DETECTION OF VENTRICULAR ARRHYTHMIAS

"EVALUATION OF CARDIAC MONITORS AND SUBCUTANEOUS DEFIBRILLATORS"

DETECTIE VAN VENTRICULAIRE RITMESTOORNISSEN

"EVALUATIE VAN HARTMONITORS EN SUBCUTANE DEFIBRILLATOREN"

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ISBN
978-94-6423-060-4

Design/lay-out
Bregje Jaspers, ProefschriftOntwerp.nl, Nijmegen

Print
ProefschirftMaken | www.proefschriftmaken.nl

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Proefschrift

ter verkrijging van de graad van doctor aan de
Erasmus Universiteit Rotterdam
op gezag van de
rector magnificus

Prof.dr. R.C.M.E. Engels

en volgens besluit van het College voor Promoties.
De openbare verdediging zal plaatsvinden op

Dinsdag 8 december 2020 om 13:30 uur

door

Rafiullah Sakhi
geboren te Kabul, Afghanistan.

Erasmus University Rotterdam

PROMOTIECOMMISSIE

Promotoren:	Prof. dr. J.W. Roos-Hesselink Prof. dr. F. Zijlstra
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Copromotoren:	Dr. S.C. Yap

Financial support by the Dutch Heart Foundation for the publication of this thesis is gratefully acknowledged

To my beloved parents, where my life began, and the love never ended.

TABLE OF CONTENS

Chapter 1.	General introduction	**9**
Part I – Clinical value of ICM for risk stratification		
Chapter 2.	Insertable cardiac monitors: current indications and devices. Expert Review Medical Devices. 2019 Jan;16(1):45-55.	**21**
Chapter 3.	Value of implantable loop recorders in patients with structural or electrical heart disease. *Journal of Interventional Cardiac Electrophysiology 2018 Jul;52(2):203-208.*	**47**
Chapter 4.	Early Detection of Ventricular Arrhythmias in adults with Congenital Heart Disease using an insertable cardiac monitor (EDVA-CHD study). *International Journal of Cardiology. 2020 Apr 15;305:63-69.*	**59**
Chapter 5.	Incremental value of an insertable cardiac monitor in patients with hypertrophic cardiomyopathy with low or intermediate risk for sudden cardiac death. *Cardiology (accepted for publication).*	**77**
Chapter 6.	Outcome of Insertable Cardiac Monitors in Symptomatic Patients with Brugada Syndrome at Low Risk of Sudden Cardiac Death. *Cardiology. 2020 Apr 22:1-8*	**91**
Chapter 7.	Increased risk of ventricular arrhythmias in survivors of out-of-hospital cardiac arrest with chronic total coronary occlusion. *Heart Rhythm. 2018 Jan;15(1):124-129.*	**107**
Part II – Eligibility for a subcutaneous ICD		
Chapter 8.	Frequency of Need for Antitachycardia or Antibradycardia Pacing or Cardiac Resynchronization Therapy in Patients with a Single-Chamber Implantable Cardioverter-Defibrillator. *America Journal of Cardiology. 2018 Dec 15;122(12):2068-2074.*	**125**

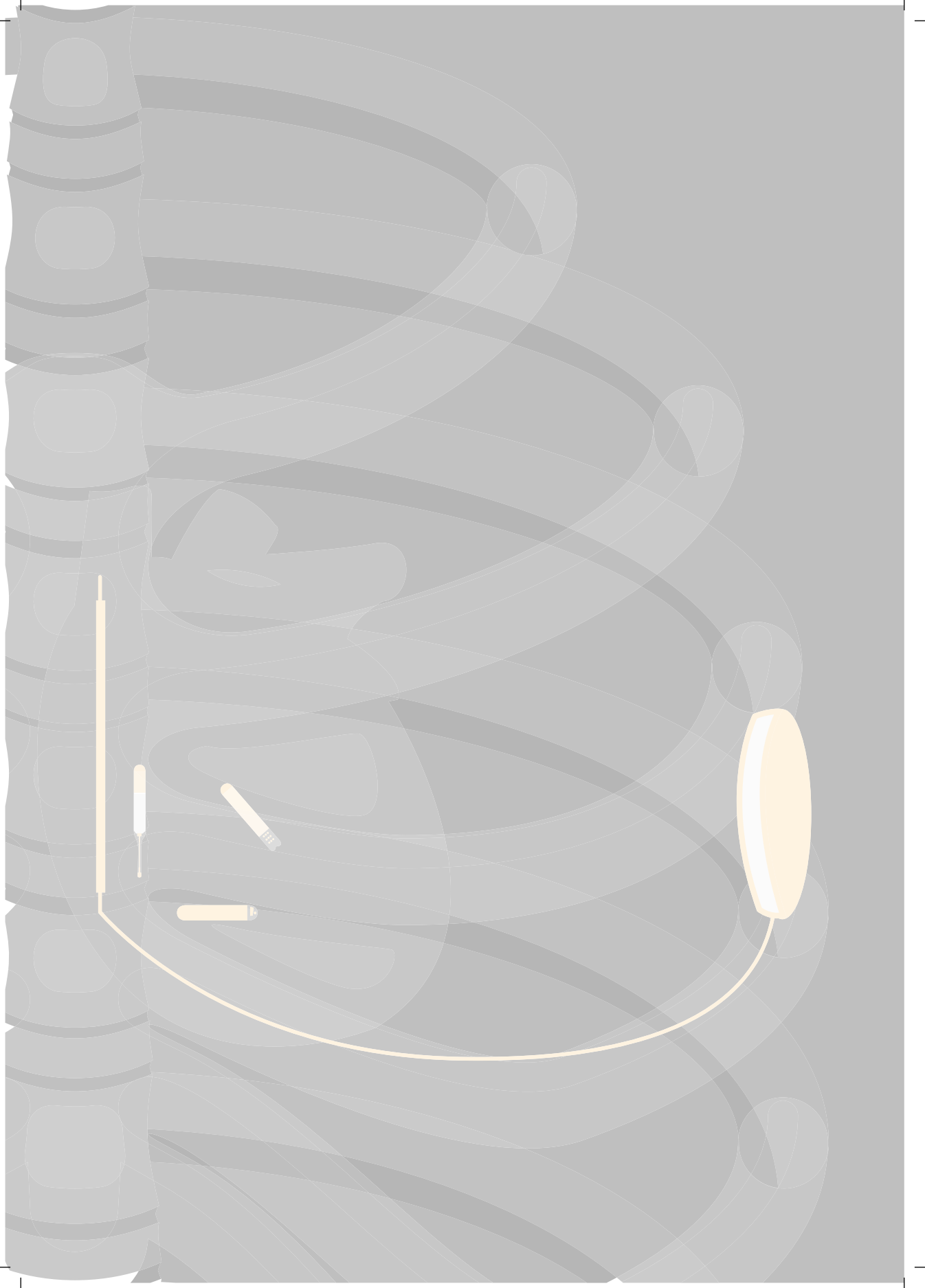
Chapter 9. Evaluation of a novel automatic screening tool for determining eligibility for a subcutaneous implantable cardioverter-defibrillator. *International Journal of Cardiology. 2018 Dec 1;272:97-101.* **141**

Editorial: Automating subcutaneous ICD screening and future sensing refinements. *International Journal of Cardiology. 2018 Dec 1;272:215-216.* **155**

Chapter 10. Usefulness of a standard 12-lead electrocardiogram to predict the eligibility for a subcutaneous defibrillator. *Journal of Electrocardiology. 2019 Jul-Aug;55:123-127.* **161**

Epilogue

Chapter 11. Summary and general discussion **179**
Dutch summary | Nederlandse samenvatting **193**
List of publications **199**
PhD portfolio **203**
About the author | Curriculum Vitae **207**
Acknowledgement | Dankwoord **209**



CHAPTER 1

General introduction

Let the beauty of what you love be what you do.

Mohamad Jalal Ad-Din Balkhi **Rumi** (Mevlana/Maulana)

Insertable cardiac monitors

Insertable cardiac monitors (ICMs) are leadless subcutaneous implantable cardiac devices that continuously monitor the heart rhythm and automatically record arrhythmias, providing the physician information on the presence, type, frequency and duration of arrhythmias.

The first ICM was introduced in the late 1980 (Medtronic, Inc., Minneapolis, MN, USA). It had the size of a pacemaker (53 x 60 x 8mm) and was implanted similarly (subcutaneous pocket). Since then, technical advancements have resulted into smaller devices, easier implantation techniques, improved detection algorithm, longer battery longevity and availability of remote monitoring[1, 2]. ICMs were primarily designed to evaluate episodes of unexplained syncope and/or to obtain symptom-rhythm correlation in patients with infrequent palpitations[1, 3-5]. However, the current ESC guideline have expanded the indication for an ICM to patients with unexplained syncope and inheritable cardiac disease at low risk of sudden cardiac death (SCD), such as those with hypertrophic cardiomyopathy, arrhythmogenic right ventricular cardiomyopathy, and inheritable primary arrhythmia syndrome[4]. Unexplained syncope in patients with inheritable cardiac disease may be associated with an arrhythmic event and is thus an important risk factor for SCD. The occurrence of unexplained syncope may qualify these patients for an implantable cardioverter-defibrillator (ICD). There may be several reasons to use an ICM in these patients. First, not all syncopal events are arrhythmogenic and proper adjudication of the syncopal event may prevent unnecessary ICD implantation. Second, the occurrence of (asymptomatic) ventricular arrhythmias (VA) is an important risk factor for SCD and continuous monitoring with an ICM may result in early VA detection. Third, symptomatic patients may be reassured when they know that their symptoms are not caused by VA. Currently, there is limited clinical evidence that the use of ICM for this purpose in this population is justified. Furthermore, there are several issues when using ICMs in this population which require further attention, such as device costs, data management, optimal duration of monitoring and clinical relevance of detected arrhythmias. The first part of the thesis is focused on evaluating the role of ICM in specific patient populations who are at potential risk of SCD and do not meet the current criteria for prophylactic ICD implantation.

Subcutaneous ICD

Transvenous ICDs are effective in preventing SCD and prolonging survival in selected patient populations[6-9]. Current guidelines recommend an ICD in patients resuscitated from near-fatal ventricular fibrillation and those with sustained ventricular tachycardia with syncope (secondary prevention)[10, 11]. Furthermore, randomized controlled trials have shown that patients with chronic heart failure secondary to ischemic or nonischemic cardiomyopathy and reduced left ventricular function (ejection fraction ≤35%) benefit from an ICD for primary prevention[7, 8]. The use of an ICD for primary prevention in patients with congenital heart disease or inheritable cardiac disease is less clear and is based on a multiparametric analysis that takes into account the recognized risk factors for VA/SCD for the specific population[10, 11].

An important disadvantage of transvenous ICDs is the long-term risk of lead-related complications, such as lead failure and lead-related endocarditis[12, 13]. This may require lead extraction which is associated with significant periprocedural risks. To overcome the lead-related complications associated with a transvenous lead, an entirely subcutaneous ICD (S-ICD) was developed[14]. Other advantages of a S-ICD are the possibility of implantation without fluoroscopy, no need of vascular access and elimination of certain periprocedural complications (i.e., pneumothorax and tamponade)[15]. The S-ICD, however, does not provide pacing or antitachycardia pacing (ATP). The 2015 ESC guidelines recommend to consider a S-ICD as an alternative to a transvenous ICD in ICD candidates without need for pacing therapy for bradycardia, cardiac resynchronization therapy, and ATP[11]. The S-ICD may be ideal in those with limited vascular access, high infection risk, or young patients with a long-term need for ICD therapy, such as those with inheritable cardiac disease or congenital heart disease[16]. Several studies have shown the efficacy and safety of the S-ICD[17-20]. While earlier S-ICD cohorts (e.g., EFFORTLESS) comprised a large proportion of young patients with inherited cardiac disease without co-morbidity, a more contemporary S-ICD cohort showed a shift towards more co-morbidities than previous cohorts with S-ICD[18, 21]. However, even the contemporary S-ICD cohort is younger with more end-stage renal disease than cohorts with a transvenous ICD[21].

Arrhythmia discrimination with a S-ICD depends on a surface electrogram and the specificity for supraventricular arrhythmias seems better in comparison to a transvenous ICD[22]. Unfortunately, inappropriate ICD shocks do occur and the main cause of inappropriate ICD shocks is T-wave oversensing[20, 22-27]. To avoid T-wave oversensing, the manufacturer recommends pre-implant ECG screening. Previously this was performed using a manual ECG-screening tool, but this has been replaced by an automatic screening tool (AST). The second part of the thesis is focused on the evaluation of AST in specific patient populations at potential risk of SCD, with a special emphasis on young patients with inherited or congenital cardiac disease.

Aim and outline of the thesis

Part I – Clinical value of ICM for risk stratification

Part I of the thesis focuses on the clinical value of ICMs in patients with structural or electrical heart disease who are deemed to be at risk for VA/SCD based on their clinical profile. In **Chapter 2** we discuss the current indications for ICMs and give an overview of the latest generation ICMs. **Chapter 3** is a pilot study in which we compared the diagnostic yield of an ICM in patients with a normal heart and patients with structural or electrical heart disease. Subsequently, in **Chapters 4-6** we evaluated the clinical value of ICMs in specific patient categories, including patients with congenital heart disease, hypertrophic cardiomyopathy and Brugada syndrome, respectively.

In **Chapter 7** we evaluated the impact of a chronic total coronary occlusion (CTO) on the occurrence of recurrent ventricular arrhythmias in survivors of out-of-hospital cardiac arrest with coronary artery disease. This study formed the basis of the ongoing multicenter VACTOR study (*Incidence of Ventricular Arrhythmias in patients with Chronic Total Occlusion Recanalization,* NCT03475888) evaluating the role of an ICM for risk stratification in patients with a CTO.

Part II – Eligibility for a subcutaneous ICD

Part II aims to identify patients who may be suitable for a S-ICD. In **Chapter 8** we retrospectively evaluated the potential eligibility for a S-ICD at the time of first replacement in a cohort of patients with a transvenous single-chamber ICD who did not need bradycardia pacing at the time of ICD implantation.

When a patient seems to be a suitable candidate for a S-ICD, it is recommended to perform a pre-implant ECG screening. This process has been automated by AST. In **Chapter 9** we evaluated the eligibility for the S-ICD using two screening methods (conventional manual method versus AST) in different patient categories. Finally, in **Chapter 10** we evaluated whether a standard 12-lead ECG can identify which patient is suitable for a S-ICD, thereby omitting the need for an additional pre-implant ECG screening.

References

1. Brignole M, Vardas P, Hoffman E, Huikuri H, Moya A, Ricci R, Sulke N, Wieling W, Committee ESD, Auricchio A, Lip GY, Almendral J, Kirchhof P, Aliot E, Gasparini M, Braunschweig F, Document R, Lip GY, Almendral J, Kirchhof P, Botto GL and Committee ESD. Indications for the use of diagnostic implantable and external ECG loop recorders. *Europace*. 2009;11:671-87.
2. Tomson TT and Passman R. The Reveal LINQ insertable cardiac monitor. *Expert review of medical devices*. 2015;12:7-18.
3. Solano A, Menozzi C, Maggi R, Donateo P, Bottoni N, Lolli G, Tomasi C, Croci F, Oddone D, Puggioni E and Brignole M. Incidence, diagnostic yield and safety of the implantable loop-recorder to detect the mechanism of syncope in patients with and without structural heart disease. *Eur Heart J*. 2004;25:1116-9.
4. Brignole M, Moya A, de Lange FJ, Deharo JC, Elliott PM, Fanciulli A, Fedorowski A, Furlan R, Kenny RA, Martin A, Probst V, Reed MJ, Rice CP, Sutton R, Ungar A, van Dijk JG and Group ESCSD. 2018 ESC Guidelines for the diagnosis and management of syncope. *Eur Heart J*. 2018;39:1883-1948.
5. Ungar A, Sgobino P, Russo V, Vitale E, Sutton R, Melissano D, Beiras X, Bottoni N, Ebert HH, Gulizia M, Jorfida M, Moya A, Andresen D, Grovale N, Brignole M and International Study on Syncope of Uncertain Etiology I. Diagnosis of neurally mediated syncope at initial evaluation and with tilt table testing compared with that revealed by prolonged ECG monitoring. An analysis from the Third International Study on Syncope of Uncertain Etiology (ISSUE-3). *Heart*. 2013;99:1825-31.
6. Moss AJ, Hall WJ, Cannom DS, Daubert JP, Higgins SL, Klein H, Levine JH, Saksena S, Waldo AL, Wilber D, Brown MW and Heo M. Improved survival with an implanted defibrillator in patients with coronary disease at high risk for ventricular arrhythmia. Multicenter Automatic Defibrillator Implantation Trial Investigators. *N Engl J Med*. 1996;335:1933-40.
7. Moss AJ, Zareba W, Hall WJ, Klein H, Wilber DJ, Cannom DS, Daubert JP, Higgins SL, Brown MW, Andrews ML and Multicenter Automatic Defibrillator Implantation Trial III. Prophylactic implantation of a defibrillator in patients with myocardial infarction and reduced ejection fraction. *N Engl J Med*. 2002;346:877-83.
8. Bardy GH, Lee KL, Mark DB, Poole JE, Packer DL, Boineau R, Domanski M, Troutman C, Anderson J, Johnson G, McNulty SE, Clapp-Channing N, Davidson-Ray LD, Fraulo ES, Fishbein DP, Luceri RM, Ip JH and Sudden Cardiac Death in Heart Failure Trial I. Amiodarone or an implantable cardioverter-defibrillator for congestive heart failure. *N Engl J Med*. 2005;352:225-37.
9. Antiarrhythmics versus Implantable Defibrillators I. A comparison of antiarrhythmic-drug therapy with implantable defibrillators in patients resuscitated from near-fatal ventricular arrhythmias. *N Engl J Med*. 1997;337:1576-83.
10. Al-Khatib SM, Stevenson WG, Ackerman MJ, Bryant WJ, Callans DJ, Curtis AB, Deal BJ, Dickfeld T, Field ME, Fonarow GC, Gillis AM, Granger CB, Hammill SC, Hlatky MA, Joglar JA, Kay GN, Matlock DD, Myerburg RJ and Page RL. 2017 AHA/ACC/HRS Guideline for Management of Patients With Ventricular Arrhythmias and the Prevention of Sudden Cardiac Death. *Circulation*. 2018;138:e272-e391.
11. Priori SG, Blomstrom-Lundqvist C, Mazzanti A, Blom N, Borggrefe M, Camm J, Elliott PM, Fitzsimons D, Hatala R, Hindricks G, Kirchhof P, Kjeldsen K, Kuck KH, Hernandez-Madrid A, Nikolaou N, Norekval TM, Spaulding C,

Van Veldhuisen DJ and Group ESCSD. 2015 ESC Guidelines for the management of patients with ventricular arrhythmias and the prevention of sudden cardiac death. *Eur Heart J*. 2015;36:2793-2867.

12. Kleemann T, Becker T, Doenges K, Vater M, Senges J, Schneider S, Saggau W, Weisse U and Seidl K. Annual rate of transvenous defibrillation lead defects in implantable cardioverter-defibrillators over a period of >10 years. *Circulation*. 2007;115:2474-80.
13. Borleffs CJ, van Erven L, van Bommel RJ, van der Velde ET, van der Wall EE, Bax JJ, Rosendaal FR and Schalij MJ. Risk of failure of transvenous implantable cardioverter-defibrillator leads. *Circ Arrhythm Electrophysiol*. 2009;2:411-6.
14. Bardy GH, Smith WM, Hood MA, Crozier IG, Melton IC, Jordaens L, Theuns D, Park RE, Wright DJ, Connelly DT, Fynn SP, Murgatroyd FD, Sperzel J, Neuzner J, Spitzer SG, Ardashev AV, Oduro A, Boersma L, Maass AH, Van Gelder IC, Wilde AA, van Dessel PF, Knops RE, Barr CS, Lupo P, Cappato R and Grace AA. An entirely subcutaneous implantable cardioverter-defibrillator. *N Engl J Med*. 2010;363:36-44.
15. Lewis GF and Gold MR. Safety and Efficacy of the Subcutaneous Implantable Defibrillator. *J Am Coll Cardiol*. 2016;67:445-454.
16. Al-Khatib SM, Friedman P and Ellenbogen KA. Defibrillators: Selecting the Right Device for the Right Patient. *Circulation*. 2016;134:1390-1404.
17. Weiss R, Knight BP, Gold MR, Leon AR, Herre JM, Hood M, Rashtian M, Kremers M, Crozier I, Lee KL, Smith W and Burke MC. Safety and efficacy of a totally subcutaneous implantable-cardioverter defibrillator. *Circulation*. 2013;128:944-53.
18. Lambiase PD, Barr C, Theuns DA, Knops R, Neuzil P, Johansen JB, Hood M, Pedersen S, Kaab S, Murgatroyd F, Reeve HL, Carter N, Boersma L and Investigators E. Worldwide experience with a totally subcutaneous implantable defibrillator: early results from the EFFORTLESS S-ICD Registry. *Eur Heart J*. 2014;35:1657-65.
19. Burke MC, Gold MR, Knight BP, Barr CS, Theuns D, Boersma LVA, Knops RE, Weiss R, Leon AR, Herre JM, Husby M, Stein KM and Lambiase PD. Safety and Efficacy of the Totally Subcutaneous Implantable Defibrillator: 2-Year Results From a Pooled Analysis of the IDE Study and EFFORTLESS Registry. *J Am Coll Cardiol*. 2015;65:1605-1615.
20. Boersma L, Barr C, Knops R, Theuns D, Eckardt L, Neuzil P, Scholten M, Hood M, Kuschyk J, Jones P, Duffy E, Husby M, Stein K, Lambiase PD and Group EI. Implant and Midterm Outcomes of the Subcutaneous Implantable Cardioverter-Defibrillator Registry: The EFFORTLESS Study. *J Am Coll Cardiol*. 2017;70:830-841.
21. Gold MR, Aasbo JD, El-Chami MF, Niebauer M, Herre J, Prutkin JM, Knight BP, Kutalek S, Hsu K, Weiss R, Bass E, Husby M, Stivland TM and Burke MC. Subcutaneous implantable cardioverter-defibrillator Post-Approval Study: Clinical characteristics and perioperative results. *Heart Rhythm*. 2017;14:1456-1463.
22. Gold MR, Theuns DA, Knight BP, Sturdivant JL, Sanghera R, Ellenbogen KA, Wood MA and Burke MC. Head-to-head comparison of arrhythmia discrimination performance of subcutaneous and transvenous ICD arrhythmia detection algorithms: the START study. *J Cardiovasc Electrophysiol*. 2012;23:359-66.
23. Jarman JW, Lascelles K, Wong T, Markides V, Clague JR and Till J. Clinical experience of entirely subcutaneous implantable cardioverter-defibrillators in children and adults: cause for caution. *Eur Heart J*. 2012;33:1351-9.
24. Olde Nordkamp LR, Dabiri Abkenari L, Boersma LV, Maass AH, de Groot JR, van Oostrom AJ, Theuns DA, Jordaens LJ, Wilde AA and Knops RE. The entirely subcutaneous implantable cardioverter-defibrillator: initial clinical experience in a large Dutch cohort. *J Am Coll Cardiol*. 2012;60:1933-9.

25. Kobe J, Reinke F, Meyer C, Shin DI, Martens E, Kaab S, Loher A, Amler S, Lichtenberg A, Winter J and Eckardt L. Implantation and follow-up of totally subcutaneous versus conventional implantable cardioverter-defibrillators: a multicenter case-control study. *Heart Rhythm*. 2013;10:29-36.
26. Kooiman KM, Knops RE, Olde Nordkamp L, Wilde AA and de Groot JR. Inappropriate subcutaneous implantable cardioverter-defibrillator shocks due to T-wave oversensing can be prevented: implications for management. *Heart Rhythm*. 2014;11:426-34.
27. Olde Nordkamp LR, Brouwer TF, Barr C, Theuns DA, Boersma LV, Johansen JB, Neuzil P, Wilde AA, Carter N, Husby M, Lambiase PD and Knops RE. Inappropriate shocks in the subcutaneous ICD: Incidence, predictors and management. *Int J Cardiol*. 2015;195:126-33.

Part I

Clinical value of ICM for risk stratification

CHAPTER 2

Insertable cardiac monitors: current indications and devices

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Expert Review Medical Devices. 2019 Jan;16(1):45-55.

Abstract

Introduction: Recurrent unexplained syncope is a well-established indication for an insertable cardiac monitor (ICM). Recently, the indications for an ICM has been expanded.

Areas covered: This review article discusses the current indications for ICMs and gives an overview of the latest generation of commercially available ICMs.

Expert commentary: The 2018 ESC Syncope guidelines have expanded the indications for an ICM to patients with inherited cardiomyopathy, inherited channelopathy, suspected unproven epilepsy, and unexplained falls. ICMs are also increasingly used for the detection of subclinical atrial fibrillation in patients with cryptogenic stroke. Whether treatment of subclinical atrial fibrillation with oral anticoagulation prevents recurrent stroke is yet unknown. The current generation of ICMs are smaller, easier to implant, have better diagnostics and are capable of remote monitoring. The Reveal LINQ (Medtronic) is the smallest ICM and has the most extensive performance and clinical data. The BioMonitor 2 (Biotronik) is the largest ICM but has excellent R-wave amplitudes, longest longevity and reliable remote monitoring. The Confirm Rx (Abbott) is capable to provide mobile data transmission enabled by a smartphone app. Future generation of ICMs will incorporate heart failures indices to facilitate remote monitoring of heart failure patients.

1. Introduction

Prolonged rhythm monitoring using a subcutaneous insertable cardiac monitor (ICM) has proven to be of incremental diagnostic value for a wide range of indications, especially in patients with unexplained recurrent syncope[1]. An ICM is not only useful for the detection of arrhythmias but can also rule out a cardiac cause of symptoms. In the most recent European Society of Cardiology (ESC) guidelines for the diagnosis and management of syncope there is an expansion of the indications for an ICM, including patients with suspected unproven epilepsy, unexplained falls, and patients with primary cardiomyopathy or inheritable arrhythmogenic disorders who are at low risk of sudden cardiac death (SCD)[1]. Technical advancements have resulted in smaller devices, easier implantation, improved atrial fibrillation (AF) detection, longer battery longevity and availability of remote monitoring. The aim of the present review is to provide an overview of the current indications (with a special focus on new indications), recent clinical trials, latest generation of ICMs, and future perspectives.

2. Indications

The indications for an ICM has expanded over the years. Table 1 provides an overview of the current indications according to the most recent guidelines[1-4].

2.1 Recurrent syncope

Syncope is a relatively common clinical symptom in the general population with a lifetime incidence of 30-40% and is responsible for 3-6% of all emergency visits[5]. Despite extensive evaluation, a significant proportion of patients remain without a diagnosis[6-8]. Several studies from the ISSUE-investigators in the early 2000s demonstrated the diagnostic value of an ICM in different syncope populations such as those with neurally-mediated syncope, bundle branch block or structural heart disease[9-11]. A meta-analysis of five randomized controlled trials comparing a conventional strategy (external loop recorder, tilt testing, and electrophysiological testing) to ICM implantation showed that an ICM provided a 3.6 increased relative probability of a diagnosis compared with the conventional strategy (46% versus 12%)[1, 12-16]. Furthermore, an ICM strategy was more cost-effective than a conventional strategy[13, 14]. Currently, an ICM is a well-established diagnostic tool in patients with recurrent unexplained syncope and should be employed in an early phase of evaluation[17].

Table 1. Recommendations for ICM implantation in current guidelines

2018 ESC guidelines for the diagnosis and management of syncope[1]	Class	LOE
ICM is indicated in an early phase of evaluation in patients with recurrent syncope of uncertain origin, absence of high-risk criteria, and a high likelihood of recurrence within the battery life of the device[8, 9, 15-17, 91, 92].	I	A
ICM is indicated in patients with high-risk criteria in whom a comprehensive evaluation did not demonstrate a cause of syncope or lead to a specific treatment, and who do not have conventional indications for primary prevention ICD or pacemaker indication[10-12, 93, 94].	I	A
ICM should be considered in patients with suspected or certain reflex syncope presenting with frequent or severe syncopal episodes[17, 95, 96].	IIa	B
Instead of an ICD, an ICM should be considered in HCM/ ARVC/ long QT syndrome or Brugada syndrome patients with recurrent episodes of unexplained syncope who are at low risk of SCD.	IIa	C
ICM may be considered in patients in whom epilepsy was suspected but the treatment has proven ineffective[34-37].	IIb	B
ICM may be considered in patients with unexplained falls[37, 42, 43].	IIb	B
Instead of an ICD, an ICM may be considered in patients with recurrent episodes of unexplained syncope with systolic impairment, but without a current indication for ICD.	IIb	C
2017 AHA/ACC/HRS guideline for management of patients with ventricular arrhythmias and the prevention of sudden cardiac death[4]		
In patients with sporadic symptoms (including syncope) suspected to be related to ventricular arrhythmias, ICMs can be useful[32, 97-99].	IIa	B
2016 ESC guidelines for the management of atrial fibrillation developed in collaboration with EACTS[2]		
In stroke patients, additional ECG monitoring by long-term non-invasive ECG monitors or ICM should be considered to document silent atrial fibrillation[47, 100].	IIa	B
2015 ESC guidelines for the management of patients with ventricular arrhythmias and the prevention of sudden cardiac death[3]		
ICMs are recommended when symptoms, e.g. syncope, are sporadic and suspected to be related to arrhythmias and when a symptom-rhythm correlation cannot be established by conventional diagnostic techniques[99].	I	B

Abbreviations: ARVC, arrhythmogenic right ventricular cardiomyopathy; HCM, hypertrophic cardiomyopathy; ICD, implantable cardioverter-defibrillator; ICM, implantable cardiac monitor.

2.2 Risk stratification

2.2.1 Inherited cardiomyopathy or channelopathy

In patients with inherited cardiomyopathy or channelopathy, the occurrence of syncope is associated with a worse prognosis and may be a harbinger of SCD. Therefore, the occurrence of syncope in this population may be an indication for an implantable cardioverter-defibrillator (ICD)[4]. However, syncope in this population is not always secondary to a life-threatening tachyarrhythmia. In fact, recent studies in Brugada patients have shown that syncope is usually neurally mediated[18, 19]. Although systematic history taking may be helpful in differentiating arrhythmic (absence of prodromes and specific triggers) and nonarrhythmic syncope[19], in clinical practice this distinction can be difficult.

In this respect, ICMs might be helpful in establishing a clear symptom-rhythm correlation. A potential down-side of using an ICM, instead of implanting an ICD, is that the next syncopal event might potentially be fatal. The experience with ICMs in patients with inherited cardiomyopathy or channelopathy is limited. A Dutch study demonstrated that the diagnostic yield of ICMs (Reveal LINQ, Medtronic) is lower in patients with channelopathy in comparison to patients with structural heart disease and healthy control patients[20]. In this study, one of five patients with hypertrophic cardiomyopathy (HCM) received an ICD based on a documented nonsustained VT. The number of patients with inherited cardiomyopathy or channelopathy who receive an ICD based on the findings of the ICM varies per underlying diagnosis. Based on the available literature, no ICM patient with Brugada syndrome[20-23], long QT syndrome[20, 24, 25], arrhythmogenic right ventricular cardiomyopathy (ARVC)[20], or noncompaction cardiomyopathy[26] received an ICD during follow-up. This might be related to the duration of follow-up. ICDs have been implanted based on ICM-findings in patients with catecholaminergic polymorphic VT (11%)[24], hypertrophic cardiomyopathy (HCM) (20%)[20], and Fabry cardiomyopathy (25%)[27]. Despite the limited available data, current guidelines give a class IIa indication for an ICM in patients with inherited cardiomyopathy (i.e., HCM and ARVC) or channelopathy (i.e., Brugada syndrome and long. QT syndrome) with recurrent episodes of unexplained syncope who are at low risk of SCD[1, 28]. ICMs may also be considered (class IIb indication) in HCM patients with frequent palpitations, in whom no cause is identified following prolonged ECG monitoring[28]. The J-wave syndromes expert consensus conference report recommends close follow-up with an ICM in presumably nonarrhythmic symptomatic patients (i.e., syncope, seizure or nocturnal agonal respiration) with Brugada or early repolarization syndrome[29].

2.2.2 Post-myocardial infarction

Post-acute myocardial infarction patients with depressed left ventricular (LV) function are at risk of SCD. However, several randomized trials have shown that prophylactic ICDs do not improve survival when implanted in patients with LV dysfunction in the early phase after an acute myocardial infarction[30, 31]. The CARISMA study investigated the incidence and prognostic significance of arrhythmias using an ICM (Reveal Plus, Medtronic) in 297 patients with a LV function ≤40% post-acute myocardial infarction (3 to 21 days)[32]. During a mean follow-up of 1.9 years, the following arrhythmias were documented: new-onset AF (28%), nonsustained ventricular tachycardia (VT) (13%), high-degree atrioventricular (AV) block (10%), sinus bradycardia (7%), sinus arrest (5%), sustained VT (3%), and ventricular fibrillation (VF) (3%). High-degree AV block was the most powerful predictor of cardiac death. In the CARISMA study, 16 patients had an electrogram recorded at the time of death, of whom 7 patients died suddenly[33]. In 6 of 7 cases of SCD (86%), VF was documented at the time of death. The clinical usefulness of ICMs in patients surviving an acute myocardial infarction is currently unclear. In the most recent ESC Syncope guidelines, there is a class IIb indication for an ICM in patients with recurrent episodes of unexplained syncope with systolic impairment, but without a current indication for an ICD[1].

2.3 Suspected unproven epilepsy

Several studies have demonstrated that up to 1 in 4 patients with 'epilepsy' may be misdiagnosed[34]. The hypothesis is that seizure-like episodes in these patients are the result from cerebral hypoperfusion due to a cardiac arrhythmia. The REVISE study included 103 patients previously diagnosed with epilepsy but considered to have a definite or likely misdiagnosis of epilepsy after neurological review[35]. Patients had to suffer at least 3 transient loss of consciousness episodes in the year before enrollment. The ICM (Reveal Plus/DX, Medtronic) recorded profound bradyarrhythmia or asystole with convulsive features in 21% of patients and they were offered a pacemaker implantation. After pacing and withdrawal of antiepileptic drugs, 60% of these patients were rendered asymptomatic. In pooled data from six studies performed in 159 patients in whom epilepsy was suspected but the treatment was ineffective, 62% had an ICM-documented attack, with an arrhythmic cause being responsible in 26%[1, 34-39].

2.4 Unexplained falls

Unexplained falls are responsible for 14% of falls in older cohorts[40]. It is important to realize that syncope in elderly can present as an unexplained fall. An Irish study included recurrent fallers over the age of 50 years with two or more unexplained falls presenting to an emergency department[41]. Seventy patients received an ICM (Reveal DX/XT, Medtronic). Fourteen patients (20%) demonstrated a cardiac arrhythmia which was attributable as the cause of their fall. Of the seventy patients, 14% received a pacemaker and 6% had treatment for supraventricular tachycardia. Early detection of an arrhythmogenic cause of falls may prevent future falls in this fragile population. In pooled data from four studies performed in 176 patients with unexplained falls who received an ICM, 70% had an ICM-documented attack, with an arrhythmic cause being responsible in 14%[1, 37, 41-43].

2.5 Unexplained palpitations

In patients with infrequent episodes of palpitations short-term ambulatory ECG monitoring is usually insufficient. In the RUP study, 50 patients with infrequent (≤1 episode per month), sustained (>1 min) palpitations and initial negative diagnostic workup were randomized to conventional strategy (24-h Holter recording, a 4-week period of ambulatory ECG monitoring with an external recorder, and electrophysiology study) or to an ICM (Reveal Plus, Medtronic) with 1-year monitoring[44]. The diagnostic yield was higher in the ICM group (73% versus 21%, P<0.001). Palpitations were completely eliminated in the patients with an arrhythmic diagnosis using ablation, pacemaker, or drugs. Furthermore, the overall cost per diagnosis in the ICM group was lower compared to the conventional strategy group. There is a class IIa indication for an ICM in selected patients with severe infrequent symptoms when other ECG monitoring systems fail to document the underlying cause[45].

2.6 Atrial fibrillation detection

The detection of AF can have therapeutic consequences for certain patient populations. Clinical AF is associated with a twofold increased risk of mortality and fivefold increased risk of stroke. Treatment with oral anticoagulation (OAC) can reduce these risks. Furthermore, previous studies have demonstrated that

device-detected subclinical AF (SCAF) has also important clinical consequences. In the ASSERT trial, SCAF (episodes of atrial rate >190 bpm with a duration of >6 minutes), was detected by a pacemaker or ICD in nearly 40% of patients during 2.5 years of follow-up. The presence of SCAF increased the risk for stroke by 2.5-fold[46]. Currently, many studies have focused on the role of SCAF detected by devices, including ICMs.

2.6.1 Cryptogenic stroke or embolic stroke of unknown origin (ESUS)

The cause of ischemic stroke remains uncertain in 20-40% of patients despite extensive testing, this is called cryptogenic stroke. Embolic stroke of unknown origin (ESUS) is a subcategory of cryptogenic stroke in patients with non-lacunar infarcts in the absence of an apparent cause. Recurrent stroke is common in cryptogenic stroke patients and early detection of SCAF in these patients may be important as timely use of OAC may prevent recurrent stroke. The CRYSTAL AF trial randomized 441 cryptogenic stroke patients (>40 years of age) to an ICM (Reveal XT, Medtronic) or conventional follow-up[47]. Sustained AF (>30 s) was observed more frequently in the ICM group in comparison to the control group (12% vs. 2% at 1 year, P<0.001; 30% vs. 3% at 3 years, P<0.001). In addition, real-world data using the Medtronic Discovery Link database demonstrated that the 2-year AF detection rate was 21.5% in cryptogenic stroke patients receiving an ICM (Reveal LINQ, Medtronic)[48]. Intermittent monitoring for AF detection was shown to be inferior to continuous ICM monitoring with sensitivities ranging from 3% (annual 24-hour Holter) to 30% (quarterly 7-day Holters). ICMs have been shown to be a cost-effective diagnostic tool for the prevention of recurrent stroke in cryptogenic stroke patients[49]. In the 2016 ESC AF guidelines there is a class IIa indication for an ICM in stroke patients to document SCAF.

Another strategy to prevent recurrent stroke in ESUS patients is to treat patients with OAC instead of aspirin. If this strategy is effective, then AF detection has less clinical implications. In the NAVIGATE-ESUS trial, 7,213 ESUS patients were randomized to 15 mg rivaroxaban (Xarelto, Bayer AG) or 100 mg aspirin[50]. At the recommendation of the Data and Safety monitoring committee, this trial was terminated on Oct. 5, 2017, due to excess risk for bleeding in the rivaroxaban arm (hazard ratio 2.72, 95% CI 1.68-4.39) and the lack of benefit for the reduction of stroke risk. Furthermore, the RE-SPECT ESUS trial (N=5,390) also failed to demonstrate superiority of dabigatran to aspirin for the prevention of recurrent stroke (4.1% versus 4.8%, HR 0.85, P=0.1)[51]. The rate of major bleeding was similar in both arms. The results were presented at the World Stroke Congress in Montreal, Canada. In this respect, it is worth to mention that in CRYSTAL AF approximately half of the patients met the inclusion criteria for NAVIGATE-ESUS and RE-SPECT ESUS. Approximately 65% of these patients did not have AF at 3 years and may thus not potentially benefit from OAC[52]. The ongoing ARCADIA and ATTICUS trials will demonstrate whether the non-vitamin K antagonist OAC (NOAC) apixaban will be beneficial in the prevention of recurrent stroke in ESUS patients in comparison to aspirin[53, 54].

2.6.2 Patients at risk of stroke

A significant number of strokes occur in patients with SCAF[46]. To improve stroke prevention, recognition of SCAF may be important in high risk patients. Several ICM trials (REVEAL AF, PREDATE AF, ASSERT-II) demonstrated a high incidence of SCAF in high-risk populations using ICMs[55-57]. The 1-year AF incidence

ranged from 20% to 31% in these studies[55-57]. In the largest of these ICM studies, the REVEAL-AF trial (Reveal XT/LINQ), 385 patients (mean age 72 years) were enrolled with a $CHADS_2$ score of ≥3, or $CHADS_2$ score of 2 and at least one of the following risk factors: coronary artery disease, renal impairment, sleep apnea, or chronic obstructive pulmonary disease[57]. The rate of AF detection (≥6 minutes) was 29% and 40% at 18 and 30 months, respectively. The mean time to AF detection was 141 days.

It is currently uncertain whether SCAF conveys the same thromboembolic risk as clinical AF[46]. Furthermore, it is also unknown whether OAC for SCAF is beneficial. Currently, there are 3 ongoing trials assessing the role of OAC in patients with device-detected SCAF (LOOP; ARTESiA; and NOAH). The Danish LOOP trial will randomize 6,000 participants 3:1 to a control group or ICM group (Reveal LINQ, Medtronic)[58, 59]. Participants should be 70-90 years at the time of screening and have at least one of the following risk factors: diabetes mellitus, hypertension, heart failure, or previous stroke. When an AF episode (≥6 minutes) is detected, OAC will be initiated. The primary endpoint will be time to stroke or systemic embolism. In the ARTESiA trial, approximately 4,000 patients with device-detected SCAF (either by pacemaker, defibrillator, or ICM) and additional risk factors for stroke will be randomized to receive either apixaban or aspirin[60, 61]. Patients with clinical AF will be excluded. The primary endpoint will be a composite of stroke, TIA and systemic embolism. Finally, the NOAH trial will randomize 3,400 patients with atrial high rate episodes (detected by pacemaker or ICD), aged 65 years or older with at least one other stroke risk factor, to edoxaban or no anticoagulation[62, 63]. The primary endpoint will be stroke or cardiovascular death.

2.6.3 Post-ablation of atrial fibrillation

To establish the efficacy of catheter ablation, reliable determination of freedom of AF is important and several studies used the ICM after surgical or percutaneous ablation[64-69]. From a clinical perspective, continuous monitoring is useful to establish a symptom-rhythm correlation. It is well established that longer arrhythmia monitoring improves the yield of AF detection. The ABACUS study compared ICM (Reveal XT, Medtronic) to conventional monitoring (30-day transtelephonic monitoring at discharge and at 6 months) in 44 post-AF ablation patients[69]. ICMs detected more AF than conventional monitoring in the first 6 months postablation (47% vs. 18%, P=0.002). Furthermore, ICMs has been used to guide treatment of early recurrence (<3 months) of AF post-ablation. In one randomized study, patients underwent early reablation when AF was triggered by supraventricular arrhythmias or premature atrial beats as detected by the ICM (Reveal XT, Medtronic)[70]. This strategy resulted in long-term success rates of 89%. According to the 2017 HRS/EHRA/ECAS/APHRS/ SOLAECE expert consensus statement on catheter and surgical ablation of AF, the minimal monitoring recommendations for paroxysmal or persistent AF recurrence post-ablation does not include an ICM, however, in the setting of clinical trials extended ECG monitoring is encouraged[71].

2.6.4 Discontinuation of oral anticoagulation

The 2017 HRS/EHRA/ECAS/APHRS/SOLAECE expert consensus statement on catheter and surgical ablation of AF gives a class IIb indication for an ICM to screen for AF recurrence in patients in whom discontinuation of OAC is being considered based on patient values and preferences[71]. One study

assessed the feasibility of discontinuation of OAC after ablation based on AF detection by an ICM (Reveal XT, Medtronic)[72]. During a mean follow-up of 32 months, 41 of 65 patients (63%) had an AF burden <1 hour per day and were able to stay off OAC. The other patients had to restart OAC. No stroke, TIA, or other thromboembolic event occurred during follow-up.

Furthermore, a small pilot study, REACT.COM, tested a targeted strategy of ICM-guided intermittent NOAC administration in patients with nonpermanent AF and a $CHADS_2$ score 1 or 2[73]. The hypothesis was that continuous monitoring using an ICM (Reveal XT, Medtronic) and the rapid onset of NOAC allowed targeted anticoagulation only around an AF episode (≥1 hour). Using this strategy there was a 94% reduction in the time on NOAC compared to chronic anticoagulation. During a mean follow-up of 466 days there were no strokes among 59 patients. Large prospective trials are needed to evaluate the safety of these approaches.

3. Current devices

Currently, there are 3 commercially-available ICMs: Reveal LINQ (Medtronic), BioMonitor 2 (Biotronik) and Confirm Rx (Abbott). Figure 1 and Table 2 provides an overview of the latest generation devices. At present, the majority of clinical and performance data is available from the Reveal LINQ device.

Figure 1. Overview of current generation ICMs. Dimensions Reveal LINQ (Medtronic): 45 x 7 x 4 mm; Confirm Rx (Abbott/ St. Jude Medical): 49 x 9 x 3 mm; and BioMonitor 2 (Biotronik): 88 x 15 x6 mm.

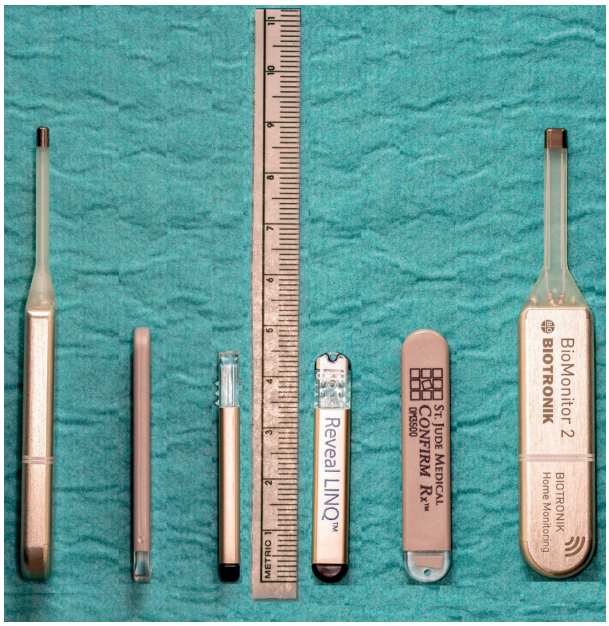


Table 2. Overview of most common current generation ICMs

	Reveal LINQ Medtronic	BioMonitor 2 Biotronik	Confirm Rx Abbott
Model:			
- Volume (cc)	1.2	4.5	1.4
- Length (mm)	45	88	49
- Width (mm)	7	15	9.4
- Thickness (mm)	4	6.5	3.1
- Weight (g)	2.5	10.1	3.0
Features:			
- Longevity (years)	3	4	2
- Remote monitoring	Wireless connection to bedside transmitter	Wireless connection to bedside transmitter	BluetoothÒ connection to personal mobile device or mobile transmitter
- MRI conditional	1.5 and 3.0 T	1.5 and 3.0 T	1.5 T
- Total EGM storage (min)	60	60	60
Regulatory approval:			
- CE Mark	Jan 2014	Aug 2015	May 2017
- FDA	Feb 2014	April 2016	Oct 2017

3.1 Initial experience

The first pilot studies focused on the sensing amplitude and remote monitoring transmission success rate. A small multicenter study of 30 patients implanted with Reveal LINQ, published in 2015, demonstrated a R-wave amplitude of 0.58±0.33 mV at implantation and a transmission success rate of 80%[74]. Incomplete data reception or patients being out of range were important reasons for transmission failures. A small Australian study of 30 patients implanted with BioMonitor 2, published in 2017, demonstrated a R-wave amplitude of 0.75±0.39mV at 1 week and a transmission success rate of 94%[75]. This high R-wave amplitude of the BioMonitor 2 has been reproduced by other groups, also when placed in the axillary region[76]. The long sensing dipole of the BioMonitor 2 not only provides better R-wave amplitude but also better P-wave visibility. A potential disadvantage is oversensing of the P-wave, as one small study demonstrated misclassification of episodes as AF or high ventricular rates due to P-wave oversensing in 16% of 19 patients[77]. So far, there is no published data on the initial experience with Confirm Rx.

3.2 Accuracy of atrial fibrillation detection

All modern ICMs are equipped with automatic AF detection. The AF detection algorithms differ per manufacturer but are primarily based on R-R interval irregularity. For example, the Reveal XT analyze R-R interval irregularity patterns during subsequent 2 minutes sampling periods using the Lorenz Plot method. Runs of ectopy with irregular coupling intervals, undersensing of beats, oversensing of myopotentials or underlying sinus arrhythmia may be sources of false positive AF detection. The Reveal

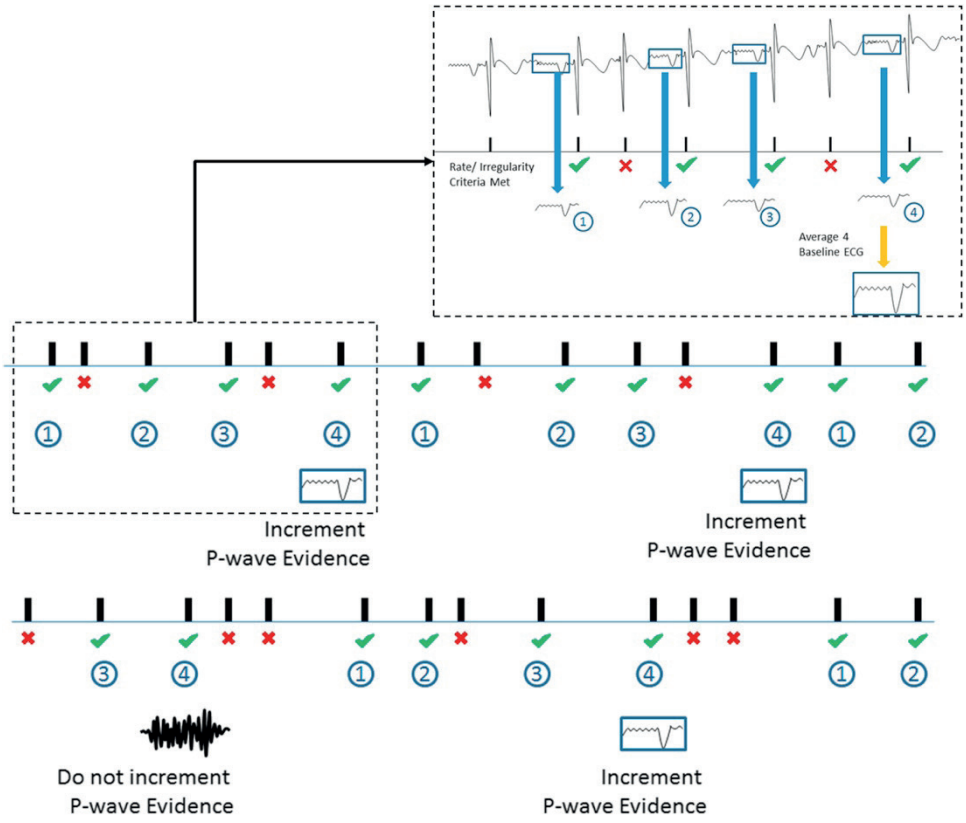
LINQ has an improved AF detection algorithm based on the recognition of a single P-wave between two R-waves using morphologic processing of the ECG signal (Figure 2). This improved detection algorithm has been tested using continuous Holter monitoring as the gold standard[78]. Valid Holter recordings (8442 hours) were analyzed from 206 patients with paroxysmal AF. The algorithm correctly identified 98% of the total AF duration (duration sensitivity) and 99% of the total sinus or non-AF rhythm duration (duration specificity). The gross AF episode detection positive predictive value (PPV) was 55%. This implies that 55% of all detected AF episodes was true AF. Using real-world data from 3,759 patients, the gross AF episode detection PPV was 84%, 73%, and 26% for all AF episodes (≥2 min) and improved to 97%, 95%, and 91% for detected AF episodes ≥1 hour in the syncope, known-AF and cryptogenic stroke cohorts, respectively[79]. Thus, the performance of the algorithm is dependent on the study population and the duration of detected AF episodes.

The BioMonitor 2 AF performance was tested in 92 patients with an indication for an ICM (AF in 44, syncope in 33, cryptogenic stroke in 15)[80]. Successful Holter recordings were completed in 82 patients. The episode sensitivity was 97% for AF episodes longer than 6 minutes (131 of 134 episodes detected). The gross AF episode detection PPV was 73%. No data on AF performance of the Confirm Rx is currently available in the literature.

3.3 Accuracy of bradycardia and pause detection

Inappropriate bradycardia and pause detection by ICMs are mainly caused by undersensing of premature ventricular beats and low-amplitude R-waves. The Reveal LINQ has an enhanced dual sense algorithm which substantially reduces inappropriate episode detection with a minimum reduction in true episode detection[81]. The original algorithm uses an auto-adjusting sensitivity threshold for R-wave (to avoid T-wave oversensing) with a short blanking period (150 ms). In the dual sense algorithm, a second sensing threshold is used with a long blanking (T-wave blanking: 530 ms; P-wave blanking: 220 ms) and fixed lower sensitivity threshold for confirmation of long detection intervals (Figure 3). Using the original algorithm 61% of 4,904 bradycardia episodes and 39% of 2,582 pause episodes were appropriately detected in 161 patients with unexplained syncope. The enhanced algorithm reduced inappropriate bradycardia and pause episodes by 95% and 47%, respectively, with 1.7% and 0.6% reduction in appropriate episodes, respectively. This new algorithm reduces episode review burden and improves episode review yield. Currently, no data on the accuracy of bradycardia and pause detection is available for BioMonitor 2 and Confirm Rx.

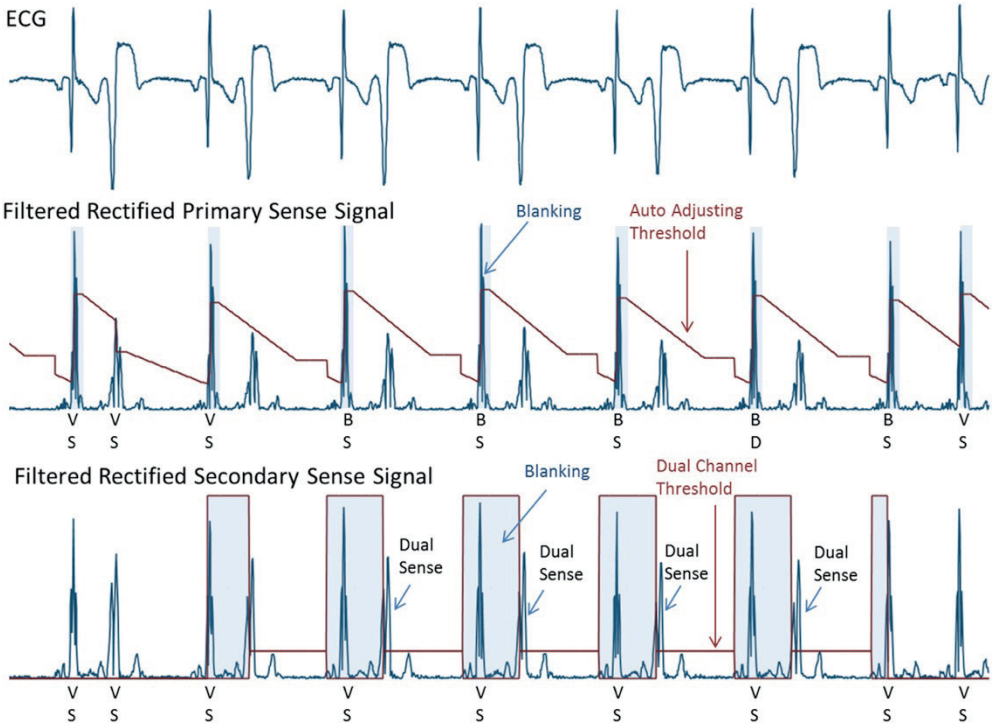
Figure 2. P-sense algorithm in the Reveal LINQ. The inset illustrates the procedure for P-wave averaging every 4 beats that meet the rate (RR >700-780 ms) and irregularity criteria. Eventual found P-wave evidence accumulates into a total P-wave evidence score over a 2-minutes AF detection period. This algorithm reduces false detection of AF due to sinus arrhythmia or runs of ectopy with irregular coupling intervals. Reprinted with permission from[78].



