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APPLICATION OF ADVANCED BIOSTATISTICAL METHODS IN CARDIAC RHYTHM MANAGEMENT RESEARCH

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ABSTRACT

Cardiac rhythm management (CRM) is a field in cardiology dedicated to the treatment of cardiac arrhythmia-related diseases. Specifically, the implantable cardioverter defibrillator (ICD) is a device implanted in patients at high risk of ventricular arrhythmias for preventing sudden cardiac death. Despite the numerous observational and randomized clinical trials conducted over recent decades, a persistent need exists for enhancing stratification models aimed at preventing and managing arrhythmias. The availability of new statistical and data science techniques has the potential to improve clinical knowledge in this field, yet their application and awareness remain limited. The primary objective of this dissertation is to implement advanced statistical methodologies to address unanswered questions in CRM and to provide clinicians with evidence-based statistical models applicable in clinical practice.

In the first part, we address the safety of ICDs by establishing evidence-based standards for estimating the reliability of ICD leads. The endocardial lead, which connects to the device and is used to deliver electrical therapies, remains a vulnerable component. We conduct a systematic review of observational studies and employ an innovative iterative method to perform a meta-analysis of survival data, effectively reconstructing individual patient data from published Kaplan-Meier curves.

Subsequently, we delve into the practice of catheter ablation for ventricular arrhythmias in patients subjected to multiple ICD shocks. The contribution focuses on the prognostic effect of early ablation after the first shock. By implementing a Bayesian adaptive design, the first planned interim analysis enables an anticipated confirmation of success for a randomized trial by demonstrating the superiority of the experimental treatment (early ablation) over standard therapy.

We further investigate potential sex-related differences in ICD effectiveness. Addressing this question through randomized trials presents ethical and practical challenges. Propensity-score matching is employed to control pre-specified confounding variables, thereby producing unbiased estimates from observational data of arrhythmic risk for both women and men.

The last part of the thesis explores machine learning techniques, with a particular emphasis on Classification and Regression Tree algorithms. The practical application demonstrated the effectiveness of this approach in predicting ICD shock based on various patient characteristics. The resulting model is interpretable and exhibits promising applicability for risk stratification in clinical practice.

LIST OF PUBLICATIONS

1. Giacopelli D, Azzolina D, Comoretto RI, Quartieri F, Rovaris G, Schillaci V, Gargaro A, Gregori D. Implantable cardioverter defibrillator lead performance: A systematic review and individual patient data Meta-analysis. Int J Cardiol. 2023;373:57-63.

2. Della Bella P, Baratto F, Vergara P, Bertocchi P, Santamaria M, Notarstefano P, Calò L, Orsida D, Tomasi L, Piacenti M, Sangiorgio S, Pentimalli F, Pruvot E, De Sousa J, Sacher F, Tritto M, Rebellato L, Deneke T, Romano SA, Nesti M, Gargaro A, Giacopelli D, Peretto G, Radinovic A. Does Timing of Ventricular Tachycardia Ablation Affect Prognosis in Patients With an Implantable Cardioverter Defibrillator? Results From the Multicenter Randomized PARTITA Trial. Circulation. 2022;145(25):1829-1838.

3. Maglia G, Giammaria M, Zanotto G, D'Onofrio A, Della Bella P, Marini M, Rovaris G, Iacopino S, Calvi V, Pisanò EC, Ziacchi M, Curnis A, Senatore G, Caravati F, Saporito D, Forleo GB, Pedretti S, Santobuono VE, Pepi P, De Salvia A, Balestri G, Maines M, Orsida D, Bisignani G, Baroni M, Lissoni F, Bertini M, Giacopelli D, Gargaro A, Biffi M. Ventricular Arrhythmias and Implantable Cardioverter-Defibrillator Therapy in Women: A Propensity Score-Matched Analysis. JACC Clin Electrophysiol. 2022;8(12):1553-1562.

4. Radinovic A, Giacopelli D, Bisceglia C, Paglino G, Gargaro A, Della Bella P. Active arrhythmia pattern: a novel predictor of ICD shocks. A sub analysis from the PARTITA study. Submitted to Circulation: Arrhythmia and Electrophysiology.

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LIST OF ABBREVIATIONS

AF: Atrial fibrillation
ATP: Anti-tachycardia pacing
AUC: Area under the curve
CART: Classification and regression tree
CI: Confidence interval
CIED: Cardiac implantable electronic device
CRM: Cardiac rhythm management
CRT-P/D: Cardiac resynchronization therapy pacemaker/defibrillator
CV: Cardiovascular
HM: Home Monitoring
HMEA: Home Monitoring Expert Alliance
HR: Hazard ratio
ICD: Implantable cardioverter defibrillator
ICM: Ischemic cardiomyopathy
IPD: Individual patient data
IQR: Interquartile range
KM: Kaplan-Meier
LVEF: Left ventricle ejection fraction
NICM: Nonischemic cardiomyopathy
NPV: Negative predictive value
NYHA: New York Heart Association
PPV: Positive predictive value
PS: Propensity score
PVS: Programmed ventricular stimulation
RM: Remote monitoring
SD: Standard deviation
SVA: Sustained ventricular arrhythmia
VF: Ventricular fibrillation
VT: Ventricular tachycardia
(w)HF: (worsening) heart failure

CHAPTER 1

INTRODUCTION

1.1 Cardiac rhythm management devices

Addressing the burden of cardiovascular diseases is the biggest health challenge in Europe. Cardiovascular (CV) diseases are the leading cause of death in the European Union and a significant contributing factor to chronic conditions and disabilities. Each year, over 13 million new cases of CV diseases are diagnosed, resulting in a population of over 60 million individuals living with CV diseases in Europe, out of a total population of 446 million [1].

Cardiac implantable electronic devices (CIEDs) play a crucial role in managing various cardiac conditions, including tachyarrhythmias, bradyarrhythmias, and medically refractory heart failure (HF). CIEDs include pacemakers, implantable cardioverter defibrillators (ICDs), cardiac resynchronization therapy pacemakers/defibrillators (CRT-Ps/CRT-Ds), and implantable cardiac monitors. The first pacemaker implantation took place in Sweden in 1958, and after decades of research, the first ICD was implanted in a patient in 1980. Since their initial clinical use, CIEDs have become standard tools in cardiology, and advancements in technology have led to their miniaturization and evolution. Presently, approximately 950 pacemakers, 170 ICDs, and 60 CRT-Ps per million inhabitants are implanted in Europe each year [1].

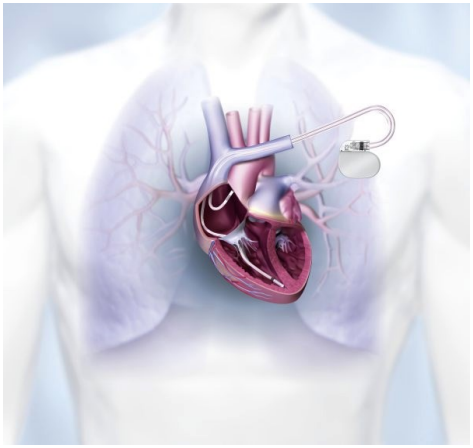
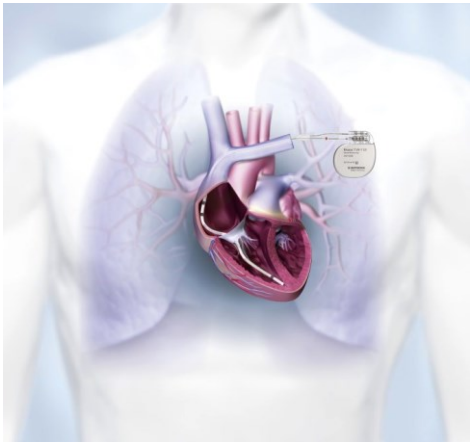
Therapies deliverable through CIEDs include:

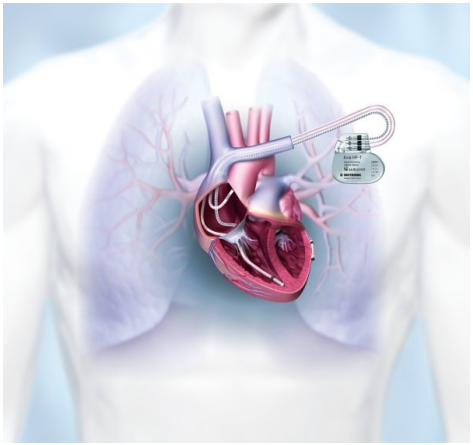
- Bradycardia pacing: This prevents bradycardia in the atria (sick sinus syndrome) and/or the ventricles (atrioventricular block).
- Cardiac resynchronization therapy (CRT)/biventricular pacing: Some patients with HF and reduced left ventricular function experience poorly coordinated ventricular contraction. Biventricular pacing (pacing both the left and right ventricles simultaneously) can improve systolic function by resynchronizing heart contractions.
- Defibrillation: An electric shock is delivered to restore a normal heart rhythm in the event of life-threatening rapid ventricular arrhythmias (ventricular fibrillation/fast ventricular tachycardia).

- Anti-tachycardia pacing (ATP): Pacing faster than an arrhythmia can sometimes break the circuit and terminate it (usually used for ventricular tachycardia with ventricular ATP; also available for atrial fibrillation/flutter with atrial ATP).
- Monitoring for heart rhythm disturbances: Implantable cardiac monitors serve as diagnostic tools and can monitor cardiac arrhythmias such as bradycardia, tachycardia, pauses, and atrial fibrillation.

Table 1.1 provides an overview of different models of transvenous CIEDs and the therapies they deliver.

Table 1.1: Different transvenous cardiac rhythm management devices and the therapies delivered.

Device		**Therapies delivered**
Pacemaker		• Bradycardia pacing • Rhythm monitoring
Implantable cardioverter defibrillator (ICD)		• Bradycardia pacing • Defibrillation • Antitachycardia pacing • Rhythm monitoring

Cardiac resynchronization therapy (CRT)		• Cardiac resynchronization • Bradycardia pacing • Defibrillation (if CRT-D device) • Rhythm monitoring
Implantable cardiac monitor (subcutaneous)		• Rhythm monitoring only (no therapies delivered)

1.2 Remote Monitoring: a source for clinical research

In patients with CIEDs, remote monitoring (RM) from home is available with most contemporary devices and is recommended as the standard of care in the 2015 Heart Rhythm Consensus Statement on RM. Numerous large randomized studies, as well as large registries and observational studies, consistently demonstrate significant organizational benefits, such as optimized follow-up, as well as clinical benefits, including improved patient management and clinical outcomes associated with RM [2].

The most commonly adopted form of RM is based on automatic transmission mechanisms that are completely independent of patient or physician interactions (Figure 1.1). An implanted device initiates daily transmissions, with additional alerts for pre-specified out-of-range parameters, using cellular or landline communication. These data are accessible for review on a website. Biotronik (Berlin, Germany) pioneered this technology with the Home Monitoring (HM) technology, which received Food and Drug Administration (FDA) approval in 2002. Other manufacturers have since followed suit, but each system is proprietary and at different stages of development [3].

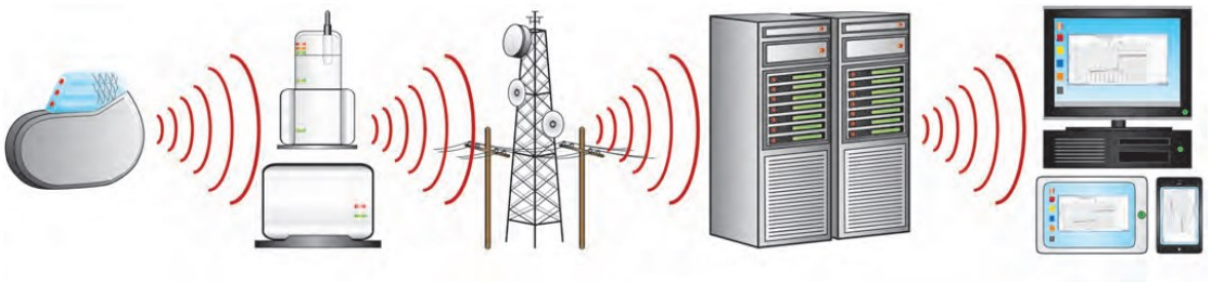


Figure 1.1: Transmission steps in a fully automatic remote monitoring system (modified from ref. 3).

In addition to organizational and clinical advantages, RM can also serve as an important technological platform for collecting a significant amount of data. This data can be efficiently utilized for the statistical detection of complex phenomena, advancing knowledge in the field of cardiology, rapidly testing study hypotheses, and providing indications on the most promising directions for medical-scientific investigation. There is a growing interest in data repositories in the medical field because, if properly utilized, they can contribute to reducing the waste of resources associated with the current paradigm primarily based on randomized clinical trials [4].

Areas of research where data transmitted by RM could be efficiently used include, but are not limited to:

- Organizational and management aspects of RM
- Atrial arrhythmias
- Ventricular arrhythmias
- HF, including cardiac resynchronization
- Optimization of programming
- Monitoring of CIED function.

With this rationale, the Home Monitoring Expert Alliance (HMEA) project was established in 2015. This is an ongoing initiative for data sharing, involving Italian clinics that incorporate the HM system into their routine medical activities with CIEDs. The goals of HMEA are to create a large dataset for continuous monitoring of medical practice performance and to facilitate hypothesis testing before investing significant resources in well-targeted prospective clinical trials.

The automatically collected RM data from CIEDs also holds potential for the application of machine learning algorithms. In the field of medicine, artificial intelligence has already been utilized in models that approximate the capabilities of cardiologists, enabling the subclassification of heart failure phenotypes, predicting mortality from coronary artery disease, and assessing the risk of atrial

fibrillation (AF) and AF-related stroke from electrocardiograms acquired in normal sinus rhythm, among other applications [5]. Recently, a machine-learning approach for analyzing daily RM data has also been proposed [6].

1.3 Advanced biostatistical methods

Statistical methods play a crucial role in all published medical research. In cardiovascular research, it has been reported that up to 50% of studies are not reproducible, partly due to the inability to evaluate the statistical analyses based on the information provided [7]. Potential issues with statistics include studies lacking sufficient statistical power, employing inappropriate statistical tests, failing to confirm test assumptions, and neglecting to account for or explain outliers or missing data [8]. Leading cardiovascular journals have recently published recommendations for statistics to provide best practices for authors, guide statistical reviewers, and help readers better understand analyses and results [9,10].

In recent years, statistical techniques and methods for data analysis have significantly advanced. However, awareness of these different statistical and probabilistic approaches may vary across different medical research fields. The CRM field may be one area where exploring the application of new data analysis techniques can improve research quality.

Secondary analysis, including meta-analyses, of time-to-event outcomes are often limited by the lack of access to individual patient data. To overcame this limitation, a new technique that combines artificial intelligence and advanced statistics, called IPDfromKM-Shiny method, has been recently developed [11]. This innovative method of survival analysis reconstructs individual-patient data from published Kaplan-Meier graphs. These reconstructed patients represent a novel form of original clinical material that can be used for systematic reviews and meta-analyses. This approach is particularly relevant in the CRM field, where time-to-event outcomes are common.

The Bayesian approach to statistical inference is another area of research. In CRM, the medical literature still predominantly relies on the frequentist approach and null hypothesis significance testing. However, Bayesian statistics are gaining popularity for their ability to incorporate prior information and directly calculate the probability of different hypotheses from the posterior distribution. This is particularly advantageous for adaptive trial designs, which allow prospectively planned modifications based on accumulating data [12]. This new concept can increase study power, reduce upfront investment, and potentially shorten trial duration.

When assessing observational studies, an important issue in evaluating outcomes is the adjustment for differences between groups. Covariate adjustment with some form of multivariable modeling is

commonly employed to control for confounding. Propensity scores are a more recent technique used to address treatment selection bias and estimate the effect of an intervention, reducing bias due to confounding variables [13]. Propensity scores can be used for matching, stratification, or weighting (e.g., inverse probability of treatment weighting) based on the specific characteristics of treated and untreated units. In the presence of large samples and datasets that include all relevant characteristics related to treatment participation and outcome, these techniques serve as powerful quasi-experimental methods to analyze observational studies, although their adoption in CRM literature remains limited.

Tree-based analysis is another novel statistical method that has become one of the most flexible, intuitive, and powerful machine learning tools for exploring complex data structures. It is expected to be increasingly used in biomedical research [14]. With these techniques, several difficulties commonly encountered in regression models, such as non-proportional hazards and nonlinear effects, can be automatically handled. Furthermore, tree-based methods can uncover factors that may act differently in different patient subgroups. The repeated partitioning creates bins of patients that are approximately homogeneous, and the interpretability of the resulting tree structure makes these methods highly suitable for use as clinical decision-making tools.

1.4 Dissertation outline

In the subsequent chapters of this dissertation, advanced statistical methodologies are implemented to address unanswered questions in CRM and to provide clinicians with evidence-based statistical models applicable in clinical practice. Our research is primarily focused on improving the risk stratification and management of patients who have received and ICD to prevent sudden cardiac death.

Chapter 2 delves into the safety of ICDs, providing a systematic review of observational studies that assess failure-free estimates of transvenous ICD leads. Additionally, an individual patient data meta-analysis is conducted using the IPDfromKM-Shiny method. This comprehensive approach synthesizes survival data from more than 44 studies and over 66,000 leads, aiming to establish standards for evaluating the clinically acceptable performance of this medical device. Furthermore, this analysis highlights the influence of study characteristics on estimates and emphasizes the importance of diligently assessing methodology and study design in clinical research.

