reduce arrhythmic mortality [relative risk (RR): 0.40; 95% confidence interval (CI): 0.27-0.67] and all-cause mortality (RR: 0.73; 95% CI: 0.64-0.82) regardless of aetiology. \(^{50}\)
<table>
<thead>
<tr>
<th>Trial</th>
<th>Year</th>
<th>No. of patients</th>
<th>Enrolment criteria</th>
<th>Aim</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>DUTCH 39</td>
<td>1995</td>
<td>60</td>
<td>Survived cardiac arrest due to VF/VT and old MI (&lt;4 weeks) and inducible VT at EPS</td>
<td>ICD as first choice therapy vs conventional therapeutic strategy (antiarrhythmic drugs and then eventual ICD)</td>
<td>73% reduction in primary end points of death, recurrent cardiac arrest and cardiac transplantation at 24 months (95% C.I., 0.09 - 0.85; P=0.02)</td>
</tr>
<tr>
<td>AVID 37</td>
<td>1997</td>
<td>1016</td>
<td>Survived VT/VF cardiac arrest or VT with Survived VT/VF cardiac arrest or VT with syncope or VT with LVEF &lt;40%</td>
<td>Antiarrhythmic treatment vs ICD</td>
<td>31% reduction of mortality with ICD at 3 years (95% C.I. 0.10-0.52; p&lt;0.02)</td>
</tr>
<tr>
<td>CASH 37</td>
<td>2000</td>
<td>288</td>
<td>Cardiac arrest due to VF or VT</td>
<td>ICD vs antiarrhythmic agents</td>
<td>Non-significant reduction in all-cause mortality at mean follow up of 57 months. 28% reduction of all-cause mortality at 3 years with ICD (97.5% C.I. upper bound 1.112; P=0.08)</td>
</tr>
<tr>
<td>CIDS 40</td>
<td>2000</td>
<td>659</td>
<td>Cardiac syncope due to VF or sustained V and syncope or poorly tolerate VT and LVEF &lt;40% or syncope and inducible or monitored VT</td>
<td>ICD vs amiodarone</td>
<td>Non-significant 19.7% reduction of all-cause mortality with ICD (95% C.I. 0.077 – 0.4) p= 0.142</td>
</tr>
</tbody>
</table>

AVID, Antiarrhythmic Versus Implantable Defibrillators; CASH, Cardiac Arrest Study Hamburg; CIDS, Canadian Implantable Defibrillator Study; EPS, electrophysiological study; ventricular fibrillation; VT, ventricular tachycardia; ICD, implantable cardioverter-defibrillator; LVEF, left ventricular ejection fraction; MI, myocardial infarction; VF, ventricular fibrillation; C.I., confidence interval.

Table 1 Summary of secondary prevention ICD trials adapted from Santini et al. Heart 2007 49
<table>
<thead>
<tr>
<th>Trial (year)</th>
<th>Patients enrolled</th>
<th>Enrolment criteria</th>
<th>Aim</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>MADIT (1995) 47</td>
<td>196</td>
<td>LVEF 35%; prior MI; asymptomatic NSVT; NYHA I–III; inducible VT refractory to iv procainamide on EP study</td>
<td>ICD vs standard medical treatment</td>
<td>54% reduction in total mortality with ICD therapy (95% C.I 0.26–0.82) P=0.009</td>
</tr>
<tr>
<td>CABG-Patch (1997) 43</td>
<td>900</td>
<td>LVEF (35%; patients scheduled for CABG; positive SAECG results</td>
<td>ICD vs. no ICD</td>
<td>Non-significant 7% increase in mortality (95% C.I 0.81 to 1.42) p=0.64</td>
</tr>
<tr>
<td>MUSTT (1999) 58</td>
<td>704</td>
<td>LVEF (40%; CAD; NSVT; inducible VT on EP study</td>
<td>EP guided therapy (antiarrhythmic or ICD) therapy vs no antiarrhythmic therapy</td>
<td>23% reduction of total mortality with ICD therapy or antiarrhythmic at 5 years (95% C.I. 0.64-0.92) p=0.005</td>
</tr>
<tr>
<td>MADIT II (2002) 48</td>
<td>1232</td>
<td>EF&lt;30% &amp; prior MI</td>
<td>Conventional therapy vs ICD</td>
<td>31% reduction of all-cause mortality with ICD (95% C.I. 0.51–0.93) P= 0.016</td>
</tr>
<tr>
<td>DEFINITE (2004) 46</td>
<td>229</td>
<td>EF &lt;36%; NICM; NSVT or PVCS at Holter monitoring</td>
<td>Conventional therapy vs conventional therapy and ICD</td>
<td>35% reduction in mortality in ICD group at 2years (95% C.I. 0.40 - 1.06) P=0.08</td>
</tr>
<tr>
<td>DINAMIT (2004) 45</td>
<td>674</td>
<td>EF &lt;35%, recent MI (within 4–40 days); impaired cardiac autonomic modulation (HR variability)</td>
<td>Conventional therapy vs ICD</td>
<td>No reduction in mortality in ICD therapy (HR for death in the ICD group, 1.08; 95% C.I., 0.76 to 1.55; P=0.66); reduction of arrhythmic deaths with ICD p &lt;0.01</td>
</tr>
<tr>
<td>COMPANION (2004) 59</td>
<td>1520</td>
<td>NYHA class III–IV due to ischaemic and non-ischaemic cardiomyopathy, QRS &lt;120ms</td>
<td>Conventional therapy vs conventional therapy and CRT-P or CRT-D</td>
<td>40% reduction in all-cause mortality with CRT-D (95% C.I. 0.49 to 0.75) P&lt;0.001</td>
</tr>
<tr>
<td>SCD-HeFT (2005) 42</td>
<td>2521</td>
<td>EF &lt;35%, NYHA class II–III (ischaemic and non-ischaemic)</td>
<td>OMT + placebo vs OMT + amiodarone vs OMT vs ICD</td>
<td>23% reduction of overall mortality with ICD (97.5% C.I. 0.62 - 0.96; P=0.007)</td>
</tr>
<tr>
<td>DANISH (2016) 60</td>
<td>1116</td>
<td>NICM EF ≤35%, NYHA II–IV</td>
<td>OMT including CRT-P if indicated vs. OMT + ICD or CRT-D if indicated</td>
<td>No reduction in mortality in ICD group (HR, 0.87; 95% C.I. 0.68 - 1.12 ;) P=0.28</td>
</tr>
</tbody>
</table>

CABG-Patch, Coronary Artery Bypass Graft Patch; COMPANION, Comparison of Medical Therapy, Pacing and Defibrillation in Heart Failure; CRT, cardiac resynchronisation therapy; DEFINITE, Defibrillators in Non-Ischemic Cardiomyopathy Treatment Evaluation; DINAMIT, Defibrillator in Acute Myocardial Infarction Trial; EF, ejection fraction; EPS, electrophysiological study; HR, heart rate; ICD, implantable cardioverter-defibrillator; LVEF, left ventricular ejection fraction; MADIT, Multicenter Automatic Defibrillator Implantation Trial; MI, myocardial infarction; MUSTT, Multicenter Unsustained Tachycardia Trial; NSVT, electrocardiogram; SCD-HeFT, Sudden Cardiac Death in Heart Failure Trial; VF, ventricular fibrillation; VT, ventricular tachycardia.

Table 2 An overview of the important primary prevention ICD trials
2.2.1 Danish trial

Investigators in Denmark published the results of a contemporary trial of ICD therapy in patients with non-ischaemic cardiomyopathy the results of which have challenged current thinking in ICD therapy in patients with non-ischaemic cardiomyopathy. This trial, named Danish (Defibrillator implantation in patients with non-ischaemic systolic heart failure), sought to evaluate the benefit of ICD therapy in non-ischaemic cardiomyopathy as until then, the data for benefit in this patient population had been derived from subgroup analysis of trials, principally, SCD-Heft.42 The study was a randomised controlled trial and 556 patients with non-ischaemic cardiomyopathy were assigned to the ICD arm and 560 patient were assigned to the usual care. There was a high uptake of cardiac resynchronisation therapy (CRT) in both arms (58%). Primary outcome of the trial was death from any cause and the secondary outcome were sudden cardiac death and cardiovascular death.

ICD therapy did not result in a mortality benefit after a median follow up of 67.6 months. The primary outcome occurred in 21.6% in the ICD group and 23.4% in the control group (hazard ratio, 0.87; 95% confidence interval, 0.68 to 1.12; P=0.28). There was a significant reduction in sudden cardiac death in the ICD compared to the control group 4.3% vs 8.2% (hazard ratio, 0.50; 95% confidence interval, 0.31 to 0.82; P=0.005). In a subgroup analysis the only group to derive a mortality benefit from ICD therapy was the younger than 68 years old (hazard ratio, 0.64; 95% confidence interval, 0.45 to 0.90; P=0.01), presumably as they survived long enough to derive benefit from the device and did not die of other causes during the follow up period.

There may be several explanations for the lack of mortality benefit in this trial. Firstly, patients with non-ischaemic cardiomyopathy may be less vulnerable to ventricular arrhythmias compared to patients with ischaemic cardiomyopathy who often have demonstrable scar which can service of a focus for re-entrant ventricular tachycardias, the most frequent mode of ventricular arrhythmia in ischaemic cardiomyopathy. Both arms had very good pharmacological therapy with high rates of angiotensin converting enzyme inhibitor, β-blocker and mineralocorticoid receptor antagonist use and high rates of CRT may have reduced the likelihood of an arrhythmic death. The event rate in this study was lower compared to other studies and this reflects excellent medical management of their heart failure, an effective method of preventing sudden cardiac death.

Secondly, it is possible that the DANISH trial was underpowered to detect a significant difference in all-cause mortality. When the DANISH trial is combined in a meta-analysis of ICDs for primary prevention of death a patients with left ventricular dysfunction with other randomised controlled
trials which recruiting patients with non-ischaemic cardiomyopathy there continues to be a clear 24% reduction in all-cause mortality in patients treated with ICDs.\textsuperscript{51}

Figure 4 Left ventricular dysfunction without ischaemic heart disease: impact of primary prevention ICD on all-cause mortality. Data from Shun-Shin MJ, Zheng SL, Cole GD, Howard JP, Whinnett ZI, Francis DP. Implantable cardioverter defibrillators for primary prevention of death in left ventricular dysfunction with and without ischaemic heart disease: a meta-analysis of 8567 patients in the 11 trials.\textsuperscript{51}

This result remained stable for the removal of any one trial. The fact that the addition of DANISH to a meta-analysis would not reduce the benefit of ICD therapy over medical therapy in non-ischaemic cardiomyopathy has been acknowledged by the authors of DANISH prior to the publication of this meta-analysis.\textsuperscript{52} The authors also acknowledge that the DANISH trial has the longest follow-up of any of the ICD trials and this may have contributed to the reduced effect of the ICD. As can be observed in the Kaplan-Meier curves, there is early separation between the ICD and control groups which later re-join (Figure 5). Any trial, if follow-up is long enough will ultimately have re-joining of survival curves as eventually all patients reach the primary end-point, death.
Figure 5 Time-to-event curves for death from any cause (A), cardiovascular death (B), and sudden cardiac death (C) from the DANISH trial.
Whilst the results of Danish have stimulated discussion amongst cardiologists, it has yet to influence policy but impacting on national and international guidelines.

2.3 Impact on policy and practice

Following the publication of these data, there were a number of international guidelines detailing the indications for primary and secondary prevention ICD implantation.\textsuperscript{53, 54} This led to a rapid expansion in the rates of ICD implantation\textsuperscript{55} particularly in the United States and in some European countries, though even within nations there existed significant geographical variation in implantation, explained by a variation physicians with a particular interest in ICD therapy driving services forward and variability in local referral pathways.\textsuperscript{56 57}

2.3.1 United Kingdom guidelines

The National Institute of Health and Clinical Excellence (NICE) issued updated guidelines on the implantation of ICD in the technology appraisal guidance in 2014 (TA314)\textsuperscript{58} and this replaced the earlier guidelines which were published in NICE technology appraisal guidance95 (published January 2006) and NICE technology appraisal guidance 120 (published May 2007).

2.3.2 The National Institute for Health and Care (clinical) Excellence guidelines for the implantation of ICDs

2.3.3 Secondary prevention of sudden cardiac death

1. ICDs are recommended for treating people with previous serious ventricular arrhythmia without a treatable cause if they

- have survived a cardiac arrest caused by either ventricular tachycardia (VT) or ventricular fibrillation 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 left ventricular ejection fraction (LVEF) of 35% or less but their symptoms are no worse than class III of the New York Heart Association (NYHA) functional classification of heart failure.
2. Treating people who:

- have a familial cardiac condition with a high risk of sudden death, such as long QT syndrome, hypertrophic cardiomyopathy, Brugada syndrome or arrhythmogenic right ventricular dysplasia or
- have undergone surgical repair of congenital heart disease.

2.3.4 Primary prevention of sudden cardiac death

Implantable cardioverter-defibrillators and cardiac resynchronisation therapy (CRT) with defibrillator (CRT-D) or CRT with pacing (CRT-P) are recommended as treatment options for people with heart failure who have left ventricular dysfunction with a left ventricular ejection fraction (LVEF) of 35% or less as specified in Table 3.

<table>
<thead>
<tr>
<th>QRS interval</th>
<th>NYHA class</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;120 milliseconds</td>
<td>ICD if there is a high risk of sudden cardiac death</td>
</tr>
<tr>
<td>120–149 milliseconds without LBBB</td>
<td>ICD</td>
</tr>
<tr>
<td>120–149 milliseconds with LBBB</td>
<td>ICB</td>
</tr>
<tr>
<td>≥150 milliseconds with or without LBBB</td>
<td>CRT-D</td>
</tr>
</tbody>
</table>

LBBB, left bundle branch block; NYHA, New York Heart Association

Table 3 Treatment options with ICD or CRT for people with heart failure who have left ventricular dysfunction with an LVEF of 35% or less (according to NYHA class, QRS duration and presence of LBBB)
2.3.5 European Society of Cardiology guidelines for the implantation of ICDs

In 2015, the European Society of Cardiology (ESC) published their updated guidelines on the management of patients with ventricular arrhythmias and the prevention of sudden cardiac death. 59

<table>
<thead>
<tr>
<th>Recommendation</th>
<th>Class</th>
<th>Level</th>
</tr>
</thead>
<tbody>
<tr>
<td>ICD implantation is recommended in patients with documented VF or haemodynamically not tolerated VT in the absence of reversible causes or within 48 h after myocardial infarction who are receiving chronic optimal medical therapy and have a reasonable expectation of survival with a good functional status &gt;1 year.</td>
<td>I</td>
<td>A</td>
</tr>
<tr>
<td>ICD implantation should be considered in patients with recurrent sustained VT (not within 48 h after myocardial infarction) who are receiving chronic optimal medical therapy, have a normal LVEF and have a reasonable expectation of survival with good functional status for &gt;1 year.</td>
<td>IIa</td>
<td>C</td>
</tr>
<tr>
<td>In patients with VF/VT and an indication for ICD, amiodarone may be considered when an ICD is not available, contraindicated for concurrent medical reasons or refused by the patient</td>
<td>IIb</td>
<td>C</td>
</tr>
</tbody>
</table>

Table 4 Summary of ICD implantation guidelines for the secondary prevention of sudden cardiac death issued by the European Society of Cardiology in 2015. 59 (LVEF, left ventricular ejection fraction; VF, ventricular fibrillation; VT, ventricular tachycardia).

<table>
<thead>
<tr>
<th>Recommendation</th>
<th>Class</th>
<th>Level</th>
</tr>
</thead>
<tbody>
<tr>
<td>ICD therapy is recommended to reduce SCD in patients with symptomatic HF (NYHA class II–III) and LVEF ≤35% after ≥3 months of optimal medical therapy who are expected to survive for at least 1 year with good functional status.</td>
<td>I</td>
<td>A</td>
</tr>
</tbody>
</table>

Table 5 Summary of ICD implantation guidelines for the primary prevention of sudden cardiac death issued by the European Society of Cardiology in 2015. 59 (LVEF, left ventricular ejection fraction).
2.4 Effectiveness of ICDs

In well selected patient populations, the ICD has been repeatedly shown to be effective in reducing arrhythmic deaths. In an analysis of the pivotal primary and secondary prevention trials, Betts et al. expressed efficacy in terms of absolute rather than relative risk reduction and number needed to treat to prevent one death (NNT).\(^6\) For secondary prevention trials (AVID, CIDS and CASH) the absolute risk reduction (ARR) at 3 year follow up ranges from 3.7% (NNT = 27) to 11.3% (NNT=8.8). For primary prevention trials (MADIT, MUSTT, MADIT II, DINAMIT and SCD-HeFT) the ARR at 3 years ranged from 0 (no benefit) to 24.6% (NNT=4). These initial trials had relatively few patients followed up beyond 2 years with the exception of the MADIT II trial. This trial reported outcomes up to eight years with ARR of 13% (NNT=7.7)\(^6\)

Many of the patients enrolled in these trials were under the age of 65 years and thus the outcomes may not reflect current clinical practice. The largest international registry of ICDs reported that of the 150 264 primary prevention patients who received ICDs from January 2006 to December 2008, 61% were aged over 65 years.\(^6\) In an analysis of over 65 000 Medicare patients with ICDs over the age of 65 mean age was 75 years, and nearly one-third had died within 3 years, reflecting a population with more advanced age and disease than seen in trial populations for primary prevention ICD.\(^6\)

In spite of the overall net benefit in terms of improved survival, clinical experience showed that there were important limitations associated with ICDs which may have limited the uptake of the technology to a degree.

2.5 Limitations of the ICD

ICD leads were introduced in 1993. This simplified the task of implanting an ICD as a thoracotomy was no longer required. However, the implantation of a ICD is associated with a small but significant risk of serious complication\(^6\) which is likely to be underreported in clinical trials.\(^6\)

These can be classified as early and late complications and are listed in Table 6 and Table 7 below. Many of these complications relate to the presence of transvenous leads.
<table>
<thead>
<tr>
<th>Complication</th>
<th>Clinical consequence</th>
<th>Incidence</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pocket haematoma</td>
<td>Surgical evacuation</td>
<td>2.2-4.7%</td>
<td>66</td>
</tr>
<tr>
<td>Pneumothorax</td>
<td>Intercostal drain</td>
<td>0.4-1.3%</td>
<td>66 67-69</td>
</tr>
<tr>
<td>Lead displacement</td>
<td>Lead reposition</td>
<td>1.80%</td>
<td>66</td>
</tr>
<tr>
<td>Lead related trauma</td>
<td>Cardiac perforation / cardiac tamponade</td>
<td>0.1-0.5%</td>
<td>67-69</td>
</tr>
<tr>
<td></td>
<td>Haemothorax or mediastinal haemorrhage</td>
<td>Rare case reports</td>
<td>70-74</td>
</tr>
<tr>
<td>Defibrillation related</td>
<td>Delayed or failed cardioversion of VF</td>
<td>0.14%</td>
<td>75</td>
</tr>
<tr>
<td></td>
<td>Left atrial thrombus-related thromboembolism</td>
<td>0.03%</td>
<td>75</td>
</tr>
<tr>
<td></td>
<td>Post shock PEA</td>
<td>Rare</td>
<td></td>
</tr>
<tr>
<td>Thrombo-embolic</td>
<td>Subclavian thrombosis / venous occlusion</td>
<td>9-28%*</td>
<td>76</td>
</tr>
<tr>
<td></td>
<td>Pulmonary embolism related to subclavian thrombosis</td>
<td>16-36%**</td>
<td>76, 77</td>
</tr>
<tr>
<td></td>
<td>Paradoxical embolism</td>
<td>Rare case report</td>
<td>77, 78</td>
</tr>
<tr>
<td></td>
<td>Coronary or systemic embolism</td>
<td>Rare case reports</td>
<td>79, 80</td>
</tr>
<tr>
<td>Any mechanical complication</td>
<td></td>
<td>3.7-6.6%</td>
<td>67-69 77</td>
</tr>
<tr>
<td>In hospital death</td>
<td></td>
<td>0.20%</td>
<td>66</td>
</tr>
</tbody>
</table>

Table 6 Summary of early complications related to transvenous-ICD implantation.

PEA (pulseless electrical activation); * the incidence of subclavian thrombus or venous occlusion is based on data from three studies in which bilateral venography was performed prior to ICD generator exchange. The incidence of abnormal venography and total venous occlusion have been presented; ** incidence of PE quoted only if subclavian thrombosis present.
<table>
<thead>
<tr>
<th>Clinical consequence</th>
<th>Incidence</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infection</td>
<td>System extraction</td>
<td>1.61%</td>
</tr>
<tr>
<td>Inappropriate shocks</td>
<td>Psychological distress and mortality association</td>
<td>6-10% †</td>
</tr>
<tr>
<td></td>
<td></td>
<td>2%‡</td>
</tr>
<tr>
<td>Tricuspid valve injury</td>
<td>Worsening tricuspid regurgitation by at least one grade</td>
<td>34.20%</td>
</tr>
<tr>
<td>Lead failure</td>
<td>Inappropriate shocks, repeat procedures</td>
<td>10.7-15%* at 5 years</td>
</tr>
<tr>
<td>Can failure</td>
<td>Generator malfunction requiring early replacement</td>
<td>26.5/1000 patient years</td>
</tr>
<tr>
<td>Psychological distress</td>
<td>PTSD*, reduced QOL, depression and anxiety related to ICD shocks</td>
<td>14-66%</td>
</tr>
<tr>
<td>Attendant complication rate at generator exchange</td>
<td>Most commonly lead fracture, infection, lead dislodgement.</td>
<td>4-15%‖</td>
</tr>
</tbody>
</table>

Table 7 Summary of late complications related to the ICD.

PTSD*, post-traumatic stress disorder, QOL, quality of life

†Annual incidence of inappropriate shocks from retrospective analysis of two prospective multicentre studies, one retrospective analysis of manufacture registry and one retrospective single centre study.

‡ Incidence of inappropriate shock at mean follow up time of 1.4 years from the high-rate programming arm of MADIT-RIT trial which represents current standard for ICD programming.

*Single centre longitudinal follow up of over 5000 ICD leads. Survival curves for recalled versus non-recalled leads separated at 2 years.

‖Data from the REPLACE registry 91. Rates of complication at pacemaker and ICD generator replacement vary from 4% with no additional lead requirement to 15% with additional lead requirement. Major complications were higher in ICD compared to pacemaker generator replacements (Odds Ratio (OR), 2.38; 95% CI 1.30 to 4.38; P<0.004).
2.5.1 Lead and generator failure

The average life of an ICD lead is approximately 10 years and 6 years for the generator. Lead failure rates have been suggested to be approximately 1% per annum and progresses over time. As patients live longer with ICD implant, the ICD hardware has longer exposure to mechanical stresses. Lead design innovation led to smaller diameter leads being developed for ease of use, this has been at the cost of reduced lead insulation with resultant lead fracture and erosion occurring in some leads. ICD leads are therefore considered to be the weak-link in conventional ICDs. The five year failure-free survival of ICD leads from three manufacturers is presented in Figure 6.