3.4 In-office insertion

The miniaturization of ICMs has enabled the routine insertion of the device outside the traditional hospital setting (operating room, cardiac catheterization or electrophysiology laboratory)[82]. Advantages of the in-office setting are lower costs, reduced resource utilization, fewer delays and lower burden to patients[83]. In the RIO 2 trial 521 patients were randomized to undergo Reveal LINQ insertion in a hospital or office environment with a follow-up of 90 days[84]. The safety profile was excellent with an untoward event rate of 0.8% in the office and 0.9% in the hospital (noninferiority: P<0.001). Patients with increased risk of bleeding or necessity of general anesthesia should, however, be treated in the operating room.

Figure 3. Dual sense algorithm in the Reveal LINQ. Auto-adjusting sensing scheme (second panel) may lead to undersensing of wide-complex shortly coupled bigeminal premature ventricular contractions, leading to inappropriate bradycardia detection. The dual sense scheme (third panel) with a long blanking and fixed threshold provides a second look for long intervals sensed in the primary sense channel (second panel). Reprinted with permission from[81].



3.5 Remote monitoring

All current generation ICMs are capable of remote monitoring. Previous ICM studies with Reveal DX/XT (Medtronic) have shown that remote monitoring improves the diagnostic yield, limits the risk of memory saturation and reduces the time to diagnosis[85]. The BioMonitor 2 using the Home Monitoring system has demonstrated a high transmission success rate, ranging from 94% to 99%[75, 86]. The Reveal LINQ using the CareLink system has demonstrated a transmission success rate of 80%[74]. While Reveal LINQ and BioMonitor 2 use a handheld activator and a home-based bedside transmitter, the Confirm Rx connects directly to the myMerlin smartphone app via Bluetooth wireless technology. This may potentially improve patients' empowerment, engagement, and compliance. There are no published reports on the transmission success of the Confirm Rx.

4. Conclusion

ICMs has been a well-established diagnostic tool for patients with recurrent unexplained syncope. The most recent guidelines expand the indication for ICMs to less well-established populations such as patients with inherited cardiomyopathies, inherited channelopathies, suspected unproven epilepsy, and unexplained falls. Furthermore, an ICM should be considered to document subclinical AF in cryptogenic stroke patients. Technological advancements have resulted in smaller devices, improved arrhythmia detection algorithms, and capability of remote monitoring. The Reveal LINQ (Medtronic) is the smallest ICM and has the most extensive performance and clinical data. The BioMonitor 2 (Biotronik) is the largest ICM but has excellent R-wave amplitudes, longest longevity and very reliable remote monitoring. Confirm Rx (Abbott) has Bluetooth wireless technology enabling monitoring via the patient's smartphone.

5. Expert commentary

An ICM is a valuable tool for the detection of arrhythmias in different patient populations, especially in patients with recurrent unexplained syncope. Recently, the indication for ICMs has expanded to other patient populations where the benefit is less clearly established. One of these patient populations are patients who are at moderate risk of SCD due to ventricular tachyarrhythmias, such as those with inherited cardiomyopathy or channelopathy. The rationale to use an ICM in this population seems logical. Risk stratification for SCD using clinical risk factors is often challenging and an ICD can have profound adverse effects. An ICM will make it possible to detect spontaneous ventricular tachyarrhythmias in an early phase and reassure patients in case of neurally mediated syncope. There are, however, several issues when using ICMs in this population which requires further attention, such as cost-effectiveness and optimal duration of monitoring.

Another field where ICMs have been used is the detection of SCAF in patients with cryptogenic stroke or patients at high risk of stroke. The most important question is whether treatment of SCAF with OAC will result in less (recurrent) stroke. Multiple randomized trials are currently ongoing to address this issue. Until we have solid evidence that treatment of SCAF is useful, the indication for an ICM in patients with cryptogenic stroke or patients with high risk of stroke is not firmly established. In this respect, data on the performance of AF detection of current and future ICMs are important.

Finally, the last decade there has been an exponential increase in the availability of wearable technologies (e.g., wristbands, in-ear monitors, electronic shirts) to detect arrhythmias[87]. Limitations of wearable technology are issues with compliance and need for recharging. Furthermore, most wearable devices use photoplethysmography technology which is less accurate than conventional electrogram-based monitoring. However, new algorithms have led to better arrhythmia detection, especially of atrial fibrillation. We expect that wearable technology will represent an important alternative for ICM considering the high consumer adoption of wearable technology (especially for the younger population), lower costs and noninvasive nature of the technology.

6. Five-Year View

In the next 5 years, ICMs will not only be capable of detecting arrhythmias but will be enhanced with new diagnostic features. One of these important features is early detection of worsening heart failure in order to provide timely intervention and prevent heart failure hospitalization. Previous studies using wireless invasive pulmonary artery pressure monitoring (CardioMEMS) have demonstrated that monitoring and timely treatment reduces heart-failure-related hospital admissions[88]. Furthermore, the MulitSENSE study demonstrated that a new algorithm (HeartLogic), combining several physiological parameters which are available from an ICD, can also predict future heart failure events[89]. It is likely that Boston Scientific will incorporate HeartLogic in their ICM (LUX-Dx) which is still under development and is expected to be launched in 2019. Medtronic has also developed a heart failure algorithm for the Reveal LINQ. Currently, the LINQ HF study is enrolling patients to test the performance of this algorithm to predict subsequent acute decompensated heart failure events[90]. The expected study completion is in October 2018. The availability of heart failure diagnostics will be an important step forward in the evolution of ICMs.

Key issues

- Recurrent unexplained syncope is a well-established indication for an ICM
- The indications for an ICM has been recently expanded to syncope patients with inherited cardiomyopathy or channelopathy, patients with suspected unproven epilepsy, and patients with unexplained falls.
- The detection of subclinical AF can be important in cryptogenic stroke patients.
- Technological advancements have resulted in smaller devices, improved arrhythmia detection algorithms, and capability of remote monitoring.
- Future ICMs will probably incorporate heart failure diagnostics to improve remote monitoring of heart failure patients.

Annotated bibliography

* Important study demonstrating that early application of an ICM allows a safe, specific, and effective therapy in patients with suspected neurally mediated syncope[17].
* This study provides important information on the incidence and prognostic significance of cardiac arrhythmias in patients with acute myocardial infarction and LV dysfunction[32].
* Interesting study demonstrating that 20% of patients >50 years with unexplained falls have a modifiable cardiac arrhythmia[41].
** Landmark paper demonstrating the clinical relevance of SCAF in relationship to the occurrence of ischemic stroke[46].

** Randomized trial demonstrating the superiority of ICM in comparison to conventional screening for the detection of AF in patients with cryptogenic stroke[47].

* Important randomized study which will determine whether treatment of device-detected SCAF with apixaban reduces the risk of stroke or systemic embolism[60].

References

Papers of special note have been highlighted as:
* of interest
** of considerable interest

1. Brignole M, Moya A, de Lange FJ, Deharo JC, Elliott PM, Fanciulli A, Fedorowski A, Furlan R, Kenny RA, Martin A, Probst V, Reed MJ, Rice CP, Sutton R, Ungar A, van Dijk JG and Group ESCSD. 2018 ESC Guidelines for the diagnosis and management of syncope. *Eur Heart J*. 2018.
2. Kirchhof P, Benussi S, Kotecha D, Ahlsson A, Atar D, Casadei B, Castella M, Diener HC, Heidbuchel H, Hendriks J, Hindricks G, Manolis AS, Oldgren J, Popescu BA, Schotten U, Van Putte B, Vardas P and Group ESCSD. 2016 ESC Guidelines for the management of atrial fibrillation developed in collaboration with EACTS. *Eur Heart J*. 2016;37:2893-2962.
3. Priori SG, Blomstrom-Lundqvist C, Mazzanti A, Blom N, Borggrefe M, Camm J, Elliott PM, Fitzsimons D, Hatala R, Hindricks G, Kirchhof P, Kjeldsen K, Kuck KH, Hernandez-Madrid A, Nikolaou N, Norekval TM, Spaulding C and Van Veldhuisen DJ. 2015 ESC Guidelines for the management of patients with ventricular arrhythmias and the prevention of sudden cardiac death: The Task Force for the Management of Patients with Ventricular Arrhythmias and the Prevention of Sudden Cardiac Death of the European Society of Cardiology (ESC). Endorsed by: Association for European Paediatric and Congenital Cardiology (AEPC). *Eur Heart J*. 2015;36:2793-867.
4. Al-Khatib SM, Stevenson WG, Ackerman MJ, Bryant WJ, Callans DJ, Curtis AB, Deal BJ, Dickfeld T, Field ME, Fonarow GC, Gillis AM, Hlatky MA, Granger CB, Hammill SC, Joglar JA, Kay GN, Matlock DD, Myerburg RJ and Page RL. 2017 AHA/ACC/HRS Guideline for Management of Patients With Ventricular Arrhythmias and the Prevention of Sudden Cardiac Death: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines and the Heart Rhythm Society. *Circulation*. 2017.
5. Ganzeboom KS, Mairuhu G, Reitsma JB, Linzer M, Wieling W and van Dijk N. Lifetime cumulative incidence of syncope in the general population: a study of 549 Dutch subjects aged 35-60 years. *J Cardiovasc Electrophysiol*. 2006;17:1172-6.
6. Kapoor WN. Evaluation and management of the patient with syncope. *JAMA*. 1992;268:2553-60.
7. Soteriades ES, Evans JC, Larson MG, Chen MH, Chen L, Benjamin EJ and Levy D. Incidence and prognosis of syncope. *N Engl J Med*. 2002;347:878-85.
8. Edvardsson N, Frykman V, van Mechelen R, Mitro P, Mohii-Oskarsson A, Pasquie JL, Ramanna H, Schwertfeger F, Ventura R, Voulgaraki D, Garutti C, Stolt P, Linker NJ and Investigators PS. Use of an implantable loop recorder to increase the diagnostic yield in unexplained syncope: results from the PICTURE registry. *Europace*. 2011;13:262-9.
9. Moya A, Brignole M, Menozzi C, Garcia-Civera R, Tognarini S, Mont L, Botto G, Giada F, Cornacchia D and International Study on Syncope of Uncertain Etiology I. Mechanism of syncope in patients with isolated syncope and in patients with tilt-positive syncope. *Circulation*. 2001;104:1261-7.
10. Brignole M, Menozzi C, Moya A, Garcia-Civera R, Mont L, Alvarez M, Errazquin F, Beiras J, Bottoni N, Donateo P and International Study on Syncope of Uncertain Etiology I. Mechanism of syncope in patients with bundle branch block and negative electrophysiological test. *Circulation*. 2001;104:2045-50.

11. Menozzi C, Brignole M, Garcia-Civera R, Moya A, Botto G, Tercedor L, Migliorini R, Navarro X and International Study on Syncope of Uncertain Etiology I. Mechanism of syncope in patients with heart disease and negative electrophysiologic test. *Circulation*. 2002;105:2741-5.
12. Da Costa A, Defaye P, Romeyer-Bouchard C, Roche F, Dauphinot V, Deharo JC, Jacon P, Lamaison D, Bathelemy JC, Isaaz K and Laurent G. Clinical impact of the implantable loop recorder in patients with isolated syncope, bundle branch block and negative workup: a randomized multicentre prospective study. *Arch Cardiovasc Dis*. 2013;106:146-54.
13. Farwell DJ, Freemantle N and Sulke N. The clinical impact of implantable loop recorders in patients with syncope. *Eur Heart J*. 2006;27:351-6.
14. Krahn AD, Klein GJ, Yee R and Skanes AC. Randomized assessment of syncope trial: conventional diagnostic testing versus a prolonged monitoring strategy. *Circulation*. 2001;104:46-51.
15. Podoleanu C, DaCosta A, Defaye P, Taieb J, Galley D, Bru P, Maury P, Mabo P, Boveda S, Cellarier G, Anselme F, Kouakam C, Delarche N, Deharo JC and investigators F. Early use of an implantable loop recorder in syncope evaluation: a randomized study in the context of the French healthcare system (FRESH study). *Arch Cardiovasc Dis*. 2014;107:546-52.
16. Sulke N, Sugihara C, Hong P, Patel N and Freemantle N. The benefit of a remotely monitored implantable loop recorder as a first line investigation in unexplained syncope: the EaSyAS II trial. *Europace*. 2016;18:912-8.
17. Brignole M, Sutton R, Menozzi C, Garcia-Civera R, Moya A, Wieling W, Andresen D, Benditt DG, Vardas P and International Study on Syncope of Uncertain Etiology G. Early application of an implantable loop recorder allows effective specific therapy in patients with recurrent suspected neurally mediated syncope. *Eur Heart J*. 2006;27:1085-92.
18. Giustetto C, Cerrato N, Ruffino E, Gribaudo E, Scrocco C, Barbonaglia L, Bianchi F, Bortnik M, Rossetti G, Carvalho P, Riccardi R, Castagno D, Anselmino M, Bergamasco L and Gaita F. Etiological diagnosis, prognostic significance and role of electrophysiological study in patients with Brugada ECG and syncope. *Int J Cardiol*. 2017;241:188-193.
19. Olde Nordkamp LR, Vink AS, Wilde AA, de Lange FJ, de Jong JS, Wieling W, van Dijk N and Tan HL. Syncope in Brugada syndrome: prevalence, clinical significance, and clues from history taking to distinguish arrhythmic from nonarrhythmic causes. *Heart Rhythm*. 2015;12:367-75.
20. Sakhi R, Theuns D, Bhagwandien RE, Michels M, Schinkel AFL, Szili-Torok T, Zijlstra F, Roos-Hesselink JW and Yap SC. Value of implantable loop recorders in patients with structural or electrical heart disease. *Journal of interventional cardiac electrophysiology : an international journal of arrhythmias and pacing*. 2018;52:203-208.
21. Champagne J, Philippon F, Gilbert M, Molin F, Blier L, Nault I, Sarrazin JF, Charbonneau L, Dufort L, Drolet B, Chahine M and O'Hara GE. The Brugada syndrome in Canada: a unique French-Canadian experience. *Can J Cardiol*. 2007;23 Suppl B:71B-75B.
22. Kubala M, Aissou L, Traulle S, Gugenheim AL and Hermida JS. Use of implantable loop recorders in patients with Brugada syndrome and suspected risk of ventricular arrhythmia. *Europace*. 2012;14:898-902.
23. Sacher F, Arsac F, Wilton SB, Derval N, Denis A, de Guillebon M, Ramoul K, Bordachar P, Ritter P, Hocini M, Clementy J, Jais P and Haissaguerre M. Syncope in Brugada syndrome patients: prevalence, characteristics, and outcome. *Heart Rhythm*. 2012;9:1272-9.

24. Avari Silva JN, Bromberg BI, Emge FK, Bowman TM and Van Hare GF. Implantable Loop Recorder Monitoring for Refining Management of Children With Inherited Arrhythmia Syndromes. *J Am Heart Assoc*. 2016;5.
25. Frangini PA, Cecchin F, Jordao L, Martuscello M, Alexander ME, Triedman JK, Walsh EP and Berul CI. How revealing are insertable loop recorders in pediatrics? *Pacing Clin Electrophysiol*. 2008;31:338-43.
26. Stollberger C, Keller H, Steger C and Finsterer J. Implantable loop-recorders in myopathic and non-myopathic patients with left ventricular hypertrabeculation/noncompaction. *Int J Cardiol*. 2013;163:146-8.
27. Weidemann F, Maier SK, Stork S, Brunner T, Liu D, Hu K, Seydelmann N, Schneider A, Becher J, Canan-Kuhl S, Blaschke D, Bijnens B, Ertl G, Wanner C and Nordbeck P. Usefulness of an Implantable Loop Recorder to Detect Clinically Relevant Arrhythmias in Patients With Advanced Fabry Cardiomyopathy. *Am J Cardiol*. 2016;118:264-74.
28. Elliott PM, Anastasakis A, Borger MA, Borggrefe M, Cecchi F, Charron P, Hagege AA, Lafont A, Limongelli G, Mahrholdt H, McKenna WJ, Mogensen J, Nihoyannopoulos P, Nistri S, Pieper PG, Pieske B, Rapezzi C, Rutten FH, Tillmanns C and Watkins H. 2014 ESC Guidelines on diagnosis and management of hypertrophic cardiomyopathy: the Task Force for the Diagnosis and Management of Hypertrophic Cardiomyopathy of the European Society of Cardiology (ESC). *Eur Heart J*. 2014;35:2733-79.
29. Antzelevitch C, Yan GX, Ackerman MJ, Borggrefe M, Corrado D, Guo J, Gussak I, Hasdemir C, Horie M, Huikuri H, Ma C, Morita H, Nam GB, Sacher F, Shimizu W, Viskin S and Wilde AA. J-Wave syndromes expert consensus conference report: Emerging concepts and gaps in knowledge. *Heart Rhythm*. 2016;13:e295-324.
30. Hohnloser SH, Kuck KH, Dorian P, Roberts RS, Hampton JR, Hatala R, Fain E, Gent M, Connolly SJ and Investigators D. Prophylactic use of an implantable cardioverter-defibrillator after acute myocardial infarction. *N Engl J Med*. 2004;351:2481-8.
31. Steinbeck G, Andresen D, Seidl K, Brachmann J, Hoffmann E, Wojciechowski D, Kornacewicz-Jach Z, Sredniawa B, Lupkovics G, Hofgartner F, Lubinski A, Rosenqvist M, Habets A, Wegscheider K, Senges J and Investigators I. Defibrillator implantation early after myocardial infarction. *N Engl J Med*. 2009;361:1427-36.
32. Bloch Thomsen PE, Jons C, Raatikainen MJ, Moerch Joergensen R, Hartikainen J, Virtanen V, Boland J, Anttonen O, Gang UJ, Hoest N, Boersma LV, Platou ES, Becker D, Messier MD, Huikuri HV, Cardiac A and Risk Stratification After Acute Myocardial Infarction Study G. Long-term recording of cardiac arrhythmias with an implantable cardiac monitor in patients with reduced ejection fraction after acute myocardial infarction: the Cardiac Arrhythmias and Risk Stratification After Acute Myocardial Infarction (CARISMA) study. *Circulation*. 2010;122:1258-64.
33. Gang UJ, Jons C, Jorgensen RM, Abildstrom SZ, Haarbo J, Messier MD, Huikuri HV, Thomsen PE and investigators C. Heart rhythm at the time of death documented by an implantable loop recorder. *Europace*. 2010;12:254-60.
34. Zaidi A, Clough P, Cooper P, Scheepers B and Fitzpatrick AP. Misdiagnosis of epilepsy: many seizure-like attacks have a cardiovascular cause. *J Am Coll Cardiol*. 2000;36:181-4.
35. Petkar S, Hamid T, Iddon P, Clifford A, Rice N, Claire R, McKee D, Curtis N, Cooper PN and Fitzpatrick AP. Prolonged implantable electrocardiographic monitoring indicates a high rate of misdiagnosis of epilepsy--REVISE study. *Europace*. 2012;14:1653-60.
36. Ho RT, Wicks T, Wyeth D and Nei M. Generalized tonic-clonic seizures detected by implantable loop recorder devices: diagnosing more than cardiac arrhythmias. *Heart Rhythm*. 2006;3:857-61.

37. Maggi R, Rafanelli M, Ceccofiglio A, Solari D, Brignole M and Ungar A. Additional diagnostic value of implantable loop recorder in patients with initial diagnosis of real or apparent transient loss of consciousness of uncertain origin. *Europace*. 2014;16:1226-30.
38. Kanjwal K, Karabin B, Kanjwal Y and Grubb BP. Differentiation of convulsive syncope from epilepsy with an implantable loop recorder. *Int J Med Sci*. 2009;6:296-300.
39. Simpson CS, Barlow MA, Krahn AD, Klein GJ, Yee R and Skanes AC. Recurrent seizure diagnosed by the insertable loop recorder. *J Interv Card Electrophysiol*. 2000;4:475-9.
40. Bhangu J, Hall P, Devaney N, Bennett K, Carroll L, Kenny RA and McMahon CG. The prevalence of unexplained falls and syncope in older adults presenting to an Irish urban emergency department. *Eur J Emerg Med*. 2018.
41. Bhangu J, McMahon CG, Hall P, Bennett K, Rice C, Crean P, Sutton R and Kenny RA. Long-term cardiac monitoring in older adults with unexplained falls and syncope. *Heart*. 2016;102:681-6.
42. Armstrong VL, Lawson J, Kamper AM, Newton J and Kenny RA. The use of an implantable loop recorder in the investigation of unexplained syncope in older people. *Age Ageing*. 2003;32:185-8.
43. Ryan DJ, Nick S, Colette SM and Roseanne K. Carotid sinus syndrome, should we pace? A multicentre, randomised control trial (Safepace 2). *Heart*. 2010;96:347-51.
44. Giada F, Gulizia M, Francese M, Croci F, Santangelo L, Santomauro M, Occhetta E, Menozzi C and Raviele A. Recurrent unexplained palpitations (RUP) study comparison of implantable loop recorder versus conventional diagnostic strategy. *J Am Coll Cardiol*. 2007;49:1951-6.
45. Brignole M, Vardas P, Hoffman E, Huikuri H, Moya A, Ricci R, Sulke N, Wieling W, Committee ESD, Auricchio A, Lip GY, Almendral J, Kirchhof P, Aliot E, Gasparini M, Braunschweig F, Document R, Lip GY, Almendral J, Kirchhof P, Botto GL and Committee ESD. Indications for the use of diagnostic implantable and external ECG loop recorders. *Europace*. 2009;11:671-87.
46. Healey JS, Connolly SJ, Gold MR, Israel CW, Van Gelder IC, Capucci A, Lau CP, Fain E, Yang S, Bailleul C, Morillo CA, Carlson M, Themeles E, Kaufman ES, Hohnloser SH and Investigators A. Subclinical atrial fibrillation and the risk of stroke. *N Engl J Med*. 2012;366:120-9.
47. Sanna T, Diener HC, Passman RS, Di Lazzaro V, Bernstein RA, Morillo CA, Rymer MM, Thijs V, Rogers T, Beckers F, Lindborg K, Brachmann J and Investigators CA. Cryptogenic stroke and underlying atrial fibrillation. *N Engl J Med*. 2014;370:2478-86.
48. Ziegler PD, Rogers JD, Ferreira SW, Nichols AJ, Richards M, Koehler JL and Sarkar S. Long-term detection of atrial fibrillation with insertable cardiac monitors in a real-world cryptogenic stroke population. *Int J Cardiol*. 2017;244:175-179.
49. Diamantopoulos A, Sawyer LM, Lip GY, Witte KK, Reynolds MR, Fauchier L, Thijs V, Brown B, Quiroz Angulo ME and Diener HC. Cost-effectiveness of an insertable cardiac monitor to detect atrial fibrillation in patients with cryptogenic stroke. *Int J Stroke*. 2016;11:302-12.
50. Hart RG, Sharma M, Mundl H, Kasner SE, Bangdiwala SI, Berkowitz SD, Swaminathan B, Lavados P, Wang Y, Wang Y, Davalos A, Shamalov N, Mikulik R, Cunha L, Lindgren A, Arauz A, Lang W, Czlonkowska A, Eckstein J, Gagliardi RJ, Amarenco P, Ameriso SF, Tatlisumak T, Veltkamp R, Hankey GJ, Toni D, Bereczki D, Uchiyama S, Ntaios G, Yoon BW, Brouns R, Endres M, Muir KW, Bornstein N, Ozturk S, O'Donnell MJ, De Vries Basson MM, Pare G, Pater C, Kirsch B, Sheridan P, Peters G, Weitz JI, Peacock WF, Shoamanesh A, Benavente OR, Joyner C, Themeles E, Connolly SJ and

Investigators NE. Rivaroxaban for Stroke Prevention after Embolic Stroke of Undetermined Source. *N Engl J Med*. 2018;378:2191-2201.

51. Diener HC, Easton JD, Granger CB, Cronin L, Duffy C, Cotton D, Brueckmann M, Sacco RL and Investigators R-SE. Design of Randomized, double-blind, Evaluation in secondary Stroke Prevention comparing the EfficaCy and safety of the oral Thrombin inhibitor dabigatran etexilate vs. acetylsalicylic acid in patients with Embolic Stroke of Undetermined Source (RE-SPECT ESUS). *Int J Stroke*. 2015;10:1309-12.
52. Verma N, Ziegler PD, Liu S and Passman RS. Incidence of atrial fibrillation among patients with an embolic stroke of undetermined source: Insights from insertable cardiac monitors. *Int J Stroke*. 2018:1747493018798554.
53. Columbia University. AtRial Cardiopathy and Antithrombotic Drugs In Prevention After Cryptogenic Stroke (ARCADIA).
54. University Hospital Tuebingen. Apixaban for Treatment of Embolic Stroke of Undetermined Source (ATTICUS).
55. Healey JS, Alings M, Ha A, Leong-Sit P, Birnie DH, de Graaf JJ, Freericks M, Verma A, Wang J, Leong D, Dokainish H, Philippon F, Barake W, McIntyre WF, Simek K, Hill MD, Mehta SR, Carlson M, Smeele F, Pandey AS, Connolly SJ and Investigators A-I. Subclinical Atrial Fibrillation in Older Patients. *Circulation*. 2017;136:1276-1283.
56. Nasir JM, Pomeroy W, Marler A, Hann M, Baykaner T, Jones R, Stoll R, Hursey K, Meadows A, Walker J and Kindsvater S. Predicting Determinants of Atrial Fibrillation or Flutter for Therapy Elucidation in Patients at Risk for Thromboembolic Events (PREDATE AF) Study. *Heart Rhythm*. 2017;14:955-961.
57. Reiffel JA, Verma A, Kowey PR, Halperin JL, Gersh BJ, Wachter R, Pouliot E, Ziegler PD and Investigators RA. Incidence of Previously Undiagnosed Atrial Fibrillation Using Insertable Cardiac Monitors in a High-Risk Population: The REVEAL AF Study. *JAMA Cardiol*. 2017;2:1120-1127.
58. Diederichsen SZ, Haugan KJ, Kober L, Hojberg S, Brandes A, Kronborg C, Graff C, Holst AG, Nielsen JB, Krieger D and Svendsen JH. Atrial fibrillation detected by continuous electrocardiographic monitoring using implantable loop recorder to prevent stroke in individuals at risk (the LOOP study): Rationale and design of a large randomized controlled trial. *Am Heart J*. 2017;187:122-132.
59. Rigshospitalet. Atrial Fibrillation Detected by Continuous ECG Monitoring (LOOP).
60. Lopes RD, Alings M, Connolly SJ, Beresh H, Granger CB, Mazuecos JB, Boriani G, Nielsen JC, Conen D, Hohnloser SH, Mairesse GH, Mabo P, Camm AJ and Healey JS. Rationale and design of the Apixaban for the Reduction of Thrombo-Embolism in Patients With Device-Detected Sub-Clinical Atrial Fibrillation (ARTESiA) trial. *Am Heart J*. 2017;189:137-145.
61. Population Health Research Institute. Apixaban for the Reduction of Thrombo-Embolism in Patients With Device-Detected Sub-Clinical Atrial Fibrillation (ARTESiA).
62. Kirchhof P, Blank BF, Calvert M, Camm AJ, Chlouverakis G, Diener HC, Goette A, Huening A, Lip GYH, Simantirakis E and Vardas P. Probing oral anticoagulation in patients with atrial high rate episodes: Rationale and design of the Non-vitamin K antagonist Oral anticoagulants in patients with Atrial High rate episodes (NOAH-AFNET 6) trial. *Am Heart J*. 2017;190:12-18.
63. Atrial Fibrillation Network. Non-vitamin K Antagonist Oral Anticoagulants in Patients With Atrial High Rate Episodes (NOAH).

64. Gersak B, Pernat A, Robic B and Sinkovec M. Low rate of atrial fibrillation recurrence verified by implantable loop recorder monitoring following a convergent epicardial and endocardial ablation of atrial fibrillation. *J Cardiovasc Electrophysiol*. 2012;23:1059-66.
65. Pokushalov E, Romanov A, Corbucci G, Artyomenko S, Turov A, Shirokova N and Karaskov A. Ablation of paroxysmal and persistent atrial fibrillation: 1-year follow-up through continuous subcutaneous monitoring. *J Cardiovasc Electrophysiol*. 2011;22:369-75.
66. Hanke T, Charitos EI, Stierle U, Karluss A, Kraatz E, Graf B, Hagemann A, Misfeld M and Sievers HH. Twenty-four-hour holter monitor follow-up does not provide accurate heart rhythm status after surgical atrial fibrillation ablation therapy: up to 12 months experience with a novel permanently implantable heart rhythm monitor device. *Circulation*. 2009;120:S177-84.
67. Pecha S, Aydin MA, Ahmadzade T, Hartel F, Hoffmann B, Steven D, Willems S, Reichenspurner H and Wagner FM. Implantable loop recorder monitoring after concomitant surgical ablation for atrial fibrillation (AF): insights from more than 200 continuously monitored patients. *Heart Vessels*. 2016;31:1347-53.
68. Perez-Castellano N, Fernandez-Cavazos R, Moreno J, Canadas V, Conde A, Gonzalez-Ferrer JJ, Macaya C and Perez-Villacastin J. The COR trial: a randomized study with continuous rhythm monitoring to compare the efficacy of cryoenergy and radiofrequency for pulmonary vein isolation. *Heart Rhythm*. 2014;11:8-14.
69. Kapa S, Epstein AE, Callans DJ, Garcia FC, Lin D, Bala R, Riley MP, Hutchinson MD, Gerstenfeld EP, Tzou W, Marchlinski FE, Frankel DS, Cooper JM, Supple G, Deo R, Verdino RJ, Patel VV and Dixit S. Assessing arrhythmia burden after catheter ablation of atrial fibrillation using an implantable loop recorder: the ABACUS study. *J Cardiovasc Electrophysiol*. 2013;24:875-81.
70. Pokushalov E, Romanov A, Corbucci G, Artyomenko S, Turov A, Shirokova N and Karaskov A. Use of an implantable monitor to detect arrhythmia recurrences and select patients for early repeat catheter ablation for atrial fibrillation: a pilot study. *Circ Arrhythm Electrophysiol*. 2011;4:823-31.
71. Calkins H, Hindricks G, Cappato R, Kim YH, Saad EB, Aguinaga L, Akar JG, Badhwar V, Brugada J, Camm J, Chen PS, Chen SA, Chung MK, Cosedis Nielsen J, Curtis AB, Davies DW, Day JD, d'Avila A, Natasja de Groot NMS, Di Biase L, Duytschaever M, Edgerton JR, Ellenbogen KA, Ellinor PT, Ernst S, Fenelon G, Gerstenfeld EP, Haines DE, Haissaguerre M, Helm RH, Hylek E, Jackman WM, Jalife J, Kalman JM, Kautzner J, Kottkamp H, Kuck KH, Kumagai K, Lee R, Lewalter T, Lindsay BD, Macle L, Mansour M, Marchlinski FE, Michaud GF, Nakagawa H, Natale A, Nattel S, Okumura K, Packer D, Pokushalov E, Reynolds MR, Sanders P, Scanavacca M, Schilling R, Tondo C, Tsao HM, Verma A, Wilber DJ, Yamane T and Document R. 2017 HRS/EHRA/ECAS/APHRS/SOLAECE expert consensus statement on catheter and surgical ablation of atrial fibrillation. *Europace*. 2018;20:e1-e160.
72. Zuern CS, Kilias A, Berlitz P, Seizer P, Gramlich M, Muller K, Duckheim M, Gawaz M and Schreieck J. Anticoagulation after catheter ablation of atrial fibrillation guided by implantable cardiac monitors. *Pacing Clin Electrophysiol*. 2015;38:688-93.
73. Passman R, Leong-Sit P, Andrei AC, Huskin A, Tomson TT, Bernstein R, Ellis E, Waks JW and Zimetbaum P. Targeted Anticoagulation for Atrial Fibrillation Guided by Continuous Rhythm Assessment With an Insertable Cardiac Monitor: The Rhythm Evaluation for Anticoagulation With Continuous Monitoring (REACT.COM) Pilot Study. *J Cardiovasc Electrophysiol*. 2016;27:264-70.

74. Purerfellner H, Sanders P, Pokushalov E, Di Bacco M, Bergemann T, Dekker LR and Reveal LUSI. Miniaturized Reveal LINQ insertable cardiac monitoring system: First-in-human experience. *Heart Rhythm*. 2015;12:1113-9.
75. Ooi SY, Ng B, Singarayar S, Hellestrand K, Illes P, Mohamed U, Razak S, Weerasooriya R and BioMonitor 2 Study I. BioMonitor 2 Pilot Study: Early Experience With Implantation of the Biotronik BioMonitor 2 Implantable Cardiac Monitor. *Heart Lung Circ*. 2017.
76. Bisignani G, De Bonis S, Bisignani A, Mancuso L and Giacopelli D. Sensing performance, safety, and patient acceptability of long-dipole cardiac monitor: An innovative axillary insertion. *Pacing Clin Electrophysiol*. 2018;41:277-283.
77. Lacour P, Dang PL, Huemer M, Parwani AS, Attanasio P, Pieske B, Boldt LH, Haverkamp W and Blaschke F. Performance of the New BioMonitor 2-AF Insertable Cardiac Monitoring System: Can Better be Worse? *Pacing Clin Electrophysiol*. 2017;40:516-526.
78. Purerfellner H, Pokushalov E, Sarkar S, Koehler J, Zhou R, Urban L and Hindricks G. P-wave evidence as a method for improving algorithm to detect atrial fibrillation in insertable cardiac monitors. *Heart Rhythm*. 2014;11:1575-83.
79. Mittal S, Rogers J, Sarkar S, Koehler J, Warman EN, Tomson TT and Passman RS. Real-world performance of an enhanced atrial fibrillation detection algorithm in an insertable cardiac monitor. *Heart Rhythm*. 2016;13:1624-30.
80. Noelker G, Busch M, Schmitt J, Roithinger F, Young G, Taborsky M and Piorkowski C. The BioMonitor 2 Master Study: Early Experience With a New Insertable Cardiac Monitor. *Circulation*. 2018;136:A16347.
81. Passman RS, Rogers JD, Sarkar S, Reiland J, Reisfeld E, Koehler J and Mittal S. Development and validation of a dual sensing scheme to improve accuracy of bradycardia and pause detection in an insertable cardiac monitor. *Heart Rhythm*. 2017;14:1016-1023.
82. Steffel J, Wright DJ, Schafer H, Rashid-Fadel T and Lewalter T. Insertion of miniaturized cardiac monitors outside the catheter operating room: experience and practical advice. *Europace*. 2017;19:1624-1629.
83. Kanters TA, Wolff C, Boyson D, Kouakam C, Dinh T, Hakkaart L and Rutten-Van Molken MP. Cost comparison of two implantable cardiac monitors in two different settings: Reveal XT in a catheterization laboratory vs. Reveal LINQ in a procedure room. *Europace*. 2016;18:919-24.
84. Rogers JD, Sanders P, Piorkowski C, Sohail MR, Anand R, Crossen K, Khairallah FS, Kaplon RE, Stromberg K and Kowal RC. In-office insertion of a miniaturized insertable cardiac monitor: Results from the Reveal LINQ In-Office 2 randomized study. *Heart Rhythm*. 2017;14:218-224.
85. Furukawa T, Maggi R, Bertolone C, Ammirati F, Santini M, Ricci R, Giada F and Brignole M. Effectiveness of remote monitoring in the management of syncope and palpitations. *Europace*. 2011;13:431-7.
86. Ciconte G, Vicedomini G, Giacopelli D, Calovic Z, Conti M, Spinelli B, Saviano M, Santinelli V and Pappone C. Feasibility of Remote Monitoring Using a Novel Long-Dipole Insertable Cardiac Monitor. *JACC Clin Electrophysiol*. 2018;4:559-561.
87. Cheung CC, Krahn AD and Andrade JG. The Emerging Role of Wearable Technologies in Detection of Arrhythmia. *Can J Cardiol*. 2018;34:1083-1087.
88. Abraham WT, Adamson PB, Bourge RC, Aaron MF, Costanzo MR, Stevenson LW, Strickland W, Neelagaru S, Raval N, Krueger S, Weiner S, Shavelle D, Jeffries B, Yadav JS and Group CTS. Wireless pulmonary artery haemodynamic monitoring in chronic heart failure: a randomised controlled trial. *Lancet*. 2011;377:658-66.

89. Boehmer JP, Hariharan R, Devecchi FG, Smith AL, Molon G, Capucci A, An Q, Averina V, Stolen CM, Thakur PH, Thompson JA, Wariar R, Zhang Y and Singh JP. A Multisensor Algorithm Predicts Heart Failure Events in Patients With Implanted Devices: Results From the MultiSENSE Study. *JACC Heart Fail*. 2017;5:216-225.
90. Medtronic Cardiac Rhythm and Heart Failure. Reveal LINQ™ Heart Failure (LINQ HF).
91. Linker NJ, Voulgaraki D, Garutti C, Rieger G, Edvardsson N and Investigators PS. Early versus delayed implantation of a loop recorder in patients with unexplained syncope--effects on care pathway and diagnostic yield. *Int J Cardiol*. 2013;170:146-51.
92. Lacunza-Ruiz FJ, Moya-Mitjans A, Martinez-Alday J, Baron-Esquivias G, Ruiz-Granell R, Rivas-Gandara N, Gonzalez-Enriquez S, Leal-del-Ojo J, Arcocha-Torres MF, Perez-Villacastin J, Garcia-Heil N and Garcia-Alberola A. Implantable loop recorder allows an etiologic diagnosis in one-third of patients. Results of the Spanish reveal registry. *Circ J*. 2013;77:2535-41.
93. Moya A, Garcia-Civera R, Croci F, Menozzi C, Brugada J, Ammirati F, Del Rosso A, Bellver-Navarro A, Garcia-Sacristan J, Bortnik M, Mont L, Ruiz-Granell R, Navarro X and Bradycardia detection in Bundle Branch Block s. Diagnosis, management, and outcomes of patients with syncope and bundle branch block. *Eur Heart J*. 2011;32:1535-41.
94. Krahn AD, Klein GJ, Norris C and Yee R. The etiology of syncope in patients with negative tilt table and electrophysiological testing. *Circulation*. 1995;92:1819-24.
95. Brignole M, Arabia F, Ammirati F, Tomaino M, Quartieri F, Rafanelli M, Del Rosso A, Rita Vecchi M, Russo V, Gaggioli G and Syncope Unit Project i. Standardized algorithm for cardiac pacing in older patients affected by severe unpredictable reflex syncope: 3-year insights from the Syncope Unit Project 2 (SUP 2) study. *Europace*. 2016;18:1427-33.
96. Brignole M, Menozzi C, Moya A, Andresen D, Blanc JJ, Krahn AD, Wieling W, Beiras X, Deharo JC, Russo V, Tomaino M, Sutton R and International Study on Syncope of Uncertain Etiology I. Pacemaker therapy in patients with neurally mediated syncope and documented asystole: Third International Study on Syncope of Uncertain Etiology (ISSUE-3): a randomized trial. *Circulation*. 2012;125:2566-71.
97. Krahn AD, Klein GJ, Yee R, Takle-Newhouse T and Norris C. Use of an extended monitoring strategy in patients with problematic syncope. Reveal Investigators. *Circulation*. 1999;99:406-10.
98. Solbiati M, Costantino G, Casazza G, Dipaola F, Galli A, Furlan R, Montano N and Sheldon R. Implantable loop recorder versus conventional diagnostic workup for unexplained recurrent syncope. *Cochrane Database Syst Rev*. 2016;4:CD011637.
99. Volosin K, Stadler RW, Wyszynski R and Kirchhof P. Tachycardia detection performance of implantable loop recorders: results from a large 'real-life' patient cohort and patients with induced ventricular arrhythmias. *Europace*. 2013;15:1215-22.
100. Gladstone DJ, Spring M, Dorian P, Panzov V, Thorpe KE, Hall J, Vaid H, O'Donnell M, Laupacis A, Cote R, Sharma M, Blakely JA, Shuaib A, Hachinski V, Coutts SB, Sahlas DJ, Teal P, Yip S, Spence JD, Buck B, Verreault S, Casaubon LK, Penn A, Selchen D, Jin A, Howse D, Mehdiratta M, Boyle K, Aviv R, Kapral MK, Mamdani M, Investigators E and Coordinators. Atrial fibrillation in patients with cryptogenic stroke. *N Engl J Med*. 2014;370:2467-77.

CHAPTER 3

Value of implantable loop recorders in patients with structural or electrical heart disease

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Journal of Interventional Cardiac Electrophysiology 2018 Jul;52(2):203-208.

Abstract

Purpose: In patients with structural heart disease (SHD) or inherited primary arrhythmia syndrome (IPAS) the occurrence of unexplained syncope or palpitations can be worrisome as they are at increased risk of sudden cardiac death. An implantable loop recorder (ILR) can be a useful diagnostic tool. Our purpose was to compare the diagnostic yield, arrhythmia mechanism and management in patients with SHD, patients with IPAS and those without heart disease.

Methods: Retrospective single-center study in consecutive patients who underwent an ILR implantation.

Results: Between March 2013 and December 2016, a total of 94 patients received an ILR (SHD, n=20; IPAS, n=14; no SHD/IPAS, n=60). The type of symptoms at the time of implantation was similar between groups. During a median follow up of 10 months, 45% had an ILR-guided diagnosis. Patients with IPAS had a lower diagnostic yield (14%) in comparison to the other groups (no SHD/IPAS 47%, P=0.03; SHD 60%, P=0.01 respectively). Furthermore, patients with SHD had a higher incidence of nonsustained VT in comparison to patients without SHD/IPAS (30% versus 3%, P<0.01). ILR-guided therapy was comparable between groups. In the SHD group, a high proportion (10%) received an implantable cardioverter-defibrillator, however this was not statistically significant higher than the other groups (no SHD/IPAS 3%, IPAS 0%, P=0.08).

Conclusions: In comparison to patients without heart disease, the diagnostic yield of an ILR was lower in patients with IPAS and the prevalence of ILR-diagnosed nonsustained VT was higher in patients with SHD.

Introduction

Implantable loop recorders (ILRs) are increasingly being used for the detection of infrequent arrhythmia episodes. Several studies have demonstrated the incremental value of ILRs over intermittent monitoring strategies for the detection of arrhythmias in patients with recurrent syncope, undocumented palpitations and cryptogenic stroke[1-4]. ILRs might also be used as a diagnostic tool in patients at risk for ventricular tachyarrhythmias (VTs), such as those with structural heart disease (SHD) or inherited primary arrhythmia syndromes (IPAS)[5-7]. The occurrence of unexplained syncope or palpitations can be worrisome in these patients. The 2009 ESC syncope guidelines recommend to consider an ILR in non-high risk patients with SHD or IPAS[7]. The recent J-wave expert consensus report also suggests the use of an ILR for close monitoring of Brugada patients with presumed non-arrhythmogenic syncope[8]. There is limited data comparing the value of an ILR in patients with and without SHD[9, 10]. Considering the nature of the underlying disease, we hypothesized that patients with SHD/IPAS would have a higher incidence of ventricular arrhythmias than patients without an underlying heart disease. The purpose of the present study was to evaluate diagnostic yield, arrhythmia mechanism and subsequent arrhythmia management in patients with and without SHD/IPAS receiving an ILR.

Methods

Study population

This observational cohort study involved consecutive patients who received an insertable ILR (Reveal LINQ, Medtronic Inc., Minneapolis, MN, USA) between March 2013 and December 2016 at our institution. The indication for the ILR was established by the treating physician and all patients gave informed consent for the implantation procedure. There were no patients who received an ILR for cryptogenic stroke. Patients with SHD included those with manifest heart disease at potential risk of arrhythmias including patients with coronary artery disease, inherited cardiomyopathy, infiltrative cardiomyopathy and congenital heart disease. Patients with IPAS included those with long QT syndrome, Brugada syndrome, catecholaminergic polymorphic VT. Carriers of a pathogenic mutation associated with cardiomyopathy or IPAS were also considered part of either the SHD or IPAS group.

ILR implantation and follow-up

ILR implantation was performed as recommended by the manufacturer using the incision and insertion tool. The device was implanted subcutaneously over the fourth intercostal space on the left hemithorax, either 45° or parallel relative to the sternal border. The incision was usually closed with one braided absorbable suture. After implantation, the patient received the remote monitoring device, as well as instructions about its use for nightly automated transmissions. Patients were discharged at the same day of implantation. Programming was optimized to maintain a high specificity, at the cost of sensitivity: detection of bradycardia (30 beats per minute; 8 beats), pause (4.5 seconds), and tachycardia (176 beats

per minute; 16 beats). Atrial fibrillation (AF) detection was set to '*AF only*'. All devices were linked to the CareLink network for remote monitoring and all episodes (automatically recorded or patient-activated episodes) were transmitted on a daily basis.

Ten days after implantation the patients were scheduled at the out-patient clinic to check their wound and interrogate their device. After this visit, patients were seen at the out-patient clinic every 6 months or earlier when necessary based on the transmitted episodes. The diagnosis was called ILR-guided if a symptom-rhythm correlation was established and/or if a VT was observed.

Statistical analysis

Continuous data are presented as mean ± standard deviation if the data were normally distributed, or as median with interquartile range (25th and 75th percentile) otherwise. Categorical variables are presented by frequencies and percentages. Differences of continuous variables between groups were analyzed with the unpaired Student's t-test or the Kruskal Wallis test, as appropriate. Differences between categorical variables were evaluated using the Chi-square test. In the case of a statistical difference between groups, posthoc pairwise analysis were performed. Event rates were estimated with the Kaplan Meier method, and differences between event rates were compared by log-rank test. Paired comparisons were made using Cox regression analysis and described with hazard ratios and 95% confidence intervals. A P-value <0.05 was considered statistically significant. Statistical analyses were performed using SPSS version 21.

Results

Between March 2013 and December 2016, a total of 94 patients underwent an ILR implantation. There were 20 patients (21%) with SHD and 14 patients (15%) with IPAS. Figure 1 provides an overview of the different underlying diagnosis in patients with SHD/IPAS. Except a higher proportion of PCI in the SHD group, there were no differences in baseline characteristics between groups (Table 1). It is also important to note that the presenting symptoms were similar between groups.

During a median follow up of 10 months (interquartile range, 3-17 months), 42 patients (45%) had an ILR-guided diagnosis. The diagnostic yield was different between groups (Figure 2, Table 2). When performing pairwise comparisons, patients with IPAS had a lower diagnostic yield in comparison to patients with SHD (P=0.01) or patients without SHD/IPAS (P=0.03). Although patients with SHD and patients without SHD/IPAS had a similar diagnostic yield, the arrhythmia mechanism was different. Using pairwise comparison, patients with SHD had a higher incidence of nonsustained VT in comparison to patients without SHD/IPAS (P<0.01).

Although there was a difference in the ILR-documented arrhythmia mechanism, the ILR-based therapy was similar between groups (Table 3). Most patients received antiarrhythmic drug therapy or had their antiarrhythmic drug dose increased. A high proportion (10%) of patients in the SHD group received an ICD, however, this was not statistically significant higher than the other groups.

Figure 1. Overview of patients with structural heart disease or inherited primary arrhythmia syndrome. Abbreviations: LQTS, long QT syndrome; CPVT, catecholaminergic polymorphic ventricular tachycardia.

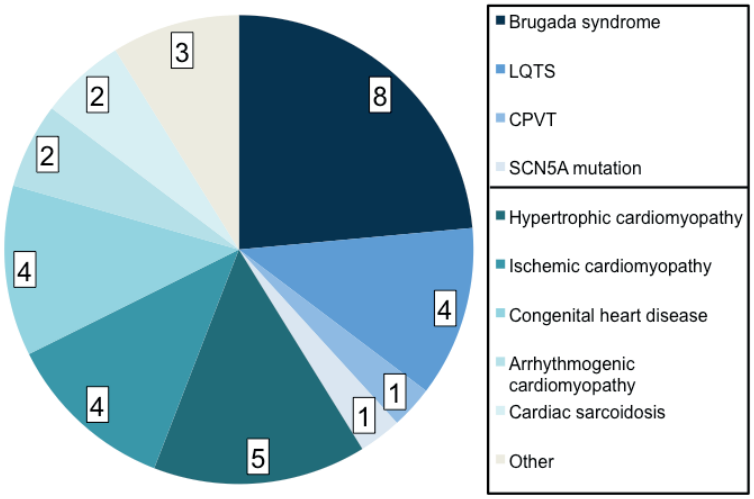

Table 1. Baseline characteristics

Variable	No SHD/IPAS N=60	SHD N=20	IPAS N=14	P-value
Demographics:				
- Age (years), mean ± SD	44 ± 17	47 ± 21	47 ± 11	0.73
- Female gender, n (%)	36 (60)	10 (50)	8 (57)	0.74
Symptoms:				
- (Near) syncope, n (%)	47 (78)	14 (70)	10 (71)	0.71
- Palpitations, n (%)	40 (67)	10 (50)	6 (43)	0.17
- Asymptomatic, n (%)	-	1 (5)	1 (7)	0.15
Co-morbidity:				
- Hypertension, n (%)	6 (10)	4 (20)	3 (21)	0.37
- Hypercholesterolemia, n (%)	8 (13)	2 (10)	1 (7)	0.79
- Diabetes mellitus, n (%)	5 (8)	1 (5)	-	0.51
- Transient ischemic attack, n (%)	4 (7)	1 (5)	-	0.61
- Stroke, n (%)	2 (3)	2 (10)	-	0.11
- Epilepsy, n (%)	2 (3)	-	2 (14)	0.11
- Renal disease, n (%)	-	1 (5)	-	0.16
- Prior PCI, n (%)	-	3 (15)	-	<0.01
- Prior CABG, n (%)	-	1 (5)	-	0.16

Abbreviations: CABG, coronary artery bypass graft; PCI, percutaneous coronary intervention.

Figure 2. Cumulative event rate for ILR-guided diagnosis

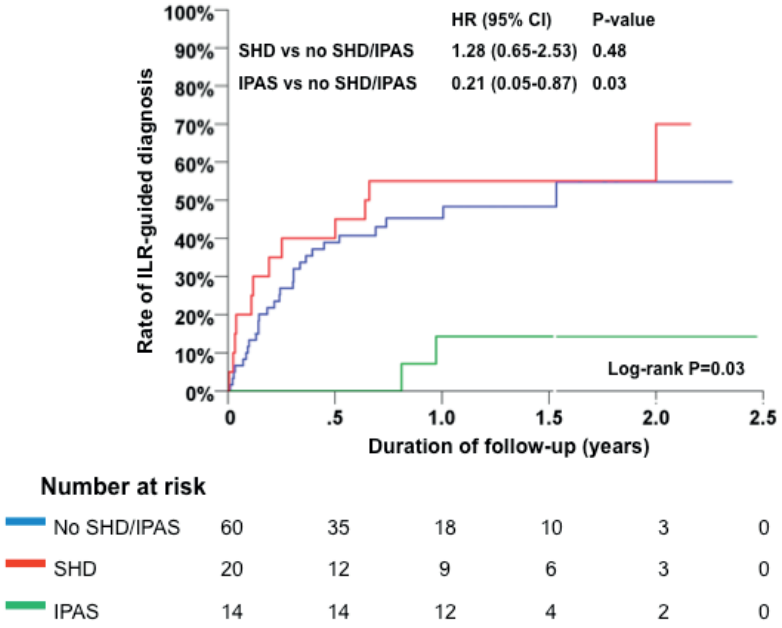

Table 2. ILR-guided arrhythmia diagnosis

Diagnosis	No SHD/IPAS N=60	SHD N=20	IPAS N=14	P-value
Any arrhythmia diagnosis, n (%)	28 (47)	12 (60)	2 (14)	0.03
- Sinus arrest, n (%)	6 (10)	1 (5)	1 (7)	0.77
- Paroxysmal AV block, n (%)	1 (2)	1 (5)	-	0.56
- Sinus bradycardia, * n (%)	2 (3)	-	-	0.56
- Progressive ST, n (%)	2 (3)	-	-	0.56
- Atrial fibrillation, n (%)	4 (7)	-	-	0.31
- SVT, n (%)	9 (15)	2 (10)	-	0.28
- Nonsustained VT, n (%)	2 (3)	6 (30)	1 (7)	<0.01
- Sustained VT, n (%)	2 (3)	2 (10)	-	0.31
No arrhythmia diagnosis, n (%)	32 (53)	8 (40)	12 (86)	0.03

Abbreviations: AV, atrioventricular; ST, sinus tachycardia; SVT, supraventricular tachycardia; VT, ventricular tachycardia.
* <40 bpm for more than 10 seconds.

Table 3. ILR-based therapy

Therapy	No SHD/IPAS N=60	SHD N=20	IPAS N=14	P-value
Antiarrhythmic drug therapy, n (%)	9 (15)	7 (35)	2 (14)	0.14
Pacemaker, n (%)	9 (15)	3 (15)	-	0.31
Catheter ablation, n (%)	8 (13)	1 (5)	-	0.24
ICD, n (%)	2 (3)	2 (10)	-	0.08

Abbreviations: ICD, implantable cardioverter-defibrillator.

Four patients received an ICD, two of them had SHD. One patient with recurrent syncope and coronary artery disease with preserved ejection fraction received an ICD for sustained monomorphic fast VT. Another patient with hypertrophic obstructive cardiomyopathy received an ICD after experiencing non-sustained VT, which increased his estimated 5-years risk of SCD from 3.6% to 8.0%. Furthermore, 2 patients without SHD/IPAS received an ICD. One woman received an ICD for syncope and sustained monomorphic fast VT and another woman received an ICD after syncope and non-sustained polymorphic fast VT. No patient died suddenly during the study period.

Discussion

The present study demonstrates that ILR patients with SHD have a higher incidence of nonsustained ventricular arrhythmias. However, there was only a trend towards a higher proportion of patients receiving an ICD in the SHD group in comparison to the other groups.

Studies which evaluated the performance of the ILR demonstrated a wide diagnostic yield ranging from 22% to 73% depending on the primary indication of the ILR[1, 3]. The diagnostic yield seems lower in patients with recurrent unexplained syncope than in patients with undocumented palpitations. Overall, the diagnostic yield in our study population was 45%, however, patients with IPAS had a lower diagnostic yield. The diagnostic yield in patients with and without SHD (60% versus 47%) was similar in our study. A previous Austrian prospective ILR study in 70 patients with unexplained syncope (including 33 patients with SHD) found a similar diagnostic yield between patients with and without SHD (45% and 51%, respectively)[9].

Patients with SHD in our study experienced a high incidence of nonsustained ventricular arrhythmias, which is not surprising considering their predisposition to ventricular arrhythmias. A previous Italian ILR study in 103 patients with unexplained syncope (including 38 patients with SHD) also found a difference in arrhythmia mechanism between patients with and without SHD[10]. Patients with SHD were more likely to have paroxysmal/persistent AV block and tachyarrhythmias in comparison to patients without SHD. The incidence of ventricular arrhythmias was 5% in patients with SHD and 0% in patients without SHD[10]. Surprisingly, the incidence of ventricular arrhythmias in our IPAS group was low. This may be related to a lower threshold to implant an ILR in IPAS patients.

Although recurrent unexplained syncope is an established indication for an ILR, a rather novel indication is the use of an ILR for risk stratification[6, 7]. An EHRA survey demonstrated that 19% of centers use ILRs in patients with borderline indications for ICD therapy[5]. Currently, the ILR does not play a major role in the current guidelines on the prevention of SCD[11]. In the most recent guidelines, ILRs are recommended after comprehensive diagnostic evaluation when symptoms (e.g. syncope) are sporadic and suspected to be related to arrhythmias[11]. In some patients with SHD/IPAS, individual risk stratification can be difficult due to atypical symptoms. In these patients, long-term monitoring by an ILR may provide valuable information by the documentation of ventricular arrhythmias. Furthermore, it might also provide reassurance in these patients when they know that their symptoms are not related to ventricular arrhythmias. Considering the fact that a purely diagnostic tool is implanted in patients at risk for VTs, it is of importance to be alerted of a potential life-threatening episode as soon as possible. This is possible due to the availability of daily remote transmissions lowering the delay to medical intervention. No patient in our study died suddenly.