In Chapter 3, we shift our focus to post-ICD implantation patient management, specifically examining the optimal timing for catheter ablation of ventricular arrhythmias. A Bayesian adaptive design for a randomized controlled trial (PARTITA, Clinicaltrials.gov Unique identifier: NCT01547208) is developed and presented. With this study design, the first planned interim analysis enabled an immediate assertion of study success by demonstrating the superiority of the experimental treatment,

consisting of an early ablation after the first ICD shock, over the standard therapy. Bayesian statistics, compared to conventional frequentist approaches, offer a robust framework for monitoring and evaluating treatment effects during the trial. In this specific case, it increased the study power, facilitating early termination of the study and providing clinical evidence in a topic where substantial gaps in knowledge still exist.

Chapter 4 concentrates on analyzing data obtained from RM of CIEDs within the HMEA framework to investigate potential sex-related differences in ICD effectiveness. Propensity-score matching technique is employed to address an unresolved scientific question in CRM research, for which the ethical and practical concerns associated with conducting randomized trials are insurmountable. By employing these methods, it becomes possible to have unbiased estimates of arrhythmic risk for both women and men.

Finally, in Chapter 5, machine learning techniques are introduced, with a particular emphasis on Classification and Regression Tree (CART) algorithms. The practical application showcased in this chapter demonstrates the effectiveness of CART in predicting ICD shock based on various patient characteristics. The resulting model is interpretable and exhibits promising applicability in clinical practice.

Collectively, these chapters contribute to the application and awareness of advanced statistical methodologies within the CRM field, addressing crucial issues related to ICD safety, timing of ablation of ventricular arrhythmias, gender disparities, and ICD shock prediction.

CHAPTER 2

SYSTEMATIC REVIEW AND INDIVIDUAL PATIENT DATA META-ANALYSIS FROM PUBLISHED KAPLAN-MEIER CURVES

Summary

Background: Reliable post-approval surveillance of ICD lead performance remains a challenge. In the past, two ICD leads were recalled due to a high frequency of failures. In this meta-analysis, we sought to provide a combined estimate of failure-free rate for ICD leads by reconstructing individual patient data from published Kaplan-Meier (KM) curves and to investigate whether estimates could be influenced by the characteristics of the study.

Methods: Observational studies assessing failure-free estimates of transvenous ICD leads with KM method, were identified through a systematic search up to November 2021.

Results: Forty-four studies were eligible that included 41,870 (63.1%) non-recalled leads and 24,493 (36.9%) recalled leads. The 8-year cumulative failure-free rate was 94.1% (CI, 93.6% - 94.6%) for contemporary non-recalled leads and 81.2% (80.3% - 82.0%) for recalled leads (hazard ratio [HR], 3.15 [2.85-3.47], p<0.001). Failure-free rate was lower in single-center studies in both the non-recalled (HR, 0.28 [0.15-0.51], p<0.001) and recalled (HR, 0.54 [0.33-0.88], p=0.014) group compared with multicenter studies. Similarly, estimates were significantly lower in small (i.e. extracted KM curve with less than 312 leads) versus large studies (HR non-recalled group, 0.54 [CI, 0.33-0.89], p=0.015; HR recalled group, 0.62 [CI, 0.43-0.89], p=0.009).

Conclusions: In this meta-analysis including more than 66,000 leads, we provide pooled survival curves that may play a role in generating evidence-based standards for assessing clinically acceptable failure rates for ICD leads. Lead performance was underestimated with single-center and small-sized studies; multicenter studies remain the main tool to reliably conduct post-market surveillance of ICD leads.

This chapter was published as:

Giacopelli D, Azzolina D, Comoretto RI, Quartieri F, Rovaris G, Schillaci V, Gargaro A, Gregori D. Implantable cardioverter defibrillator lead performance: A systematic review and individual patient data Meta-analysis. Int J Cardiol. 2023;373:57-63. doi: 10.1016/j.ijcard.2022.11.048.

2.1 Introduction

ICDs are effective devices for preventing sudden cardiac death in patients at high risk of ventricular arrhythmias and has been proven to be highly reliable over time [15,16]. With respect to the latter, the high energy lead is the most vulnerable component of this system that can fail due to mechanical stress and cause inappropriate shock or ineffective therapy [17]. In the past decade, two ICD leads have been recalled due to a high frequency of reported failures [18,19]. Contemporary leads have safer reputations, but reliable post-approval surveillance of ICD lead performance remains challenging due to discrepancies among published studies and the limitations of product performance reports by manufacturers, which rely primarily on voluntary reporting of adverse events by hospitals [20].

Published studies typically report aggregated failure-free data using KM curves along with the number of patients at risk. The lack of access to individual patient data (IPD) makes it difficult to perform meta-analysis on this topic, where detailed data on the survival over time after implantation can play a significant role in generating evidence-based standards. Recently, an iterative method based on KM estimation has been developed to perform a secondary analysis of IPD on published survival curves [21,22].

In this systematic review and meta-analysis, we sought to provide a pooled risk of lead failure in contemporary ICD leads. Furthermore, we investigated whether failure-free estimates could be influenced by the characteristics of the study design.

2.2 Methods

2.2.1 Study Selection

The manuscript was developed and reported according to the Meta-analysis of Observational Studies in Epidemiology (MOOSE) reporting guideline [23]. An electronic search was performed using the database of MEDLINE (PubMed) from January 1, 1990, until November 30, 2021, using the following search string: ("implantable cardioverter-defibrillator" OR "ICD") AND ("lead failure" OR "failure" OR "early failure" OR "lead survival" OR "leads"). A manual search for additional pertinent studies was also completed by systematically check the references from the retrieved records and review articles.

Eligibility criteria included observational studies aimed at assessing failure-free rates of recalled and contemporary non-recalled transvenous ICD leads in a general population implanted with pectoral ICD with or without CRT function. The recalled group included the Sprint Fidelis (Medtronic) and Riata/Riata ST (St. Jude Medical) lead families. The non-recalled group included the most used contemporary families: Endotak Reliance (Boston Scientific), Sprint Quattro (Medtronic), Linox

(Biotronik), and Durata (Abbott). Lead failure was defined as a lead that does not perform as expected, presenting structural (externalization of the conductors, insulation defect, or fracture) or electrical malfunction. The lead did not necessarily need to be extracted.

To be included, studies had to report the KM survival or failure curve with numbers at risk at given time points and the total number of events. The absence of reported numbers at risk was not an exclusion criterion, as the algorithm can still provide an estimate of reconstructed IPD in this setting, but at the price of lower accuracy [21]. The exclusion criteria included (i) studies with less than 100 leads, (ii) case and series reports, (ii) studies with abdominal implants, (iii) studies in a specific subgroup of patients (eg, pediatric), and (iv) studies in which the definition of lead failure consisted of dislodgments and/or cardiac perforations. Data from industry and published in nonpeer reviewed sources were deemed inappropriate for inclusion.

The eligibility for the study was independently determined by two investigators. Divergent opinions were resolved by mutual consensus.

2.2.2 Data extraction

The following information was collected from each study: name of the first author, year of publication, country of origin, characteristics of the study population, group of leads (recalled / non-recalled), number of failed leads, total number of leads, maximum time of survival estimate, and study design (single-center / multicenter). The definition of lead failure was also collected.

The primary outcome was failure-free estimates during study follow-up. To pool survival data, we used the approach as described by Liu et al. [22]. Raw data coordinates (time, survival probability) were extracted manually from the selected KM curves by mouse clicks using the web-based Shiny application that was developed with the R package IPDfromKM (https://CRAN.R-project.org/package=IPDfromKM). A screenshot of the application is displayed in Figure 2.1.

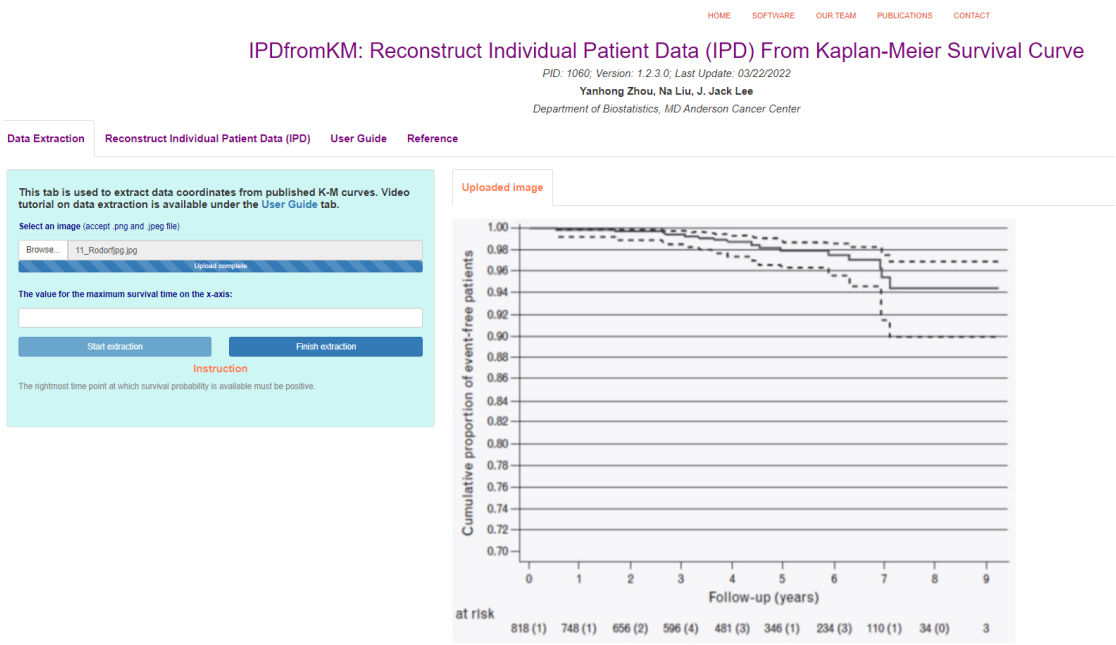


Figure 2.1**:** Screenshot of the web-based Shiny application developed with R package IPDfromKM.

In a second stage, combining information on numbers at risk at given time points, number of events and the extracted data coordinates, the R package IPDfromKM allowed reconstructing survival IPD. Finally, the reconstructed IPD from all studies were merged to create the study dataset. Studies from the same hospitals were compared to exclude double inclusion of patients in the analysis by evaluating potential overlaps in the enrolment period for the study cohorts.

2.2.3 Quality and Risk of Bias Assessment

Quality was independently assessed by two researchers in a blinded fashion, and disagreements were discussed and resolved by consensus. The risk of bias was evaluated using a validated tool for prevalence studies [24]. The tool assesses the internal and external validity of the studies, rating the overall risk of bias as low (score >8), moderate (score 6-8), or high (score≤5).

2.2.4 Statistical analysis

An accuracy assessment of the estimated number at risk as resolved by the data-extraction procedure and the number of events at each risk time point was performed for each reconstructed IPD before pooling, using the Kolmogorov-Smirnov test. Survival rates were estimated with the product-limit method and reported along with the 95% confidence interval (CI). KM plots were generated with the pooled dataset. The difference between recalled and non-recalled leads was tested with a mixed effects proportional-hazard Cox model including study identifier as random effect to model between-studies heterogeneity. Results were reported with HR and 95% CI. In each group, the impact of study design and size was then investigated with mixed-effects proportional hazard Cox models including

the single-/multicenter variable and the size of the extracted KM curve (dichotomized variable based on the median number of leads across all studies) as fixed effects, and study identifier and lead model as random effects. Analysis was performed with RStudio statistical software (version 4.0.3, R Development Core Team; R Foundation for Statistical Computing). Statistical significance was set at p=0.05 in all tests.

2.3 Results

2.3.1 Search results

The database search yielded a total of 8,263 records. After removal of title abstract screening, 265 original full-text articles were reviewed in more detail. Forty-four studies [25-68] were eventually included in the meta-analysis, comprising a total of 66,363 patients (Figure 2.2).

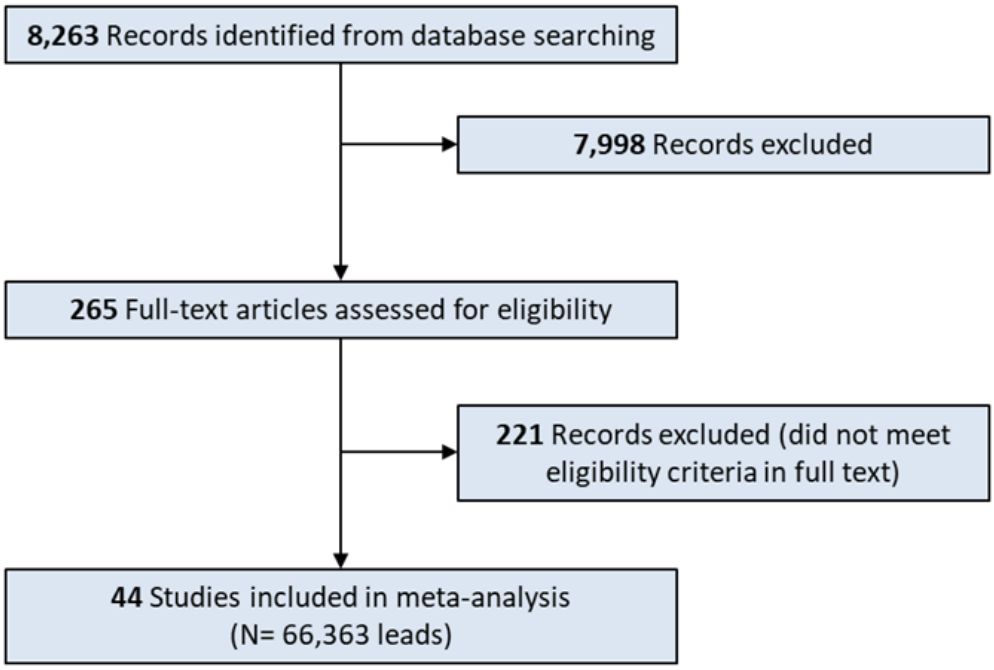


Figure 2.2: Flow diagram of study identification, eligibility assessment and inclusion.

A detailed overview is provided in Table 2.1.

Table 2.1: Main characteristics of the studies (n=44) included in the meta-analysis and summary study quality assessment.

Study	Number of sites	Number of leads	Population	Time of survival estimate (months)	Risk of bias
Abdelhadi et al, 2013, USA[25]	Multicenter (7 sites)	1,081	Adults (>18 years) who received Riata or Riata ST leads from 2002 to 2010; age 63.5 ± 13.5 years and 74% male for RIATA cohort; age 64.8 ± 13.1 years and 74% male for RIATA ST cohort.	96	low
Akhtar et al, 2021, UK[26]	Multicenter (3 sites)	575	Patients with a CRT-D implant between October 2008 and September 2017; age 64 ± 9.7 years and 44% male for failed lead; age 69.5 ± 11.6 years and 82% male for non-failed lead.	130	moderate
Alasti et al, 2020, Australia[27]	Single-center	187	Retrospective review of all patients who underwent ICD implantation for primary or secondary prevention with Biotronik Linox S/SD or Sorin Vigila 1CR/2CR lead at a large tertiary center (from 2007 to 2015); age 66.5 (55-74) years and 82% male.	140	moderate
Barbhaiya et al, 2020, USA[28]	Single-center	657	Retrospective review of patients of all ICD leads implanted from December 2011 to June 2017 at their institution; age 64 ± 16 years and 72% male.	50	high
Cairns et al, 2014, USA / Canada[29]	Multicenter (216 sites)	11,016	Data from 3 prospective registries of Optim-insulated ICD leads from 2006 to 2013. Patients were eligible if they had implantation of a St. Jude Medical ICD or CRT-D with an Optim-insulated lead (age >18 years); mean age from 64.8 to 66.4 and 71% to 74% male according to subgroup.	60	low
Cheung et al, 2012, USA[30]	Single-center	604	Retrospective evaluation of all patients who underwent implantation of a Sprint Fidelis lead at the Long Island Jewish Medical Center between 2004 and 2007; age 67 (56-76) years and 76% male.	72	moderate
Cheung et al, 2013, USA[31]	Single-center	316	Retrospective evaluation of all patients who underwent implantation of a Riata or Riata ST lead at the Weill Cornell Medical Center New York Presbyterian Hospital between 2002 and 2007; age 65 (55-76) years and 68% male.	96	moderate
Cobb et al, 2020, UK[32]	Single-center	656	Retrospective evaluation of all patients who underwent implantation of Riata or Endotak leads from 2003 to 2008 at the Heart Hospital; age 56 (range 16-84) years and 70% male for Riata cohort; age 64 (range 18-90) years and 71% male for Endotak cohort.	144	moderate