Two ICD leads, the Sprint Fidelis (Medtronic Inc. Minneapolis, Minnesota) and the Riata (St Jude Medical, Sylmar, California) have been recalled by the US Food and Drug Administration in 2007 and 2011 respectively. ICD lead failure are associated with inappropriate shock in 76% of cases. Serious complications can result from a failing lead as evidenced by the high frequency of inappropriate shocks seen with the Sprint Fidelis and Riata leads. Rates of psychological distress are higher amongst patients who have received shocks of any kind. The young and woman have been reported to be the most affected by Riata lead failures. It is recommended to extract fractured leads and to replace recalled leads with no signs of fracture at the time of generator exchange. Whilst the extraction of a transvenous endocardial lead has improved significantly, it is still associated with occasional serious complications and a small risk of death.

Patients with ICDs can also experience inappropriate shocks due to inappropriate identification and classification of non-lethal arrhythmias as potentially lethal. This occurs in about 10-20% of ICD recipients and is associated with pro-arrhythmia, anxiety, depression, poor quality of life and increased mortality. The data are conflicting on whether the inappropriate shocks increase mortality directly or whether they occur more frequently in a sicker population (increased incidence of atrial fibrillation etc.). Optimising the programming of the ICD can reduce the likelihood of inappropriate shocks due to incorrect identification and classification of arrhythmias. Improved rhythm discrimination algorithms can also reduce inappropriate shocks and thus provide direct benefit to the patient.
Figure 6 Five year failure-free survival of ICD leads from 3 manufactures.
Survival curves for the 2 leads with advisories diverged from the other ICD leads at 2 years. This occurred due to deficiencies in lead design Re-used with permission Elsevier, from Liu et al.
Longitudinal follow-up of implantable cardioverter defibrillator leads. The American journal of cardiology 2014; 113: 103-106. 85

2.6 Evolution of the S-ICD

The landmark primary prevention ICD trials using TV-ICD described above 42, 47, 48 meant that a large number of patients with a history of previous myocardial infarction or heart failure could be eligible for ICD therapy. However, due to the limitations of the TV-ICD, the perceived cost of the devices and other factors, there rates of implantation did not meet this increased need. 105-110 There were also cases of patients with a need for ICD but in whom TV-ICD leads were not suitable due to the young age of the patient or the presence of complex venous anatomy. 111 In order to address some of the limitations the subcutaneous ICD (S-ICD) was developed. 112, 113 However, there were several problems that needed to be overcome such elevated defibrillation
requirements, lack of safety and efficacy data of shock efficacy and issues surrounding appropriate sensing in S-ICD. These shall be considered in next sections.

### 2.6.1 Defibrillation energy requirements

Defibrillation requires the generation of a sufficient voltage gradient over the myocardium to terminate fibrillation. It is hypothesised that a voltage gradient of \( \approx 5 \text{V/cm} \) over \( \approx 90\% \) of the myocardium is required for efficient defibrillation. TV-ICD s are easily able to achieve this threshold, however, due to the close proximity of the shock coil within the heart, much greater gradients of over \( 30 \text{V/cm} \) are achieved near the shock coil. Defibrillation with such high voltages has been shown to damage myocytes, a term known as electroporation. This can result in transient reduction in contractility and troponin release and a voltage gradients greater than \( 50 \text{V/cm} \) electrical stunning and post-shock ventricular arrhythmias.

Early S-ICD trials focused on the defibrillation energy requirements (DER) for the S-ICD, as unlike the TV-ICD, an S-ICD lacked a defibrillation electrode within the heart, and therefore the potential energy requirements were likely to be much greater. This has resulted in reduced battery longevity and larger generator size in S-ICDs compared to TV-ICDs.

A study designed to estimate the subcutaneous DER using a subcutaneous to cutaneous (SQ to Q) electrode configuration in the left upper anterior chest region in patients undergoing TV-ICD implantation using additional two VF inductions was performed. Twenty patients were recruited and were entered into either a high (70 joule) or low (50 joule) stage with an energy step up or down for the second shock dependent of the success of the first shock. The results were as follows: Q-SQ defibrillation at 50 J was successful in 17/18 patients (94%); Q-SQ defibrillation at 30 J was successful in 7/9 patients (78%), and two patients (10%) required 100 J for successful SQ defibrillation. This suggested that there was considerable variability in the DER between patients and was considerably more than the latest iterations of TV-ICDs. Therefore a change in the device size, components and possible SQ vectors was considered.

In a subsequent study evaluating the efficacy of a novel anteroposterior defibrillation shock pathway using a long time-constant shock waveform found that over 80\% of patients were successfully defibrillated using 35J or less.

Finite element computer modelling was then used in a study designed to determine factors affecting optimal lead positions for S-ICD. This technique is able to explore the electric fields generated by electrodes placed in arbitrary locations and orientations in the human torso as a way of estimating the relative defibrillation efficacies on S-ICD orientations. Pseudo-DFTs were
generated. In total 122 single-electrode/array configurations and 28 dual-electrode configurations were tested. This study concluded that the choice of electrode configuration which maximises shock vector alignment with the centre of the myocardial mass and the use of longer leads is more likely to result in lower DFT.

Whilst the DER of the S-ICD are nearly three times greater compared to the TV-ICD, the energy is dissipated in a more uniform manner through the thorax, with only approximately 10% reaching the myocardium. This resembles the ideal model of defibrillation and is evidenced by significantly lower troponin I release from pigs hearts following 80J S-ICD shocks compared to 35J transvenous shocks.\(^{118}\) The cost however, is increased skeletal muscle damage with the S-ICD shocks. No pulmonary damage was reported in pigs either type of shock.

In summary the elevated DER in S-ICDs was overcome by developing S-ICD with a capacity to deliver 80J rather than the 35-40J seen with TV-ICDs.

### 2.7 Shock efficacy and safety

#### 2.7.1 Preclinical

Cappato et al. described the process that led to the development of the S-ICD to be used in humans. They tested the combination of an anterior electrode adjacent to the left edge of the sternum and a lateral electrode at the site along the axillary line between the 4th and 6th intercostal space in two acute defibrillation studies, the first to test the DFT and the second to test the S-ICD’s ability to induce, detect and shock VF in canines. Shock energies of less than 80J terminated all induced VFs as well as providing effecting detection of activation of shock therapy in all cases.\(^{127}\)

#### 2.7.2 Clinical

Two short-term small, non-randomised clinical trials were then conducted to identify suitable device configuration and assess energy requirements.\(^{128}\) The results were published in the New England Journal of Medicine and has become the seminal paper for S-ICDs. Four S-ICD configurations were evaluated in 78 patients and subsequently tested in 49 patients to determine the S-ICD DFT in comparison with that of the standard TV-ICD. (Figure 7) The optimal configuration consisted of a left parasternal electrode and a left thoracic pulse generator located in the 5\(^{th}\) and 6\(^{th}\) intercostal space in the mid axillary line. This configuration was as effective for terminating induced ventricular fibrillation as a TV-ICD albeit with significantly higher energy requirements (36.6±19.8J vs. 11.1±8.5J).
Four configurations of an S-ICD as tested by Bardy et al. Panel A (top left) ultimately became the preferred configuration for lead and generator placement. Reproduced with permission from (Bardy GH, Smith WM, Hood MA, Crozier IG, Melton IC, Jordaens L, et al. An entirely subcutaneous implantable cardioverter-defibrillator. NEJM 2010; 363: 36-44.), Copyright Massachusetts Medical Society.

Induced ventricular fibrillation was successfully converted twice in 58/59 patients (98%) with a 65J shock. In a longer follow up (mean 10±1 months) the device successfully detected and treated all 12 episodes of spontaneous sustained ventricular tachyarrhythmia.

A prospective nonrandomised, multicentre trial confirmed the safety and efficacy of the S-ICD. The acute conversion rate for ventricular fibrillation was >90% for the 330 patients with a 180 day system complication-free rate of 99%.
2.8 S-ICD screening

In contrast to patients receiving a TV-ICD, potential S-ICD recipients must have an ECG with an appropriate morphology as the sensing occurs from the subcutaneous electrodes (resembling a surface ECG) and not an endocardial lead. Pre-implant screening is therefore mandated prior to implantation of an S-ICD. This is achieved by recording a three-lead electrocardiogram with surface electrodes placed over the 5th intercostal space in the mid-axillary line, 1cm lateral to the xiphoid midline, on the patient’s left and 14 cm superior to this. This configuration replicates the S-ICD sensing vectors. The ECG is acquired in the supine and standing postures. The acquired electrograms are then analysed using a proprietary ECG screening tool prior to device implantation. (Figure 8) As the morphology analysis is crucial to S-ICD rhythm detection and discrimination, this screening process is to ensure reliable sensing. Patients need to have an ECG that suitably matches the template in at least one vector in both postures to pass the screening process. Patients who fail this screening process are not suitable for S-ICD implantation.

Figure 8 Pre-implant screening tool.

Appropriate and inappropriate pre S-ICD ECG screening. Only one of the ECGs fits the ECG template (top right) all others failed as part of the P-QRS-T complex fell outside or below the pre-

2.9 Sensing with the subcutaneous implantable cardioverter

The S-ICD senses cardiac signals very differently from a TV-ICD. This is because electrocardiograms derived subcutaneously resemble a surface ECG rather than the unique signal obtained from an intracardiac electrode. 130 The morphology of normal sensed beats differs significantly from ventricular tachycardia sensed beats in the surface ECG and the S-ICD ECG. (Figure 9) This is one of the strengths of the S-ICD as it uses morphology based discrimination to accurately distinguish SVTs from ventricular arrhythmias. 131

![Surface ECG, IEGM and S-ICD electrograms.](http://events.medtelligence.net/2012/may9/Boersma/index.htm)

A comparison of the sensed signal with the surface ECG, the intracardiac electrogram and the S-ICD ECG in normal rhythm and in ventricular tachycardia. Adapted from slide in presentation by Dr Boersma, St Antonius Hospital, Nieuwegein, The Netherlands available at http://events.medtelligence.net/2012/may9/Boersma/index.htm
Chapter 2

The S-ICD uses 3 sensing electrodes to generate 3 sensing vectors. Two electrodes, distal and proximal, flank the parasternal defibrillation coil. The distal electrode is located at the level of the manubriosternal joint and the proximal electrode is located adjacent to the xiphoid. The third sensing electrode is the active can. (S-ICD generator) This configuration generates three sensing vectors, primary vector (between the distal electrode and the can), secondary vector (between the distal electrode and the can) and the alternative vector (between the distal and proximal electrode). (Figure 2).

The S-ICD automatically selects the sensing vector with the best signal for rhythm detection and in clinical practice, this is usually the primary vector. The QRS template is sampled in 41 locations along the QRS contour and are compared with subsequently sensed signals. This is conceptually similar to the TV-ICD morphology based comparison algorithm but the resolution is considerably higher with the S-ICD.

Recent work has identified that approximately 85% of patients with an indication for an ICD on primary or secondary prevention grounds have an ECG that meets the S-ICD screening criteria. Hypertrophic cardiomyopathy, a heavy weight, prolonged QRS duration and an R:T ratio <3 in the ECG lead with the largest T wave were independently associated with failure to pass the screening test.

2.10 Overview of S-ICD sensing algorithms

The S-ICD sensing the cardiac signal very differently from TV-ICDs. The S-ICD utilises a morphology based sensing algorithm that uses the rich signal of the QRS-T complex which resembles the surface ECG. This signal is analysed by the S-ICD in a similar manner to how a clinician would analyse an ECG, by assessing the rate and the morphology of the QRS-T complexes. The main advantage of this method is that discrimination between supraventricular tachycardia (narrow and regular) and ventricular arrhythmias (broad and regular) is as good as if not better with S-ICDs than TV-ICD. This was demonstrated in a head-to-head comparison of the S-ICD and TV-ICDs form three manufactures and well as in clinical practice. However, the advantages of morphology based sensing are off-set by the disadvantages caused by the presence of T-waves which can lead to T-wave oversensing and inappropriate shocks. This is one of the most common causes of inappropriate shocks in patients with S-ICD at the current incidence is approximately 5-7% per annum.

To prevent this, commercially available S-ICD system employ several strategies to risk the likelihood of T wave oversensing:
1. The pre-implant screening tool to exclude patients with large T waves who may be prone to T wave oversensing

2. Automatic setup whereby the S-ICD selects the optimal vector out of the three available for sensing

3. Variable threshold detection profiles to avoid T wave detection
   a. This a relatively commonly employed technique in implantable cardiac electronic devices the ‘window’ or threshold for detecting cardiac signal decays rapidly after a sensed R wave but not too rapidly in order to avoid the T wave. The threshold for detection needs to be lowered so that the device can detect low amplitude ventricular fibrillation waves should they arise. An example of a profile of a variable threshold detection taken from a patent submitted by the S-ICD engineers is shown in Figure 10. ¹³⁴

   ![Figure 10](image)

   Figure 10 Illustration of the use of a variable threshold detection profile to avoid the unnecessary detection of the T wave after having detected the preceding QRS complex.

   Taken from patent application ‘Accurate cardiac event detection in an implantable cardiac stimulus device ‘US 20140046394 A1¹³⁴

   b. These algorithms employ S-ICD hardware features that measure the minimum and maximum amplitudes of each potential QRS complex, time intervals between detections, widths of each detected complex, and morphologic comparison of the currently detected complex to both the previous complex and to a stored normal sinus rhythm, known as the Reference ECG. Software algorithms then look for patterns in either the morphologic comparison to the Reference ECG (Figure 11A) or the intervals (Figure 11B) to recognize and discard the inappropriate detections and correct the time interval between the appropriate detections. ¹³⁵
c. The most recent of these compares the morphology of 3 successive detections to identify when 2 similar QRS complexes (N vs. N-2) are separated by a dissimilar T-wave complex (N vs. N-1; see Figure 11C). In addition to comparing complexes N to N-1 and N to N-2, the width of each complex and the intervals between detections were used to enhance algorithm performance. When 3 successive detections fit the rules of the algorithm, detection N-1 is deemed to be a T-wave and is discarded. The authors of the article that describes this algorithm claim that it will reduce the incidence of T-wave oversensing by 40% and that it is hoped that this will translate into a meaningful reduction in inappropriate shocks.

4. SMARTPASS filter
   a. This is a high-pass filter designed to reduce oversensing while maintaining an appropriate sensing margin, though the details of this a commercially sensitive and have not been released into the public domain.

5. The use of a conditional zone for the detection of tachycardias (see below).
Chapter 2

Figure 11 Novel sensing algorithm to reduce T wave oversensing

A: An S-ICD sensing algorithm that compares detected complexes to a normal sinus rhythm reference and identifies repeated patterns of match–no match to discard over-detections.

Panel B: An S-ICD sensing algorithm that identifies repeated patterns of short to long intervals to discard over-detections.

Panel C: This algorithm was developed to reduce T wave oversensing. The most recently detected complex (N) is compared to both the previous (N-1) and the 2nd previous complex (N-2). Patterns where N matches N-2 but not N-1 could be used to remove T-waves. *Dashed red lines and solid blue lines indicate that the algorithms depicted in Panels A and B, respectively, would not detect the T-wave in this example.
Chapter 2

2.11 Rhythm discrimination in S-ICD

2.11.1 The Insight™ algorithm

The Insight™ algorithm is used by the current version of the S-ICD (Boston Scientific, 1 Boston Scientific Pl, Natick, MA 01760, United States) to discriminate between different arrhythmias to prevent inappropriate shocks.

There are 3 tiers of rhythm analysis that it runs simultaneously once the rate falls within the tachycardia zone.

2.11.2 Static morphology analysis

A sensed tachycardia beat morphology is compared with a stored template. If there is a good match between the sensed beat and the stored template it is considered to be supraventricular in origin and labelled a sensed beat ‘S’, otherwise it is considered to be ventricular and the algorithm continues.

2.11.3 Dynamic morphology analysis

A sensed tachycardia beat morphology is compared with the preceding beat. This assesses for a polymorphic relationship between beats. If there is polymorphic relationship, the beat is labelled a tachycardia beat ‘T’ and if it is a good match the algorithm continues. If not the device assumes the rhythm is ventricular fibrillation and commences capacity charging for preparation of shock delivery.

2.11.4 QRS width analysis

The QRS width of the sensed tachycardia beat is compared with the stored template (recorded at the time of implant and representing a ‘normal beat’). If the QRS width is narrow, the beat is considered supraventricular and is labelled a sensed beat ‘S’ otherwise it is considered ventricular and it is labelled as a tachycardia beat ‘T’.

Table 8 summarises the interventions that have been shown to reduce the incidence of inappropriate shock or T wave oversensing.
## 2.12 Calculation of heart rate

The S-ICD uses a mean of four sensed QRS complexes to determine heart rate. Once the heart rate falls within the tachycardia zone the Insight\textsuperscript{TM} algorithm is triggered.

### 2.12.1 The importance of accurate heart rate detection

An alternative method to reduce oversensing would be to find an alternative method of calculating the heart rate by detecting the QRS in a way that oversensing of the cardiac signal is avoided completely. The importance of accurate heart rate detection is illustrated in the following clinical case that I reported.\textsuperscript{136}

### 2.12.2 Five shocks two mechanisms

A 69 year-old male was recommended to have an implantable cardioverter-defibrillator for secondary prevention of sudden cardiac death. The patient had a relative contraindication to a transvenous ICD by having a large right atrial thrombus despite being on warfarin with a therapeutic INR. The patient was assessed for suitability for an S-ICD and successfully passed the ECG screening process. An S-ICD (Model number 1010, Boston Scientific, 1 Boston Scientific Pl, Natick, MA 01760, United States) was implanted without complication prior to the patient’s discharge home. The device was programmed with a conditional zone between 190-230 bpm and a shock zone for rates greater than 230 bpm. Sensing was from the secondary vector.

The patient subsequently presented on four occasions having received a total of five inappropriate shocks from the S-ICD. The first four episodes were from the same mechanism. The patient underwent VT ablation which was successful at preventing VT recurrence. The patient then had a fifth episode of inappropriate therapy. The S-ICD was replaced with a TV-ICD. No further inappropriate shocks have occurred since.

### Table 8 Interventions that have been shown to reduce the incidence of inappropriate shock or T wave oversensing.

<table>
<thead>
<tr>
<th>Intervention</th>
<th>Reduction in incidence of inappropriate shock\textsuperscript{1} / TWOS\textsuperscript{2}</th>
</tr>
</thead>
<tbody>
<tr>
<td>Appropriate use of screening tool</td>
<td>Unknown</td>
</tr>
<tr>
<td>Use of dual zone programming</td>
<td>15.9% (1)</td>
</tr>
<tr>
<td>Use of 3 successive complexes algorithm</td>
<td>39.8 +/- 11.4% (2)</td>
</tr>
</tbody>
</table>

1. TWOS = Tachycardia-Waveform Oversensing System
2. S-ICD = Subcutaneous Implantable Cardioverter-Defibrillator

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Inspection of stored subcutaneous ECGs (S-ECGs) for the first four inappropriate shocks reveals an identical mechanism of onset. (Figure 12 and 13)

2.12.2.1 Explanation of the electrograms

The heart rate is between 140-150 bpm and the complexes are broad and the rhythm is regular. Monomorphic ventricular tachycardia is the most likely cause (Figure 12). The S-ICD ascribed the largest positive or negative wave as an R wave. There are sensing markers throughout the recording. Some of these complexes are sensed on the R-wave (positive wave) and some on the T-wave (negative wave). We speculate that this occurred because rhythm had positive and negative wave of equivalent amplitudes. At a critical moment (Figure 12 and Figure 13; red circles) sensing of both the R-wave and the T-wave occurs within a single VT complex (T-wave oversensing) resulted in the calculated heart rate falling into the shock zone.

The S-ICD calculates heart rate by measuring the mean of 4 consecutive RR intervals. The initial rate 140 bpm (Figure 12), which is well below the tachycardia zones (conditional zone rate 190-230 bpm and shock zone >230 bpm). At the point the duration of 4 sequential sensed beats is 920ms and the calculated heart rate is therefore 920ms/4 = 230ms or 260 bpm, thus falling into the shock zone. It is important to note that the S-ICD initially employs rate criteria alone to trigger tachycardia detection (unlike TV-ICD which variously employ onset, stability, duration etc.). In summary, a single double counted beat during monomorphic VT resulted in the first four inappropriate shocks.
Figure 12 Stored S-ICD ECG from the alternate vector taken from treated episode in November 2013.

The rhythm is monomorphic VT rate 140 bpm. This image illustrates the variation in where the S-ICD senses each complex (S): * R-wave sensed and ^ T-wave sensed (0-24 seconds). However each complex is only counted once. The red circle (38 seconds) highlights single complex that has been double counted (T-wave oversensing). This marks the point where the calculated heart rate falls within the shock zone. Dashed red arrow indicates increased sensitivity within conditional zone with multiple complexes double counting (●●) resulting in tachycardia confirmation, device charging (C) and shock delivery (знак Разряд) and termination of the tachycardia.
Figure 13 Subcutaneous ECG from the secondary vector taken from treated episode in October 2013.

The rhythm is monomorphic VT rate 150 bpm. Red circle highlights single complex that has been double counted. This marks the point where the calculated heart rate falls within the conditional zone. The dashed red arrow indicates increased sensitivity within conditional zone with multiple complexes double counting resulting in tachycardia confirmation, device charging(C) and shock delivery (✔) and termination of the tachycardia.
Once in the shock zone the sensing characteristics within the S-ICD become much more aggressive. However, in this case, there is clear evidence of frequent T-wave oversensing that was not apparent prior to triggering the shock zone (Figure 12 and Figure 13). Ultimately, sufficient number complexes were labelled as tachycardia beats to fulfil the predetermined criteria for device charging and subsequent shock delivery.

2.12.3 How does sensing influence tachycardia therapy?

The principal function of any defibrillator is to sense the cardiac signal. Once this is achieved then the heart rate can be determined and detection of ventricular arrhythmias can occur. Accurate sensing is likely to influence the tachycardia therapy appropriately and inaccurate sensing is likely to misinform the tachycardia therapy.

In a study comparing the sensing and discrimination performances of the S-ICD and three commercial available TV-ICD devices, the S-ICD performed better than two of the three TV-ICD devices in SVT discrimination. Ventricular arrhythmia detection was comparable between the technologies and was >99% accurate in all 4.