Several small ILR studies in patients with SHD or IPAS demonstrated that the proportion of ILR patients that received an ICD varies. Based on the available literature, no ILR patient with Brugada syndrome[12-14], long QT syndrome[15, 16], hypertrophic cardiomyopathy[9], or noncompaction cardiomyopathy[17] received an ICD during follow-up. In contrast, ICDs were implanted, based on the findings of the ILR, in patients with catecholaminergic polymorphic VT (11%)[15], congenital heart disease (0-9%)[16, 18, 19], Fabry cardiomyopathy (25%)[20], and SHD (0-28%)[9, 10, 21]. In our study, 10% of the SHD cohort received an ICD. Abovementioned data supports the use of ILRs in symptomatic patients with SHD for early detection of ventricular arrhythmias.

Study limitations

The present study is small and the patient population is highly selected, thereby limiting generalizability of the data. Furthermore, the lack of a control group (close follow-up with repeated ambulatory Holter monitoring) hampers conclusions on the incremental benefit of an ILR in comparison to alternative methods of monitoring. Therefore, all conclusions of the present study must be drawn with caution.

References

1. Edvardsson N, Frykman V, van Mechelen R, Mitro P, Mohii-Oskarsson A, Pasquie JL, Ramanna H, Schwertfeger F, Ventura R, Voulgaraki D, Garutti C, Stolt P, Linker NJ and Investigators PS. Use of an implantable loop recorder to increase the diagnostic yield in unexplained syncope: results from the PICTURE registry. *Europace*. 2011;13:262-9.
2. Farwell DJ, Freemantle N and Sulke N. The clinical impact of implantable loop recorders in patients with syncope. *Eur Heart J*. 2006;27:351-6.
3. Giada F, Gulizia M, Francese M, Croci F, Santangelo L, Santomauro M, Occhetta E, Menozzi C and Raviele A. Recurrent unexplained palpitations (RUP) study comparison of implantable loop recorder versus conventional diagnostic strategy. *J Am Coll Cardiol*. 2007;49:1951-6.
4. Sanna T, Diener HC, Passman RS, Di Lazzaro V, Bernstein RA, Morillo CA, Rymer MM, Thijs V, Rogers T, Beckers F, Lindborg K, Brachmann J and Investigators CA. Cryptogenic stroke and underlying atrial fibrillation. *N Engl J Med*. 2014;370:2478-86.
5. Proclemer A, Lewalter T, Bongiorni MG, Svendsen JH, Pison L, Lundqvist CB and Scientific Initiative Committee EHRA. Screening and risk evaluation for sudden cardiac death in ischaemic and non-ischaemic cardiomyopathy: results of the European Heart Rhythm Association survey. *Europace*. 2013;15:1059-62.
6. Task Force m, Brignole M, Vardas P, Hoffman E, Huikuri H, Moya A, Ricci R, Sulke N, Wieling W, Committee ESD, Auricchio A, Lip GY, Almendral J, Kirchhof P, Aliot E, Gasparini M, Braunschweig F, Document R, Lip GY, Almendral J, Kirchhof P, Botto GL and Committee ESD. Indications for the use of diagnostic implantable and external ECG loop recorders. *Europace*. 2009;11:671-87.
7. Task Force for the D, Management of S, European Society of C, European Heart Rhythm A, Heart Failure A, Heart Rhythm S, Moya A, Sutton R, Ammirati F, Blanc JJ, Brignole M, Dahm JB, Deharo JC, Gajek J, Gjesdal K, Krahn A, Massin M, Pepi M, Pezawas T, Ruiz Granell R, Sarasin F, Ungar A, van Dijk JG, Walma EP and Wieling W. Guidelines for the diagnosis and management of syncope (version 2009). *Eur Heart J*. 2009;30:2631-71.
8. Antzelevitch C, Yan GX, Ackerman MJ, Borggrefe M, Corrado D, Guo J, Gussak I, Hasdemir C, Horie M, Huikuri H, Ma C, Morita H, Nam GB, Sacher F, Shimizu W, Viskin S and Wilde AAM. J-Wave syndromes expert consensus conference report: Emerging concepts and gaps in knowledge. *Europace*. 2017;19:665-694.
9. Pezawas T, Stix G, Kastner J, Schneider B, Wolzt M and Schmidinger H. Implantable loop recorder in unexplained syncope: classification, mechanism, transient loss of consciousness and role of major depressive disorder in patients with and without structural heart disease. *Heart*. 2008;94:e17.
10. Solano A, Menozzi C, Maggi R, Donateo P, Bottoni N, Lolli G, Tomasi C, Croci F, Oddone D, Puggioni E and Brignole M. Incidence, diagnostic yield and safety of the implantable loop-recorder to detect the mechanism of syncope in patients with and without structural heart disease. *Eur Heart J*. 2004;25:1116-9.
11. Priori SG, Blomstrom-Lundqvist C, Mazzanti A, Blom N, Borggrefe M, Camm J, Elliott PM, Fitzsimons D, Hatala R, Hindricks G, Kirchhof P, Kjeldsen K, Kuck KH, Hernandez-Madrid A, Nikolaou N, Norekval TM, Spaulding C and Van Veldhuisen DJ. 2015 ESC Guidelines for the management of patients with ventricular arrhythmias and the prevention of sudden cardiac death: The Task Force for the Management of Patients with Ventricular Arrhythmias and the Prevention of Sudden Cardiac Death of the European Society of Cardiology (ESC). Endorsed by: Association for European Paediatric and Congenital Cardiology (AEPC). *Eur Heart J*. 2015;36:2793-867.

12. Champagne J, Philippon F, Gilbert M, Molin F, Blier L, Nault I, Sarrazin JF, Charbonneau L, Dufort L, Drolet B, Chahine M and O'Hara GE. The Brugada syndrome in Canada: a unique French-Canadian experience. *Can J Cardiol*. 2007;23 Suppl B:71B-75B.
13. Kubala M, Aissou L, Traulle S, Gugenheim AL and Hermida JS. Use of implantable loop recorders in patients with Brugada syndrome and suspected risk of ventricular arrhythmia. *Europace*. 2012;14:898-902.
14. Sacher F, Arsac F, Wilton SB, Derval N, Denis A, de Guillebon M, Ramoul K, Bordachar P, Ritter P, Hocini M, Clementy J, Jais P and Haissaguerre M. Syncope in Brugada syndrome patients: prevalence, characteristics, and outcome. *Heart Rhythm*. 2012;9:1272-9.
15. Avari Silva JN, Bromberg BI, Emge FK, Bowman TM and Van Hare GF. Implantable Loop Recorder Monitoring for Refining Management of Children With Inherited Arrhythmia Syndromes. *J Am Heart Assoc*. 2016;5.
16. Frangini PA, Cecchin F, Jordao L, Martuscello M, Alexander ME, Triedman JK, Walsh EP and Berul CI. How revealing are insertable loop recorders in pediatrics? *Pacing Clin Electrophysiol*. 2008;31:338-43.
17. Stollberger C, Keller H, Steger C and Finsterer J. Implantable loop-recorders in myopathic and non-myopathic patients with left ventricular hypertrabeculation/noncompaction. *Int J Cardiol*. 2013;163:146-8.
18. Kenny D, Chakrabarti S, Ranasinghe A, Chambers A, Martin R and Stuart G. Single-centre use of implantable loop recorders in patients with congenital heart disease. *Europace*. 2009;11:303-7.
19. Sanatani S, Peirone A, Chiu C, Human DG, Gross GJ and Hamilton RM. Use of an implantable loop recorder in the evaluation of children with congenital heart disease. *Am Heart J*. 2002;143:366-72.
20. Weidemann F, Maier SK, Stork S, Brunner T, Liu D, Hu K, Seydelmann N, Schneider A, Becher J, Canan-Kuhl S, Blaschke D, Bijnens B, Ertl G, Wanner C and Nordbeck P. Usefulness of an Implantable Loop Recorder to Detect Clinically Relevant Arrhythmias in Patients With Advanced Fabry Cardiomyopathy. *Am J Cardiol*. 2016;118:264-74.
21. Schernthaner C, Danmayr F, Altenberger J, Pichler M and Strohmer B. High incidence of tachyarrhythmias detected by an implantable loop recorder in patients with unexplained syncope. *Kardiol Pol*. 2008;66:37-44; discussion 45-6.

CHAPTER 4

Early Detection of Ventricular Arrhythmias in adults with Congenital Heart Disease using an insertable cardiac monitor (EDVA-CHD study)

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International Journal of Cardiology. 2020 Apr 15;305:63-69

Abstract

Background: Sudden cardiac death (SCD) due to ventricular arrhythmias (VA) is an important mode of death in adults with congenital heart disease (CHD). Risk stratification is difficult in this heterogenous population. Insertable cardiac monitors (ICM) may be useful for risk stratification. Our purpose was to evaluate the use of ICM for the detection of VA in adults with CHD.

Methods: In this prospective single-center observational study we included consecutive adults with CHD deemed at risk of VA who received an ICM between March 2013 and February 2019. The decision to implant an ICM was made in a Heart Team consisting of a cardiac electrophysiologist and a cardiologist specialized in CHD.

Results: A total of 30 patients (mean age, 38 ± 15 years; 50% male) received an ICM. During a median follow-up of 16 months, 8 patients (27%) had documented nonsustained VA. Of these 8 patients, 3 (10%) received a prophylactic ICD. Furthermore, ICM-detected arrhythmias were present in 22 patients (73%) leading to a change in clinical management in 16 patients (53%). Besides the patients receiving an ICD, 10 patients (33%) had a change in their antiarrhythmic drugs, 6 patients (20%) underwent an electrophysiology study, and 1 patient (3%) received a pacemaker.

Conclusions: The detection of VA by the ICM contributed to the clinical decision to implant a prophylactic ICD. Furthermore, ICM-detected arrhythmias led to important changes in the clinical management. Therefore, long-term arrhythmia monitoring by an ICM seems valuable for risk stratification in adults with CHD.

Introduction

Sudden cardiac death (SCD) is an important mode of death in adults with congenital heart disease (CHD) and is mainly driven by ventricular arrhythmias (VA)[1-4]. Identification of patients with CHD at risk for VA is important to determine which patients may benefit from a prophylactic implantable cardioverter-defibrillator (ICD). Risk stratification is hampered by the low predictive value of clinical risk factors[5]. This is not surprising considering Bayes theorem and the low absolute incidence of SCD in adults with CHD[6]. For patients with tetralogy of Fallot there is some guidance on selecting patients for a prophylactic ICD[7, 8]. In other CHD lesions, the decision is challenging and the indication for an ICD is largely based on systemic ventricular dysfunction, syncope and/or documented VA. The decision to implant an ICD is also hampered by potential ICD complications, such as shocks, device or lead malfunction, inappropriate shocks, and psychological burden[9-11].

Considering the clinical relevance of documented VA for risk stratification, we adopted a strategy focusing on early detection of VA using insertable/implantable cardiac monitors (ICMs). ICM-detected VA may provide a tipping point in decision-making in patients who are considered at risk of SCD but who do not qualify for an ICD according to current guidelines. Long-term arrhythmia monitoring using ICMs already have an established role in patients with recurrent syncope[12]. In the most recent ESC Syncope guidelines there is an expanding role for ICMs for risk stratification in patients with primary cardiomyopathy or inheritable arrhythmogenic disorders, but not for patients with CHD[13]. The purpose of the present study was to evaluate the strategy of using ICMs for the early detection of VA in adults with CHD who are deemed at risk of VA based on their clinical profile.

Methods

Study design

The *Early Detection of Ventricular Arrhythmias in adults with Congenital Heart Disease using an insertable cardiac monitor* (EDVA-CHD) study is a prospective observational study which included consecutive adults with CHD who received an ICM between March 2013 and February 2019. The starting date was chosen based on the availability of the Reveal LINQ (Medtronic Inc., Minneapolis, MN, USA) in our center. Patients who were deemed to be at risk of VA by their treating physician were eligible for an ICM. The reason for monitoring could be a combination of symptoms (e.g., (near)syncope, palpitations), prior nonsustained VA, wide QRS, and/or systemic ventricular dysfunction. The decision to implant an ICM was made in a Heart Team consisting of at least a cardiac electrophysiologist and a cardiologist specialized in CHD. The study was approved by the institutional review board of the Erasmus Medical Center. Our center is a tertiary referral center with the largest population of adults with CHD in the Netherlands.

Device programming and follow-up

All ICMs were implanted subcutaneously as recommended by the manufacturer using the incision and insertion tool. Furthermore, all patients received a handheld activator to indicate their symptoms when necessary. The ICM was usually programmed according to local settings: tachycardia-detection was set to 176 bpm for 16 beats; bradycardia-setting to 30 bpm for 8 beats; pause-setting to 4.5 sec; and atrial fibrillation (AF) setting to 'AF only'. Based on the implanting physician preferences other settings could be programmed. All devices were connected to the Medtronic CareLink network for remote monitoring. Patients were discharged on the same day of implantation. Ten days after implantation the patients were seen at the out-patient clinic to check their wound and to interrogate the ICM. Afterwards, the patients were seen regularly at the outpatient clinic according to routine patient care. ICM check-ups were performed at the outpatient clinic every 6 months or earlier when necessary based on symptoms or transmitted episodes. Remote monitoring was performed on a daily basis during weekdays.

Classification of episodes and endpoints

All patient activated episodes and automatically detected episodes were classified. In the case of an inappropriate automatically detected episode, the cause of inappropriate detection was specified, if possible.

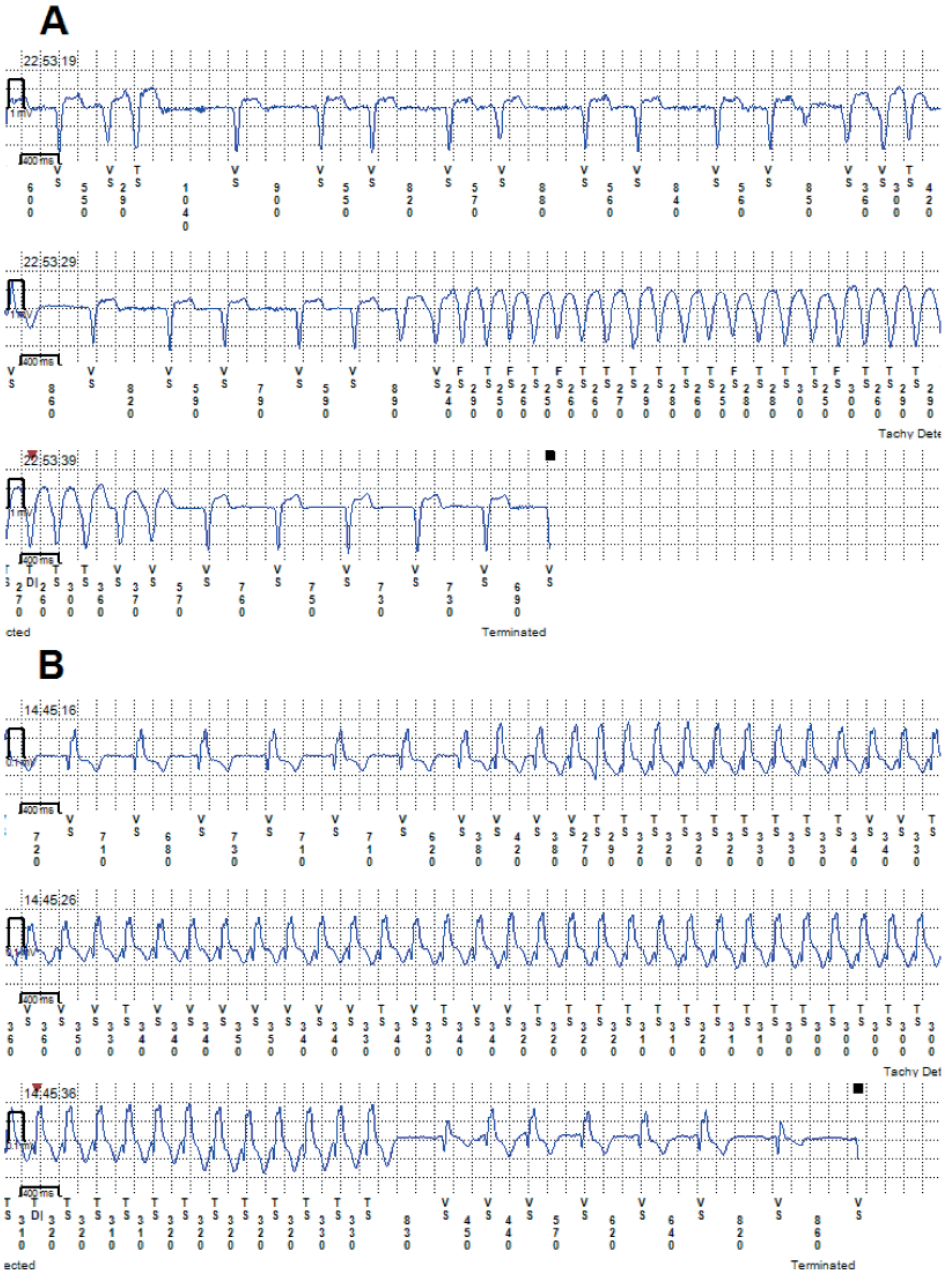
The primary endpoint of the present study was the occurrence of VA. A regular broad complex tachycardia was considered a VA if there was a sudden onset and a change in the QRS morphology in comparison to the baseline rhythm (Figure 1A). An irregular broad complex tachycardia was considered a VA if there was a sudden onset and a polymorphic QRS morphology. A regular broad or small complex tachycardia was considered a supraventricular tachycardia (SVT) if there was a sudden onset and no change in QRS morphology (Figure 1B). In the case of doubt, a second electrophysiologist was consulted for the final diagnosis.

The secondary endpoint was the occurrence of other arrhythmias during follow-up. Finally, it was established whether a detected arrhythmia resulted in a change in patient management ('actionable event').

Statistical analysis

Continuous data are presented as mean ± standard deviation or as median with corresponding 25^{th} and 75^{th} percentile, as appropriate. Categorical variables are presented by frequencies and percentages. Statistical analyses were performed using SPSS version 21.

Figure 1. Example ICM-detected episode of (A) ventricular tachycardia, (B) supraventricular tachycardia with pre-existing intraventricular conduction delay.



Results

Study population

A total of 30 CHD patients (mean age, 38 ± 15 years; 50% male) received an ICM during the study period. Baseline characteristics of the study population are listed in Table 1. The majority of patients had moderate or severe complexity CHD. The 3 most common diagnoses were aortic coarctation, tetralogy of Fallot (TOF) and d-transposition of the great arteries (d-TGA). The majority of patients had symptoms at the time of ICM implantation (93%). An impaired systemic ventricular function was present in 17 patients (57%). A previous nonsustained VA was documented in 20% of the study population. A detailed patient-level description of CHD diagnosis, previous cardiac surgery, and reason for ICM is presented in Appendix A. There were no ICM- or procedure-related complications.

Table 1. Clinical baseline characteristics

	Total group (n=30)
Age, years	38 ± 15
Gender, male	15 (50%)
Hypertension	8 (27%)
Diabetes Mellitus	1 (3%)
Surgical repair	25 (83%)
Symptoms	
- Palpitations	12 (40%)
- (near) Syncope	10 (33%)
- Palpitations and (near) syncope	6 (20%)
- Asymptomatic	2 (7%)
Congenital diagnosis	
- Aortic coarctation	7 (23%)
AVR	3 (10%)
- Tetralogy of Fallot	5 (17%)
Transannular patch	2 (7%)
- ASD	5 (17%)
Direct surgical closure of ASD	3 (10%)
- TGA corrected by atrial switch	2 (7%)
Mustard repair	1 (7%)
- TGA corrected by arterial switch	2 (7%)
- Congenital corrected TGA	2 (7%)
Tricuspid valvuloplasty	1 (3%)
- VSD	2 (7%)
VSD patch	2 (7%)
- Other	5 (17%)

Systemic systolic ventricular function	
- Normal (EF ≥55%)	13 (43%)
- Mild impaired (EF 54-45%)	10 (33%)
- Moderate impaired (EF 36-44%)	7 (23%)
Electrocardiography	
- Sinus rhythm	27 (90%)
- Other rhythm	3 (10%)
- PR interval, if sinus rhythm, ms	180 ± 49
- QRS duration, ms	136 ± 31
- QRS duration >120ms	17 (57%)
24-48h Holter monitoring	
- <1% PVCs	25 (83%)
- 1-10% PVCs	1 (3%)
- Non-sustained VT	6 (20%)
- Supra ventricular tachycardia	2 (7%)
Cardiac medication	19 (63%)
- ACE-inhibitor/ ARB	8 (27%)
- Diuretics	3 (10%)
- Beta blocker	11 (37%)
- Amiodarone/Sotalol/Digoxin	3 (10%)
- Digoxin/calcium channel blocker	3 (10%)
- Oral anticoagulants	6 (23%)

Data is presented as n (%), mean ± SD. Abbreviations: AVR, aortic valve replacement; ASD, atrial septal defect; TGA, transposition of the great arteries; VSD, ventricle septal defect; EF, ejection fraction; PVC, premature ventricular complex; VT, ventricular tachycardia; ACE, angiotensin converting enzyme; ARB, angiotensin receptor blocker.

ICM-detected episodes

During a median follow-up of 16 months (interquartile range 9-21 months), a total of 1,689 episodes were transmitted to the CareLink network system (Table 2). There were 538 (32%) patient-activated episodes and 1,151 (68%) automatically detected episodes. The majority of patient-activated episodes (88%) comprised sinus rhythm with or without ectopy, thus, only 12% of patient-activated episodes comprised a significant arrhythmia (Table 2).

Table 2. Overview ICM-detected arrhythmia episodes

	Total episodes (n=1689)
Symptom episode*	**538 (32%)**
- Sinus rhythm	473 (88%)
without ectopy	314 (58%)
with PACs	19 (4%)
with PVCs	140 (26%)
- Atrial fibrillation	33 (6%)
- Regular small complex tachycardia	12 (2%)
- Regular broad complex tachycardia	20 (4%)
Tachy episode*	**666 (39%)**
- Sinus rhythm	510 (77%)
without ectopy	268 (40%)
with PACs	20 (3%)
with PVCs	214 (32%)
with noise	8 (1%)
- Atrial fibrillation	8 (1%)
- Regular small complex tachycardia	118 (18%)
- Regular broad complex tachycardia	30 (5%)
AF episode*	**213 (13%)**
- Sinus rhythm	18 (9%)
with PACs	2 (<1%)
with PVCs	16 (8%)
- Atrial fibrillation	180 (85%)
- Small complex tachycardia	15 (7%)
with intermittent AV-block	15 (7%)
Brady episode*	**147 (9%)**
- Sinus rhythm	41(28%)
with undersensing of PVCs	41(28%)
- Sinus bradycardia	103 (70%)
- AV block	3 (2%)
Pause episode*	**108 (6%)**
- Sinus rhythm	63 (58%)
with sudden drop of R-wave	28 (26%)
with small R-waves	17 (16%)
with undersensing of PVCs	15 (14%)
with loss of contact	3 (3%)
- Sinus bradycardia	29 (27%)

- AV block	3 (3%)
- Sinus arrest or SA block	13 (12%)
AT episodes*	**17 (1%)**
- Atrial fibrillation	10 (59%)
- Sinus tachycardia	5 (29%)
- Regular small complex tachycardia	2 (12%)

Data is presented as n (%). * Episode classification by ICM. Abbreviations: ICM, insertable cardiac monitor; PAC, premature atrial complex; AF, atrial fibrillation; AV, atrioventricular; SA, sinoatrial; AT, atrial tachycardia; other abbreviations as defined by Table 1.

Primary and secondary endpoints

During follow-up, 8 patients (27%) developed nonsustained VA. Four of 8 patients (50%) had a history of nonsustained VA, thus 4 patients (13%) had a de novo nonsustained VA and 4 patients (13%) had recurrent nonsustained VA. In 7 of 8 patients (88%) the VA episodes were detected by patient-activated episodes. Most patients had monomorphic VA episodes and 1 patient experienced polymorphic VA episodes. Of the 8 patients with VA, 3 patients had an impaired systemic ventricular function. Of the 8 patients with VA, 3 patients received a prophylactic ICD after consultation with their treating physician and 3 patients had a change in their antiarrhythmic drug therapy. The remaining 2 patients did not have a change in their clinical management.

A 19-year-old man with surgical corrected Shone's complex (coarctation resection, subvalvular aortic membrane resection, mitral valve and aortic valve replacement) received a dual-chamber ICD after detection of recurrent symptomatic nonsustained fast polymorphic VA (mean CL 240-270 ms, maximal 7 beats) 3 months post-ICM implantation. He received an ICM due to combination of palpitations, exercise-induced ventricular ectopy, signs of inferior wall infarction and mild impaired systemic ventricular function. After ICD implantation, he experienced two episodes of nonsustained fast polymorphic VA without ICD therapy during a follow-up of 17 months.

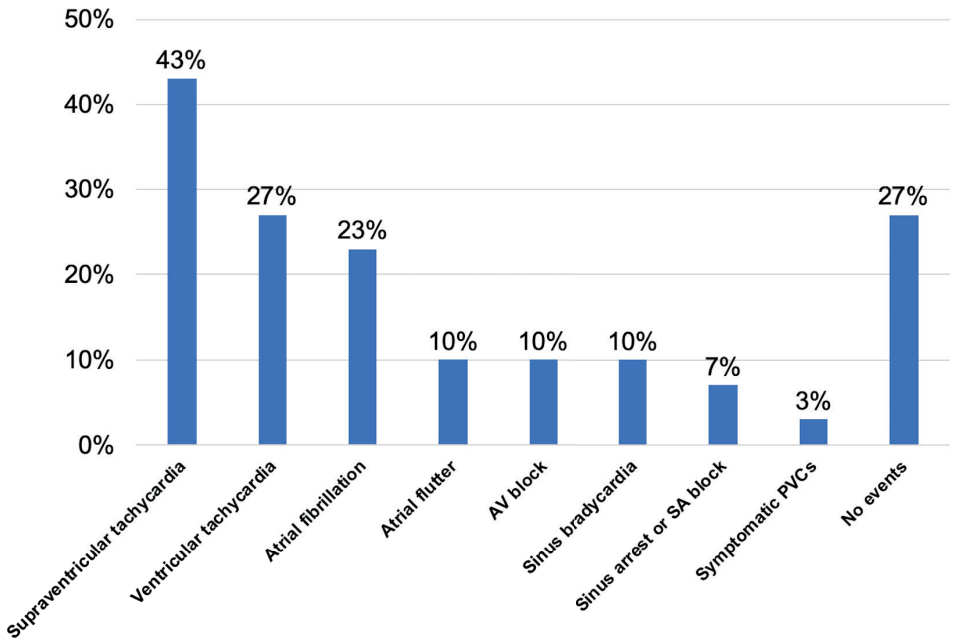
The second patient who received a dual-chamber ICD was a 42-year-old woman with surgical corrected TOF who experienced recurrent symptomatic nonsustained monomorphic VA (mean CL 490-520 ms, maximal 11 beats) 3 months post-ICM implantation. She received an ICM for the combination of palpitations and near-syncope. She did not experience VA post-ICD implantation during a follow-up of 27 months.

The last patient who received a dual-chamber ICD was a 44-year-old man with congenital corrected transposition of the great arteries and tricuspid valvuloplasty who developed an asymptomatic nonsustained fast monomorphic VA (mean CL 280 ms, 27 beats) 18 months post-ICM implantation (Figure 1A). He received an ICM for a combination of syncope and dilated systemic ventricle with moderate-to-severe systolic ventricular dysfunction. During a follow-up of 12 months post-ICD implantation he experienced one episode of nonsustained fast monomorphic VA without ICD therapy.

Any significant arrhythmia was detected in 22 patients (73%). Figure 2 shows the proportion of patients with a specific arrhythmia and Appendix A provides an overview of detected arrhythmias per

patient. In 16 patients (53%) the detected arrhythmia was considered an actionable event. Management included initiation or change of antiarrhythmic drug therapy (n=10, 33%), electrophysiology study (n=6, 20%), ICD implantation (n=3, 10%), electrical cardioversion (n=2, 7%), and pacemaker implantation (n=1, 3%).

Figure 2. Proportion of patients with an ICM-detected arrhythmia.



Discussion

The incidence of ICM-detected VA in a selected CHD population was relatively high (27%). The ICM-detected VA contributed to the decision to implant a prophylactic ICD in 10% of the study population. Furthermore, the detection of other arrhythmias by the ICM resulted in a significant change in clinical management in a majority of patients. The present study is the first prospective study focusing specifically on the use of an ICM for risk stratification in adults with CHD.

Risk of sudden death

Although the risk of SCD is higher in patients with CHD than in the general population, the absolute risk is still relatively low (approximately 0.1% per year)[3]. This has stimulated the search for risk factors

which may help identify patients at risk for SCD, who may benefit from a prophylactic ICD implantation. Important risk factors for SCD include among others (recurrent) (non)sustained VA, inducible VA, atrial tachyarrhythmias, prolonged QRS duration, systemic ventricular dysfunction, and subpulmonary ventricular dysfunction[4, 14-17]. Despite the multitude of identified risk factors, the indication for ICD implantation remains challenging in clinical practice, especially regarding the potential downside of ICD therapy[9-11]. Furthermore, risk stratification is not uniform for the CHD population. For example, inducible sustained VA during programmed ventricular stimulation is useful for risk stratification in patients with TOF[7, 8], but has not been demonstrated to predict VA/SCD in other CHD populations[18].

Risk stratification using ICM

In patients with certain high-risk features presenting with symptoms (i.e., syncope, near-syncope, palpitations), it is of importance for both patients and caregivers to rule out VA. This can be attempted using short-term monitoring, however, when symptoms are infrequent longer arrhythmia monitoring is necessary. For this purpose, an ICM is a valuable diagnostic tool for detecting paroxysmal arrhythmias as well as establishing a symptom-rhythm correlation. We provide data on the diagnostic yield of an ICM in a selected adult CHD population deemed at risk for VA. The incidence of VA was high in this population and resulted in implantation of an ICD for primary prevention in 10% of the study population. This is slightly higher than previous retrospective studies in patients with CHD who received an ICM[19, 20]. These studies focused on the overall diagnostic yield of an ICM and not specifically on the role of an ICM for risk stratification. Kenny et al. described the diagnostic outcome of an ICM (Reveal or Reveal Plus, Medtronic Inc., Minneapolis, MN, USA) in a predominantly pediatric CHD population (median age 15 years)[20]. In this study, 1 of 18 patients (6%) received an ICD during a median follow-up of 19 months. The patient who received an ICD was known with Ebstein's anomaly and developed monomorphic VA at the age of 16 years. A more recent retrospective study from Boston Children's Hospital included 34 patients with CHD and an ICM (Reveal LINQ, Medtronic Inc., Minneapolis, MN, USA)[19]. In this study, 1 of 34 patients (3%) received an ICD during a median duration of follow-up of 11.8 months. The patient who received an ICD was a patient with Fontan circulation who received an ICM at the age of 32 years. Other series reporting the use of ICM in patients with CDH are smaller and mostly performed in a pediatric population[21-28].

Cost-benefit of ICMs for risk stratification

Besides the use of an ICM for risk stratification, the ICM detected a significant arrhythmia in 73% of the population and this led to a change in clinical management in 53% of patients. Therefore, an ICM can be used to titrate medication and identify candidates for an electrophysiologic procedure (i.e., pacemaker, ICD or electrophysiological study). An important aspect is the ability to differentiate between benign (near)syncope and arrhythmogenic (near)syncope. Providing reassurance to a symptomatic patient is valuable in daily clinical practice.

Although the use of ICMs for risk stratification seems promising, there are some factors which should be considered such as device costs, data overload, clinical relevance of device-detected VA and medical overuse. The issue of data overload is exemplified by the recording of more than 1,600

episodes in 30 patients in a relatively short follow-up period in our study population. This requires a proper logistic organization with a dedicated telemonitoring staff. There is some controversy with regard to the clinical relevance of device-detected arrhythmias, especially for atrial fibrillation[12]. With regard to the clinical relevance of device-detected VA, it is important to stress that in our population the majority of VA episodes were detected as patient-activated episodes, indicating that the patient experienced symptoms. Koyak et al. previously identified that symptomatic but not asymptomatic nonsustained VA was associated with appropriate ICD therapy in TOF patients who receive an ICD for primary prevention[29].

Study limitations

A limitation of the present study is the small size and lack of a control group. Therefore, no conclusion can be made regarding the incremental value of an ICM compared to standard clinical practice with intermittent Holter monitoring. Ideally, a randomized clinical trial would be conducted where patients are randomized to an ICM or conventional follow-up. Obstacles for such a clinical trial are the heterogeneity of the population and challenges in defining appropriate endpoints. In this regard, it is important to stress that our study population was a highly selected population. The usefulness of an ICM may not apply to an unselected CHD population. Finally, the classification of broad complex tachycardia as either VA or SVT can be challenging considering that only a single surface EGM is available. To reduce the risk of misclassification, difficult EGMs were reevaluated by an electrophysiologist.

Conclusion

There was a high incidence of ICM-detected VA in adults with CHD who were deemed at risk of VA. ICM results led to implantation of an ICD in 10% of the study population. The detection of arrhythmias by the ICM led to important changes in the clinical management of patients. Our prospective pilot study suggests that the use of ICMs for risk stratification in selected adults with CHD is helpful.

Appendix

Appendix A. Overview of baseline characteristics and clinical outcome

	Underlying diagnosis	Surgical status	Age at repair (years)	QRS duration (ms)	Reason for ICM	Age at ICM implantation (years)	FU with ICM (months)	ICM-detected arrhythmia	ICM-guided therapy
1	Aortic coarctation	Surgical repair, AVR	8	190	Syncope, bifascicular block with first-degree AV block	56	10	Sinus arrest	AAD
2	Aortic coarctation	Surgical repair	3	117	Prior NSVT (asymptomatic)	26	12	NSVT	Conservative
3	Aortic coarctation	Surgical repair, PDA closure	11	148	Syncope, mild systemic ventricular dysfunction	71	15	SVT, AF, AFL	Ablation, ECV, AAD
4	Aortic coarctation	Surgical repair, AVR, MVR	<1	109	Palpitations, exercise-induced PVCs, mild systemic ventricular dysfunction	19	3	NSVT, SVT, SA block, AF	DDD-ICD, AAD
5	Aortic coarctation	Surgical repair, PDA closure	14	124	Palpitations, syncope, prior NSVT, mild systemic ventricular dysfunction	19	32	SVT	Ablation
6	Aortic coarctation	Surgical repair	38	81	Palpitations	41	1		
7	Aortic coarctation	Surgical repair, AVR	10	174	Palpitations, mild systemic ventricular dysfunction	55	21		
8	TOF	Total repair, PVR	30	180	Palpitations, QRS 180 ms	52	17	AF, AV block	Conservative
9	TOF	Total repair (transannular patch), PVR	<1	176	Palpitations, mild systemic ventricular dysfunction	33	17	SVT, Bradycardia	Conservative
10	TOF	Total repair (Hancock conduit)	11	155	Palpitations, near syncope	41	3	NSVT	DDD-ICD

Appendix A. continued

11	TOF	Total repair	8	176	Near syncope, prior NSVT	39	21		
12	TOF	Total repair (transannular patch)	5	161	Palpitations, syncope	25	32		
13	ASD	Surgical closure ASD, PV repair	11	114	Palpitations, near syncope, mild systemic ventricular dysfunction	56	4	SVT	AAD, EPS
14	ASD	Percutaneous ASD closure	27	168	Syncope, mild systemic ventricular dysfunction	36	31	SVT, bradycardia	AAD, EPS
15	ASD			106	Syncope	74	3	AF, AV block	Pacemaker
16	ASD	Surgical closure ASD, PV repair, TV repair	8	109	Palpitations, mild systemic ventricular dysfunction	43	16	AF, SVT	Conservative
17	ASD	Surgical closure ASD, TV repair	20	116	Near syncope, mild systemic ventricular dysfunction	24	10		
18	d-TGA	Mustard repair	5	146	Near syncope, moderate systemic ventricular dysfunction, exercise-induced PVCs	39	15	AV block	Conservative
19	d-TGA	Mustard repair	4	99	Palpitations, moderate systemic ventricular dysfunction	47	4		
20	d-TGA	Arterial switch and VSD closure (patch)	<1	136	Palpitations, moderate systemic ventricular dysfunction	29	21	SVT, NSVT	Conservative
21	d-TGA	Arterial switch, VSD closure (patch)	<1	118	Palpitations, prior NSVT	18	36	SVT, NSVT	AAD
22	cc-TGA	TV repair	40	152	Syncope, prior SVT, moderate systemic ventricular dysfunction	43	18	NSVT, AF, Bradycardia	DDD-ICD

23	cc-TGA			97	Palpitations, moderate systemic ventricular dysfunction	29	30	SVT, AFL	Ablation
24	VSD	VSD closure (patch) and PDA closure	<1	104	Near syncope, prior NSVT	20	29	NSVT, SVT, AF	AAD
25	VSD	VSD closure (patch) and ASD repair	2	118	Palpitations, prior NSVT	19	12	NSVT, SVT	AAD
26	Tricuspid atresia	TCPC with lateral tunnel	11	130	Palpitations, near syncope	50	2	SVT	AAD, Ablation
27	Bicuspid aortic valve			88	Exercise-induced PVCs (asymptomatic)	41	27	Symptomatic PVCs	AAD
28	DOLV	Rastelli repair	11	174	Palpitations, prior SVT, moderate systemic ventricular dysfunction	43	12	AFL	ECV
29	Congenital PV stenosis	PV and TV repair	11	153	Palpitations, near syncope, mild systemic ventricular dysfunction	20	19		
30	Ebstein's anomaly		1	151	Near syncope, moderate systemic ventricular dysfunction	24	16		

Abbreviations: AAD, antiarrhythmic drug; AF, atrial fibrillation; AFL, atrial flutter; ASD, atrial septal defect; AV, atrioventricular; AVR, aortic valve replacement; cc-TGA, congenital corrected transposition of the great arteries; d-TGA, d-transposition of the great arteries; DOLV, double outlet left ventricle; ECV, electrical cardioversion; EPS, electrophysiology study; ICD, implantable cardioverter-defibrillator; ICM, insertable cardiac monitor; FU, follow-up; MVR, mitral valve replacement; NSVT, nonsustained ventricular tachycardia; PDA, patent ductus arteriosus; PV, pulmonary valve; PVC, premature ventricular complex; SA, sino-atrial; SVT, supraventricular tachycardia; TCPC, total cavopulmonary connection; TOF, tetralogy of Fallot; TV, tricuspid valve; VSD, ventricular septal defect.

References

1. Nieminen HP, Jokinen EV and Sairanen HI. Causes of late deaths after pediatric cardiac surgery: a population-based study. *J Am Coll Cardiol*. 2007;50:1263-71.
2. Oechslin EN, Harrison DA, Connelly MS, Webb GD and Siu SC. Mode of death in adults with congenital heart disease. *Am J Cardiol*. 2000;86:1111-6.
3. Silka MJ, Hardy BG, Menashe VD and Morris CD. A population-based prospective evaluation of risk of sudden cardiac death after operation for common congenital heart defects. *J Am Coll Cardiol*. 1998;32:245-51.
4. Koyak Z, Harris L, de Groot JR, Silversides CK, Oechslin EN, Bouma BJ, Budts W, Zwinderman AH, Van Gelder IC and Mulder BJ. Sudden cardiac death in adult congenital heart disease. *Circulation*. 2012;126:1944-54.
5. Yap SC and Harris L. Sudden cardiac death in adults with congenital heart disease. *Expert Rev Cardiovasc Ther*. 2009;7:1605-20.
6. Khairy P. Programmed ventricular stimulation for risk stratification in patients with tetralogy of Fallot: a Bayesian perspective. *Nat Clin Pract Cardiovasc Med*. 2007;4:292-3.
7. Khairy P, Harris L, Landzberg MJ, Viswanathan S, Barlow A, Gatzoulis MA, Fernandes SM, Beauchesne L, Therrien J, Chetaille P, Gordon E, Vonder Muhll I and Cecchin F. Implantable cardioverter-defibrillators in tetralogy of Fallot. *Circulation*. 2008;117:363-70.
8. Khairy P, Landzberg MJ, Gatzoulis MA, Lucron H, Lambert J, Marcon F, Alexander ME and Walsh EP. Value of programmed ventricular stimulation after tetralogy of fallot repair: a multicenter study. *Circulation*. 2004;109:1994-2000.
9. Yap SC, Roos-Hesselink JW, Hoendermis ES, Budts W, Vliegen HW, Mulder BJ, van Dijk AP, Schalij MJ and Drenthen W. Outcome of implantable cardioverter defibrillators in adults with congenital heart disease: a multi-centre study. *Eur Heart J*. 2007;28:1854-61.
10. Vehmeijer JT, Brouwer TF, Limpens J, Knops RE, Bouma BJ, Mulder BJ and de Groot JR. Implantable cardioverter-defibrillators in adults with congenital heart disease: a systematic review and meta-analysis. *Eur Heart J*. 2016;37:1439-48.
11. Opic P, Utens EM, Moons P, Theuns DA, van Dijk AP, Hoendermis ES, Vliegen HW, de Groot NM, Witsenburg M, Schalij M and Roos-Hesselink JW. Psychosocial impact of implantable cardioverter defibrillators (ICD) in young adults with Tetralogy of Fallot. *Clin Res Cardiol*. 2012;101:509-19.
12. Sakhi R, Theuns D, Szili-Torok T and Yap SC. Insertable cardiac monitors: current indications and devices. *Expert review of medical devices*. 2019;16:45-55.
13. Brignole M, Moya A, de Lange FJ, Deharo JC, Elliott PM, Fanciulli A, Fedorowski A, Furlan R, Kenny RA, Martin A, Probst V, Reed MJ, Rice CP, Sutton R, Ungar A, van Dijk JG and Group ESCSD. 2018 ESC Guidelines for the diagnosis and management of syncope. *Eur Heart J*. 2018;39:1883-1948.
14. Kammeraad JA, van Deurzen CH, Sreeram N, Bink-Boelkens MT, Ottenkamp J, Helbing WA, Lam J, Sobotka-Plojhar MA, Daniels O and Balaji S. Predictors of sudden cardiac death after Mustard or Senning repair for transposition of the great arteries. *J Am Coll Cardiol*. 2004;44:1095-102.

15. Gatzoulis MA, Balaji S, Webber SA, Siu SC, Hokanson JS, Poile C, Rosenthal M, Nakazawa M, Moller JH, Gillette PC, Webb GD and Redington AN. Risk factors for arrhythmia and sudden cardiac death late after repair of tetralogy of Fallot: a multicentre study. *Lancet*. 2000;356:975-81.
16. Diller GP, Kempny A, Liodakis E, Alonso-Gonzalez R, Inuzuka R, Uebing A, Orwat S, Dimopoulos K, Swan L, Li W, Gatzoulis MA and Baumgartner H. Left ventricular longitudinal function predicts life-threatening ventricular arrhythmia and death in adults with repaired tetralogy of fallot. *Circulation*. 2012;125:2440-6.
17. Gallego P, Gonzalez AE, Sanchez-Recalde A, Peinado R, Polo L, Gomez-Rubin C, Lopez-Sendon JL and Oliver JM. Incidence and predictors of sudden cardiac arrest in adults with congenital heart defects repaired before adult life. *Am J Cardiol*. 2012;110:109-17.
18. Khairy P, Harris L, Landzberg MJ, Fernandes SM, Barlow A, Mercier LA, Viswanathan S, Chetaille P, Gordon E, Dore A and Cecchin F. Sudden death and defibrillators in transposition of the great arteries with intra-atrial baffles: a multicenter study. *Circ Arrhythm Electrophysiol*. 2008;1:250-7.
19. Bezzerides VJ, Walsh A, Martuscello M, Escudero CA, Gauvreau K, Lam G, Abrams DJ, Triedman JK, Alexander ME, Bevilacqua L and Mah DY. The Real-World Utility of the LINQ Implantable Loop Recorder in Pediatric and Adult Congenital Heart Patients. *JACC Clin Electrophysiol*. 2019;5:245-251.
20. Kenny D, Chakrabarti S, Ranasinghe A, Chambers A, Martin R and Stuart G. Single-centre use of implantable loop recorders in patients with congenital heart disease. *Europace*. 2009;11:303-7.
21. Frangini PA, Cecchin F, Jordao L, Martuscello M, Alexander ME, Triedman JK, Walsh EP and Berul CI. How revealing are insertable loop recorders in pediatrics? *Pacing Clin Electrophysiol*. 2008;31:338-43.
22. Sanatani S, Peirone A, Chiu C, Human DG, Gross GJ and Hamilton RM. Use of an implantable loop recorder in the evaluation of children with congenital heart disease. *Am Heart J*. 2002;143:366-72.
23. Gass M, Apitz C, Salehi-Gilani S, Ziemer G and Hofbeck M. Use of the implantable loop recorder in children and adolescents. *Cardiol Young*. 2006;16:572-8.
24. Kothari DS, Riddell F, Smith W, Voss J and Skinner JR. Digital implantable loop recorders in the investigation of syncope in children: benefits and limitations. *Heart Rhythm*. 2006;3:1306-12.
25. Rossano J, Bloemers B, Sreeram N, Balaji S and Shah MJ. Efficacy of implantable loop recorders in establishing symptom-rhythm correlation in young patients with syncope and palpitations. *Pediatrics*. 2003;112:e228-33.
26. Sreeram N, Gass M, Apitz C, Ziemer G, Hofbeck M, Emmel M, Brockmeier K, Hitchcock F and Bennink G. The diagnostic yield from implantable loop recorders in children and young adults. *Clin Res Cardiol*. 2008;97:327-33.
27. Yeung B and McLeod K. The implantable loop recorder in children. *Heart*. 2008;94:888-91.
28. Dodeja AK, Thomas C, Daniels CJ, Kertesz N and Kamp A. Detection of arrhythmias in adult congenital heart disease patients with LINQ(TM) implantable loop recorder. *Congenit Heart Dis*. 2019.
29. Koyak Z, de Groot JR, Bouma BJ, Van Gelder IC, Budts W, Zwinderman AH and Mulder BJ. Symptomatic but not asymptomatic non-sustained ventricular tachycardia is associated with appropriate implantable cardioverter therapy in tetralogy of Fallot. *Int J Cardiol*. 2013;167:1532-5.

CHAPTER 5

Incremental value of an insertable cardiac monitor in patients with hypertrophic cardiomyopathy with low or intermediate risk for sudden cardiac death

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Cardiology (accepted for publication).

Abstract

Aims: The aim of the present study was to compare the rate of actionable arrhythmic events between patients with hypertrophic cardiomyopathy (HCM) who are monitored with an insertable cardiac monitor (ICM) or Holter monitoring.

Methods: We studied 50 patients (mean age 52 years, 72% men) with HCM at low or intermediate risk for SCD of whom 25 patients received an ICM between November 2014 and February 2019. We retrospectively identified a control group of 25 patients who were matched on age, sex and HCM Risk-SCD score category. The mean HCM Risk SCD-score was 3.41±1.31 and 3.31±1.43 for the ICM group and Holter group, respectively. The primary endpoint was an actionable event which was defined as an arrhythmic event resulting in a change in patient management. The secondary endpoint was the occurrence of ventricular tachycardia (VT).

Results: The cumulative actionable event rate at 30 months was higher in the ICM group (51% versus 27%, log-rank P-value <0.01). De novo atrial fibrillation requiring oral anticoagulation occurred only in the ICM group (N=3). Overall, 4 implantable cardioverter defibrillators were implanted for primary prevention (N=2 in each group). The cumulative rate of VT episodes at 30 months was similar between groups (23% [ICM group] versus 42% [Holter group], log-rank P-value=0.71). Furthermore, the characteristics of the VT were similar between groups with regard to the number of beats and rate.

Conclusions: In adults with HCM, an ICM will detect more arrhythmic events requiring an intervention than a conventional Holter strategy. In contrast, the diagnostic yield of detecting VT seems similar for both groups.

Introduction

Insertable cardiac monitors (ICMs) provide continuous rhythm monitoring and are useful for the detection of infrequent arrhythmias, especially in patients with recurrent unexplained syncope[1]. The exact role of ICMs in patients with hypertrophic cardiomyopathy (HCM) is less clear. The current ESC guidelines recommend that HCM patients with recurrent episodes of unexplained syncope, who are at low risk of sudden cardiac death (SCD), should be considered for an ICM[1, 2]. Furthermore, an ICM may be considered for HCM patients with frequent unexplained palpitations[2]. However, these recommendations are based on scarce data and there is no comparative data with ambulatory Holter monitoring[3-5]. The 2014 ESC HCM guidelines recommend the use of ambulatory Holter monitoring to detect atrial and ventricular arrhythmias every 12-24 months or more often in the case of symptoms or left atrial dilatation[2]. Theoretically, the diagnostic yield for the detection of arrhythmias is higher for an ICM in comparison to intermittent Holter monitoring. This higher diagnostic yield may be clinically relevant in this patient population. For example, the detection of ventricular tachycardia (VT) may have an impact on risk stratification for SCD and the decision to implant an implantable cardioverter-defibrillator (ICD)[2, 6, 7]. Furthermore, HCM patients with documented AF should receive oral anticoagulation to prevent stroke[2]. In the past 5 years, we adopted a strategy to use an ICM in HCM patients at low to intermediate risk of SCD for the detection of subclinical arrhythmias, with a particular emphasis on the detection of VT. The aim of the present study was to evaluate the incremental value of ICMs compared to a conventional strategy (i.e., Holter monitoring) in adults with HCM and a low- or intermediate HCM Risk-SCD score.

Methods

Study population

This was a prospective observational study which included all consecutive adults with HCM who received a Reveal LINQ (Medtronic Inc., Minneapolis, MN, USA) between November 2014 and February 2019. All patients had an HCM Risk-SCD score <6%. The reason for an ICM was a combination of symptoms (e.g., recurrent (near)syncope, palpitations), presence of myocardial fibrosis (determined by the presence of late gadolinium enhancement [LGE] on cardiac MRI [CMR]) and/or an intermediate risk for SCD (5-year risk of SCD ≥4 to <6%). The decision to implant an ICM was made during a Heart Team consisting of a cardiac electrophysiologist and a cardiologist specialized in HCM.

The control group was retrospectively identified from our prospective HCM registry and consisted of a matched cohort who received conventional follow-up (intermittent Holter monitoring every 6-24 months based on treating physician's discretion). Matching was based on age (with a margin of 5 years), sex and HCM Risk-SCD score category (<4% or ≥4 to <6%). Patients in the control group required a minimum of 1 Holter study during follow-up and at least a clinical follow-up of 1 year. The study was approved by the Ethics Committee of the Erasmus MC.

ICM settings

All ICMs were implanted subcutaneously as recommended by the manufacturer using the incision and insertion tool. Furthermore, all patients received a handheld activator to indicate their symptoms when necessary. The ICM was routinely programmed with the following settings: tachycardia-detection was set to 176 bpm for 16 beats; bradycardia-setting to 30 bpm for 8 beats; pause-setting to 4.5 sec; and atrial fibrillation (AF) setting to 'AF only'. Based on the implanting physician's preferences other settings could be programmed. All devices were connected to the Medtronic CareLink network for remote monitoring.

Clinical follow-up of ICM group

ICM patients were discharged on the day of implantation. Ten days after implantation the patients were seen at the out-patient clinic to check the implantation site and to interrogate the ICM. Afterwards, the patients were seen regularly at the outpatient clinic according to routine patient care. ICM check-ups were performed at the outpatient clinic every 6 months or earlier when necessary based on symptoms or transmitted episodes. Remote monitoring was performed on a daily basis during weekdays. All patient activated episodes and automatically detected episodes were classified. In case of an inappropriate automatically detected episode, the cause of inappropriate detection was specified, if possible. Multiple actionable events could occur in 1 patient.

Study endpoints

The primary endpoint of the study was the occurrence of an actionable event which was defined as an arrhythmic event resulting in any change in patient management (e.g., start or increase of medication, implantation of pacemaker or ICD, catheter ablation, etc.). The secondary endpoint was the occurrence of any VT (at least 3 beats), irrespective if this resulted in an actionable event or not. A regular wide complex tachycardia was considered a VT if there was a sudden onset and a change in the QRS morphology in comparison to the baseline rhythm. An irregular wide complex tachycardia was considered a VT if there was a sudden onset and a polymorphic QRS morphology. A regular wide or narrow complex tachycardia was considered a supraventricular tachycardia (SVT) if there was a sudden onset and no change in QRS morphology. In case of doubt, a second electrophysiologist was consulted for the final diagnosis. For both endpoints, the cumulative event rate was determined at 30 months considering the estimated battery lifetime of the ICM.

Statistical analysis

Continuous data are presented as mean ± standard deviation or as median with interquartile range (IQR) (25^{th} and 75^{th} percentile), as appropriate. Categorical variables are presented by frequencies and percentages. Differences of continuous variables between groups were analyzed with the unpaired Student's t test or the Kruskal-Wallis test, as appropriate. Differences between categorical variables were evaluated using the chi-square test. Cumulative event rates were estimated with the Kaplan-Meier method and differences were compared by log-rank test. Statistical analyses were performed using SPSS version 25 (IBM Corp., Somers, NY).

Results

A total of 25 HCM patients received an ICM between 2014 and 2019. We identified 25 matched controls with HCM who were seen at the outpatient clinic in the same study period. Baseline characteristics of the study population are presented in Table 1. The ICM group more often had a history of syncope (32% versus 4%, P=0.01). Other baseline characteristics, including a history of nonsustained VT (NSVT), were similar between groups.

Table 1. Clinical baseline characteristics

	ICM group (n=25)	Control group (n=25)	P value
Age, years	51 ± 16	52 ± 16	0.94
Sex, man	18 (72%)	18 (72%)	1.00
NYHA functional class ≥II	7 (28%)	7 (28%)	1.00
History of myectomy	2 (8%)	3 (12%)	0.64
Left ventricular systolic function			1.00
- Normal (EF ≥50%)	25 (100%)	24 (96%)	
- Mildly impaired (EF 45-49%)	0	1 (4%)	
Genetic testing	21 (84%)	23 (92%)	0.67
Pathogenic mutation	12 (48%)	14 (56%)	0.57
- MYBPC3	8 (32%)	11 (44%)	0.38
- MYH7	3 (12%)	1 (4%)	0.30
- TPM1	1 (4%)	0	1.00
- TNNI3	0	2 (8%)	0.49
History of NSVT	13 (52%)	8 (32%)	0.15
History of unexplained syncope	8 (32%)	1 (4%)	0.01
Peak LVOT gradient	6 (5-17)	12 (6-82)	0.19
Family history of SCD	3 (12%)	3 (12%)	1.00
Left atrial size	43 ± 9	45 ± 7	0.23
Maximum left ventricular wall thickness	18 ± 5	18 ± 5	0.49
HCM Risk-SCD score	3.41 ± 1.31	3.31 ± 1.43	0.79
- <4%	13 (52%)	13 (52%)	1.00
- ≥4 to ≤6%	12 (48%)	12 (48%)	1.00
Electrocardiography	25 (100%)	25 (100%)	1.00
- Sinus rhythm	24 (96%)	25 (100%)	1.00
- Atrial fibrillation	1 (4%)	0	1.00
- PR interval, if sinus rhythm	164 ± 25	182 ± 25	0.85
- QRS duration, ms	105 ± 18	102 ± 28	0.56
- QTc duration, ms	426 ± 25	416 ± 28	0.61

Table 1. continued

Holter monitoring	25 (100%)	25 (100%)	1.00
- <1% PVCs	23 (92%)	25 (100%)	0.49
- 1-10% PVCs	2 (8%)	0	0.49
- NSVT	11 (44%)	6 (24%)	0.14
- Supraventricular tachycardia	7 (28%)	12 (48%)	0.15
- Atrial fibrillation	2 (8%)	0	0.49
Cardiac medication	16 (64%)	19 (76%)	0.35
- Beta blocker	12 (48%)	14 (56%)	0.57
- Loop diuretics	5 (20%)	0	0.05
- ACE-inhibitor/ ARB	6 (24%)	3 (12%)	0.27
- Oral anticoagulants	5 (20%)	5 (20%)	1.00
- Calcium channel blocker	3 (16%)	4 (16%)	0.68
- Amiodarone/Sotalol	2 (8%)	2 (8%)	1.00

Data are presented as n (%), mean ± SD or median with interquartile range. Abbreviations: ACE, angiotensin converting enzyme; ARB, angiotensin receptor blocker; CAD, coronary artery disease; EF, ejection fraction; HCM, hypertrophic cardiomyopathy; LVOT, left ventricular outflow tract; NSVT, nonsustained ventricular tachycardia; NYHA, New York Heart Association; PVC, premature ventricular complex; SCD, sudden cardiac death.