Cohen et al, 2015, USA[33]	Single-center	4,078	Retrospective evaluation of all patients who underwent implantation of ICD leads from 1996 to 2011 at the Winthrop University Hospital; age 70 ± 13 years and 74% male.	120	moderate
Davidsson et al, 2020, Iceland[34]	Single-center	102	Restrospective analysis of all individuals who had the recalled lead implanted from 2002 to 2009 in Iceland along with individuals who had ICDs from other manufacturers from 2010 to 2012 to serve as controls; age 54.5 (16-80) years and 77% male for recalled led cohort; age 56 (12-77) years and 72% male for control cohort.	96	high
Demirel et al, 2014, The Netherlands[35]	Single-center	147	Prospective investigation all patients who underwent implantation of a Riata lead in their centre according to the Netherlands Heart Rhythm Association protocol; age 71.4 ± 8.4 years and 69% male for failed lead; age 70.6 ± 10.1 years and 84% male for non-failed lead.	80	moderate
Erkapic et al, 2011, Germany[36]	Single-center	357	Retrospective analysis on data from consecutive patients who received a single-, dual-, or triple-chamber ICD with Riata family lead at their institution from 2000 to 2010; age 66 ± 9 years and 90% male for failed lead; age 61 ± 12 years and 83% male for non-failed lead.	72	moderate
Farwell et al, 2008, Canada[37]	Single-center	480	All patients who were implanted with an ICD and a Sprint Fidelis lead in the centre between 2004 and 2007; age 54.2 ± 13.5 years and 88% male for failed lead; age 62.2 ± 11.0 years and 85% male for non-failed lead.	30	high
Fazal et al, 2013, UK[38]	Single-center	219	All patients implanted with Sprint Fidelis or Riata leads at the centre between 2003 and 2008 were retrospectively identified; age 64.7 ± 21.9 years and 88% male for Sprint Fidelis lead; age 64.0 ± 13.9 years and 78% male for Riata lead.	84	moderate
Forleo et al, 2014, Italy[39]	Single-center	225	All patients implanted with Optim-coated leads as part of an ICD or CRT-D system in their institution between 2007 and 2011 were contacted to perform fluoroscopic screening of the lead; age 67.5 ± 10.6 years and 84% male.	48	moderate
Frey et al, 2019, Switzerland[40]	Multicenter (2 sites)	145	Retrospective analysis of all patients who received a passive SFL model at the University Hospital Basel and at the Kantonsspital St.Gallen between 2004 and 2007; patients characteristics are not reported.	144	moderate

Girerd et al, 2011, France[41]	Single-center	269	Retrospective analysis on all patients who received a Sprint Fidelis lead at the centre between 2004 and 2007; age 60.6 ± 13.7 years and 87% male.	60	moderate
Good et al, 2016, USA[42]	Multicenter (98 sites)	3,933	Data from two prospective registries (GALAXY and CELESTIAL) on safety and reliability of Linox leads implanted between 2008 and 2013; age 67.0 ± 12.2 years and 73% male.	60	low
Hauser et al, 2011, USA[43]	Multicenter (3 sites)	2,691	Retrospective analysis on adults ≥18 years of age who received a Sprint Fidelis or Quattro lead at the Minneapolis Heart Institute (Minneapolis, MN), Mayo Clinic (Rochester, MN), and Beth Israel Deaconess Medical Center (Boston, MA) between 2001 and 2009; age 64.7 ± 14.2 years and 75% male for Sprint Fidelis cohort; age 65.2 ± 13.5 years and 79% male for Sprint Quattro cohort.	48	moderate
Kawada et al, 2017, Japan[44]	Single-center	204	Retrospective review of patients with ICD lead implanted between 2000 and 2013 at their hospital; mean age ranged from 55.5 to 60.0 years and male prevalence between 63% to 85% according to groups.	120	high
Kleeman et al, 2019, Germany[45]	Single-center	1,407	Analysis of a prospective registry (ICD-registry Ludwigshafen) of patients implanted with a St Jude Medical lead between 2002 and 2017; age 64 ± 12 years and 80% male for Durata cohort; age 63 ± 11 years and 83% male for Riata cohort.	120	moderate
Kondo et al, 2020, Japan[46]	Single-center	297	Retrospectively review on consecutive patients who underwent ICD system implantation at Chiba University Hospital, Japan, between 2008 and 2017; mean age ranged from 62.6 to 64.1 years and male prevalence between 75% to 82% according to groups.	108	high
Lam et al, 2019, Switzerland[47]	Single-center	260	Retrospective analysis on all Linox/Vigila, Riata and Sprint Fidelis ICD leads implanted in the their centre; mean age ranged from 55.3 to 60.9 years and male prevalence between 77% to 91% according to groups.	120	high
Liu et al, 2014, USA[48]	Single-center	5,288	Analysis of all patients receiving a Medtronic, Boston Scientific, or St. Jude Medical transvenous ICD lead at the University of Pittsburgh Medical Center from 2000 to 2012; mean age ranged from 64 to 72 years and male prevalence between 75% to 78% according to groups.	96	moderate

Marai et al, 2019, Israel[49]	Single-center	722	All patients who underwent implantation of Linox and Sprint Quattro ICD leads between 2007 and 2016 were included in this study; age 64.4 ± 11.8 years, prevalence of male not reported.	100	moderate
Mori et al, 2021, Japan[50]	Single-center	306	Retrospective study on consecutive cases of patients from 2007 to 2017 who underwent an initial transvenous ICD implantation; age 63.3 ± 13.4 years, 75% male.	116	high
Noti et al, 2016, Switzerland[51]	Single-center	392*	Retrospective analysis on all Linox/Vigila, Sprint Quattro, and Endotak ICD leads implanted in the their centre; mean age ranged from 55.6 to 59.6 years and male prevalence between 71% to 82% according to groups.	96	high
O'Connor et al, 2018, New Zealand[52]	Single-center	279	A retrospective cohort study of all patients with an ICD implanted between January 2007 and December 2012 from the Wellington Hospital region, New Zealand; mean age ranged from 57.6 to 60.2 years and male prevalence between 73% to 81% according to groups.	120	moderate
Padfield et al, 2015, Canada[53]	Multicenter (3 sites)	1,315	Analysis on all recipients of Linox and Durata leads in the BC Cardiac Registry, a mandatory Governmental database of ICD implants between 2008 and 2012; age 63 (51-71) years and 81% male for Linox cohort; age 66 (57-74) years and 79% male for Durata cohort.	56	low
Parkash et al, 2012, Canada / USA[54]	Multicenter (25 sites)	818	Patients enrolled in the randomized RAFT trial who received a Sprint Fidelis lead from 2004 to 2007; age 66.0 ± 9.5 years, 83% male.	48	low
Parkash et al, 2018, Canada[55]	Multicenter (17 sites)	3,762	Using the Canadian Registry of Electronic Device Outcomes, prospective follow-up data were collected on Riata leads under advisory; age 60.9 ± 11.7 years, 80% male.	144	low
Pérez Dìez et al, 2018, Spain[56]	Single-center	438	Ambispective study of all consecutive first implantations of defibrillator leads carried out in the center between 2008 and 2013; median age ranged from 61 to 64 years and male prevalence between 85% to 87% according to groups.	96	moderate
Ricci et al, 2011, Italy[57]	Single-center	414	Retrospective collection of data from 2004 to 2010; age 67 ± 12 years, 86% male.	54	moderate

Rodorf et al, 2013, Italy[58]	Single-center	890	Consecutive patients in whom a right ventricular ICD lead had been implanted in the center from 2003 to 2010 were included in the analysis; mean age ranged from 56 to 59 years and male prevalence between 79% to 86% according to groups.	60	high
Rodorf et al, 2019, Italy[59]	Multicenter (11 sites)	818	Prospective registry, including all consecutive Durata ICD leads implanted in the participating centers; age 67 ± 12 years, 81% male.	96	moderate
Shariff et al, 2015, USA[60]	Single-center	631**	Retrospective analysis on all patients receiving a Sprint Quattro lead at the center from 2000 to 2014; age 63 ± 15 years, 74% male.	36	high
Stroker et al, 2016, Belgium[61]	Multicenter (2 sites)	143	Retrospective evaluation on all patients implanted with a Riata lead from 2003 to 2008; age 63 ± 14 years, 80% male.	120	moderate
Sung et al, 2012, USA[62]	Multicenter (more than 50 sites)	14,968	Retrospective analysis of the VANCDSC registry, including ICD leads implanted from 2002 to 2012; patients' characteristics not reported.	72	moderate
Theuns et al, 2012, The Netherlands[63]	Multicenter (12 sites)	1,029	In 2012, all ICD implantation centers were contacted by the Netherlands Heart Rhythm Association Device Advisory Committee to identify all patients with an active Riata ICD lead and to perform fluoroscopic screening of the lead; patients' characteristics not reported.	120	low
Valk et al, 2013, The Netherlands[64]	Single-center	374	Retrospective analysis on all consecutive patients implanted with Riata ICD leads between 2003 and 2007 at the Erasmus Medical Center; age 60 (52-70) years, 78% male.	108	high
van Malderen et al, 2016, The Netherlands[65]	Single-center	1,091	Analysis on patients who underwent implantation of Linox, Durata, Endotak ICD lead from 2003 and 2011 included in the continuous ICD registry of the Erasmus Medical Center; median age ranged from 61 to 63 years and male prevalence between 76% to 81% according to groups.	84	moderate
van Rees et al, 2012, The Netherlands[66]	Single-center	2,163	Retrospective analysis on patients who received an ICD system at the Leiden University Medical Center, Leiden, the Netherlands, mean age ranged from 61 to 63 years and male prevalence between 80% to 89% according to groups.	120	high

Vollmann et al, 2013, Germany[67]	Single-center	642	Analysis on all patients who received a Sprint Fidelis or Quattro ICD lead at the centre between 1998 and 2008; age 63.3 ± 14.9 years and 81% male for Sprint Fidelis cohort; age 60.9 ± 14.8 years and 81% male for Quattro cohort.	72	moderate
Weberndorfer et al, 2018, Switzerland[68]	Single-center	220	All patients receiving high-voltage leads at the center between 2009 and 2017 were retrospectively analyzed; median age ranged from 61 to 62 years and male prevalence between 81% to 82% according to groups.	84	moderate

*93 Linox leads were excluded because already included in the study from Lam et al, 2018.
**dual-coil leads were excluded because already included in the study from Liu et al, 2014.

They were published between 2011 and 2021 and most of them were conducted in Europe (52%) or North America (34%). Thirty-one (70%) were single-center studies and 13 (30%) were multicenter studies. Seven studies had low risk of bias, 25 studies had moderate risk of bias and 12 had high risk of bias (Table 2.2). The main issues detected during quality evaluation were retrospective data collection without active systematic screening (n=35), no description of the adjudication process of events (n=32), characteristics of the sample frame poorly described or sample frame not representative of the target population (n=17), unclear definition of lead failure (n=8), lack of information on units at risk (n=8), inappropriate length of the follow-up period (n=13).

Table 2.2: Risk of Bias of included studies.

	External Validity Items					**Internal Validity Items**					**Overall Score**	**Overall Risk of Bias**
Author, year	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**		
Abdelhadi et al, 2013	1	1	1	1	1	1	1	0	1	1	9	low
Akhtar et al, 2021	0	1	1	1	1	1	0	0	1	0	6	moderate
Alasti et al, 2020	0	0	1	1	1	1	0	0	1	1	6	moderate
Barbhaiya et al, 2020	1	0	1	1	1	1	0	0	0	0	5	high
Cairns et al, 2014	1	1	1	1	1	0	1	1	1	1	9	low
Cheung et al, 2012	1	0	1	1	1	1	0	0	1	1	7	moderate
Cheung et al, 2013	0	0	1	1	1	1	0	0	1	1	6	moderate
Cobb et al, 2020	1	0	1	1	1	1	0	0	1	1	7	moderate
Cohen et al, 2015	0	0	1	1	1	1	0	0	1	1	6	moderate
Davidsson et al, 2020	0	0	1	1	1	1	0	0	1	0	5	high
Demirel et al, 2014	1	0	1	1	1	1	0	1	1	1	8	moderate
Erkapic et al, 2011	1	0	1	1	1	1	0	0	1	1	7	moderate
Farwell et al, 2008	0	0	1	1	1	0	0	0	0	1	4	high
Fazal et al, 2013	1	0	1	1	1	0	0	0	1	1	6	moderate
Forleo et al, 2014	1	0	1	1	1	1	1	1	0	1	8	moderate
Frey et al, 2019	0	1	1	1	1	1	0	0	1	1	7	moderate
Girerd et al, 2011	1	0	1	1	1	1	0	0	0	1	6	moderate
Good et al, 2016	1	1	1	1	1	1	1	1	1	1	10	low
Hauser et al, 2011	0	1	1	1	1	1	0	0	1	1	7	moderate
Kawada et al, 2017	1	0	1	1	1	1	0	0	0	0	5	high
Kleeman et al, 2019	1	0	1	1	1	1	0	1	0	1	7	moderate
Kondo et al, 2020	1	0	1	1	1	1	0	0	0	0	5	high
Lam et al, 2019	0	0	1	1	1	1	0	0	1	0	5	high
Liu et al, 2014	1	0	1	1	1	1	0	0	0	1	6	moderate
Marai et al, 2019	0	0	1	1	1	1	0	0	1	1	6	moderate
Mori et al, 2021	0	0	1	1	1	1	0	0	0	1	5	high
Noti et al, 2016	0	0	1	1	1	1	0	0	0	1	5	high
O'Connor et al, 2018	1	0	1	1	1	1	0	0	1	0	6	moderate
Padfield et al, 2015	1	1	1	1	1	1	1	0	1	1	9	low
Parkash et al, 2012	1	1	1	1	1	1	1	1	1	1	10	low
Parkash et al, 2018	0	1	1	1	1	1	1	1	1	1	9	low
Pérez Dìez et al, 2018	0	0	1	1	1	1	0	0	1	1	6	moderate

Ricci et al, 2011	1	0	1	1	1	1	0	0	0	1	6	moderate
Rodorf et al, 2013	1	0	1	1	1	0	0	0	0	0	4	high
Rodorf et al, 2019	1	1	1	1	1	1	0	0	1	1	8	moderate
Shariff et al, 2015	1	0	1	1	1	0	0	0	0	1	5	high
Stroker et al, 2016	1	1	1	1	1	1	0	0	1	1	8	moderate
Sung et al, 2012	0	1	1	1	1	1	1	0	1	1	8	moderate
Theuns et al, 2012	0	1	1	1	1	1	1	1	1	1	9	low
Valk et al, 2013	1	0	1	1	1	0	0	0	0	1	5	high
van Malderen et al, 2016	1	0	1	1	1	1	0	1	1	1	8	moderate
van Rees et al, 2012	0	0	1	1	1	0	0	0	1	1	5	high
Vollmann et al, 2013	1	0	1	1	1	1	0	0	1	1	7	moderate
Weberndorfer et al, 2018	1	0	1	1	1	0	0	0	1	1	6	moderate

Footnote: 0: no, 1: yes, overall risk of bias: low (score >8), moderate (score 6-8), or high (score ≤5). Items scored: 1) Was the study's target population a close representation of the national population in relation to relevant variables, e.g., age, sex?; 2) Was the sampling frame a true or close representation of the target population?; 3) Was some form of random selection used to select the sample, OR, was a census undertaken?; 4) Was the likelihood of non-response bias minimal?; 5) Were data collected directly from the subjects (as opposed to a proxy)?; 6) Was an acceptable case definition used in the study?; 7) Had the study instrument that measured the parameter of interest (e.g., prevalence of comorbidity) been tested for reliability and validity (if necessary)?; 8) Was the same mode of data collection used for all subjects?; 9) Was the length of the shortest prevalence period for the parameter of interest appropriate?; 10) Were the numerator(s) and denominator(s) for the parameter of interest appropriate?

The definition of lead failure was consistent across most studies including at least one of the following criteria: nonphysiological high-rate sensing (electrical noise) unrelated to external electromagnetic interference or T-wave oversensing; a sudden rise or fall of impedance outside the range of 200-2000 Ohm or 20-200 Ohm for the pace/sense and high voltage circuits, respectively (unrelated to perforation or lead dislodgement); or abnormal lead parameters clearly associated with evidence of lead fracture or insulation failure at reoperation. Lead dislodgments or perforations and lead revisions due to electrical abnormalities that normalized with the reuse of the lead were not considered lead failures. The definitions of lead failure for each study are reported in Table 2.3.

Table 2.3: Lead failure definition.

Study	**Lead failure definition**
Abdelhadi et al, 2013	A lead with an externalized conductors was a failure even if it was functioning normally and electrically intact. A lead failed owing to an electrical malfunction if it exhibited abnormal impedance leading to replacement, electrical noise as manifested by nonphysiologic signals, increase in pacing threshold or decrease in R-wave amplitude necessitating lead replacement, or inability to provide effective therapy owing to a lead defect.
Akhtar et al, 2021	High-voltage leads were considered to have failed if they exhibited: persistent oversensing of non-physiological rapid signals, the abnormal impedance in the pace/sense or the shock component, an increase in right-ventricular lead threshold, and/or decrease in sensing sufficient to make the lead unreliable.
Alasti et al, 2020, Australia	Lead failure in this study was defined as the presence of at least one of the following criteria: 1. Non-physiological high-rate signals (noise) not related to electromagnetic interference or T-wave oversensing. 2. Sudden rise or fall in impedance in either the pace/sense system outside the range of 200–2000 Ohm or high voltage system outside the range of 20–200 Ohm. 3. Sudden decrease in the ventricular sensing threshold to ≤ 2 mV or increase in the ventricular pacing threshold > 5 V at pulse width of 0.5 msec.