The aim of all ICDs is to achieve 100% sensitivity in detecting potentially lethal arrhythmias. However, this is often achieved at the expense of reduced specificity, in other words inappropriate detections and potentially shock delivery for non-lethal arrhythmias such as supraventricular tachycardia (SVT).

Registry data suggests that the S-ICD is effective in sensing and then terminating ventricular arrhythmias, but with nearly 1 in 8 patients receiving inappropriate shocks, mainly due to T-wave over sensing. This is relatively high rate of inappropriate therapy and one of the main drawbacks of this technology as discussed in the section on complications above.

T-wave oversensing occurs when the S-ICD misinterprets the T wave as an R wave, and therefore double counts each beat. Thus an episode of oversensing occurring whilst an individual is exercising with a heart rate of 125bpm will result in the ‘inaccurate’ sensed heart rate to be 250bpm. This falls in the S-ICD tachycardia window (maximum programmed rate is 240bpm) and therefore if the oversensing is sustained it would probably result in the delivery of an inappropriate shock.

Inappropriate shocks due to T wave oversensing can be significantly reduced by reprogramming the sensing vector and / or the therapy zones of the device using a template acquired during exercise. Inappropriate shocks were also significantly reduced when dual zone versus single
zone programming was used (two-year inappropriate shock free rate 89.7% vs 73.6%; respectively (hazard ratio 0.38, P < .001).138

2.12.4 Previous experience analysing sensing vectors

Burke et al. identified variances in QRS and T wave signal amplitudes that were due to changes in body posture.139 This was the stimulus to introduce two postures into the ECG screening process for the S-ICD.
2.13 Clinical experience with S-ICD

Early experience supported the efficacy and safety the S-ICD \(^{25}\) though there were concerns regarding the rate of inappropriate therapy and other adverse events. \(^{23, 24}\) This was thought partly to represent the learning curve associated with new technologies. However, the EFFORTLESS S-ICD registry has reported appropriate system performance with clinical events equivalent to conventional TV-ICDs. \(^{133}\) Rates of inappropriate shock were 7% per annum which is equivalent to rates of inappropriate therapy with TV-ICD prior to the MADIT RIT trial. The principal cause of the inappropriate therapy in the EFFORTLESS registry was due to oversensing (85%) most frequently of the cardiac signal (94% of oversensed episodes). T waves or low amplitude signals (31 and 53% respectively) were the principal cause of such signal oversensing.

2.14 Comparison of S-ICD and TV-ICDs

There are a number of important differences between TV-ICDs and S-ICDs. (Table 9) Some of these differences are clear advantages for the S-ICD over the TV-ICD such as the reduced risk of pulmonary and cardiac complications at the time of device implantation whereas some are clear disadvantages such as the absence of long term outcome data and lack of bradycardia pacing. Other potential disadvantages such as the elevated shock strength with S-ICD are offset by a reduced myocardial voltage gradient. The results of a prospective randomised comparison of TV-ICDs and S-ICDs are awaited when the outcomes from the PRETORIAN trial are published. \(^{140}\)
<table>
<thead>
<tr>
<th></th>
<th>TV-ICD</th>
<th>S-ICD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pre-implant screening ECG</td>
<td>Not required</td>
<td>Mandated</td>
</tr>
<tr>
<td>Implant Technique</td>
<td>Need for transvenous puncture and endocardial lead with attendant risk of pneumothorax and cardiac tamponade</td>
<td>No transvenous lead with no risk of pneumothorax or cardiac tamponade</td>
</tr>
<tr>
<td>Venous anatomy</td>
<td>Requires venous and right ventricular access</td>
<td>Can be implanted in patients without venous access or with complex cardiac anatomy</td>
</tr>
<tr>
<td>Shock efficacy</td>
<td>Effectively detects and terminates ventricular fibrillation</td>
<td>Effectively detects and terminates ventricular fibrillation</td>
</tr>
<tr>
<td>Shock strength</td>
<td>Lower shock strength (35-40J)</td>
<td>High shock strength (80J)</td>
</tr>
<tr>
<td>Myocardial voltage gradients</td>
<td>High myocardial voltage gradients</td>
<td>Lower myocardial voltage gradients</td>
</tr>
<tr>
<td>Bradycardia pacing</td>
<td>Provides pacing for bradycardia, resynchronization, and tachycardia termination</td>
<td>Does not pace, apart from limited postshock pacing</td>
</tr>
<tr>
<td>Lead reliability</td>
<td>Dependent on transvenous lead with documented reliability issues</td>
<td>Subcutaneous lead with potential but not proven long-term reliability</td>
</tr>
<tr>
<td>Lead explantation</td>
<td>Device and lead explantation moderately risky</td>
<td>Explantation easy and low risk (initial experience only)</td>
</tr>
<tr>
<td>Programmability</td>
<td>Highly programmable</td>
<td>Limited programmability</td>
</tr>
<tr>
<td>Size of generator</td>
<td>Small device (30cm³)</td>
<td>Larger device (60cm³)</td>
</tr>
<tr>
<td>Track record</td>
<td>Established technology with proven benefits</td>
<td>Novel technology with limited experience and follow-up</td>
</tr>
</tbody>
</table>

Table 9 A comparison of transvenous-ICDs and subcutaneous-ICDs.

Adapted from Crozier et al. How the Subcutaneous Implantable Cardioverter Defibrillator Works: Indications/Limitations and Special Groups to Consider Cardiac Electrophysiology Clinics 2014 6; 2: 285-295 119
2.15 S-ICDs in patients with complex anatomy

The advent of new surgical techniques in the 1970s and 1980s has led to an increase in the survival of patients with congenital heart disease who would have otherwise died in childhood. The majority of these patients now survive into adulthood and there are now more adults with congenital heart disease (ACHD) alive than there are children with congenital heart disease. Historically there has been a paucity of data on the clinical features that predicted risk of SCD. This is because ACHD is relatively rare compared to acquired heart disease, though recently there has been much interest in the occurrence of late onset arrhythmia in this population group. Often arrhythmias in ACHD do not become manifest until the third decade, suggesting that a period of negative remodelling is important in the development of these arrhythmias. This is a good reason why it is important to understand the mechanism effective treatment of potentially lethal arrhythmias in this population.

2.15.1 Causes of arrhythmias in ACHD

There are two main reasons that arrhythmias arise in ACHD. The first is due to the abnormal physiology (pressure and volume loads) and certain anatomical features associated with the various congenital lesions. The second is as a consequence of previous surgery as the surgical scars form an anatomic barrier to normal electrical impulse thereby promoting macro re-entrant circuits as a mechanism for both atrial and ventricular arrhythmias. Longitudinal follow-up of these patients has demonstrated that a) approximately 1% of all patients with some form of ACHD will develop a malignant arrhythmia over a mean follow-up of 10 years, b) these events will usually occur in patients with more complex haemodynamic and anatomical lesions (Transposition of the Great Arteries (TGA) Single Ventricular Physiology (SVP), Tetralogy of Fallot (ToF) and patients with LV outflow obstruction) and in these patients the SCD may reach 10% over a 10 year period c) abnormal systemic ventricular function is one of the strongest predictors of malignant arrhythmia.

2.15.2 Causes of SCD in ACHD

In a study of 25 790 adults with a broad spectrum of CHD, 1189 deaths (5%) were identified, of whom 213 patients (19%) died suddenly. Arrhythmic death occurred in 171 of 25790 patients. The underlying cardiac lesions were mild, moderate, and severe CHD in 12%, 33%, and 55% of the SCD cases, respectively. Clinical variables associated with SCD were supraventricular tachycardia (odds ratio [OR], 3.5; 95% confidence interval [C.I., 1.5–7.9; P<0.004), moderate to severe
systemic ventricular dysfunction (OR, 3.4; 95% CI, 1.1–10.4; P<0.034), moderate to severe subpulmonary ventricular dysfunction (OR, 3.4; 95% CI, 1.1–10.2; P<0.030), increased QRS duration (OR, 1.34 [per 10-ms increase]; 95% CI, 1.10–1.34; P<0.008), and QT dispersion (OR, 1.22 [per 10-ms increase]; 95% CI, 1.22–1.48; P<0.008).

With respect to specific ACHD lesions, there are the most data on ToF as it one of the most common complex ACHD lesions, with a long follow-up into adulthood. A summary of the commonly accepted risk factors for the development of malignant arrhythmias after surgical repair in TGA, ToF, SVP and LV outflow obstruction are presented in Table 10 Risk factors for SCD in complex ACHD.

...
<table>
<thead>
<tr>
<th>After repair of tetralogy of Fallot</th>
<th>After atrial switch for transposition</th>
<th>Repair for Single Ventricle Physiology</th>
<th>LV outflow obstruction</th>
</tr>
</thead>
<tbody>
<tr>
<td>Older age at the time of complete repair</td>
<td>Longer duration of follow-up</td>
<td>Longer duration of follow-up</td>
<td>Longer duration of follow-up</td>
</tr>
<tr>
<td>Longer duration of follow-up since complete repair</td>
<td>History of syncope or rapid palpitation</td>
<td>History of syncope or rapid palpitation</td>
<td>History of ≥2 episodes of syncope</td>
</tr>
<tr>
<td>History of syncope</td>
<td>Atrial tachycardia</td>
<td>Atrial tachycardia</td>
<td>Outflow gradient of &gt;50mmHg</td>
</tr>
<tr>
<td>Severe pulmonary incompetence</td>
<td>Depressed systemic RV function</td>
<td>Depressed systemic ventricular function</td>
<td>Aortic regurgitation</td>
</tr>
<tr>
<td>Severe RV enlargement</td>
<td></td>
<td>Older Fontan technique (atriopulmonary connection)</td>
<td>Elevated LV end-diastolic pressure</td>
</tr>
<tr>
<td>Moderate to severe RV systolic dysfunction</td>
<td></td>
<td></td>
<td>Depressed LV systolic function</td>
</tr>
<tr>
<td>Extensive RV fibrosis</td>
<td></td>
<td></td>
<td>Severe LV hypertrophy</td>
</tr>
<tr>
<td>Moderate to severe LV systolic dysfunction</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Elevated LV end-diastolic pressure</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>QRS duration ≥180ms</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nonsustained VT on ambulatory monitoring</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>History of atrial tachycardia</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Inducible VT at EPS</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

EPS, electrophysiology study; RV, right ventricle; LV, left ventricle

Table 10 Risk factors for SCD in complex ACHD

Table adapted from Walsh Review in Sudden death in adult congenital heart disease: risk stratification in 2014 Heart Rhythm 11; 12: 1735-42 141
2.15.3 Outcomes of patients with ACHD and ICDs

Data on outcomes of patients with ACHD with ICDs has historically been based largely on single centre studies. However, a recent systematic review meta-analysis of 24 studies involving over 2000 patients (50% ToF) with ACHD and ICDs with a mean follow-up of 3.6 ± 0.9 years has demonstrated that overall 24% (18.6-31.3) of patients received one of more appropriate ICD therapies (ATP or shock), 25% of patients received inappropriate shocks in 25% (20.1-31.0) and lead-related complications occurred in 26% (18.9-33.6) of patients. This study included any type of ICD (epicardial, TV and S-ICD) though the majority of patients received TV-ICDs (96.1%).

The S-ICD is an ideal tool to treat the elevated risk of SCD in patients with complex ACHD as no transvenous leads are required to negotiate the often challenging venous anatomy and the risk of pneumothorax and endocarditis are markedly reduced. There is however a limited amount of data available on outcomes of patients with ACHD treated with S-ICDs. Initial reports have been mixed with critics citing problems relating to T wave oversensing and delays to therapy. Alternative strategies such as improved screening and non-standard leads positions may help reduce some of these problems.
2.16 Need for research and development

A number of questions arise from the preceding discussion. Firstly, there is a need to understand whether any change in the location of the parasternal sensing electrode would improve the S-ICD sensing characteristics in patients with ACHD. Secondly, there is a need to understand whether increasing the number of postures during the screening process would improve the S-ICD sensing characteristics in patients with ACHD. Thirdly, there is a need to understand what the electrocardiographic features are that predispose to T wave oversensing. Lastly, as S-ICD technology is new, there is scope for research and development that may the potential of the device, in particular with reference to personalised medicine in order to improve outcome that remain hitherto unexplored.

Given this, in this thesis I will explore the following areas relating to this:

1. The impact of right parasternal versus left parasternal sensing electrode position on the amplitude and ratio of ECG waves in controls and adults with complex congenital heart disease.
2. The impact of postural change on the amplitude and ratio of ECG waves in controls and adults with complex congenital heart disease.
   A multicentre study.
4. Calculation of the transformational coordinates to generate an 8-lead ECG from the two S-ICD sensing electrode positions.
2.17 Outline of thesis

This thesis contains four separate studies corresponding to the research question and aims outlined in the introduction, each detailed in individual chapters. Each study is presented in full, including the methodology, results and discussion pertinent to the specific work.

2.18 Setting

All original research was conducted at University Hospital Southampton NHS Foundation Trust. This hospital serves 1.3 million people living in Southampton and South Hampshire, in addition to tertiary cardiac services to around 3 million people in central southern England and the Channel Islands. Two studies involved collaboration with other UK centres. Bristol Heart Institute, University Hospitals Bristol NHS Foundation Trust for the impact of age on ICD outcomes (Chapter 3) and the Dudley Group NHS Foundation trust for the T wave oversensing study (Chapter 6).

2.19 Ethical considerations

All work was undertaken in accordance with the Declaration of Helsinki and according to the principles of Good Clinical Practice. Ethical approval for prospective study was granted by the Southampton University Hospital and South West Hampshire Research Ethics Committee B (REC 08/H0503/55) (Chapters 3 and 4), the NRES Committee for the East of England – Norfolk (REC 14/EE/0197) (Chapter 5) and the Proportionate Review Sub-committee of the NRES Committee London-Brent (REC 13/LO/1800) (Chapter 6).

2.20 Data handling and record keeping

Data was collected and retained in accordance with the Data Protection Act 1998. Study documents (paper and electronic) were retained in a secure location during and after the relevant trial had finished. All essential documents and source data, including any medical records where entries related to the research have been made, will be retained for a minimum period of 5 years following the end of the study. A ‘DO NOT DESTROY’ label stating the time after which the documents can be destroyed was placed on the outer cover of relevant medical records.
Chapter 3: Evaluating the use of right parasternal versus left parasternal ECG parameters using surface electrodes as surrogates for sensed ECG signal from subcutaneous implantable cardioverter defibrillator in adult congenital heart disease patients and normal controls

3.1 Abstract

3.1.1 Aim

This study investigated the impact of a right parasternal sensing electrode position on the R and T wave amplitudes and the R:T ratio using surface electrodes as surrogates for the S-ICD vectors in patients with adult congenital heart disease (ACHD) and normal controls.

3.1.2 Methods

Conventional left parasternal sensing electrode position and right parasternal sensing electrode positions were used to collect 10-second electrograms, recorded through an 80-electrode body surface mapping technology (Prime ECG ™ system). Recordings were made in the supine, prone, left lateral, right lateral, sitting and standing positions in using both the standard electrode vector position and the right parasternal positions.

3.1.3 Results

Forty patients were recruited and 37 patients were used for analysis. Twenty-seven (73%) had complex ACHD, 10 patients had normal hearts and acted as controls. A total of 3708 data points were analysed. There were no significant differences in the R:T ratio when measured in ACHD patients in the right compared to the left parasternal lead position. In contrast there were important differences in the magnitude of the R:T ratio when measured in control patients in the right compared to the left parasternal lead position; in the primary vector, the R:T ratio was greater in right than left by 2.99 (p=0.0002 95% C.I. 1.48 to 4.50) and in the secondary vector, the R:T ratio was smaller in the right than in the left by 0.77 (p=0.004 95% C.I. -1.58 to 0.05).
3.1.4 Conclusion

In selected patients, a right parasternal lead position may provide a useful alternative sensing configuration for the S-ICD.
3.2 Introduction

The subcutaneous ICD (S-ICD) provides effective shock therapy for defibrillation/cardioversion in patients with potentially life threatening ventricular arrhythmias. However, as the S-ICD relies on subcutaneous rather than endocardial electrogram sensing, its facility for arrhythmia sensing and discrimination requires specific scrutiny. Registry data has reported rates of inappropriate therapy of 7% per annum, mostly due problems arising from algorithm driven interpretation of the sensed cardiac signal. This incidence of inappropriate shocks may exceed that for contemporary TV-ICD devices. The S-ICD employs a morphology-based sensing algorithm and in its application a R:T signal ratio of <3 on the standard surface ECG has been identified as an important predictor of arrhythmia discrimination such that a potential S-ICD recipient would be identified as having failed S-ICD screening because of a high risk of inappropriate shock therapy.

The S-ICD system comprises three sensing electrodes: the first is located on the can in the 5th intercostal space in the mid-axillary line; the second is a proximal electrode located 1cm lateral to the xiphoid midline, on the patient’s left; the third is a distal electrode placed 14 cm superior. This configuration can produce three vectors: primary (horizontal, proximal electrode to can), secondary (diagonal, distal electrode to can) and alternate (vertical, distal to proximal electrode). The manufacturer of the only clinically released S-ICD recommends pre-implant ECG screening using three cutaneous sensing electrodes that are placed overlying the intended S-ICD sensing electrode locations, to demonstrate electrogram characteristics that will allow optimal operation of the device’s sensing and arrhythmia discrimination algorithm.

The use of a right parasternal lead position has been shown to achieve satisfactory S-ICD electrogram sensing in selected patients with atypical cardiac morphology and ECG characteristics. However, to date the impact on sensing of a right parasternal lead position has not been systematically assessed and the differences between right and left parasternal sensing characteristics are not currently known. We speculated that a right parasternal lead position might offer particular sensing advantage in the ACHD population, particularly because of the associated abnormalities in cardiac morphology and topology.

Therefore, the aim of this study was to investigate impact of a right parasternal sensing electrode position on sensed R wave and T wave amplitudes, and the magnitude of the R:T ratio, in three S-ICD vectors in patients with ACHD and normal controls.
3.3 Methods

This was a non-randomised, observational study conducted in tertiary referral cardiac centre. Willing participants aged over 16 years were recruited. Patients were recruited into four groups: Tetralogy of Fallot (ToF), Transposition of the Great Arteries (TGA) and Single Ventricle Physiology (SVP) and controls with structurally normal hearts as defined by normal transthoracic echocardiography and magnetic resonance imaging. Exclusion criteria were inability to provide informed consent and participation in other studies and patients with paced ventricular rhythm.

3.3.1 Use of surface ECG data

We used ECG data collected from surface electrodes a surrogates for the S-ICD sensing vectors rather than implanting S-ICDs into participants as this was non-invasive, easier to recruit participants and considered to be a reasonable proxy for S-ICD sensing.

Ten-second electrograms were recorded (sampling rate 1000Hz) in using body surface mapping technology (Prime ECG™ system, Heartscape Technologies Inc. now Verathon, Columbia, Maryland, United States). Recordings were made in the supine, prone, left lateral, right lateral, sitting and standing positions in using both the standard electrode vector position and the right parasternal positions. (Figure 14) The PRIME ECG™ system is a validated form of body surface mapping (BSM) that can accurately detect cardiac electrical activity. It consists of a flexible plastic anterior and posterior electrode vest and portable recording unit. The anterior vest contains 64 electrodes and the posterior vest 16 electrodes enabling the recording of 80 simultaneous unipolar ECG signals. The vests are arranged in vertical strips reference to their anatomical landmarks. Prior to recording, signal quality is checked in banks of 8 leads and any poor signal is identified and corrected. Previous studies have validated cutaneous-derived electrocardiography signals (e.g. body surface mapping) as reliable surrogates for subcutaneous sensing algorithm testing. Sensing vectors were recreated using bipolar signals from one electrode position to another according to the standard S-ICD vector configuration described above with the alternate (vertical) vector being recreated using electrodes located on the left and right parasternal positions as necessary. (Figure 14) The amplitudes were analysed based on the beat-annotations by calculating the maximum rectified waveform within the P, QRS, T windows based on annotations at the raw sampling rate=1000Hz. The peak amplitudes of the R wave, T wave served as comparators for analysis, rather than the morphology of the of the recorded wave forms.
Figure 14 Illustration of the sensing electrodes used in the recording of the right parasternal and left parasternal lead position.

For generating the right parasternal lead set, the Primary vector equivalence was recreated from recording electrodes e14 to e58, the secondary vector was recreated from recording electrodes e9 to e58 and the alternate vector was recreated from recording electrodes e9 to e4. For generating the left parasternal lead set, the Primary vector equivalence was recreated from recording electrodes e24 to e58, the secondary vector was recreated from recording electrodes e19 to e58 and the alternate vector was recreated from recording electrodes e19 to e24.

### 3.3.2 Statistical methods

Continuous variables are reported as mean (range), mean (SD) or median and inter-quartile range (IQR) for data with distribution that deviated from the normal one, and categorical variables as frequency (%). The test of Shapiro-Wilk for normality of distributions was applied.

Descriptive statistics and univariate statistical comparisons of R wave amplitude, T wave amplitude and RT ratio magnitude between and within the groups were applied: for continuous variables: a two-sample t-test when relevant distributional assumptions were met and the Mann–Whitney U-test or Wilcoxon signed ranks test for paired data, otherwise. For categorical variables, \( \chi^2 \) test or Fisher’s exact test were applied, as appropriate.

SPSS was the statistical software package used for the analysis (SPSS Statistics for Windows, Version 17.0. Chicago: SPSS Inc. Released 2008.). Three dimensional charts were constructed to illustrate the amplitude of the R wave, T wave and RT ratios.

For the subgroup analysis, generalized linear mixed models (‘proc glimmix’) with random and repeated effects for the comparison between the paired measurements, were used to obtain
restricted maximum likelihood (REML) solutions with a diagonal type of the covariance matrices for all or selected measurements between or within the groups.

Least square means with 95% CIs were obtained. The value of P<0.05 was considered statistically significant. Three dimensional charts were constructed to illustrate the amplitude of the R wave, T wave and RT ratios. The sub-group analyses was performed with the statistical software SAS Ver.9.3 (SAS Institute Inc. Cary, NC, USA).