ICM-detected arrhythmias and Holter follow-up

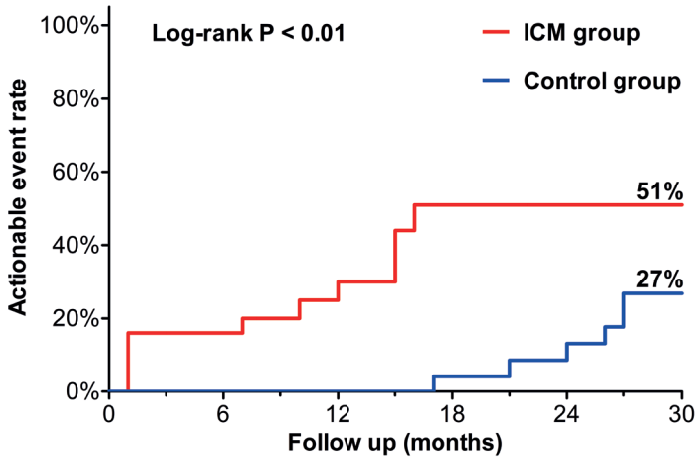
During a mean follow-up of 17±10 months with the ICM, a total of 1,015 episodes were transmitted to the CareLink network system. There were 270 (27%) patient-activated episodes and 745 (73%) automatically detected episodes. The majority of patient-activated episodes (93%) comprised of sinus rhythm with or without ectopy. In the control group, 48 Holter recordings were performed during follow-up. The median number of Holter recordings per patient was 2 (IQR, 1-3). The median interval between Holter recordings was 12 (IQR, 5-23) months.

Primary end-point

The cumulative event rate for an actionable event was higher in the ICM group (51% versus 27% at 30 months, log-rank P-value <0.01) (Figure 1). In the ICM group the following actionable events occurred: antiarrhythmic drug therapy (or change in dose) for documented arrhythmias (n=6, 24%), start of non-vitamin K antagonist oral anticoagulation for documented AF (n=3, 12%), electrophysiology study for symptomatic SVT (n=2, 8%), implantation of ICD for primary prevention (n=2, 8%), pacemaker implantation for sinus node dysfunction (n=1, 4%) and external electrical cardioversion for AF (n=1, 4%). In the control group the following actionable events occurred: antiarrhythmic drug therapy (or change in dose) for documented arrhythmias (n=6, 24%), implantation of ICD for primary prevention (n=2, 8%) and electrophysiology study for symptomatic SVT (n=1, 4%). De novo AF only occurred in

the ICM group. Of the 3 patients with de novo AF, only 1 patient experienced symptoms required an electrical cardioversion for persistent AF.

Figure 1. Cumulative event rate for actionable events



Numbers at risk						
	0	6	12	18	24	30
ICM group	25	21	15	7	5	2
Control group	25	25	25	23	20	13

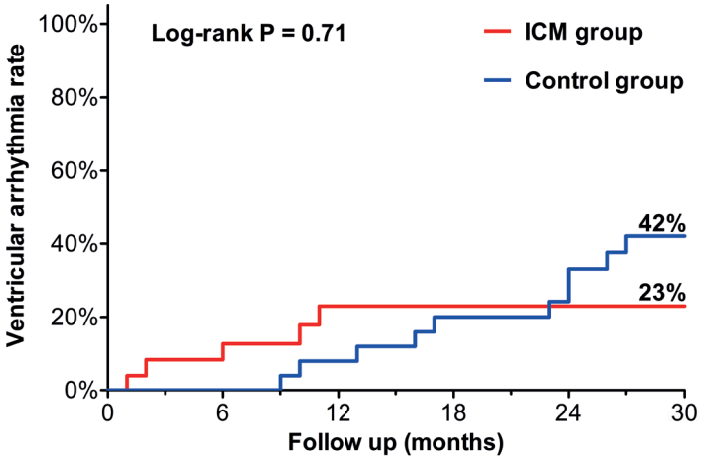
Overall, 4 patients received an ICD for primary prevention (2 in each group). A patient in the ICM group had an ICM-detected NSVT (7 beats, 171 bpm, patient-activated) which increased his HCM Risk-SCD score from 3.6% to 8.0%. He received a prophylactic ICD 15 months after his ICM implantation. The other patient in the ICM group had a history of NSVT, HCM Risk-SCD score of 4.44% and patchy LGE anterior wall and interventricular septum on his CMR. He experienced an episode of fast monomorphic NSVT (32 beats, 200 bpm, automatically detected) 12 months post-ICM implantation. This did not increase his HCM Risk-SCD score, but based on his clinical profile and the malignant character of the VT, the patient received an ICD. In the control group, a patient received a prophylactic ICD after a Holter-detected monomorphic VT episode (3 beats, 135 bpm) increased his HCM Risk-SCD score from 4.4% to 9.6% at 27 months after initial risk evaluation. The second patient in the control group who received a prophylactic ICD had an HCM Risk-SCD score of 4.2% and had a history of NSVT. The combination of Holter-detected recurrent VT and recurrent near-syncope was the indication for an ICD 26 months after initial risk evaluation.

Secondary end-point

The cumulative event rate for VT was 23% in the ICM group and 42% in the control group at 30 months (log-rank P-value = 0.71) (Figure 2). Most VT episodes (4 of 5, 80%) in the ICM group were patient-activated

episodes, thus, were detected while patients experienced symptoms. One patient of the ICM group had a VT episode which was automatically detected (32 beats, 200 bpm). The characteristics of documented VT episodes were similar between groups with regard to the median number of documented beats (5 [IQR, 5-7] versus 6 [IQR, 4-11], for ICM group and control group, respectively, P=1.00) and median rate (150 bpm [IQR, 145-155 bpm] versus 136 bpm [IQR, 125-168 bpm], for ICM group and control group, respectively, P=0.21).

Figure 2. Cumulative event rate for ventricular arrhythmias



Numbers at risk						
	0	6	12	18	24	30
ICM group	25	21	15	10	7	3
Control group	25	25	23	20	17	10

Discussion

The present study is the first study comparing the value of an ICM to conventional Holter monitoring in HCM patients with a low or intermediate HCM Risk-SCD score. The main finding is that actionable arrhythmic events occurred more frequently in the ICM group in comparison to the Holter group. In contrast, the cumulative rate of detected VT was similar between both groups.

It is well-known that prolonged arrhythmia monitoring increases the yield of arrhythmia detection. The indications for an ICM has expanded over the years and its use is currently not only limited to patients with recurrent unexplained syncope[1,8]. Other important indications include the detection of subclinical AF, risk stratification in patients with inheritable heart disease by the detection of VT and establishing a symptom-rhythm correlation in symptomatic patients[9]. In patients with HCM who are at low risk for SCD according to the HCM Risk-SCD score, the current ESC guidelines recommends that

an ICM should be considered in patients with recurrent unexplained syncope and may be considered in those with unexplained palpitations[1, 2]. However, limited data exists on the clinical impact of ICMs in HCM patients and most studies comprised less than 10 patients[3-5].

The present study is the first to provide insight in the incremental value of an ICM in patients with HCM. The rate of actionable arrhythmic events was higher in the ICM group in comparison to a matched group who had intermittent Holter monitoring. Interestingly, de novo AF requiring oral anticoagulation only occurred in the ICM group. It is known that AF occurs in approximately 20% of patients with HCM and is associated with impaired quality of life, thromboembolism and mortality[10-15]. To prevent thromboembolic complications, the guidelines recommend the use of lifelong oral anticoagulation, irrespective of the CHADS-VASc score, when AF occurs in patients with HCM[2]. Several studies in HCM patients with a cardiac implantable electronic device have demonstrated a high incidence of clinically silent AF episodes which may have important implications[13, 16]. In our study, 3 patients (12%) were started on oral anticoagulation after the detection of de novo AF detected by the ICM. Thus, an ICM may play a role in the detection of subclinical AF in this specific population.

SCD is the most feared consequence of HCM, which has led to meticulous efforts to identify those patients who may benefit from a prophylactic ICD. Since 2014, the HCM Risk-SCD model provides guidance to physicians to identify patients deemed to be at high risk for SCD, and thus eligible for a prophylactic ICD[17, 18]. In clinical practice however, we are confronted with patients with a low or intermediate risk who have additional risk factors which are not incorporated in the HCM Risk-SCD model, such as extensive LGE on CMR[19], LV apical aneurysms, multiple pathogenic sarcomere protein variants, and LV dysfunction. The presence of NSVT is an important risk factor, especially in those patients younger than 30 years of age[20, 21]. In the American guidelines there is class IIa indication for an ICD in patients with NSVT who have additional SCD modifiers (i.e, age <30 years, LGE on CMR, LVOT obstruction, LV aneurysm, syncope >5 years ago)[6]. Considering the clinical relevance of documenting VT in this population, routine ambulatory Holter monitoring is recommended[2, 6, 7].

We expected that continuous monitoring with an ICM would improve VT detection. Interestingly, in our study the diagnostic yield for detecting VT was similar between the ICM and the Holter group. This apparent paradox can be partly explained by the ICM settings. Only longer and faster runs of VT (≥16 beats at a rate of >176 bpm) or symptomatic VT (patient-activated episodes) will be detected by the ICM, while with Holter monitoring a VT of ≥3 beats at a rate of >120 bpm will suffice. The Reveal LINQ can be programmed to detect a tachycardia of 5 beats at a rate of >120 bpm. However, this sensitive programming setting will result in a suboptimal signal-to-noise ratio, as many tachycardia episodes will be due to sinus tachycardia.

There is some inconsistency in the literature with regard to the prognostic significance of specific characteristics of documented VT. Studies in unselected HCM cohorts have shown no association between characteristics of the detected VT on ambulatory Holter monitoring and the occurrence of SCD[21]. However, several HCM cohorts with ICDs (higher-risk cohorts) demonstrated that longer-lasting and faster VT were more predictive of the occurrence of appropriate ICD therapy[22-24]. For example, in 160 HCM patients with ICDs, Wang et al. reported the independent association of fast (>200 bpm), long (>7

beats) and repetitive runs of VT with the occurrence of ICD therapy, whereas this association was not shown for slower, shorter and single-run of VT[24]. These data are important and support the use of ICMs as these devices are able to capture the more predictive longer and faster VT.

Finally, there are some factors that need to be considered when using ICMs in this patient population, including device costs, data overload, the clinical relevance of detected arrhythmias and medical overuse. A dedicated telemonitoring staff is a requirement before providing such a service to patients.

Study limitations

Although we used a matched control group, the present study is a nonrandomized study and selection bias is possible. The control group had a lower proportion of patients with a history of syncope. It is important to stress that the ICM population was not a general HCM population, but a selected cohort of HCM patients with symptoms or additional risk factors for SCD. Finally, the classification of wide complex tachycardia as either VT or SVT can be challenging considering that only a single surface electrogram is available. To reduce the risk of misclassification, difficult electrograms were reevaluated by an electrophysiologist.

Conclusions

In patients with HCM, the use of an ICM resulted in more actionable arrhythmic events if compared to intermittent Holter monitoring. Interestingly, de novo AF was only detected in the ICM group. The diagnostic yield of detecting VT appeared similar between both rhythm detection strategies, which may be explained by the ICM not detecting short runs of VT.

References

1. Brignole M, Moya A, de Lange FJ, Deharo JC, Elliott PM, Fanciulli A, Fedorowski A, Furlan R, Kenny RA, Martin A, Probst V, Reed MJ, Rice CP, Sutton R, Ungar A, van Dijk JG and Group ESCSD. 2018 ESC Guidelines for the diagnosis and management of syncope. *Eur Heart J*. 2018;39:1883-1948.
2. Elliott PM, Anastasakis A, Borger MA, Borggrefe M, Cecchi F, Charron P, Hagege AA, Lafont A, Limongelli G, Mahrholdt H, McKenna WJ, Mogensen J, Nihoyannopoulos P, Nistri S, Pieper PG, Pieske B, Rapezzi C, Rutten FH, Tillmanns C and Watkins H. 2014 ESC Guidelines on diagnosis and management of hypertrophic cardiomyopathy. *Eur Heart J*. 2014;35:2733-79.
3. Sakhi R, Theuns D, Bhagwandien RE, Michels M, Schinkel AFL, Szili-Torok T, Zijlstra F, Roos-Hesselink JW and Yap SC. Value of implantable loop recorders in patients with structural or electrical heart disease. *Journal of interventional cardiac electrophysiology : an international journal of arrhythmias and pacing*. 2018;52:203-208.
4. Pezawas T, Stix G, Kastner J, Schneider B, Wolzt M and Schmidinger H. Implantable loop recorder in unexplained syncope: classification, mechanism, transient loss of consciousness and role of major depressive disorder in patients with and without structural heart disease. *Heart*. 2008;94:e17.
5. Magnusson P and Morner S. EvaLuation Using Cardiac Insertable Devices And TelephonE in Hypertrophic Cardiomyopathy (ELUCIDATE HCM)-rationale and design: a prospective observational study on incidence of arrhythmias in Sweden. *BMJ Open*. 2017;7:e019541.
6. Al-Khatib SM, Stevenson WG, Ackerman MJ, Bryant WJ, Callans DJ, Curtis AB, Deal BJ, Dickfeld T, Field ME, Fonarow GC, Gillis AM, Hlatky MA, Granger CB, Hammill SC, Joglar JA, Kay GN, Matlock DD, Myerburg RJ and Page RL. 2017 AHA/ACC/HRS Guideline for Management of Patients With Ventricular Arrhythmias and the Prevention of Sudden Cardiac Death. *Circulation*. 2017.
7. Priori SG, Blomstrom-Lundqvist C, Mazzanti A, Blom N, Borggrefe M, Camm J, Elliott PM, Fitzsimons D, Hatala R, Hindricks G, Kirchhof P, Kjeldsen K, Kuck KH, Hernandez-Madrid A, Nikolaou N, Norekval TM, Spaulding C, Van Veldhuisen DJ and Group ESCSD. 2015 ESC Guidelines for the management of patients with ventricular arrhythmias and the prevention of sudden cardiac death. *Eur Heart J*. 2015;36:2793-2867.
8. Brignole M, Vardas P, Hoffman E, Huikuri H, Moya A, Ricci R, Sulke N, Wieling W, Committee ESD, Auricchio A, Lip GY, Almendral J, Kirchhof P, Aliot E, Gasparini M, Braunschweig F, Document R, Lip GY, Almendral J, Kirchhof P, Botto GL and Committee ESD. Indications for the use of diagnostic implantable and external ECG loop recorders. *Europace*. 2009;11:671-87.
9. Sakhi R, Theuns D, Szili-Torok T and Yap SC. Insertable cardiac monitors: current indications and devices. *Expert review of medical devices*. 2019;16:45-55.
10. Olivotto I, Cecchi F, Casey SA, Dolara A, Traverse JH and Maron BJ. Impact of atrial fibrillation on the clinical course of hypertrophic cardiomyopathy. *Circulation*. 2001;104:2517-24.
11. Ho CY, Day SM, Ashley EA, Michels M, Pereira AC, Jacoby D, Cirino AL, Fox JC, Lakdawala NK, Ware JS, Caleshu CA, Helms AS, Colan SD, Girolami F, Cecchi F, Seidman CE, Sajeev G, Signorovitch J, Green EM and Olivotto I. Genotype and Lifetime Burden of Disease in Hypertrophic Cardiomyopathy: Insights from the Sarcomeric Human Cardiomyopathy Registry (SHaRe). *Circulation*. 2018;138:1387-1398.

12. Healey JS, Connolly SJ, Gold MR, Israel CW, Van Gelder IC, Capucci A, Lau CP, Fain E, Yang S, Bailleul C, Morillo CA, Carlson M, Themeles E, Kaufman ES, Hohnloser SH and Investigators A. Subclinical atrial fibrillation and the risk of stroke. *N Engl J Med*. 2012;366:120-9.
13. van Velzen HG, Theuns DA, Yap SC, Michels M and Schinkel AF. Incidence of Device-Detected Atrial Fibrillation and Long-Term Outcomes in Patients With Hypertrophic Cardiomyopathy. *Am J Cardiol*. 2017;119:100-105.
14. Guttmann OP, Rahman MS, O'Mahony C, Anastasakis A and Elliott PM. Atrial fibrillation and thromboembolism in patients with hypertrophic cardiomyopathy: systematic review. *Heart*. 2014;100:465-72.
15. Rowin EJ, Hausvater A, Link MS, Abt P, Gionfriddo W, Wang W, Rastegar H, Estes NAM, Maron MS and Maron BJ. Clinical Profile and Consequences of Atrial Fibrillation in Hypertrophic Cardiomyopathy. *Circulation*. 2017;136:2420-2436.
16. Rowin EJ, Orfanos A, Estes NAM, Wang W, Link MS, Maron MS and Maron BJ. Occurrence and Natural History of Clinically Silent Episodes of Atrial Fibrillation in Hypertrophic Cardiomyopathy. *Am J Cardiol*. 2017;119:1862-1865.
17. O'Mahony C, Akhtar MM, Anastasiou Z, Guttmann OP, Vriesendorp PA, Michels M, Magri D, Autore C, Fernandez A, Ochoa JP, Leong KMW, Varnava AM, Monserrat L, Anastasakis A, Garcia-Pavia P, Rapezzi C, Biagini E, Gimeno JR, Limongelli G, Omar RZ and Elliott PM. Effectiveness of the 2014 European Society of Cardiology guideline on sudden cardiac death in hypertrophic cardiomyopathy: a systematic review and meta-analysis. *Heart*. 2019;105:623-631.
18. O'Mahony C, Jichi F, Pavlou M, Monserrat L, Anastasakis A, Rapezzi C, Biagini E, Gimeno JR, Limongelli G, McKenna WJ, Omar RZ, Elliott PM and Hypertrophic Cardiomyopathy Outcomes I. A novel clinical risk prediction model for sudden cardiac death in hypertrophic cardiomyopathy (HCM risk-SCD). *Eur Heart J*. 2014;35:2010-20.
19. Briasoulis A, Mallikethi-Reddy S, Palla M, Alesh I and Afonso L. Myocardial fibrosis on cardiac magnetic resonance and cardiac outcomes in hypertrophic cardiomyopathy: a meta-analysis. *Heart*. 2015;101:1406-11.
20. Christiaans I, van Engelen K, van Langen IM, Birnie E, Bonsel GJ, Elliott PM and Wilde AA. Risk stratification for sudden cardiac death in hypertrophic cardiomyopathy: systematic review of clinical risk markers. *Europace*. 2010;12:313-21.
21. Monserrat L, Elliott PM, Gimeno JR, Sharma S, Penas-Lado M and McKenna WJ. Non-sustained ventricular tachycardia in hypertrophic cardiomyopathy: an independent marker of sudden death risk in young patients. *J Am Coll Cardiol*. 2003;42:873-9.
22. Francia P, Santini D, Musumeci B, Semprini L, Adduci C, Pagannone E, Proietti G, Volpe M and Autore C. Clinical impact of nonsustained ventricular tachycardia recorded by the implantable cardioverter-defibrillator in patients with hypertrophic cardiomyopathy. *J Cardiovasc Electrophysiol*. 2014;25:1180-7.
23. Viswanathan K, Suszko AM, Das M, Jackson N, Gollob M, Cameron D, Spears D, Woo A, Rakowski H, Khurana M and Chauhan VS. Rapid Device-Detected Nonsustained Ventricular Tachycardia in the Risk Stratification of Hypertrophic Cardiomyopathy. *Pacing Clin Electrophysiol*. 2016;39:642-51.
24. Wang W, Lian Z, Rowin EJ, Maron BJ, Maron MS and Link MS. Prognostic Implications of Nonsustained Ventricular Tachycardia in High-Risk Patients With Hypertrophic Cardiomyopathy. *Circ Arrhythm Electrophysiol*. 2017;10.

CHAPTER 6

Outcome of Insertable Cardiac Monitors in Symptomatic Patients with Brugada Syndrome at Low Risk of Sudden Cardiac Death

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Cardiology. 2020 Apr 22:1-8.

Abstract

Introduction: There is limited data on the experience with insertable cardiac monitors (ICMs) in patients with Brugada syndrome.

Objective: To evaluate the outcome of ICM in symptomatic patients with Brugada syndrome who are at suspected low risk of sudden cardiac death (SCD).

Methods: We conducted a prospective single-center cohort study including all symptomatic patients with Brugada syndrome who received an ICM (Reveal LINQ) between July 2014 and October 2019. The main indication for monitoring was to exclude ventricular arrhythmias as the cause of symptoms and to establish a symptom-rhythm relationship.

Results: A total of 20 patients (mean age, 39 ± 12 years; 55% male) received an ICM during the study period. Nine patients (45%) had a history of syncope (presumed nonarrhythmogenic) and 5 patients had a recent syncope (<6 months). During a median follow-up of 32 months (interquartile range, 11-36 months), 3 patients (15%) experienced an episode of nonsustained ventricular arrhythmia. No patient died suddenly, nor experienced a sustained ventricular arrhythmia, and no patient had a recurrence of syncope. Overall, 17 patients (85%) experienced symptoms during follow-up, of whom 10 patients had an ICM-detected arrhythmia. In 4 patients (20%) the ICM-detected arrhythmia was an actionable event. ICM-guided management included antiarrhythmic drug therapy for symptomatic ectopic beats (n=3), pulmonary vein isolation and oral anticoagulation for atrial fibrillation (n=1), electrophysiological study for risk stratification (n=1), and pacemaker implantation for atrioventricular block (n=1).

Conclusions: An ICM can be used to exclude ventricular arrhythmias in symptomatic patients with Brugada syndrome at low risk of SCD. Furthermore, an ICM-detected arrhythmia changed clinical management in 20% of patients.

Introduction

Risk stratification in patients with Brugada syndrome is challenging[1-3]. Several risk factors for arrhythmic events (sustained ventricular arrhythmia or sudden cardiac death [SCD]) have been identified but the most robust predictors are a spontaneous type 1 Brugada electrocardiogram (ECG) pattern and presumed arrhythmogenic syncope[1-3]. There is controversy over the predictive role of inducible sustained ventricular arrhythmia during electrophysiological study (EPS), but it seems to be informative for predicting arrhythmic risk in moderate-risk patients when using less aggressive stimulation protocols (up to double extrastimuli)[1-5].

The current guidelines recommend an implantable cardioverter-defibrillator (ICD) in patients with Brugada syndrome with aborted cardiac arrest, documented spontaneous sustained ventricular arrhythmias or a combination of spontaneous type 1 Brugada ECG pattern and a history of syncope[6, 7]. The downside of ICD therapy is the risk of late complications, inappropriate ICD shocks and psychological burden[8].

In clinical practice, physicians are confronted with patients with Brugada syndrome who have symptoms such as palpitations, near-syncope, or nonarrhythmic syncope[5, 9]. Some symptoms are caused by anxiety for arrhythmic events, but it may be difficult to differentiate this from clinically relevant arrhythmias. Insertable cardiac monitors (ICM) are increasingly being used in doubtful cases to exclude ventricular arrhythmias as the cause of symptoms[5, 10, 11]. The recent ESC guidelines and expert consensus conference report support the use of ICMs in patients with Brugada syndrome and recurrent unexplained syncope[12, 13]. The aim of the present study is to evaluate the use of ICMs in symptomatic patients with Brugada syndrome who are presumed to be at low risk of SCD.

Methods

Study design and population

The present study is a prospective single-center cohort study which included all symptomatic adults with Brugada syndrome who received an ICM between July 2014 and October 2019.The main indication for arrhythmia monitoring was to exclude ventricular arrhythmias as the cause of symptoms. Most patients have received a 24-hour Holter monitoring prior to ICM implantation. Patients with high risk features, such as a spontaneous sustained ventricular arrhythmia, a combination of spontaneous type 1 Brugada ECG pattern and arrhythmic syncope, or positive EPS, were not considered for an ICM but were recommended an ICD[6, 14]. Until 2014, we recommended EPS to all patients with spontaneous or drug-induced Brugada ECG pattern. Thereafter, EPS was only proposed to doubtful cases. The study was approved by the institutional review board of the Erasmus MC.

Device programming and follow-up

All ICMs (Reveal LINQ, Medtronic) were implanted subcutaneously using the incision and insertion tool. Furthermore, all patients received a handheld activator to indicate their symptoms when necessary.

The ICM was programmed according to local settings: tachycardia-detection was set to 176 bpm for 16 beats (nominal setting); bradycardia-setting to 30 bpm for 8 beats (nominal 4 beats); pause-setting to 4.5 sec (nominal 3.0 sec); and atrial fibrillation (AF) setting to 'AF only'. These settings were chosen to improve the signal-to-noise ratio. All devices were connected to the CareLink network (Medtronic) for remote monitoring. Patients were discharged on the same day of implantation. Ten days after implantation the patients were seen at the out-patient clinic to check their wound and to interrogate the ICM. Afterwards, the patients were seen regularly at the outpatient clinic according to routine patient care. ICM check-ups were performed at the outpatient clinic every 6 months or earlier when necessary based on symptoms or transmitted episodes. Remote monitoring was performed on a daily basis during weekdays. Remote monitoring involves automatic unscheduled transmission of alert events.

Classification of episodes and endpoints

All patient activated episodes and automatically detected episodes were classified. In the case of an inappropriate automatically detected episode, the cause of inappropriate detection was specified, if possible. A regular broad complex tachycardia (BCT) was considered a ventricular arrhythmia if there was a sudden onset and a change in the QRS morphology in comparison to the baseline rhythm. An irregular BCT was considered a ventricular arrhythmia if there was a sudden onset and a polymorphic QRS morphology. A regular broad or small complex tachycardia was considered a supraventricular tachycardia if there was a sudden onset and no change in QRS morphology. In the case of doubt, a second electrophysiologist was consulted for the final diagnosis. Finally, it was established whether a detected arrhythmia resulted in a change in patient management ('actionable event').

Statistical analysis

Data are presented as mean ± standard deviation or as median with corresponding 25^{th} and 75^{th} percentile, as appropriate. Categorical variables are presented by frequencies and percentages. Statistical analyses were performed using SPSS version 21.

Results

Study population

A total of 20 patients with Brugada syndrome (mean age, 39 ± 12 years; 55% male) received an ICM during the study period. Baseline characteristics of the study population are listed in Table 1 and 2. Symptoms before ICM implantation consisted of syncope suggestive of a non-arrhythmogenic cause (n=9, 45%), palpitations (n=7, 35%) or a combination of near-syncope and palpitations (n=4, 20%). Of the 9 patients with syncope, 7 patients (78%) had only 1 syncopal event and 5 patients (56%) had a recent syncope (<6 months before ICM implantation). A detailed patient-level description of patient characteristics is presented in Table 2. There were no ICM- or procedure-related complications.

Table 1. Clinical baseline characteristics.

	Total group (n=20)
Age, years	39 ± 12
Gender, male	11 (55%)
Family history of SCD in first-degree relatives	8 (40%)
History of atrial flutter at age <35 years	1 (5%)
Symptoms	
- Palpitations	11 (55%)
- Syncope	9 (45%)
- Near syncope	4 (20%)
Systemic systolic ventricular function	
- Normal left ventricular ejection fraction (≥55%)	20 (100%)
Genetic variance	
- No (likely) pathogenic SCN5A variant	14 (70%)
- No genetic testing	4 (20%)
- Pathogenic SCN5A variant	2 (10%)
Clinical presentation	
- Ajmaline induced Brugada ECG	14 (70%)
- Fever induced Brugada ECG	4 (20%)
- Spontaneous Brugada ECG	2 (10%)
Electrocardiography	
- Sinus rhythm	20 (100%)
- PR interval, ms	169 ± 28
- QRS duration, ms	103 ± 18
- QTc duration, ms	391 ± 22
- Fragmented QRS	4 (20%)
EP-study	7 (35%)
- No inducible sustained VA	7 (35%)
- VERP <200ms	2 (10%)
Holter monitoring	16 (80%)
- No PVCs	10 (50%)
- ≤1% PVCs	6 (30%)
- Supraventricular tachycardia	0
- Ventricular tachycardia	0
SA-ECG	16 (80%)
- Late potentials	10 (50%)

Data are presented as n (%) or mean with standard deviation. Abbreviations: ECG, electrocardiogram; EP, electrophysiology; PVC, premature ventricular arrhythmia; SCD, sudden cardiac death; VA, ventricular arrhythmia; VERP, ventricular effective refractory period.

Table 2. Detailed overview of baseline characteristics and clinical outcomes

Age* (years), gender (M/F)	Type of Brugada	Symptoms before ICM	SCD first-degree relatives	SCD <35 years first-degree relatives	Proband status	SND	History of inducible VA	SCN5A variant	Symptoms during follow-up	ICM detected rhythm	Management
20, M	Ajmaline	Syncope	-	-	+	-	NA	NA	Symptoms (not specified)	SR	-
22, M	Ajmaline	Syncope	+	+	-	-	NA	-	Asymptomatic	-	-
23, M	Ajmaline	Near-syncope, palpitations	-	-	+	-	NA	-	Near-syncope, palpitations	PAC/PVC, SVT, NSVT	AAD, EPS
24, F	Ajmaline	Near-syncope, palpitations	+	-	-	-	-	NA	Asymptomatic	-	-
29, M	Ajmaline	Palpitations	-	-	-	-	-	-	Asymptomatic	ST, SB	-
30, F	Ajmaline	Palpitations	+	-	+	-	NA	-	Symptoms (not specified)	SR	-
35, M	Ajmaline	Palpitations	-	-	+	-	-	-	Palpitations, amaurosis fugax	PAC, AF	AAD, NOAC, PVI
37, M	Ajmaline	Syncope	+	+	+	-	-	-	Palpitations	PAC	-
41, M	Ajmaline	Syncope	+	-	+	-	NA	-	Palpitations	PVC	-
41, F	Ajmaline	Near-syncope, palpitations	+	+	+	-	NA	NA	Palpitations	SR	-
41, F	Ajmaline	Syncope	+	-	+	-	NA	-	Palpitations	PVC, NSVT	-
43, M	Ajmaline	Syncope	+	+	-	-	-	+	Palpitations	SA	-
44, F	Ajmaline	Near-syncope, palpitations	-	-	-	-	-	-	Palpitations	PVC	-
55, F	Ajmaline	Syncope	-	-	+	-	NA	-	Symptoms (not specified)	SR	-

25, F	Fever	Palpitations	-	-	-	-	NA	+	Near-syncope, palpitations	PAC/PVC, SA	-
39, M	Fever	Syncope	-	-	-	-	NA	-	Symptoms (not specified)	SR	-
42, M	Fever	Palpitations	-	-	+	-	-	-	Palpitations	PAC/PVC, NSVT	AAD
50, F	Fever	Syncope	-	-	+	+	NA	-	Near-syncope, palpitations	PAC, SVT, AVB, SA	PM
53, F	Spontaneous	Palpitations	-	-	+	-	NA	-	Symptoms (not specified)	SR	-
63, M	Spontaneous	Palpitations	-	-	+	-	NA	NA	Palpitations	SR	-

Patients are sorted on age at diagnosis and type of Brugada syndrome. Abbreviations: AAD, antiarrhythmic drug therapy; AF, atrial fibrillation; AVB, atrioventricular block; ICM, insertable cardiac monitor; NA, not available; NSVT, nonsustained ventricular tachycardia; PAC, premature atrial complexes; PM, pacemaker; PVC, premature ventricular complexes; SA, sinus arrest; SB, sinus bradycardia; SCD, sudden cardiac death; SND, sinus node disease; SR, sinus rhythm; ST, sinus tachycardia; SVT, supraventricular tachycardia; VA, ventricular arrhythmia. + denotes present; - denotes absent, *age at diagnosis.

ICM-detected episodes

During a median follow-up of 32 months (IQR, 11-36 months), a total of 1,912 episodes were transmitted to the CareLink network system (Appendix A). There were 904 (47%) patient-activated episodes and 1,008 (53%) automatically detected episodes. The majority of patient-activated episodes (98%) comprised sinus rhythm with or without ectopy, thus, only a minority of patient-activated episodes comprised a significant arrhythmia.

Detection of ventricular arrhythmias episodes

During follow-up, 3 patients (15%) experienced an episode of nonsustained ventricular arrhythmia (Table 2, Figure 1).

The first patient was a 23-year-old male with ajmaline-induced Brugada syndrome and an anxiety disorder (treated by psychiatrist) who received an ICM due to recurrent unexplained symptoms (i.e. near-syncope and palpitations). During follow-up, he experienced 6 episodes of symptomatic regular slow monomorphic nonsustained ventricular arrhythmia (4-8 beats, patient-activated). It is important to note, that the majority of his patient-activated episodes did not show any arrhythmia. The patient underwent an EPS which was negative and based on the negative EPS he was treated conservatively.

The second patient was a 41-year-old female with ajmaline-induced Brugada syndrome and a positive family history of SCD who received an ICM for a history of presumed nonarrhythmogenic syncope. She experienced one symptomatic episode of irregular nonsustained ventricular arrhythmia (9 beats, patient-activated) with palpitations five months post ICM-implantation. It was decided to continue arrhythmia monitoring and to perform an EPS if there was a recurrent ventricular arrhythmia episode.

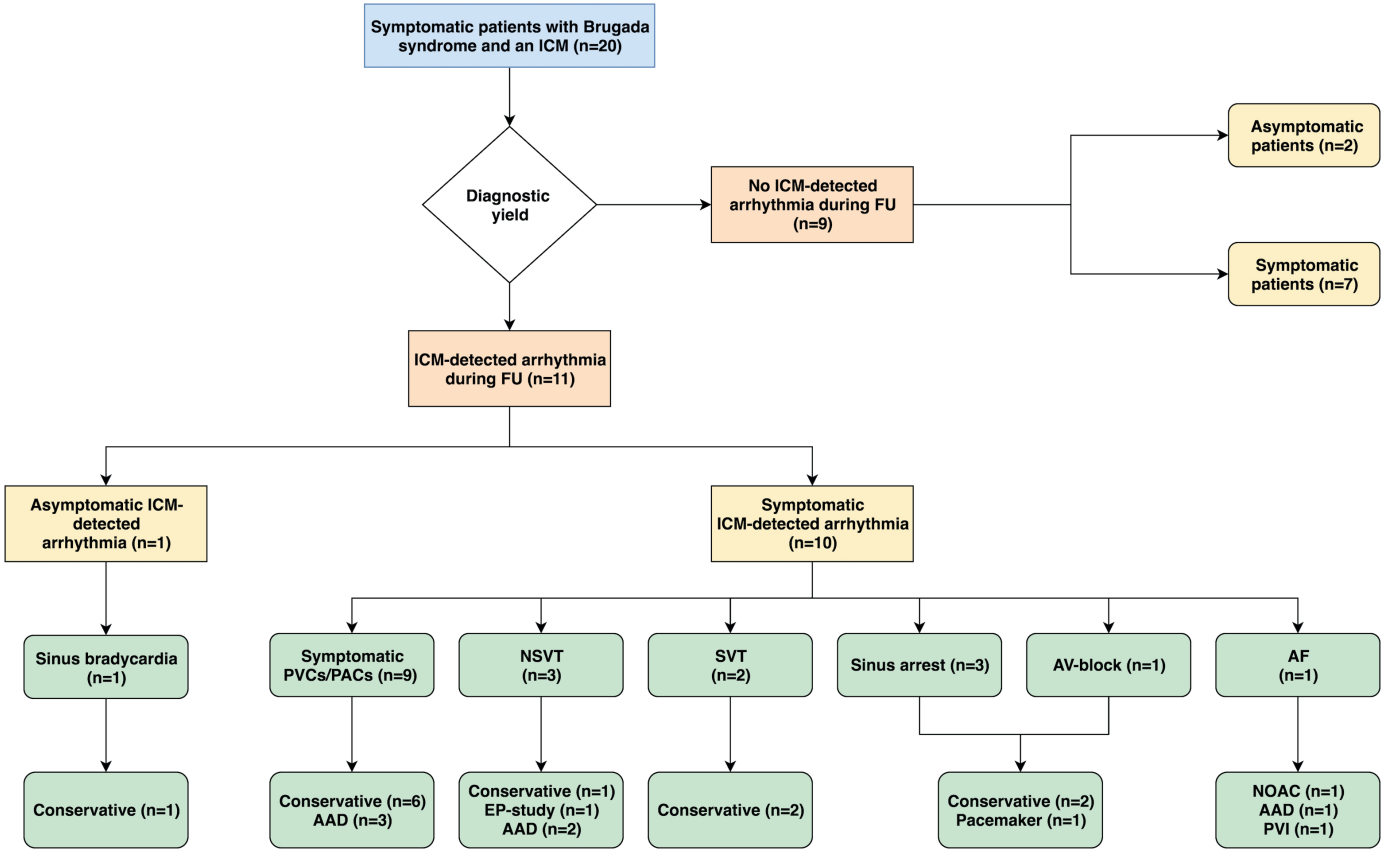
The third patient was a 42-year-old male with fever-induced Brugada syndrome, fragmented QRS and a negative EPS who received an ICM for palpitations. He experienced a symptomatic regular monomorphic nonsustained ventricular arrhythmia (7 beats, patient-activated) 16 months post ICM-implantation. Because he also had symptomatic ventricular ectopic beats, he was treated successfully with quinidine sulphate. No ventricular arrhythmia was seen thereafter. His ICM was explanted 3.5 years after implantation.

No patient died suddenly or experienced a sustained ventricular arrhythmia.

Symptom-rhythm correlation

No patient experienced syncope during a median follow-up of 32 months (IQR, 11-36 months). Overall, 17 patients (85%) experienced any symptom during follow-up (Figure 1, Table 2). Ten of 17 (59%) symptomatic patients had an ICM-detected arrhythmia. In 4 patients (20%) the ICM-detected arrhythmia was considered an actionable event. ICM-guided management included antiarrhythmic drug therapy for symptomatic ectopic beats (n=3), pulmonary vein isolation and oral anticoagulation for atrial fibrillation (n=1), electrophysiological study for risk stratification (n=1), and pacemaker implantation for high-degree atrioventricular block (n=1).

Figure 1. Overview of ICM-detected arrhythmias and the therapeutic management. Abbreviations: AAD, anti-arrhythmic drug; AF, atrial fibrillation; AV, atrioventricular; EPS, electrophysiology study; ICM, insertable cardiac monitor; NSVT, nonsustained ventricular tachycardia; PAC, premature atrial complex; PVC, premature ventricular complex; PVI, pulmonary vein isolation; VT, supraventricular tachycardia



Two patients with ventricular arrhythmia episodes and actionable events have been described previously. Furthermore, a 35-year-old male with ajmaline-induced Brugada syndrome experienced symptomatic paroxysmal AF detected by the ICM. He was started on oral anticoagulation and sotalol. In addition, he was scheduled for a pulmonary vein isolation.

A 50-year-old female with recurrent syncope, fever-induced Brugada syndrome and a positive family history of SCD at young age (third-degree relative) received a dual-chamber pacemaker after her ICM detected a 10-seconds pause due to high-degree AV block. During a follow-up of 18 months after pacemaker implantation, no episode of ventricular arrhythmia was documented by her pacemaker.

Overall, in 10 patients (45%) the ICM was explanted. In 9 patients the ICM was explanted due to end of battery life.

Discussion

The present study is one of the largest case series evaluating the outcome of continuous monitoring in adults with Brugada syndrome with low risk of SCD. During almost 3 years of follow-up, there was a low risk of nonsustained ventricular arrhythmia and an absence of sustained ventricular arrhythmia. In 4 patients (20%), an ICM-guided diagnosis resulted in a change of patient management. No patient required an ICD during follow-up. Thus, an ICM may provide reassurance to a symptomatic patient with Brugada syndrome.

Risk stratification

Brugada syndrome is characterized by an increased risk of SCD. Several risk factors for SCD have been identified including among others spontaneous type 1 Brugada ECG pattern, history of arrhythmogenic syncope, positive EPS, family history of SCD <35 years, fractionated QRS, early repolarization in the peripheral leads, increased T_{peak}-T_{end} interval, sinus node dysfunction, first-degree AV block and nonsustained ventricular arrhythmia[1-4]. The role of EPS in patients with Brugada syndrome is controversial. A recent meta-analysis demonstrated that ventricular arrhythmia induction using single or double extrastimuli was associated with a 2- to 3-fold increased risk of arrhythmic events[4]. However, it is important to note that a negative EPS alone is not sufficient to preclude arrhythmia risk, especially in patients with clinical high-risk features. Using a recently developed risk score (published in 2017) based on clinical parameters, the risk score in our study population ranged from 0 to 3 points corresponding to an estimated 5-year event rate ranging from 1.6% to 16.6%[1]. The arrhythmic event rate in our study population was 0% during a median follow-up of almost 3 years, supporting the clinical judgment not to implant a prophylactic ICD in our study population.

Role of ICM in Brugada syndrome

An ICM is a sensitive tool to detect paroxysmal arrhythmias and is particularly useful for establishing a symptom-rhythm correlation. In the general population, there is a clear indication for an ICM in patients

with recurrent unexplained syncope[12, 15]. Interestingly, the recent ESC guidelines give a class IIa indication (level of evidence C) for an ICM (instead of an ICD) in Brugada patients with recurrent unexplained syncope who are at low risk of SCD[12]. Currently, there is limited published data on the use of ICM in patients with Brugada syndrome[5, 10, 11, 16-18]. A few case reports in Brugada patients with presumed non-arrhythmogenic syncope have demonstrated the detection of self-terminating sustained ventricular arrhythmia by the ICM[16, 17]. These patients received a prophylactic ICD. Until now, there are 2 reported case series with >10 patients. In 2012, Kubala et al. reported a retrospective analysis of 11 patients (mean age 44 years) with Brugada syndrome and ICM (Reveal DX, Medtronic)[10]. Most patients were symptomatic and had a previous EPS, furthermore, half of the study population had a spontaneous type 1 Brugada ECG pattern. During a mean follow-up of 33 months, no ventricular arrhythmic event was documented in patients with recurrence of symptoms. In 2017, Giustetto et al. reported the experience with ICMs in the Piedmont Brugada registry[5]. In this study, 13 patients with neurally mediated syncope and 14 patients with unexplained, suspected arrhythmia-related syncope received an ICM. During follow-up, no patient had an arrhythmic event (defined as ventricular fibrillation, sustained ventricular arrhythmia or SCD). Our study expands the experience with ICM in symptomatic patients with Brugada syndrome and is in line with previous studies by demonstrating no sustained ventricular arrhythmias during follow-up. In contrast to previous studies, we reported all ICM-detected arrhythmic events independent of initial symptoms.

Considerations

There seems to be a role to use ICM in selected symptomatic Brugada patients. Patients who are recently diagnosed with Brugada syndrome usually experience increased anxiety considering the increased risk of SCD. The heightened awareness of palpitations or near-syncope may be troublesome for patients, and in this respect an ICM with remote monitoring may provide reassurance by excluding clinically relevant arrhythmias during symptoms.

On the other hand, when using an ICM there are some limiting factors which should be considered such as device costs, data overload, clinical relevance of device-detected ventricular arrhythmia and medical overuse. The issue of data overload is highlighted by the recording of almost 2,000 episodes in 20 patients in our study population. A dedicated telemonitoring staff with a proper infrastructure is advised before providing such a service to patients

Study limitations

Although this is one of the largest reported series on the use of ICM in Brugada patients, the sample size is still relatively small. This may impact on the external validity of the study results. Furthermore, a longer follow-up duration may potentially increase the likelihood of detecting ventricular arrhythmias. However, the average battery life time of the Reveal LINQ is 3 years. A longer follow-up would thus require replacement of the ICM. Finally, asymptomatic ventricular arrhythmia episodes which are shorter (<16 beats) or slower (<176 bpm) than the programmed cutoff values will be missed. Therefore, the true incidence of ventricular arrhythmia episodes will most likely be higher in this population.

Conclusion

An ICM can be used to exclude ventricular arrhythmias in symptomatic patients with Brugada syndrome at presumed low risk of SCD and thereby providing reassurance. Furthermore, an ICM-detected arrhythmia changed clinical management in 20% of patients.

Appendix

Appendix A. Overview of ICM-detected arrhythmias

	Total episodes (n=1912)
Symptom episodes*	**904 (47%)**
- Sinus rhythm	888 (98%)
without ectopy	411
with PVCs	255
with PACs	222
- Regular broad complex tachycardia	8 (<1%)
- Regular small complex tachycardia	4 (<1%)
- Atrial fibrillation	4 (<1%)
Brady episodes*	**822 (43%)**
- Sinus bradycardia	818 (99%)
- Sinus rhythm	2
with undersensing of PVCs	2
- Sinus arrest	2 (<1%)
Tachycardia episodes*	**121 (6%)**
- Sinus rhythm	121 (100%)
without ectopy	98
with oversensing	13
with noise	9
with PACs	1
Pause episodes*	**53 (3%)**
- Sinus rhythm	48 (91%)
with sudden drop of R-wave	41
with small R-waves	6
with undersensing of PVCs	1
- Sinus arrest	4 (8%)
- AV-block	1 (2%)
Atrial tachycardia*	**11 (<1%)**
Sinus rhythm	11 (100%)
Atrial fibrillation*	**1 (<1%)**
Sinus rhythm with PACs	1 (100%)

Data are presented as n (%). * Episode classification by ICM. Abbreviations: AV-block, atrio-ventricular block; PAC, premature atrial complex; PVC, premature ventricular complex; SA, sino-atrial.

References

1. Sieira J, Conte G, Ciconte G, Chierchia GB, Casado-Arroyo R, Baltogiannis G, Di Giovanni G, Saitoh Y, Julia J, Mugnai G, La Meir M, Wellens F, Czapla J, Pappaert G, de Asmundis C and Brugada P. A score model to predict risk of events in patients with Brugada Syndrome. *Eur Heart J*. 2017;38:1756-1763.
2. Priori SG, Gasparini M, Napolitano C, Della Bella P, Ottonelli AG, Sassone B, Giordano U, Pappone C, Mascioli G, Rossetti G, De Nardis R and Colombo M. Risk stratification in Brugada syndrome: results of the PRELUDE (PRogrammed ELectrical stimUlation preDictive valuE) registry. *J Am Coll Cardiol*. 2012;59:37-45.
3. Probst V, Veltmann C, Eckardt L, Meregalli PG, Gaita F, Tan HL, Babuty D, Sacher F, Giustetto C, Schulze-Bahr E, Borggrefe M, Haissaguerre M, Mabo P, Le Marec H, Wolpert C and Wilde AA. Long-term prognosis of patients diagnosed with Brugada syndrome: Results from the FINGER Brugada Syndrome Registry. *Circulation*. 2010;121:635-43.
4. Sroubek J, Probst V, Mazzanti A, Delise P, Hevia JC, Ohkubo K, Zorzi A, Champagne J, Kostopoulou A, Yin X, Napolitano C, Milan DJ, Wilde A, Sacher F, Borggrefe M, Ellinor PT, Theodorakis G, Nault I, Corrado D, Watanabe I, Antzelevitch C, Allocca G, Priori SG and Lubitz SA. Programmed Ventricular Stimulation for Risk Stratification in the Brugada Syndrome: A Pooled Analysis. *Circulation*. 2016;133:622-30.
5. Giustetto C, Cerrato N, Ruffino E, Gribaudo E, Scrocco C, Barbonaglia L, Bianchi F, Bortnik M, Rossetti G, Carvalho P, Riccardi R, Castagno D, Anselmino M, Bergamasco L and Gaita F. Etiological diagnosis, prognostic significance and role of electrophysiological study in patients with Brugada ECG and syncope. *Int J Cardiol*. 2017;241:188-193.
6. Priori SG, Blomstrom-Lundqvist C, Mazzanti A, Blom N, Borggrefe M, Camm J, Elliott PM, Fitzsimons D, Hatala R, Hindricks G, Kirchhof P, Kjeldsen K, Kuck KH, Hernandez-Madrid A, Nikolaou N, Norekval TM, Spaulding C, Van Veldhuisen DJ and Group ESCSD. 2015 ESC Guidelines for the management of patients with ventricular arrhythmias and the prevention of sudden cardiac death: The Task Force for the Management of Patients with Ventricular Arrhythmias and the Prevention of Sudden Cardiac Death of the European Society of Cardiology (ESC). Endorsed by: Association for European Paediatric and Congenital Cardiology (AEPC). *Eur Heart J*. 2015;36:2793-2867.
7. Al-Khatib SM, Stevenson WG, Ackerman MJ, Bryant WJ, Callans DJ, Curtis AB, Deal BJ, Dickfeld T, Field ME, Fonarow GC, Gillis AM, Granger CB, Hammill SC, Hlatky MA, Joglar JA, Kay GN, Matlock DD, Myerburg RJ and Page RL. 2017 AHA/ACC/HRS Guideline for Management of Patients With Ventricular Arrhythmias and the Prevention of Sudden Cardiac Death. *Circulation*. 2018;138:e272-e391.
8. Dereci A, Yap SC and Schinkel AFL. Meta-Analysis of Clinical Outcome After Implantable Cardioverter-Defibrillator Implantation in Patients With Brugada Syndrome. *JACC Clin Electrophysiol*. 2019;5:141-148.
9. Olde Nordkamp LR, Vink AS, Wilde AA, de Lange FJ, de Jong JS, Wieling W, van Dijk N and Tan HL. Syncope in Brugada syndrome: prevalence, clinical significance, and clues from history taking to distinguish arrhythmic from nonarrhythmic causes. *Heart Rhythm*. 2015;12:367-75.
10. Kubala M, Aissou L, Traulle S, Gugenheim AL and Hermida JS. Use of implantable loop recorders in patients with Brugada syndrome and suspected risk of ventricular arrhythmia. *Europace*. 2012;14:898-902.

11. Sakhi R, Theuns D, Bhagwandien RE, Michels M, Schinkel AFL, Szili-Torok T, Zijlstra F, Roos-Hesselink JW and Yap SC. Value of implantable loop recorders in patients with structural or electrical heart disease. *J Interv Card Electrophysiol*. 2018;52:203-208.
12. Brignole M, Moya A, de Lange FJ, Deharo JC, Elliott PM, Fanciulli A, Fedorowski A, Furlan R, Kenny RA, Martin A, Probst V, Reed MJ, Rice CP, Sutton R, Ungar A, van Dijk JG and Group ESCSD. 2018 ESC Guidelines for the diagnosis and management of syncope. *Eur Heart J*. 2018;39:1883-1948.
13. Antzelevitch C, Yan GX, Ackerman MJ, Borggrefe M, Corrado D, Guo J, Gussak I, Hasdemir C, Horie M, Huikuri H, Ma C, Morita H, Nam GB, Sacher F, Shimizu W, Viskin S and Wilde AA. J-Wave syndromes expert consensus conference report: Emerging concepts and gaps in knowledge. *Heart Rhythm*. 2016;13:e295-324.
14. Priori SG, Wilde AA, Horie M, Cho Y, Behr ER, Berul C, Blom N, Brugada J, Chiang CE, Huikuri H, Kannankeril P, Krahn A, Leenhardt A, Moss A, Schwartz PJ, Shimizu W, Tomaselli G and Tracy C. HRS/EHRA/APHRS expert consensus statement on the diagnosis and management of patients with inherited primary arrhythmia syndromes: document endorsed by HRS, EHRA, and APHRS in May 2013 and by ACCF, AHA, PACES, and AEPC in June 2013. *Heart Rhythm*. 2013;10:1932-63.
15. Sakhi R, Theuns D, Szili-Torok T and Yap SC. Insertable cardiac monitors: current indications and devices. *Expert Rev Med Devices*. 2019;16:45-55.
16. Boule S, Kouakam C and Brigadeau F. Very prolonged episode of self-terminating ventricular fibrillation in a patient with Brugada syndrome. *Can J Cardiol*. 2013;29:1742 e1-3.
17. Hamilton G, O'Donnell D and Han HC. Brugada syndrome and undifferentiated syncope: use of an implantable loop recorder to document causation. *Med J Aust*. 2018;209:113-114.
18. Champagne J, Philippon F, Gilbert M, Molin F, Blier L, Nault I, Sarrazin JF, Charbonneau L, Dufort L, Drolet B, Chahine M and O'Hara GE. The Brugada syndrome in Canada: a unique French-Canadian experience. *Can J Cardiol*. 2007;23 Suppl B:71B-75B.

CHAPTER 7

Increased risk of ventricular arrhythmias in survivors of out-of-hospital cardiac arrest with chronic total coronary occlusion

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Heart Rhythm. 2018 Jan;15(1):124-129.

Abstract

Background: A chronic total occlusion (CTO) is common in out-of-hospital cardiac arrest (OHCA) survivors with coronary artery disease. It is unclear whether a CTO contributes to ventricular arrhythmias in this population.

Objective: This study sought to evaluate the impact of unrevascularized CTO's on the occurrence of appropriate implantable cardioverter-defibrillator (ICD) therapy and all-cause mortality in OHCA survivors with coronary artery disease.

Methods: This was a retrospective study that included all consecutive OHCA survivors with coronary artery disease who received an ICD from 1999 until 2015. Study endpoints were appropriate ICD therapy and all-cause mortality.

Results: We identified 217 OHCA survivors (mean age 63±10 years, 86% man) with coronary artery disease. An unrevascularized CTO was present in 71 of 217 patients (33%) at the time of ICD implantation. During a median follow-up of 61 months (interquartile range, 28-97 months), 57 of 217 patients (26%) experienced an appropriate ICD therapy. CTO patients had a higher incidence of appropriate ICD therapy in comparison to non-CTO patients (logrank P=0.002). Multivariate Cox regression analysis identified CTO (hazard ratio, 2.07; 95% confidence interval, 1.23-3.50; P=0.007) as an independent predictor of appropriate ICD therapy. The presence of a CTO was not associated with a higher mortality rate (logrank P=0.18).

Conclusions: In OHCA survivors with coronary artery disease receiving an ICD for secondary prevention, a CTO was an independent predictor for the occurrence of ventricular arrhythmias but not for mortality.

Introduction

The exact role of a chronic total occlusion (CTO) in causing a life-threatening ventricular arrhythmias (VA) is not clear. In clinical practice we encounter out-of-hospital cardiac arrest (OHCA) survivors with a CTO who have a relatively preserved left ventricular function and no significant rise in cardiac enzymes. One may speculate that the presence of a CTO may contribute to the VA event by a complex interplay of scar and ischemia. A previous nonrandomized study showed that failed or unattempted CTO recanalization in stable coronary artery disease patients was associated with increased risk of sudden cardiac death in comparison to those with revascularized CTO[1]. Furthermore, several studies in patients with ischemic cardiomyopathy and severe LV dysfunction who receive an ICD for primary prevention have shown that a CTO is an independent predictor of VA[2, 3]. Currently, there is limited data on the prognostic implications of a CTO in patients with coronary artery disease who present with OHCA due to VA. The aim of the present study was to evaluate the impact of a CTO on the occurrence of VA and all-cause mortality in survivors of OHCA with coronary artery disease.

Methods

Study Population

The study population was identified using the prospective ICD registry of the department of cardiology of the Erasmus Medical Center in Rotterdam, the Netherlands. Baseline clinical and echocardiography data, characteristics of the implant procedure, and data for all follow-up visits were prospectively recorded in a dedicated database. We identified all consecutive patients with coronary artery disease who received an ICD for secondary prevention after OHCA due to VA between December 1999 and June 2015. Coronary artery disease was defined as the presence of significant coronary artery stenosis (>50%) or a history of percutaneous or surgical revascularization.