Barbhaiya et al, 2020	Patients with recurrent, non-physiological high-rate sensing, a change in pace/sense or high-voltage impedance increase >100% or decrease >50%), or values outside of 200 to 1500 ohms, for pace/sense, or 20 to 200 ohms for high voltage and a sudden or incremental increase in right-ventricular threshold, and/or decrease in sensing, without an alternate explanation.
Cairns et al, 2014	All-cause mechanical lead failure was defined as any failure of the structural integrity of the lead with the following subtypes: (1) conductor fracture; (2) all-cause insulation abrasion or externalized conductor; (3) miscellaneous mechanical failure; and (4) unclassified mechanical failure.
Cheung et al, 2012	Lead failure was defined as one of the following: (1) sudden increase in chronic pacing threshold or defibrillation lead impedance of >20% during a 24-hour period, (2) oversensing of nonphysiological electric noise artifacts because of make-break potentials, or (3) failure to deliver defibrillation therapy because of lead fracture or insulation break.
Cheung et al, 2013	Electrical lead failure was defined as one of the following: (1) sudden change in pacing or defibrillation lead impedance (>50%) over a 3-month period, (2) sudden increase in pacing thresholds (>100% baseline)over a 3-month period, (3) oversensing of nonphysiologic electrical noise artifacts due to make-break potentials, (4) failure to deliver defibrillation therapy due to lead fracture or insulation break, or (5) decreasein R-wave amplitude(>50%) over a 3-month period, leading to undersensing of induced ventricular fibrillation during ICD testing.
Cobb et al, 2020	Lead failure was defined by on the following electrical parameters: >1V threshold increase, oversensing of noise, persistent fall of R wave <2 mV or >50%, fall to <300 Ohm or rise >1500 Ohm of pacing impedance, fall to <20 Ohm or rise to >200 Ohm of high-voltage impedance.
Cohen et al, 2015	Lead failure was included failure to capture and sense, abnormal pacing impedance (less than 400 ohms or greater than 2000 ohms), abnormal defibrillation impedance (less than 20 ohms or greater than 200 ohms), insulation defect, lead fracture, extracardiac stimulation, cardiac perforation, tricuspid valve entrapment, lead tip fracture, and/or lead dislodgment.
Davidsson et al, 2020	Occurrence of lead failure was determined by (1) externalization of the conductor, defined as direct visualization of the conductor wires outside the lead body on fluoroscopy or being visualized on a chest radiograph; (2) electrical dysfunction, high-frequency, low-amplitude irregular signal (electrical noise) between ventricular signals on the intracardiac ICD electrogram; and (3) lead fracture.
Demirel et al, 2014	Electrical lead failure was considered if it met one of the following criteria: (i) presence of non-physiological signals on the intracardiac ventricular electrogram, (ii) pacing impedance outside the interval 200–2000 V or >100% increase or >50% decrease of the stable baseline impedance, (iii) change in high-voltage impedance to >200 or <25 V, (iv) pacing threshold >5 V or >100% increase, (v) R-wave sensing <3.0 mV or >50% reduction.
Erkapic et al, 2011	Lead failure was defined as a malfunction of the high-voltage ICD lead necessitating surgical intervention. Thus, at least one of the following criteria had to be present: (1) A visible insulation defect of the lead observed on fluoroscopy with the conductors breaking through the lead insulation; (2) oversensing that could not be overcome by reprogramming of the device (excluding T-wave oversensing); (3) undersensing of the ventricular signal (<3.0 mV); (4) lead impedance out of normal limits (i.e., <200 or >2000 Ohm); and (5) documentation of exit block (excluding lead dislocation or perforation).
Farwell et al, 2008	A sudden increase in chronic pacing or defibrillation impedance (>20% increase over a 24-hour period) and/or inappropriate shock secondary to sensing of electrical noise artifacts from make break potentials.
Fazal et al, 2013	Lead failure was diagnosed if any of the following occurred: 1) sudden increase in pacing or defibrillation impedance from baseline without alternative explanation; 2) frequent short V–V intervals implying fracture of the conductor, contact between the two components generating electrical “noise” (sensing artefact); 3) delivery of inappropriate shock(s) as a consequence of interpretation of these sensing artefacts as ventricular arrhythmia; and 4) failure of effective electrical therapy including sensing, pacing or defibrillation.
Forleo et al, 2014	Lead failure was defined as electrical malfunction or abnormality resulting in lead replacement, excluding infections, dislodgements, or perforations. A lead was determined to have externalized conductors in the case of fluoroscopic evidence of conductors outside the lead body due to an abrasion related breach of the outer insulation.
Frey et al, 2019	Failure due to any of these reasons: - Lead fracture with inappropriate discharge due to noise sensing; - sudden increase in lead impedance to >1500 Ω; - sudden increase in the high-voltage circuit impedance to >100 Ω; - >300 occurrences of nonphysiological short VV-intervals.
Girerd et al, 2011	A lead was considered fractured if there was a sudden increase of impedance over 1500 ohms for the pace/sense portion of the lead or over 200 ohms for the defibrillation portions of the lead and/or inappropriate shock(s) secondary to oversensing of electrical noise artefacts on electrogram review. Functional abnormalities and physiological oversensing without lead electrical dysfunction were not considered as failures.

Good et al, 2016	The analysis was performed using the categories of lead observations (i.e., cardiac perforation, conductor fracture, lead dislodgement, etc.) as defined in the third edition of the international standard ISO 5841-2. Conductor fracture was observed visually, electrically, or radiographically, and in some cases via returned lead analysis. Failure to capture was intermittent or complete non-capture or sudden or significant increase in pacing threshold. Insulation breach was observed visually, electrically, or radiographically, and in some cases via returned lead analysis. Pacing impedance was considered abnormal if a measurement was <200 Ohm or > 3,000 Ohm or there was a sudden or significant change in impedance. The analysis excluded events that were resolved with successful lead repositioning.
Hauser et al, 2011	Lead failed if it exhibited abnormal impedance; if it exhibited electrical noise as manifested by nonphysiological signals on the electrogram or by pulse generator diagnostic data suggesting rapid oversensing (eg, nonphysiological short intervals and/or recurrent nonsustained ventricular tachycardia with intervals usually <220 milliseconds); or if it could not sense R waves and/or provide effective electrical therapy as a result of an apparent structural defect such as a conductor fracture or insulation breach.
Kawada et al, 2017	Lead failure was defined as one of the following: (1) recurrent nonphysiological high rate sensing (electrical noise); (2) a sudden pace/sense or high-voltage impedance change (>100% increase or >50% decrease) or values outside the interval of 200–1500 Ohm or 20–200 Ohm, respectively; (3) a sudden or intermittent increase in right ventricular threshold and/ or decrease in R-wave amplitude, without alternative explanation.
Kleeman et al, 2019	Lead failure was suspected if one or more of the following criteria were fulfilled: (a) noise artifacts from nonphysiologic potentials after excluding electromagnetic interferences from electrical devices, (b) a sudden change of the lead impedance to abnormal range (high voltage or pace-sense lead), (c) a sudden pacing threshold rise or exit block, for which no other cause was found, (d) visible disruption of the lead on radiographic examination or (e) visible damage of lead isolation on x-ray or intraoperatively during lead revision.
Kondo et al, 2020	Lead failure was defined as one of the following: (1) recurrent nonphysiological high rate sensing (electrical noise); (2) a sudden pace/sense or high-voltage impedance change (>100% increase or >50% decrease) or values outside the interval of 200–1500 Ohm or 20–200 Ohm, respectively; (3) a sudden or intermittent increase in right ventricular threshold and/ or decrease in R-wave amplitude, without alternative explanation.
Lam et al, 2019	Lead failure was defined by the presence of any of the following criteria: – Non-physiological high rate signals, not attributable to electromagnetic interferences, myopotential or T wave oversensing, with or without inappropriate shocks; – Sudden change of long-term pace/sense or high voltage impedance (> 100% increase or > 50% decrease) or values outside the interval of 200–2000 Ω or 20–200 Ω, respectively, and loose set screw excluded at revision; – Fluoroscopic observation of an externalized conductor; – Visual observation of an exposed or externalized conductor; – Sudden increase in right ventricular threshold and/or decrease of R wave sensing, without alternative explanation.
Liu et al, 2014	Lead failure was defined as electrical malfunction resulting in lead extraction or replacement with a new ICD lead. Specifically, electrical malfunction was defined as abnormal pace-sense or high-voltage impedance values, decrease in R-wave amplitude, increase in pacing threshold necessitating lead replacement; or the presence of electrical noise leading to inappropriate ICD therapy.
Marai et al, 2019	Lead failures were defined as abnormally low- or high-voltage impedances, failure to capture, failure to sense or defibrillate, or the presence of nonphysiological signals that are not due to external interference.
Mori et al, 2021	Lead failure was diagnosed if one or more of the following criteria were fulfilled and required a surgical operation: (1) an impedance failure that resulted in an increase in the pacing or defibrillation impedance out of the normal range that required a surgical revision as suggested by the experts of the manufacturer; (2) exit block exhibiting an increase in the pacing threshold without a remarkable change in the lead impedance; (3) fractures resulting in the appearance of a translucent area of the lead observed on x-ray; (4) sensing failures resulting in an amplitude decrease to less than the sensing threshold; and (5) an insulation defect exhibiting sensing noise artifact or major pectoral muscle stimulation related to the body motion.
Noti et al, 2016	Lead failure was defined by the presence of any of the following criteria: – Non-physiological high rate signals, not attributable to electromagnetic interferences, myopotential or T wave oversensing, with or without inappropriate shocks; – Sudden change of long-term pace/sense or high voltage impedance (> 100% increase or > 50% decrease) or values outside the interval of 200–2000 Ω or 20–200 Ω, respectively, and loose set screw excluded at revision; – Fluoroscopic observation of an externalized conductor; – Visual observation of an exposed or externalized conductor; – Sudden increase in right ventricular threshold and/or decrease of R wave sensing, without alternative explanation.

O'Connor et al, 2018	Lead failure in this study was defined as the requirement to deactivate, extract, and/or replace a lead due to at least one of the following: 1. Nonphysiological high-rate sensing not as a consequence of electromagnetic interference or T-wave oversensing; 2. Sudden rise or fall in impedance in either the pace/sense or high voltage components beyond the reported limits for the lead; 3. Sudden decrease in the ventricular sensing threshold to ≤2 mV or complete failure of ventricular capture; 4. Radiographic evidence of lead fracture or insulation breach.
Padfield et al, 2015	Lead failure was defined as recurrent nonphysiological high-rate sensing unrelated to external electromagnetic interference or T-wave oversensing; a sudden rise in impedance unrelated to perforation or lead dislodgement; or abnormal lead parameters with definite evidence of lead fracture or insulation failure.
Parkash et al, 2012	Lead fractures were classified as confirmed if 2 of the 3 following criteria were present: (1) Impedance rise (>50% or 500 Ohm in 1 week), (2) short interval count >10 times per day or 300 times per month, and (3) inappropriate shock because of noise recorded on the electrogram.
Parkash et al, 2018	Electrical lead failure was defined as 1 of the following: a sudden change in impedance (high voltage or other) (rise or drop >50% over a 3-month period) or inappropriate shocks/nonsustained ventricular tachycardia secondary to sensing of electrical noise artifacts from nonphysiologic potentials or sudden pacing threshold rise for which no other cause was found; a loose set screw was required to be excluded at the time of replacement (if a revision was performed). Structural lead failure was defined as a visible disruption of the lead on radiographic examination by either cinefluoroscopy or chest radiographs.
Pérez Dìez et al, 2018	Structural failure was defined as an insulation defect, conductor fracture, or externalization. Electrical failure was defined as the presence of at least one of the following: (1) anomalous low-voltage impedance (< 200 or > 2,000 Ω), (2) anomalous highvoltage impedance (< 20 or > 200 Ω), (3) failure to capture, (4) the presence of unexplained recurrent nonphysiologic electrical signals unrelated to external interference, and (5) loss of sensing, with detection <2mV.
Ricci et al, 2011	The occurrence of noise-induced inappropriate shocks was considered the most important signla of lead failure. In the absence of noise-induced shocks, lead failure evidence was derived from the analysis of signals such as a significant decrease or increase in lead impedance; presence of false non-sustained ventricular tachycardia episodes; significant increase in the sensing integrity counter, which counts the number of sensed, non-physiologic short ventricular intervals near the ICD blanking period; oversensing or undersensing of the normal cardiac electrical activity, as registered on the right ventricular channel; or any change in electrical parameters which may prevent detection or interruption of potentially lethal arrhythmias.
Rodorf et al, 2013	Lead failure was defined as a sudden change (≥50% as compared with chronic values) in long-term pacing and high-voltage impedance and/or electrical noise artifacts from rapid, nonphysiological make-break potentials recorded on the sensing channel.
Rodorf et al, 2019	Lead failure was defined as electrical malfunction (sudden change ≥50% as compared with chronic values in long-term pacing and high-voltage impedance, reduction in R-wave sensing, increase in capture threshold and/or presence of electrical noise artifacts from rapid, nonphysiological make-break potentials recorded on the sensing channel) or lead structural malfunction (externalization of conductors, insulation defect or fracture).
Shariff et al, 2015	Lead failure was defined as electrical malfunction resulting in lead extraction or replacement with a new ICD lead.
Stroker et al, 2016	Electrical lead failure was defined as one of the following: (1) pace/sense conductor impedance out of range (outside 200 to 2000 Ohm interval) or a sudden change >100% increase or >50% decrease of the stable baseline, (2) change in high-voltage impedance (>200 or <50 Ohm), (3) increase in capture threshold >5V or >100%, (4) decrease in R-wave sensing (<3 mV or >50%), and (5) oversensing of nonphysiological electrical noise artifacts, not due to external interference such as electromagnetic interference.
Sung et al, 2012	A lead was considered to have failed if it met 1 of the following criteria: (1) presence of nonphysiologic noise not due to external interference such as electromagnetic interference; (2) rise in pace/sense (p/s) conductor impedance to >2,000 Ohm usually from baseline impedance <1,000 Ohm or greater than double rise in stable baseline impedance; (3) drop in p/s conductor impedance to less than half of the previously stable baseline value or to impedance <200 Ohm from baseline impedance >300 Ohm; (4) change in superior vena cava (SVC) or high-voltage coil impedance to >200 or <25 Ohm; and (5) rise in capture threshold to greater than double of the previously stable value.
Theuns et al, 2012	Electrical dysfunction of the lead was considered if it met 1 of the following Criteria: (1) the presence of nonphysiological signals on the intracardiac ventricular electrogram; (2) increase in pacing impedance to >2000 Ω or to greater than double the increase in stable baseline impedance; (3) decrease in pacing impedance to <200 Ω or to less than half of stable baseline value; or (4)

	change in high-voltage impedance to >200 Ω or <25 Ω. The presence of externalized conductors was defined as conductor cables visible outside the lead body on fluoroscopy in any of the views.
Valk et al, 2013, The Netherlands	Capture thresholds, sensing amplitudes and pacing and shock impedance were routinely measured and checked for abnormal changes.
van Malderen et al, 2016	Lead failure was defined as a lead not performing to its specifications because of a specific structural or electrical failure requiring removal from service. Structural failure was defined as insulation breach, externalization of conductors, or fracture. Electrical failure was defined as (1)abnormal low-voltage impedance (outside the range 200–2000 Ω); (2)abnormal high-voltage impedance (outside the range of 20–200 Ω); (3) failure to capture; (4) presence of nonphysiological signals not due to external interference (noise); or (5) failure to sense when ventricular sensing signal decreased ≤2 mV.
van Rees et al, 2012	Defibrillation lead removal or capping was classified as lead failure if one of the following criteria was met: (1) undersensing or oversensing of normal electrical cardiac activity; (2) incapability of sensing, pacing, or defibrillation; (3) inappropriate shocks secondary to electrical noise artifacts; (4) abnormal lead impedance; (5) Lead Integrity Algorithm triggering an ICD alert.
Vollmann et al, 2013	Lead failed if one or more of the following criteria applied: (i) a sudden rise in long-term pacing or high-voltage impedance, (ii) electrical noise artefacts as manifested by non-physiological signals on the electrogram or by device diagnostics (e.g. non-physiological short intervals and/or recurrent non-sustained ventricular tachycardia with intervals usually ,220 ms), (iii) failure to sense R-waves or ineffective electrical therapy due to an apparent structural lead defect.
Weberndorfer et al, 2018	Lead failure was defined as the occurrence of one of the following: non-physiological high rate—sensing not caused by external interference (noise), low-voltage impedance outside the interval of 200–2000 Ohm, high-voltage impedance outside the interval 20– 150 Ohm, failure to sense, capture, or defibrillate.

A total of 89 KM curves were extracted, including a median number of 312 leads (interquartile range, IQR 120-774) each. The accuracy assessment performed on each KM curve showed that the reconstructed IPD was accurate (p-values of the Kolmogorov-Smirnov test >0.05).

2.3.2 Non-recalled versus Recalled leads

Our meta-analysis included 41,870 (63.1%) non-recalled and 24,493 (36.9%) recalled leads with 1,018 and 2,610 failures, respectively. The cumulative failure-free rate was 97.4% (95% CI, 97.2% - 97.6%) at 5 years and 94.1% (95% CI, 93.6% - 94.6%) at 8 years for non-recalled leads with a failure rate of 0.62x100 patient-years (CI, 0.58-0.66); and 92.3% (CI, 91.9% - 92.7%) at 5 years and 81.2% (95% CI, 80.3% - 82.0%) at 8 years for recalled leads with a failure rate of 2.20x100 patient-years (95% CI, 2.11-2.28). The difference was statistically significant in the mixed effects Cox model (HR, 3.15 [95% CI, 2.85-3.47], p<0.001) with a 0.625 standard deviation of the random effect (ie, study identifier). Figure 2.3 shows the reconstructed IPD KM survival curves by lead recalled status.