### 3.3.3 Explanation of statistical methods used

a. Shapiro-Wilk
   - This test determines whether a population is normally distributed

b. Two-sample t-test
   - This tests evaluates the null hypothesis that two means from independent groups are equal. This test is used for data that follow a normal distribution.

c. Mann–Whitney U-test
   - This is a non-parametric (does not require the data to be normally distributed) test comparing whether the means of paired observations from independent samples are equal. This test is the alternative to the independent T test.

d. Wilcoxon signed ranks test for paired data
   - This is a non-parametric (does not require the data to be normally distributed) test comparing whether the means of paired observations from independent samples are equal.

e. \( \chi^2 \) test (Chi-square)
   - This test is used on frequency data and to test differences in proportions using 2x2 table showing the distribution of one variable in rows and another in columns, (contingency) table.

f. Fisher’s exact test
   - This test is similar to the \( \chi^2 \) test in that it evaluates whether frequencies using a 2x2 contingency table, but it provides exact probabilities (rather than approximations used in the \( \chi^2 \) test) and is valid when the expected frequencies are small.

g. Generalised linear mixed models
   - This is an advanced form of statistical analysis that is an extension of generalised linear model for example regression analysis. Regression analysis attempts to identify how a dependent variable (y axis) relates to independent data.\(^{157}\) This
assumes a linear relationship between the independent and dependent variable and can be expressed mathematically as:

\[ Y = a + bx \]

Y is the dependent variable, x is the independent variable, a is the intercept of the estimated line and b is the gradient of the estimated line.

![Estimated linear regression line showing the intercept a and the slope b, (the mean increase in Y for a unit increase in x). Taken with permission from Medical Statistics at a Glance Third Edition Petrie and Sabin Wiley & Blackwell.](image)

In generalised linear mixed modelling, both fixed and random effects rather than just (fixed effects as in simple linear regression) hence the terms mixed. This study, this test was selected due to the complexity of the data and the high number of variables. We wanted to compare the difference between ECG parameters when measured from the right versus the left parasternal side. However, within this, patients also had six changes in posture (repeated measures), three vectors (within group changes) and four subgroups (independent variables). The use of an ANOVA analysis (analysis of variance) was considered because of the repeated measures recorded in the postural change but this discounted a there were a small percentage of data points missing and therefore a mixed model was selected. Given the complexity and high number of interacting variables, the help of a statistician was sought who designed the generalised linear mixed model to address this question.

This method resulted in a highly detailed analysis of the interaction of posture on the ECG parameters such that each parameter in each posture was compared to each other rather than to a reference posture. Thus for example, the R wave recorded in the supine posture in the primary vector for the subgroup Tetralogy of Fallot for example, would be compared to all other R waves recorded in the
five other postures in that vector and subgroup. Each posture would in turn be compared to the other postures and between the left and right parasternal group. This would be repeated for all R wave, T wave and R:T ratios for all subgroups in all 3 vectors and parasternal groups. The high volume of data that was generated are succinctly presented in summary tables. Please see explanation below.

3.4 Results

Of 40 patients recruited, 37 were suitable for the analysis (3 were excluded due to poor quality signal in the right parasternal region). Twenty-seven (73%) had ACHD: 10 with Transposition of the Great Arteries (TGA); 10 with Tetralogy of Fallot (TOF) and 7 with single ventricle physiology (SVP). The remaining 10 patients had normal hearts, confirmed on transthoracic echocardiography and magnetic resonance imaging. The mean age of the patients was 36 years, 62% male. A total of 3708 valid data points were used for the analysis. A total of 3708 valid data points were used for the analysis.

The mean amplitude of the R wave and T wave in the left and right parasternal lead positions are summarised in Table 11.
Overall, there were no significant differences in any vector in the magnitude of the R:T ratio when measured in ACHD patients in the right compared to the left parasternal lead position. The magnitude of the R:T ratio in the primary vector in controls was greater in right compared to the left by 2.99 (p=0.0002 95% C.I. 1.48 to 4.50). The magnitude of the R:T ratio in the secondary vector was smaller in the right than in the left by 0.77 (p=0.004 95% C.I. -1.58 to 0.05). The magnitude of the R:T ratio in the alternate vector tended to be greater in the right parasternal lead position (4.05) compared to the low R:T ratio in the left parasternal lead position (1.16) (95% C.I -0.03 to .31) but not with statistical significance (p=0.07).

Three-dimensional charts of the R and T wave amplitudes and R:T ratio magnitudes in the right and left parasternal sensing positions are presented in Figure 16 and Figure 17.
Figure 16 Three-dimensional charts of the R and T wave amplitudes and R:T ratio magnitudes in the right and left parasternal sensing positions in the ACHD group.
Figure 17 Three-dimensional charts of the R and T wave amplitudes and R:T ratio magnitudes in the right and left parasternal sensing positions in the control group.
3.4.1 Subgroup analysis

In order to determine whether pooling of the ACHD groups may mask differences between the amplitude of R and T waves recorded in the right and left parasternal lead position a subgroup analysis was performed using a generalised linear mixed model. The results are illustrated using summary boxes which indicate which results are statistically different (p<0.05). A detailed explanation of how to interpret the summary boxes is presented in Figure 18.

<table>
<thead>
<tr>
<th>R wave</th>
<th>Right parasternal</th>
<th>Primary vector</th>
<th>posture</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
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<td></td>
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<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
<td>6</td>
</tr>
</tbody>
</table>

Figure 18 The panel is a representation of the results recorded in the R wave in the primary vector in all 6 postures.

3.4.2 Explanation of how to interpret sub-group summary boxes

Sub-group summary boxes were developed specifically for demonstration of the results of subgroup analyses of this study. The summary boxes provide a good overview of which parameter is significantly different from other parameters. In this study the mean amplitude of each R wave, T wave and R:T ratio in each sub-group recorded in one posture in the left parasternal lead position is compared to the mean amplitude of each R wave, T wave and R:T ratio in the same sub-group recorded in all postures in the right parasternal lead position.

The example in Figure 18 uses the imaginary results of the analysis of the R wave amplitude result when measured in the primary vector. Results from posture 1 in the left parasternal lead position will be compared to results from posture 1-6 in the right parasternal lead position, results from posture 2 will be compared to results from posture 2-6 and so on and so forth. Results that are statistically significant within a parasternal group (adjusted p value <0.05) are coded red, in this example, only the posture 1 when measured from the left parasternal side is significantly different to posture 3 when measured from the right parasternal side. Thus for each sub-group a total of 324 comparisons were made (6x6 postures in 3 vectors for 3 ECG parameters – R wave T wave and
Posture 1 corresponds to the left posture, posture 2 corresponds to the prone posture, posture 3 corresponds to the right posture, posture 4 corresponds to the sitting posture, posture 5 corresponds to the standing posture and posture 6 corresponds to the supine posture.

The subgroup analysis (Figure 19) demonstrates that there is variation the differences between amplitude of the R and T waves and the R:T ratio when measured in the right and left parasternal lead position between the ACHD groups. The Transposition of the Great Arteries group has a greater number of statistically significant differences (27/324) in the amplitudes of the R and T waves and R:T ratio between left and right parasternal lead positions compared with the Tetralogy of Fallot (5/324) and Single Ventricle Physiology group (0/324). However, the control group has the largest number of statistically significant differences in the amplitudes of the R and T waves and R:T ratio between left and right parasternal lead positions (54/324). Most of the statistically significant differences occurred in the alternate (vertical) vector, with the R wave in the alternate vector accounting for most of the differences in the TGA group and the T wave in the alternate vector accounting for most of the differences in the control group.
Figure 19 Subgroup analysis of impact of parasternal lead position on amplitude of the R wave, T wave and the R:T ratio.

1 = left posture, 2 = prone posture, 3 = right posture, 4 = sitting posture, 5 = standing posture and 6 = supine posture.
3.5 Discussion

In this prospective clinical study we investigated how using a right parasternal lead sensing electrode position would impact on the R wave and T wave amplitudes and R:T ratio compared to the left parasternal lead position in patients with ACHD and controls with structurally normal hearts.

We observed that overall, using a right parasternal lead position did not impact on the R:T ratio in patients with ACHD. In the control group by contrast, in two of the three vectors, there were statistically significant differences in the magnitude of the R:T ratio (greater in the primary and smaller in the secondary vector). In the alternate vector the magnitude of the R:T ratio tended to be greater in the right parasternal lead position but this did not achieve statistical significance.

In a detailed subgroup analysis of differences between left and right parasternal lead positions taking account of postural change, more significant differences were identified in the alternate vector than in the primary or secondary vectors. The TGA group and the control group accounted for most of the statistically significant differences whereas there were very few significant differences the ECG parameters when measured from the left and right parasternal lead position in the TOF and SVP groups.

The geometric position of the heart within the chest wall has been shown to be a large source of variation in body surface potentials and may help explain the differences observed between groups in this study. Patients with ACHD tend to have a more centrally located heart in the thorax with larger right hearts and this is likely to explain the lack of variation in the R wave and T wave amplitude and the R:T ratio when measured from the right and left parasternal sensing positions. In contrast in normal controls, the right parasternal sensing electrode position is further away from the structurally normal heart, and therefore differences appear more marked compared to the left parasternal sensing position. We have not tested this using cross-sectional imaging. This may explain the larger variation in sensing parameters between the left and right parasternal positions in the control group.

The clinical uptake of S-ICDs, for the conventional ICD indication of primary prevention of sudden cardiac death in ischemic heart disease patients with severely impaired left ventricular ejection fraction, is rapidly increasing. These patients have leftward orientated hearts. We speculate that such patients are likely to exhibit similar sensed electrogram characteristics to the normal (control) group in this study. In fact, we observed improvements in the R:T ratio from R:T<3 in the left parasternal sensing position to R:T of approximately 4 in the right parasternal position. This
has clinical relevance. It is preferable to have more than one vector which satisfies implant S-ICD screening criteria, as this enhances the likelihood of later successful configuration of the S-ICD system for the avoidance of inappropriate shock therapy in the event of unexpected T wave oversensing in the right parasternal lead position may provide this facility. However, the true clinical value needs to be tested in a larger cohort of patients with coronary artery disease and poor left ventricular function.

Non-standard lead positions are being increasingly employed as experience and confidence grows with implanting S-ICDs. This study supports the use of screening patients using a right parasternal sensing position in those patients where poor or borderline sensing parameters are identified at the pre-implant screen.

There are a number of potential disadvantages with use of a right parasternal sensing position. Firstly, a right parasternal sensing position may be advantageous in one or two vectors, but at the cost of potentially worsening sensing characteristics in the remaining third vector. At present we are not able to reliably predict specific patients who might benefit from a right parasternal position. Therefore, the approach needs to be individualised on a case by case basis.

Secondly, this study focused on how the sensing parameters might change by utilising a right parasternal lead position but not on the defibrillation effectiveness of the S-ICD system in this lead configuration. In the early clinical trial investigating the optimal electrode/can configuration for the S-ICD, four different positions were tested, all of which utilised a left parasternal defibrillation/sensing electrode.  We speculate however that a right parasternal lead position (with Can in the standard axillary position) is likely to offer similar defibrillation efficacy to that seen with a left parasternal lead position. Again, this needs to be tested prospectively.

Lastly, to implant an S-ICD with a right parasternal electrode, it is necessary for the defibrillation lead body to cross the midline at the level of the xiphisternum. This area has reduced amounts of subcutaneous tissue and the lead may be more vulnerable to erosion through the skin at this location.

3.5.1 Limitations

There are a number of limitations to this study. There is a modest number of participants. However, a total of 27 ACHD patients compares favourably to the number of such patients enrolled in the Effortless Registry Furthermore, the number of data points generated is large and this goes some way to mitigating the effects of participants. The second limitation is that all
the data were collected at rest. Therefore there is the possibility of variability in ECG parameters with exercise and during arrhythmia.

3.6 Conclusion

This study has not demonstrated any significant differences in S-ICD sensing parameters using a right parasternal lead position compared to a left parasternal lead position in a broad range of adult patients with complex ACHD. However, a right parasternal lead position showed significant differences in the R:T ratio in the primary and secondary vector and a clinically important improvement in the R:T ratio in the alternate vector in participants with structurally normal hearts. In a subgroup analysis the alternate vector accounted for most of significant differences between the sensing parameters measured in the left and right parasternal leads position. In selected patients, a right parasternal lead position may provide a useful alternative for sensing in the S-ICD configuration.
Chapter 4: Evaluating the impact of postural change on ECG parameters using surface electrodes as surrogates for sensed ECG signal from subcutaneous implantable cardioverter defibrillator in adult congenital heart disease patients and normal controls

4.1 Abstract

4.1.1 Introduction

The aim of this study was to compare the R and T wave amplitudes and the R:T ratio magnitude in three S-ICD vectors in patients with ACHD and normal controls in 6 different postures.

4.1.2 Methods

A non-randomised, observational study was conducted. Patients were recruited into four groups: Tetralogy of Fallot (TOF), Transposition of the Great Arteries (TGA) and Single Ventricle Physiology (SVP) and controls with structurally normal hearts. 10-second electrograms were recorded using body surface mapping technology. Recordings were made in the supine, prone, left lateral, right lateral, sitting and standing positions in using both the standard electrode vector position

4.1.3 Results

Forty patients were recruited, 37 patients were suitable for the analysis. Overall, the R and T wave amplitudes and R:T ratio recorded in the right lateral posture was ranked the smallest in both the ACHD and control groups (mean rank 2.6 ± 1.3 and 2.3 ± 1.4) respectively, where rank 1 is the lowest and 6 the highest. The R and T wave amplitudes and R:T ratio in the prone posture was ranked the largest in both the ACHD and control groups (mean rank 4.7 ± 1.6 and 4.7 ±1.9) respectively. In a subgroup analysis, posture had a more significant impact on the R and T wave amplitude and R:T ratio in controls than in the ACHD subgroups.
4.1.4 Conclusion

Postural change has a greater impact on the R and T wave amplitude and R:T ratio magnitude in patients with structurally normal hearts than in patients with complex ACHD. The left lateral, right lateral and prone postures account the extremes in R and T wave amplitude and R:T ratio magnitude. Introducing ECG screening in all 6 postures would make the process more robust.
4.2 Introduction

The subcutaneous implantable cardioverter-defibrillator S-ICD has a proven track record in delivering life safe and effective shock therapy for patients with lethal arrhythmias,\textsuperscript{148} and has the advantage of not requiring intravenous lead placement. Patients with complex congenital heart disease tend to be younger and often have the combination of a high incidence of sudden cardiac death, accounting for nearly 1 in 5 deaths in the population,\textsuperscript{159} and have more complex anatomy.\textsuperscript{143} Given this, the S-ICD appears to be well suited to meet their requirements.

Registry data has reported rates of inappropriate therapy of up to 7% per annum,\textsuperscript{133} mostly due to T-wave oversensing and undersensing of the cardiac signal. The S-ICD consists of three sensing electrodes, the first, the can is located in the 5\textsuperscript{th} intercostal space in the mid-axillary line, the second, a proximal electrode located 1cm lateral to the xiphoid midline and the third is a distal electrode placed 14 cm superior. Three cutaneous sensing electrodes are placed overlying the intended S-ICD sensing electrode locations for the purposes of the pre-implant screen and recordings are made in two postures (supine and standing) at three gain settings.

The S-ICD appears more challenged in its ability to sense appropriately all of the time. Accurate sensing requires an adequate R wave with a minimal T wave amplitude to reduce the likelihood of T wave oversensing. An R:T of <3 on a surface ECG has been found to be a risk factor of inappropriate therapy in S-ICD patients.\textsuperscript{129} Thus, changes in the R wave or T wave caused by postural change alone may result in changes to the R:T ratio. There are anecdotal reports of episodes of oversensing occurring whilst patients are in non-standard pre-implant screen postures e.g. prone and whilst in bed. Whilst the effect of changes in body posture on the electrocardiogram has been known about for over 70 years,\textsuperscript{160} it is not known how postural change may impact upon the R wave, T wave and R:T in the S-ICD sensing vectors or in which postures is the signal sensed well (maximal amplitude) or less well (minimal amplitude) or indeed whether certain vectors are more vulnerable to postural change than others.

The aim of this study was to compare the R and T wave amplitudes and the R:T ratio magnitude in three S-ICD vectors in patients with ACHD and normal controls in 6 different postures.

4.3 Methods

This non-randomised, observational study was conducted in tertiary referral cardiac centre. Willing participants aged over 16 years were recruited. All the study subjects were adults and had the ability to give informed consent. Patients were recruited into four groups: Tetralogy of Fallot
(TOF), Transposition of the Great Arteries (TGA) and Single Ventricle Physiology (SVP) and controls with structurally normal hearts as defined by transthoracic echocardiography and magnetic resonance imaging. We used ECG data collected from surface electrodes as surrogates for the S-ICD sensing vectors rather than implanting S-ICDs into participants as this was non-invasive, easier to recruit participants and considered to be a reasonable proxy for S-ICD sensing Exclusion criteria were inability to provide informed consent and participation in other studies and patients with paced ventricular rhythm.

10-second electrograms were recorded (sampling rate 1000Hz) using body surface mapping technology (Prime ECG™ system). Recordings were made in the supine, prone, left lateral, right lateral, sitting and standing positions in using both the standard electrode vector position. The PRIME ECG™ system is a validated form of body surface mapping (BSM) that can accurately detect cardiac electrical activity. It consists of a flexible plastic anterior and posterior electrode vest and portable recording unit. The anterior vest contains 64 electrodes and the posterior vest 16 electrodes enabling the recording of 80 simultaneous unipolar ECG signals. (Figure 20) The vests are arranged in vertical strips reference to their anatomical landmarks. Prior to recording, signal quality is checked in banks of 8 leads and any poor signal is identified and corrected. Previous studies have validated cutaneous-derived electrocardiography signals (i.e. body surface mapping) as reliable surrogates for subcutaneous sensing algorithm testing.130
Figure 20 Illustration of the sensing electrodes used in the recording of the electrode lead positions utilising the Prime ECG™ system.
The Primary vector equivalence was recreated from recording electrodes e24 to e58, the secondary vector was recreated from recording electrodes e19 to e58 and the alternate vector was recreated from recording electrodes e19 to e24.

4.3.1 Statistical methods

Continuous variables are reported as mean (range), mean (SD) or median and inter-quartile range (IQR) for data with distribution that deviated from the normal one, and categorical variables as frequency (%).

Postural variation within each parameter was expressed as a percentage of the lowest value and categorised as low (<25% variation), medium (25-49% variation) and high (>50% variation).

Differences within groups caused by postural changed was assessed using a generalised linear model ‘proc glimmix’ model with random and repeated effects for the comparison between the paired measurements, used to obtain restricted maximum likelihood (REML) solutions with a diagonal type of the covariance matrices for all or selected measurements between or within the groups. Least square means with 95% CIs were obtained. The value of P<0.05 was considered
statistically significant. Three dimensional charts were constructed to illustrate the amplitude of the R wave, T wave and RT ratios. The sub-group analyses was performed with the statistical software SAS Ver.9.3 (SAS Institute Inc. Cary, NC, USA).

This sophisticated novel approach used to analyse complex, non-normally distributed data whilst adjusting for multiple comparisons and was devised entirely for the purposes of this analysis. The estimation technique used was the restricted maximum likelihood method. The least-squares means adjustment for multiple comparisons using Tukey-Kramer analysis was used. This resulted in each parameter being compared to all other parameters within that field (e.g. the R wave in a control patient in the primary vector in left lateral posture was compared to the five other postures in that vector in the left parasternal group and all six postures in the right parasternal group. This was repeated for all three vectors for the T wave and R wave in all four groups. A p value <0.05 was used to determine statistical significance.

Matrix comparison boxes were generated to illustrate the within and between parasternal group statistical differences (adjusted p<0.05). Three dimensional charts were constructed to illustrate the amplitude of the R wave, T wave and RT ratios.

4.3.2 Explanation of statistical methods used

a. Shapiro-Wilk
   a. This test determines whether a population is normally distributed.

b. Two-sample t-test
   a. This test evaluates the null hypothesis that two means from independent groups are equal. This test is used for data that follow a normal distribution.

c. Mann–Whitney U-test
   a. This is a non-parametric (does not require the data to be normally distributed) test comparing whether the means of paired observations from independent samples are equal. This test is the alternative to the independent T test.

d. Wilcoxon signed ranks test for paired data
   a. This is a non-parametric (does not require the data to be normally distributed) test comparing whether the means of paired observations from independent samples are equal.

e. $\chi^2$ test (Chi-square)
   a. This test is used on frequency data and to test differences in proportions using 2x2 table showing the distribution of one variable in rows and another in columns, (contingency) table.
f. Fisher’s exact test
   a. This test is similar to the $\chi^2$ test in that it evaluates whether frequencies using a 2x2 contingency table, but it provides exact probabilities (rather than approximations used in the $\chi^2$ test) and is valid when the expected frequencies are small.

g. Generalised linear mixed models
   a. This is an advanced form of statistical analysis that is an extension of generalised linear model for example regression analysis. Regression analysis attempts to identify how a dependent variable (y axis) relates to independent data. This assumes a linear relationship between the independent and dependent variable and can be expressed mathematically as:

   $Y = a + bx$

   $Y$ is the dependent variable, $x$ is the independent variable, $a$ is the intercept of the estimated line and $b$ is the gradient of the estimated line.

   ![Figure 21 Estimated linear regression line showing the intercept $a$ and the slope $b$, (the mean increase in $Y$ for a unit increase in $x$). Taken with permission from Medical Statistics at a Glance Third Edition Petrie and Sabin Wiley & Blackwell.](image)

   In generalised linear mixed modelling, both fixed and random effects rather than just (fixed effects as in simple linear regression) hence the terms mixed. This study, this test was selected due to the complexity of the data and the high number of variables. We wanted to compare the impact of postural change between ECG parameters when controlling for all the other variables. However, within this, patients also had six changes in posture (repeated measures), three vectors (within group changes) and four subgroups (independent variables). The use of an ANOVA analysis (analysis of variance) was considered because of the repeated measures recorded in the postural change but this discounted a there were a small percentage of data points missing and therefore a mixed model was
selected. Given the complexity and high number of interacting variables, the help of a statistician was sought who designed the generalised linear mixed model to address this question.

This method resulted in a highly detailed analysis of the interaction of posture on the ECG parameters such that each parameter in each posture was compared to each other rather than to a reference posture. Thus for example, the R wave recorded in the supine posture in the primary vector for the subgroup Tetralogy of Fallot for example, would be compared to all other R waves recorded in the five other postures in that vector and subgroup. Each posture would in turn be compared to the other postures. This would be repeated for all R wave, T wave and R:T ratios for all subgroups in all 3 vectors.

The high volume of data that was generated are succinctly presented in summary tables. Please see explanation below.

4.4 Results

Forty patients were recruited, 37 patients were suitable for the analysis (three excluded due to poor quality signal). Twenty-seven (73%) had ACHD: 11 with Transposition of the Great Arteries (TGA); 10 with Tetralogy of Fallot (TOF) and 6 with single ventricle physiology (SVP). The remaining 10 patients had normal hearts, confirmed on transthoracic echocardiography and magnetic resonance imaging. The mean age of the patients was 36 years, 62% male. A total of 1863 valid data points were used for the analysis.