For analysis of the association between CTO and VA, 2 researchers (S.C.Y. and E.Y.) analyzed every patient in our cohort for the presence of a CTO at the time of ICD implantation by evaluating the coronary angiograms and catheterization reports before ICD implantation. This study was approved by the institutional review board of the Erasmus Medical Center.

Definition of study variables

Chronic total occlusion was defined as complete vessel occlusion with TIMI 0 flow within the occluded segment and an estimated occlusion duration of ≥3 months[4, 5]. Occluded vessels that were surgically or percutaneously revascularized and secondary occluded vessels (i.e., diagonal branch, posterior descending artery, and posterolateral branches) were not classified as CTO in this study. Multivessel disease was defined as the presence of 2 or more coronary arteries with significant non-revascularized lesions at the time of ICD implantation.

Device Programming

Devices were programmed with 2-3 consecutive zones (monitor zone, ventricular tachycardia zone and ventricular fibrillation zone, usually 2 zones) with limits slightly varying per manufacturer. The cut-off rate for the VT zone was usually set at 171-182 bpm and the cut-off rate for the VF zone was usually set at 222-230 bpm. In the VT zone, arrhythmias were initially treated with a series of antitachycardia pacing (ATP) bursts followed by shocks. In the VF zone, device shocks were the initial therapy or, when available, "ATP during charging". If a patient had a VA with cycle length lower than the initially programmed cut-off, another detection zone for slow VT was added. Conventional programming was used for detection duration. Detection in the VF zone was usually programmed at 18 of 24 intervals or a 2.5-second delay depending on manufacturer. Detection in the VT zone was usually programmed at 16-20 intervals or a 5-second delay depending on manufacturer.

Follow-up and endpoints

Patients were usually followed every 3-6 months. The follow-up visits included clinical assessment and device interrogation. Unscheduled device interrogations were performed in case of symptomatic episodes of arrhythmia and during unplanned hospitalization. All spontaneous VA episodes were prospectively reviewed and classified (D.A.M.J.T). The primary endpoint was appropriate ICD therapy defined as the delivery of ATP or shock for VA (either ventricular tachycardia or ventricular fibrillation). The secondary endpoint was all-cause mortality.

Statistical Analysis

Continuous data are presented as mean ± standard deviation if the data were normally distributed, or as median with interquartile range (25^{th} and 75^{th} percentile) otherwise. Categorical variables are presented by frequencies and percentages. Differences of continuous variables between the two groups were analyzed with the unpaired Student's t-test or the Mann-Whitney U-test, as appropriate. Differences between categorical variables were evaluated using the Chi-square test or the Fisher's exact test in case of small expected cell frequencies.

The cumulative event rate of appropriate ICD therapy was calculated using the Kaplan-Meier method. Predictors of appropriate ICD therapy were determined using univariable and multivariable Cox regression analysis. Potential predictors were presence of CTO, left ventricular ejection fraction (LVEF) <35%, coronary artery bypass graft, multivessel disease, age >70 years, NYHA class III and renal dysfunction (GFR <60 mL/min). Any variable with a *P* value <0.10 and CTO status were entered in the multivariable model. Data are presented as hazard ratios (HR) and 95% confidence intervals (CI). A subgroup analysis was also performed where patients with unrevascularized CTO were compared to patients with recent (i.e., between OHCA and ICD implantation) successful CTO revascularization (surgical or percutaneous). Statistical analyses were performed using SPSS V.21.0. All statistical tests were two-sided. *P* values <0.05 were considered statistically significant.

Results

Study population

A total of 217 patients received an ICD as secondary prevention after experiencing OHCA for VA during the study period. The CTO group consisted of 71 patients (33%) with an unrevascularized CTO before ICD implantation. Baseline characteristics are depicted in Table 1. The CTO group was older, had more multivessel disease and had less coronary artery bypass grafts (CABG). Of the 71 CTO patients, 23 patients (32%) underwent myocardial perfusion scintigraphy. Of the patients who underwent imaging stress testing, the majority (21 of 23 patients, 91%) demonstrated no or limited myocardial ischemia.

Table 1. Baseline characteristics

Characteristic	**All patients (n=217)**	**Non-CTO group (n=146)**	**CTO group (n=71)**	**P-value**
Age (years), mean±SD	63±10	62±11	65±9	0.03
Male gender	187 (86)	123 (84)	64 (90)	0.24
Medical history				
- Diabetes mellitus	39 (18)	26 (18)	13 (18)	0.93
- Renal dysfunction (GFR <60 mL/min)	50 (23)	31 (21)	19 (27)	0.36
- Previous CABG	66 (30)	55 (38)	11 (16)	0.001
- Previous PCI	121 (56)	81 (56)	40 (56)	0.91
- NYHA class ≥II	144 (66)	95 (65)	49 (69)	0.56
- Multivessel disease	40 (18)	7 (5)	33 (47)	<0.001
- LVEF <35%	112 (52)	71 (49)	41 (58)	0.21
- QRS ≥130 ms	55 (25)	33 (23)	22 (31)	0.18
Medication at ICD implantation				
- ACE inhibitor	177 (82)	120 (82)	57 (80)	0.73
- Beta-blocker	177 (82)	121 (83)	56 (79)	0.48
- Statin	171 (79)	115 (79)	56 (79)	0.99
- Diuretic	106 (49)	71 (49)	35 (49)	0.93
- Amiodarone	39 (18)	29 (20)	10 (14)	0.30
- Digoxin	20 (9)	14 (10)	6 (9)	0.79
ICD type				0.81
- Single-chamber	135 (62)	93 (64)	42 (59)	
- Dual-chamber	59 (27)	38 (26)	21 (30)	
- CRT-D	23 (11)	15 (10)	8 (11)	

Data are presented as n (%), unless stated otherwise. ACE indicates angiotensin-converting-enzyme; CABG, coronary artery bypass graft; CRT-D, cardiac resynchronization therapy with defibrillator; GFR, glomerular filtration rate; ICD, implantable cardioverter-defibrillator; LVEF, left ventricular ejection fraction; NYHA, New York Heart Association; PCI, percutaneous coronary intervention. * >50% luminal stenosis.

Appropriate ICD therapy

During a median follow-up of 61 months (28-97 months), 57 of 217 patients (26%) of the total group experienced an appropriate ICD therapy. The incidence of appropriate ICD therapy was higher in the CTO group in comparison to the non-CTO group (logrank P=0.002, Figure 1). The cumulative event rates for appropriate ICD therapy (ATP and ICD shock) in the CTO group were 19.7%, 37.3% and 37.3% at 1, 3 and 5 years, respectively. The cumulative event rates for appropriate ICD therapy in the non-CTO group were 9.4%, 21.9% and 24.8% at 1, 3 and 5 years, respectively. Using univariate Cox regression analysis, the presence of a CTO was associated with an increased risk of appropriate ICD therapy (HR 2.20; 95% CI 1.31-3.72; P=0.003) (Table 2). Multivariate Cox regression analysis demonstrated that CTO and LVEF <35% were independent predictors of appropriate ICD therapy (Table 2). The cumulative event rate for appropriate ICD therapy in the CTO and non-CTO group stratified by left ventricular function is depicted in Figure 2.

When restricting the outcome data to appropriate ICD therapy in the VF zone, the CTO group only showed a trend towards a higher rate of appropriate ICD therapy in comparison to the non-CTO cohort (logrank P=0.08). The 5-year event rate of appropriate ICD therapy in the VF zone was 20.6% and 15.8% in the CTO and non-CTO group, respectively.

Figure 1. Cumulative event rate for appropriate ICD therapy in CTO and non-CTO populations - CTO indicates chronic total occlusion; ICD, implantable cardioverter-defibrillator.

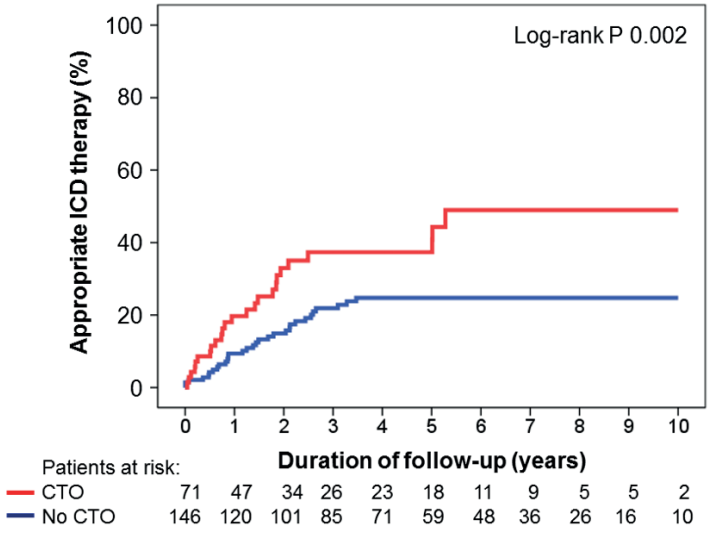
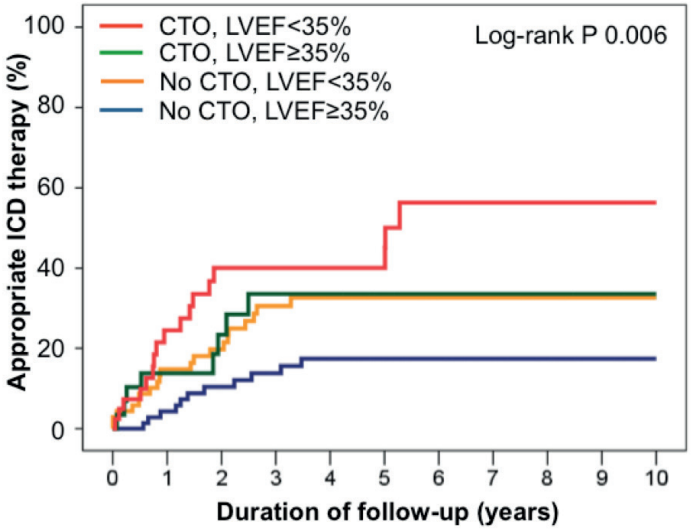


Table 2. Predictors of appropriate ICD therapy

	Univariable		Multivariable	
	HR (95%CI)	**P-value**	**HR (95%CI)**	**P-value**
CTO	2.20 (1.31-3.72)	0.003	2.07 (1.23-3.50)	0.007
LVEF <35%	2.07 (1.19-3.59)	0.01	1.94 (1.11-3.38)	0.02
Multivessel disease	1.64 (0.89-3.03)	0.11		
CABG	1.35 (0.79-2.31)	0.27		
Age >70 years	1.11 (0.62-1.98)	0.73		
NYHA class III	1.06 (0.33-3.39)	0.92		
Renal dysfunction	0.80 (0.42-1.51)	0.49		

CABG indicates coronary artery bypass graft; CTO, chronic total occlusion; LVEF, left ventricular ejection fraction; NYHA, New York Heart Association.

Figure 2. Cumulative event rate for appropriate ICD therapy in patients with CTO and non-CTO stratified by LV ejection fraction below and above 35%. Abbreviations: CTO indicates chronic total occlusion; ICD, implantable cardioverter-defibrillator; LVEF, left ventricular ejection fraction.



Mortality

A total of 58 patients (27%) died during follow-up. The survival rate was similar between the CTO and non-CTO group (logrank P=0.18, Figure 3). The cumulative survival rates in the CTO group were 94.2%, 83.9% and 81.6% at 1, 3 and 5 years, respectively. The cumulative survival rates in the non-CTO group were 99.2%, 85.9% and 82.2% at 1, 3 and 5 years, respectively. Univariate and multivariate Cox regression analysis demonstrated that the presence of a CTO was not a predictor of all-cause mortality (Table

3). Univariate Cox regression analysis showed that LVEF <35%, age >70 years and renal dysfunction were associated with increased all-cause mortality. However, multivariate Cox regression analysis demonstrated that LVEF <35% and age >70 years were independent predictors of all-cause mortality.

Figure 3. Cumulative survival rate in CTO and non-CTO populations. Abbreviations: CTO indicates chronic total occlusion.

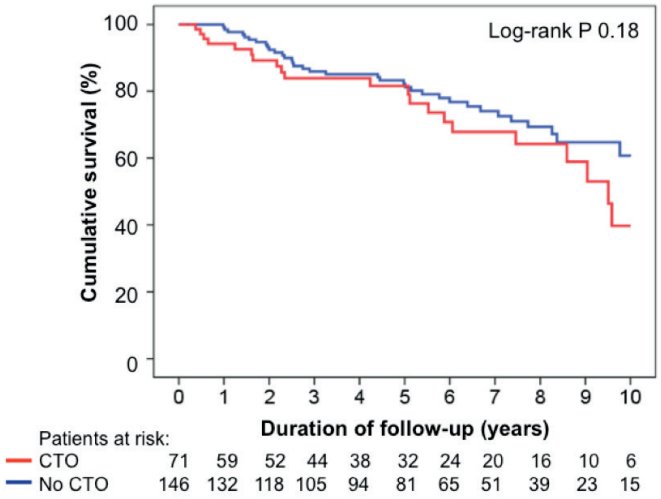


Table 3. Predictors of all-cause mortality

	Univariable		Multivariable	
	HR (95%CI)	**P-value**	**HR (95%CI)**	**P-value**
CTO	1.44 (0.85-2.45)	0.18	0.97 (0.51-1.87)	0.93
Age >70 years	3.19 (1.90-5.38)	<0.001	2.84 (1.64-4.92)	<0.001
LVEF <35%	2.20 (1.23-3.92)	0.008	2.07 (1.15-3.73)	0.02
Renal dysfunction	2.19 (1.29-3.72)	0.004	1.63 (0.94-2.81)	0.08
Multivessel disease	1.76 (0.97-3.19)	0.06	1.35 (0.65-2.80)	0.42
NYHA class III	1.75 (0.70-4.39)	0.24		
CABG	1.23 (0.72-2.09)	0.45		

CABG indicates coronary artery bypass graft; CTO, chronic total occlusion; LVEF, left ventricular ejection fraction; NYHA, New York Heart Association.

Recent CTO revascularization and appropriate ICD therapy

There was a subgroup of patients (n=25) who underwent successful CTO revascularization in the period between OHCA and ICD implantation. The cumulative event rate of appropriate ICD therapy within this group was similar to the unrevascularized CTO group (n=71) (logrank P=0.48).

Discussion

The present study demonstrates that a CTO was an independent predictor of appropriate ICD therapy, but was not associated with all-cause mortality. This work also found that LVEF<35% was an independent predictor of both appropriate ICD therapy and all-cause mortality.

Chronic total occlusion and ventricular arrhythmias

CTO is a very common condition among patients with coronary artery disease, with a reported prevalence between 30% to 50% in patients with ischemia referred to the catheterization laboratory[6, 7]. Therefore, it is not surprisingly that there was a high prevalence of CTO in our population of out-of-hospital cardiac survivors with coronary artery disease who received an ICD. The exact role of a CTO in causing or triggering the initial ventricular fibrillation episode is not fully understood. However, there are several observations that may suggest that the presence of a CTO play an important role in the development of VA in patients with coronary artery disease.

A recent study showed that patients with previously failed or not attempted CTO recanalization had a higher incidence of sudden cardiac death (2.7% versus 0.5% at 4-years of follow-up) in comparison to those with successful CTO recanalization[1]. These observations may imply that ischemia associated with a CTO renders a patient vulnerable for VA. This is strengthened by the observation that CTO's are an independent predictor of VA in patients with ischemic cardiomyopathy and ICDs for primary prevention[2, 3]. Our study is, to the best of our knowledge, the first study which shows that a CTO is also an independent predictor of VA in survivors of OHCA with coronary artery disease who receive an ICD.

There are several explanations for the increased risk of VA in CTO patients. The substrate of VA in patients with ischemic cardiomyopathy is usually a myocardial scar[8]. Channels of slow conduction, a pre-requisite for reentry, can be found within the scar or, more commonly, in the scar-border zone[8-10]. It is known that the presence of a CTO is associated with ischemia, as measured by fractional flow reserve, even in the presence of well-developed collaterals[11, 12]. Ischemia around the post-infarction necrotic core may increase electrical instability and the development of VA.

Chronic total occlusion and all-cause mortality in ICD recipients

Prior studies in ischemic cardiomyopathy patients who received an ICD as primary prevention have shown conflicting results of the effect of a CTO on all-cause mortality[2, 13]. It is important to realize that primary prevention patients have a low ejection fraction, which is a strong predictor of all-cause mortality.

In our study cohort of patients who received an ICD for secondary prevention, of which approximately half (52%) had a LVEF<35%, the presence of CTO was not associated with a higher mortality rate.

The lack of a clear adverse effect of a CTO on all-cause mortality in ICD recipients (either primary or secondary prevention) is in contrast to data from non-ICD carriers. A recent meta-analysis, not specifically including ICD recipients, showed that failed CTO recanalization is associated with a higher risk of all-cause mortality in comparison to those with successful CTO recanalization (odds ratio 1.92; 95% CI 1.59-2.33)[14]. This discrepancy in the effect of a CTO on all-cause mortality may be partially explained by the prevention of SCD due to VA in ICD recipients.

Clinical implications and future directions

The results of the present study may have several implications. First, due to technical advances in percutaneous coronary intervention techniques, CTO recanalization can be achieved with high success rates and low complication rates[15]. At this moment, there is no compelling evidence that successful CTO recanalization during initial hospitalization may reduce VA burden in survivors of OHCA. In the small substudy in our cohort, there was no reduction in appropriate ICD therapy in patients who underwent recent CTO revascularization before ICD implantation. However, this analysis is hampered by the small sample size (n=25, underpowered) and the observational nature of the study design. Appropriately designed prospective randomized trials can elucidate this issue.

Second, our study supports the causative role of a CTO in the development of VA irrespective of the left ventricular function. Interestingly, CTO patients with a LVEF>35% had a similar incidence of VA in comparison to non-CTO patients with severe LV dysfunction (LVEF<35%). Previous studies have shown that severe LV dysfunction is an important predictor of sudden cardiac death and ICDs are indicated as primary prevention in ischemic cardiomyopathy patients with severe LV dysfunction primarily based on the results of the MADIT II and SCD-HeFT trials (median LVEF 23-24%)[16-18]. Previous CTO studies demonstrated a higher risk of all-cause mortality and sudden cardiac death rate in patients with failed CTO recanalization despite the fact that only a minority (7-11%) had severe LV dysfunction[1, 19]. In our study, the presence of a CTO had a similar predictive power as severe LV dysfunction. More research is needed to investigate the incidence of VA and the role of a prophylactic ICD in patients with failed CTO recanalization and preserved LV function.

Study limitations

There are several limitations. The current guidelines recommend prolonged detection settings and higher tachycardia therapy zone limits to reduce ICD therapy primarily based on the MADIT-RIT trial[20]. These guidelines were published in 2015 and we changed our clinical practice in 2016 (these patients are not included in this study). We do not know whether these new settings will change the conclusions of our study as they will probably lower the incidence of appropriate ICD therapy both in the CTO and non-CTO groups. In addition, we have no complete data on the extent of ischemia in the CTO population and thus cannot make a distinction between those with small or moderate/large ischemic burden. One can imagine that patients with moderate or large ischemic burden are more prone to VA.

Finally, the single-center design may limit generalizability of the data. However, the 3-year mortality rate in our study (15%) was similar to the ICD arms of secondary prevention randomized controlled trials[21-23].

Conclusion

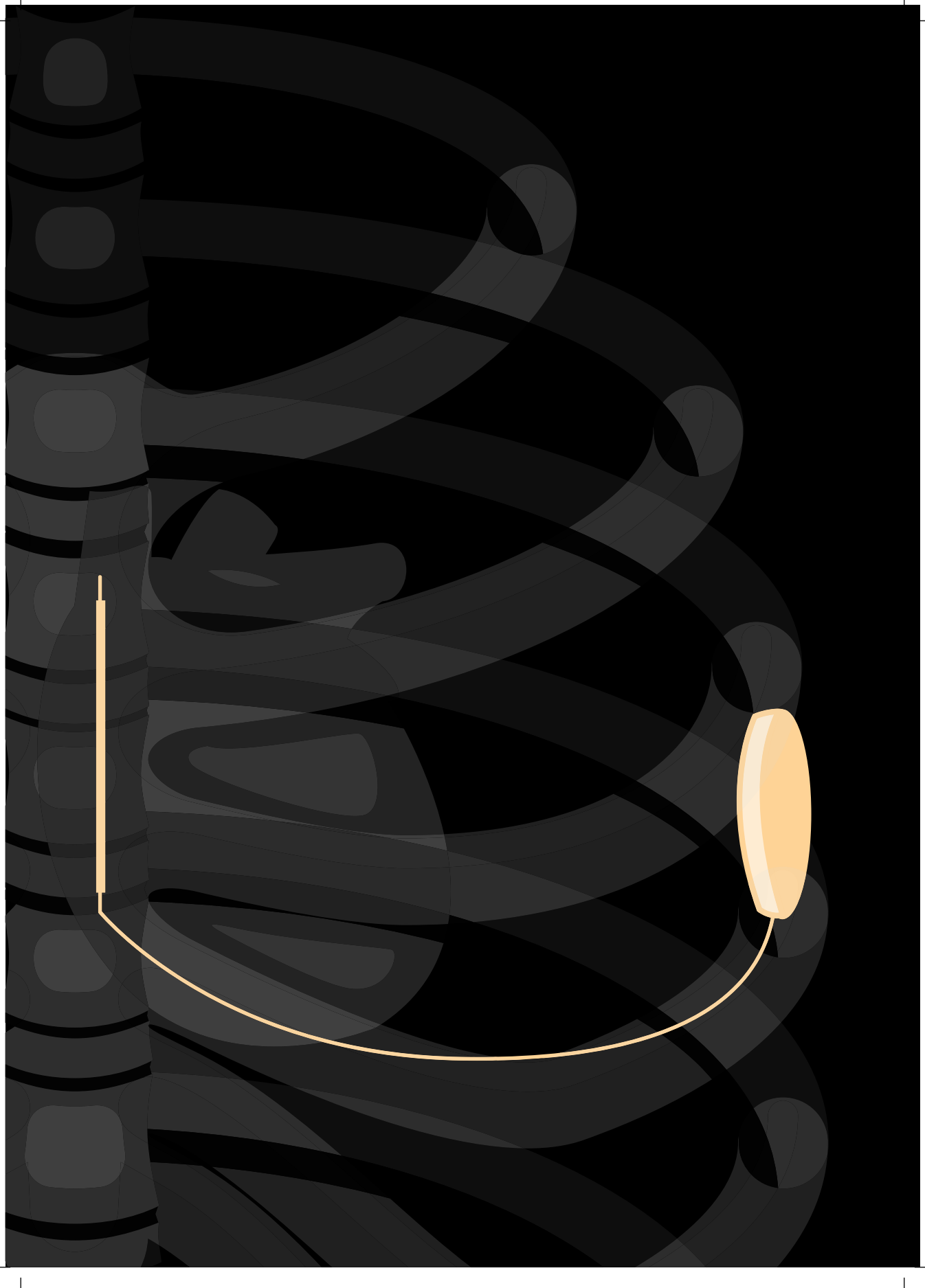
In OHCA survivors with coronary artery disease, the presence of a CTO is common and is an independent predictor of future VA. A CTO was not associated with a higher mortality rate in this secondary prevention ICD group. The data support the causative role of a CTO in the development of VA. Further studies are needed to investigate whether CTO revascularization can reduce the arrhythmic risk in OHCA survivors.

References

1. Godino C, Bassanelli G, Economou FI, Takagi K, Ancona M, Galaverna S, Mangieri A, Magni V, Latib A, Chieffo A, Carlino M, Montorfano M, Cappelletti A, Margonato A and Colombo A. Predictors of cardiac death in patients with coronary chronic total occlusion not revascularized by PCI. *Int J Cardiol*. 2013;168:1402-9.
2. Nombela-Franco L, Mitroi CD, Fernandez-Lozano I, Garcia-Touchard A, Toquero J, Castro-Urda V, Fernandez-Diaz JA, Perez-Pereira E, Beltran-Correas P, Segovia J, Werner GS, Javier G and Luis AP. Ventricular arrhythmias among implantable cardioverter-defibrillator recipients for primary prevention: impact of chronic total coronary occlusion (VACTO Primary Study). *Circulation Arrhythmia and electrophysiology*. 2012;5:147-54.
3. Di Marco A, Anguera I, Teruel L, Dallaglio P, Gonzalez-Costello J, Leon V, Nunez E, Manito N, Gomez-Hospital JA, Sabate X and Cequier A. Chronic total occlusion of an infarct-related artery: a new predictor of ventricular arrhythmias in primary prevention implantable cardioverter defibrillator patients. *Europace*. 2016.
4. Di Mario C, Werner GS, Sianos G, Galassi AR, Buttner J, Dudek D, Chevalier B, Lefevre T, Schofer J, Koolen J, Sievert H, Reimers B, Fajadet J, Colombo A, Gershlick A, Serruys PW and Reifart N. European perspective in the recanalisation of Chronic Total Occlusions (CTO): consensus document from the EuroCTO Club. *EuroIntervention*. 2007;3:30-43.
5. Authors/Task Force m, Windecker S, Kolh P, Alfonso F, Collet JP, Cremer J, Falk V, Filippatos G, Hamm C, Head SJ, Juni P, Kappetein AP, Kastrati A, Knuuti J, Landmesser U, Laufer G, Neumann FJ, Richter DJ, Schauerte P, Sousa Uva M, Stefanini GG, Taggart DP, Torracca L, Valgimigli M, Wijns W and Witkowski A. 2014 ESC/EACTS Guidelines on myocardial revascularization: The Task Force on Myocardial Revascularization of the European Society of Cardiology (ESC) and the European Association for Cardio-Thoracic Surgery (EACTS)Developed with the special contribution of the European Association of Percutaneous Cardiovascular Interventions (EAPCI). *European heart journal*. 2014;35:2541-619.
6. Christofferson RD, Lehmann KG, Martin GV, Every N, Caldwell JH and Kapadia SR. Effect of chronic total coronary occlusion on treatment strategy. *The American journal of cardiology*. 2005;95:1088-91.
7. Werner GS, Gitt AK, Zeymer U, Juenger C, Towae F, Wienbergen H and Senges J. Chronic total coronary occlusions in patients with stable angina pectoris: impact on therapy and outcome in present day clinical practice. *Clin Res Cardiol*. 2009;98:435-41.
8. Horowitz LN, Josephson ME and Harken AH. Epicardial and endocardial activation during sustained ventricular tachycardia in man. *Circulation*. 1980;61:1227-38.
9. Arenal A, del Castillo S, Gonzalez-Torrecilla E, Atienza F, Ortiz M, Jimenez J, Puchol A, Garcia J and Almendral J. Tachycardia-related channel in the scar tissue in patients with sustained monomorphic ventricular tachycardias: influence of the voltage scar definition. *Circulation*. 2004;110:2568-74.
10. de Bakker JM, van Capelle FJ, Janse MJ, Wilde AA, Coronel R, Becker AE, Dingemans KP, van Hemel NM and Hauer RN. Reentry as a cause of ventricular tachycardia in patients with chronic ischemic heart disease: electrophysiologic and anatomic correlation. *Circulation*. 1988;77:589-606.
11. Sachdeva R, Agrawal M, Flynn SE, Werner GS and Uretsky BF. The myocardium supplied by a chronic total occlusion is a persistently ischemic zone. *Catheterization and cardiovascular interventions : official journal of the Society for Cardiac Angiography & Interventions*. 2014;83:9-16.

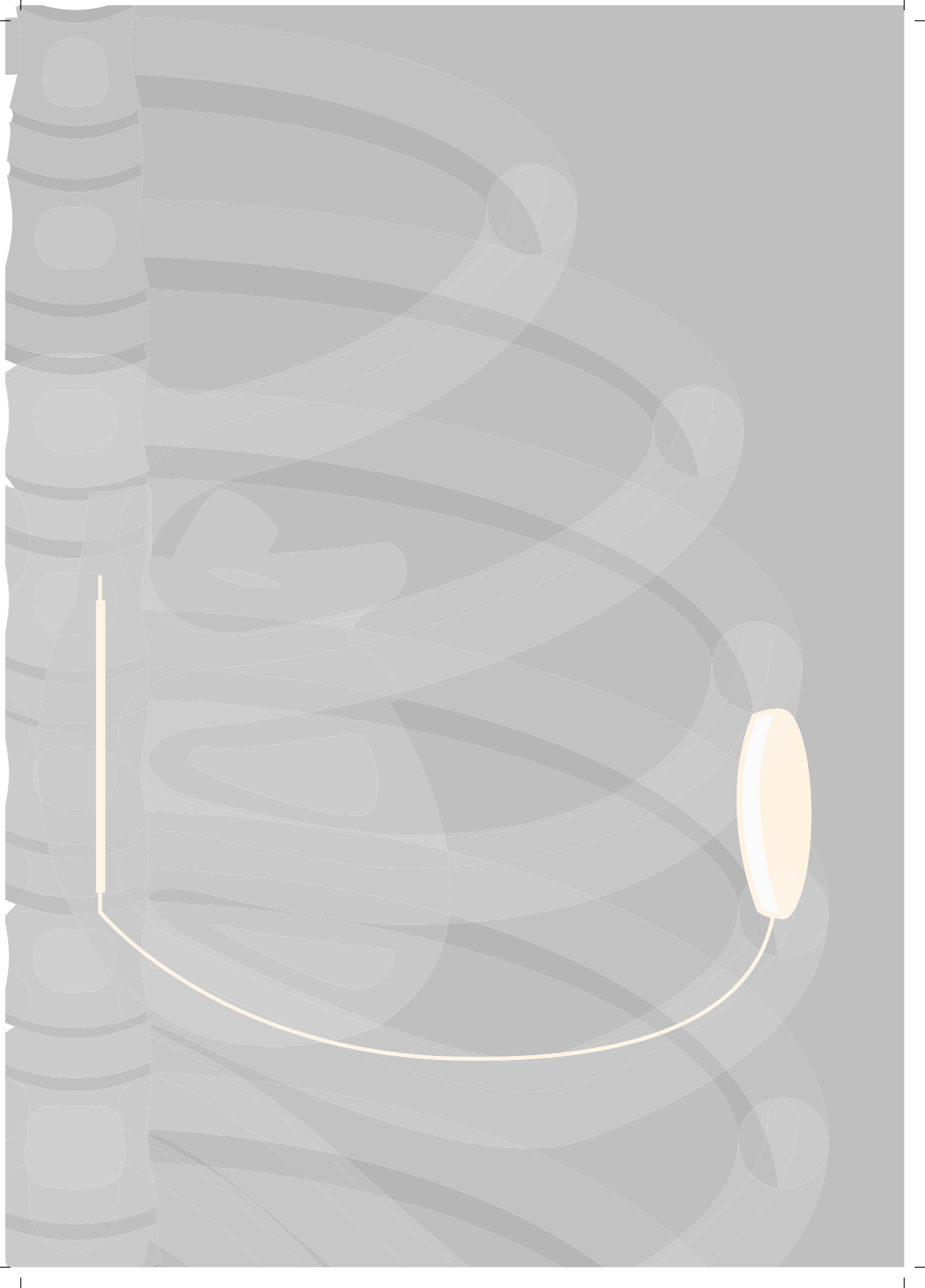
12. Werner GS, Surber R, Ferrari M, Fritzenwanger M and Figulla HR. The functional reserve of collaterals supplying long-term chronic total coronary occlusions in patients without prior myocardial infarction. *European heart journal*. 2006;27:2406-12.
13. Raja V, Wiegn P, Obel O, Christakopoulos G, Christopoulos G, Rangan BV, Roesle M, Abdullah SM, Luna M, Addo T, Ayers C, Garcia S, de Lemos JA, Banerjee S and Brilakis ES. Impact of Chronic Total Occlusions and Coronary Revascularization on All-Cause Mortality and the Incidence of Ventricular Arrhythmias in Patients With Ischemic Cardiomyopathy. *The American journal of cardiology*. 2015;116:1358-62.
14. Christakopoulos GE, Christopoulos G, Carlino M, Jeroudi OM, Roesle M, Rangan BV, Abdullah S, Grodin J, Kumbhani DJ, Vo M, Luna M, Alaswad K, Karmpaliotis D, Rinfret S, Garcia S, Banerjee S and Brilakis ES. Meta-analysis of clinical outcomes of patients who underwent percutaneous coronary interventions for chronic total occlusions. *The American journal of cardiology*. 2015;115:1367-75.
15. Patel VG, Brayton KM, Tamayo A, Mogabgab O, Michael TT, Lo N, Alomar M, Shorrock D, Cipher D, Abdullah S, Banerjee S and Brilakis ES. Angiographic success and procedural complications in patients undergoing percutaneous coronary chronic total occlusion interventions: a weighted meta-analysis of 18,061 patients from 65 studies. *JACC Cardiovascular interventions*. 2013;6:128-36.
16. Bardy GH, Lee KL, Mark DB, Poole JE, Packer DL, Boineau R, Domanski M, Troutman C, Anderson J, Johnson G, McNulty SE, Clapp-Channing N, Davidson-Ray LD, Fraulo ES, Fishbein DP, Luceri RM, Ip JH and Sudden Cardiac Death in Heart Failure Trial I. Amiodarone or an implantable cardioverter-defibrillator for congestive heart failure. *The New England journal of medicine*. 2005;352:225-37.
17. Moss AJ, Zareba W, Hall WJ, Klein H, Wilber DJ, Cannom DS, Daubert JP, Higgins SL, Brown MW, Andrews ML and Multicenter Automatic Defibrillator Implantation Trial III. Prophylactic implantation of a defibrillator in patients with myocardial infarction and reduced ejection fraction. *The New England journal of medicine*. 2002;346:877-83.
18. Priori SG, Blomstrom-Lundqvist C, Mazzanti A, Blom N, Borggrefe M, Camm J, Elliott PM, Fitzsimons D, Hatala R, Hindricks G, Kirchhof P, Kjeldsen K, Kuck KH, Hernandez-Madrid A, Nikolaou N, Norekval TM, Spaulding C, Van Veldhuisen DJ, Authors/Task Force M and Document R. 2015 ESC Guidelines for the management of patients with ventricular arrhythmias and the prevention of sudden cardiac death: The Task Force for the Management of Patients with Ventricular Arrhythmias and the Prevention of Sudden Cardiac Death of the European Society of Cardiology (ESC)Endorsed by: Association for European Paediatric and Congenital Cardiology (AEPC). *European heart journal*. 2015;36:2793-867.
19. Jones DA, Weerackody R, Rathod K, Behar J, Gallagher S, Knight CJ, Kapur A, Jain AK, Rothman MT, Thompson CA, Mathur A, Wragg A and Smith EJ. Successful recanalization of chronic total occlusions is associated with improved long-term survival. *JACC Cardiovascular interventions*. 2012;5:380-8.
20. Wilkoff BL, Fauchier L, Stiles MK, Morillo CA, Al-Khatib SM, Almendral J, Aguinaga L, Berger RD, Cuesta A, Daubert JP, Dubner S, Ellenbogen KA, Mark Estes NA, 3rd, Fenelon G, Garcia FC, Gasparini M, Haines DE, Healey JS, Hurtwitz JL, Keegan R, Kolb C, Kuck KH, Marinskis G, Martinelli M, McGuire M, Molina LG, Okumura K, Proclemer A, Russo AM, Singh JP, Swerdlow CD, Teo WS, Uribe W, Viskin S, Wang CC and Zhang S. 2015 HRS/EHRA/APHRS/SOLAECE expert consensus statement on optimal implantable cardioverter-defibrillator programming and testing. *Heart rhythm : the official journal of the Heart Rhythm Society*. 2016;13:e50-86.

21. Connolly SJ, Gent M, Roberts RS, Dorian P, Roy D, Sheldon RS, Mitchell LB, Green MS, Klein GJ and O'Brien B. Canadian implantable defibrillator study (CIDS) : a randomized trial of the implantable cardioverter defibrillator against amiodarone. *Circulation*. 2000;101:1297-302.
22. Kuck KH, Cappato R, Siebels J and Ruppel R. Randomized comparison of antiarrhythmic drug therapy with implantable defibrillators in patients resuscitated from cardiac arrest : the Cardiac Arrest Study Hamburg (CASH). *Circulation*. 2000;102:748-54.
23. A comparison of antiarrhythmic-drug therapy with implantable defibrillators in patients resuscitated from near-fatal ventricular arrhythmias. The Antiarrhythmics versus Implantable Defibrillators (AVID) Investigators. *The New England journal of medicine*. 1997;337:1576-83.



Part II

Eligibility for a subcutaneous ICD



CHAPTER 8

Frequency of Need for Antitachycardia or Antibradycardia Pacing or Cardiac Resynchronization Therapy in Patients with a Single-Chamber Implantable Cardioverter-Defibrillator

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America Journal of Cardiology. 2018 Dec 15;122(12):2068-2074

Abstract

The subcutaneous implantable cardioverter-defibrillator (S-ICD) is unable to deliver antitachycardia pacing (ATP), bradycardia pacing, and cardiac resynchronization therapy (CRT). However, little is known about the proportion of patients that develop the need for one of these features. We evaluated the potential suitability for a S-ICD at the time of first replacement in a cohort of patients with a transvenous single-chamber device who did not need bradycardia pacing at the time of implantation. The study cohort consisted of patients who received a transvenous single-chamber ICD between 1998 and September 2017. The primary endpoint was a combined endpoint of the need for atrial or ventricular pacing, development of a CRT indication, or termination of ventricular arrhythmias by ATP delivery. During a mean follow-up of 5.6 ± 1.9 years, 78 out of 254 (31%) patients reached the primary endpoint. The 7-years cumulative S-ICD suitability rate was 65.6% (95% CI 58.5% – 71.7%). Event rates were 9.5% (95% CI 6.5% – 13.9%) at 1-year follow-up, and 28.0% (95% CI 22.8% – 34.2%) at 5-years follow-up. For individual endpoints incidence rates were 1.8 (95% CI 1.2 – 2.6) per 100-patient-years for CRT, 0.3 (95% CI 0.1 – 0.8) per 100-patient-years for pacing-dependency, and 4.9 (95% CI 3.8 – 6.3) per 100-patient-years for appropriate ATP therapy. No baseline variables for predicting S-ICD unsuitability were found. In conclusion, at the time of the first replacement, 69% of the patients with a single-chamber device would have been clinically eligible for the S-ICD. Incidence rates of developing a bradycardia pacing and CRT indication are low.

Introduction

The implantable cardioverter defibrillator (ICD) has proven to be effective both in primary and secondary prevention of sudden cardiac death[1-4]. However, the transvenous ICD (TV-ICD) has been associated with acute and chronic complications due to the use of endovascular leads[5-7]. Lead failure and infection might require extraction, which is associated with a risk of severe complications, reported up to 1.7%[8,9]. Based on this, an entirely subcutaneous implantable defibrillator (S-ICD) has been developed as an alternative to the TV-ICD system[10]. The S-ICD has proven to be competent in terminating ventricular arrhythmias with defibrillation[11-14]. However, a trade-off of the S-ICD is the inability to deliver bradycardia pacing, cardiac resynchronization therapy (CRT) and antitachycardia pacing (ATP). Therefore, patients who qualify for a single-chamber TV-ICD without an indication for bradycardia pacing or ATP can be considered clinically eligible for a S-ICD. When considering these patients, many physicians are still reluctant to implant the S-ICD due to potential need for pacing or ATP. However, there is limited data on the proportion of patients who actually develop an indication for bradycardia pacing or CRT during follow-up. The aim of the study is to determine the need for pacing or ATP at the time of elective device replacement in a cohort of patients with a single-chamber TV-ICD who were theoretical eligible for a S-ICD at baseline. Predictors of development of an indication for bradycardia pacing or CRT, and predictors of monomorphic ventricular arrhythmias which can be terminated by ATP were identified.

Methods

Patients for this retrospective observational cohort study were obtained from the prospectively collected registry of all patients who underwent ICD implantation at the Erasmus Medical Centre, Rotterdam, the Netherlands. All patients who received a transvenous single-chamber ICD were identified. Patients who were pacemaker dependent or had another indication for bradycardia pacing and those who had a secondary prevention indication based on sustained monomorphic ventricular tachycardia (VT) were excluded from analysis. For the purpose of the study, the cohort comprised of those who underwent generator replacement or upgrade. The study period for inclusion was from November 1998 to September 2017. The administrative censoring date for analyses was September 2017 for all patients alive until that date. The study protocol was approved by the IRB of the Erasmus MC. The ethics committee waived the need for written informed consent, since the present study was a retrospective cohort analysis of patients with a clinical indication for ICD implantation.

Data on baseline clinical characteristics, implantation procedures, and scheduled or unscheduled follow-up visits were prospectively collected in the Erasmus Medical Center ICD registry. This registry and medical records were reviewed to obtain data on clinical variables at baseline and replacement.

The endpoint of the current study was the inappropriateness for an S-ICD system, which was defined as the occurrence of one of the following individual endpoints which ever occurred first: The development of an indication for bradycardia therapy, defined as the need for atrial and/or right ventricular pacing. If the bradycardia settings of the ICD required reprogramming to a higher lower rate or rate adaptive pacing mode, this was also considered an indication for bradycardia therapy. If the patient required reprogramming of bradycardia settings or required an upgrade to a dual-chamber device, the date of replacement or upgrade was considered the date of endpoint. The development of an indication for CRT. If the patient required an upgrade to a CRT-D, the date of upgrade was considered the date of endpoint. Termination of ventricular arrhythmias by ATP delivery was considered an endpoint. The date of first successful termination of VT by ATP was considered the endpoint. If a patient did not reach one of the above endpoints, the patient was censored at the date of elective generator replacement.

Statistical analysis

Normality of distribution was assessed by using the Shapiro-Wilk test. Continuous variables are presented as mean ± SD or as median with 25th and 75th percentiles, where appropriate. Data were compared by the Student t or Mann-Whitney U test, as appropriate. Categorical data are expressed as percentages and compared with Fisher's exact test. The event-free rate of unsuitability for an S-ICD system was calculated using the Kaplan-Meier method. The incidence rates of the endpoints upgrade (dual-chamber ICD/CRT-D) and ATP delivery were calculated and expressed per 100-patient-years with a 2-sided 95% confidence interval (CI). Univariate logistic regression analyses were used to determine potential clinical baseline predictors for unsuitability for a S-ICD, with the calculation of ORs with 95% CIs. Any variable with a P value < 0.10 was analyzed in a multivariate model. A P value < 0.05 was considered significant. All statistical analyses were performed using SPSS, version 24 (IBM Corp, Armonk, NY, USA) and STATA, version 12 (Statacorp, College Station, TX, USA.

Results

During the study period, a total of 1174 patients received a single-chamber TV-ICD. Excluding patients that had a secondary prevention indication based on sustained monomorphic VT, 977 patients remained. Of these, 269 patients received at least 1 replacement or upgrade. Nine patients were pacing-dependent at baseline, 5 patients received a re-implantation shortly after the first implantation due to an infection, and 1 patient received a replacement in another hospital. Consequently, these patients were excluded (Figure 1). The remaining 254 patients were considered the study cohort, with a mean age of 53 ± 14 years, majority were male (72%), and structural heart disease was present in 78% of patients. Most patients were in sinus rhythm at baseline (91%), with a mean heart rate of 69 ± 13 bpm. Other baseline characteristics are presented in Table 1. Beta-blockers were used in 187 (74%) of the patients, most of them used bisoprolol (24%), carvedilol (15%), or metoprolol (34%).

Table 1. Baseline clinical characteristics

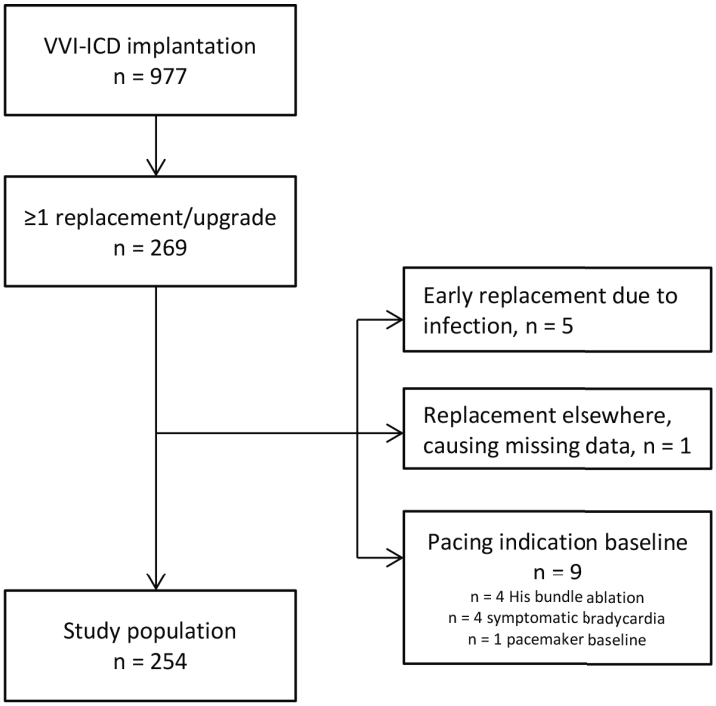
	Total group (n=254)
Age (years)	53 ± 14
Men	183 (72%)
Indication ICD therapy	
- Primary prevention	160 (63%)
- Secondary prevention	94 (37%)
Coronary artery disease	144 (57%)
- Myocardial infarction	127 (50%)
Atrial fibrillation	50 (20%)
Inherited primary arrhythmia syndrome	13 (5%)
- Cardiomyopathy	121 (48%)
- Dilated	35 (14%)
- Ischemic	59 (24%)
- Hypertrophic	14 (6%)
- Non compaction	11 (4%)
Left ventricular ejection fraction (%)	31 (25, 40)
New York Heart Association class	
- 1	99 (39%)
- 2	135 (53%)
- 3	18 (7%)
Diabetes mellitus	41 (16%)
Creatinine (µmol/L)	80 (70, 95)
Electrocardiographic parameters	
Rhythm	
- Sinus	232 (91%)
- Atrium fibrillation	22 (9%)
Heart rate (bpm)	69 ± 13
PR interval (ms)	171 ± 29
QRS duration (ms)	108 (98, 125)
QRS morphology	
- Normal	160 (63%)
- Left bundle branch block	34 (13%)
- Right bundle branch block	22 (9%)
- Intraventricular conduction delay	23 (9%)
Atrioventricular conduction disorder	28 (11%)
- 1st degree	28 (11%)

Table 1. continued

Medication	
Antiarrhythmic medication	214 (84%)
- Sodium channel blocker*	2 (1%)
- β-blocker*	187 (74%)
- Sotalol*	10 (4%)
- Amiodarone*	30 (12%)
- Digoxin*	30 (12%)
Calcium antagonists	27 (11%)
ACE inhibitors / ARBs	193 (76%)
Diuretics	126 (50%)
Statins	147 (58%)

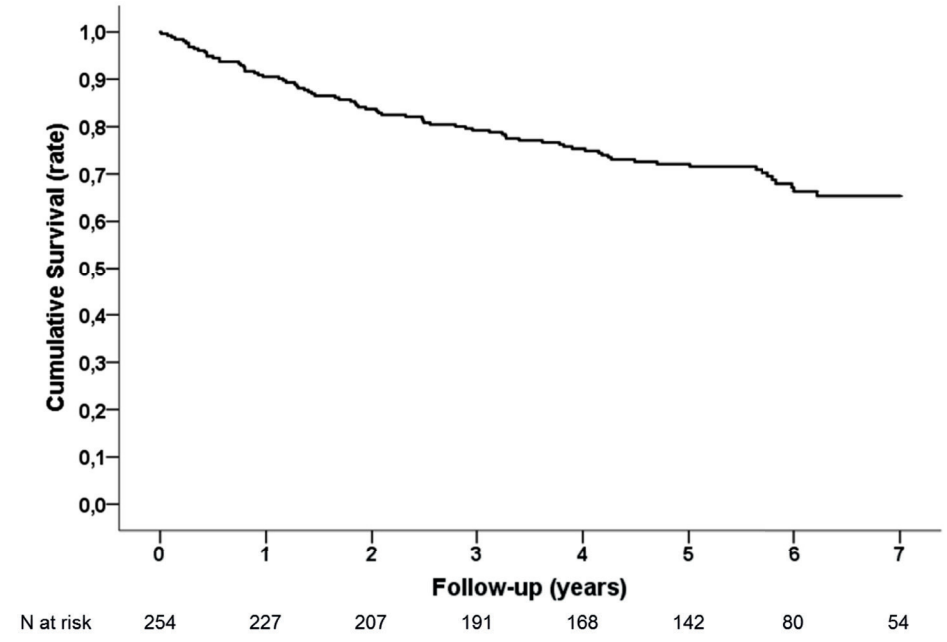
Normally distributed continuous data is presented as mean ±SD, non-Gaussian distributed continuous data as median (IQR), and categorical data as count (%). *Patients could be using more than 1 antiarrhythmic drug.

Figure 1. Flowchart describing the study population selection. Abbreviation: VT = Ventricular Tachycardia



The mean interval from first implantation to first elective replacement or upgrade was 5.6 ± 1.9 years. During follow-up, 78 patients (31%) developed an indication for bradycardia pacing, CRT, and/or received ATP for termination of ventricular arrhythmias. These patients are considered non-eligible for the S-ICD. In Figure 2, the eligibility rate for S-ICD over time is shown. At 7 years follow-up, S-ICD eligibility rate was 66% (95% CI 59% – 72%). Event-rates for unsuitability were 10% (95% CI 7% – 14%) at 1-year follow-up, 28% (95% CI 23% – 34%) at 5-years follow-up, and 34% (95% CI 28% – 41%) at 7-years follow-up.

Figure 2. Cumulative eligibility rate for the S-ICD over time



Eight (3.1%) patients developed a bradycardia pacing indication; of which 3 (1.2%) received a dual-chamber ICD, 3 received a CRT-D, and 2 patients retained their single-chamber device. In total, 25 (10%) patients received a CRT-D. The total follow-up period until the first re-implantation was 1358.1 years, which yields a total upgrade and bradycardia pacing indication rate of 2.1 (95% CI 1.4 – 3.0) per 100-patient-years, 1.8 (95% CI 1.2 – 2.6) per 100-patient-years in case of CRT-D, and 0.3 (95% CI 0.1 – 0.8) per 100-patient-years in case of dual-chamber ICD and bradycardia pacing. The indications for an upgrade to a dual-chamber ICD were symptomatic bradycardia in 2 patients and the presence of supraventricular tachycardia's in 1 patient. Thirteen patients received a CRT-D upgrade based a class I recommendation, 1 based on a class IIa recommendation, and 2 based on a class IIb recommendation.[15] The remaining 9 patients (36%) received a CRT-D at the discretion of the physician. Monomorphic VT terminated by ATP was observed in 57 patients (22%), yielding an incidence rate of 4.9 (95% CI 3.8 – 6.3)

per 100-patient-years. The mean cycle length of the VT was 315 ± 36 ms. In Figure 3, the cumulative event-rates for individual and combined endpoints are presented.

Univariate regression analysis was performed in order to establish baseline predictors of unsuitability for a S-ICD (Table 2). Multivariate logistic regression analysis controlling for variables with a univariate P-value < 0.1 revealed that none were significant predictive variables. A regression analysis specifically to predict ATP therapy identified no variables. An analysis to predict bradycardia pacing and/or CRT indication was not possible due to small sample size.

Figure 3. Cumulative event rates for the individual endpoints and combined endpoint. Solid line – combined endpoint; long dashed line – ATP therapy; squared dotted line – bradycardia pacing and CRT indication. Abbreviations: ATP = Antitachycardia Pacing; CRT = Cardiac Resynchronization Therapy.

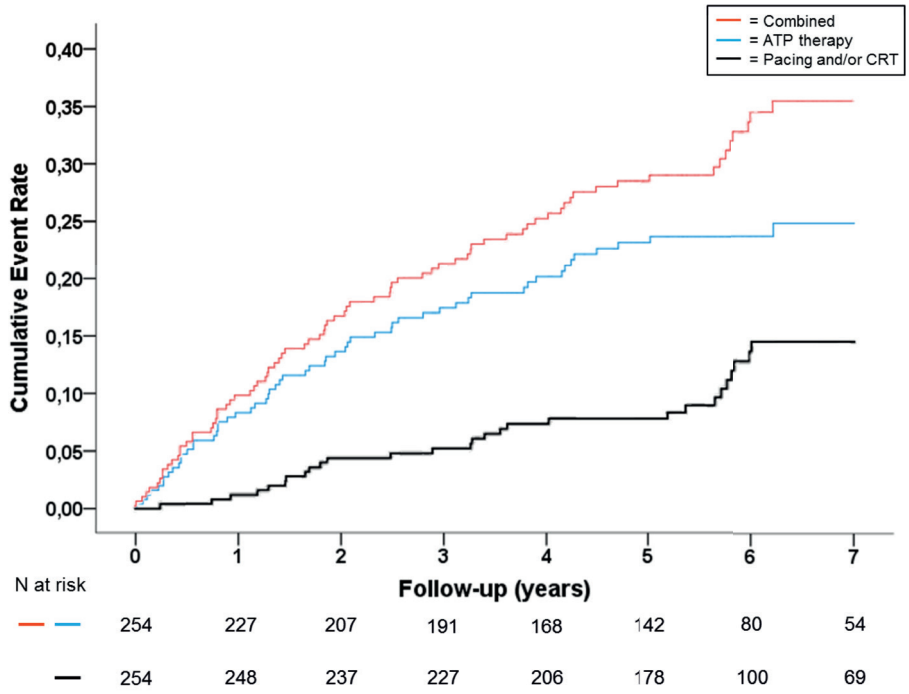


Table 2. Univariate and multivariate regression analysis for the occurrence of the primary endpoint

Logistic regression analysis		**Univariate analysis**		**Multivariate analysis**
Variables	**OR**	**95% CI**	***P*-value**	***P*-value**
IPAS	0.17	(0.02 - 1.36)	0.10	1.00
Cardiomyopathy	1.60	(0.94 - 2.73)	0.09	0.59
LVEF (%)	0.97	(0.94 - 0.99)	0.01	0.08
Creatinine (µmol/L)	1.01	(0.99 - 1.02)	0.10	0.90
PR duration (ms)	1.01	(1.00 - 1.02)	0.02	0.05
QRS duration (ms)	1.01	(1.00 - 1.02)	0.03	0.36
Non-normal QRS morphology	1.97	(1.14 - 3.39)	0.02	0.05
Amiodarone therapy	2.50	(1.16 - 5.41)	0.02	0.71

Abbreviations: IPAS = Inherited Primary Arrhythmia Syndromes; LVEF = left ventricular ejection fraction.

The mean interval until re-implantation was significantly different between elective replacement and upgrade for bradycardia pacing and CRT indication group, respectively 5.8 ± 1.7 years vs. 3.6 ± 2.2 years (P < 0.001). Differences in ECG parameters between groups are presented in Table 3. No difference in heart rate was seen in the upgrade group over time. Beta-blocker therapy is presented in Table 4. In total, 187 (74%) at baseline vs. 191 patients (75%) at the time of the first replacement were taking beta-blockers (P = 0.52). For the replacement and upgrade group respectively, 166 (74%) vs. 168 (75%) (P = 0.64), and 21 (70%) vs. 23 (77%) (P = 0.56). Pearson correlation showed no correlation between difference in heart rate over time and difference in daily dosage of bisoprolol over time (r = -0.21, P = 0.16), carvedilol over time (r = -0.17, P = 0.95), and metoprolol over time (r =-0.08, P = 0.56.

Table 3. Electrocardiographic parameters at baseline and follow-up

	Baseline (t_0)	**Replacement (t_1)**	***P*-value**
Heart rate (bpm)			
- Total	69 ± 13	65 ± 12	<0.001*
- Replacement	69 ± 13	65 ± 12	<0.001*
- Bradycardia/CRT	68 ± 14	68 ± 16	0.88
PR interval (ms)			
- Total	171 ± 26	182 ± 33	<0.001*
- Replacement	168 ± 25	179 ± 31	<0.001*
- Bradycardia/CRT	192 ± 30	208 ± 40	0.003*
QRS duration (ms)			
- Total	114 ± 24	125 ± 31	<0.001*
- Replacement	112 ± 22	121 ± 28	<0.001*
- Bradycardia/CRT	129 ± 29	156 ± 33	<0.001*

Data are presented as mean ± SD. *P*-values are computed by (paired) Student *T* test. * *P*-value < 0.05 was considered significant. Abbreviation: CRT = Cardiac Resynchronization Therapy.