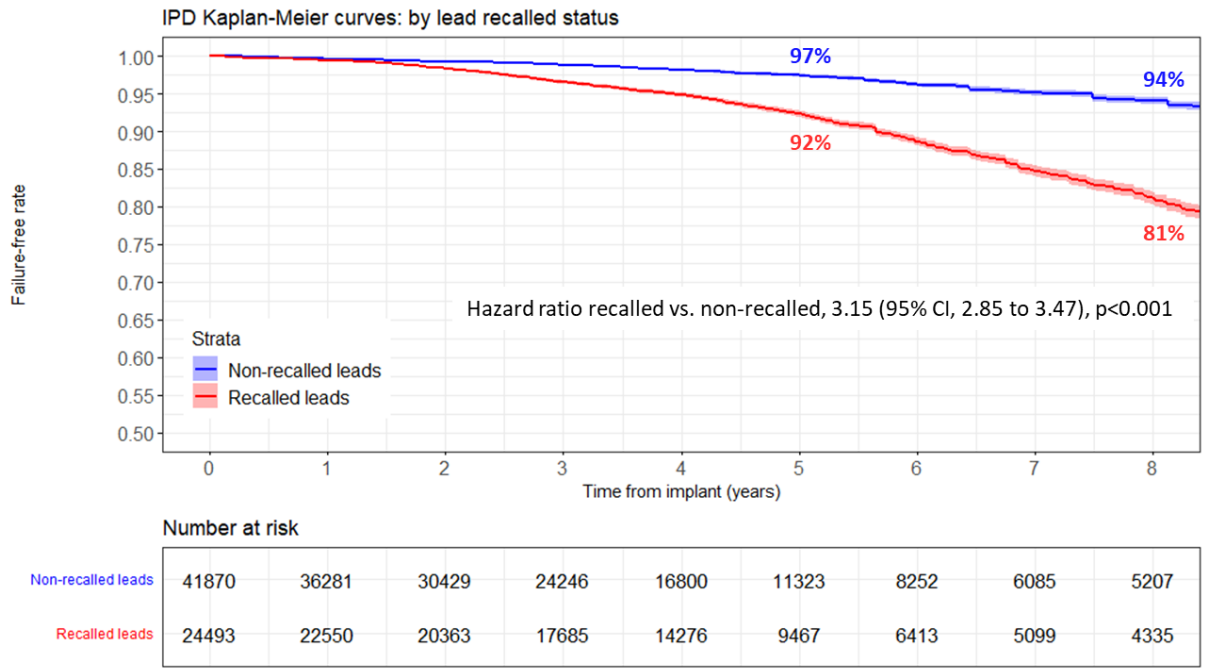


Figure 2.3: reconstructed IPD Kaplan-Meier survival curves with 95% confidence interval by recalled status.

2.3.3 Single- versus Multicenter studies

Failure-free rate was lower in single-center studies in both the non-recalled group (HR, 0.28 [95% CI, 0.15-0.51], p<0.001) and the recalled group (HR, 0.54 [95% CI, 0.33-0.88], p=0.014) group compared with multicenter studies. In the non-recalled group, the cumulative failure-free rate was 96.2% (95% CI, 95.8% - 96.5%) at 5 years and 92.5% (95% CI, 91.9% - 93.1%) at 8 years in single-center studies; and 98.6% (95% CI, 98.3% - 98.8%) at 5 years and 97.1% (95% CI, 96.2% - 98.1%) at 8 years in multicenter studies. In the recalled group, the cumulative failure-free rate was 88.8% (95% CI, 88.0% - 89.7%) at 5 years and 74.5% (95% CI, 72.9% - 76.3%) at 8 years in single-center studies; and 94.2% (95% CI, 93.7% - 94.6%) at 5 years and 84.3% (95% CI, 83.3% - 85.2%) at 8 years in multicenter studies. Figure 2.4 shows the reconstructed IPD KM survival curves by single-center / multicenter design.

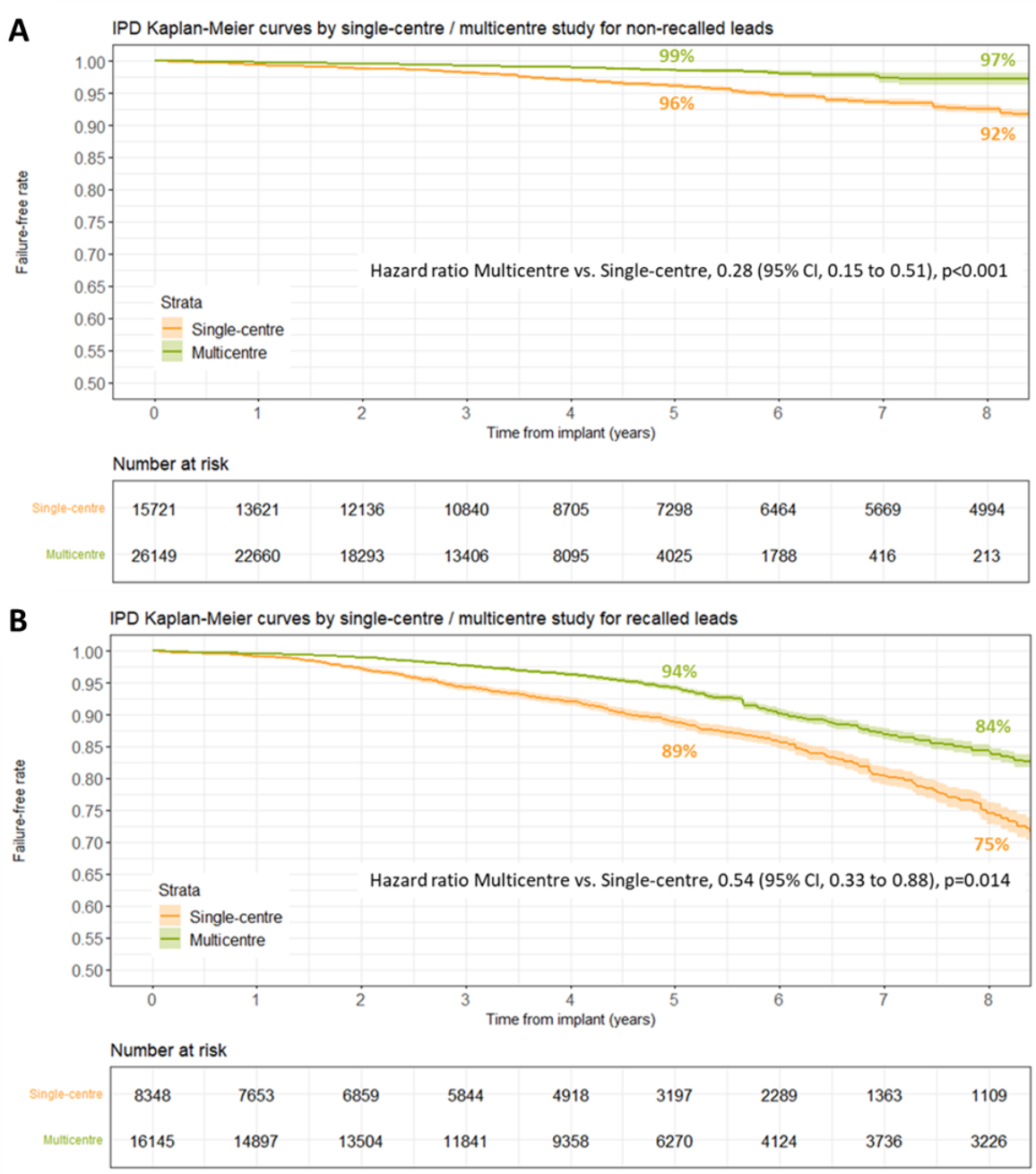


Figure 2.4: Reconstructed IPD Kaplan-Meier survival curves with 95% confidence interval by single-center / multicenter design the study for contemporary non-recalled leads (A) and recalled leads (B).

2.3.4 Impact of study size

The cumulative failure-free probability was significantly lower in small (i.e. extracted KM curve with less than 312 leads) versus large studies for both non-recalled (HR, 0.54 [CI, 0.33-0.89], p=0.015) and recalled (HR, 0.62 [CI, 0.43-0.89], p=0.009) leads. In the non-recalled group, the cumulative failure-free rate was 96.8% (CI, 96.0% - 97.5%) at 5 years and 91.0% (CI, 89.3% - 92.8%) at 8 years in small studies; and 97.5% (CI, 97.3% - 97.7%) at 5 years and 94.5% (CI, 94.0% - 95.0%) at 8 years in large studies. In the recalled group, the cumulative failure-free rate was 88.3% (CI, 86.7% - 90.0%)

at 5 years and 75.7% (CI, 72.7% - 78.9%) at 8 years in small studies; and 92.7% (CI, 92.3% - 93.2%) at 5 years and 81.7% (CI, 80.9% - 82.6%) at 8 years in large studies. Figure 2.5 shows the reconstructed IPD KM survival curves by study size.

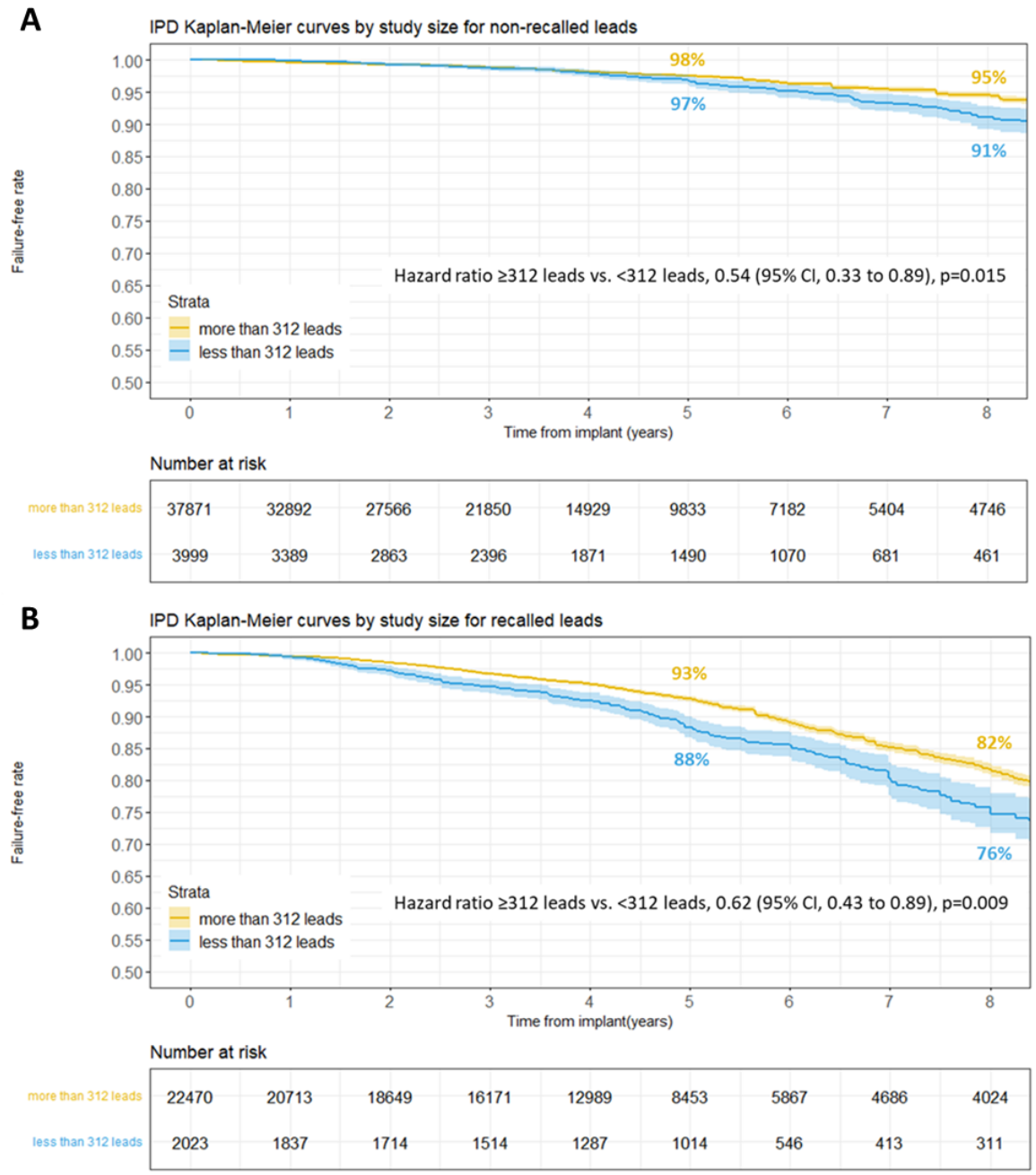


Figure 2.5: Reconstructed IPD Kaplan-Meier survival curves with 95% confidence interval by study size for contemporary non-recalled leads (A) and recalled leads (B).

2.4 Discussion

Despite recent advances in lead technology, physicians will likely continue to need to understand how to manage patients with lead failures. Regulatory authorities have identified high-quality post-approval surveillance for these devices as a priority [69], but reliable safety monitoring remains a challenge. In the last decade, many studies have investigated this topic using time-to-event outcomes, which is the more informative analysis of time-dependent data. However, an overall estimate of contemporary ICD lead performance is not available, as a meta-analysis of all published data is lacking. The main reason is that a reliable pooled analysis can only be performed if access to IPD is available for each source, and this is rarely possible. To address this knowledge gap, we used a new validated algorithm to recreate KM data on which the published survival curves are based [21,22]. This allowed us to fit survival models on a very large aggregated data set. This IPD meta-analysis on more than 66,000 transvenous ICD leads highlighted a substantial difference in performance between recalled and contemporary non-recalled leads. These figures could help identify reliable standards to evaluate clinically acceptable survival rates for transvenous ICD leads. The failure-free estimate at 8 years for recalled leads was 81.2% with a failure rate of 2.20x100 patient-years. These results are slightly worse than those reported in a 2015 review [70], which indicated an annual incidence of lead failure between 1.2% and 2.2% with shorter follow-up. Our pooled KM curve (Figure 2.3) diverged from non-recalled leads after 2 years of implantation and showed a marked performance decline after 5 years. For contemporary leads, we showed an estimate of failure-free rate of 97.4% at 5 years and 94.1% at 8 years. These results are reassuring and demonstrate remarkably improved ICD lead durability. A recent propensity-matched survival analysis of contemporary high-energy ICD leads in data generated using an active surveillance software tool reported similar rates of freedom from lead failure at 5 years (from 97.7% to 98.9%) [70]. Comparisons with manufacturer's product performance reports are difficult because these reports also include lead dislodgments that were excluded in our meta-analysis. Although this is a different definition of lead failure, the reported survival probabilities were close to ours, ranging between 99% and 97% at 5 years [71-74]. This could be explained by the potential underreporting of performance issues that is a well-known drawback of this surveillance methodology, being based on analysis of voluntary product returns and not subject to active surveillance.

We also showed that failure-free estimates could be influenced by the characteristics of the study. Specifically, we observed a significant difference in estimates between single-center and multicenter studies consistently in the recalled and non-recalled groups. Single-center studies tend to underestimate lead performance compared with studies that involve at least 2 sites. The difference between failure-free rates could be quantified in an absolute value of 5% and 9% at 8 years for

contemporary and recalled leads, respectively. This is not totally unexpected. Although single-center studies are valuable and an essential part of clinical investigations, there is evidence to suggest that their results may be seriously flawed due to potential limited external validity [76,77]. The failure rate of ICD leads estimated in a single clinical environment is not necessarily generalizable to a broader population, for example, due to the operator-specific implantation technique. Furthermore, single-center studies can be prone to reporting and publication biases [78], generally induced by a much greater propensity to publish warning abnormal rather than within-range normal lead performance. This effect could specifically explain the systematic underestimation of failure-free rates from single-center compared with multicenter studies that we found for both contemporary and recalled leads. Interestingly, we observed that the size of the cohort included in the survival analysis also tends to introduce bias in failure-free estimates. KM curves with fewer than 312 leads estimated a significantly lower survival rate than analyses with larger samples. The difference could be quantified in an absolute value of 4% and 6% at 8 years for contemporary and recall leads, respectively. The observed effect of study characteristics on lead performance estimates recommends carefully assessing methodology and study design when conducting research on this topic. A single-center, small-sized study should be a major caveat in the journal peer review process and should be used with caution for decision making. Meta-analyses mitigate, but do not totally abolish, such biases. Multicenter follow-up studies including at least a few hundred leads for each model considered are the main tool to reliably conduct post-market surveillance of ICD leads.

This study has some limitations. First, published KM curves tend to pool data over different covariates that might affect survival (e.g., patient age, sex, vascular access, etc.), and the method is still not quite the same as having true IPD. The inability to derive separate KM curves for different subgroups can have an impact on estimates. However, this is an issue for all meta-analysis where a covariate adjustment could not be performed. Second, although the definition of lead failure was similar in all studies, there are some minor differences (Table 2.3). We mitigated this potential bias, including the definition of lead failure in the risk of bias assessment. Finally, several studies included in the meta-analysis reported aggregated survival curves for a mix of different leads; therefore, no comparison was made among lead models.

In conclusion, in this systematic review and IPD meta-analysis on published survival curves, we provided pooled survival KM curves on more than 66,000 ICD leads. The overall failure-free rate for contemporary leads was markedly higher than for recalled leads with estimates of 97% and 94% at 5 and 8 years, respectively. These figures may play a significant role in generating evidence-based standards for assessing clinically acceptable failure rates for transvenous ICD leads. Lead

performance was underestimated with single-center and small-sized studies; large multicenter studies remain the main tool to reliably conduct post-market surveillance of ICD leads.

CHAPTER 3

BAYESIAN ADAPTIVE DESIGN FOR THE MULTICENTER RANDOMIZED PARTITA TRIAL

Summary

Background: Optimal timing for catheter ablation of ventricular tachycardia is an important unresolved issue. There are no randomized trials evaluating the benefit of ablation after the first ICD shock.

Methods: We conducted a 2-phase, prospective, multicenter, randomized clinical trial. Patients with ischemic or nonischemic dilated cardiomyopathy and primary or secondary prevention indication for ICD were enrolled in an initial observational phase until first appropriate shock (phase A). After reconsenting, patients were randomly assigned 1:1 in phase B to immediate ablation (within 2 months from shock delivery) or continuation of standard therapy. The primary end point was a composite of death from any cause or hospitalization for worsening heart failure. Amiodarone intake was not allowed except for documented atrial tachyarrhythmias. On July 23, 2021, phase B of the trial was interrupted as a result of the first interim analysis on the basis of the Bayesian adaptive design.