The mean amplitude of the R wave and T wave in the left and right parasternal lead positions are summarised in Table 12. Three dimensional charts are shown in Figure 22 and Figure 23.
Table 12 Mean amplitude of the R wave and T wave in millivolts and the R:T ratio in all patients in primary, secondary and alternate vectors. (Standard deviation and percent difference between maximal and minimal recording).

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<th></th>
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<th>Upper Bound</th>
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<th>95%</th>
<th>% difference between max and min.</th>
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4.4.1 Ranking position

In order to determine which postures had the maximal and minimal recorded amplitudes, postures were ranked from 1-6 (smallest to largest) for the R and T wave amplitudes and R:T ratio in all vectors in the ACHD group and the control group. (Table 13) Overall, the R and T wave amplitudes and R:T ratio recorded in the right lateral posture was ranked the smallest in both the ACHD and control groups (mean rank 2.6 ± 1.3 and 2.3 ± 1.4) respectively. The R and T wave amplitudes and R:T ratio in the prone posture was ranked the largest in both the ACHD and control groups (mean rank 4.7 ±1.6 and 4.7 ±1.9) respectively.
The right lateral and left lateral and prone postures accounted for 17/18 (94.4%) of the postures that were ranked largest or smallest in the control group ($p = 0.0027$ for differences between groups) in the control group compared to 8/18 (44.4%) vector-postures that were ranked largest or smallest in the ACHD group.

**4.4.2 Magnitude of postural variation**

Overall, there were 18 vector-postures (3 vectors x 6 postures). The left lateral posture exhibited the greatest variability in ranking of the R and T wave amplitudes and R:T ratio in both ACHD and control groups (standard deviation 2.1 in the ACHD group and 2.4 in the control group).

In order to determine the influence of postural change on the consistency in the measured ECG parameter, postural variation within each parameter was expressed as a percentage of the lowest value and categorised as low (<25% variation), medium (25-49% variation) and high (>50% variation). Overall, there were 9 outcomes, three ECG parameters (R wave, T wave and R:T ratio) measured in 3 vectors.

Overall, in the ACHD group, the influence of posture on the R wave, T wave and R:T ratio was classified as low or medium in 7/9 (77.8%, 95% C.I. 50.6 - 100) and high in 2/9 (22.2, 95% C.I. 0 - 49.4) possible outcomes. (Table 13) In the control group, the influence of posture on the R wave, T wave and R:T ratio was classified as high, with 8/9 (88.9% 95% C.I. 68.4 - 100) and low in 1/9 (11.1% 95% C.I. 0 – 31.6) possible outcomes.
Figure 22 Three dimensional charts depicting the postural variation in amplitude of the R and T wave in millivolts (mV) and R:T ratio magnitude in all three vectors for the ACHD group.
Figure 23 Three dimensional charts depicting the postural variation in amplitude of the R and T wave in millivolts (mV) and R:T ratio magnitude in all three vectors for the ACHD group.
4.4.3 Subgroup analysis

In order to determine whether pooling of the ACHD groups may mask differences between the amplitude of R and T waves recorded in the right and left parasternal lead position, a subgroup analysis was performed of the ACHD groups (Tetralogy of Fallot, single ventricular physiology and Transposition of the Great Arteries) and controls. The following tables summarise the statistically significant differences between R and T wave amplitude and the magnitude of the R:T ratio when all postures are compared to each other within each group using the Glimmix model.

4.4.4 Explanation of matrix comparison boxes

<table>
<thead>
<tr>
<th>R wave primary vector</th>
<th>Left parasternal leads</th>
</tr>
</thead>
<tbody>
<tr>
<td>posture</td>
<td>Left</td>
</tr>
<tr>
<td>Left</td>
<td></td>
</tr>
<tr>
<td>Prone</td>
<td></td>
</tr>
<tr>
<td>Right</td>
<td></td>
</tr>
<tr>
<td>Sitting</td>
<td></td>
</tr>
<tr>
<td>Standing</td>
<td></td>
</tr>
<tr>
<td>Supine</td>
<td></td>
</tr>
</tbody>
</table>

Figure 24 Explanation of matrix comparison boxes

The panel in Figure 24 is a representation of the results recorded in the R wave in the primary vector in all 6 postures. Each result is compared to all other results. For example, results from the left posture will be compared to results from all the other five postures, results from the prone posture will be compared to results from the outstanding four postures and so on and so forth. Results that are statistically significant within a parasternal group (adjusted p value <0.05) are coded red, in this example, the left posture is significantly different to the right posture.

The matrix comparison boxes for the three ACHD subgroups and normal controls is presented in Figure 25.

Overall, the R wave in the right posture was significantly smaller than the R wave in the left posture in the TGA group (p<0.05). Otherwise there were no significant differences between any of the R or T wave amplitudes in any of the ACHD sub-groups.

In contrast in the control group, the R wave amplitude in the left posture was significantly larger than the R wave in all other postures in the control group in the secondary vector. The T wave was significantly smaller in the right and standing posture compared to the left posture in the
secondary vector (p<0.05). The T wave was significantly smaller in the prone and sitting posture compared to the left posture in the alternate vector (p<0.05) in the secondary vector.

Figure 25 Subgroup analysis of impact of postural change on amplitude of the R wave, T wave and the R:T ratio.

1 = left posture, 2 = prone posture, 3 = right posture, 4 = sitting posture, 5 = standing posture and 6 = supine posture.
4.5 Discussion

4.5.1 Effect of postural change on signal variation in S-ICD

Postural change has been known to affect the electrocardiogram for over 70 years and has been reported as a cause of T wave oversensing in a patient with a transvenous ICD. In the context of S-ICDs, data published in abstract form compared QRS amplitude and QRS:T wave ratio made during multiple postures using standard S-ICD vectors. Significant variance in QRS amplitude was observed, though the details of this variation remain unpublished.

In this prospective clinical study, we have identified that postural variation appears to have little impact on the R and T wave amplitude and R:T ratio magnitude in patients with complex ACHD. However in contrast, in patients with structurally normal hearts, posture has a large impact on the R and T wave amplitude and R:T ratio magnitude. Furthermore, we have identified that the right lateral, left lateral and prone postures account the extremes in R and T wave amplitude and R:T ratio magnitude in both patients with ACHD group and patients with structurally normal hearts.

It is unclear why patients with ACHD have less variation in R wave and T wave amplitude and R:T ratio compared to normal controls. We hypothesise that is may be due to a smaller relative change of the heart within the chest cavity with postural variation. This may be due to the larger size of the heart which may restrict movement within the mediastinum. Fibrous adhesion from previous surgical interventions may restrict movement caused by postural change. Alternatively, autonomic changes caused by postural change may modify the amplitude of the R wave, T wave and R:T ratio. It would be important to test these hypotheses prospectively. The finding of such a study would have potential implications in the screening procedure prior to S-ICD implantation.

Our finding that patients with structurally normal hearts exhibit significant variation in the R and T wave amplitude and R:T ratio magnitude has important clinical relevance. Firstly, approximately 21% of the patients enrolled in the Effortless registry could be considered to have a structurally normal heart (idiopathic VF (8%) and inherited channelopathies (13%)). No data currently exist of which population of patients received inappropriate shock. Secondly, the S-ICD pre-implant screening template tool is designed to select patients who have a QRS-T complex for the morphology-based sensing algorithm employed by the device. The current recommendations mandate the use of only two postures, supine and standing. Patients who do not satisfy the screening tool and not recommended to proceed with S-ICD implantation. The potential consequence of a patient who does not satisfy the screening template is inappropriate sensing from the device, including T wave oversensing and inappropriate shock delivery. We would therefore recommend the use of the left lateral, right lateral and prone postures at the pre-
implant screen in order to challenge the S-ICD screening tool with the extremes of the R and T wave and R:T ratio magnitude. We speculate that this may improve the negative predictive value of the pre-implant screen (i.e. better at excluding patients who will subsequently have poor S-ICD sensing) and help to reduce the number proportion of patients who receive inappropriate shock caused by T wave oversensing or undersensing of the cardiac signal.

### 4.5.2 Limitations

There are a number of limitations to this study. Firstly, in this study there are relatively modest number of participants. However, all 27 of patients with complex anatomical lesions and this number compares well to the number of patients enrolled in the Effortless registry. Furthermore, the number of data points generated is large and this goes in some way to mitigate the effects of a modest number of participants. Secondly, we have speculated that postural change may influence the success of the pre-implant ECG screen, though we have not tested this assumption.

### 4.6 Conclusion

Postural change appears to have a greater impact on the R and T wave amplitude and R:T ratio magnitude in patients with structurally normal hearts than in patients with complex ACHD. The left lateral, right lateral and prone postures account the extremes in R and T wave amplitude and R:T ratio magnitude. This may have implications at the time of screening patients for suitability for S-ICD implantation. Including postures that account for the extremes in R and T wave amplitude may identify patients at higher risk of T wave oversensing and therefore preventing these patients from having S-ICD implanted may help reduce the burden of inappropriate shock delivery in S-ICDs.
Chapter 5: ECG predictors of T wave oversensing in S-ICD recipients

5.1 Abstract

5.1.1 Introduction

T-wave over-sensing is the commonest cause of inappropriate shocks in subcutaneous implantable cardioverter defibrillators (S-ICDs). We hypothesise, that predictors of T-wave oversensing can be derived from surface ECG parameters.

5.1.2 Methods

In a cohort of SICD recipients in two UK centres, all patients who had T-wave oversensing (study group) were compared to all those who had not (control group). The pre-implant screen was scanned and the R wave, T wave amplitudes, QRS interval, time to peak T wave, QT interval and R:T ratio were measured using digital callipers. Logistic regression was performed to identify ECG predictors of T-wave oversensing.

5.1.3 Results

One hundred and one patients were studied. Six (5.9%) had T-wave oversensing. The mean age of the population was 58.6 years ± 18 years and the median follow-up from implantation was 19.5 months. By univariate analysis, the predictors of T-wave oversensing are QRS duration (140.7 ± 28.7 vs. 105.9 ± 24.6, p = 0.007), time to peak T wave (corrected for heart rate, pTc) (403.9 ± 22.6 vs. 347.8 ± 41.4, p =0.006), QTc interval (500.4 ± 41.2 vs. 446.8 ± 49.7, p=0.021) and R:T ratio (3.5 ± 1.1 vs. 9.5 ± 13.2, p=0.034). By multivariate analysis, time to pTc is the most predictive of T-wave oversensing. A time to pTc of 390ms cut-off point provided a sensitivity 38.5%, a specificity of 98.9%, a positive predictive value for T-wave oversensing of 83.3%, and a negative predictive value of 91.6%. For every 10ms increase in the pTc there is a 30% increase in the odds of an inappropriate shock from T wave oversensing.

5.1.4 Conclusion

In this pilot study, time to pTc was the most powerful ECG predictor of T-wave oversensing. This may have important implications in screening patients who may be at high risk of inappropriate
shocks from T-wave oversensing, however, the number of patients affected by T wave oversensing was small so need larger study is required with enough oversensing events to allow multivariate prediction score development and validation.
5.2 Introduction

The S-ICD has a proven track record in delivering life safe and effective shock therapy for patients with lethal arrhythmias. The S-ICD performs well in a head-to-comparison with transvenous implantable cardioverter defibrillators in discriminating supraventricular tachyarrhythmia from ventricular tachyarrhythmia, though results of a randomised trial comparing S-ICD to transvenous ICDs has yet to be published. Clinical experience has demonstrated that the S-ICD has limited sensing specificity due to failure to appropriately sense or discriminate electrical signals unrelated to supraventricular tachycardia. Indeed, registry data has reported rates of inappropriate therapy of approximately 7% per annum, mostly due to T-wave oversensing and undersensing of the cardiac signal. This rate is considerably higher than rates of inappropriate shocks reported in contemporary TV-ICD device.

The pre-implant ECG screen is an integral part of selecting potential S-ICD recipients and excluding patients whose QRS-T wave morphology does not satisfy the screening tool. As the S-ICD employs an ECG morphology-based sensing algorithm, we hypothesise that ECG markers may prove be useful predictors of T wave oversensing.

5.3 Methods

The pre-implant ECGs of patients who had successfully passed the pre-implant ECG screen and had an S-ICD implanted at two UK centres were studied. The study group comprised of patients who had experienced T-wave oversensing and had received an inappropriate shock due to T-wave oversensing. Patients with oversensing of the cardiac signal were excluded if they had experienced oversensing due to noise, a change in QRS morphology (e.g. monomorphic ventricular tachycardia or aberrantly conducted beats). Patients who had not received an inappropriate shock due to T-wave oversensing comprised the control group. The pre-implant ECG screen was scanned and the amplitude of the R/S wave and T wave was measured. The QRS interval, time to peak T wave (measured from the onset of the Q wave to the peak of the T wave), QT interval and R:T ratio was measured using digital callipers (Cardio callipers, On-screen electrocardiogram callipers, version 3.3, Iconico Inc.) with the ECG magnified to 500%. The amplitude of the R/S wave and the T wave was measured in all three vectors. The QRS duration, QT interval, time to peak interval were measured in the secondary vector where possible as this vector approximates the vector of lead II of a standard 12-lead ECG which tends to have a symmetrical positive T wave. When a T wave was of low amplitude or biphasic in the secondary vector, another vector with the maximal T wave amplitude was sought. The mean of four
consecutive complexes were used for each parameter to reduce measurement error. Patient clinical and demographic characteristics were recorded including heart failure aetiology, co-morbidities and medication at the time of S-ICD implant.

5.3.1 Statistical analysis

Continuous variables are expressed as the mean±1 standard error of measurement and were compared using Student’s t test or nonparametric analysis where appropriate. A two-tailed p value of <0.05 indicated statistical significance. A univariate analysis was performed to determine factors that predicted T-wave oversensing (factors with univariable P<0.1). Binary logistic analysis was performed using a backward elimination method to determine the most fitted model for the parameters that influence the outcomes with an adjusted P<0.05 needed for entry into the model and an adjusted P>0.1 for removal at any stage. Odds ratios were reported for those covariates that were significantly associated with T wave oversensing. Statistical analysis was performed using the STATA statistical package (Stata/IC 13.0 for Windows. StataCorp LP, USA).

5.3.2 Explanation of statistical analyses

1. Student’s t test
   a. This tests evaluates the null hypothesis that two means from independent groups are equal. This test is used for data that follow a normal distribution.

2. Univariate analysis
   b. This is also known as a simple regression model and consists of one variable and one explanatory variable. Regression analysis attempts to identify how a dependent variable (y axis) relates to independent data. This assumes a linear relationship between the independent and dependent variable and can be expressed mathematically as:

   \[ Y = a + bx \]

   Y is the dependent variable, x is the independent variable, a is the intercept of the estimated line and b is the gradient of the estimated line. See Figure 15

3. Logistic analysis
   a. Is a regression model, specifically a type of generalised linear model, which relates one or more explanatory variables to a categorical dependent (outcome) variable. Thus, in this study, the binary outcome variable was the occurrence of T wave over sensing and the explanatory variables were the ECG predictors of this.

4. Odds
a. The ratio of probabilities of two complementary events. In this study it would be the odds of T wave oversensing divided by the odds of no T wave oversensing.

5. Odds ratio
   a. The ratio of two odds (e.g. the odds of T wave oversensing). It can be considered to be an estimate of the relative risk in a case-control study.

5.4 Results

Complete datasets could be recorded in 101 patients, 10 (9.9%) of whom were not enrolled in the EFFORTLESS registry. The mean age of the population was 58.6 years ±18 years and the S-ICD was implanted for a primary prevention indication in 75 (75%). Mean follow-up was 19.5 months. In total 93% had dual zone programming, the most frequent setting being conditional zone 200 bpm and shock zone of 220 bpm in 54/94 (57.4%). The primary vector was programmed in 49 (48.5%), the secondary vector in 44 (43.6%) and the alternate vector in 8 (7.9%) of patients.

Fifteen (14.9%) patients were identified as having episodes of oversensing and 6 patients (5.9%) were identified as having received an inappropriate shock due to T wave oversensing that could not be explained by a change in morphology, noise or non-cardiac signal. (Table 14) These patients experienced 25 separate episodes of T-wave oversensing and received a total of 14 shocks (mean 0.56 shocks per episode). Their clinical history is summarised in Table 15 and baseline demographics are presented in Table 16. Given an oversensed signal, the odds ratio of a patient receiving a shock of the cause of the oversensed signal is due to T-wave oversensing is 3.27 (95% confidence interval 1.03 – 10.4). The T-wave oversensing group was compared with a control group of 95 patients who had not experienced T-wave oversensing. Baseline ECG characteristics are presented in Table 17.
Table 14 Summary of the number of episodes of oversensed signal.

TWOS, T wave oversensing, MMVT, monomorphic ventricular tachycardia

<table>
<thead>
<tr>
<th>Oversensing type</th>
<th>Number of patients</th>
<th>Number of episodes</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Shock</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>No shock</td>
<td></td>
</tr>
<tr>
<td>TWOS</td>
<td>6</td>
<td>14</td>
<td>25</td>
</tr>
<tr>
<td>Noise / ectopy</td>
<td>4</td>
<td>2</td>
<td>17</td>
</tr>
<tr>
<td>Morphology change - MMVT</td>
<td>3</td>
<td>4</td>
<td>15</td>
</tr>
<tr>
<td>Morphology change - other</td>
<td>2</td>
<td>1</td>
<td>5</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>15</strong></td>
<td><strong>21</strong></td>
<td><strong>50</strong></td>
</tr>
</tbody>
</table>

Table 15 Summary of baseline characteristics of patients who experienced T wave oversensing. Yrs, years, PP, primary prevention of sudden cardiac death, SP, secondary prevention of sudden cardiac death, ST, sinus tachycardia, A Flutter, atrial flutter, SR, sinus rhythm.

<table>
<thead>
<tr>
<th>ID</th>
<th>Age (yrs)</th>
<th>Gender</th>
<th>Implant date</th>
<th>Indication</th>
<th>Date of episode</th>
<th>time of episode</th>
<th>ECG characteristics at time of TWOS</th>
<th>Number of episodes</th>
<th>Number of shocks</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>75</td>
<td>Male</td>
<td>13/02/2009</td>
<td>PP</td>
<td>05/06/2009</td>
<td>14h13</td>
<td>Low amplitude signal. ST rate 110 bpm</td>
<td>7</td>
<td>3</td>
</tr>
<tr>
<td>2</td>
<td>63</td>
<td>Male</td>
<td>31/12/2009</td>
<td>SP</td>
<td>19/10/2011</td>
<td>19h05</td>
<td>Low amplitude signal. A flutter rate 140 bpm</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>3</td>
<td>77</td>
<td>Male</td>
<td>29/11/2012</td>
<td>PP</td>
<td>12/02/2015</td>
<td>13h10</td>
<td>Low amplitude signal. ST rate 120 bpm</td>
<td>4</td>
<td>2</td>
</tr>
<tr>
<td>4</td>
<td>54</td>
<td>Male</td>
<td>28/11/2013</td>
<td>PP</td>
<td>21/04/2014</td>
<td>01h15</td>
<td>Low amplitude signal. SR rate 98 bpm</td>
<td>6</td>
<td>2</td>
</tr>
<tr>
<td>5</td>
<td>12</td>
<td>Male</td>
<td>07/08/2012</td>
<td>SP</td>
<td>26/09/2012</td>
<td>15h48</td>
<td>High amplitude T waves. ST rate 170 bpm</td>
<td>2</td>
<td>5</td>
</tr>
<tr>
<td>6</td>
<td>70</td>
<td>Male</td>
<td>09/07/2013</td>
<td>SP</td>
<td>04/02/2014</td>
<td>11h48</td>
<td>Low amplitude signal. AF rate 110 bpm</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Demographics</td>
<td>TWOS (n=6)</td>
<td>No TWOS (n=95)</td>
<td>p value</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>------------------------------------</td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male (%)</td>
<td>100.0</td>
<td>77.4</td>
<td>0.17</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td>55.8 ± 23.1</td>
<td>59.3 ± 17.9</td>
<td>0.65</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Primary prevention (%)</td>
<td>50.0</td>
<td>75.8</td>
<td>0.16</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ischaemic (%)</td>
<td>50.0</td>
<td>56.8</td>
<td>0.70</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NICM (%)</td>
<td>33.3</td>
<td>25.3</td>
<td>0.69</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<td></td>
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<tr>
<td>Valvular (%)</td>
<td>0.0</td>
<td>1.0</td>
<td>0.80</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>HCM (%)</td>
<td>0.0</td>
<td>5.3</td>
<td>0.56</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>EF</td>
<td>38.8 ± 15.4</td>
<td>32.9 ± 15.9</td>
<td>0.38</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypertension (%)</td>
<td>16.7</td>
<td>52.2</td>
<td>0.16</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diabetes mellitus (%)</td>
<td>0.0</td>
<td>25.8</td>
<td>0.18</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Atrial fibrillation (%)</td>
<td>16.7</td>
<td>28.4</td>
<td>0.53</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Myocardial infarction (%)</td>
<td>40.0</td>
<td>54.0</td>
<td>0.54</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CABG (%)</td>
<td>66.7</td>
<td>14.6</td>
<td>0.00</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PCI (%)</td>
<td>16.7</td>
<td>21.6</td>
<td>0.78</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Two zone programming</td>
<td>83.3</td>
<td>93.5</td>
<td>0.34</td>
<td></td>
<td></td>
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<td></td>
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<td></td>
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<tr>
<td>Conditional zone</td>
<td>202 ± 10.9</td>
<td>201.8 ± 8.7</td>
<td>0.96</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Shock zone</td>
<td>231.7 ± 21.4</td>
<td>227.3 ± 12.7</td>
<td>0.43</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sensing vector</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Primary</td>
<td>50.0</td>
<td>48.4</td>
<td>0.75</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Secondary</td>
<td>50.0</td>
<td>43.2</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Alternate</td>
<td>0.0</td>
<td>8.4</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>R:T ratio</td>
<td>3.5 ± 1.1</td>
<td>9.5 ± 13.2</td>
<td>0.27</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Aspirin (%)</td>
<td>50.0</td>
<td>48.4</td>
<td>0.61</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Warfarin (%)</td>
<td>16.7</td>
<td>27.2</td>
<td>0.72</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ACEi (%)</td>
<td>66.7</td>
<td>59.6</td>
<td>0.63</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Angiotensin receptor blocker (%)</td>
<td>0.0</td>
<td>21.6</td>
<td>0.24</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>β blocker (%)</td>
<td>80.0</td>
<td>85.1</td>
<td>0.76</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Aldosterone antagonist (%)</td>
<td>33.3</td>
<td>26.4</td>
<td>0.50</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Loop diuretic (%)</td>
<td>50.0</td>
<td>55.9</td>
<td>0.86</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Amiodarone (%)</td>
<td>33.3</td>
<td>11.4</td>
<td>0.06</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Statin (%)</td>
<td>33.3</td>
<td>62.0</td>
<td>0.33</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Table 16 Baseline clinical characteristics.