Table 4. Beta-blocker therapy at baseline and follow-up

	Baseline (t_0)	**Replacement (t_1)**	***P*-value**
Daily dose bisoprolol (mg)			
- Total	4.3 ± 3.7	5.4 ± 3.7	0.07
- Replacement	4.4 ± 3.8	5.6 ± 3.8	0.09
- Bradycardia/CRT	3.3 ± 2.4	4.0 ± 2.9	0.58
Daily dose carvedilol (mg)			
- Total	26.5 ± 20.7	33.2 ± 23.5	0.20
- Replacement	27.6 ± 20.7	33.5 ± 24.5	0.30
- Bradycardia/CRT	6.25, 6.25*	31.3 ± 12.5	0.06
Daily dose metoprolol (mg)			
- Total	90.5 ± 59.7	80.4 ± 48.3	0.25
- Replacement	89.6 ± 59.0	77.6 ± 46.5	0.18
- Bradycardia/CRT	96.6 ± 67.1	107 ± 60.7	0.74

Data are presented as mean ± SD. *P*-values are computed by Student *T* test. * Only two patients, daily dose carvedilol in both patients 6.25 mg

Discussion

We found that the majority of the patients (69%) implanted with a transvenous single-chamber ICD would still have been theoretical eligible for the S-ICD, retrospectively, at time of replacement of the device. Non-eligibility was caused more often by appropriate ATP therapy (4.9 per 100-patient-years), than by the development of bradycardia pacing or CRT indication (2.1 per 100-patients-years). We did not find any baseline determinants that could be used to predict if a patient is unsuitable for a S-ICD.

So far little was known about the proportion of patients that develop a bradycardia pacing indication and the need for CRT. It is difficult to place our findings in relation to those of other studies, due to differences in sample size, study design, definitions and follow-up duration. Analysis of the IDE trial and the EFFORTLESS S-ICD registry showed very low explantation rates of the S-ICD for both the need for bradycardia pacing and CRT (0.1 – 0.4%)[13,14]. Other studies described a higher need for bradycardia pacing. Namely, De Bie et al.[16] evaluated in a comparable study that the S-ICD eligibility was 55% after 5-years follow-up, compared to 72% after 5-years follow-up in our study. It is striking that they found that 11% had developed a bradycardia pacing indication. However, this might be an overestimation, as a 20% ventricular pacing burden was used as a cut-off for pacing-dependency. Besides, they included patients with a dual-chamber ICD with a DDI 40 non-tracking backup mode at baseline. The development of a CRT indication is comparable, given follow-up duration. Also, the DAVID trial[17] mentioned in 2002 that 3.9% of the VVI patients crossed over to a dual-chamber device in a median follow-up of only 8.4 (0 – 23.6) months. Finally, Grett et al.[18] found in a retrospective study that in 2.2 years of follow-up 15% developed a pacemaker indication, and 0.8% developed the need for CRT. However, the indication for a pacemaker

may be overestimated, as some patients (7.4%) already had a high risk of pacemaker dependency at baseline. Thus, it seems that event-rates for both indications are low, as seen in our results.

One of the most important disadvantage of the S-ICD is the incapability to deliver ATP therapy, since painful ICD shocks are associated with a reduced quality of life[19]. We found that 22% of the patients experienced appropriate ATP therapy. A median of 4 (1;8) VT episodes per patient were treated with ATP during 5.6 ± 1.9 years of follow-up. Grett et al.[18] found a comparable amount of ATP therapy, given follow-up duration. De Bie et al.[16] found that 27% have had ATP therapy, but in a shorter follow-up period. Yet, Auricchio et al.[20] found, during a follow-up of 22 ± 9 months, an 1-year incidence rate of 4.3% for appropriate ATP therapy in patients with a single-chamber ICD, and a 2-years incidence rate of 7.2%. However, these studies did not assess the number of ATP treatments per person, so no statements can be made about grading how much a patient would have benefitted from ATP therapy. In addition, Burke et al.[13] found that after a mean follow-up of 1.8 ± 0.9 years only 0.1% of the S-ICDs were explanted because of the need for ATP, and 0.1% because of VT storms attempted to suppress with overdrive pacing. In the long-term follow-up of the EFFORTLESS registry, Boersma et al.[14] showed that 5.8% of patients experienced a shock for at least 1 sustained monomorphic VT episode in 3.1 years; 2.2% of patients experienced shocks for more than 1 monomorphic VT episodes. Only 0.5% had their S-ICD removed for perceived need for ATP over a follow-up of 3.1 ± 1.5 years. Therefore, the actual rate of patients that would benefit ATP therapy, once implanted with the S-ICD, is probably lower than seen in our results. Unfortunately, our study did not find any baseline characteristics that could predict the need for ATP in the future.

The differences in ECG parameters between patients that develop the need for bradycardia pacing or CRT and patients with an elective replacement, may be due to worsening of the heart function mainly in the CRT group at time of the upgrade. The association between beta-blockers and the proportion of patients that develop a pacing indication was not objectified before. Our results suggest that the association between increasing of the dosage beta-blockers and lowering of the heart rate is not clinically relevant. For those who received an upgrade no increase in daily dosage beta-blocker has been observed between baseline and the time of upgrade.

Although we did not find any predictive variables for unsuitability for the S-ICD, QRS duration had a P-value below 0.05 in the univariate regression. De Bie et al.[16] found QRS duration as a significant predictive variable in the multivariate analysis. Possibly, patients with a wider QRS complex at baseline will benefit less from a S-ICD, due to a larger chance of needing CRT in the future. Given the outcome that only a small amount of patients develop the need for pacing and/or CRT, the inability to give ATP still remains the biggest disadvantage of the S-ICD. Future studies should investigate if patients with a S-ICD receive more appropriate shocks, because ATP therapy is not possible. A randomized clinical trial like PRAETORIAN is needed to assess the superiority or non-inferiority of the S-ICD compared to the contemporary TV-ICD[21]. Also, a new subcutaneous device should be generated, with the same advantages of the current S-ICD, only with the ability to give ATP therapy.

Since this was a retrospective study, potential limitations regarding uniformity of data collection, clinical missing data and ascertainment bias could not be excluded. Based on the inclusion

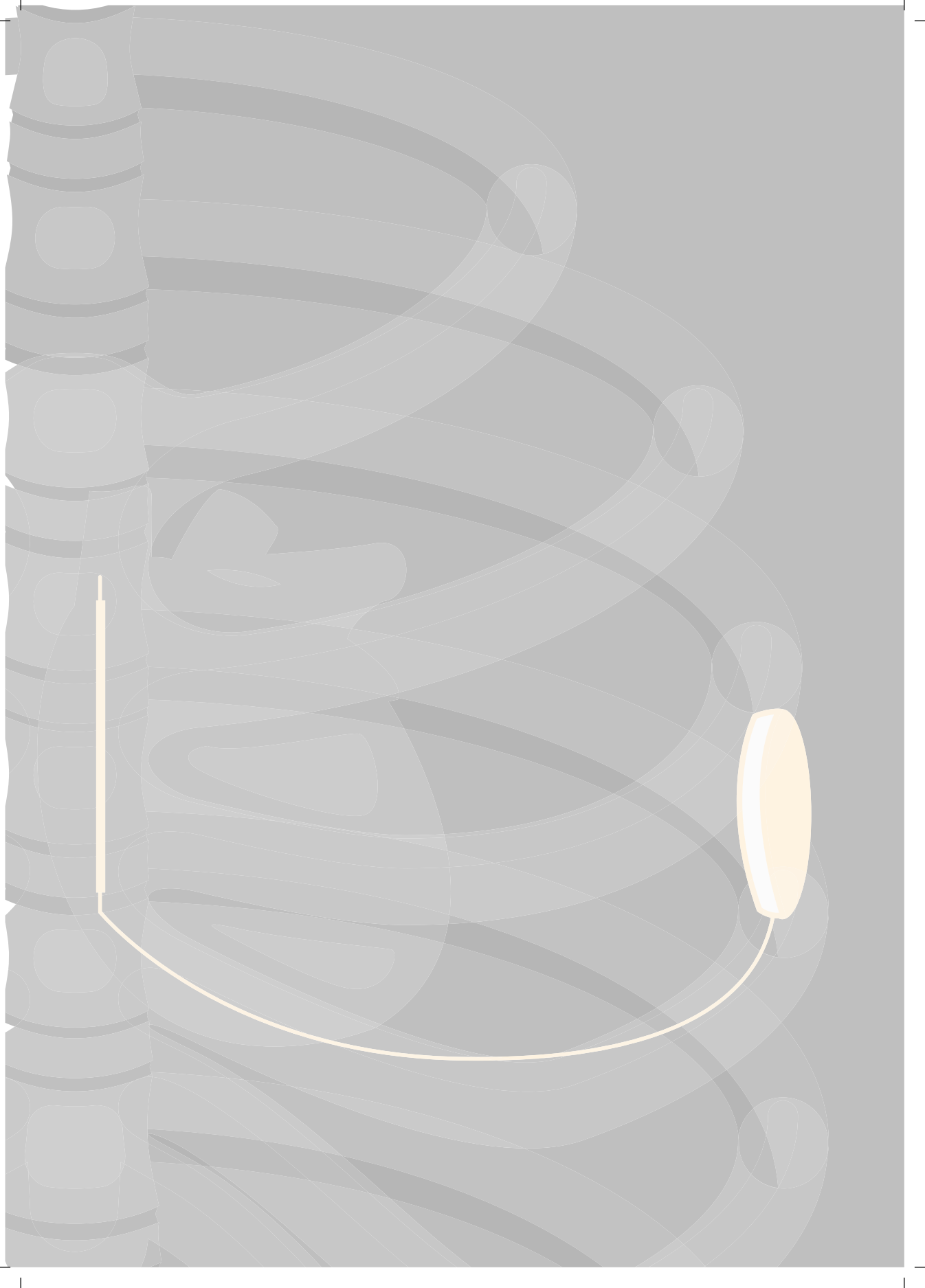
criteria of the study, potential selection bias could not be excluded. Also, some subgroups have a small sample size. Finally, all patients who did not reach the endpoint of this study were considered potential candidates for the S-ICD, however, other factors that determine eligibility for the S-ICD, like QRS and T-wave morphology and vector screening, and patients' preference were not assessed.

At time of the first replacement of the device, 69% of the patients implanted with a single-chamber TV-ICD would still have been potentially eligible for the S-ICD. Only a small amount of patients that are suitable for a S-ICD at baseline developed an indication for bradycardia pacing and/or CRT. Distinguishing patients at baseline that would be ineligible for the S-ICD during follow-up is not possible on the basis of our study.

References

1. Moss AJ, Hall WJ, Cannom DS, Daubert JP, Higgins SL, Klein H, Levine JH, Saksena S, Waldo AL, Wilber D, Brown MW, Heo M. Improved survival with an implanted defibrillator in patients with coronary disease at high risk for ventricular arrhythmia. Multicenter Automatic Defibrillator Implantation Trial Investigators. *N Engl J Med* 1996;335:1933-1940.
2. Antiarrhythmics versus Implantable Defibrillators I. A comparison of antiarrhythmic-drug therapy with implantable defibrillators in patients resuscitated from near-fatal ventricular arrhythmias. *N Engl J Med* 1997;337:1576-1583.
3. Moss AJ, Zareba W, Hall WJ, Klein H, Wilber DJ, Cannom DS, Daubert JP, Higgins SL, Brown MW, Andrews ML, Multicenter Automatic Defibrillator Implantation Trial III. Prophylactic implantation of a defibrillator in patients with myocardial infarction and reduced ejection fraction. *N Engl J Med* 2002;346:877-883.
4. Bardy GH, Lee KL, Mark DB, Poole JE, Packer DL, Boineau R, Domanski M, Troutman C, Anderson J, Johnson G, McNulty SE, Clapp-Channing N, Davidson-Ray LD, Fraulo ES, Fishbein DP, Luceri RM, Ip JH, Investigators SCDiHFTS-H. Amiodarone or an implantable cardioverter-defibrillator for congestive heart failure. *N Engl J Med* 2005;352:225-237.
5. Reynolds MR, Cohen DJ, Kugelmass AD, Brown PP, Becker ER, Culler SD, Simon AW. The frequency and incremental cost of major complications among medicare beneficiaries receiving implantable cardioverter-defibrillators. *J Am Coll Cardiol* 2006;47:2493-2497.
6. Kleemann T, Becker T, Doenges K, Vater M, Senges J, Schneider S, Saggau W, Weisse U, Seidl K. Annual rate of transvenous defibrillation lead defects in implantable cardioverter-defibrillators over a period of >10 years. *Circulation* 2007;115:2474-2480.
7. Borleffs CJ, van Erven L, van Bommel RJ, van der Velde ET, van der Wall EE, Bax JJ, Rosendaal FR, Schalij MJ. Risk of failure of transvenous implantable cardioverter-defibrillator leads. *Circ Arrhythm Electrophysiol* 2009;2:411-416.
8. Eckstein J, Koller MT, Zabel M, Kalusche D, Schaer BA, Osswald S, Sticherling C. Necessity for surgical revision of defibrillator leads implanted long-term: causes and management. *Circulation* 2008;117:2727-2733.
9. Bongiorni MG, Kennergren C, Butter C, Deharo JC, Kutarski A, Rinaldi CA, Romano SL, Maggioni AP, Andarala M, Auricchio A, Kuck KH, Blomstrom-Lundqvist C, Investigators EL. The European Lead Extraction ConTRolled (ELECTRa) study: a European Heart Rhythm Association (EHRA) Registry of Transvenous Lead Extraction Outcomes. *Eur Heart J* 2017;38:2995-3005.
10. Bardy GH, Smith WM, Hood MA, Crozier IG, Melton IC, Jordaens L, Theuns D, Park RE, Wright DJ, Connelly DT, Fynn SP, Murgatroyd FD, Sperzel J, Neuzner J, Spitzer SG, Ardashev AV, Oduro A, Boersma L, Maass AH, Van Gelder IC, Wilde AA, van Dessel PF, Knops RE, Barr CS, Lupo P, Cappato R, Grace AA. An entirely subcutaneous implantable cardioverter-defibrillator. *N Engl J Med* 2010;363:36-44.
11. Weiss R, Knight BP, Gold MR, Leon AR, Herre JM, Hood M, Rashtian M, Kremers M, Crozier I, Lee KL, Smith W, Burke MC. Safety and efficacy of a totally subcutaneous implantable-cardioverter defibrillator. *Circulation* 2013;128:944-953.

12. Lambiase PD, Barr C, Theuns DA, Knops R, Neuzil P, Johansen JB, Hood M, Pedersen S, Kaab S, Murgatroyd F, Reeve HL, Carter N, Boersma L, Investigators E. Worldwide experience with a totally subcutaneous implantable defibrillator: early results from the EFFORTLESS S-ICD Registry. *Eur Heart J* 2014;35:1657-1665.
13. Burke MC, Gold MR, Knight BP, Barr CS, Theuns D, Boersma LVA, Knops RE, Weiss R, Leon AR, Herre JM, Husby M, Stein KM, Lambiase PD. Safety and Efficacy of the Totally Subcutaneous Implantable Defibrillator: 2-Year Results From a Pooled Analysis of the IDE Study and EFFORTLESS Registry. *J Am Coll Cardiol* 2015;65:1605-1615.
14. Boersma L, Barr C, Knops R, Theuns D, Eckardt L, Neuzil P, Scholten M, Hood M, Kuschyk J, Jones P, Duffy E, Husby M, Stein K, Lambiase PD, Group EI. Implant and Midterm Outcomes of the Subcutaneous Implantable Cardioverter-Defibrillator Registry: The EFFORTLESS Study. *J Am Coll Cardiol* 2017;70:830-841.
15. Ponikowski P, Voors AA, Anker SD, Bueno H, Cleland JG, Coats AJ, Falk V, Gonzalez-Juanatey JR, Harjola VP, Jankowska EA, Jessup M, Linde C, Nihoyannopoulos P, Parissis JT, Pieske B, Riley JP, Rosano GM, Ruilope LM, Ruschitzka F, Rutten FH, van der Meer P, Authors/Task Force M, Document R. 2016 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure: The Task Force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC). Developed with the special contribution of the Heart Failure Association (HFA) of the ESC. *Eur J Heart Fail* 2016;18:891-975.
16. de Bie MK, Thijssen J, van Rees JB, Putter H, van der Velde ET, Schalij MJ, van Erven L. Suitability for subcutaneous defibrillator implantation: results based on data from routine clinical practice. *Heart* 2013;99:1018-1023.
17. Wilkoff BL, Cook JR, Epstein AE, Greene HL, Hallstrom AP, Hsia H, Kutalek SP, Sharma A, Dual C, Investigators VVIIDT. Dual-chamber pacing or ventricular backup pacing in patients with an implantable defibrillator: the Dual Chamber and VVI Implantable Defibrillator (DAVID) Trial. *JAMA* 2002;288:3115-3123.
18. Grett M, Christ M, Trappe HJ. Pradiktoren fur die Notwendigkeit antibradykarder und antitachykarder Stimulation nach ICD-Implantation : Implikationen fur den subkutanen ICD. *Herzschr Elektrophysiol* 2016;27:390-395.
19. Schron EB, Exner DV, Yao Q, Jenkins LS, Steinberg JS, Cook JR, Kutalek SP, Friedman PL, Bubien RS, Page RL, Powell J. Quality of life in the antiarrhythmics versus implantable defibrillators trial: impact of therapy and influence of adverse symptoms and defibrillator shocks. *Circulation* 2002;105:589-594.
20. Auricchio A, Schloss EJ, Kurita T, Meijer A, Gerritse B, Zweibel S, AlSmadi FM, Leng CT, Sterns LD, PainFree SSTI. Low inappropriate shock rates in patients with single- and dual/triple-chamber implantable cardioverter-defibrillators using a novel suite of detection algorithms: PainFree SST trial primary results. *Heart Rhythm* 2015;12:926-936.
21. Olde Nordkamp LR, Knops RE, Bardy GH, Blaauw Y, Boersma LV, Bos JS, Delnoy PP, van Dessel PF, Driessen AH, de Groot JR, Herrman JP, Jordaens LJ, Kooiman KM, Maass AH, Meine M, Mizusawa Y, Molhoek SG, van Opstal J, Tijssen JG, Wilde AA. Rationale and design of the PRAETORIAN trial: a Prospective, RAndomizEd comparison of subcuTaneOus and tRansvenous ImplANtable cardioverter-defibrillator therapy. *Am Heart J* 2012;163:753-760 e752.



CHAPTER 9

Evaluation of a novel automatic screening tool for determining eligibility for a subcutaneous implantable cardioverter-defibrillator

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International Journal of Cardiology. 2018 Dec 1;272:97-101

Abstract

Background: The manufacturer has developed a new ECG screening tool to determine eligibility for the subcutaneous ICD (S-ICD), the "automatic screening tool" (AST), which may render manual ECG-screening unnecessary. The aim of the study was to determine the eligibility for the S-ICD using two methods (manual ECG-screening versus AST) in different patient categories including patients with cardiomyopathy, congenital heart disease and inherited primary arrhythmia syndrome.

Methods: We prospectively evaluated the ECG suitability for an S-ICD in consecutive patients at our outpatient clinic between February and June 2017. The primary endpoint of the study was ECG eligibility defined as at least 1 successful vector in both supine and sitting postures.

Results: A total of 254 patients (167 men; mean age 45 ± 16 years) were screened using both methods. Overall, there was a high ECG eligibility using either method (93% versus 92%, P=0.45). Overall agreement between both methods was 94%. Patients with hypertrophic cardiomyopathy (HCM) more often had a failed screening test using either test in comparison to the patients without HCM (manual: odds ratio [OR] 3.3, 95% confidence interval [CI] 1.2-9.3, P=0.02; AST: OR 3.0, 95% CI 1.2-7.6, P=0.02).

Conclusion: AST showed a high agreement with manual ECG-screening for S-ICD. Overall there was a high ECG eligibility for S-ICD, although patients with HCM had a lower passing rate irrespective of the screening method.

Introduction

Implantable cardiac defibrillators (ICD) are highly effective in preventing sudden cardiac death (SCD) due to malignant ventricular arrhythmias[1-4]. Conventional transvenous ICD (TV-ICD) systems are often associated with short- and long-term complications due to placement of endovascular leads[5, 6]. Therefore, an entirely subcutaneous implantable defibrillator (S-ICD) system has been developed as an alternative to TV-ICD[7]. Previous studies have proven the efficacy and safety of S-ICD therapy in primary and secondary prevention of SCD[8-10]. However, the advantage of the S-ICD is partially offset by the presence of inappropriate shocks due to QRS/T-wave oversensing[11-13]. In order to prevent S-ICD implantation in patients susceptible for sensing problems, a pre-implantation ECG screening has been developed to identify patients that are likely to have an unsuitable subcutaneous ECG. Conventionally, the eligibility for S-ICD is mainly based on template ECG morphology screening, in which QRS-complex and T-wave morphology are manually evaluated (manual ECG-screening). Approximately 7% to 11% of patients are considered not eligible for S-ICD implantation based on manual ECG screening [14-16]. Recently, the manufacturer (Boston Scientific, Natick, MA, USA) developed an automatic screening tool (AST), which aims to automatically identify the eligibility for S-ICD. The performance of AST has not been assessed.

The aim the study was to determine the difference between manual ECG-screening and AST, and to determine the eligibility of patients with structural heart disease (SHD) or an inherited primary arrhythmia syndrome (IPAS) for an S-ICD using both screening methods.

Methods

Study population

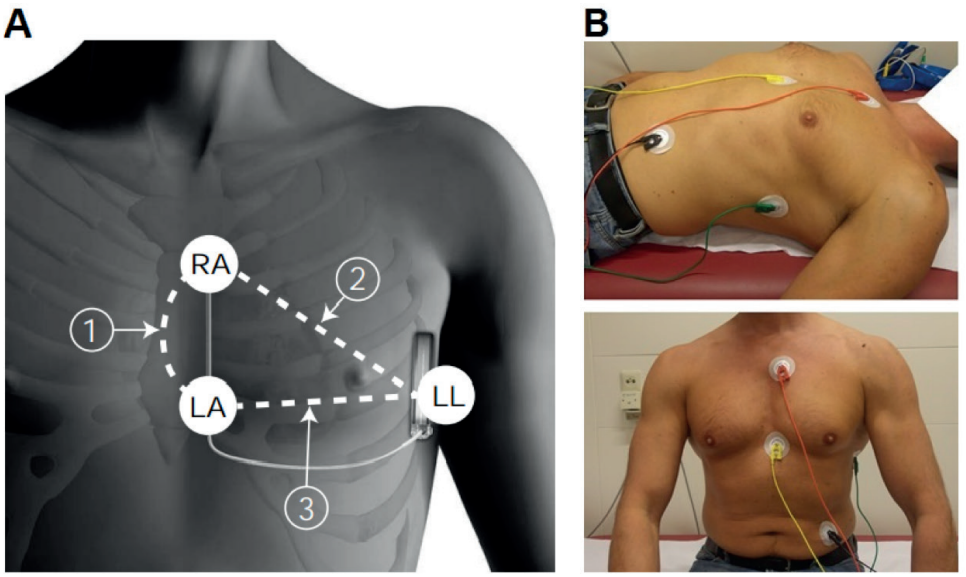
This single center, prospective study evaluates the eligibility for S-ICD by using the conventional manual ECG-screening and the novel AST. From February 2017 to June 2017, all consecutive patients with SHD or IPAS were screened during their routine visit at the outpatient clinic. Exclusion criteria were ≥ 3% ventricular pacing, cardiac resynchronization therapy and patients with paced QRS-complex during screening. All included patients provided informed consent to participate in the study, and the study was approved by the institutional review board of the Erasmus Medical Center, MEC-2017-035.

ECG data collection

The S-ICD system (Boston Scientific, Natick, MA, USA) utilizes 3 sensing electrodes to monitor the cardiac electrical activity (A, distal from the sternal defibrillation coil; B, proximal from the sternal defibrillation coil; C, pulse generator (CAN) implanted at the left-lateral midaxillary line). These electrodes represent 3 vector projections of cardiac electrical conduction (secondary: A-to-CAN, primary: B-to-CAN, and alternate: A-to-B). In order to mimic the S-ICD sensing vectors, 3 bipolar limb lead electrodes were placed in the same configuration as advised by the manufacturer. The left arm (LA) electrode was placed one cm

left lateral of the xiphoid, the right arm (RA) electrode was placed 14 cm cranial to the LA-electrode and the left leg (LL) electrode was placed at the 5th intercostal space along the mid-axillary line representing the proximal, distal sensing electrode and pulse generator of the S-ICD system, respectively. The ground electrode (RL) was placed on the lower torso to ensure that other leads positions were undisturbed. The derived bipolar leads represent the S-ICD sense vectors (Alternate = Lead I, Secondary = Lead II, and Primary = Lead III) (Figure 1A).

Figure 1. Panel A. Diagram of S-ICD sensing vectors and the exact placements limb-lead electrodes; Panel B. Diagram of S-ICD sensing vectors and placements limp-lead electrodes.



Manual ECG screening

A 3-lead ECG was obtained by a standard ECG-recorder at a paper speed of 25mm/s for a period of 10 seconds. This process was repeated in both supine and sitting posture at three different ECG-gains (5, 10 and 20 mm/mV). The recorded ECGs were evaluated by using the standard manual ECG-screening tool provided by Boston Scientific. This tool consists of six colored profiles that corresponds to the automatic gain settings of the S-ICD. Based on current recommendation, a patient is considered eligible for S-ICD if all complexes in 10-second strip of at least one sense vector pass the screening process in at least 2 postures. The manual ECG screening tool rejects complexes in which the QRS amplitude is too large, too small, or the ratio of QRS amplitude to T-wave amplitude is insufficient. The availability of a second appropriate sensing vector may reduce the chance of cardiac signal oversensing by reprogramming a different sensing vector. In order to allow both the physician and the device to optimize the sensing vector after implantation, multiple appropriate (≥2 vector) sensing vector was evaluated.

In order to assess the inter-observer variability of the manual ECG-screening, the surface ECGs of 50 randomly selected patients were reevaluated. This was performed independently in a blind fashion by two investigators (SCY and DAMJT).

Automatic screening tool

The automatic screening tool (AST, Model 2889, EMBLEM S-ICD) is a new application that automatically determines the eligibility for S-ICD. This novel application is available on the Boston Scientific Zoom programmer (3120 zoom LATITUDE) and is a proposed alternative to the manual ECG-screening. Using the Boston Scientific Zoom programmer, a 3-lead surface ECG, with the same configuration as for the manual ECG-screening, was recorded for at least 10 seconds in both supine and sitting postures (Figure 1B). Subsequently, AST summarized the eligibility for S-ICD per sense vector for both postures and provided for each vector-posture combination the ECG data that were used during the screening. A patient was considered eligible for S-ICD if at least 1 vector passed the screening process in both supine and sitting postures.

AST uses the measured QRS amplitude and QRS/T-wave ratio to determine the appropriateness of the sensing vectors just like the Vector Select™ algorithm when the S-ICD system is implanted. In fact, AST resembles the S-ICD sensing scheme which reduces subjectivity associated with the manual ECG screening.

Statistical analysis

Continuous data are presented as mean ± standard deviation if the data were normally distributed, or as median with interquartile range (25^{th} and 75^{th} percentile), where appropriate. Categorical variables are presented by frequencies and percentages. Differences of continuous variables between groups were analyzed with the unpaired Student's t-test. Differences between unpaired categorical variables were evaluated using the Chi-square test or the Fisher's exact test, as appropriate. Paired nominal data were compared with the McNemar Chi-square test. In the absence of a gold standard, the manual ECG-screening method was considered the reference method. Inter-observer agreement was evaluated using the Cohen's Kappa statistics. A P-value <0.05 was considered statistically significant. Statistical analyses were performed using SPSS version 21.

Results

Study population

The study cohort consisted 254 patients who underwent both manual ECG-screening and AST in both supine and sitting postures at the same day. The population was predominantly male (66%) with a mean age of 45 ± 16 years. SHD was present in 194 patients (76%); cardiomyopathies (n=126) and congenital heart disease (CHD, n=68), and IPAS was present in 60 patients (24%). Further baseline characteristics are presented in Table 1. Seventy-five patients already had a transvenous ICD system, single-chamber in

61 patients and dual-chamber in 14. For all patients, the percentage right ventricular pacing was < 3%. Twenty-five patients already carried an S-ICD, while 10 received a subcutaneous system after screening.

Table 1. Baseline demographic and clinical characteristics

	Total (n=254)	**Pass (n=237)**	**Fail (n=17)**	**P-value**
Male gender	167 (66%)	154 (65%)	13 (76%)	0.34
Age, *years*	45 ± 16	45 ± 16	44 ± 16	0.70
Body mass index, *kg/m²*	26.1 ± 4.5	26.2 ± 4.5	25.0 ± 5.0	0.39
Implantable cardioverter-defibrillator	110 (43%)	104 (44%)	6 (35%)	0.49
- Primary prevention indication	70 (28%)	67 (28%)	3 (18%)	0.67
- Secondary prevention indication	40 (16%)	37 (16%)	3 (18%)	0.74
Cardiac diagnosis				
Structural heart disease	194 (76%)	180 (76%)	14 (82%)	0.77
- Cardiomyopathy	126 (50%)	117 (49%)	9 (53%)	0.78
Hypertrophic cardiomyopathy	48 (19%)	41 (17%)	7 (41%)	0.02
Ischemic cardiomyopathy	31 (12%)	29 (12%)	2 (12%)	1.00
Non-ischemic cardiomyopathy	22 (9%)	22 (9%)	0	0.38
Non-compaction cardiomyopathy	11 (4%)	11 (5%)	0	1.00
Arrhythmogenic right ventricular cardiomyopathy	14 (6%)	14 (6%)	0	0.61
- Congenital heart disease	68 (27%)	63 (27%)	5 (29%)	0.80
Tetralogy of Fallot	25 (10%)	22 (9%)	3 (18%)	0.23
TGA-arterial switch	15 (6%)	14 (6%)	1 (6%)	1.00
TGA-Mustard/Senning	18 (7%)	18 (8%)	0	0.62
Fontan circulation	10 (4%)	9 (4%)	1 (6%)	0.51
Inherited primary arrhythmia syndrome	60 (24%)	57 (24%)	3 (18%)	0.77
- Brugada syndrome	37 (15%)	35 (15%)	2 (12%)	1.00
Ajmaline induced type 1 ECG	27 (11%)	26 (11%)	1 (6%)	1.00
Spontaneous type 1 ECG	10 (4%)	9 (4%)	1 (6%)	0.51
- Idiopathic VF	13 (5%)	12 (5%)	1 (6%)	0.60
- Long QT syndrome	10 (4%)	10 (4%)	0	1.00

Data are presented as mean ± SD, categorical data as n(%). Abbreviations: TGA = transposition of the great arteries; VF = ventricular fibrillation

S-ICD eligibility rate

Overall, 237 patients (93%) were eligible for S-ICD implantation and 17 (7%) ineligible using the ≥ 1 vector pass criterion (manual ECG-screening). Baseline characteristics stratified by S-ICD eligibility are presented in Table 1. There were no differences in demographics, ICD indication, and underlying etiology between patients who passed and those who failed manual ECG screening (Table 1). However, hypertrophic cardiomyopathy (HCM) was more prevalent in patients who were ineligible for S-ICD implantation compared to those who were eligible (41% vs. 17%; P = 0.02).

When using AST, 233 patients (92%) were eligible for S-ICD. Similar to manual ECG-screening, no differences in baseline characteristics were found between patients who passed and those who failed screening by AST, except for HCM. Proportionally, HCM patients who were ineligible for S-ICD implantation were higher compared to those who were eligible (38% vs. 17%; P = 0.02). Taken together, HCM patients had a higher risk to fail ECG screening test using either method in comparison to the total population (manual ECG-screening: odds ratio [OR] 3.3, 95% confidence interval [CI] 1.2 - 9.3, P = 0.02; AST: OR 3.0, 95% CI 1.2 - 7.6, P = 0.02). When using the stringent ≥ 2 vector pass criterion, the S-ICD eligibility rate was 80% for manual ECG-screening and 83% for AST. Considering inter-observer agreement, manual ECG-screening proved to be reproducible, with a Cohen's Kappa of 0.88 and 0.79, for ≥ 1 and ≥ 2 vector pass criterion, respectively.

Overall vector eligibility

In order for a vector to pass, that vector had to satisfy the ECG screening template (at any gain) in both the erect and supine position. In manual ECG-screening the highest pass rate was observed for the primary sensing vector (78%), followed by the secondary sensing vector (75%). The alternate sensing vector had the lowest pass rate (57%). Similar pass rates were found when using AST; 80%, 77%, and 59%, for primary, secondary, and alternate sensing vector respectively. Overall, pass rates were higher for the primary and secondary sensing vector compared to the alternate sensing vector in both manual ECG-screening and AST (P < 0.001).

Comparison manual and automatic ECG-screening

The S-ICD eligibility rates for both screening methods are presented in Table 2. Overall, the S-ICD eligibility rate was not different between manual ECG-screening and AST (93%, 95% CI [90%-96%] vs. 92%, 95% CI [88% - 95%]; P = 0.45). The overall agreement for the patient population between manual ECG-screening and AST was 94%. Discrepancy between the two screening methods was observed in 16 patients (6%). In 4% of the patients manual ECG-screening showed at least 1 suitable vector while AST demonstrated no suitable vector. In contrast, in 2% of patients AST showed at least 1 suitable vector while manual ECG-screening demonstrated no suitable vector.

Table 2. Eligibility for subcutaneous ICD implantation based on ≥ 1 vector passing

	Manual	AST	P-value
Structural heart disease (n=194)	180 (93)	175 (90)	0.30
- Cardiomyopathy (n=126)	117 (93)	115 (91)	0.75
Hypertrophic cardiomyopathy (n=48)	41 (85)	40 (83)	1.00
Ischemic cardiomyopathy (n=31)	29 (94)	29 (94)	1.00
Non-ischemic dilated cardiomyopathy (n=22)	22 (100)	21 (96)	1.00
Non-compaction cardiomyopathy (n=11)	11 (100)	11 (100)	1.00
Arrhythmogenic right ventricular cardiomyopathy (n=14)	14 (100)	14 (100)	1.00
- Congenital heart disease (n=68)	63 (93)	60 (88)	0.76
Tetralogy of Fallot (n=25)	22 (88)	22 (88)	1.00
TGA-arterial switch (n=15)	14 (93)	13 (87)	1.00
TGA-Mustard/Senning (n=18)	18 (100)	17 (94)	1.00
Fontan circulation (n=10)	9 (90)	8 (80)	1.00
Inherited primary arrhythmia syndrome (n=60)	57 (95)	58 (97)	1.00
- Brugada syndrome (n=37)	35 (95)	36 (97)	1.00
Ajmaline induced type 1 ECG (n=27)	26 (96)	26 (96)	1.00
Spontaneous type 1 ECG (n=10)	9 (90)	10 (100)	1.00
- Idiopathic VF (n=13)	12 (92)	12 (92)	1.00
- Long QT syndrome (n=10)	10 (100)	10 (100)	1.00
Total (n=254)	237 (93)	233 (92)	0.45

Data are presented as categorical data as n(%). Abbreviations: TGA = transposition of the great arteries; VF = ventricular fibrillation

Considering a vector-based analysis, the frequency of pass and failure per vector for both screening methods are presented in Table 3. Discordance between manual ECG-screening and AST was highest in the alternate sensing vector (24%), followed by primary (16%) and secondary sensing vector (15%). When comparing both screening methods per sensing vector, no significant difference in agreement/discordance was observed.

Follow-up of S-ICD patients

The median follow-up of the S-ICD patients was 34 months (interquartile range: 11 to 62 months). Inappropriate ICD therapy was observed in 4 patients. Of these, one patient experienced an inappropriate shock due to QRS/T-wave oversensing caused by attenuation of the QRS complex. Two patients experienced an inappropriate due to a supraventricular arrhythmia detected in the shock zone. One patient received an inappropriate shock immediately post-implantation due to oversensing of low-amplitude signals and artefacts. These signals were caused by air entrapment at the proximal sensing electrode. All patients with inappropriate shocks had ≥ 2 suitable vectors with either screening method.

Table 3. Eligibility for S-ICD implantation per vector for manual and automatic ECG screening

		Automatic Screening Tool					
		Primary vector		Secondary vector		Alternate vector	
Manual ECG-screening		**Fail**	**Pass**	**Fail**	**Pass**	**Fail**	**Pass**
Primary vector	**Fail**	**33**	**23**	-	-	-	-
	Pass	**17**	**181**	-	-	-	-
Secondary vector	**Fail**	-	-	**42**	**22**	-	-
	Pass	-	-	**16**	**174**		--
Alternate vector	**Fail**	-	-	-	-	**75**	**34**
	Pass	-	-	-	-	**28**	**117**

Data are presented as frequencies

Discussion

In the present study, we compared the eligibility for the S-ICD system in a large cohort of patients using the conventional (manual ECG-screening) and novel (AST) ECG-screening system. The main finding of the study was that AST had a similar performance as manual ECG-screening. In addition, we provide an overview of the passing rates in different patient categories using the both screening methods. In comparison to other structural or electrical heart diseases, patients with HCM demonstrated a lower passing rate.

Advantages of AST

The manual ECG-screening for S-ICD was developed by the manufacturer to identify patients who might be susceptible to QRS-T-wave oversensing and, therefore, are at higher risk for inappropriate shocks. According to the current literature, the overall eligibility rate for S-ICD, based on manual ECG-screening, range from 85% to 93% for ≥ 1 successful vector in an unselected cardiac patient cohort[14, 15]. This is in line with the results of the present study (93% passing rate for manual ECG-screening).

Despite the high inter-observer and inter-test agreement, manual ECG-screening system is time consuming and is subject to the clinicians observation and interpretations. Investigators should also be briefly trained before using the manual ECG-screening system. In contrast to the manual ECG-screening, AST eliminates the inter- and intra-observer variability. In our study, AST has a similar performance as manual ECG-screening with a low proportion of disagreement. This result is in line with 2 recent published studies evaluating the performance of AST compared to manual ECG-screening. The study by Francia et al.[17] reported similar eligibility rates, 91% with manual ECG-screening and 94% with AST in 235 patients with an indication for ICD. More recently, Bogeholz et al.[18] found that eligibility was similar for AST (94%) and manual ECG screening (97%) in 33 consecutive patients with an already implanted S-ICD system.

S-ICD eligibility in different patient populations

There are limited studies addressing the eligibility for S-ICD in patients with SHD and IPAS. Only three studies have assessed the eligibility for S-ICD in patients with cardiomyopathy, however, these studies specifically addressed patients with HCM[19-21]. The 1-vector passing rate using manual ECG-screening in our HCM population was 85% which is in agreement with the data of 2 previous papersa[19, 20]. However, the study by Srinivasan et al.[21] reported a much lower passing rate of 62%. This may be to the requirement of a suitable vector during exercise testing in the last study, which we did not perform. However, the present study followed the pre-implant screening method for S-ICD, as recommended by the manufacturer, which does not require exercise testing.

Despite the promising advantages of the S-ICD in patients with CHD, there are limited data available whether the sensing algorithm of the S-ICD is appropriate in these patients. According to the study of Zeb et al.[22], which evaluated the eligibility of patients with CHD for S-ICD based on ≥ 1 successful vector, 88% of the patients with CHD were considered eligible for S-ICD. Our study reported a similar passing rate for both screenings methods (manual ECG-screening 93% and AST 88%). The screening tools were developed using data from normal heart orientation. However, in line with the latter study, there were no differences in the eligibility for S-ICD between the different CHD diagnosis. We recognize that some patients with CHD may require a personalized position of their subcutaneous electrode due to unusual cardiac anatomy and atypical ECG characteristics. The use of right-sided parasternal lead position has been shown to achieve appropriate S-ICD sensing vector in selected patients with transposition of the great arteries, tetralogy of Fallot and Fontan circulation[23-25].

Limited studies investigated the eligibility for S-ICD in patients with IPAS, most studies involved patients with Brugada syndrome. In the study of Conte et al.[26], 87% of the patients with IPAS passed the screening for S-ICD based on ≥1 successful vector, which was similar to the results of both manual ECG-screening and AST of the present study. Previous studies demonstrated a lower passing rate (81%-82%) for Brugada patients, especially in those with spontaneous type 1 Brugada syndrome[26-28]. In our study, the passing rate was high (95%). Patients with spontaneous type 1 Brugada syndrome had numerically a lower passing rate (90%), but this was not statistically different from patients with ajmalin-induced Brugada syndrome (P=0.47 manual ECG-screening and P=0.73 AST). This discrepancy in passing rate with previous publication may be explained by the lower proportion of patients with spontaneous Brugada pattern in our cohort.

The eligibility for S-ICD based on ≥ 2 successful vectors has been investigated in only two studies[16, 20]. In line with the study of Randles et al.[16], which reported an overall passing rate of 85% for ≥2 successful vectors in an unselected cardiac patient cohort, the overall passing rate of the present study was 80% for the manual ECG-screening and 83% for AST.

Clinical implications

The manual ECG-screening method has been developed to identify patients that are likely to have an unsuitable subcutaneous ECG. Zeb et al.[29] investigated the performance of the manual ECG-screening tool and reported a sensitivity of 95% and specificity of 79%. Despite the high sensitivity of manual

ECG screening, inappropriate shocks are still mainly caused by QRS/T-wave oversensing[30]. The current study evaluated the performance of AST compared to manual ECG-screening and no differences in S-ICD eligibility rate were observed. During follow-up, one patient experienced an inappropriate shock due to QRS/T-wave oversensing caused by attenuation of the QRS complex. The question arises how to increase specificity in order to decrease the number of patients experiencing inappropriate shocks? Brouwer et al. investigated algorithm-based screening by using an external S-ICD[31]. This method may improve the identification of eligible S-ICD candidates but needs further investigation. Despite the fact that AST resembles the Vector Select™ algorithm of the S-ICD, a mismatch between the selected sensing vector by the S-ICD and AST in a considerable fraction of patients[18]. Of note, one has to keep in mind that transient causes of QRS/T-wave oversensing due to attenuation of the QRS complex or air entrapment cannot be detected by ECG screening methods.

Study limitations

The present study addressed the eligibility for S-ICD in a large cohort of patients with SHD and IPAS using both manual ECG-screening and AST, certain limitations are present. Since the ECGs were collected from awake individuals at rest, the passing rate for an S-ICD might be overestimated due to ECG changes under certain conditions such as enhanced vagal tone during sleeping or exercise. Application of S-ICD screening test during exercise is suggested to identify T-wave oversensing and would likely result in a greater failure rate. Another limitation might be that the study cohort consisted of patients with and without an ICD indication. However, when comparing the S-ICD eligibility rate between patients with and without an ICD indication, no difference was found ($P = 0.61$).

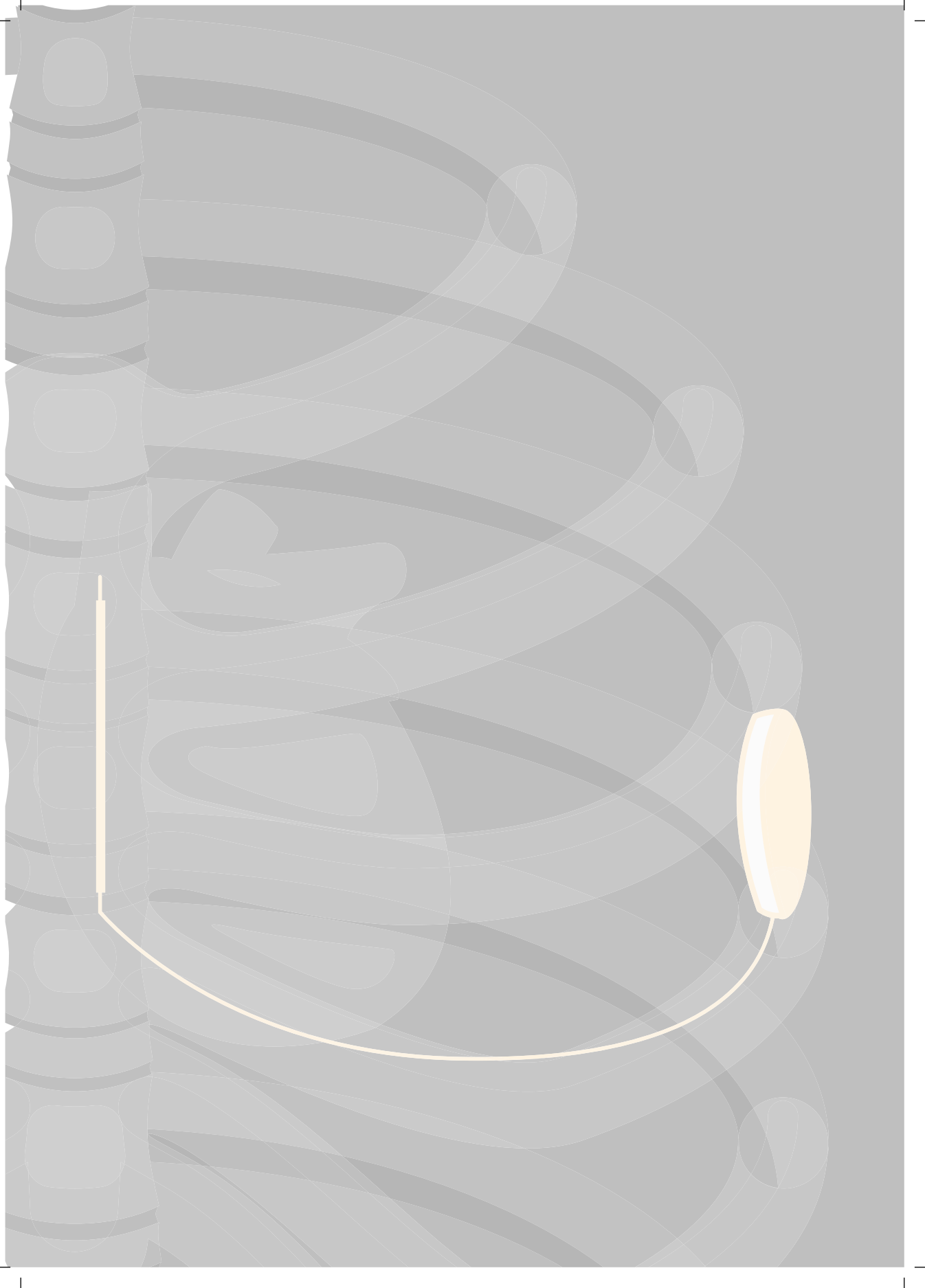
Conclusion

The present study shows that AST is an appropriate alternative to the manual ECG-screening for S-ICD systems. The eligibility for S-ICD implantation is high in patients with SHD and IPAS, although patients with HCM seem to have a lower passing rate, irrespective of the screening method.

References

1. Moss AJ, Hall WJ, Cannom DS, et al. Improved survival with an implanted defibrillator in patients with coronary disease at high risk for ventricular arrhythmia. Multicenter Automatic Defibrillator Implantation Trial Investigators. N Engl J Med. 1996;335:1933-1940.
2. Antiarrhythmic versus Implantable Defibrillator Investigators. A comparison of antiarrhythmic-drug therapy with implantable defibrillators in patients resuscitated from near-fatal ventricular arrhythmias. N Engl J Med. 1997;337:1576-1583.
3. Moss AJ, Zareba W, Hall WJ, et al. Prophylactic implantation of a defibrillator in patients with myocardial infarction and reduced ejection fraction. N Engl J Med. 2002;346:877-883.
4. Bardy GH, Lee KL, Mark DB, et al. Amiodarone or an implantable cardioverter-defibrillator for congestive heart failure. N Engl J Med. 2005;352:225-237.
5. Kleemann T, Becker T, Doenges K, et al. Annual rate of transvenous defibrillation lead defects in implantable cardioverter-defibrillators over a period of >10 years. Circulation. 2007;115:2474-480.
6. Borleffs CJ, van Erven L, van Bommel RJ, et al. Risk of failure of transvenous implantable cardioverter-defibrillator leads. Circ Arrhythm Electrophysiol. 2009;2:411-416.
7. Bardy GH, Smith WM, Hood MA, et al. An entirely subcutaneous implantable cardioverter-defibrillator. N Engl J Med. 2010;363:36-44.
8. Weiss R, Knight BP, Gold MR, et al. Safety and efficacy of a totally subcutaneous implantable-cardioverter defibrillator. Circulation. 2013;128:944-953.
9. Lambiase PD, Barr C, Theuns DA, et al. Worldwide experience with a totally subcutaneous implantable defibrillator: early results from the EFFORTLESS S-ICD Registry. Eur Heart J. 2014;35:1657-1665.
10. Burke MC, Gold MR, Knight BP, et al. Safety and Efficacy of the Totally Subcutaneous Implantable Defibrillator: 2-Year Results From a Pooled Analysis of the IDE Study and EFFORTLESS Registry. J Am Coll Cardiol. 2015;65:1605-1615.
11. Jarman JW, Lascelles K, Wong T, Markides V, Clague JR, Till J. Clinical experience of entirely subcutaneous implantable cardioverter-defibrillators in children and adults: cause for caution. Eur Heart J. 2012;33:1351-1359.
12. Olde Nordkamp LR, Dabiri Abkenari L, Boersma LV, et al. The entirely subcutaneous implantable cardioverter-defibrillator: initial clinical experience in a large Dutch cohort. J Am Coll Cardiol. 2012;60:1933-1939.
13. Kobe J, Reinke F, Meyer C, et al. Implantation and follow-up of totally subcutaneous versus conventional implantable cardioverter-defibrillators: a multicenter case-control study. Heart Rhythm. 2013;10:29-36.
14. Groh CA, Sharma S, Pelchovitz DJ, et al. Use of an electrocardiographic screening tool to determine candidacy for a subcutaneous implantable cardioverter-defibrillator. Heart Rhythm. 2014;11:1361-1366.
15. Olde Nordkamp LR, Warnaars JL, Kooiman KM, et al. Which patients are not suitable for a subcutaneous ICD: incidence and predictors of failed QRS-T-wave morphology screening. J Cardiovasc Electrophysiol. 2014;25:494-499.
16. Randles DA, Hawkins NM, Shaw M, Patwala AY, Pettit SJ, Wright DJ. How many patients fulfil the surface electrocardiogram criteria for subcutaneous implantable cardioverter-defibrillator implantation? Europace. 2014;16:1015-1021.

17. Francia P, Ziacchi M, De Filippo P, et al. Subcutaneous implantable cardioverter defibrillator eligibility according to a novel automated screening tool and agreement with the standard manual electrocardiographic morphology tool. J Interv Card Electrophysiol. 2018;52:61-67.
18. Bogeholz N, Pauls P, Guner F, et al. Direct comparison of the novel automated screening tool (AST) versus the manual screening tool (MST) in patients with already implanted subcutaneous ICD. Int J Cardiol. 2018;265:90-96.
19. Francia P, Adduci C, Palano F, et al. Eligibility for the Subcutaneous Implantable Cardioverter-Defibrillator in Patients With Hypertrophic Cardiomyopathy. J Cardiovasc Electrophysiol. 2015;26:893-899.
20. Maurizi N, Olivotto I, Olde Nordkamp LR, et al. Prevalence of subcutaneous implantable cardioverter-defibrillator candidacy based on template ECG screening in patients with hypertrophic cardiomyopathy. Heart Rhythm. 2016;13:457-463.
21. Srinivasan NT, Patel KH, Qamar K, et al. Disease Severity and Exercise Testing Reduce Subcutaneous Implantable Cardioverter-Defibrillator Left Sternal ECG Screening Success in Hypertrophic Cardiomyopathy. Circ Arrhythm Electrophysiol. 2017;10 doi: 10.1161/CIRCEP.117.004801.
22. Zeb M, Curzen N, Veldtman G, et al. Potential eligibility of congenital heart disease patients for subcutaneous implantable cardioverter-defibrillator based on surface electrocardiogram mapping. Europace. 2015;17:1059-1067.
23. Okamura H, McLeod CJ, DeSimone CV, et al. Right Parasternal Lead Placement Increases Eligibility for Subcutaneous Implantable Cardioverter Defibrillator Therapy in Adults With Congenital Heart Disease. Circ J. 2016;80:1328-1335.
24. Wilson DG, Zeb M, Veldtman G, Dimitrov BD, Morgan JM. Left and Right Parasternal Sensing for the S-ICD in Adult Congenital Heart Disease Patients and Normal Controls. Pacing Clin Electrophysiol. 2016;39:282-290.
25. Alonso P, Osca J, Cano O, et al. The Role of Conventional and Right-Sided ECG Screening for Subcutaneous ICD in a Tetralogy of Fallot Population. Pacing Clin Electrophysiol. 2017;40:145-153.
26. Conte G, Kawabata M, de Asmundis C, et al. High rate of subcutaneous implantable cardioverter-defibrillator sensing screening failure in patients with Brugada syndrome: a comparison with other inherited primary arrhythmia syndromes. Europace. 2017 doi: 10.1093/europace/eux009.
27. Olde Nordkamp LR, Conte G, Rosenmoller BR, et al. Brugada Syndrome and the Subcutaneous Implantable Cardioverter-Defibrillator. J Am Coll Cardiol. 2016;68:665-666.
28. Tachibana M, Nishii N, Morita H, et al. Exercise stress test reveals ineligibility for subcutaneous implantable cardioverter defibrillator in patients with Brugada syndrome. J Cardiovasc Electrophysiol. 2017;28:1454-1459.
29. Zeb M, Curzen N, Allavatam V, et al. Sensitivity and specificity of the subcutaneous implantable cardioverter defibrillator pre-implant screening tool. Int J Cardiol. 2015;195:205-209.
30. [30] Boersma L, Barr C, Knops R, et al. Implant and Midterm Outcomes of the Subcutaneous Implantable Cardioverter-Defibrillator Registry: The EFFORTLESS Study. J Am Coll Cardiol. 2017;70:830-841.
31. Brouwer TF, Kooiman KM, Olde Nordkamp LR, van Halm VP, Knops RE. Algorithm-based screening may improve patient selection for the subcutaneous implantable defibrillator. J Am Coll Cardiol EP. 2017;2:605-614



EDITORIAL

Automating subcutaneous ICD screening and future sensing refinements

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International Journal of Cardiology. 2018 Dec 1;272:215-216.

The avoidance of transvenous leads is the key innovation of the Subcutaneous ICD (S-ICD) carrying the benefits of preventing long-term vascular complications & lead issues requiring potentially hazardous interventions especially extraction. However, this brings the challenge of ensuring optimal sensing of ventricular arrhythmias in the absence of intracardiac electrograms. By utilizing the 3 sensing vectors to differentiate the R wave from the T wave, very effective sensing is possible avoiding unnecessary shocks for SVT outperforming transvenous device algorithms for the latter[1]. However, there are two major sources of concern: Surface ECG screening could "rule out" potentially eligible patients and the risk of T wave oversensing causing inappropriate shocks.

The risk of unnecessary exclusion relates to the possibility of human error with manual screening using a "ruler and paper". Also, the printed ECG does not fully represent the signal the device actually sees because it is derived between 2 skin electrodes rather than between the subcutaneous lead & generator, it is also processed by a VectorSelectTM sensing algorithm in the implanted S-ICD.