Results: Of the 517 patients enrolled in phase A, 154 (30%) had VTs, 56 (11%) received an appropriate shock in a median follow-up of 2.4 (1.4, 4.4) years, and 47 (9%) accepted to participate in the phase B. After 24.2 (8.5, 24.4) months, the primary endpoint occurred in 1 (4%) of 23 patients in the ablation group and 10 (42%) of 24 patients in the control group (hazard ratio, 0.11; 95% confidence interval, 0.01-0.85; P = 0.034). The results met the pre-specified termination criteria of >99% Bayesian posterior probability of superiority of treatment over standard therapy. No deaths were observed in the ablation group versus 8 deaths (33%) in the control group (P = 0.004); there was 1 wHF hospitalization in the ablation group (4%) versus 4 in the control group (17%; P = 0.159). ICD shocks were less frequent in the ablation group (9%) than in the control group (42%; P=0.039).

Conclusions: VT ablation after the first appropriate shock was associated with a reduced risk of the combined death or wHF hospitalization endpoint. Catheter ablation was also associated with lower recurrence of VTs treated by shock and lower mortality. These findings support a referral for VT ablation after the first ICD shock.

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3.1 Introduction

Current guidelines indicate ventricular tachycardia (VT) ablation in the setting of structural heart disease in cases of recurrent episodes causing ICD interventions [79]. It is known that the occurrence of appropriate shocks negatively affects quality of life and survival [80-84]. Retrospective observational studies demonstrated that freedom from VT recurrence after catheter ablation is associated with improved survival [85]. It has been shown that an earlier ablation of VT, both in ischemic (ICM) and nonischemic cardiomyopathy (NICM) is associated with a lower recurrence rate although a survival benefit could not be demonstrated [86,87]. Randomized controlled trials, that studied the importance of timing, addressed the issue of prophylactic catheter ablation in ICM with discordant results in terms of reduction of VT episodes and no significant benefit in terms of mortality [88-91]. On the other hand, deferring the timing of ablation to an undefined future poses an increased risk of VT recurrence with a probable adverse effect on the clinical course. It is therefore important to define when the ablation procedure should be performed between these two extreme timings. The aim of the PARTITA trial was to verify the prognostic impact of early VT ablation, after the first ICD shock, on the endpoints of mortality and worsening heart failure (wHF). In addition, due to its prospective nature the study was designed to provide data on the natural history of VT following ICD implantation and the identification of specific arrhythmia patterns could predict a subsequent shock.

3.2 Methods

This is a multicenter, randomized, controlled two-stage clinical investigation that included 16 sites (12 in Italy, 1 in Switzerland, 1 in Portugal, 1 in France and 1 in Germany). The study was approved by the institutional review committees of the respective participating centers. Written informed consent was obtained from all subjects. The trial is registered with the NCT01547208 identifier on ClinicalTrials.gov.

3.2.1 Phase A

Patients with ischemic or non-ischemic dilated cardiomyopathy with primary or secondary prevention indication to ICD were enrolled in the initial observational stage (Phase A). Exclusion criteria were general contraindication to transcatheter ablation or antithrombotic therapy and chronic treatment with class I and class III antiarrhythmic drugs (amiodarone was only allowed for the treatment of atrial fibrillation). Patients received a Biotronik-manufactured ICD or CRT-D). The study protocol

required a uniform ICD setting for the detection and therapy of ventricular arrhythmias. The follow-up was based on RM verification. Additional in-hospital visits were scheduled according to the standard site routine. All episodes of ventricular tachyarrhythmia were collected and classified as non-sustained ventricular arrhythmias (i.e. lasting less than 30 s and without ICD therapy), sustained VT, or ventricular fibrillation (VF). Patients remained in phase A until the first VT episode treated with an appropriate ICD shock or until the end of the study.

3.2.2 Phase B

After reconsenting, patients who received the first shock for VT were randomly assigned 1:1 to immediate ablation or continuation of standard therapy. Catheter ablation was performed within 2 months after the ICD shock, while patients assigned to standard therapy did not undergo any ablation procedure until an electrical storm episode. Patients were followed up for 2 years after the randomization or until the end of the study.

3.2.3 Study procedures

Baseline programmed ventricular stimulation (PVS) was performed (up to 4 extrastimuli, from 2 ventricular sites), before general anesthesia, to obtain the 12 lead ECG of the VT. Endocardial or endoepicardial ventricular high density electroanatomic mapping was performed in sinus rhythm with the CARTO 3 (Biosense Webster, Diamond Bar, CA) or NavX Ensite (Abbott, MN) systems. Standard voltage criteria were used to identify scar low voltage areas, while activation maps were performed to identify areas of late potentials, defined as local ventricular potentials occurring after the terminal portion of the surface QRS and early potentials, defined as fractionated (EGM containing >4 sharp deflections) or isolated (≥2 sharp EGMs separated by an isoelectric segment) within the QRS. Catheter ablation was performed preferably in sinus rhythm with standard power settings (50W) aiming at complete abolition of late potentials when present or early potentials when absent. Remaps were performed until no residual potentials were recorded. PVS was repeated attempting to reinduce VT after completing ablation in sinus rhythm. If the VT was still inducible and hemodynamically tolerated by the patient, activation mapping and ablation aimed at the termination of the ongoing VT. The aim of the ablation procedure was the combined procedural endpoint of abolition of late potentials and VT non-inducibility with the complete stimulation protocol.

3.2.4 Endpoints

The primary endpoint was a composite of death from any cause or worsening of heart failure that led to hospitalization. Secondary outcome measures were (i) death resulting from cardiac causes; (ii) sustained VT or VF recurrences; (iv) appropriate ICD shock; (v) electrical storm.

3.2.5 Sample size

The study was powered to detect an absolute difference between groups of 20% in the primary endpoint rate, assuming an 84% event-free rate at 2 years for the ablation group [92] and with type I and type II errors of 0.05 and 0.20 (80% power), respectively. With the assumption that primary prevention patients would have a shock rate of 20% in 5 years (0.4% incidence per month) [93] while secondary prevention patients of 53% in 2 years (3.1% incidence per month) [93], the sample size of 586 patients was planned to reach 176 randomizations.

3.2.6 Bayesian adaptive design

During the study, data from randomized clinical trials on safety and efficacy of prolonged VT detection in ICD programming became available [94] inducing a revision of the VT detection settings recommended in our clinical investigation plan. This further contributed to a lower than expected percentage of patients experiencing shocks for VTs, leading to an unrealistic prolongation of the study. In view of that, in December 2017 the clinical investigation plan was amended to include an adaptive design of the randomized study stage using a Bayesian approach [95]. Specifically, two interim analyses were planned at 25% (n=44) and 50% (n=88) of the 176 initially estimated sample size. Study success required a probability of superiority of ablation over standard treatment in the primary endpoint at the final analysis of at least 98% to control the type I error rate at no more than 2.5% which was verified by simulations (Table 3.1). Simulations were performed with the assumption of a primary endpoint event-free probability in the control group (pC) of 0.64 and with a rate in the ablation group (pA) ranging from 0.50 to 0.95. According to the Bayesian adaptive design, the trial would have been stopped with the declaration of study success, if the predictive probability of superiority was ≥99% at any interim analysis (including +1%-penalty). Conversely, the study would have been stopped for futility, if the predictive probability of superiority was less than 5%.

Table 3.1: Results of 1,000 simulated trials.

pA	pC	P(win)	Mean SS	SD SS	P(n=44)	P(n=88)	P(n=176)
0.50	0.64	0.001	176	0	0	0	1.000
0.60	0.64	0.013	174	12	0.008	0.003	0.989
0.70	0.64	0.247	160	39	0.068	0.077	0.855
0.75	0.64	0.620	137	54	0.170	0.190	0.639
0.80	0.64	0.921	102	55	0.317	0.316	0.334
0.85	0.64	0.994	72	41	0.584	0.305	0.110
0.90	0.64	0.999	53	22	0.819	0.167	0.013
0.95	0.64	1.000	46	8	0.963	0.037	0

pA = event-free probability in the ablation group; pC = event-free probability in the control group; P(win) = probability of study success; SD = standard deviation; SS = sample size; P(n=44) = probability of study termination at the first interim analysis; P(n=88) = probability of study termination at the second interim analysis; P(n=176) = probability of study termination at final analysis.

3.2.7 Statistics

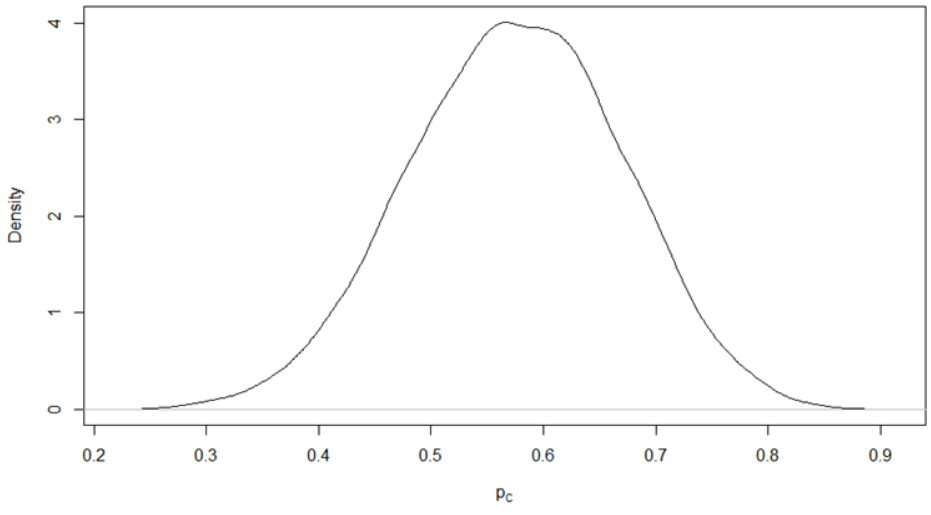
The primary endpoint was analyzed using the KM methods with the intention-to-treat approach. We used Cox's proportional hazards regression models to estimate the HR and the corresponding 95% CI. Differences in outcome measures were evaluated also by using the two-sided log-rank test. Multivariable Cox's models were also used to identify predictors of appropriate shocks in the registry phase and estimate respective HR (CI) adjusting by covariates based on known clinical relevance.

Continuous variables are presented as mean (standard deviation, SD) or median (interquartile range, IQR) and compared using the Mann-Whitney U test. Categorical variables are presented by absolute and relative frequencies and compared with the $\chi 2$ test or Fisher's exact test.

The median missing data for the baseline variables was 2.3% (IQR, 1.2% - 8.1%). Multiple imputations were then generated with predictive mean matching (for numeric data) and logistic regression imputation (for binary data) under the missing-at-random assumption. Imputed datasets were thereafter pooled for outcome analysis. All tests were considered significant with $P< 0.05$. Data were managed with Stata/MP 17.0 statistical software (StataCorp LLC, Texas, USA) and R Studio 4.0.3 (Boston, MA, USA).

3.2.8 Interim analysis

By July 2021, the number of randomized patients required for the first planned interim analysis completed their follow-up. This analysis showed that the predictive probability of success was 99.9% (Figure 3.1). This was more than the protocol-specified boundary of 99% and allowed an immediate claim of study success (i.e. superiority of immediate ablation over standard therapy). The investigators were asked to terminate study procedures and competent Ethics committees were informed.



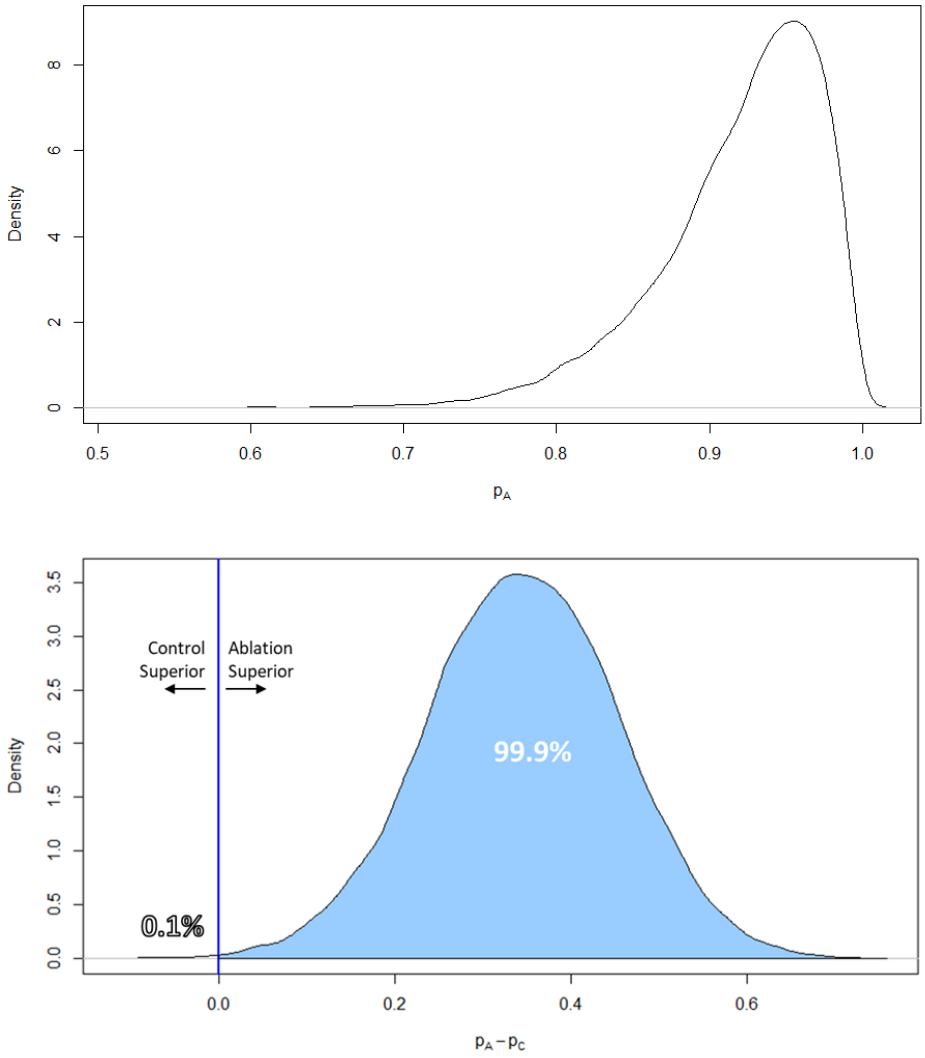


Figure 3.1: Posterior probability of primary endpoint event-free in the control group (pC), in the ablation group (pA), and of the difference between ablation over standard treatment in the primary endpoint at the first interim analysis.

3.3 Results

3.3.1 Study population

Figure 3.2 shows the trial profile. From September 2012 to July 2021, a total of 517 patients were enrolled in 16 sites.

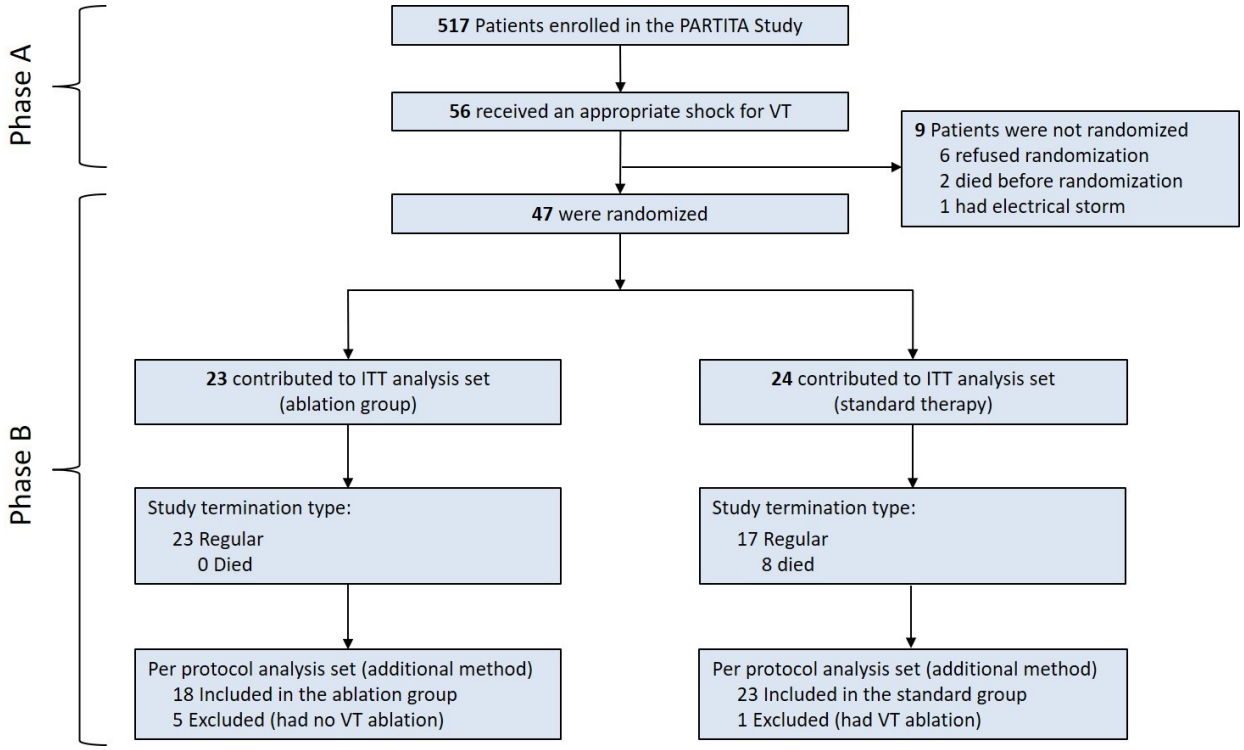


Figure 3.2**:** Patient allocation and analysis.