NICM, non-ischaemic cardiomyopathy, HCM, hypertrophic cardiomyopathy, EF, ejection fraction, CABG, coronary artery bypass graft, PCI, percutaneous coronary intervention, CKD, chronic kidney disease, PVD, peripheral vascular disease, NOAC, novel oral anticoagulant, ACEi, angiotensin converting enzyme.
Sample baseline screen ECGs, episodes of T-wave oversensing and clinic downloaded strips are shown in Figure 26.

<table>
<thead>
<tr>
<th>ECG variable</th>
<th>TWOS (N=6)</th>
<th>No TWOS (N=95)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heart rate (bpm)</td>
<td>74.1 ± 25.3</td>
<td>71.6 ± 18.4</td>
<td>0.760</td>
</tr>
<tr>
<td>R/S wave amplitude (mV)</td>
<td>1.3 ± .4</td>
<td>1.9 ± .9</td>
<td>0.124</td>
</tr>
<tr>
<td>T wave amplitude (mV)</td>
<td>0.4 ± .1</td>
<td>0.3 ± .2</td>
<td>0.564</td>
</tr>
<tr>
<td>QRSd (ms)</td>
<td>140.7 ± 28.7</td>
<td>105.9 ± 24.6</td>
<td>0.001</td>
</tr>
<tr>
<td>Time to peak T wave (ms)</td>
<td>369.9 ± 52.2</td>
<td>322.7 ± 41.0</td>
<td>0.008</td>
</tr>
<tr>
<td>Corrected time to peak T wave (ms)</td>
<td>403.9 ± 22.6</td>
<td>347.2 ± 41.4</td>
<td>0.001</td>
</tr>
<tr>
<td>QT interval</td>
<td>462.5 ± 58.4</td>
<td>417.6 ± 51.9</td>
<td>0.040</td>
</tr>
<tr>
<td>QTc interval</td>
<td>500.4 ± 41.2</td>
<td>446.8 ± 49.7</td>
<td>0.011</td>
</tr>
<tr>
<td>R:T ratio</td>
<td>3.5 ± 1.1</td>
<td>9.5 ± 13.2</td>
<td>0.316</td>
</tr>
<tr>
<td>atrial fibrillation (%)</td>
<td>16.7</td>
<td>28.4</td>
<td>0.53</td>
</tr>
</tbody>
</table>

Table 17 Baseline ECG characteristics

Figure 26 Montage of selection of four patients (1-4) who experienced T wave oversensing. Pre-implant screen is shown in image A, a screen shot of an episode of T-wave oversensing is shown in B, and a baseline electrogram at clinic prior to the episode is shown in C.
5.4.1 Clinical and electrocardiographic predictors of T-wave oversensing

By univariate analysis, the predictors of T-wave oversensing are QRS duration (140.7 ± 28.7 vs. 105.9 ± 24.6, p=0.007), time to peak T wave (369.9 ± 52.2 vs. 322.7 ± 41.0, p=0.014) time to peak T wave (corrected for heart rate) (403.9 ± 22.6 vs. 347.8 ± 41.4, p=0.006), QT interval (462.5 ± 58.4 vs. 417.6 ± 51.9, p=0.021), QTc interval (500.4 ± 41.2 vs. 446.8 ± 49.7, p=0.021) and R:T ratio (3.5 ± 1.1 vs. 9.5 ± 13.2, p=0.034). By multivariate analysis, time to pTc is the most predictive of T-wave oversensing Table 18. For every 10ms increase in the tPc there is a 30% increase in the odds of an inappropriate shock from T wave oversensing.

Table 18. Results of univariate and multivariate analysis.

<table>
<thead>
<tr>
<th>Logistic regression</th>
<th>Coefficient (β)</th>
<th>Odds ratio</th>
<th>p value</th>
<th>95% Confidence interval</th>
</tr>
</thead>
<tbody>
<tr>
<td>Univariate model</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>QRSd (ms)</td>
<td>0.04</td>
<td>1.04</td>
<td>0.007</td>
<td>1.01 - 1.07</td>
</tr>
<tr>
<td>Time to pT (ms)</td>
<td>0.03</td>
<td>1.03</td>
<td>0.014</td>
<td>1.00 - 1.05</td>
</tr>
<tr>
<td>Time to pTc (ms)</td>
<td>0.03</td>
<td>1.03</td>
<td>0.006</td>
<td>1.01 - 1.05</td>
</tr>
<tr>
<td>QT interval</td>
<td>0.02</td>
<td>1.02</td>
<td>0.053</td>
<td>1.00 - 1.03</td>
</tr>
<tr>
<td>QTc interval</td>
<td>0.02</td>
<td>1.02</td>
<td>0.021</td>
<td>1.00 - 1.03</td>
</tr>
<tr>
<td>R:T ratio</td>
<td>-0.65</td>
<td>0.52</td>
<td>0.034</td>
<td>0.29 - 0.95</td>
</tr>
<tr>
<td>Multivariate model</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Time to pTc (ms)</td>
<td>0.03</td>
<td>1.03</td>
<td>0.011</td>
<td>1.00 - 1.05</td>
</tr>
</tbody>
</table>

Results for all clinical and electrocardiographic variables that predicted T wave oversensing. QRSd, QRS duration, Time to pT, time to peak T wave, Time to pTc, time to peak T wave corrected for heart rate.

5.4.2 Predictive accuracy for determining T-wave oversensing.

Receiver operating characteristic (ROC) curves of time to pTc and CABG for T-wave oversensing were constructed. The area under the curve (AUC) were 0.88 and 0.76 respectively. The time to pTc of 390ms cut-off point provided a sensitivity 38.5% of a specificity of 98.9% a positive predictive value for T-wave oversensing of 83.3% and a negative predictive value of 91.6% (AUC = 0.687).

5.5 Discussion

In this study 5.9% of patients experienced T-wave oversensing over a median follow up of 19.5 months with a mean of 1.8 shocks per patient with T-wave oversensing. This incidence is similar to that for inappropriate shocks reported in the Effortless Registry. Patients who experienced
T-wave oversensing had significantly broader QRS complexes, lower R:T ratios and greater time to peak T wave amplitude and QTc. On analysis using a univariate statistical model all these parameters were predictive of T-wave oversensing. With multivariate analysis, only time pTc was predictive.

Although T-wave oversensing and inappropriate shock occurred relatively infrequently in this study and in the literature, we believe that any inappropriate shock is too many and that all avenues should be explored in order to reduce the burden of inappropriate therapy to levels that approach those of transvenous ICDs. T-wave oversensing is an important cause of inappropriate shock therapy in S-ICD recipients, the adverse consequences of which are of major importance for patient wellbeing and acceptance of ICD therapy. We believe T-wave oversensing can be reduced with careful attention to pre-implantation ECG characteristics. T-wave oversensing arises due to double counting of the QRS-T complex, which is more likely to occur when the QRS-T complex falls outside of an algorithm-specific timing window. This concept is captured within the pre-implant ECG screening template area. The S-ICD utilises a morphology based sensing algorithm that uses the pre-implant screening ECG to exclude patients from S-ICD therapy because of possibility of inappropriate shock therapy and/or failed rhythm discrimination. Therefore, we hypothesised that refined analysis of the pre-implant ECG screen could better predict T-wave oversensing.

Whilst the number of patients in this study who experienced T-wave oversensing is small (5.9% over a median follow up of 19.5 months) the consequence is important with a mean of 1.8 shocks per patient with T-wave oversensing. This incidence is similar to that for inappropriate shocks reported in the Effortless registry. 133, 164-166

In this study, patients who had T-wave oversensing had significantly broader QRS complexes, lower R:T ratios and greater time to peak T wave amplitude and QTc. On analysis using a univariate statistical model all these parameters were predictive of T-wave oversensing. With multivariate analysis, only time pTc was predictive.

All patients in the study had passed the pre-implant ECG screen in at least one vector in 2 postures using the patient screening template as recommended by the manufacturer. T-wave oversensing appears to occur early after S-ICD implantation (median time 4.2 months). Two cases required system extraction. One was in the context of recurrent shocks caused by T-wave oversensing and the second due to new RBBB developing which lead to vector change and failure to continue to satisfy and concomitant development of sustained monomorphic VT amenable to ATP. It is our observation that the pre-implant ECG screen, in its current form, is suboptimal in determining risk of T-wave oversensing. Using ECG parameters such as QRS duration and time to pTc may provide added value in the pre-implant ECG evaluation. On ROC analysis, the AUC is high.
for pTc (0.88), demonstrating that time pTc could be a clinically reliable predictor of T-wave oversensing. At a cut-off of 390ms for pTc, there is a high sensitivity, acceptable specificity and excellent positive and negative predictive values.

Oversensing that may be predicted and oversensing that can’t be predicted. In this study, we have been careful to distinguish between patients who have had T-wave oversensing during sinus rhythm and patients who have had oversensing and inappropriate shocks due to other causes. We have classified oversensing according to underlying rhythm and cause and distinguished whether the oversensing resulted in shock delivery or not. In a recent publication reported on the incidence, predictors and management of inappropriate shocks in the Effortless registry, patients with a history of atrial fibrillation (HR 2.4) and patients with hypertrophic cardiomyopathy (HR 4.6) had an increased risk for inappropriate shocks, while programming the primary vector for sensing (from xyphoid to V6) reduced this risk. 129

In our study, one patient developed RBBB following VT ablation and subsequently received an inappropriate shock for T-wave oversensing. Nine other patients experienced oversensing, eight of which received inappropriate shocks for causes that would have been difficult to predict at the time of S-ICD implantation – noise, QRS morphology change due to monomorphic VT and other types of QRS morphology change (e.g. aberrant conduction).

5.5.1 Dynamic nature of electrocardiogram

Electrocardiographic parameters are dynamic in nature reflecting changes in transmembrane ionic gradients, ischaemia, parasympathetic tone, serum electrolyte levels to name but a few factors. There are four scenarios whereby changes in ECG parameters may render a patient with an S-ICD vulnerable to T-wave oversensing: attenuation of the R/S, an increase in the T wave amplitude, broadening of QRS complex and changes in the QT interval. In patients with oedematous states, the amplitude of the QRS complexes can be reduced, though they recover following treatment. 167 In heart failure patients the mean change in QRS duration is 1.36ms/year, though in some patients the rate of change is significantly more rapid at over 10ms/year. 168 T wave amplitude varies with exercise, ischaemia, haemodialysis, hypertension and medication 169–172 and the QT interval is affected by a wide range of drugs which include anti-arrhythmic medication, antibiotics and antipsychotics that have potassium channel blocking characteristics, predominantly affecting the rapidly activating current I(Kr). 173 Thus it may be prudent to re-evaluate the ECG of any patient who may be at risk of T-wave oversensing in light of a change in their heart failure status, ischaemic status or medication that may affect repolarisation or serum potassium levels.
Programming changes to reduce T-wave oversensing

The manufacturer of the currently available S-ICD has recently developed a refined sensing algorithm which has been shown to reduce T-wave oversensing by up to 51% in independent validation studies without impacting on tachycardia detection and discrimination. Whether this results in an appreciable reduction in T-wave oversensing in clinical practice remains to be seen.

5.5.2 Limitations

This study only looked at T-wave oversensing. There is no process that predicts which patients will develop noise, aberrancy or MMVT at present. This study is a retrospective study, though the majority of the clinical data had been recorded prospectively as part of clinical trials or registries therefore we are confident that the data are accurate and reliable. The number of patients in this pilot study who have had T-wave oversensing is very small and therefore interpretation of the results must take this into account. In order to perform multivariate analyses, there must be at least 10 outcomes for each explanatory variable and this is something that was not present in this study. Therefore, the results of this study must be interpreted with a degree of caution.

We further conducted a calculation of a sample size that would be required to adequately power a study investigating the use of time to pTc in predicting T-wave oversensing. We used an information from the T-wave oversensing pilot study with an assumed T-wave oversensing incidence of 5% among a population of S-ICD patients and an odds ratio (OR) for “time to pTc” for predicting time to pTc of 1.03 per ms increase in time to pTc (95% confidence interval 1.00-1.05). At a power of 80%, a one-sided p<0.05 was assumed as only a prolonged time to pTc would be associated with an increase in probability for T-wave oversensing.

We estimated conservatively that a minimum of 756 patients would be required to be included in the analysis, with a minimal number of 38 T-wave oversensing cases, possibly increasing to 55. All calculations were performed on G*power 3.1.9 for Windows (1, 2).

We determined that a conservative estimate would require 756 patients to be included in the study in which the minimal number of cases of T-wave oversensing would be 38, and increasing up to 55. All calculations were performed on G*power 3.1.9 for Windows (1, 2).

5.6 Conclusion

The ECG parameters that predict T-wave oversensing are QRS duration, time to peak T wave, QT interval and R:T ratio with time to pTc being the most powerful predictor of T-wave oversensing on multivariate analysis. However, the number of patients affected by T wave oversensing was
small so need larger study is required with enough oversensing events to allow multivariate prediction score development and validation.
Chapter 6: Reconstruction of an 8–lead ECG from two S-ICD vectors

6.1 Abstract

6.1.1 Background

Techniques exist which allow surface ECGs to be reconstructed from reduced lead sets. We aimed to reconstruct an 8-lead ECG from two independent S-ICD sensing electrodes vectors as proof of this principle.

6.1.2 Methods

Participants with ICDs (N=61) underwent 3 minute ECGs using a TMSi Porti7 multi-channel signal recorder (TMS international, The Netherlands) with electrodes in the standard S-ICD and 12-lead positions. Participants were randomised to either a training (N=31) or validation (N=30) group. The transformation used was a linear combination of the 2 independent S-ICD vectors to each of the 8 independent leads of the 12-lead ECG, with coefficients selected that minimized the root mean square error (RMSE) between recorded and derived ECGs when applied to the training group. The transformation was then applied to the validation group and agreement between the recorded and derived lead pairs was measured by Pearson correlation coefficient (r) and normalised RMSE (NRMSE).

6.1.3 Results

In total 27 patients with complete data sets were included in the validation set consisting of 57 888 data points from 216 full lead sets. The distribution of the r and NRMSE were skewed. Mean r = 0.770 (SE 0.024), median r = 0.925. NRMSE mean = 0.233 (SE 0.015) median = 0.171.

6.1.4 Conclusions

We have demonstrated that the reconstruction of an 8-lead ECG from two S-ICD vectors is possible. The agreement between derived and measured signals was generally good to excellent though there were some negative correlations. If perfected, the ability to generate accurate multi-lead surface ECG data from an S-ICD would potentially allow recording and review of clinical arrhythmias at follow-up.
6.2 Introduction

The standard 12-lead electrocardiogram (ECG) represents the summed electrical forces of the heart as measured between limb lead electrodes (Einthoven leads, lead I, II and III), reconstructed combination of these directly recorded leads via simple mathematical formulae (Goldberger augmented leads, aVF, AVL and aVR), or directly recorded “unipolar” traces referenced to a fixed central dipole (precordial leads, V1-V6). Numerous studies have demonstrated the feasibility of generating and accuracy of using reconstructed 12-lead ECG from a reduced lead set. Of these, the EASI ECG system has gained widespread appeal and is used derive continuous 12-lead ECG data for adult and paediatric patients.

Reconstruction of a 12-lead ECG can be achieved by one of two methods. Single stationary dipole reconstruction (exact solution, or deterministic approach) and linear and non-linear filtering methods (statistical approach). When the two methods are compared, the statistical approach is preferred as it is less affected by collinearity (when predictors are highly correlated).

The underlying principle in limited lead systems is the transformation of information recorded from a ‘source’ lead system to another ‘target’ lead system. This idea relies on identifying a set of transformation coefficients that manipulate the signals in the source lead system to produce the signals in the target lead system. The target lead can then be estimated using a weighted sum of the measured signals. Each new, or derived lead is defined as in equation (1):

\[ \text{Derived lead} = (\text{coef1} \times \text{lead1}) + (\text{coef2} \times \text{lead2}) + (\text{coef3} \times \text{lead3}) \ldots \]

(1)

Where Derived lead is the estimated ECG signal, lead1, lead2 and lead3 are the measured signals and coef1, coef2 and coef3 are the coefficients that weight the measured signals.

Recent attempts have been made to generate 12-lead surface ECGs from endocardial electrograms recorded from cardiac implantable devices, such as implantable cardioverter defibrillators (ICDs) and cardiac resynchronization therapy devices with and without a defibrillator (CRT-P/D). The ICD is limited by the use of intravascular leads which can compromise the venous circulation, can become infected or can fracture and result in inappropriate shocks. The subcutaneous implantable cardioverter-defibrillator (S-ICD) has developed as an alternative to transvenous implantable cardioverter-defibrillators. The S-ICD system comprises three sensing electrodes: the first is located on the can in the 5th intercostal space in the mid-axillary line; the second is a proximal electrode located 1cm lateral to the xiphoid midline; the third is a distal...
electrode placed 14 cm superior to the second electrode, 1 cm lateral to the midline. Bellardine et al. have demonstrated good correlation between subcutaneous and corresponding transcutaneous body surface ECGs.\textsuperscript{130}

To date, a surface ECG has not been transformed from S-ICD vectors. The objective of this proof of principle study is to reconstruct an 8-lead ECG from two independent S-ICD sensing vectors and to determine the accuracy of the reconstructed ECG.

6.3\hspace{1em} Materials and methods

6.3.1\hspace{1em} Study population

All patients with an ICD indication aged at 18 years and over attending the ICD clinic at Southampton General Hospital were eligible for this study. Informed, written consent was obtained before the participation in the study. The study was approved by the London and Surrey borders NHS research and ethics committee.

6.3.2\hspace{1em} Study procedure

Simultaneous 12-lead ECG recording using the Mason-Likar 12-lead electrode arrangement and three study S-ICD surface electrodes placed in the conventional S-ICD electrode positions were recorded for three minutes. (Figure 27) ECGs were recorded with the participant in a supine position with the head and shoulders raised to approximately 45 degrees. The electrodes used were Ambu Blue Sensor SP single patient use ECG electrodes (Ambu, Denmark), connected to the Porti7 system with ExG shielded carbon cable (1.5m), microcoax to unipolar snap (TMS international, The Netherlands). ECGs were recorded using a TMSi Porti7 multi-channel signal recorder (TMS international, The Netherlands) attached to a laptop running TMSi polybench v1.30.3.3521 software (TMS international, The Netherlands). The sampling rate was set at 2000Hz. ECGs were stored in poly5 format.
Figure 27 Illustration of the Mason-Likar 12-lead electrode arrangement

12-lead electrode arrangement (red dots) and three study S-ICD electrodes placed in the conventional S-ICD electrode positions, (blue dots) and the location of the horizontal (H), vertical (V) and diagonal (D) vectors.

6.3.3 Randomisation

Participants were allocated to the ‘training dataset’ or to the ‘validation dataset’ using a random number generator. The training dataset was used to generate the transformation coefficients. The validation dataset was then used to test the coefficients, see Figure 28.
Chapter 6

Figure 28 Representation of how the transformation was created with the training dataset and used with the validation dataset.

Schematic illustrating how the transformation matrix was generated from the recordings from both the S-ICD vectors and the 12-lead ECGs (A) and how the transformation matrix containing the coefficients were combined with the S-ICD vectors to generate the reconstructed 12-lead ECGs (B).
### 6.3.4 Selection of representative beat for analysis

The representative QRST complexes that were compared were average beats over each of the recorded ECG leads generated in the following way: QRS complexes were sensed using an R-wave amplitude adaptively decaying sense threshold and any oversensed beats were manually removed. The QRS fiducial point for each patient was aligned for all leads by selecting the median QRS peak sample in time with the first beat in each lead used as the starting template beginning 100 milliseconds (ms) prior to sensed fiducial points and ending 450ms following sensed fiducial point.

### 6.3.5 Generation a signal averaged beat

The correlation coefficient of the template vs. each of the following beats was calculated. Initially, only beats with a correlation > 0.80 were included in the average. Then, the correlation coefficient was adjusted per lead between 0.5 and 0.9 to ensure the numbers of beats in each lead were similar. In addition, the difference in area between the template and the following beats were assessed for similarity and following beats were excluded if the area was not similar. The resulting signal averaged QRST complex from each patient and lead was used as the “representative” beat for which the transformation coefficients were computed.

### 6.3.6 Generation of coefficients, conversion matrix and derived ECGs

The following model was created for the matrix calculation from two independent S-ICD vectors to the 12-lead ECG:

\[
\begin{align*}
    \text{lead } I &= a_1 \times H + b_1 \times V \\
    \text{lead } II &= a_2 \times H + b_2 \times V \\
    \text{lead } V_1 &= a_3 \times H + b_3 \times V \\
    \text{lead } V_2 &= a_4 \times H + b_4 \times V \\
    \text{lead } V_3 &= a_5 \times H + b_5 \times V \\
    \text{lead } V_4 &= a_6 \times H + b_6 \times V \\
    \text{lead } V_5 &= a_7 \times H + b_7 \times V \\
    \text{lead } V_6 &= a_8 \times H + b_8 \times V
\end{align*}
\]

In which H is the horizontal vector, V is the vertical vector and a1...a8 and b1...b8 are the transformation coefficients. Leads III, aVR, aVL, and aVF are redundant (12) and are calculated from known geometries in the Einthoven triangle and therefore these leads were not included in the analysis.

The transformation coefficients were derived using the least squared difference approach, in which they are optimized for minimum root mean squared (RMS) difference between measured and derived vectors when applied to the training dataset. The optimization was performed in...
MATLAB (MathWorks, 2014a, Natick, USA) using the optimization toolbox function ‘fmincon’ which is a constrained nonlinear optimization method using the interior-point algorithm. This optimization algorithm is designed to efficiently determine the transformation matrix from the two subcutaneous leads to the 12-lead ECG that minimizes the RMSD between measured and computed 12-lead ECGs over all patients and leads.

6.3.7 Application of matrix to validation dataset

The measured ECG data for the validation dataset were imported into RashLab (a program for data processing, using the libRasch library (http://www.librasch.org/libRASCH-0.8.35)) where QRS complexes were automatically identified for all beats in the signal. The starting position of the P wave was stored into an array.

Each lead signal was then filtered in MATLAB using a 1st order high pass filter. For each starting position element in the array the next 520 samples were collected to ensure that the entire signal of interest was identified. Once all beats were acquired in this way for each lead, these were averaged for each lead, resampled from 1000 to 256 Hz and stored. This produced an averaged beat for each lead and each patient of 134 samples.