Manual screening has a positive predictive value of only 59% and negative predictive value of 98% when compared to the S-ICD's sensing[2]. This has resulted in a drive to standardize the screening process and ideally match the signals & processing to the in-situ S-ICD. The introduction of the Automated Screening Tool (AST) is the first step in this direction. In this issue, Sakhi et al. & Theuns compared 256 patients with the manual (MST) versus the AST[3]. They demonstrate no significant difference in overall eligibility between the 2 techniques reflecting the findings of two other groups who have undertaken similar studies[4,5]. However, there are important differences in the details of the findings. Francia et al.[4], showed that there were significant much larger differences in the vector selection: At least two vectors were appropriate in 69% patients with MST and 80% patients with AST ($p = 0.008$) as opposed to only a 6% difference between the tools. This is important as having at least one vector gives increased room for maneuvers if subsequent oversensing issues arise and raises confidence in prescribing

S-ICD over transvenous devices even though only 1 vector is required. The most frequent reason for screening failure with MST was a high- amplitude T-wave (31% of failures)[4]. With AST, 23% of recordings that failed with MST for high-amplitude T-wave were acceptable. This can be partially addressed by using right sided or sternal lead positions. Bogeholz et al., showed similar rule out rates between the MST: 3.0% and AST: 6.1% but the implanted S-ICD worked flawlessly in all these patients[5]. Furthermore, the AST did not predict the finally selected sensing vector better than MST with a clear mismatch between AST and MST for the predicted eligibility of single vectors- only 49% of patients have identical single vectors selected by both approaches. These data highlight the discrepancies between the S-ICD VectorSelectTM sensing algorithm and the AST/MST parameters that are tested and raise some controversial questions as to the benefits of screening at all-this needs to be fully determined in a large S-ICD implanted cohort.

The populations screened also differ: Francia 90% cardiomyopathies, Bogeholtz 27% versus 50% in Sakhi et al. which has implications in dissecting the details of the screening differences. The overall single vector pass rates for both the techniques at a level of N90% are certainly higher than in inherited cardiac conditions such as HCM with manual screening where 38% patients were ineligible for S-ICD with a single vector on the left side: 10% failed on exercise with large R waves being an important

factor[6]. No studies have systematically compared left, sternal & right sided screening with both AST and MST. Generally, the main determinants of likelihood of screening failure in the overall S-ICD population using the AST are QRS widening/bundle branch block, decreased R/T-wave ratio in lead I and T-wave inversion in I, II, or aVF[5].

Sakhi et al.'s study is an important step to standardize screening. It is vital to ensure a rigorous screening approach to maximize eligibility using all available lead positions, maximize the number of sensing vectors & avoid inappropriate therapies or undersensing especially if patients have dynamic T wave changes on exercise e.g. Long QT Syndrome and Cardiomyopathy cases: these are the main reasons to justify pre-operative screening.

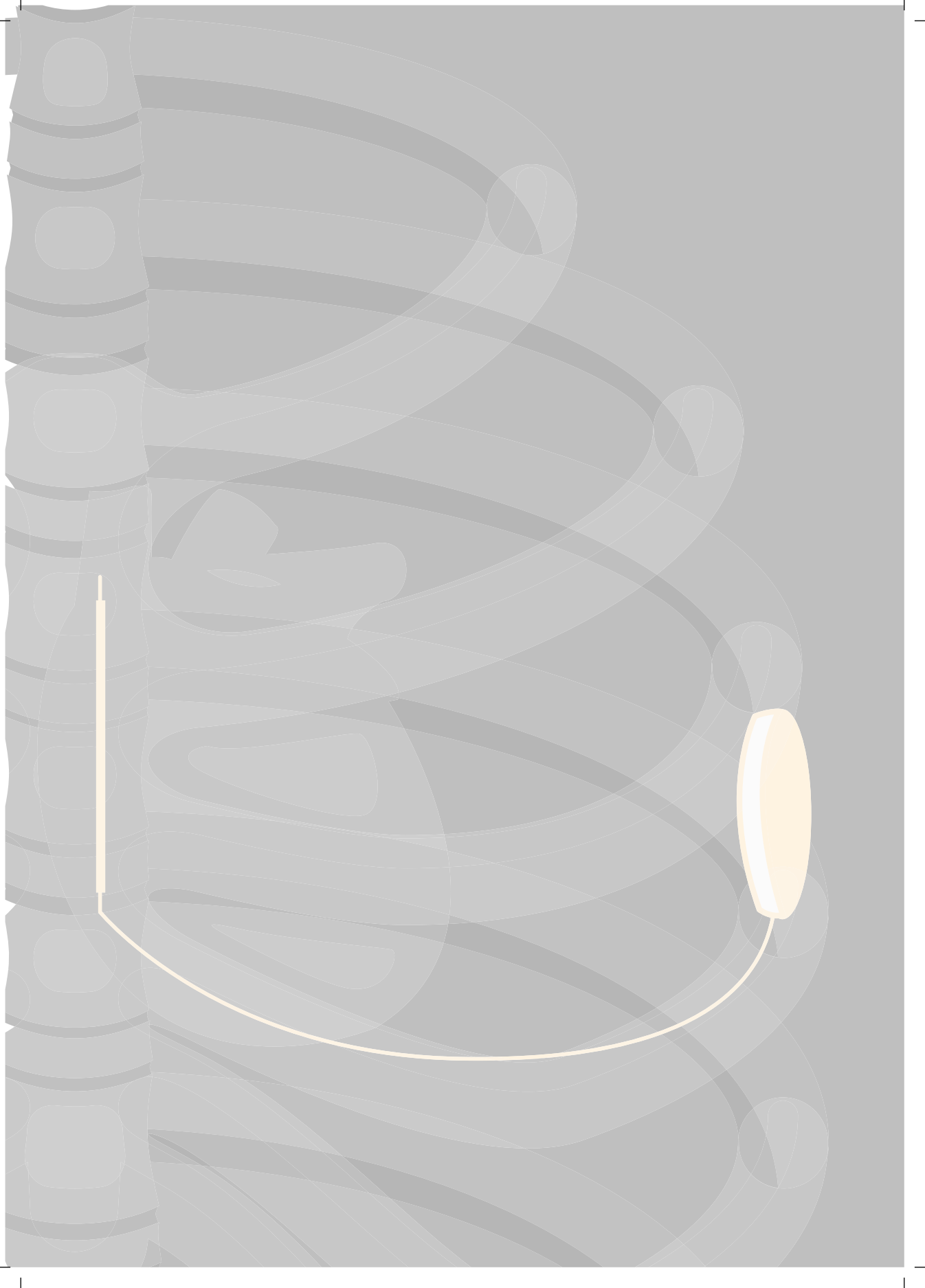
The key problem of T wave oversensing has been effectively addressed with the SMARTPASS filter. The SMARTPASS filter applies a high pass filter to remove low frequency T waves enabling only R waves to be detected by the device. This was initially tested on a retrospective dataset of inappropriate shock signals demonstrating a 40% re- duction in T wave oversensing[7]. Subsequent clinical testing by Theuns et al. in the LATTITUDE Remote Monitoring Registry has vindicated these findings: 1984 patients S-ICD were compared with the filter enabled or off- inappropriate shocks were reduced to just 4.3% vs 9.7% matching that seen with transvenous systems without compromising appropriate therapies[8].

Can the vectors that are sensed be further improved to reduce patient exclusion? Refinement could come from a more detailed vector analysis of the signal between the S-ICD lead configurations to provide a reconstructed ECG for sensing. This concept is well established in the literature and was recently tested in a series of S-ICD recipients where 3 ECG vectors can be utilized to reconstruct the QRS-T wave morphology of an 8 lead ECG[9,10]. Therefore, every patient could have a personalized ideal ECG vector to enable optimal sensing with a maximum R:T wave ratio difference & the 8 lead ECG could be reconstructed after an event from the S-ICD signals to provide diagnostic information and potentially guide VT ablation. Indeed, discrimination algorithms could combine vectors to optimize discrimination further.

In conclusion, Theuns and his co-authors work to enhance S-ICD screening and sensing is to be commended[3,8]. Automatic screening should enable standardization of S-ICD patient selection and with suit- able software and hardware enhancements we will see further refinements in sensing and event data. Leadless pacing for ATP and bradycardia may also enable hybrid S-ICD systems to further reduce T wave oversensing & discrimination errors.

References

1. M.R.Gold,D.A.Theuns,B.P.Knight,J.L.Sturdivant,R.Sanghera,K.A.Ellenbogen,M.A. Wood, M.C. Burke, Head-to-head comparison of arrhythmia discrimination perfor- mance of subcutaneous and transvenous ICD arrhythmia detection algorithms: the START study, J. Cardiovasc. Electrophysiol. 23 (4) (2012) 359–366
2. M.Zeb,N.Curzen,V.Allavatam,D.Wilson,A.Yue,P.Roberts,J.Morgan,Sensitivity and specificity of the subcutaneous implantable cardioverter defibrillator pre- implant screening tool, Int. J. Cardiol. 195 (2015 Sep 15) 205–209
3. R. Sakhi, S.C. Yap, M. Michels, A.F.L. Schinkel, R.M. Kauling, J.W. Roos-Hesselink, D.A.M.J. Theuns, Evaluation of a novel automatic screening tool for determining eligibility for a subcutaneous implantable cardioverter-defibrillator, Int. J. Cardiol. (2018 Jul 6)
4. P.Francia,M.Ziacchi,P.DeFilippo,etal.,Subcutaneousimplantablecardioverterde- fibrillator eligibility according to a novel automated screening tool and agreement with the standard manual electrocardiographic morphology tool, J. Interv. Card. Electrophysiol. 52 (2018) 61–67.
5. N. Bogeholz, P. Pauls, F. Guner, et al., Direct comparison of the novel automated screening tool (AST) versus the manual screening tool (MST) in patients with already implanted subcutaneous ICD, Int. J. Cardiol. 265 (2018) 90–96.
6. N.T. Srinivasan, K.H. Patel, K. Qamar, A. Taylor, M. Bacà, R. Providência, M. Tome-Esteban, P.M. Elliott, P.D. Lambiase, Disease severity and exercise testing reduce subcutaneous implantable cardioverter-defibrillator left sternal ECG screen- ing success in hypertrophic cardiomyopathy, Circ. Arrhythm. Electrophysiol. 10 (4) (2017)
7. A.J. Brisben, M.C. Burke, B.P. Knight, S.J. Hahn, K.L. Herrmann, V. Allavatam, D. Mahajan, R. Sanghera, M.R. Gold, A new algorithm to reduce inappropriate therapy in the S-ICD system, J. Cardiovasc. Electrophysiol. 26 (2015) 417–423.
8. D.A.M.J. Theuns, T.F. Brouwer, P.W. Jones, V. Allavatam, S. Donnelley, A. Auricchio, R.E. Knops, M.C. Burke, Prospective blinded evaluation of a novel sensing methodol- ogy designed to reduce inappropriate shocks by the subcutaneous implantable cardioverter-defibrillator, Heart Rhythm (2018 Jun 8)
9. G.E. Dower, A. Yakush, S.B. Nazzal, R.V. Jutzy, C.E. Ruiz, Deriving the 12-lead electrocardiogram from four (EASI) electrodes, J. Electrocardiol. 21 (Suppl) (1988) S182–S187.
10. D.G. Wilson, P.L. Cronbach, D. Panfilo, S.E. Greenhut, B.P. Stegemann, J.M. Morgan, Reconstruction of an 8-lead surface ECG from two subcutaneous ICD vectors, Int. J. Cardiol. 236 (2017 Jun 1) 194–197



CHAPTER 10

Usefulness of a standard 12-lead electrocardiogram to predict the eligibility for a subcutaneous defibrillator

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Journal of Electrocardiology. 2019 Jul-Aug;55:123-127.

Abstract

Background: Currently, the eligibility for a subcutaneous implantable defibrillator (S-ICD) system relies on a pre-implant vector screening based on the automated screening tool (AST). We investigated which 12-lead ECG characteristics are associated with eligibility for an S-ICD in a heterogeneous population at risk for sudden cardiac death (SCD). The goal is to determine patient eligibility for S-ICD using the standard 12-lead ECG, thereby avoiding additional AST screening.

Methods: We evaluated the eligibility for an S-ICD in 254 consecutive patients at risk for SCD. We identified 12-lead ECG parameters which were independently associated with AST passing (≥1 vector) using multivariable logistical regression analysis in our derivation cohort. The final model was tested in a separate validation cohort.

Results: The overall passing rate was 92% in our derivation cohort. Independent 12-lead ECG characteristics associated with AST passing were QRS≤130 ms, absence of QRS/T discordance in lead II and R/T-ratio ≥3.5 in lead II. Eighty-three of 254 patients (33%) fulfilled these three criteria and had a passing rate of 100%. Of the validation cohort, 37 of 60 patients (62%) fulfilled all three criteria and also had a passing rate of 100%. The interobserver agreement for applying the ECG model was 90% (Cohen's Kappa= 0.80).

Conclusion: Using the standard 12-lead ECG, we developed a simple screening model with a high specificity for S-ICD eligibility. Our results suggest that patients who fulfill the three ECG criteria do not need additional AST-screening.

Introduction

The efficacy and safety of the subcutaneous implantable defibrillator (S-ICD) has been demonstrated in both primary and secondary prevention of sudden cardiac death (SCD)[1]. However, the advantage of the S-ICD is partially offset by the presence of inappropriate shocks that is mainly attributed to T-wave oversensing[1-4]. Therefore, it is recommended that every S-ICD candidate needs to be screened before S-ICD implantation to reduce the likelihood of T-wave oversensing. In current practice, the eligibility for a subcutaneous implantable defibrillator system relies on a pre-implant vector screening based on the automated screening tool (AST). Several studies have investigated the feasibility of AST for S-ICD eligibility screening[5-7].

Previous studies demonstrated several standard 12-lead ECG characteristics associated with the eligibility for an S-ICD. However, these associations were based on the manual ECG screening tool[8-10]. We investigated which 12-lead ECG characteristics are associated with eligibility for an S-ICD in a heterogeneous population at risk for sudden cardiac death (SCD). The goal is to determine patient eligibility for S-ICD using the standard 12-lead ECG, thereby avoiding additional AST screening. Quick assessment of eligibility for a S-ICD based on a standard 12-lead ECG may be useful as the healthcare provider immediately knows if a patient is eligible for a S-ICD.

Methods

Study design

This was a retrospective study evaluating 12-lead ECG characteristics associated with AST passing in consecutive patients with cardiomyopathy, congenital heart disease, and inherited primary heart disease. The purpose of the present study was to develop a 12-lead ECG screening model which can identify patients who are eligible for an S-ICD, thereby omitting additional AST screening. The standard 12-lead ECG was acquired directly after the AST-screening. A patient was considered eligible for S-ICD if at least one sensing vector passed the AST in both supine and sitting posture. The screening model was developed using a derivation cohort. This derivation cohort consisted of 254 patients which was previously described by our group.[7] In this study we investigated the eligibility for S-ICD using both AST and manual ECG screening. In brief, all consecutive patients at risk for SCD were screened for their eligibility for S-ICD during their routine outpatient clinic using both AST and manual ECG screening between February and June 2017. Exclusion criteria were ≥3% ventricular pacing, cardiac resynchronization therapy and patients with paced QRS-complex during screening.

Finally, the derived 12-lead ECG screening model was tested in an independent validation cohort consisting of implantable cardioverter defibrillator (ICD) candidates who underwent AST-screening in a clinical setting after June 2017. All included patients provided informed consent to participate in the study, and the study was approved by the institutional review board of the Erasmus Medical Center (MEC 2017-035).

ECG analysis

Standard 12-lead ECG characteristics, such as PR interval, QRS duration, presence of interventricular conduction delay and QT(c) interval (as determined by Fridericia formula), JTc (JTc= QTc - QRS duration) were extracted from the baseline standard 12-lead ECG. Furthermore, maximum QRS and T-wave amplitude (absolute maximum deflection from the isoelectric line), absence of T-wave inversion (TWI) and QRS/T-wave discordance, and R/T-ratio were manually determined using E-scribe software (E-scribe™ ECG Workstation version 8.16.1). The characteristics were specifically analyzed in lead I, II and aVF, since these leads have a vector direction which are comparable to the primary, secondary and alternate sensing vector of the S-ICD, respectively. T-wave was considered inverted when the highest amplitude had a negative polarity and QRS/T-wave discordance was noticed when the T-wave had an opposite direction as the QRS complex. For the purpose of determining TWI and QRS/T-wave discordance the T-wave should be ≥0.1 mV.

ECG characteristics of the patients who passed the AST were compared to the patients who failed. Furthermore, a specific vector-based analysis was performed to investigate which ECG characteristics were associated with eligibility for S-ICD at the corresponding vector level.

Statistical analysis

Continuous data are presented as mean ± standard deviation or as median with interquartile range (25^{th} and 75^{th} percentile), where appropriate. Categorical variables are presented by frequencies and percentages. Differences between groups were analyzed with the unpaired Student's t-test, Chi-square test or the Fisher's exact test, as appropriate. Univariable and multivariable logistic regression analysis were performed to identify factors associated with AST passing. Any univariable variable with a P-value <0.05 was entered in a multivariable forward conditional model. Inter-observer agreement between 2 observers (RS and SCY) was evaluated using Cohen's Kappa statistics. A P-value <0.05 was considered statistically significant. Statistical analyses were performed using SPSS version 24.

Results

Baseline characteristics

A total of 254 consecutive patients were screened for their S-ICD eligibility using the AST. Among them 167 (66%) patients were males and the mean age of the study population was of 51±16 years. The majority of the patients had structural heart disease (SHD; n=194, 76%). Inherited primary arrhythmia syndrome (IPAS) was present in 60 (24%) patients. Hundred and ten (43%) patients had an ICD at the time of enrollment. The majority (64%) of the indications were for primary prevention.

Comparative demographic and clinical characteristics of those who passed (n=233, 92%) and those who failed (n=21, 8%) the AST are listed in Table 1. The passing rate varied from 83% for hypertrophic cardiomyopathy (HCM) to 100% for long QT syndrome (LQTS). There were no statistically significant differences in demographics, ICD indication, and underlying etiology between patients who

passed and those who failed the screening. Detailed overview of the baseline characteristics has been previously reported by Sakhi *et al.*[7]

Table 1. Demographics and clinical characteristics

	Total (n=254)	Pass (n=233)	Fail (n=21)	P-value
Male gender (%)	167 (66)	154 (66)	13 (62)	0.70
Age, years, ±SD	51 ± 16	51 ± 16	56 ± 16	0.17
BMI, kg/m2, ± SD	26.1 ± 4.5	26.0 ± 4.5	26.5 ± 5.0	0.68
Implantable cardioverter-defibrillator	110 (43)	103 (44)	7 (33)	0.36
Primary prevention	70 (28)	65 (28)	5 (24)	0.69
Secondary prevention	40 (16)	38 (16)	2 (10)	0.41
Cardiac diagnosis*				
Structural heart disease (%)	194 (76)	175 (75)	19 (90)	0.11
- Cardiomyopathy	126 (50)	115 (49)	11 (52)	0.79
- Congenital heart disease	68 (27)	60 (26)	8 (38)	0.22
Inherited primary arrhythmia syndrome (%)	60 (24)	58 (25)	2 (10)	0.11

Data are presented as mean ± SD, categorical data as n (%). BMI: body-mass index.

Patient based ECG analysis

ECG characteristics stratified by S-ICD eligibility are listed in Table 2. Patients who passed the screening had a higher proportion of QRS≤130 ms and QTc≤450 ms in comparison to those who failed the screening. When looking at specific leads, the patients who passed the screening had less TWI in lead II; less QRS/T-wave discordance in lead II and aVF; and a higher R/T-ratio in lead II and aVF in comparison to those who failed the screening.

Vector-based ECG analysis

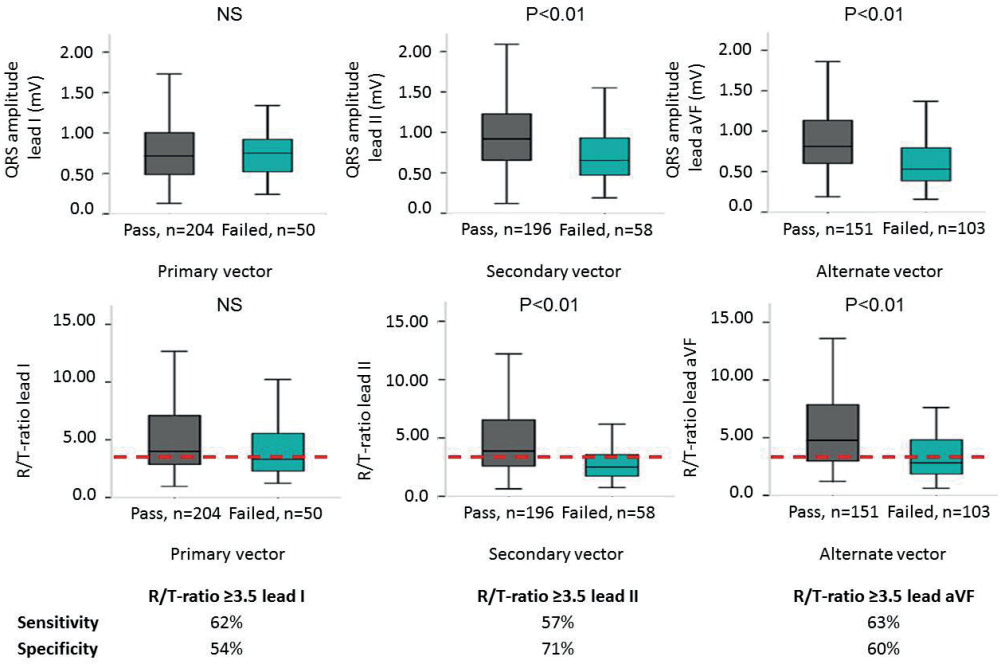
The primary, secondary and alternate sensing vectors of 254 patients, both supine and sitting postures, were analyzed separately, resulting in 762 vectors. The primary sensing vector was the most appropriate (80%, n=204), followed by the secondary vector (77%, n=196) and the alternate vector (59%, n=151). Results of the absolute QRS amplitude and R/T-ratio of lead I, lead II and lead aVF with the corresponding vectors are demonstrated in Figure 1. Patients who passed the secondary or alternate vector had a higher absolute QRS amplitude in their corresponding leads (lead II and aVF, respectively) in comparison to those who failed (lead II: 0.92 mV versus 0.66 mV, P<0.01; lead aVF: 0.81 mV versus 0.53 mV, P<0.01). Furthermore, they also had a higher R/T-ratio in leads II and aVF (lead II: 3.88 versus 2.50, P<0.01; lead aVF: 4.77 versus 2.82, P<0.01). A R/T-ratio of ≥3.5 was deemed as the optimal cutoff based on the highest sensitivity and specificity for the specific leads (Figure 1). A more detailed overview of ECG characteristics with the matching screening vectors are provided in supplementary material (Appendix A). Patients who passed the screening had a higher proportion of R/T-ratio ≥3.5 in lead II and aVF (Table 2).

Table 2. Baseline 12-lead ECG characteristics

	Total (n=254)	Pass (n=233)	Fail (n=21)	P-value
Sinus rhythm (%)	229 (90)	209 (90)	20 (95)	0.41
PR interval (IQR)*	169 (152-189)	168 (151-187)	188 (161-193)	0.06
QRS≤130 ms	200 (79)	193 (83)	7 (33)	<0.01
QT≤450 ms	227 (89)	210 (90)	17 (81)	0.19
QTc≤450 ms	223 (88)	208 (89)	15 (71)	0.02
JTc duration	294 (275-316)	295 (275-316)	289 (273-322)	0.36
Maximal QRS amplitude in mV (IQR)				
- lead I	0.72 (0.49-0.99)	0.70 (0.49-0.99)	0.88 (0.55-1.00)	0.34
- lead II	0.87 (0.60-1.18)	0.89 (0.63-1.20)	0.63 (0.45-1.01)	0.08
- lead aVF	0.71 (0.48-1.00)	0.72 (0.50-1.03)	0.58 (0.34-0.87)	0.36
Absence of T-wave inversion (%)				
- lead I	211 (83)	197 (85)	14 (67)	0.04
- lead II	225 (89)	210 (90)	15 (71)	0.02
- lead aVF	215 (85)	200 (86)	15 (71)	0.09
Absence of QRS/T-wave discordance (%)				
- lead I	179 (70)	167 (72)	12 (57)	0.16
- lead II	198 (78)	188 (81)	10 (48)	<0.01
- lead aVF	163 (64)	156 (67)	7 (33)	<0.01
R/T-ratio per lead (IQR)				
- lead I	3.87 (2.58-6.85)	3.88 (2.59-6.94)	3.44 (2.56-5.54)	1.00
- lead II	3.52 (2.33-5.71)	3.61 (2.42-5.94)	2.52 (1.58-3.10)	0.02
- lead aVF	3.66 (2.33-6.84)	4.08 (2.38-7.09)	2.36 (1.42-3.60)	0.02
R/T-ratio of ≥3.5 per lead (%)				
- lead I	149 (59)	139 (60)	10 (48)	0.28
- lead II	128 (50)	123 (53)	5 (24)	0.02
- lead aVF	136 (54)	130 (56)	6 (29)	0.02

* Only in patients with sinus rhythm, IQR= interquartile range.

Figure 1. Eligibility for S-ICD of the different screening vectors based on the QRS-amplitude and R/T-ratio of the corresponding leads. NS= no significant p-value.



	R/T-ratio ≥3.5 lead I	R/T-ratio ≥3.5 lead II	R/T-ratio ≥3.5 lead aVF
Sensitivity	62%	57%	63%
Specificity	54%	71%	60%

ECG characteristics associated with S-ICD eligibility

Univariable and multivariable analysis for S-ICD eligibility are presented in Table 3. Univariable analysis demonstrated that QRS duration ≤130 ms, QTc duration ≤450 ms, absence of TWI in lead I and lead II, absence of QRS/T-wave discordance in lead II and aVF, and R/T-ratio ≥3.5 in II and aVF were associated with AST passing based on ≥1-vector pass rule. Independent ECG characteristics associated with AST passing were QRS≤130 ms, absence of QRS/T-wave discordance in lead II and R/T-ratio ≥3.5 in lead II.

When applying the ECG criteria in the derivation cohort, 83 patients (33%) fulfilled all three ECG criteria. In these patients, the eligibility for S-ICD based on ≥1 vector passing rate was 100%, When using the more stringent ≥2 vector pass criteria for S-ICD eligibility, the passing rate was 96%.

Table 3. ECG characteristics associated with S-ICD eligibility

Variables	Univariable		Multivariable	
	OR (95% CI)	P-value	OR (95% CI)	P-value
QRS≤130 ms	**9.65 (3.66-25.43)**	**<0.01**	**8.09 (2.88-22.77)**	**<0.01**
QTc≤450 ms	3.33 (1.18-9.54)	0.02		
Absence of T-wave inversion in lead I	2.74 (1.03-7.25)	0.04		
Absence of T-wave inversion in lead II	3.65 (1.29-10.33)	0.02		
Absence of QRS/T-wave discordance in lead II	**5.05 (1.98-12.92)**	**<0.01**	**4.19 (1.49-11.74)**	**<0.01**
Absence of QRS/T-wave discordance in lead aVF	3.95 (1.53-10.19)	<0.01		
R/T-ratio ≥3.5 in lead II	**3.58 (1.27-10.01)**	**0.02**	**4.21 (1.27-13.95)**	**0.02**
R/T-ratio ≥3.5 in lead aVF	3.16 (1.18-8.42)	0.02		

Abbreviations: OR= odds ratio; CI= confidence interval.

Validation analysis

The 12-lead ECG screening model was evaluated in a validation cohort consisting of 60 ICD candidates who underwent AST-screening as part of their clinical workup for ICD implantation. The mean age of the validation cohort was 49 ± 17 years and the majority of the patients were male (76%). In total, 50 patients had SHD (83%) and IPAS was present in 10 (17%) patients. The ≥1 vector pass rate was 90% for this cohort, 6 patients (10%) failed the AST screening. When applying the derived screening model, 37 of 60 patients (62%) fulfilled all three 12-lead ECG criteria. The ≥1 vector pass rate was 100% for this selected cohort, thus all patients who fulfilled the three ECG criteria were eligible for S-ICD. Furthermore, when using the stringent criteria for S-ICD eligibility (≥2 vector pass rule) the eligibility increased from 78% to 89% in patients. The interobserver agreement of the screening model was good with a Cohen's Kappa of 0.80 and an overall agreement of 90%.

Follow- up of S-ICD patients

Of the patients who fulfilled all the three ECG criteria in the derivation cohort, 18 of 83 patients (22%) had an S-ICD. During a median follow-up of 66 months (interquartile range: 35-85 months), two patients experienced an inappropriate shock. One patient received an inappropriate shock due to R-wave attenuation and the other patient due to a supraventricular tachyarrhythmia detected in the shock zone. In the validation cohort, 28 of the 37 patients (76%) who fulfilled the three ECG criteria received an S-ICD and during a median follow-up of 11 months (interquartile range: 3-15 months) none of the patients experienced an inappropriate shock.

Discussion

The present study demonstrated that QRS duration ≤130 ms, absence of QRS/T-wave discordance in lead II and R/T-ratio ≥3.5 in lead II were independently associated with eligibility for S-ICD based on AST-screening. Interestingly, the eligibility for S-ICD was 100% in patients who fulfilled all three criteria in both the derivation and validation cohort.

Using the AST as a pre-implant screening tool, eligibility rates from 92% to 96% have been reported[5-7]. The study by Francia *et al*., reported eligibility rates of 94% and 80% when using ≥1-vector and ≥2-vector pass rule, respectively[5]. This is in line with the results of the present study (92% for ≥1-vector pass and ≥ 80% 2-vector pass). More recently, Bogeholz *et al*., found a ≥1-vector AST passing rate of 94% in 33 consecutive patients who already had an S-ICD system implanted[6]. Comparable results were demonstrated by Sakhi *et al*., in S-ICD patients in whom eligibility for S-ICD had already been determined with manual ECG screening (n=35, 100% ≥1-vector pass rule)[7].

ECG characteristics associated with S-ICD eligibility

Previous studies have identified 12-lead ECG characteristics associated with S-ICD ineligibility based on manual ECG screening, such as prolonged QRS duration, low R/T-ratio, T-wave inversion and QRS/T-wave discordance[8-10]. Considering the high agreement between manual ECG screening and AST on a patient level, one would expect the same factors to be associated with S-ICD ineligibility based on AST[7]. We identified similar factors associated with S-ICD ineligibility: prolonged QRS duration, presence of QRS/T-wave discordance in lead II, and low R/T-ratio in lead II. Bogeholz *et al*. also demonstrated that prolonged QRS duration, presence of T-wave inversion and a low R/T-ratio were more common in patients who failed AST-screening.

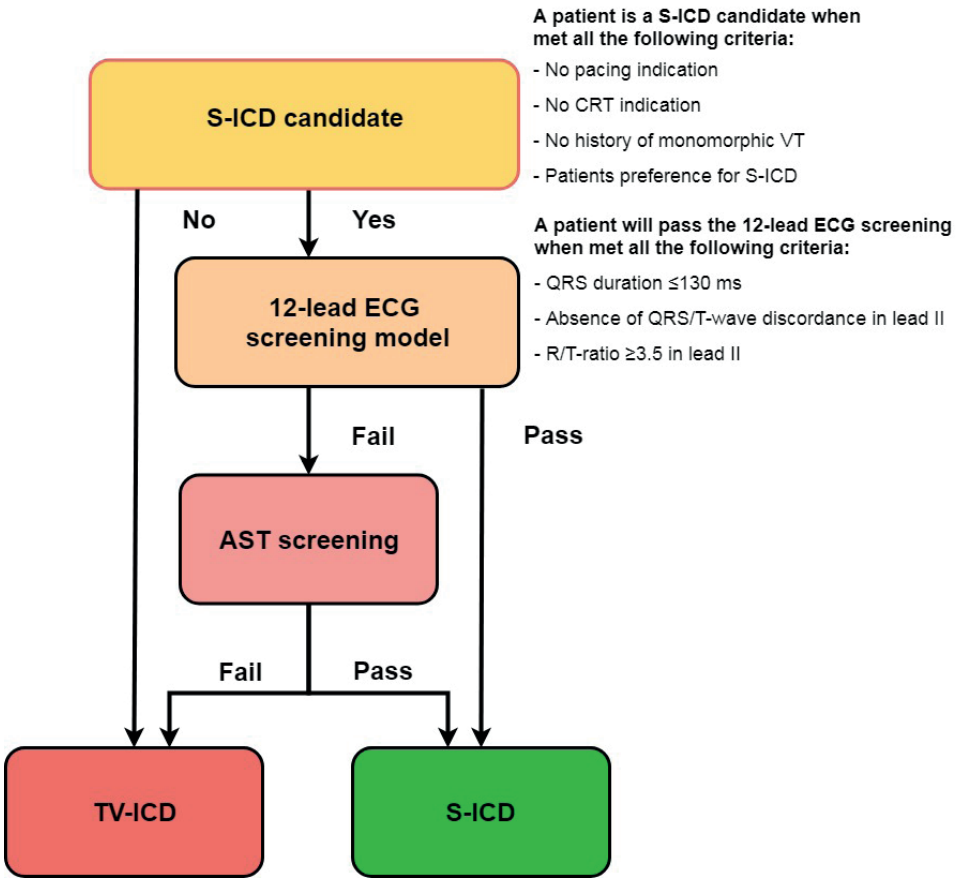
The purpose of AST screening is to select patients who are at low risk of T-wave oversensing. Our proposed screening model achieves the same result albeit at the cost of sensitivity (patients who fail our screening model, may still be suitable based on AST). The identified ECG factors are probably associated with a normal repolarization with a good signal-to-noise ratio. It is known that prolonged QRS duration and QRS/T-wave discordance are associated with repolarization abnormalities. By excluding patients with repolarization abnormalities and a low R/T-ratio, it seems logical that the chance of T-wave oversensing is low.

Clinical implications

When a patient is a potential ICD candidate and does not have an indication for pacing, biventricular pacing or ATP then the patient is a potential candidate for an S-ICD. In clinical practice, a potential S-ICD candidate undergoes vector screening using AST and when at least 1 vector is suitable then we will discuss the pros and cons of transvenous and subcutaneous ICDs. Based on previous studies it is known that the S-ICD eligibility rate based on AST is relatively high (>90%). Some implanters have argued to abolish vector screening considering this high passing rate. Unfortunately, inappropriate shocks due to T-wave oversensing do occur and this should be prevented. We developed a simple screening model

using the standard 12-lead ECG which can identify patients who have a very high likelihood to pass the vector screening based on AST. When patients fulfill all three ECG criteria, it seems safe to omit vector screening considering the 100% ≥1 vector passing rate and even 96% ≥2 vector passing rate. Despite the excellent specificity (100%), the sensitivity of the proposed screening model varied between 36-67%. This means that a substantial proportion of ICD candidates still requires AST screening. Based on the results of the present study, we propose a simple flowchart to determine eligibility for an S-ICD that can be easily implemented in daily clinical practice (Figure 2).

Figure 2. Proposed screening procedure for S-ICD screening in daily clinical practice. CRT= cardiac resynchronization therapy; VT= ventricular tachycardia; TV-ICD= transvenous implantable cardioverter defibrillator.



Study limitations

Several limitations are important to highlight. It has been previously shown that S-ICD screening during exercise can identify T-wave oversensing and results in a greater failure rate, especially in certain patients with HCM[3, 11, 12]. We did not test our study population during exercise, therefore we cannot draw conclusions on the validity of our model in patients undergoing exercise testing as part of the screening. Furthermore, the combination of the small number of patients in the validation cohort and high passing rate may affect the accuracy of the specificity of our model. Therefore, the 12-lead ECG screening model should be validated in a larger population before widespread clinical adoption. Finally, the safety of the proposed algorithm can be evaluated when comparing the inappropriate shock rates of patient populations screened with the proposed algorithm versus AST only.

Conclusion

Using the standard 12-lead ECG we developed a simple screening model with a high specificity for S-ICD eligibility. Our results suggest that patients who fulfill the three ECG criteria do not need additional AST-screening.

Appendix

Appendix A. Baseline 12-lead ECG characteristics with the matching screening vectors

	PRIMARY VECTOR			SECONDARY VECTOR			ALTERNATE VECTOR		
	Pass (n=204)	**Fail (n=50)**	**P-value**	**Pass (n=196)**	**Fail (n=58)**	**P-value**	**Pass (n=151)**	**Fail (n=103)**	**P-value**
Maximal QRS amplitude in mV (IQR)									
- lead I	0.72 (0.48-1.01)	0.75 (0.51-0.93)	0.83	0.70 (0.49-1.00)	0.78 (0.48-0.93)	0.42	0.73 (0.49-1.05)	0.70 (0.48-0.92)	0.88
- **lead II**	0.89 (0.62-1.21)	0.74 (0.51-1.12)	0.51	**0.92 (0.65-1.23)**	**0.66 (0.47-0.93)**	**<0.01**	0.93 (0.67-1.34)	0.72 (0.50-0.99)	0.01
- **lead aVF**	0.69 (0.48-0.99)	0.76 (0.50-1.08)	0.27	0.72 (0.50-1.03)	0.66 (0.40-0.96)	0.65	**0.81 (0.59-1.14)**	**0.53 (0.38-0.80)**	**<0.01**
T-wave inversion (%)									
- lead I	35 (17)	8 (16)	0.85	19 (10)	10 (17)	0.10	23 (15)	20 (19)	0.38
- lead II	21 (10)	8 (16)	0.26	29 (15)	14 (24)	0.11	14 (9)	15 (15)	0.19
- lead aVF	28 (14)	11 (22)	0.15	30 (15)	9 (16)	0.97	23 (15)	16 (16)	0.95
QRS/T-wave discordance (%)									
- **lead I**	**53 (26)**	**22 (44)**	**0.01**	50 (26)	25 (43)	0.03	46 (30)	29 (28)	0.74
- **lead II**	40 (20)	16 (32)	0.13	**32 (16)**	**24 (41)**	**<0.01**	30 (20)	26 (25)	0.06
- **lead aVF**	66 (32)	25 (50)	0.05	60 (31)	31 (53)	0.01	51 (34)	40 (39)	0.61
R/T-ratio per lead (IQR)									
- lead I	4.00 (2.86-7.11)	3.30 (2.25-5.63)	0.27	3.84 (2.41-6.99)	4.22 (2.71-6.14)	0.65	4.11 (2.86-7.11)	3.76 (2.46-6.00)	0.31
- **lead II**	3.69 (2.36-6.40)	2.70 (2.06-3.85)	0.01	**3.88 (2.58-6.58)**	**2.49 (1.72-3.57)**	**<0.01**	3.84 (2.66-6.67)	2.75 (1.94-4.52)	0.01
- **lead aVF**	3.72 (2.34-7.37)	3.52 (2.03-5.62)	0.88	4.21 (2.58-7.60)	2.76 (1.81-5.40)	0.03	**4.77 (2.97-7.89)**	**2.82 (1.85-4.82)**	**<0.01**
R/T-ratio≥3.5 per lead (%)									
- **lead I**	**126 (62)**	**23 (46)**	**0.04**	115 (59)	34 (59)	0.99	95 (63)	54 (52)	0.10
- **lead II**	112 (55)	16 (32)	<0.01	**111 (57)**	**17 (29)**	**<0.01**	86 (57)	42 (41)	0.01
- **lead aVF**	111 (54)	25 (50)	0.58	114 (58)	22 (38)	<0.01	**95 (63)**	**41 (40)**	**<0.01**

References

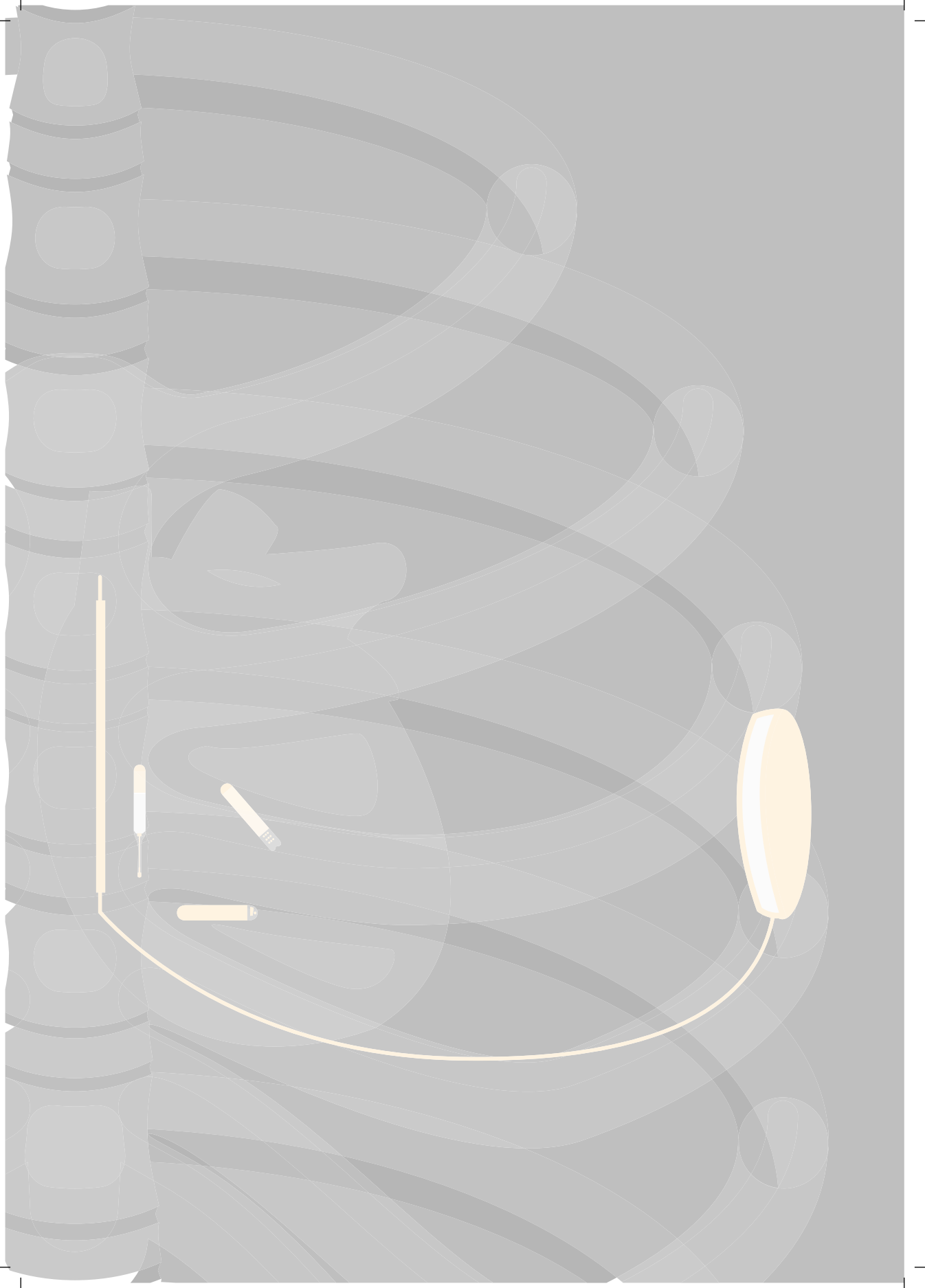
1. Boersma L, Barr C, Knops R, Theuns D, Eckardt L, Neuzil P, Scholten M, Hood M, Kuschyk J, Jones P, Duffy E, Husby M, Stein K, Lambiase PD and Group EI. Implant and Midterm Outcomes of the Subcutaneous Implantable Cardioverter-Defibrillator Registry: The EFFORTLESS Study. *J Am Coll Cardiol*. 2017;70:830-841.
2. Gold MR, Theuns DA, Knight BP, Sturdivant JL, Sanghera R, Ellenbogen KA, Wood MA and Burke MC. Head-to-head comparison of arrhythmia discrimination performance of subcutaneous and transvenous ICD arrhythmia detection algorithms: the START study. *J Cardiovasc Electrophysiol*. 2012;23:359-66.
3. Kooiman KM, Knops RE, Olde Nordkamp L, Wilde AA and de Groot JR. Inappropriate subcutaneous implantable cardioverter-defibrillator shocks due to T-wave oversensing can be prevented: implications for management. *Heart Rhythm*. 2014;11:426-34.
4. Olde Nordkamp LR, Brouwer TF, Barr C, Theuns DA, Boersma LV, Johansen JB, Neuzil P, Wilde AA, Carter N, Husby M, Lambiase PD and Knops RE. Inappropriate shocks in the subcutaneous ICD: Incidence, predictors and management. *Int J Cardiol*. 2015;195:126-33.
5. Francia P, Ziacchi M, De Filippo P, Viani S, D'Onofrio A, Russo V, Adduci C, Biffi M, Ferrari P, Bianchi V, Ammendola E, Palano F, Frisoni J, Valsecchi S, Lovecchio M and Bongiorni MG. Subcutaneous implantable cardioverter defibrillator eligibility according to a novel automated screening tool and agreement with the standard manual electrocardiographic morphology tool. *J Interv Card Electrophysiol*. 2018;52:61-67.
6. Bogeholz N, Pauls P, Guner F, Bode N, Fischer A, Dechering D, Frommeyer G, Kobe J, Wasmer K, Eckardt L and Reinke F. Direct comparison of the novel automated screening tool (AST) versus the manual screening tool (MST) in patients with already implanted subcutaneous ICD. *Int J Cardiol*. 2018;265:90-96.
7. Sakhi R, Theuns D, Bhagwandien RE, Michels M, Schinkel AFL, Szili-Torok T, Zijlstra F, Roos-Hesselink JW and Yap SC. Value of implantable loop recorders in patients with structural or electrical heart disease. *Journal of interventional cardiac electrophysiology : an international journal of arrhythmias and pacing*. 2018;52:203-208.
8. Groh CA, Sharma S, Pelchovitz DJ, Bhave PD, Rhyner J, Verma N, Arora R, Chicos AB, Kim SS, Lin AC, Passman RS and Knight BP. Use of an electrocardiographic screening tool to determine candidacy for a subcutaneous implantable cardioverter-defibrillator. *Heart Rhythm*. 2014;11:1361-6.
9. Olde Nordkamp LRA, Warnaars JLF, Kooiman KM, de Groot JR, Rosenmoller B, Wilde AAM and Knops RE. Which patients are not suitable for a subcutaneous ICD: incidence and predictors of failed QRS-T-wave morphology screening. *J Cardiovasc Electrophysiol*. 2014;25:494-499.
10. Randles DA, Hawkins NM, Shaw M, Patwala AY, Pettit SJ and Wright DJ. How many patients fulfil the surface electrocardiogram criteria for subcutaneous implantable cardioverter-defibrillator implantation? *Europace*. 2014;16:1015-21.
11. Srinivasan NT, Patel KH, Qamar K, Taylor A, Baca M, Providencia R, Tome-Esteban M, Elliott PM and Lambiase PD. Disease Severity and Exercise Testing Reduce Subcutaneous Implantable Cardioverter-Defibrillator Left Sternal ECG Screening Success in Hypertrophic Cardiomyopathy. *Circ Arrhythm Electrophysiol*. 2017;10.
12. Francia P, Adduci C, Palano F, Semprini L, Serdoz A, Montesanti D, Santini D, Musumeci B, Salvati A, Volpe M and Autore C. Eligibility for the Subcutaneous Implantable Cardioverter-Defibrillator in Patients With Hypertrophic Cardiomyopathy. *J Cardiovasc Electrophysiol*. 2015;26:893-899.

Epilogue

Tali sono tutte le cose vere, dopo che son trovate;
ma il punto sta nel saperle trovare.

(All truths are easy to understand once they are discovered;
the point is to discover them)

Galileo Galilei
(Dialogo sopra i due massimi sistemi del mondo, 1632)



CHAPTER 11

Summary and general discussion

Nederlandse samenvatting

List of publications

PhD-portfolio

Curriculum Vitae

Dankwoord

SUMMARY

Introduction

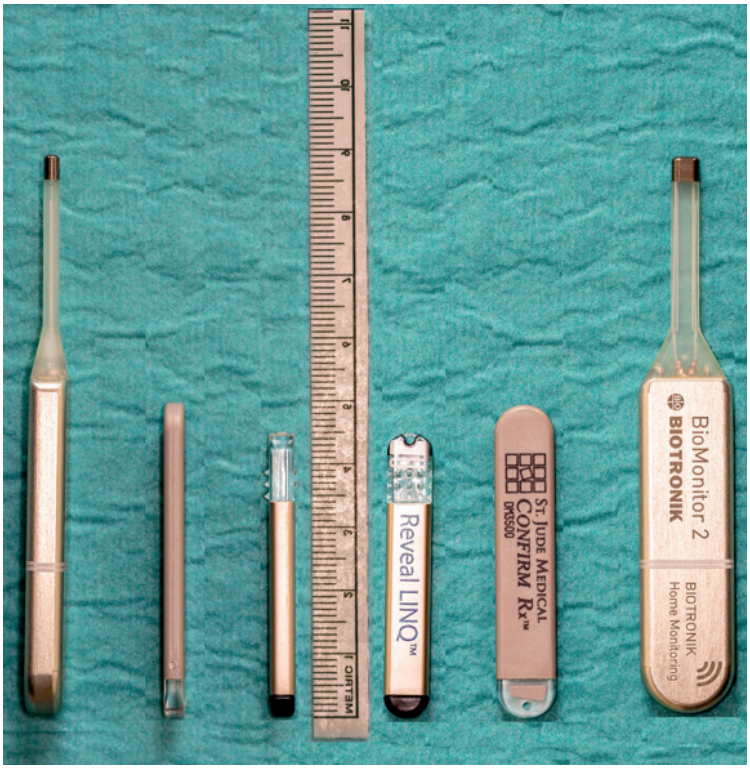
Prolonged rhythm monitoring using a subcutaneous insertable cardiac monitor (ICM) has proven to be of incremental diagnostic value for a wide spectrum of indications, especially in patients with recurrent unexplained syncope[1, 2]. The aim of the present thesis (**Part I**) was to investigate the clinical value of ICMs as part of risk stratification in different patients with inherited and/or structural heart disease who are susceptible to sudden cardiac death (SCD) but who do not have a clear indication for an implantable cardioverter-defibrillator (ICD) for primary prevention. Furthermore, given the fact that the majority of patients with inherited and/or structural heart disease are young and do not require bradycardia pacing or resynchronization therapy, we wanted to investigate their suitability for a completely subcutaneous ICD system (**Part II).** The following summary addresses the main findings of the studies included in this thesis and discuss their clinical features and future perspectives.

Part I – Summary

In Part I of the present thesis we focus on the clinical usefulness of ICMs as diagnostic tool for risk stratification in patients who are at low to moderate risk of SCD. First, we provide a review in **Chapter 2**, in which we discuss the current indications for ICMs and give an overview of the latest generation of commercially available ICMs. According to the current guidelines and expert consensus, the indications for ICMs are expanding to patients with primary cardiomyopathy (e.g., hypertrophic cardiomyopathy, arrhythmogenic right ventricular cardiomyopathy), inherited primary arrhythmia syndrome (e.g., long-QT syndrome, Brugada syndrome), suspected unproven epilepsy, and unexplained falls[1-5]. The current generation ICMs are smaller, easier to implant, have better diagnostics, and are capable of remote monitoring. Figure 1 provide an overview of the current ICMs on the market. The Reveal LINQ (Medtronic) is the smallest ICM and has the most extensive performance and clinical data. The BioMonitor 2 (Biotronik) is the largest ICM but has excellent R-wave amplitudes, longest longevity, and reliable remote monitoring. The Confirm Rx (Abbott) is capable of providing mobile data transmission enabled by a smartphone app.

Considering the expanding role for ICMs for risk stratification in patients with primary cardiomyopathy or inherited arrhythmia syndrome, we performed a pilot study in which we described our initial experience with the current generation of ICM (Reveal LINQ) (**Chapter 3**). We hypothesized that patients with structural or electrical heart disease would have a higher incidence of ventricular arrhythmia (VA) compared to those without underlying heart disease. We found that in comparison to patients without heart disease, the diagnostic yield of an ICM was lower in patients with inherited arrhythmia syndrome and the incidence of ICM-diagnosed nonsustained VA was higher in patients with structural heart disease Interestingly, 4 patients (4%) received an ICD based on the findings of the ICM.

Figure 1. Overview of current generation ICMs. Reveal LINQ (Medtronic), Confirm Rx (Abbott/St. Jude medical), and BioMonitor 2 (Biotronik), respectively.



Based on the results of our pilot study, we specifically evaluated the value of ICMs in specific patient categories at low to moderate risk of SCD. The occurrence of syncope in patients who are potentially susceptible to SCD could be the result of a self-terminating VA and is considered a risk factor for SCD in certain heart conditions. Furthermore, symptoms like palpitations and near-syncope may also be associated with other significant arrhythmias. Considering the potential adverse effects of ICD therapy, the decision to implant an ICD is not easy, especially in young patients. In this regard, an ICM can be used to exclude VA as the cause of symptoms. Furthermore, continuous arrhythmia monitoring will also provide the physician the assurance that any VA, also those that are asymptomatic, will be documented. The strategy of using an ICM for this purpose in different patient population is described in **Chapter 4-6**.

An important mode of death in adults with congenital heart disease (CHD) is SCD and is mainly driven by VA. In current practice, the decision to implant an ICD in patients with CHD is challenging and is largely based on the physician's clinical judgement[6-9]. In **Chapter 4** (**EDVA-CHD** study), we prospectively evaluated the usefulness of ICMs in adults with CHD who deemed at risk of SCD. The **EDVA-CHD** study demonstrated that long-term arrhythmia monitoring by an ICM seems valuable for

risk stratification in adults with CHD resulting in an ICD for 10% of the study population. Furthermore, ICM-detected arrhythmias leading to changes in clinical management occurred in 73% of patients.

The ESC guidelines recommend the use of the HCM Risk-SCD model to identify ICD candidates in patients with hypertrophic cardiomyopathy (HCM). One important risk factor in this model is the occurrence of (non)sustained VA[3, 5, 10]. In **Chapter 5**, we compared the diagnostic yield of ICMs in the detection of VA with conventional Holter monitoring. The study was performed in patients with HCM who are deemed to be at low to moderate risk of SCD based on the HCM Risk-SCD model. This study demonstrated that in adults with HCM, the diagnostic yield of detecting a VA is similar for ICMs and conventional Holter monitoring. However, compared to conventional strategy, ICMs detected more arrhythmic events requiring a therapeutic intervention.

Brugada syndrome is an inherited syndrome associated with a risk of SCD due to VA[11, 12]. Risk stratification in patients with Brugada syndrome is challenging and there is debate on the prognostic role of an electrophysiology study[13-15]. In clinical practice, physicians are confronted with patients with Brugada syndrome who have symptoms such as palpitations, near-syncope, or nonarrhythmogenic syncope[16, 17]. Some symptoms are caused by anxiety for arrhythmic events, but it may be difficult to differentiate this from clinically relevant arrhythmias. The purpose of the study in **Chapter 6** was to evaluate the value of ICMs in symptomatic patients with Brugada syndrome who are at low risk of SCD. The main reason for arrhythmia monitoring was to exclude VA as the cause of symptoms and to establish a symptom-rhythm relationship. Half of the population had a history of syncope. There was no sustained VA during follow-up of almost 3 years. The majority of patients had symptoms during follow-up, and 20% required a change in clinical management based on an ICM-detected arrhythmia.

Finally, chronic coronary total occlusion (CTO) has been identified as a risk factor for VA in primary prevention ICD recipients with LV dysfunction. CTO is a very common condition among patients with coronary artery disease, with a reported prevalence between 30 to 50% in patients with referred to catheterization laboratory[18, 19]. In **Chapter 7**, we conducted a retrospective single-center study in which we evaluated the impact of unrevascularized CTOs on the occurrence of appropriate ICD therapy in out-of-hospital cardiac arrest survivors with coronary artery disease. A CTO was an independent predictor of appropriate ICD therapy, even after correcting for severe LV dysfunction.