The median age at enrollment was 67.3±10.7 years and 449 (87%) patients were men. Twenty one percent (n=107) of the patients were implanted for secondary prevention and the prevalence of CRT-D was 24%. The most frequent etiology was ischemic cardiomyopathy (78%). Complete baseline characteristics are reported in Table 3.2.

Table 3.2: Patients' characteristics.

	Overall, N=517[1]	**Randomized patients, N=47[1]**	**Ablation, N=23[1]**	**Standard therapy, N=24[1]**	**P value**
Male	449 (87%)	40 (85%)	19 (83%)	21 (88%)	0.7
Age (years)	67.3 (10.7)	68.4 (9.3)	71.2 (8.1)	65.6 (9.6)	0.059
NYHA					0.5
Class I	95 (20%)	8 (18%)	3 (13%)	5 (24%)	
Class II	291 (62%)	29 (66%)	17 (74%)	12 (57%)	
Class III	82 (17%)	7 (16%)	3 (13%)	4 (19%)	
Class IV	1 (0.2%)	0 (0%)	0 (0%)	0 (0%)	
LV Ejection Fraction (%)	34.0 (9.5)	32.2 (8.6)	31.9 (9.0)	32.4 (8.3)	>0.9
QRS duration (ms)	120.8 (31.1)	123.6 (30.1)	126.3 (35.0)	120.9 (25.2)	>0.9
Device					0.5
Single-chamber ICD	177 (35%)	13 (28%)	5 (22%)	8 (33%)	
Dual-chamber ICD	209 (41%)	19 (40%)	11 (48%)	8 (33%)	
CRT-D	123 (24%)	15 (32%)	7 (30%)	8 (33%)	
ICD Indication					0.5
Primary prevention	403 (79%)	35 (74%)	16 (70%)	19 (79%)	
Secondary prevention	107 (21%)	12 (26%)	7 (30%)	5 (21%)	
Cardiomyopathy					0.5
Ischemic	397 (78%)	38 (81%)	20 (87%)	18 (75%)	
Idiopathic dilated	114 (22%)	9 (19%)	3 (13%)	6 (25%)	

Comorbidities					
Hypertension	355 (77%)	32 (74%)	17 (81%)	15 (68%)	0.3
Diabetes	165 (36%)	13 (30%)	4 (19%)	9 (41%)	0.12
Chronic renal failure	66 (14%)	9 (21%)	3 (14%)	6 (27%)	0.5
COPD	50 (11%)	7 (16%)	2 (9.5%)	5 (23%)	0.4
Stroke/TIA	37 (8.1%)	3 (7.0%)	2 (9.5%)	1 (4.5%)	0.6
Liver disease	28 (6.1%)	3 (7.0%)	1 (4.8%)	2 (9.1%)	>0.9
History of atrial fibrillation	144 (29%)	18 (38%)	9 (39%)	9 (37%)	0.7
Drug therapy					
ACE inhibitors	327 (67%)	34 (72%)	17 (74%)	17 (71%)	0.8
ARBs	79 (16%)	8 (17%)	3 (13%)	5 (21%)	0.7
Aspirin	326 (67%)	32 (68%)	16 (70%)	16 (67%)	0.8
Betablockers	423 (97%)	47 (100%)	23 (100%)	24 (100%)	-
Diuretics	381 (78%)	40 (85%)	20 (87%)	20 (83%)	>0.9
Statins	343 (70%)	36 (77%)	17 (74%)	19 (79%)	0.7
Amiodarone	56 (13%)	5 (12%)	1 (5%)	4 (21%)	0.2

[1]Mean (SD); n (%)
[2]Wilcoxon rank sum test; Pearson's Chi-squared test; Fisher's exact test.
Abbreviations: ARBs, angiotensin receptor blockers; COPD, chronic obstructive pulmonary disease; ICD, implantable-cardioverter defibrillator; CRT-D, cardiac resynchronization therapy defibrillator; LV, left ventricle; NYHA, New York Heart Association; TIA, transient ischemic attack.

3.3.2 Phase A

During a median follow-up of 2.4 years (IQR 1.4, 4.4) years, 246 (48%) patients had episodes of ventricular tachycardia, 154 had sustained VTs, and 56 (11%) received a first appropriate shock for VT of whom 49 priorly had a median of 3 ATPs. Among secondary prevention patients, 50% did not have VT episodes. The shock incidence per month was 0.30% (95% CI 0.22-0.40%) for primary prevention and 0.34% (0.18-0.56%) for secondary prevention patients, with an overall rate of 0.31% (0.23%-0.40%). The incidence of ventricular arrhythmias and ICD therapies is summarized in Table 2. Both the occurrence of VT treated with ATP and terminated by ATP were associated with an increased risk of subsequent appropriate shock (respectively: HR 22.2, 95% CI 9.78-50.5 and HR: 4.20, 95% CI, 2.41-7.30, both with $p<0.001$). In addition, each delivered and successful ATP increased this risk by 6% ($p<0.001$) and 4% ($p<0.001$), respectively. Non-sustained VTs were not associated with increased shock risk. Among the baseline characteristics, only left ejection fraction below 35% was associated with the risk of shock for VT.

Table 3.3: Ventricular arrhythmias and device therapies during Phase A.

Patients with	**Overall, N = 517**
Any ventricular tachycardia	246 (47.6%)
Non-sustained ventricular tachycardia	145 (28.0%)
Sustained ventricular tachycardia	154 (29.8%)

With no device therapy*	36 (7.0%)
Treated with ATP only	62 (12.0%)
Treated with shock only	6 (1.2%)
Treated with ATP and shock	50 (9.7%)
Ventricular fibrillation	29 (5.6%)
Inappropriate shock	19 (3.7%)

Abbreviations: ATP, antitachycardia pacing.
* VT episodes in the VT1 monitor zone (<167 bpm as reported in the Supplemental Material). All these patients underwent subsequent ICD reprogramming.

3.3.3 Phase B

Forty-seven patients were randomized to the ablation group (n = 23) or the standard therapy group (n = 24) and were included in the intention-to-treat analysis. The mean age of the randomized patients was 68.4±9.3 years, 81% had a prior myocardial infarction and 74% had an implantation for primary prevention (Table 3.2). There were no significant differences between the 2 groups, although there was a trend of older age in patients randomized to ablation (p=0.059).

At the time of first interim analysis (median follow-up 24.2 [8.5, 24.4] months), the composite primary endpoint of death or wHF hospitalization occurred in significantly less patients in the ablation group as compared to standard therapy (1 patient [4%] versus 10 patients [42%], logrank p=0.010).

The KM curves for the primary analysis are shown in Figure 3.3 (HR, 0.11; 95% CI, 0.01-0.85; p= 0.034).

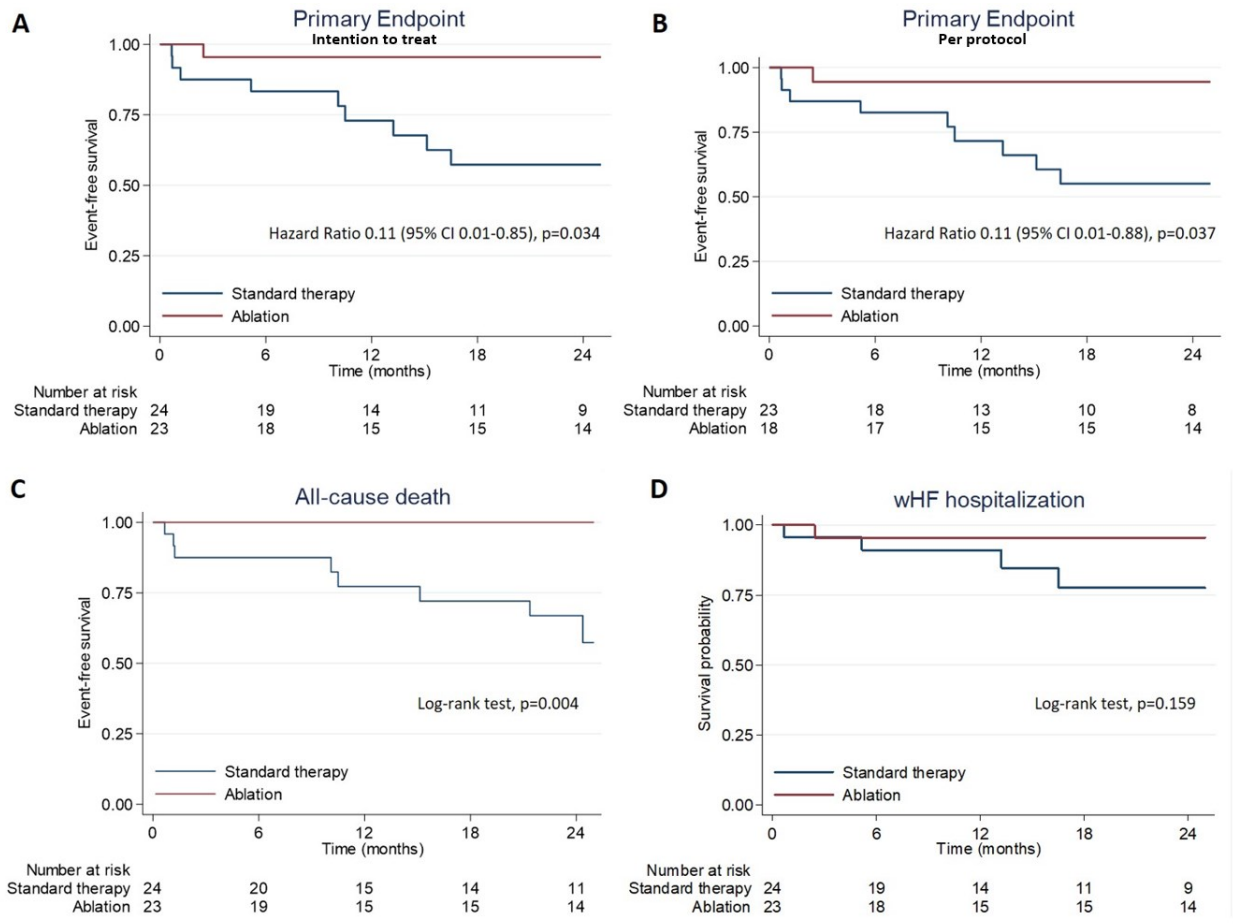


Figure 3.3: Primary endpoint and its components.

The results of the per-protocol analysis were consistent with the results of the primary analysis (Figure 3.3 and Table 3.4).

Table 3.4: Results of proportional hazard model of primary endpoint recurrence in the ablation versus standard therapy group (per-protocol analysis).

Predictor	Model	Hazard Ratio	95% Confidence Interval	p-value
Ablation vs. standard therapy	Cox	0.11	0.01, 0.88	0.037

Among secondary outcomes (Table 3.5), the proportions of patients with all-cause death (0% versus 33%, p=0.004) and recurrent VTs with shock (9% versus 42%, p=0.039) were significantly lower in the ablation group. There was a trend in the reduction of cardiac deaths (0% versus 13%, p=0.087), while no differences were observed for wHF hospitalizations (4% versus 17%, p=0.159), recurrences of any VTs (30% versus 50%, p=0.434), and electrical storms (0% versus 8%, p=0.280).

Table 3.5: Secondary outcomes and comparison between ablation and standard therapy group by log-rank test.

	Ablation	Standard therapy	P value
All-cause death	0 (0%)	8 (33.3%)	0.004
wHF hospitalization	1 (4.3%)	4 (16.7%)	0.159
Cardiac death	0 (0%)	3 (12.5%)	0.087
Recurrent VTs	7 (30.4%)	12 (50.0%)	0.434
Recurrent VTs with shock	2 (8.7%)	10 (41.7%)	0.039
Electrical storm	0 (0%)	2 (8.3%)	0.280

Figure 3.3 shows the KM curves for all-cause death and wHF hospitalization; Figure 3.4 shows VT recurrences with ICD shock.

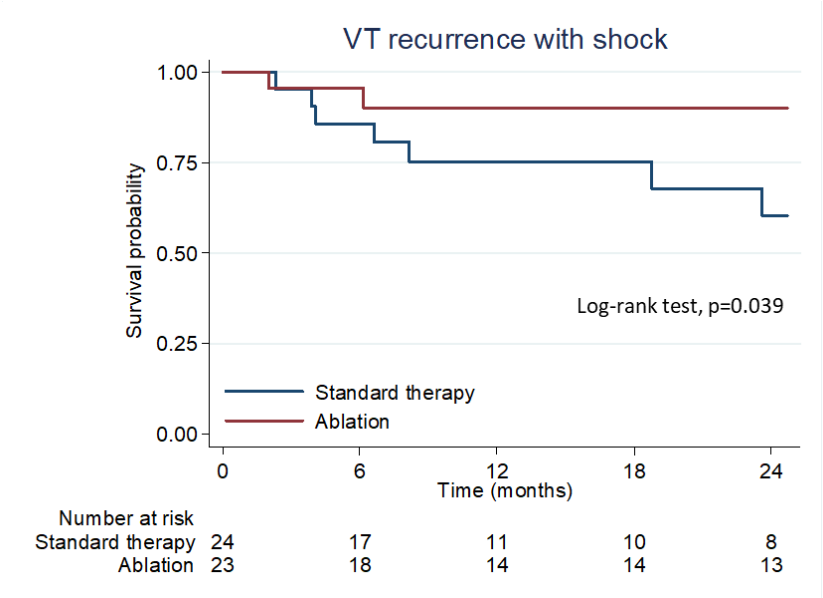


Figure 3.4: Kaplan-Meier survival curves of ventricular tachycardia recurrences with shock.

There were no procedure-related complications among patients who underwent VT ablation during the study. Among the randomized patients, there were 8 deaths in the control group. Two patients died of heart failure after 5 and 10 days of hospitalization, one patient had a fatal cardiac arrest outside the hospital. Five patients died from non-cardiac causes: two deaths were attributed to malignant tumors (sarcoma and squamous cell carcinoma of the skin), one to sepsis, and in 2 reasons were unknown. There were 5 cases of wHF: one patient in the ablation group and four in the control group; all patients were treated by optimizing medical therapy. Of note, all patients in the control group had VT recurrences treated by the device.

3.4 Discussion

The PARTITA trial is the first prospective randomized study to demonstrate a survival benefit of catheter ablation of ventricular tachycardia in patients with ischemic and non-ischemic cardiomyopathy, compared to the control population. The benefit reported for the composite endpoint was driven by the significant impact of ablation on mortality alone. These results were observed both in the intention to treat and per-protocol analyses. After 24 months, 95% of the patients in the ablation arm were free of death or wHF compared to 57% of patients in the control arm. In addition, there was a significant reduction in recurrent VTs treated with shock, 9% in the ablation arm compared to 42% in the control group.

Previously published randomized trials on the timing of ablation were mainly focused on prophylactic catheter ablation [88-91]. The results were heterogenous in terms of VT recurrences and there was no benefit in terms of mortality. The SMASH-VT [88] findings supported the hypothesis that a decreased rate of VT recurrences may have an impact on subsequent mortality. There was a trend in the reduction of mortality although not significant. Two later studies, the VTACH [89] and SMS [90] trial, failed to prove a survival benefit also because the rate of VT recurrences was significantly higher in both arms, compared to the SMASH VT and our own data. The SMS trial did not demonstrate a benefit in VT recurrence rate in the active arm. These discordant results may be explained by the different ablation strategy, that did not include substrate modification as an endpoint and the fact that the ablation protocol was heterogenous allowing variations among centers. The BERLIN VT [91] ultimately demonstrated the lack of benefit of preventive ablation as it was interrupted for futility because the primary endpoint (all-cause death and hospitalization for HF or arrhythmia) increased sufficiently in the prophylactic treatment arm. The reasons why prophylactic catheter ablation failed to prove a net benefit were probably multiple. One of the main explanations could be that a truly prophylactic ablation strategy may include patients that would not suffer from arrhythmia recurrences in the future. From this standpoint our study randomized to ablation patients with an active arrhythmia pattern, as documented by the finding that 88% of patients before the first shock had multiple episodes of VTs treated by ATP. The inclusion of patients with secondary prevention does not warrant a higher rate of shock, as in our series among 107 included for secondary prevention, 50% had no ventricular arrhythmias and the rate of shock was similar to the patients included for primary prevention. On top of the different selection criteria, other trials did not always report strict ICD programming [88], had drug management fluctuations [90], mapping and ablation strategies were not uniform among centers [89,90].

An alternative design was proposed in the VANISH study [96], where patients with ischemic cardiomyopathy were randomized to catheter ablation or escalated drug therapy after failing amiodarone treatment, showing a significant benefit in the composite endpoint of death, VT storm or ICD shock in the ablation arm. Results were mainly driven by a reduction in VT recurrences. This trial targeted a population with a more advanced arrhythmia pattern, despite similar LVEF, as it included only patients in whom antiarrhythmic drug therapy failed, whereas in our group it was substantially banned.

Although in our series there were no complications reported, it is common knowledge that VT ablation is a complex procedure that might be related to complications and risks. From this perspective the time selection proposed in our study provides an efficient indication to treatment for patients with an active arrhythmia pattern, while avoiding potentially unnecessary prophylactic VT ablation procedures.