The averaged beats from study leads H and V were then combined with the transformation matrix to generate eight independent derived beats (lead I, II, V1-V6). Leads III, aVR, aVL, and aVF are redundant and were not calculated in this study so as not over-estimate the value of the vectors in the frontal plane. The derived leads were compared to the measured leads for each patient in RAW format.

6.3.8 Statistical analysis

Continuous data were presented as mean and standard deviation and categorical variables were presented as frequencies and percentages. The quantitative measures of similarity between the original (measured) ECG and the corresponding derived (reconstructed) ECG were determined using Pearson r correlation and root mean square error (RMSE) analysis for each derived lead. The Pearson r was considered to show high positive correlation at r ≥ 0.7. The RMSE is a parameter that indicates the average voltage error (microvolts) across the ECG leads studied. These parameters have been used by other investigators who have recorded this type of data for derived ECG leads. All analyses were performed in Stata 13 (StataCorp., College Station, TX: StataCorp LP.)
6.3.9 Explanation of statistical analyses

1. Pearson’s r correlation
   a. This is a quantative measure of the linear relationship between two variables with results ranging from -1 (total negative relationship, as one variable increase a unit, so does the other variable decrease by the same amount), 0 (no relationship) and 1 (perfect positive relationship). In this study pearson’s r correlation was used to assess for how well the measured ECG correlated with the derived ECG.

2. Root mean square error
   a. This is a measure of the differences between two sets of values. The RMSE represents the sample standard deviation of the differences between predicted values and observed values. In this case it is the difference between the measured and derived ECGs.

6.4 Results

A total of 63 cases were recruited, mean age 66.5 ± 14.2 years and 76.4% male. A summary of the characteristics of participants assigned to each group are presented in Table 19. Four participants were excluded after enrolment (Figure 29).

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Training dataset (n=31)</th>
<th>Validation dataset (n = 30)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>65.6 ± 15.9</td>
<td>67.1 ± 12.6</td>
<td>0.688</td>
</tr>
<tr>
<td>Male</td>
<td>23 (74.2)</td>
<td>24 (80)</td>
<td>0.59</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>173.0 ± 4.5</td>
<td>174.0 ± 9.5</td>
<td>0.698</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>79.5 ± 11.2</td>
<td>83.4 ± 14.8</td>
<td>0.44</td>
</tr>
<tr>
<td>BMI (kg/m^2)</td>
<td>26.4 ± 3.3</td>
<td>27.5 ± 5.7</td>
<td>0.554</td>
</tr>
<tr>
<td>Primary prevention</td>
<td>15 (55.5)</td>
<td>11 (40.7)</td>
<td>0.519</td>
</tr>
</tbody>
</table>

Table 19 Summary of participants assigned to training and validation datasets
Figure 29 Flow chart for selection of participants
6.4.1 Transformation coefficients

The transformation coefficients optimised from the training dataset are shown in Table 20.

<table>
<thead>
<tr>
<th>Lead</th>
<th>Horizontal vector</th>
<th>Vertical vector</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>-0.1615</td>
<td>-0.0692</td>
</tr>
<tr>
<td>II</td>
<td>-0.3746</td>
<td>-0.7210</td>
</tr>
<tr>
<td>V1</td>
<td>0.6175</td>
<td>0.1131</td>
</tr>
<tr>
<td>V2</td>
<td>0.7862</td>
<td>-0.0531</td>
</tr>
<tr>
<td>V3</td>
<td>0.3587</td>
<td>-0.4372</td>
</tr>
<tr>
<td>V4</td>
<td>-0.0152</td>
<td>0.6531</td>
</tr>
<tr>
<td>V5</td>
<td>-0.3947</td>
<td>-0.6139</td>
</tr>
<tr>
<td>V6</td>
<td>-0.5059</td>
<td>0.5118</td>
</tr>
</tbody>
</table>

Table 20 Transformation coefficients for all 8-leads

6.4.2 Reconstructed signal

Overall, 57,888 data points from 216 full lead sets over the 27-patient validation dataset were compared. Distribution of \( r \) and NRMSE were skewed. The distribution of the \( r \) and NRMSE were skewed. Mean \( r = 0.770 \) (SE 0.024), median \( r = 0.925 \) (interquartile range 0.76-0.97). NRMSE mean = 0.233 (SE 0.015) Median = 0.171 (interquartile range 0.10–0.29). The correlation coefficients and RMSE for each lead are summarised in Table 21. A scatter plot for each lead is presented in Figure 30.
6.4.3 Validation group

Lead-specific coefficients are summarised in Table 21. Table 22 describes Pearson correlation coefficient for all cases. From this, it can be observed that the data are skewed towards high correlation coefficients. Overall 123/216 (56.9%, 95% confidence interval 50.3 – 63.5) had an r value of >0.9 and 171/216 (79.2%, 95% confidence interval 73.8 - 84.6) had an r value >0.7. Reconstructed chest leads V3, V4 and lead I had significantly lower r values compared to the other leads (0.70 ± 0.40 vs 0.82 ± 0.32, p=0.0013). Examples of a case with a highly correlated reconstructed ECG and a case with a moderately correlated reconstructed ECG is shown in Figure 31.

<table>
<thead>
<tr>
<th>Lead</th>
<th>RMSE</th>
<th>Pearson r in µV</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>292.6</td>
<td>0.585</td>
<td>&lt;0.00001</td>
</tr>
<tr>
<td>II</td>
<td>275.1</td>
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<tr>
<td>V1</td>
<td>359.58</td>
<td>0.8413</td>
<td>&lt;0.00001</td>
</tr>
<tr>
<td>V2</td>
<td>643.93</td>
<td>0.719</td>
<td>&lt;0.00001</td>
</tr>
<tr>
<td>V3</td>
<td>638.76</td>
<td>0.6802</td>
<td>&lt;0.00001</td>
</tr>
<tr>
<td>V4</td>
<td>618.2</td>
<td>0.5989</td>
<td>&lt;0.00001</td>
</tr>
<tr>
<td>V5</td>
<td>455.88</td>
<td>0.7287</td>
<td>&lt;0.00001</td>
</tr>
<tr>
<td>V6</td>
<td>242.99</td>
<td>0.8841</td>
<td>&lt;0.00001</td>
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Table 21 Pearson correlation coefficients and RMSE for all leads
<table>
<thead>
<tr>
<th>Case</th>
<th>I</th>
<th>II</th>
<th>V1</th>
<th>V2</th>
<th>V3</th>
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<tr>
<td>1</td>
<td>0.463</td>
<td>0.945</td>
<td>0.984</td>
<td>0.664</td>
<td>0.738</td>
<td>0.817</td>
<td>0.903</td>
<td>0.944</td>
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<td>2</td>
<td>0.661</td>
<td>0.985</td>
<td>-0.442</td>
<td>0.771</td>
<td>0.948</td>
<td>0.975</td>
<td>0.980</td>
<td>0.984</td>
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<td>3</td>
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<td>0.847</td>
<td>0.981</td>
<td>0.949</td>
<td>0.949</td>
<td>0.930</td>
<td>0.859</td>
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<tr>
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<td>0.924</td>
<td>0.574</td>
<td>0.692</td>
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<td>0.960</td>
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<td>0.768</td>
<td>0.597</td>
<td>0.960</td>
<td>0.967</td>
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<td>0.217</td>
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<td>0.995</td>
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<td>0.575</td>
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<td>9</td>
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<td>0.993</td>
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<td>0.938</td>
<td>0.896</td>
<td>0.866</td>
<td>0.949</td>
</tr>
<tr>
<td>10</td>
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<td>0.954</td>
<td>0.992</td>
<td>0.919</td>
<td>0.832</td>
<td>0.862</td>
<td>0.986</td>
<td>0.991</td>
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<td>0.992</td>
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<td>0.866</td>
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<td>0.768</td>
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<td>0.849</td>
<td>0.891</td>
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<tr>
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<td>0.981</td>
<td>0.973</td>
<td>0.901</td>
<td>0.949</td>
</tr>
</tbody>
</table>

Table 22 Pearson correlation coefficients ($r$) for all patients and leads
6.5 Discussion and Conclusion

6.5.1 Feasibility and accuracy of S-ICD derived 12-lead ECGs

This study confirms the proof of concept that it is possible to create transformation coefficients and to reconstruct an 8-lead ECG using two independent S-ICD electrode vectors. Overall the accuracy has been good to excellent with a median $r = 0.925$ (interquartile range 0.76-0.97) for all reconstructed signals. Over 79% of reconstructed leads had an $r$ value >0.7 and 50% of reconstructed leads had an $r$ value >0.9. The coefficients we achieved are comparable to those published in other studies. $^{176, 181, 188-190}$ However, in some leads the reconstruction did not work well. In 27/216 (12.5%) of leads the $r$ value was <0.5 with many examples of negative correlations. The reconstructed lateral limb leads Lead I and the chest leads V3 and V4 significantly lower $r$ values compared to the other leads. In general leads II and V6 were most accurately predicted. We speculate that these differences are explained by differences in the heart and torso anatomy between patients resulting in variation in the spatial relationships between ECG electrodes.
We utilised a linear transformation model to reconstruct the 12-lead ECGs from two independent S-ICD vectors. It would have been feasible to utilise a fixed dipole method, though this would require a number of assumptions to be made regarding the conductively of the body tissues and fluid, would be more complex and time-consuming and thus would probably not have improved on these results.

The concept that all possible theoretical ECG vectors can be reconstructed using data from suitable measured independent vectors has been applied to create reduced lead ECG systems such as the EASI ECG system. In this study we have used only 2 measured vectors on a 2-dimensional plane to reconstruct the ECG. Traditionalists would argue that a larger part of the information that can be obtained from surface ECG recording is in three dimensions and therefore the results of this study represent a break from this traditionalist view. Adding a third dimension to the S-ICD sensing configuration is challenging given the generator and lead location on the chest wall, therefore our statistical solution is likely to remain the preferred option for this technology.

6.5.2 Clinical applications

At present the S-ICD will only store electrograms from the vector that has been selected as the sensing vector and only once a tachycardia has been detected. The ability to generate a 12-lead ECG from S-ICDs is novel and would provide the clinician with considerably more information than currently available. In particular, detailed information on the morphology, axis and origin of ventricular tachycardia which would inform future catheter ablation strategies.

6.5.3 Personalised coefficients

The accuracy of the derived ECGs for any given patient is dependent on the spatial arrangement of electrodes on that patient relative to each other and to the electric heart vector and the conductivity of the underlying tissue. A close match with those of the participants used to derive the conversion matrix will result in ECGs that are highly correlated with the patient’s own measured ECG. Conversely, a poor match with those of the participants used to derive the conversion matrix will result in ECGs that are poorly correlated with the patient’s own measured ECG. Therefore any factors that affect the size and shape of the thorax, the composition of the underlying tissue and position and pathology of the heart itself will affect the accuracy of the derived ECG. The accuracy of the derived ECGs could be improved if the coefficients were generated for specific sub-groups of patients stratified by these confounders. A more elegant solution may be to derive transformation coefficients on a patient by patient basis. Simultaneous
readings could be taken from a surface ECG and the S-ICD in-situ, and these used to generate coefficients which could then be uploaded to the S-ICD.

6.5.4 Limitations

The main limitation of this pilot study was the relatively small number of patients in the training and validation groups and the presence of a small but significance proportion of reconstructed leads having a low correlation with the measured signal. Notwithstanding this, we achieved our objective, to derive the transformation coefficients and to generate transformed ECGs most of which are highly correlated with the measured ECG. However, some of the derived ECGs would not be of sufficient quality to be used in a clinical setting and therefore repeating this study using a larger cohort, as was done with the original EASI coefficients would be necessary. In order for this technology to be incorporated into subsequent versions of the S-ICD, future studies should also repeat this study whilst the patient is experiencing arrhythmias to test how precise the reconstructed ECGs are during arrhythmia. In addition to quantitative comparisons (Pearson correlation and RMSE), qualitative comparisons interpreted by 2 blinded physicians for adjudication and agreement may add clinical context.

6.6 Conclusions

We have demonstrated that the reconstruction of an 8-lead ECG from two S-ICD vectors is possible. The agreement between derived and measured signals was generally good to excellent though there were some negative correlations. If perfected, the ability to generate accurate multi-lead surface ECG data from an S-ICD would potentially allow recording and review of clinical arrhythmias at follow-up.
Chapter 7: Discussion and conclusion

Implantable cardioverter-defibrillator therapy can be life saving for an individual patient. In recent years the S-ICD has emerged as an alternative to the transvenous ICD though problems with S-ICD sensing of the cardiac signal has limited its uptake.

This thesis has covered a broad range of topics on the subject of S-ICD sensing: the impact of a right parasternal lead position and postural change on S-ICD sensing, ECG predictors of T-wave oversensing and reconstructing an 8-lead ECG from two S-ICD vectors. The theme that links these studies together is the concept of developing a tailored assessment of patient’s suitability for S-ICD therapy. Most of the studies in this thesis are small and are exploratory in nature, due to the low incidence of T wave oversensing in the ECG predictors of T-wave oversensing, the relatively rarity of patient with complex congenital heart disease in the impact of right parasternal lead position and posture on S-ICD sensing studies demonstrate. As a consequence larger confirmatory studies would be required to corroborate my findings.

7.1 Summary of original findings

7.1.1 Assessment of a patient’s suitability for an S-ICD and implications on S-ICD implantation

The impact of parasternal lead position and posture on sensing with the S-ICD.

In the linked studies of parasternal lead position and S-ICD sensing and postural change and S-ICD sensing, I have demonstrated that the current pre-implant screening process does not account for how the R wave and T wave amplitude vary with posture and placement of the sternal sensing electrode. I have demonstrated that by adopting an individualised approach at the time of the pre-implant ECG screen and prior to S-ICD implantation, S-ICD sensing parameters may be optimised and thus reduce some of the adverse events associated with S-ICD therapy, namely inappropriate shock due to T-wave oversensing. Changing the location of the parasternal lead position in an individual patient in response to results of pre-implant screen with more than two postures or using a right parasternal lead screening position may maximise the sensing capabilities of the S-ICD.
7.1.2 Assessment and follow-up of patients with S-ICDs

T-wave oversensing study

In this study I have demonstrated how the pre-implant ECG can be used to identify the ECG predictors of T-wave oversensing. I have identified the pTc as a marker for inappropriate shocks due to T wave oversensing and that there is a 30% increase in the odds of receiving an inappropriate shock due to T wave oversensing for every 10ms increase in this index. Thus, patient care can be individualised at the time of the assessment of the patient’s suitability for the device and if they have ECG markers which places them at risk of T-wave oversensing then they may be advised that S-ICD treatment may not be in their interests. Alternative treatments include a cardiac resynchronisation therapy device with ICD (CRT-D) if there QRS is also broad. The incidence of T-wave oversensing in S-ICD is reducing due to improvements in discrimination algorithms and improved screening practices. This study was underpowered and the number of patients with T-wave oversensing was low thus reducing the value of the multivariable logistic analysis that was performed, therefore should be considered a pilot study. A post-hoc power calculation however has determined that over 750 patients would need to be recruited into a study in order for it to be powered adequately. Such a trial would be impractical to arrange given that the most recent published data on S-ICDs which pooled the original IDE trial and the international Effortless Registry has recruited a total of 882 patients implanted in 61 centres by 107 implanters in over 5 years. 192

7.1.3 Follow up of S-ICDs

Reconstructing an 8-lead ECG from 2-independent S-ICD vectors

In this study, I have demonstrated the feasibility of reconstructing an 8-lead ECGs from 2 independent S-ICD vectors. The accuracy of the reconstructed ECGs was generally good, but in some individuals and in some leads, the accuracy was poor. However, I propose that if the transformation matrix was individualised at the time of the assessment of the patient’s suitability for the device the resultant reconstructed would likely be highly correlated to the individual's ECG.
7.2 Contemporary challenges to defibrillator therapy and how findings from this thesis may influence these

The ICD has a clear benefit in preventing arrhythmic death in appropriately selected individuals, and this benefit is probably greatest in secondary prevention patients as they are at greater overall risk of SCD and have a higher incidence of appropriate therapy.\textsuperscript{193} In an analysis by Betts et al.\textsuperscript{60} of the absolute risk reduction (ARR) in total mortality with primary and secondary prevention ICDs, data from eight primary prevention (PP) trials, three secondary prevention (SP) trials and one SP meta-analyses were analysed. The ARR at 3-year follow-up ranged from 0 (no benefit) to 24.6\% (NNT = 4) for PP. For SP the ARR at 3-year follow up ranged from 3.7\% (NNT = 27) to 11.3\% (NNT = 9). Absolute risk reduction increased with follow-up in PP trials, whereas there was considerable variation in SP trials. Data from extended follow up of the landmark trial in primary prevention of SCD with ICDs,\textsuperscript{61} where the number needed to treat to prevent 1 death is six over an eight year time horizon.

From a technical perspective, the biggest challenge to the modern day defibrillator occurred approximately 7 years ago with the problems encountered with the transvenous lead failures associated with the Medtronic Sprint Fidelis leads and the St Jude Medical Riata lead failures. As discussed in the introduction, the perception was that the presence of a transvenous lead was the ‘Achilles heel’ of the ICD and this led to the development of the S-ICD. The S-ICD has become increasingly popular amongst physicians who implant defibrillators mainly due to the advantages of not having a transvenous lead in situ. However, there remain a number of important limitations of the S-ICD, mainly to do with accurate sensing of the cardiac signal and this will be the focus of the subsequent discussion.

7.2.1 Current challenges to S-ICD sensing

Many of the studies in this thesis have focused upon features that are specific to the sensing characteristics of the S-ICD (Chapters 3-6). In particular, the importance of how a small change in the location of where an electrogram is recorded (e.g. left versus right parasternal location), or how the change in the posture may influence the sensed electrogram by altering the amplitude of the R wave or the T wave, both fundamental to accurate sensing in the S-ICD. In addition the ECG predictors of T-wave oversensing highlights the importance of accurate S-ICD sensing capabilities.

The S-ICD is an evolving technology. Some critics were concerned that high rates of inappropriate therapy would limit the uptake of the device.\textsuperscript{24} There is undoubtedly a learning curve for the implanters\textsuperscript{192} but also for the manufacturers. As more data from international registries becomes
available, there is a greater understanding of the challenges that the S-ICD faces. One of the main challenges is improving the accuracy of the sensing function of the S-ICD and this follows on from the work carried out as part of this thesis.

### 7.2.2 Novel solutions

Whilst these new algorithms are welcomed they may be ineffective if the patient develops bundle branch block during SVT unless an ECG template recording aberrant beat morphology if it has been recognised during screening or if there electromechanical noise.

In addition to continuously monitoring the heart rate, the S-ICD also compares the QRS-complex and T-wave morphology to a template registered and stored by the S-ICD immediately after implantation to discriminate between SVT and ventricular arrhythmias. For this reason also, QRS-T wave morphology screening and analysis is integral to assessing device eligibility and efficacy prior to implantation.

It is in this context that the work done as part of this thesis must be viewed. In the studies investigating the impact of postural change and parasternal lead position I have demonstrated that the location of the sensing electrodes can alter the sensed amplitude of the R and T waves and R:T ratios. Thus adopting an individualised approach to pre-implant ECG screening in order to achieve the optimum R wave, T wave and R: T ratio to prevent complication such as oversensing appears to be a valid option. This method has been successfully used in clinical practice. However, adopting an individualised approach to where the sensing electrodes of an S-ICD are placed has yet to be proven as a strategy that translates into fewer oversensing episodes.

### 7.2.3 Difficulties of calculating heart rates

Given the ubiquity of the ECG, and the ease with which clinicians (and non-clinicians) are able to calculate accurate heart rates it is surprising that a robust 100% accurate computer-based method has yet to be developed. Indeed, if such a method were to be developed and integrated into S-ICD firmware, then that would become the ‘gold-standard’ heart rate monitor against which the other sensing processes which current sensing and analyse the a cardiac signal could be continuously compared. If the detected rate was found greater than the ‘gold-standard’ method, then it would mean oversensing was occurring, and inappropriate therapy could be withheld.

However, there are several reasons why creating a 100% accurate heart rate detector is challenging. The ECG is a non-stationary signal and is subject to a variety of corrupting sources of noise in a clinical environment, for example, power line interference, muscle contraction noise,
poor electrode contact, patient movement, and baseline wandering due to respiration any of which can degrade the quality of the ECG signal.

Since the advent of telemedicine, there has been increasing interest in the signal processing literature about developing accurate and efficient heart rate monitors. One of the more promising methods is the use of wavelet analysis which employs time-domain gradient based approach and spectral energy analysis to process the acquired ECG signal.

7.2.4 Overview of QRS detectors:

The algorithms for QRS detectors can be classified into three categories:

1) No syntactic, which are generally inefficient
2) Syntactic, which are used widely and
3) Hybrid.

Previously applied algorithms commonly use computing technique to detect QRS complexes using thresholding, artificial intelligence using hidden Markov models, and time recursive prediction techniques. Normally the recorded signal is filtered to enhance the QRS complexes to suppress the P and T wave and noise and finally determining the presence of QRS complexes using a decision tool. The main drawbacks of these techniques is that frequency variation in QRS complexes adversely affects their performance. The frequency band of QRS complexes generally overlaps the frequency band of noise, resulting in both false positives and false negatives. Methods using artificial intelligence are time consuming due to the use the necessary computational rules.

Wavelet analysis is a very promising mathematical tool that gives good estimation of time and frequency localization. Wavelet analysis has become a useful tool for characterizing ECG signal and some very efficient algorithms has been reported using wavelet transform as QRS detectors (Figure 32).

Table 23 provides a comparison of published ECG detection algorithms.
Figure 32 An example of wavelet based QRS identification.
A, ECG signal from a patient in normal sinus rhythm. Numbers denote cumulative number of detected R waves. B, Coefficient plot after application of wavelet transform with numbering indicating cumulative number of detected beats.
Table 23 Comparison of published ECG detection algorithms.


Wavelet based heart rate technology has not to my knowledge been applied in S-ICD technology at present, but may do so in the future. An alternative method for improving the accuracy of QRS detection would be to use more than one S-ICD vector to determine the heart rate. At present, only the vector that is in use is capable to sensing all the time. Newer versions of the S-ICD may employ more than one of the S-ICD vectors to sense the cardiac signal and thus calculate the heart rate. An advantage of such a system would be a theoretically improved accuracy of the heart rate determination.

In summary, within this thesis, I have discussed some of the problems related to oversensing of the cardiac signal that can occur with the S-ICD and this has led me to hypothesise that by improving the mechanism by which the S-ICD counts the heart beat in a way that eliminates the T wave, any oversensing may be dramatically reduced. Whether this occurs remains to be seen in future studies in this area.