Part I - Discussion

There is a clear indication to use an ICM as a diagnostic tool in patients with recurrent unexplained syncope without high-risk features[20]. A history of syncope in patients with structural heart disease or inheritable arrhythmia syndrome is associated with an increased risk of SCD. When the mechanism of syncope is nonarrhythmogenic, the management of patients with high-risk features is similar to those without syncope. The clinical problem is that the distinction between nonarrhythmogenic and arrhythmogenic syncope can be difficult. In this respect, an ICM can be useful. The recent European guidelines expand the role of ICM to patients with structural heart disease or inheritable arrhythmia

syndrome who have recurrent episodes of unexplained syncope who are at low risk of SCD[2]. We evaluated a strategy of using an ICM in symptomatic patients with congenital heart disease, HCM and Brugada syndrome who were at low to moderate risk of SCD. It is good to realize that these patients already underwent comprehensive evaluation before ICM implantation which did not lead to a specific treatment. The goal of continuous monitoring in these patients was to establish a symptom-rhythm correlation and to detect asymptomatic VA. We demonstrated that the incidence of VA was relatively low during follow-up, but up to 10% of patients received an ICD, depending on the patient population. In addition, ICM-detected arrhythmias led to a change in clinical management in a 20-53% of the patients. Finally, it is important to highlight that the exclusion of VA as the cause of symptoms and continuous monitoring provides reassurance to patients who have an underlying disease predisposing them to malignant arrhythmias.

Though the use of ICMs in patients with high-risk features seems promising, there are several factors that should be considered, including device costs, data overload, clinical relevance of device-detected VA and medical overuse. The issue of data overload is exemplified by the recording of more than 4,600 episodes in 75 patients during the follow-up period of our studies. This requires a proper logistic organization with a dedicated telemonitoring staff. Furthermore, since the insertion procedure can take place outside the catheterization laboratory in a less resource intensive environment and can be performed by trained nurses, we expect that the costs related to ICM implantation will decrease[21-24].

In conclusion, an ICM can be a useful diagnostic tool in symptomatic patients with structural heart disease or inheritable arrhythmia syndrome who are at low to moderate risk of SCD when comprehensive evaluation has not led to a specific treatment.

Part I – Future perspective

Since the introduction of the ICMs in 1980, technological improvements have led to miniaturization of the device, improved sensing capabilities, atrial fibrillation detection algorithms, and availability of remote monitoring[25, 26]. Recently, the indications for ICMs have expanded to other populations. While previously it was mainly used for patients with recurrent unexplained syncope, the ICM can be used for risk stratification or to detect atrial fibrillation after cryptogenic stroke or after catheter ablation[27]. ICMs can also be useful for research purposes to clarify the mechanism of clinical events. For example, CTO has been identified as a risk factor for VA in patients who received an ICD for primary or secondary prevention[28-30]. Patients with a failed CTO revascularization have a higher mortality rate in comparison to those with successful recanalization[31]. Based on these observations we hypothesize that CTO is an important predictor of VA, especially after a failed recanalization. Currently, we are evaluating 3 groups of patients with a CTO for the occurrence of VA with an ICM (NCT03475888, VACTOR study). These groups are patients with successful percutaneous CTO recanalization, failed percutaneous CTO recanalization and untreated CTO. The results are expected in 2023.

Currently, ICMs are used for continuous monitoring of the heart rhythm. Considering the remote monitoring capabilities, the diagnostic capabilities may expand to other fields. The most promising field is to remotely monitor patients with heart failure in order to detect early signs of worsening heart failure. The CHAMPION study has demonstrated that patients with NYHA III heart failure who are managed with remote monitoring using a wireless implantable hemodynamic monitoring system (CardioMEMS™, Abbott) have a reduction in heart-failure-related hospitalizations[32]. The CardioMEMS™ system monitors the pulmonary artery pressure using a small pressure sensor which is permanently implanted in the distal pulmonary artery. It is also possible to use physiological trends for detecting early signs of worsening heart failure. The MultiSENSE study demonstrated that the HeartLogic™ diagnostic (Boston Scientific) can predict future heart failure events[33]. HeartLogic™ uses multiple sensors in an ICD to track changes in heart sounds, intrathoracic impedance, respiration, heart rate and patient activity metrics. When the composite index crosses a certain threshold, the clinician is proactively alerted via remote monitoring. It is likely that heart failure diagnostics can be incorporated in an ICM providing the possibility to remotely monitor patients with heart failure who do not have an ICD. For example, the purpose of the currently ongoing LINQ HF study (Medtronic) is to assess the relationship between changes in LINQ derived data and other physiologic parameters with subsequent acute decompensated heart failure events (NCT02758301). No results have been published yet. In conclusion, we expect that the availability of heart failure diagnostics will be an important mile stone in the evolution of ICMs.

Part II – Summary

In **part II** of this thesis we evaluated the suitability of different patient categories for a subcutaneous ICD (S-ICD, Figure 2). The current guidelines give a class IIa recommendation for an S-ICD as an alternative to a transvenous ICD if there is no need for pacing therapy, cardiac resynchronization therapy (CRT) or antitachycardia pacing (ATP). Furthermore, to prevent inappropriate shocks due to T-wave oversensing it is recommended that every candidate undergo vector screening to check if they qualify for an S-ICD. In **Chapter 8** we evaluated the potential candidacy for an S-ICD at the time of first replacement in a cohort of patients with a transvenous single chamber ICD who did not need pacing at the time of implantation. At the time of first ICD replacement, 69% of patients was potentially suitable for an S-ICD. Thus, 31% needed either ATP, CRT and/or bradypacing during the first battery-lifetime. For individual end points, annual incidence rates were 4.9% appropriate ATP, 1.8% for CRT, and 0.3% for pacing-dependency. No baseline variables could predict which patient would potentially be suitable for an S-ICD.

If a patient is considered a candidate for an S-ICD (no need for pacing, ATP or CRT), then vector screening is performed to check if the patient has a suitable QRS-T morphology. Usually this was done manually using a manual ECG-screening tool and a vector electrocardiogram. Recently, an Automated Screening Tool (AST) became available, fully automating this process of vector screening. In **Chapter 9** we prospectively evaluated the eligibility for a S-ICD using the two screening tools (manual vector screening versus AST) in different patient categories including patients with cardiomyopathy, congenital heart disease and inherited primary arrhythmia syndrome. There was a high vector eligibility

using either method (93% versus 92%, P = 0.45). Furthermore, agreement between the two screening methods was 94%. Patients with hypertrophic cardiomyopathy more often had a failed screening test in comparison to other patients.

Figure 2. The current (second) generation of the S-ICD system (Boston Scientific).

Previous studies have demonstrated that several standard 12-lead ECG characteristics are associated with the eligibility for a S-ICD based on manual vector screening[34-36]. In **Chapter 10**, we investigated which 12-lead ECG characteristics were associated with eligibility for an S-ICD based on AST in a heterogenous population. We found that QRS ≤ 130 ms, absence of QRS/T discordance in lead II and R/T-ratio ≥3.5 in lead II were independently associated with S-ICD eligibility based on AST. Patients who fulfilled all three criteria (n=83, 33%) had a passing rate of 100%. Therefore, our results suggest that patients who fulfill the three 12-lead ECG criteria do not need additional vector screening for S-ICD eligibility.

Part II - Discussion

There are several advantages of an S-ICD in comparison to a transvenous ICD. These include the reduced risk of lead dysfunction, elimination of risk of endocarditis, lower procedural risk and relative ease of extraction. Disadvantages of an S-ICD are the inability to provide pacing (including ATP and CRT), larger pulse generator size, shorter battery longevity and requirement of a pre-implant ECG screening. Although the current guidelines recommend that an S-ICD should be considered as an alternative to a transvenous ICD, there is only a modest implementation of this technology in clinical practice[37]. A physician may have the opinion that a patient without immediate need for pacing therapy or ATP may

potentially require these therapies in the future, thereby opting for a transvenous ICD to be on the safe side.

We demonstrated that the majority (69%) of patients who have a transvenous single chamber ICD would have qualified for an S-ICD at the time of first replacement. The most important reason not to qualify for an S-ICD was the occurrence of ATP (4.9% per year). Interestingly, the risk of pacing dependency was low in this population (0.3% per year). Thus, based on our data we can conclude that the potential need for future pacing therapy is low in a standard ICD population who do not have a need for pacing therapy at implantation. With regard to the development of the need of CRT, it is important to realize that a de novo CRT-implantation is easier than an upgrade to CRT in a patient who have a transvenous ICD[38, 39].

If a patient is a potential candidate for a S-ICD, then a pre-implant vector screening is recommended by the manufacturer to avoid the risk of QRS/T-wave oversensing. Previously, this was done using a ruler and printed vector electrocardiogram. To automate this process, the manufacturer has developed the Automated Screening Tool (AST). We demonstrated that AST has a good agreement with the previous manual vector screening for identifying suitable patients for an S-ICD. Furthermore, we demonstrated that the single-vector passing rate was high (92%) in a heterogenous patient population including patients with congenital heart disease and inheritable primary arrhythmia syndromes. The only exception were patients with hypertrophic cardiomyopathy, who had a lower passing rate (83%) based on AST. Importantly, previous studies have demonstrated that the passing rate may further decline when testing was done during exercise[40-42]. Furthermore, we demonstrated that a pre-implant vector screening can potentially be omitted if the patient fulfills specific criteria on a standard 12-lead ECG (i.e., QRS duration of ≤130ms, R/T-ratio ≥3.5 in lead II and absence of T-wave discordance in lead II). Although we tested our model in a validation cohort, external validation in a larger population is necessary. Furthermore, we don't know the risk of inappropriate shocks when patients with an S-ICD are screened based on our 12-lead ECG model.

Finally, the risk of inappropriate shocks due to cardiac oversensing has been reduced by the recent introduction of SMART Pass technology. The SMART Pass feature activates an additional high-pass filter thereby reducing the amplitude of lower frequency signals (e.g., T-waves). This feature has resulted in reduction of first inappropriate shock by 50%[43]. Considering this technological improvement, some physicians have chosen not to perform pre-implant vector screening.

Future perspectives

Although the S-ICD has several theoretical advantages in comparison to the traditional transvenous ICD, the ongoing PRAETORIAN trial will provide more insight in the advantages and disadvantages of the S-ICD[44]. The primary endpoint is a composite of inappropriate shocks and ICD-related complications.

An interesting concept that is being explored is the modular S-ICD system, consisting of a combined system including a leadless cardiac pacemaker (LCP) and S-ICD system[45, 46]. This combined

system will be able to provide ATP, which is currently one of the major disadvantages of the current S-ICD system. Reliable device-device communication between the EMPOWER™ LCP and EMBLEM™ S-ICD, through the use of galvanic coupling, has been confirmed in animal studies[45, 46]. Furthermore, firmware upgrade of the S-ICD to enable the ability to communicate with the LCP can be performed in existing S-ICD without replacement or explantation of the device. The advantage of the modular S-ICD system is that an S-ICD can be implanted in eligible patients and an EMPOWER™ LCP be implanted later when patients develop the need for ATP. Human clinical studies are expected soon.

References

1. Brignole M, Vardas P, Hoffman E, Huikuri H, Moya A, Ricci R, Sulke N, Wieling W, Committee ESD, Auricchio A, Lip GY, Almendral J, Kirchhof P, Aliot E, Gasparini M, Braunschweig F, Document R, Lip GY, Almendral J, Kirchhof P, Botto GL and Committee ESD. Indications for the use of diagnostic implantable and external ECG loop recorders. *Europace*. 2009;11:671-87.
2. Brignole M, Moya A, de Lange FJ, Deharo JC, Elliott PM, Fanciulli A, Fedorowski A, Furlan R, Kenny RA, Martin A, Probst V, Reed MJ, Rice CP, Sutton R, Ungar A, van Dijk JG and Group ESCSD. 2018 ESC Guidelines for the diagnosis and management of syncope. *European heart journal*. 2018;39:1883-1948.
3. Al-Khatib SM, Stevenson WG, Ackerman MJ, Bryant WJ, Callans DJ, Curtis AB, Deal BJ, Dickfeld T, Field ME, Fonarow GC, Gillis AM, Granger CB, Hammill SC, Hlatky MA, Joglar JA, Kay GN, Matlock DD, Myerburg RJ and Page RL. 2017 AHA/ACC/HRS Guideline for Management of Patients With Ventricular Arrhythmias and the Prevention of Sudden Cardiac Death. *Circulation*. 2018;138:e272-e391.
4. Antzelevitch C, Yan GX, Ackerman MJ, Borggrefe M, Corrado D, Guo J, Gussak I, Hasdemir C, Horie M, Huikuri H, Ma C, Morita H, Nam GB, Sacher F, Shimizu W, Viskin S and Wilde AA. J-Wave syndromes expert consensus conference report: Emerging concepts and gaps in knowledge. *Heart Rhythm*. 2016;13:e295-324.
5. Priori SG, Blomstrom-Lundqvist C, Mazzanti A, Blom N, Borggrefe M, Camm J, Elliott PM, Fitzsimons D, Hatala R, Hindricks G, Kirchhof P, Kjeldsen K, Kuck KH, Hernandez-Madrid A, Nikolaou N, Norekval TM, Spaulding C, Van Veldhuisen DJ and Group ESCSD. 2015 ESC Guidelines for the management of patients with ventricular arrhythmias and the prevention of sudden cardiac death: *Eur Heart J*. 2015;36:2793-2867.
6. Yap SC, Roos-Hesselink JW, Hoendermis ES, Budts W, Vliegen HW, Mulder BJ, van Dijk AP, Schalij MJ and Drenthen W. Outcome of implantable cardioverter defibrillators in adults with congenital heart disease: a multi-centre study. *Eur Heart J*. 2007;28:1854-61.
7. Khairy P, Landzberg MJ, Gatzoulis MA, Lucron H, Lambert J, Marcon F, Alexander ME and Walsh EP. Value of programmed ventricular stimulation after tetralogy of fallot repair: a multicenter study. *Circulation*. 2004;109:1994-2000.
8. Khairy P. Programmed ventricular stimulation for risk stratification in patients with tetralogy of Fallot: a Bayesian perspective. *Nat Clin Pract Cardiovasc Med*. 2007;4:292-3.
9. Khairy P, Harris L, Landzberg MJ, Viswanathan S, Barlow A, Gatzoulis MA, Fernandes SM, Beauchesne L, Therrien J, Chetaille P, Gordon E, Vonder Muhll I and Cecchin F. Implantable cardioverter-defibrillators in tetralogy of Fallot. *Circulation*. 2008;117:363-70.
10. Elliott PM, Anastasakis A, Borger MA, Borggrefe M, Cecchi F, Charron P, Hagege AA, Lafont A, Limongelli G, Mahrholdt H, McKenna WJ, Mogensen J, Nihoyannopoulos P, Nistri S, Pieper PG, Pieske B, Rapezzi C, Rutten FH, Tillmanns C and Watkins H. 2014 ESC Guidelines on diagnosis and management of hypertrophic cardiomyopathy. *European heart journal*. 2014;35:2733-79.
11. Giuseppe C, Egle C, Antonio C, Giampiero M, Domenico O, Antonino M and Brugada P. Update on Brugada Syndrome 2019. *Curr Probl Cardiol*. 2019:100454.

12. Nademanee K, Veerakul G, Nimmannit S, Chaowakul V, Bhuripanyo K, Likittanasombat K, Tunsanga K, Kuasirikul S, Malasit P, Tansupasawadikul S and Tatsanavivat P. Arrhythmogenic marker for the sudden unexplained death syndrome in Thai men. *Circulation*. 1997;96:2595-600.
13. Sieira J, Conte G, Ciconte G, Chierchia GB, Casado-Arroyo R, Baltogiannis G, Di Giovanni G, Saitoh Y, Julia J, Mugnai G, La Meir M, Wellens F, Czapla J, Pappaert G, de Asmundis C and Brugada P. A score model to predict risk of events in patients with Brugada Syndrome. *European heart journal*. 2017;38:1756-1763.
14. Priori SG, Gasparini M, Napolitano C, Della Bella P, Ottonelli AG, Sassone B, Giordano U, Pappone C, Mascioli G, Rossetti G, De Nardis R and Colombo M. Risk stratification in Brugada syndrome: results of the PRELUDE (PRogrammed ELectrical stimUlation preDictive valuE) registry. *Journal of the American College of Cardiology*. 2012;59:37-45.
15. Probst V, Veltmann C, Eckardt L, Meregalli PG, Gaita F, Tan HL, Babuty D, Sacher F, Giustetto C, Schulze-Bahr E, Borggrefe M, Haissaguerre M, Mabo P, Le Marec H, Wolpert C and Wilde AA. Long-term prognosis of patients diagnosed with Brugada syndrome: Results from the FINGER Brugada Syndrome Registry. *Circulation*. 2010;121:635-43.
16. Giustetto C, Cerrato N, Ruffino E, Gribaudo E, Scrocco C, Barbonaglia L, Bianchi F, Bortnik M, Rossetti G, Carvalho P, Riccardi R, Castagno D, Anselmino M, Bergamasco L and Gaita F. Etiological diagnosis, prognostic significance and role of electrophysiological study in patients with Brugada ECG and syncope. *International journal of cardiology*. 2017;241:188-193.
17. Olde Nordkamp LR, Vink AS, Wilde AA, de Lange FJ, de Jong JS, Wieling W, van Dijk N and Tan HL. Syncope in Brugada syndrome: prevalence, clinical significance, and clues from history taking to distinguish arrhythmic from nonarrhythmic causes. *Heart rhythm*. 2015;12:367-75.
18. Christofferson RD, Lehmann KG, Martin GV, Every N, Caldwell JH and Kapadia SR. Effect of chronic total coronary occlusion on treatment strategy. *Am J Cardiol*. 2005;95:1088-91.
19. Werner GS, Gitt AK, Zeymer U, Juenger C, Towae F, Wienbergen H and Senges J. Chronic total coronary occlusions in patients with stable angina pectoris: impact on therapy and outcome in present day clinical practice. *Clin Res Cardiol*. 2009;98:435-41.
20. Ungar A, Sgobino P, Russo V, Vitale E, Sutton R, Melissano D, Beiras X, Bottoni N, Ebert HH, Gulizia M, Jorfida M, Moya A, Andresen D, Grovale N and Brignole M. Diagnosis of neurally mediated syncope at initial evaluation and with tilt table testing compared with that revealed by prolonged ECG monitoring. An analysis from the Third International Study on Syncope of Uncertain Etiology (ISSUE-3). *Heart (British Cardiac Society)*. 2013;99:1825-31.
21. Lim WY, Papageorgiou N, Sukumar SM, Alexiou S, Srinivasan NT, Monkhouse C, Daw H, Caldeira H, Harvie H, Kuriakose J, Baca M, Ahsan SY, Chow AW, Hunter RJ, Finlay M, Lambiase PD, Schilling RJ, Earley MJ and Providencia R. A nurse-led implantable loop recorder service is safe and cost effective. *Journal of cardiovascular electrophysiology*. 2019;30:2900-2906.
22. Sanders P, Piorkowski C, Kragten JA, Goode GK, Raj SR, Dinh T, Sohail MR, Anand R, Moya-Mitjans A, Franco N, Stromberg K and Rogers JD. Safety of in-hospital insertable cardiac monitor procedures performed outside the traditional settings: results from the Reveal LINQ in-office 2 international study. *BMC cardiovascular disorders*. 2019;19:132.

23. Beinart SC, Natale A, Verma A, Amin A, Kasner S, Diener HC, Del Greco M, Wilkoff BL, Pouliot E, Franco N and Mittal S. Real-world comparison of in-hospital Reveal LINQ insertable cardiac monitor insertion inside and outside of the cardiac catheterization or electrophysiology laboratory. *American heart journal*. 2019;207:76-82.
24. Kanters TA, Wolff C, Boyson D, Kouakam C, Dinh T, Hakkaart L and Rutten-Van Molken MP. Cost comparison of two implantable cardiac monitors in two different settings: Reveal XT in a catheterization laboratory vs. Reveal LINQ in a procedure room. *Europace*. 2016;18:919-24.
25. Tomson TT and Passman R. The Reveal LINQ insertable cardiac monitor. *Expert review of medical devices*. 2015;12:7-18.
26. Sakhi R, Theuns D, Szili-Torok T and Yap SC. Insertable cardiac monitors: current indications and devices. *Expert review of medical devices*. 2019;16:45-55.
27. Kirchhof P, Benussi S, Kotecha D, Ahlsson A, Atar D, Casadei B, Castella M, Diener HC, Heidbuchel H, Hendriks J, Hindricks G, Manolis AS, Oldgren J, Popescu BA, Schotten U, Van Putte B and Vardas P. 2016 ESC Guidelines for the management of atrial fibrillation developed in collaboration with EACTS. *European heart journal*. 2016;37:2893-2962.
28. Yap SC, Sakhi R, Theuns D, Yasar YE, Bhagwandien RE, Diletti R, Zijlstra F and Szili-Torok T. Increased risk of ventricular arrhythmias in survivors of out-of-hospital cardiac arrest with chronic total coronary occlusion. *Heart rhythm*. 2018;15:124-129.
29. Nombela-Franco L, Iannaccone M, Anguera I, Amat-Santos IJ, Sanchez-Garcia M, Bautista D, Calvelo MN, Di Marco A, Moretti C, Pozzi R, Scaglione M, Canadas V, Sandin-Fuentes M, Arenal A, Bagur R, Perez-Castellano N, Fernandez-Perez C, Gaita F, Macaya C, Escaned J and Fernandez-Lozano I. Impact of Chronic Total Coronary Occlusion on Recurrence of Ventricular Arrhythmias in Ischemic Secondary Prevention Implantable Cardioverter-Defibrillator Recipients (VACTO Secondary Study): Insights From Coronary Angiogram and Electrogram Analysis. *JACC Cardiovascular interventions*. 2017;10:879-888.
30. Nombela-Franco L, Mitroi CD, Fernandez-Lozano I, Garcia-Touchard A, Toquero J, Castro-Urda V, Fernandez-Diaz JA, Perez-Pereira E, Beltran-Correas P, Segovia J, Werner GS, Javier G and Luis AP. Ventricular arrhythmias among implantable cardioverter-defibrillator recipients for primary prevention: impact of chronic total coronary occlusion (VACTO Primary Study). *Circulation Arrhythmia and electrophysiology*. 2012;5:147-54.
31. Hannan EL, Zhong Y, Jacobs AK, Stamato NJ, Berger PB, Walford G, Sharma S, Venditti FJ and King SB, 3rd. Patients With Chronic Total Occlusions Undergoing Percutaneous Coronary Interventions: Characteristics, Success, and Outcomes. *Circulation Cardiovascular interventions*. 2016;9:e003586.
32. Abraham WT, Adamson PB, Bourge RC, Aaron MF, Costanzo MR, Stevenson LW, Strickland W, Neelagaru S, Raval N, Krueger S, Weiner S, Shavelle D, Jeffries B, Yadav JS and Group CTS. Wireless pulmonary artery haemodynamic monitoring in chronic heart failure: a randomised controlled trial. *Lancet*. 2011;377:658-66.
33. Boehmer JP, Hariharan R, Devecchi FG, Smith AL, Molon G, Capucci A, An Q, Averina V, Stolen CM, Thakur PH, Thompson JA, Wariar R, Zhang Y and Singh JP. A Multisensor Algorithm Predicts Heart Failure Events in Patients With Implanted Devices: Results From the MultiSENSE Study. *JACC Heart Fail*. 2017;5:216-225.
34. Groh CA, Sharma S, Pelchovitz DJ, Bhave PD, Rhyner J, Verma N, Arora R, Chicos AB, Kim SS, Lin AC, Passman RS and Knight BP. Use of an electrocardiographic screening tool to determine candidacy for a subcutaneous implantable cardioverter-defibrillator. *Heart Rhythm*. 2014;11:1361-6.

35. Olde Nordkamp LRA, Warnaars JLF, Kooiman KM, de Groot JR, Rosenmoller B, Wilde AAM and Knops RE. Which patients are not suitable for a subcutaneous ICD: incidence and predictors of failed QRS-T-wave morphology screening. *J Cardiovasc Electrophysiol*. 2014;25:494-499.
36. Randles DA, Hawkins NM, Shaw M, Patwala AY, Pettit SJ and Wright DJ. How many patients fulfil the surface electrocardiogram criteria for subcutaneous implantable cardioverter-defibrillator implantation? *Europace*. 2014;16:1015-21.
37. Huang XM, Fu HX, Zhong L, Cao J, Asirvatham SJ, Baddour LM, Sohail MR, Nkomo VT, Nishimura RA, Greason KL, Suri RM, Friedman PA and Cha YM. Outcomes of Transvenous Lead Extraction for Cardiovascular Implantable Electronic Device Infections in Patients With Prosthetic Heart Valves. *Circ Arrhythm Electrophysiol*. 2016;9.
38. Kirkfeldt RE, Johansen JB, Nohr EA, Jorgensen OD and Nielsen JC. Complications after cardiac implantable electronic device implantations: an analysis of a complete, nationwide cohort in Denmark. *European heart journal*. 2014;35:1186-94.
39. Poole JE, Gleva MJ, Mela T, Chung MK, Uslan DZ, Borge R, Gottipaty V, Shinn T, Dan D, Feldman LA, Seide H, Winston SA, Gallagher JJ, Langberg JJ, Mitchell K and Holcomb R. Complication rates associated with pacemaker or implantable cardioverter-defibrillator generator replacements and upgrade procedures: results from the REPLACE registry. *Circulation*. 2010;122:1553-61.
40. Kooiman KM, Knops RE, Olde Nordkamp L, Wilde AA and de Groot JR. Inappropriate subcutaneous implantable cardioverter-defibrillator shocks due to T-wave oversensing can be prevented: implications for management. *Heart rhythm*. 2014;11:426-34.
41. Srinivasan NT, Patel KH, Qamar K, Taylor A, Baca M, Providencia R, Tome-Esteban M, Elliott PM and Lambiase PD. Disease Severity and Exercise Testing Reduce Subcutaneous Implantable Cardioverter-Defibrillator Left Sternal ECG Screening Success in Hypertrophic Cardiomyopathy. *Circ Arrhythm Electrophysiol*. 2017;10.
42. Francia P, Adduci C, Palano F, Semprini L, Serdoz A, Montesanti D, Santini D, Musumeci B, Salvati A, Volpe M and Autore C. Eligibility for the Subcutaneous Implantable Cardioverter-Defibrillator in Patients With Hypertrophic Cardiomyopathy. *J Cardiovasc Electrophysiol*. 2015;26:893-899.
43. Theuns D, Brouwer TF, Jones PW, Allavatam V, Donnelley S, Auricchio A, Knops RE and Burke MC. Prospective blinded evaluation of a novel sensing methodology designed to reduce inappropriate shocks by the subcutaneous implantable cardioverter-defibrillator. *Heart rhythm*. 2018;15:1515-1522.
44. Olde Nordkamp LR, Knops RE, Bardy GH, Blaauw Y, Boersma LV, Bos JS, Delnoy PP, van Dessel PF, Driessen AH, de Groot JR, Herrman JP, Jordaens LJ, Kooiman KM, Maass AH, Meine M, Mizusawa Y, Molhoek SG, van Opstal J, Tijssen JG and Wilde AA. Rationale and design of the PRAETORIAN trial: a Prospective, RAndomizEd comparison of subcuTaneOus and tRansvenous ImplANtable cardioverter-defibrillator therapy. *Am Heart J*. 2012;163:753-760 e2.
45. Tjong FVY, Brouwer TF, Kooiman KM, Smeding L, Koop B, Soltis B, Shuros A, Wilde AAM, Burke M and Knops RE. Communicating Antitachycardia Pacing-Enabled Leadless Pacemaker and Subcutaneous Implantable Defibrillator. *Journal of the American College of Cardiology*. 2016;67:1865-1866.

46. Tjong FVY and Koop BE. The modular cardiac rhythm management system: the EMPOWER leadless pacemaker and the EMBLEM subcutaneous ICD. *Herzschrittmachertherapie & Elektrophysiologie*. 2018;29:355-361.

DUTCH SUMMARY | NEDERLANDSE SAMENVATTING

Inleiding

Implanteerbare loop recorders (ILR) zijn effectief voor het detecteren van sporadische hartritmestoornissen. In **deel I** van dit proefschrift hebben wij de klinische waarde van een ILR onderzocht bij patiënten met een erfelijke of verworven hartziekte met een potentieel risico op plotse hartdood. Aangezien de meerderheid van patiënten met een erfelijke hartziekte jong is, wilden wij in **deel II** van dit proefschrift onderzoeken of deze patiënten geschikt zijn voor een volledig subcutane ICD (S-ICD) systeem. De onderstaande samenvatting geeft de belangrijkste bevindingen van de studies weer die in dit proefschrift zijn opgenomen.

Deel I – Nut van een ILR voor risicostratificatie

In **deel I** van dit proefschrift richten we ons op de klinisch waarde van een ILR als diagnostisch instrument voor risicostratificatie bij patiënten met een laag tot matig risico op plotse hartdood. In **hoofdstuk 2** geven we een overzicht van de huidige indicaties voor een ILR en bespreken we de verschillende commercieel verkrijgbare ILR's. Volgens de huidige richtlijnen kunnen ILR's ook toegepast worden bij patiënten met een erfelijke cardiomyopathie (bijv. hypertrofische cardiomyopathie, aritmogene rechter ventriculaire cardiomyopathie) en een erfelijke elektrische hartziekte (bijv. long-QT syndroom, Brugada syndroom). De huidige generatie ILR's zijn kleiner, makkelijker te implanteren, beter in het detecteren van ritmestoornissen en in staat om op afstand het hartritme te monitoren (*remote monitoring*). De Reveal LINQ (Medtronic) is de kleinste en meest gebruikte ILR. De BioMonitor 2 (Biotronik) is qua afmetingen de grootste ILR, maar heeft wel een goed signaalkwaliteit en de langste batterijlevensduur. De Confirm Rx (Abbott) is in staat tot mobiele datatransmissie met behulp van een smartphone app.

Met het oog op de uitbreiding van het indicatiegebied van ILR's tot patiënten met een erfelijke cardiomyopathie of een elektrische hartziekte, hebben we een pilotstudie uitgevoerd waarin we onze eerste ervaringen met de Reveal LINQ hebben beschreven (**hoofdstuk 3**). De diagnostische opbrengst van de ILR hebben we bij 3 groepen (structurele hartafwijking, erfelijke elektrische hartziekte, normaal hart) onderzocht. Opvallend genoeg was de diagnostische opbrengst het laagst bij patiënten met een erfelijke elektrische hartziekte. Daarnaast was het risico op kamerritmestoornissen het hoogst bij patiënten met een structurele hartafwijking. Bovendien kreeg 4% van de studiepopulatie een implanteerbare cardioverter-defibrillator (ICD) op basis van de bevindingen van de ILR.

Het optreden van syncope bij patiënten met een hartziekte kan het gevolg zijn van een kamerritmestoornis. Daarom wordt onverklaarbare syncope vaak beschouwd als een risicofactor voor plotse hartdood. Ook al is syncope een risicofactor voor plotse hartdood, het besluit om een ICD als primaire preventie te geven is niet eenvoudig. Zeker niet bij jonge patiënten met bijvoorbeeld een

erfelijke hartziekte. Een ICD heeft namelijk ook nadelige gevolgen zoals onterechte ICD-therapie, malfunctie en ICD-gerelateerde infectie. Aan de andere kant kan het optreden van klachten bij een patiënt die een risico heeft op plotse hartdood beangstigend zijn. Een ILR kan nuttig zijn om het ritme te detecteren tijdens het optreden van klachten. Daarnaast kan continue ritmebewaking middels een ILR de behandelend arts de zekerheid te bieden dat elke kamerritmestoornis, ook als deze asymptomatisch is, wordt gedocumenteerd. In **hoofdstuk 4-6** hebben wij in drie specifieke patiëntencategorieën met een laag tot matig risico op plotse hartdood de klinische meerwaarde van een ILR onderzocht.

Plotse hartdood is een belangrijke doodsoorzaak bij volwassenen met een aangeboren hartafwijking en wordt voornamelijk veroorzaakt door een kamerritmestoornis. In de huidige praktijk is de beslissing om een ICD te implanteren bij deze patiënten een uitdaging en dit is grotendeels gebaseerd op het klinisch oordeel van de behandelend arts. In **hoofdstuk 4** hebben wij prospectief de klinische meerwaarde van een ILR onderzocht bij volwassenen met een aangeboren hartafwijking. Dit waren voornamelijk symptomatische patiënten met een aantal risicofactoren voor een kamerritmestoornis. Gedurende een mediane follow-up van 16 maanden, kreeg 27% een kamerritmestoornis en uiteindelijk kreeg 10% een ICD. Bovendien leidde de bevindingen op de ILR tot wijzigingen van het klinisch beleid in 73% van de studiepopulatie.

In de huidige Europese richtlijnen wordt het gebruik van de risicocalculator (*HCM Risk-SCD model*) aanbevolen bij patiënten met hypertrofische cardiomyopathie om potentiële ICD-kandidaten te identificeren. Bij een berekende 5-jaars risico op plotse hartdood van 6% wordt een ICD aanbevolen. Een belangrijke risicofactor in deze calculator is het optreden van kortdurende kamerritmestoornissen (>120/min, minimaal 3 complexen). In **hoofdstuk 5** hebben wij de meerwaarde van een ILR boven een conventionele strategie onderzocht bij patiënten met hypertrofische cardiomyopathie. De patiënten in deze studie hadden een laag tot matig risico op plotse hartdood volgens de risicocalculator. De gekozen controlegroep was vergelijkbaar met de ILR-groep op basis van leeftijd, geslacht en berekende risicoscore. Dit onderzoek toonde aan dat de detectie van kamerritmestoornissen vergelijkbaar was tussen beide groepen. Echter, in de ILR-groep werden er meer ritmestoornissen gedetecteerd die resulteerde in een wijziging van het klinisch beleid.

Brugada syndroom is een erfelijke elektrische hartziekte dat geassocieerd is met een verhoogd risico op plotse hartdood ten gevolge van een kamerritmestoornis. Risicostratificatie bij patiënten met Brugada syndroom is lastig en er is discussie over de prognostische rol van een elektrofysiologisch onderzoek voor risicostratificatie. Indien patiënten zich presenteren met klachten die mogelijk gerelateerd zijn aan hartritmestoornissen dan is het wenselijk om te weten of een ritmestoornis hieraan ten grondslag ligt. Het doel van onze studie in **hoofdstuk 6** is te evalueren wat de opbrengst is van een ILR bij symptomatische Brugada patiënten. De belangrijkste reden voor een ILR was het uitsluiten van kamerritmestoornis als oorzaak van de symptomen en het documenteren van een symptoom-ritme correlatie. De helft van de studiepopulatie had een keer syncope gehad voor de ILR-implantatie. Gedurende een gemiddelde follow-up van bijna 3 jaar werd er bij 15% van de studiepopulatie een kortdurende kamerritmestoornis gedetecteerd. Geen patiënt kreeg een ICD. Daarnaast werd er bij 20% van de populatie het klinisch beleid gewijzigd o.b.v. een ritmestoornis gedetecteerd door de ILR.

Tot slot, een chronische totale occlusie van een kransslagader komt veel voor bij patiënten met coronairlijden. Eerdere studies hebben aangetoond dat een chronische totale occlusie een belangrijke risicofactor is voor het krijgen van kamerritmestoornissen bij patiënten die een ICD hebben gekregen voor primaire preventie van plotse hartdood. In **hoofdstuk 7** hebben we retrospectief onderzocht of een chronische totale occlusie een voorspeller was van kamerritmestoornissen bij patiënten die een ICD kregen na een hartstilstand (secundaire preventie). Een chronische totale occlusie bleek een onafhankelijke voorspeller te zijn van terechte ICD-therapie. Het 5-jaars risico op een terechte ICD-therapie was 37% in de groep met een chronische totale occlusie en 25% in de groep zonder een chronische totale occlusie. Op dit moment onderzoeken wij de incidentie van kamerritmestoornissen bij patiënten met een chronische totale occlusie middels een ILR (*VACTOR* studie, NCT03475888).

Deel II – Subcutane ICD

In **deel II** van dit proefschrift hebben wij de geschiktheid voor een subcutane ICD onderzocht bij verschillende patiënten groepen. De huidige richtlijnen geven aan dat een S-ICD een alternatief is voor een transveneuze ICD indien er geen noodzaak is voor bradypacing, cardiale resynchronisatie therapie (CRT) of antitachycardie pacing (ATP). De S-ICD maakt gebruik van een oppervlakte vector om de hartfrequentie te bepalen. Indien de S-ICD ten onrechte andere signalen oppikt (*oversensing*) dan kan dat leiden tot een onterechte ICD schok. Derhalve wordt aanbevolen om bij elke S-ICD kandidaat de vectoren te screenen om te bepalen of hij/zij geschikt is voor een S-ICD.

In **hoofdstuk 8** hebben wij retrospectief onderzocht of patiënten met een transveneuze ICD geschikt waren geweest voor een S-ICD. Dit waren patiënten die op het moment van de implantatie geen pacing indicatie hadden. Ten tijde van de eerste ICD-wissel bleek 69% van de patiënten achteraf gezien potentieel geschikt voor een S-ICD. Gedurende de eerste levensduur van de ICD had namelijk slechts 31% van de patiënten CRT, ATP en/of bradypacing therapie nodig. De jaarlijkse incidentie voor ATP, CRT en bradypacing was 4.9%, 1.8% en 0.3%, respectievelijk. Echter, er waren geen klinische parameters ten tijde van de initiële ICD-implantatie die voorspelden of iemand geschikt was voor een S-ICD. Daarnaast weten we niet bij hoeveel patiënten de vectoren geschikt waren voor een S-ICD.

Bij een S-ICD kandidaat wordt standaard een vectorscreening uitgevoerd om te controleren of de kandidaat een geschikte QRS-T-morfologie heeft. Voorheen werd dit gedaan middels een vectorelektrocardiogram en een vector screening tool waarbij handmatig bekeken werd of de QRS-T-morfologie geschikt was. In 2016 heeft de fabrikant software ontwikkeld waarmee dit proces geautomatiseerd werd, de zogenaamde *Automated Screening Tool* (AST). In **hoofdstuk 9** hebben wij prospectief in een heterogene populatie de geschiktheid voor een S-ICD onderzocht met behulp van de twee methoden (manuele vectorscreening versus AST). De S-ICD geschiktheid op basis van beide screeningsmethoden was vergelijkbaar (93% versus 92%) en de overeenkomst tussen de twee methoden was 94%. Patiënten met een hypertrofische cardiomyopathie hadden 3x meer kans op ongeschikte

vectoren dan andere patiënten. Dit komt waarschijnlijk door de abnormale T-top morfologie in deze populatie.

Eerdere studies hebben aangetoond dat een 12-afleidingen ECG kan voorspellen of iemand geschikt is voor een S-ICD op basis van de manuele vectorscreening. Dit is handig in de klinische praktijk omdat je dan geen aparte vector screening hoeft te doen. In **hoofdstuk 10** hebben wij in een heterogene populatie onderzocht welke parameters op een standaard 12-afleidingen ECG geassocieerd zijn met S-ICD geschiktheid gemeten met AST. Wij vonden dat een QRS-duur van ≤130 ms, afwezigheid van QRS/T-discordantie in lead II en R/T-ratio ≥3.5 in lead II onafhankelijke voorspellers zijn voor S-ICD geschiktheid. Patiënten die aan alle drie de criteria voldeden (33% van de studiepopulatie) waren 100% geschikt voor een S-ICD op basis van AST. De belangrijkste boodschap van deze studie is dat indien patiënten voldoen aan alle 3 criteria, een additionele vector screening niet noodzakelijk is.

LIST OF PUBLICATIONS

1. Early detection of ventricular arrhythmias in adults with congenital heart disease using an insertable cardiac monitor (EDVA-CHD study). **Sakhi R**, Kauling RM, Theuns DA, Szili-Torok T, Bhagwandien RE, van den Bosch AE, Cuypers JAAE, Roos-Hesselink JW, Yap SC. *Int J Cardiol. 2020 Feb 4. pii: S0167-5273(19)34124-5. doi: 10.1016/j.ijcard.2020.02.009.*

2. Usefulness of a standard 12-lead electrocardiogram to predict the eligibility for a subcutaneous defibrillator. **Sakhi R**, Theuns DAMJ, Cosgun D, Michels M, Schinkel AFL, Kauling RM, Roos-Hesselink JW, Yap SC. *J Electrocardiol. 2019 Jul - Aug;55:123-127. doi: 10.1016/j.jelectrocard.2019.05.014. Epub 2019 May 24.*

3. Insertable cardiac monitors: current indications and devices. **Sakhi R**, Theuns DAMJ, Szili-Torok T, Yap SC. *Expert Rev Med Devices. 2019 Jan;16(1):45-55. doi: 10.1080/17434440.2018.1557046. Epub 2018 Dec 11. Review.*

4. Frequency of Need for Antitachycardia or Antibradycardia Pacing or Cardiac Resynchronization Therapy in Patients With a Single-Chamber Implantable Cardioverter-Defibrillator. Melles MC, Yap SC, Bhagwandien RE, **Sakhi R**, Szili-Torok T, Theuns DAMJ. *Am J Cardiol. 2018 Dec 15;122(12):2068-2074. doi: 10.1016/j.amjcard.2018.08.059. Epub 2018 Sep 23.*

5. Evaluation of a novel automatic screening tool for determining eligibility for a subcutaneous implantable cardioverter-defibrillator. **Sakhi R**, Yap SC, Michels M, Schinkel AFL, Kauling RM, Roos-Hesselink JW, Theuns DAMJ. *Int J Cardiol. 2018 Dec 1;272:97-101. doi: 10.1016/j.ijcard.2018.07.037. Epub 2018 Jul 6.*

6. Impact of device-host interaction on paravalvular aortic regurgitation with different transcatheter heart valves. Rodríguez-Olivares R, El Faquir N, Rahhab Z, van Gils L, Ren B, **Sakhi R**, Geleijnse ML, van Domburg R, de Jaegere PPT, Zamorano Gómez JL, Van Mieghem NM. Cardiovasc Revasc Med. 2019 Feb;20(2):126-132. doi: 10.1016/j.carrev.2018.05.004. Epub 2018 May 6.

7. Value of implantable loop recorders in patients with structural or electrical heart disease. **Sakhi R**, Theuns DAMJ, Bhagwandien RE, Michels M, Schinkel AFL, Szili-Torok T, Zijlstra F, Roos-Hesselink JW, Yap SC. *J Interv Card Electrophysiol. 2018 Jul;52(2):203-208. doi: 10.1007/s10840-018-0354-y. Epub 2018 Mar 13.*

8. Increased risk of ventricular arrhythmias in survivors of out-of-hospital cardiac arrest with chronic total coronary occlusion. Yap SC, **Sakhi R**, Theuns DAMJ, Yasar YE, Bhagwandien RE, Diletti R, Zijlstra F, Szili-Torok T. *Heart Rhythm. 2018 Jan;15(1):124-129. doi: 10.1016/j.hrthm.2017.09.004. Epub 2017 Sep 14.*

9. Outcome of Insertable Cardiac Monitors in Symptomatic Patients with Brugada Syndrome at Low Risk of Sudden Cardiac Death. **Sakhi R**, Assaf A, Theuns DAMJ, Verhagen JMA, Szili-Torok T, Roos-Hesselink JW, Yap SC. *Cardiology. 2020 Apr 22:1-8. doi: 10.1159/000507075.*

10. Cardio-Room Rotterdam: Monthly Multidisciplinary Educational Meetings for Cardiac Surgery and Cardiology residents. A.H Sadeghi, A. Dereci, **R.Sakhi**, R. Muslem, A.R. Wahadat, M. Arslan. *2020 EACTS newsletter; resident section.*

11. Incremental value of an insertable cardiac monitor in patients with hypertrophic cardiomyopathy with low or intermediate risk for sudden cardiac death. **Sakhi R**, Huurman R, Theuns DAMJ, Schinkel AFL, Assaf A, Szili-Torok T, Roos-Hesselink JW, Michels M, Yap SC. *Cardiology (accepted for publication).*

PHD-PORTFOLIO

Name Phd-Student	Rafiullah Sakhi
Department	Cardiology
Research school	Cardiovascular Research School Erasmus MC (COEUR)
Phd-period	November 2016 – March 2020
Title thesis	Detection of ventricular arrhythmias Evaluation of cardiac monitors and subcutaneous defibrillators
Promotors	Prof. dr. J.W. Roos-Hesselink Prof. dr. F. Zijlstra
Co promotor	Dr. S.C.Yap
Date defense	08-12-2020

PhD Training	**Year**	**Workload**
General academic skills		
Principles of Research in Medicine, NIHES	2017	0,7
Basis Cursus Regelgeving en Organisatie voor Klinische Onderzoeken (BROK)		1.5
Research Integrity	2019	0,3
In-depth courses (COEUR, NIHES, MOLMED)		
Arrhythmia Research Methodology, COEUR	2017	1,5
Heart Failure Research, COEUR	2017	1,5
Intensive Care Part I and Part II, COEUR	2017	0,5
Cardiovascular Imaging and Diagnostics Part I, COEUR	2017	0.5
Discoveries in Atrial Fibrillation Pathophysiology: Implications for AF Therapy, COEUR	2017	0.4
Biomedical English Writing Course, Molmed,	2017	0.4
Biostatistical methods I: Basic principles, NIHES	2017	5,7
Biostatistical methods II: classical regression models, NIHES	2017	4,3
Arrhythmia Research, COEUR	2018	0.4
Congenital Heart Disease Part I, COEUR	2018	1
Pathophysiology of ischemic heart disease, COEUR	2018	0.8
Oral presentation		
The Netherlands Society of Cardiology (NVVC), Noordwijkerhout, Nederland	2017	1.1
The Netherlands Society of Cardiology (NVVC), Noordwijkerhout, Nederland	2018	1.1
Heart Rhythm Society, Boston (HRS), U.S.A	2018	1.7
The Netherlands Society of Cardiology (NVVC), Rotterdam, Nederland	2019	1.1
European Heart Rhythm Association (EHRA), Barcelona, Spain	2019	1.7

Dutch Revascularization and Electrophysiology (DRESS), Nijkerk, Nederland	2019	1.1
Heart Rhythm Society (HRS), San Diego, U.S.A, cancelled due to Covid-19	2020	
European Heart Rhythm Association (EHRA), Vienna, Austria, cancelled due to Covid-19	2020	

Poster presentation		
European Heart Rhythm Association (EHRA), Vienna, Austria	2017	1.4
European Heart Rhythm Association (EHRA), Lisbon, Portugal	2018	1.4
European Society of Cardiology (ESC), Paris, France	2019	1.9
Heart Rhythm Society (HRS), San Diego, U.S.A, cancelled due to Covid-19	2020	
European Heart Rhythm Association (EHRA), Vienna, Austria, cancelled due to Covid-19	2020	

Teaching activities/Supervising		
Supervising Master Thesis	2018	0.6
Supervising Master Thesis	2018	0.6
Supervising physician assistants in implanting cardiac monitors	2019	0.3

Symposia, Seminar and workshops		
Er komt een device bij de dokter, Boston Scientific, Amsterdam, Nederland	2017	0.4
ICD-Basics, Boston Scientific, Amsterdam, Nederland	2018	0.4
Pacemaker Basics, Boston Scientific, Amsterdam, Nederland	2018	0.4
Ambassadors meeting insertable cardiac monitors, Munich, Germany	2018	0.4
Basis Cardiac Rhythm Management, St. Jude Medical, Veenendaal, Nederland		0.8
Workshop InDesign CS6, Molmed, Rotterdam, Nederland	2018	0.4
Workshop Pacemaker and ICD, Boston Scientific, Amsterdam, Nederland	2018	0.4
Workshop Cardiac Rhythm Management Training, Abbott,Veenendaal, Nederland	2018	0.8
Fundamental Critical Care Support (NVIC), Simulatie en Trainingscentrum voor Zorg (NSTZ), Ede, Nederland	2020	1.5

Grant / Prize		
EHRA Congress Travel Grant	2018	-
Research Grant Biotronik	2019	-
EHRA Congress Travel Grant	2019	-
EHRA Congress Educational Grant	2019	-

Total workload (ECTS)	38.4

ABOUT THE AUTHOR | CURRICULUM VITAE

Rafiullah (Rafi) Sakhi was born on January 10th, 1989 in Kabul, Afghanistan. At the age of nine, he and his family fled the war in Afghanistan and settled in the Netherlands in 1998. After graduating high school in 2008 (Jan Tinbergen College, Roosendaal), he studied Electrical-Engineering at the Technical University of Delft and Biomedical Science at the University of Amsterdam. In 2010 he started medical school at the Erasmus University in Rotterdam. It was during this period that he became familiar with clinical research. After acquiring his Medical Doctor's degree in 2016, he started a (clinical) research fellowship at the department of Cardiology of the Erasmus Medical Center Rotterdam which resulted in this thesis: ''*Detection of ventricular arrhythmias. Evaluation of cardiac monitors and subcutaneous defibrillators*'', supervised by dr. S.C. Yap (co-promotor), Prof. dr. J.W. Roos-Hesselink (promotor) and Prof. dr. F. Zijlstra (promotor). During his fellowship, he had the opportunity to present his work on national and international conferences and to publish his study results in several international peer reviewed medical journals.

DANKWOORD/ ACKNOWLEDGEMENT

Aan het eind van dit proefschrift is een dankwoord aan allen die een bijdrage hebben geleverd aan de totstandkoming van dit proefschrift op zijn plaats. Graag wil ik een aantal personen in het bijzonder noemen.

Allereerst wil ik alle patiënten die betrokken waren geweest bij dit proefschrift bedanken. Geweldig dat jullie bereid waren om mee te werken aan onze onderzoeken.

Beste Sing, doste aziez (dierbare vriend), het lijkt als de dag van gisteren dat ik als medisch student bij je solliciteerde. Vanaf ons eerste gesprek was voor mij duidelijk dat ik onder jouw begeleiding wilde promoveren. In de afgelopen jaren heb ik enorm veel van je geleerd en ik ben blij dat ik die keuze heb gemaakt. Jij kon de chaos in mijn hoofd laten verdwijnen alleen door jouw visie met mij te delen. Sing, ik heb ongelofelijk veel respect voor je en ik wil je bedanken voor je vertrouwen, betrokkenheid en strenge maar toch rechtvaardige begeleiding. Het is een eer om jou als leermeester en vriend te hebben.

Graag wil ik mijn promotoren professor J.W. Roos-Hesselink en professor F. Zijlstra bedanken voor hun begeleiding en inzet. Beste Jolien, ik heb altijd met veel plezier met u mogen werken. Hoe u uw PhD-studenten onder uw hoede neemt en hoe u ze beschermt, zegt veel over u. Ik wil u hartelijk bedanken voor uw begeleiding en betrokkenheid. Het is een eer om onder u te promoveren. Beste professor Zijlstra, u was vanaf het begin af aan betrokken bij mijn onderzoek. Ik dank u voor u kritische en verhelderende blik. Ik vind het fascinerend hoe u met weinig woorden veel zegt.

Beste Dominic, jouw visie was vaak doorslaggevend. Ik denk nog steeds dat jij de beste device (tachy) specialist van Nederland bent. Stiekem was je ook een vaste begeleider. Dominic, ik wil je bedanken voor je inzet en jouw betrokkenheid. Beste Agnes en Astrid, het was altijd heel fijn om met jullie samen te werken. Beste Petter, jij kan ongelooflijk mooi vertellen over muziek en de geschiedenis daarvan. Bedankt voor de prettige samenwerking.

Beste professor Bogers, professor Boersma en dr. Szili-Torok, ik wil u hartelijk danken voor uw deelname in de leescommissie en voor uw tijd en moeite voor het beoordelen van het proefschrift. Professor Decker, professor Dekker en professor Vernooy: hartelijk dank voor uw deelname aan de grote commissie.

Graag wil ik ook alle cardiologen en medewerkers van de afdeling cardiologie bedanken. In het bijzonder wil ik Michelle, Arend, Judith, Martijn, Annemien, en Alexander bedanken voor hun inzet en bereidheid om altijd mee te denken en te werken aan onze studies. Tevens wil ik hierbij graag alle EFO-cardiologen/ fellows en medewerkers bedanken voor jullie behulpzaamheid en de fijne samenwerking. Ik zal de congressen en de daarbij behorende uitjes niet vergeten. Ik dank jullie voor de mooie en leerzame jaren.

Ook mijn (ex) lotgenoten, onderzoekcollega's, wil ik bedanken voor hun ondersteuning gedurende de afgelopen 3 jaren: bedankt voor de leerzame en vooral toch leuke onderzoeksperiode.

Beste Roy, ik heb met veel plezier met je samengewerkt aan het HCM-project. Wat was dat een klus, maar aangezien jij een uiterste goed bijgehouden database hebt (want zo werk jij…), kon je binnen no-time de gewenste data leveren. Ik vergeet onze uitjes in Parijs (alhoewel sommige wel) en het feit dat je mij nog een 'halve' vinger verschuldigd bent niet. Roy, ik wens je veel succes met je verdere loopbaan.

Beste Demet, jij hebt hard gewerkt gedurende je masteronderzoek en het resultaat mocht er zijn. Ik wil je bedanken voor de mooie samenwerking en ik wens je veel succes met je carrière.

Beste leden van de cardiokamer (Ali, Adem, Amir, Murat en Rahat): wat zijn wij toch nerds! In onze (sporadische) vrije tijd kwamen wij samen om richtlijnen en nieuwe studies te bespreken. We hebben er zelfs over gepubliceerd! Gedurende de afgelopen jaren zijn we van studiegenoten vrienden geworden en nu beschouw ik jullie als familie. Ik ben trots om jullie als vrienden en familie te beschouwen.
Beste Ali, van allebei uitgeloot naar allebei getrouwd, twee kinderen, arts en (bijna) gepromoveerd. Wat is de tijd snel gegaan! Ik heb altijd veel van jou kunnen leren, jij was en bent de stille kracht tussen ons. Beste Adem, wat hebben we veel gelachen samen. Ik vind het altijd mooi hoe jij het eerst en het hardst om je eigen grappen lacht. Ik wens je veel succes met je carrière en ik ben ervan overtuigd dat je een top (interventie-) cardioloog wordt (met veel humor). Beste Amir, ik denk dat wij de term 'vrienden voor het leven' heel serieus nemen. In de korte tijd dat ik met jou heb mogen samen werken op de afdeling CTC, heb ik gezien dat jij die ene 'top' assistent bent. Ik ben ervan overtuig dat jij ook een topchirurg wordt. Beste Murat, ik vind het altijd knap hoe het jou lukt om met zeeën van tijd altijd net te laat te zijn of net te weinig tijd te hebben. Murat, ik wil je bedanken voor je vriendschap en ik wens je veel succes met je carrière. Welke kant je ook op gaat, jij zult er het altijd beste uithalen. Beste Rahat, jij bent die duizendpoot die alles tegelijk kan doen. Een woord voor jou: afarin! Rahat, ik ben trots op je. Zet dit door en je wordt een top cardioloog of een topbestuurder of toch een politicus…

Lieve familie, promoveren kost veel tijd en heeft met periodes dan ook invloed gehad op mijn leven. Ondanks dat we elkaar soms minder vaak zagen hebben jullie daar nooit een probleem van gemaakt. Bedankt daarvoor!
Modar jaan en Padar jaan, bedankt voor jullie onvoorwaardelijke liefde, steun en betrokkenheid. Jullie gedrevenheid en steun heeft mij gebracht tot waar ik ben. Zabi jaan, als oude broer heb jij ons altijd onder je hoede genomen. Jouw draagkracht en liefde voor ons familie is ongeëvenaard. Ik dank je daarvoor en ik ben trots om jou als broer te hebben. Graag wil ik hierbij ook Goeban, Pakiza, Diba, Ania, Farid en al mijn lieve neefjes en nichtjes bedanken voor al de mooie en gezellige momenten (chronologisch volgorde: Rayaan, Noorzia, Savash, Lamar, Laily, Shirin (boef), Sam, Ferouza en Saffier). Ania jaan, lieve schoonzus, jij bent een geschenk voor ons familie.

Als laatst wil ik mijn gezin bedanken: mijn lieve vrouw Jullieta, mijn zoontje Zahir en dochtertje Neyla. Jullie zijn de bron van mijn leven! Nafas, het is ons gelukt! Bedankt voor je steun, liefde en vertrouwen. Ik hou van jullie!

Financial support for the publication of this thesis was generously provided by:

Erasmus MC
Nederlandse hartstichting
Servier Nederland Farma B.V.
Biotronik Nederland B.V.
Medtronic Trading NL B.V.