### 7.3 S-ICD sensing in the future

#### 7.3.1 Automated screening

It is likely that in the future the manual screening process with the coloured ECG template will be replaced with an automated screening process whereby the patient’s ECG will be recorded directly by the S-ICD manufacturer’s pacing system analyser (PSA) which will have the up to date
sensing algorithms discussed in chapter 2 installed as software. This is likely to improve the proportion of patients who are appropriately selected for S-ICD therapy and could help identify patients who may go on to have inappropriate sensing with an S-ICD and recommend that these patients not receive an ICD.

7.3.2 Floating bipole away from the heart to provide optimal sensing and reducing the risk of inappropriate sensing

At present the S-ICD is limited to sensing via one of 3 vectors created from the lead/can interface. As this thesis has discussed, this paradigm has its limitations. The incorporation of an additional sensing electrode but separate from the S-ICD may offer alternative solutions for the problem of S-ICD sensing. This ‘floating dipole’ may potentially take the form an implantable loop recorder placed at the optimal location to provide useful additional information for accurate cardiac signal sensing. This floating bipole would communicate remotely (e.g. Bluetooth) with the S-ICD can to deliver this additional sensing information. 207

7.3.3 Integrating the signals from more than 1 vector to achieve the best sensing vector

At present the majority of patients who are deemed suitable for S-ICD implantation on the basis of a successful template screening assessment have at least 2 vectors that passed the screen. In a study of 230 ICD patients with no pacing indication, 78% of the patients had ≥2 appropriate sensing vectors. 129 However, only one sensing vector will be used at any one time. It would therefore seem logical to attempt to incorporate the use of more than one vector in the assessment of the cardiac signal. This however may take up valuable computing power and jeopardise the duration of the battery, therefore these issues may need to be resolved before this incorporated into newer iterations of the S-ICD.

7.3.4 Combining transvenous, epicardial or leadless pacemakers with the S-ICD

One of the limitations of the S-ICD is the absence of durable bradycardia pacing capability. Physicians have overcome this by combining transvenous permanent pacemakers (PPM) or epicardial pacemakers (in cases where venous access is not feasible) with the S-ICD. In doing so, the PPM will provide the backup pacing and the S-ICD will provide the defibrillation capability should a ventricular arrhythmia occur. 208 209 Prior to implanting the S-ICD in a patient with an incumbent PPM, both the intrinsic QRS complex and the paced QRS complex must satisfy the S-ICD screening template as described in Chapter 2.
The main risk of combining these two technologies is two-fold. Firstly, the S-ICD may over-sense the pacing spike and thus deliver inappropriate therapy. It is therefore important that the pacemaker be programmed in bipolar mode in order to minimise the amplitude of the pacing spike. It must be noted that after the delivery of a full output shock for ventricular tachycardia or ventricular fibrillation, the pacemaker would revert to unipolar pacing and therefore there is a risk of inadvertent oversensing and further, this time, inappropriate shock delivery. Secondly, during ventricular tachycardia or ventricular fibrillation, the PPM will continue to attempt to deliver paced beats (though these will not capture the myocardium and will be ineffectual). However, there is a risk that the S-ICD would sense these pacing spikes and therefore undersense the ventricular tachycardia/ventricular fibrillation and thus lifesaving therapy may not be delivered. It is therefore vital that intraoperative cross talk testing takes place to evaluate for the presence of either of the above scenarios.

As discussed in chapter 2, the presence of transvenous leads are a weak point of the TV-ICD. So are the presence the transvenous leads in PPM and therefore leadless pacemakers have been developed. These miniaturised pacing systems are implanted via the femoral vein and delivered to the right ventricular by means of a catheter delivery system. To date, the data on the safety and efficacy of the Micra (Medtronic Minneapolis) device in particular appear very encouraging. One advantage that a leadless pacemaker would offer is the ability to deliver anti-tachycardia pacing in order to terminate ventricular tachycardia painlessly, which the S-ICD is unable to do at present. It seems logical therefore to explore the use of leadless pacemakers and the S-ICD.

Early experiments in sheep and humans have tested leadless pacemakers and S-ICD with evidence that this is feasible and safe, though more data are required. Data from this study support using this combined therapy in clinic, aiming to benefit patients in whom transvenous access is not feasible or desired. This combined therapy is the next step in multi-component leadless cardiac rhythm management, with the objective to eliminate transvenous lead-related complications.

In conclusion, the combination of permanent (transvenous, epicardial and leadless) pacemakers is being tested. At present the pacemaker serves as a tool to deliver bradycardia pacing, however, it is entirely conceivable that they may also serve as an additional sensing tool to help eliminate the problems of oversensing with the S-ICD.
7.4 The future role of S-ICD in an ACHD population

In a subset of patients with ACHD there is a small but ongoing risk of SCD. As discussed in Chapters 3 and 4, the S-ICD is well suited to some patients with ACHD at high risk of SCD due in part due to the absence of a transvenous lead and also that postural change and parasternal lead position do not affect the sensed ECG signal as much in patients with ACHD compared to normal controls. A recent systematic review and meta-analysis of ACHD patients with ICDs (transvenous ICD 96.1%) has reported remarkably high rates of appropriate ICD therapy (ATP and shocks) in both primary and secondary prevention (24% (18.6-31.3)) and that due to the younger age at implant and lower death rates from non-cardiac causes, the cumulative benefits are thought to be greater in ACHD patients compared to acquired heart disease patients. However, the drawback is a high rate of inappropriate therapy (25% (18.9-33.6)) in 3.7 +/- 0.8 years. Supraventricular tachycardia (68%), sinus tachycardia (17%) and oversensing and lead failure (13%) were the most common reasons for the first occurrence of inappropriate shock. This highlights the importance of accurate sensing discussed in detail above (improve pre-implant screening protocol, minimising risk of T-wave oversensing by appropriately selecting patients with surface ECGs that are less likely to have oversensed signal). Importantly, the S-ICD has been shown to have an excellent capacity (better than two of the three commonly used transvenous ICDs) to discriminate ventricular from supraventricular rhythms and therefore if S-ICDs were used from frequently in the ACHD population, one may speculate that the rate of inappropriate therapy may actually reduce, assuming no risk of T-wave oversensing from high amplitude T waves. Whether this is true remains to be seen in future studies.

7.4.1 Vector transformation

From the lead transformation study, I have demonstrated that it is feasible to reconstruct a 12 lead ECG from 2 independent S-ICD vectors with good overall accuracy. This entirely novel concept in the S-ICD does not resolve any specific sensing problems associated with S-ICD but rather provides insight into additional functionality associated with the S-ICD, which may eventually help resolve oversensing issues by optimising the sensing vector. The theory underlying this transformation is relatively simple. Any desired vector (lead) can be reconstructed if the known coefficients are multiple by the know vectors (leads).

\[
\text{Derived lead} = (\text{coef1 } \times \text{ lead1}) + (\text{coef2 } \times \text{ lead } 2) + (\text{coef3 } \times \text{ lead3})...
\]

Applying this theory may help allow us to reconstruct sensing vectors that reduce the amplitude of the T wave, thus reducing the likelihood of T-wave oversensing.
The S-ICD sensing configuration is in the shape of a right angle triangle. (Figure 33). This allows us to easily calculate the QRS and T wave axis. I have observed that the R wave axis and the T wave axis differ. (Figure 34). We know that ECG leads that record the cardiac signal in the same axis as that of the cardiac (QRS) axis have the maximal positive amplitude signal and those leads that are orthogonal to the cardiac axis have the lowest amplitude signal. Thus, if a sensing vector 90 degrees to the T wave axis then the resultant complex should have the smallest recordable T wave amplitude. The R wave would still be present assuming the QRS axis differs from the T wave axis. It is conceivable therefore that one could ‘dial-up’ the optimal sensing vector by transform the signal from the 3 S-ICD vectors to generate the new complex with the smallest T wave. This transformed complex would act as the principle sensing vector. This would be another step towards personalisation of the ICD therapy.
Figure 34 Transforming vectors to reduce the amplitude of the T wave

A: A pre-implant ECG screen taken from a patient who went on to receive an inappropriate shock due to T wave oversensing. B: A schematic to illustrate the QRS and T wave vectors. C: An illustration of where an orthogonal angle to the T wave axis would lie. This new vector would theoretically have the lowest amplitude T wave.
This hypothesis would need to be tested to prove that 1) it is possible to create the necessary coefficients required to transform the signal to the desired vector and 2) the transformed signal is superior to the native S-ICD signals in terms of sensing accuracy, discrimination and reduction in rates of T wave oversensing.

7.4.2 Identification of patients at risk of T-wave oversensing prior to inappropriate therapy

One of the limitations of the current iteration of the S-ICD is its ability to store electrograms only once the capacitors start charging. This contrasts with transvenous ICDs which are capable of storing considerably more data (episodes of atrial tachyarrhythmia, non-sustained ventricular tachycardia in the monitor zones etc.). At present, we are therefore unable to identify episodes of T-wave oversensing that do not result in inappropriate therapy. It is possible that there are patients who are experiencing T-wave oversensing but that these are occurring at rates below the tachycardia detection window even accounting for the double counted beat. It would be important to identify this cohort of patients as they may be at higher risk of subsequent inappropriate shock from T-wave oversensing.

7.4.2.1 Research implications

A study to identify episodes of subclinical T-wave oversensing is being designed in order to test this hypothesis. Holter monitors with electrodes placed over the S-ICD sensing electrodes will be attached to patients with S-ICDs who have a prolonged pTc. Data from the holter monitors will be sent to Boston Scientific (S-ICD manufacturer) for further analysis. The data will be run through their proprietary sensing algorithm to detect episodes of T-wave oversensing that would not have been identified previously. This might have important implications as it may lead to better identification and of patients at risk of T-wave oversensing. Interventions that may reduce their risk of subsequent clinical T-wave oversensing and inappropriate shock include S-ICD reprogramming (using different vectors, modifying tachycardia therapy zones, updating discrimination algorithms), medication changes (stopping medication that prolong the QT intervals), lead re-positioning or even device explantation if the risks of T-wave oversensing are thought to be too great.
7.4.3 Does device therapy for prevention of sudden cardiac death need to be tailored to the individual?

At present clinicians only have relatively crude tools to guide them in the decision to implant a defibrillator: the clinical history, the surface ECG and the ejection fraction. There are several novel risk markers that have been used for the assessment of increased risk in SCD, however, at present, none of these have been accepted into routine clinical practice. Technology could help. As this thesis has demonstrated, much could be done at an individual level (optimise lead position, identify patients at risk of T wave oversensing and using vector transformation to reduce the likelihood of inappropriate therapy) to maximise the potential benefit (and reduce the unwanted consequences) of subcutaneous implantable defibrillators in particular.

Therefore, it seems logical that that ICD therapy ought to be tailored to the individual as much as possible. However, the hypothesis of whether a truly personalised approach to device therapy to reduce sudden cardiac death may be superior to ‘off the shelf therapy’ is valid but would need to be answered in future studies.

7.5 Final conclusion

Progress is being made towards the goal of an individual approach to the assessment and treatment in patients with subcutaneous implantable cardioverter defibrillators. Population studies are required to develop more sophisticated discrimination algorithms, vector transformation to reduce T wave oversensing and reducing morbidity associated with ICDs due to inappropriate therapy, individualisation of electrode placement and risk assessment for inappropriate shock occurs. A future of inappropriate shock free sudden cardiac death treatment which is appropriate for all patients with subcutaneous ICDs is a tangible reality.
Appendices

Appendix A

<table>
<thead>
<tr>
<th>Monitor Zone</th>
<th>Zone 1</th>
<th>Zone 2</th>
<th>Zone 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Medtronic</td>
<td>133</td>
<td>167</td>
<td>250 (via VF)</td>
</tr>
<tr>
<td>St Jude</td>
<td>-</td>
<td>166</td>
<td>200</td>
</tr>
<tr>
<td>Boston</td>
<td>-</td>
<td>165</td>
<td>200</td>
</tr>
<tr>
<td>Sorin</td>
<td>135</td>
<td>165</td>
<td>200</td>
</tr>
</tbody>
</table>

Primary prevention ICD setting for University Hospital Southampton NHS Foundation Trust

Table 1 Standardised hospital programming for tachycardia zones for major ICD manufacturers in primary prevention patients with structural heart disease at University Hospital Southampton NHS Foundation Trust.
<table>
<thead>
<tr>
<th></th>
<th>Monitor Zone</th>
<th>Zone 1</th>
<th>Zone 2</th>
<th>Zone 3</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Medtronic</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Detection</td>
<td>36 intervals</td>
<td>32 intervals</td>
<td>(via VF)</td>
<td>30/40 intervals</td>
</tr>
<tr>
<td>Redetection</td>
<td>12 intervals</td>
<td>(via VF)</td>
<td>12/16 intervals</td>
<td></td>
</tr>
<tr>
<td><strong>St Jude</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Detection</td>
<td>-</td>
<td>25 intervals</td>
<td>25 intervals</td>
<td>25 intervals</td>
</tr>
<tr>
<td>Redetection</td>
<td>-</td>
<td>9 intervals</td>
<td>9 intervals</td>
<td>9 intervals</td>
</tr>
<tr>
<td><strong>Boston</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Detection</td>
<td>-</td>
<td>9.0s</td>
<td>7.0s</td>
<td>6.0s</td>
</tr>
<tr>
<td>Redetection</td>
<td>-</td>
<td>3.0s</td>
<td>3.0s</td>
<td>1.0s (fixed)</td>
</tr>
<tr>
<td><strong>Sorin</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Detection</td>
<td>50 intervals</td>
<td>30 intervals</td>
<td>20 intervals</td>
<td>20 intervals</td>
</tr>
<tr>
<td>Redetection</td>
<td>-</td>
<td>(fixed)</td>
<td>(fixed)</td>
<td>(fixed)</td>
</tr>
</tbody>
</table>

Table 2 Standardised hospital programming for discrimination settings for major ICD manufacturers in primary prevention patients with structural heart disease at University Hospital Southampton NHS Foundation Trust.
Primary Prevention Settings

The following protocols are a robust guide for PRIMARY PREVENTION patient settings. They do not take away the responsibility of clinicians and physiologists to consider individual patient requirements, patient heart rates, underlying rhythm, and the indication for device.

**Contraindications:** Secondary prevention, and inherited cardiac diseases and syndromes.

### Medtronic

<table>
<thead>
<tr>
<th>Zone</th>
<th>Thresholds</th>
<th>Interval</th>
<th>SVT Disc</th>
<th>Therapy</th>
</tr>
</thead>
</table>
| VF         | 200bpm (300ms) | 30 of 40 | On         | ATP during charging on  
  - Deliver ATP if last 8 RR ≥ 200ms  
  - Burst 8 at 88%  
  - Charge saver ON, smart mode on  
  All Shocks 35J  
  - Reverse polarity of penultimate shock  
  - Confirmation+ On |
| FVT via VF | 240bpm (250ms) | On       | Therapy 1: ATPx2  
  - Burst 8, 88%, 10ms, smart off  
  Therapy 2: ATPx1  
  - Ramp 8, 84%, 10ms, smart off  
  Therapy 3-6: Full output Shocks  
  - Reversed polarity of penultimate shock |
| VT Monitor | 172 (370ms) | 32       | On         | On for Ischaemic patients only, but use discretion.                      |

### Shared Settings

- V-V Minimum ATP interval: 170ms
- Off

### SVT Discrimination

- As per out of the box setting (Unless contraindicated)
- Collect morphology template (Test -> Wavelet) >70%?

### Brady Setting:

- If no pacing indication limit V-pacing 40bpm, AAI <->DDD (MVP)
# Boston Scientific

<table>
<thead>
<tr>
<th>Zone</th>
<th>Threshold</th>
<th>Duration</th>
<th>Detection Enhance</th>
<th>Therapy</th>
</tr>
</thead>
</table>
| VF   | 240bpm (250ms) | 2.5s | N/A | Quick Convert ATP (300bpm) Full output shocks  
  - Lead configuration |
| VT | 200bpm (300ms) | 12s | On | ATP  
  - 2x Scan, 8 initial, 88%, min interval 200ms, Scan decrement 10ms  
  - 1x Ramp, 8 initial, 84%, min interval 200ms  
  ATP Time-out: OFF  
  Full output shocks |

| Post Therapy | Post tachycardia pacing on |

| SVT Discrimination |  
  - Rhythm ID (Unless contraindicated)  
  - Turn *Sustained rate duration OFF* in pre and post therapy |

| Brady Settings: | If no pacing indication limit V-pacing 40bpm DDD with Rhythm IQ  
  ATR mode switch is set to 0, 4, 4 DDIR. |
## St Jude Medical

<table>
<thead>
<tr>
<th>Zone</th>
<th>Threshold</th>
<th>Interval</th>
<th>SVT Disc</th>
<th>Therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>VT-1</td>
<td>170 bpm (370 ms)</td>
<td>35</td>
<td>On</td>
<td>Monitor Only</td>
</tr>
</tbody>
</table>
| VT-2 | 200 bpm (300 ms) | 35 | On | Therapy 1: ATP Burstx2  
8 stimuli, 88%, add stim off, 200ms min burst, re-adaptive on  
Therapy 2: ATP Rampx1  
8 stimuli, 84%, 200ms min burst, re-adaptive on  
Therapy 3-4: Full output shocks |
| VT-3 | 240 bpm (250 ms) | 12 | | Therapy 1: ATP whilst charging  
Upper cut off 300 bpm  
Therapy 2-4: Full output shocks  
Max number of shocks (6) |
| **SVT Discrimination** | | | | As per out of the box setting (Unless contraindicated)  
Collect morphology template |
| **Brady Setting:** | | | | If no pacing indication limit V-pacing 40 bpm, DDI (VIP) |
## Appendix B

<table>
<thead>
<tr>
<th>ID</th>
<th>Age at implant</th>
<th>Date of therapy</th>
<th>Details</th>
</tr>
</thead>
<tbody>
<tr>
<td>302</td>
<td>60.6</td>
<td>01/04/2010</td>
<td>ATP for FVT CL 300ms</td>
</tr>
<tr>
<td>262</td>
<td>61.6</td>
<td>19/09/2013</td>
<td>ATP and shock for FVT CL250ms.</td>
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<tr>
<td>335</td>
<td>61.7</td>
<td>14/03/2014</td>
<td>VT 205 bpm ATP to SR</td>
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<tr>
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<td>61.7</td>
<td>18/11/2014</td>
<td>Shock for VF 400bpm</td>
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<td>393</td>
<td>62.3</td>
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<td>ATP for FVT 231 BPM</td>
</tr>
<tr>
<td>389</td>
<td>63.0</td>
<td>26/03/2014</td>
<td>ATP and shock for FVT CL260ms</td>
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<td>391</td>
<td>64.6</td>
<td>14/11/2014</td>
<td>ATP then shock for FVT / VF</td>
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<tr>
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<td>ATP for FVT 240ms</td>
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<td>ATP for FVT via VF 290 msec</td>
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<td>ATP for VT 214bpm</td>
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<td>65.7</td>
<td>17/07/2013</td>
<td>Shock for FVT CL 260msec</td>
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<tr>
<td>366</td>
<td>66.7</td>
<td>13/03/2013</td>
<td>ATP for VF CL 230ms</td>
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<tr>
<td>248</td>
<td>68.0</td>
<td>11/10/2010</td>
<td>ATP CL 260 msec on 11/10/2010</td>
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<tr>
<td>289</td>
<td>68.1</td>
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<td>ATP for FVT CL 240ms</td>
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<tr>
<td>266</td>
<td>68.3</td>
<td>20/05/2010</td>
<td>ATP for FVT 213 bpm</td>
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<tr>
<td>246</td>
<td>68.9</td>
<td>13/01/2012</td>
<td>ATP for VT 210bpm</td>
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<tr>
<td>225</td>
<td>69.2</td>
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<td>ATP then shock FVT CL 240 msec</td>
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<tr>
<td>242</td>
<td>69.2</td>
<td>20/10/2011</td>
<td>Shock for FVT CL 230 msec</td>
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<td>69.3</td>
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<td>ATP for VT CL 300 msec.</td>
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<td>111</td>
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<td>112</td>
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<td>ATP for CL &lt;290ms then acceleration to shock zone</td>
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<td>110</td>
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<td>ATP and shock during VT storm</td>
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<td>Shock for VF</td>
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<tr>
<td>124</td>
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<td>ATP for VT rate 200bpm which accelerated rhythm to VF &lt;300bpm &gt; shocked</td>
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<td>104</td>
<td>72.7</td>
<td>29/03/2013</td>
<td>ATP and shock FVT at 240BPM</td>
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<td>102</td>
<td>73.5</td>
<td>13/05/2008</td>
<td>ATP In FVT zone</td>
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<td>74.4</td>
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<td>74.8</td>
<td>28/02/2011</td>
<td>ATP for VT CL 290ms</td>
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<td>75.6</td>
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<td>ATP for VT CL 280ms</td>
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<td>77.5</td>
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<td>ATP for VT rate 200bpm</td>
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<td>105</td>
<td>77.7</td>
<td>02/11/2011</td>
<td>Shock for VF</td>
</tr>
<tr>
<td>91</td>
<td>78.0</td>
<td>21/04/2009</td>
<td>ATP for VT CL 280ms</td>
</tr>
<tr>
<td>107</td>
<td>78.7</td>
<td>21/11/2009</td>
<td>ATP and shock for FVT and syncope</td>
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<tr>
<td>135</td>
<td>78.8</td>
<td>23/05/2011</td>
<td>ATP for VT CL 280ms</td>
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<tr>
<td>100</td>
<td>78.9</td>
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<td>79.7</td>
<td>07/08/2012</td>
<td>ATP and shock for FVT</td>
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<td>47</td>
<td>80.3</td>
<td>27/11/2011</td>
<td>ATP and shock for FVT/VF CL 270ms</td>
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<td>80.4</td>
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<td>82.8</td>
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<td>Shock and shock for FVT CL 270ms</td>
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<td>83.9</td>
<td>06/05/2013</td>
<td>ATP for VT CL 300ms</td>
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<tr>
<td>451</td>
<td>89.9</td>
<td>13/10/2014</td>
<td>Shock for FVT 243ms</td>
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</tbody>
</table>

Table Details of therapy delivered for ventricular arrhythmias with rates ≥200bpm. ATP, anti-tachycardia pacing; VT, ventricular tachycardia; CL, cycle length; SR, sinus rhythm; VF, ventricular fibrillation; FVT, fast ventricular tachycardia; PMVT, polymorphic VT; VP, ventricular paced rhythm.
<table>
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Table: Details of therapy delivered for ventricular arrhythmias with rates < 200bpm. ATP, anti-tachycardia pacing; VT, ventricular tachycardia; CL, cycle length; SR, sinus rhythm; VF, ventricular fibrillation; FVT, fast ventricular tachycardia; PMVT, polymorphic VT; VP, ventricular paced rhythm
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