In spite of the high incidence (48%) of any ventricular arrhythmia in the study population, a striking minority was treated with an ICD shock (11%). The incidence of non-sustained VT was fairly high (28%), as a consequence of the long-time detection criteria that were uniformly adopted and strictly observed based on previously published trials [94,97]. Furthermore, the extensive utilization of ATP, both bursts and ramps, led to a very high number of ATPs that successfully terminated VT episodes without shocks. Aside from an ejection fraction below 35%, the only predictors of subsequent shocks were the delivery of any ATP treatment and effective ATP treatment. Among clinical variables we found that AF was not associated with VT shocks, nor were non-sustained ventricular tachycardias. The occurrence of NSVT with long detection intervals seems to be a benign finding that does not require specific treatment. On the other hand, any appropriate ATP or successful ATP were strong predictors of subsequent shock. It is estimated that every ATP intervention increased the risk of a shock by 4-6%.

For the first time, the PARTITA trial provides evidence that catheter ablation should be performed after the first ICD shock as it improves survival over a later referral in patients with ischemic and non-ischemic cardiomyopathy. Furthermore, as the number of ATP treatments is strongly predictive of subsequent shock treatment, future studies may aim at the evaluation of a threshold of ATP treatments that might warrant an ablation procedure.

There was a small number of randomized patients due to the lower-than-expected number of ICD shocks and this did not allow us to demonstrate a benefit for all the secondary endpoints. The rate of amiodarone therapy was very low, however it was still prescribed in cases of atrial arrhythmias, this might have affected the natural history of VT episodes and ICD therapy.

In conclusion, VT ablation after the first appropriate shock was associated with a reduced risk of the combined death or wHF hospitalization endpoint. Catheter ablation was also associated with lower recurrence of VTs treated by shock and lower mortality. These findings support a referral for VT ablation after the first ICD shock.

CHAPTER 4

REMOTE MONITORING DATA FROM IMPLANTABLE DEVICES: A PROPENSITY SCORE-MATCHED ANALYSIS

Summary

Objectives: To investigate sex-specific risk of sustained ventricular arrhythmias (SVA) and device therapies, by balancing sex groups in relation to several baseline characteristics with the propensity score (PS).

Background: Causes of sex differences in incidence of SVAs are poorly understood.

Methods: We used a large remote monitoring dataset from ICDs and CRT-Ds. Study endpoints were time to the first appropriate SVA, time to the first device therapy for SVA, and time to the first ICD shock. Results were compared between women and a PS-matched men subgroup.

Results: In a cohort of 2,532 patients with an ICD or CRT-D (median age, 70 years), 488 patients (19.3%) were women. After selecting 488 men PS-matched for 19 variables relative to baseline demographics, implant indications, principal comorbidities, and concomitant therapy, yet SVA rate in 2.1-year median follow-up was significantly lower in women than in man (adjusted HR, 0.65; 95% CI, 0.51-0.81; p<0.001). Women also showed a reduced risk of any device therapy (HR, 0.59; CI, 0.45-0.76; p<0.001) and shocks (HR, 0.66; CI, 0.47-0.94, p=0.021). Differences in sex-specific SVA risk profile were not confirmed in CRT-D patients (HR, 0.78; CI, 0.55-1.09; p=0.14) and in those with an ejection fraction <30% (HR, 0.80; CI, 0.52-1.23; p=0.31).

Conclusions: After matching demographics, indications, principal comorbidities, and concomitant therapy, women still exhibited a lower SVA risk profile than men, except in the subgroups of CRT-D or/and ejection fraction <30%.

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4.1 Introduction

ICD is an established therapy for the prevention of sudden cardiac death in selected patients [98]. Although current guidelines apply to both women and men, there is a growing awareness that the incidence of cardiac arrhythmias and device interventions is sex-dependent [99]. Reasons are poorly understood as women have been underrepresented in previous landmark trials on ICD and cardiac resynchronization therapy [100]. The design of randomized trials to assess sex differences in ICD prevention of sudden cardiac death poses unsolvable ethical and practical concerns. In this perspective PS matching methods are appealing, as they allow to control pre-specified confounding variables and efficiently reduce related bias. Balancing variables relative to demographics, device indication, comorbidities, concomitant therapy, would help clarify whether the observed sex-specific differences in incidence of ventricular arrhythmias are secondary to variable disproportions or further mechanisms still need to be investigated.

To examine sex-related differences in the incidence of ventricular arrhythmia and device therapy, we used a large dataset of RM data obtained daily from ICD and CRT-D devices, ensuring reporting of arrythmia occurrences, with no limitations relative to device memory storage capacity and in-hospital device interrogations. Potential confounding factors were then controlled by a women-to-men, 1:1 nearest neighbor PS method.

4.2 Methods

4.2.1 Study population and follow-up

The present analysis was designed by the first and last authors within the HMEA, an independent network of clinics using RM during routine follow-up of cardiac implantable electronic devices [101]. The data included in the analysis were collected from daily remote transmissions of the Home Monitoring system (BIOTRONIK, Berlin, Germany). The HMEA project was approved by competent ethics committees and all patients gave their written informed consent to data processing for research purposes.

Patients were included in the analysis if they had received a de novo ICD or CRT-D device for primary or secondary prevention of sudden cardiac death. Patient characteristics including demographic information, device indication, comorbidities, and medical therapy were collected at the time of ICD/CRT-D implantation. Devices were programmed according to clinical practice. Patients were classified as a high-rate (or a low-rate) therapy group if the first detection zone with therapies was programmed to ≥200 (or <200) beats/min.

Follow-up data were automatically generated by daily RM transmissions including atrial and ventricular electrograms and far field signal (sensed between right ventricular coil and device can) recorded upon detection of a SVA.

4.2.2 Study endpoints and adjudication of ventricular arrhythmia

The primary endpoint of the analysis was the time to the first appropriate post-implant SVA detection. Secondary endpoints were the time to the first appropriate device therapy (antitachycardia pacing or ICD shock, whichever came first) and to the first appropriate shock. The results were compared between women and men.

Two independent electrophysiologists adjudicated appropriateness of SVA detection while being blinded to patient characteristics and investigational site. In the event of disagreement, the vote of a third independent electrophysiologist was requested.

4.2.3 Statistics

Distributions of continuous variables were described as median (IQR) and compared between groups with the Wilcoxon rank-sum test. Binary and categorical variables were described as absolute and relative frequencies and compared with the Pearson's chi-square or Fisher's exact test.

The PS was based on 19 baseline variables: age, ICD/CRT-D device, New York Heart Association (NYHA) functional class, secondary prevention, ischemic etiology, congenital cardiomyopathy, left ventricular ejection fraction (LVEF), QRS duration, hypertension, diabetes, chronic obstructive pulmonary disease, stroke or transient ischemic attack, renal dysfunction, history of atrial fibrillation, beta-blocker, angiotensin-converting enzyme and/or angiotensin II receptors blocker, diuretic, amiodarone, and high-rate therapy programming. After verifying a satisfactory common support between women and men (Figure 4.1), a PS-based 1:1 match was performed with the nearest-neighbor method to control for potential confounders in the selected men subset. After PS matching, the absolute between-group standardized mean difference was verified for all baseline variables.

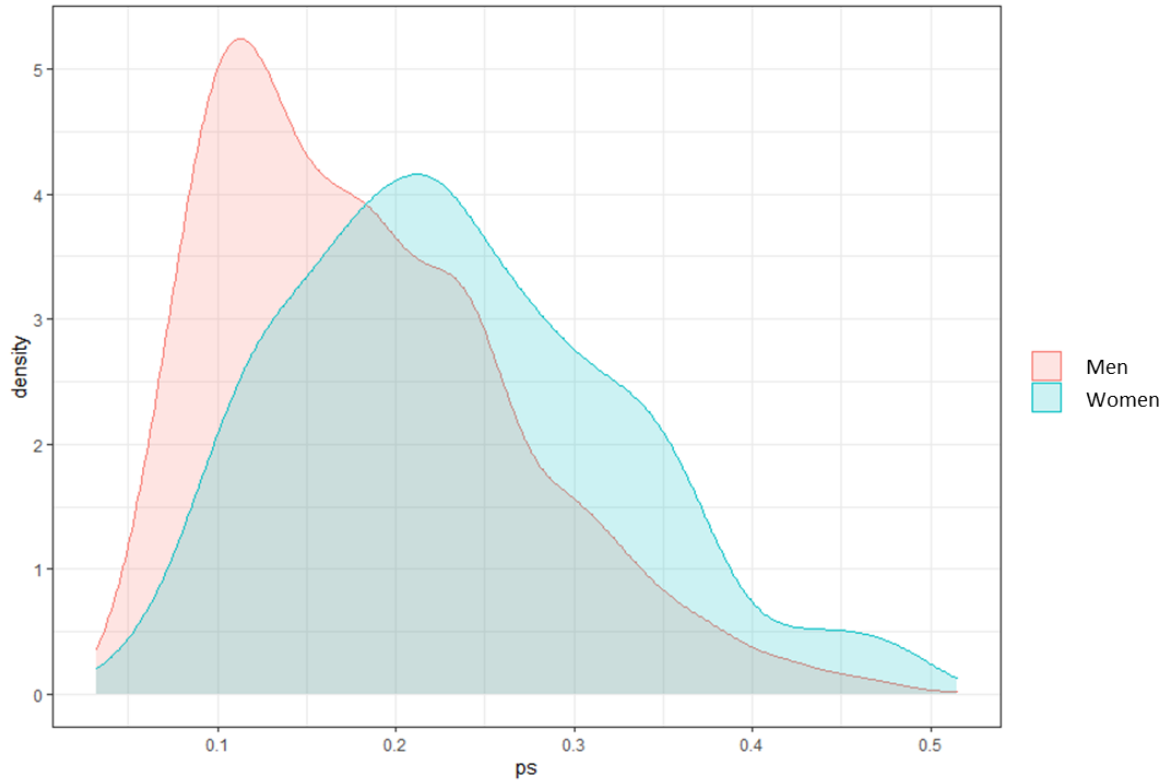

Figure 4.1: Common support of propensity score between women and men.

KM plots were generated for study endpoints, reporting free rate estimates with the 95% CI. HRs of endpoint events in women versus men were estimated using both the PS-matched and unmatched men groups for univariable and multivariable proportional hazard Cox regressions. Age, secondary prevention, ischemic etiology, ICD/CRT-D, and LVEF were further used as adjusting covariates. All tests were considered significant with a p-value <0.05. Packages MatchIt and survival of the R Studio software version 4.0.3 were used for the analysis.

4.3 Results

4.3.1 Baseline characteristics

A total of 2,532 patients with a median age of 70 years (IQR, 60-77) met the selection criteria, 488 (19.3%) were women and 2,044 (80.7%) were men. As compared to men, women had a higher prevalence of CRT-D devices (51% vs. 40%, p<0.001), more frequent diagnosis of non-ischemic cardiomyopathy (65% vs. 45%, p<0.001), and more advanced NYHA functional class (p=0.037). Device programming did not differ significantly between groups with a high-rate therapy setting used in about 40% of patients. A median detection counter was set to 28 beats for ventricular tachycardia zones and “16 out of 20” for ventricular fibrillation zone.

PS-matching identified a subset of 488 males showing an absolute standardized mean difference of <0.1 in all baseline variables (Figure 4.2).

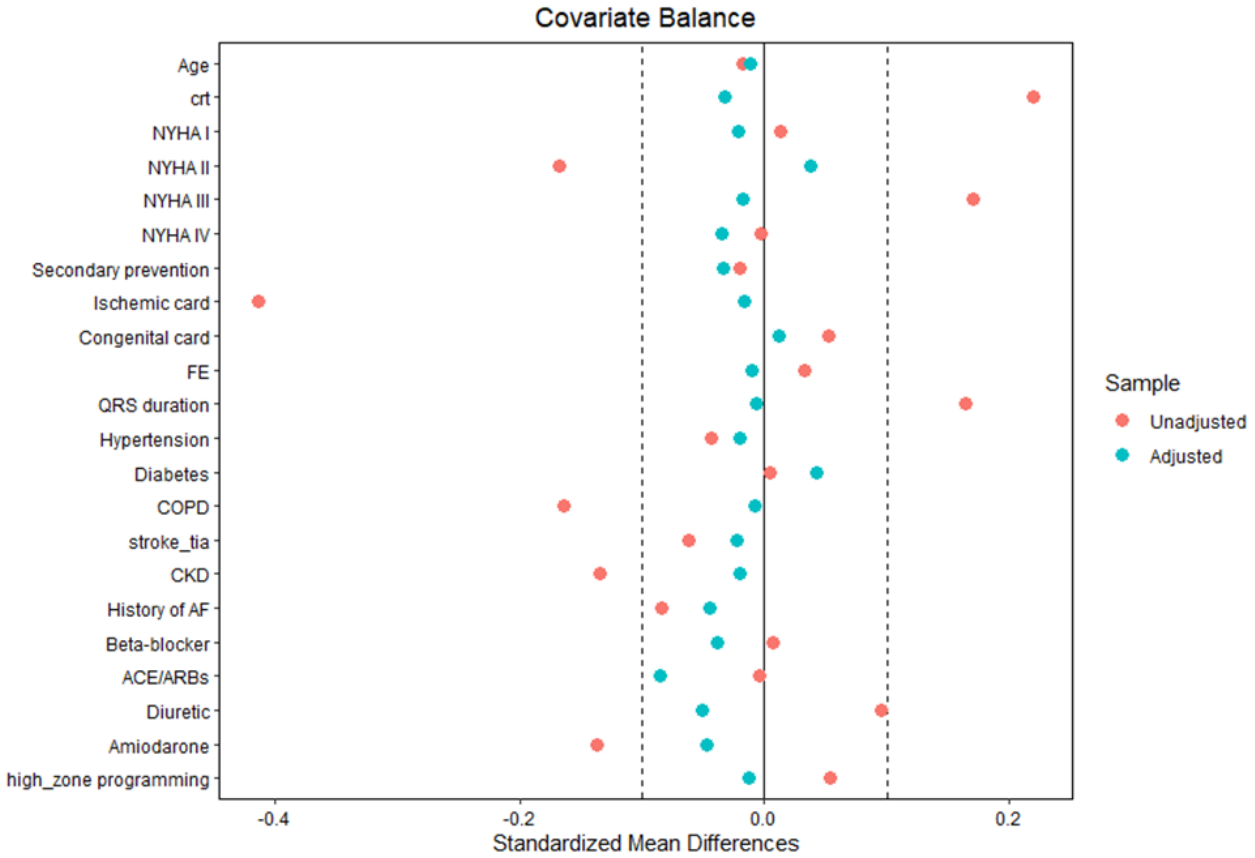

Figure 4.2: Absolute mean differences for the propensity score variables before matching ("Unadjusted") and after the matching ("Adjusted"). A 1:1 match identified a subset of 488 males showing <0.1 absolute standardized mean difference in all baseline variables.

Baseline patient characteristics are detailed in Table 4.1 for all study groups.

Table 4.1**:** Comorbidities, baseline, and device characteristics at implant.

Characteristic	**All patients,** N = 2,532	**Women,** N = 488	**Men,** N = 2,044	**p-value**	**PS-matched men group,** N = 488	**p-value**
Age, years	70 (60-77)	70 (59-78)	69 (61-77)	0.74	69 (60-76)	0.78
Device				<0.001		0.62
ICD	58%	49%	60%		47%	
CRT-D	42%	51%	40%		53%	
NYHA class				0.037		0.92
I	10%	10%	10%		10%	
II	62%	55%	63%		54%	
III	28%	34%	26%		34%	
IV	1%	1%	1%		2%	
Prevention				0.72		0.68
Primary	84%	85%	84%		83%	
Secondary	16%	15%	16%		17%	
Cardiomyopathy				<0.001		0.80
Non-ischemic	49%	65%	45%		63%	
Ischemic	49%	31%	53%		34%	
Non-ischemic genetic	2%	4%	2%		3%	
LVEF, %	30 (26-35)	30 (25.5-35)	30 (26-35)	0.44	30 (28-35)	0.13

QRS duration, ms	120 (100-140)	130 (104-150)	120 (100-140)	<0.001	126 (100-146)	0.90
Comorbidities						
Hypertension	52%	52%	52%	0.95	51%	0.76
Diabetes	24%	24%	24%	0.93	24%	0.55
COPD	11%	8%	11%	0.06	8%	0.92
Stroke/TIA	9%	7%	9%	0.22	9%	0.76
CKD	13%	10%	13%	0.07	11%	0.83
History of AF	24%	20%	25%	0.07	23%	0.56
Medications						
Beta-blocker	78%	81%	78%	0.2	78%	0.82
ACE/ARBs	64%	66%	63%	0.4	67%	0.28
Diuretic	72%	77%	71%	0.022	76%	0.44
Amiodarone	13%	9%	14%	0.023	12%	0.52
High-rate therapy programming[1]	41%	43%	40%	0.38	44%	0.86
Follow-up, years	2.1 (1.1-3.7)	2.0 (1.0-3.6)	2.1 (1.1-3.8)	0.26	2.3 (1.2-3.9)	0.08

Data are shown as median (interquartile range) or relative frequency (%). P-values were determined by Wilcoxon rank-sum test, chi-square test of independence, or Fisher's exact test, as appropriate.
[1]First therapy zone ≥200 beats/min.
Abbreviations: ACE, angiotensin-converting enzyme; AF, atrial fibrillation; ARBs, angiotensin II receptors blockers; COPD, chronic obstructive pulmonary disease; CKD, chronic kidney disease; CRT-D, cardiac resynchronization therapy defibrillator; ICD, implantable cardioverter-defibrillator; LVEF, left ventricular ejection fraction; NYHA, New York Heart Association; PS, propensity score; TIA, transient ischemic attack.

4.3.2 Primary endpoint

The median post-implant follow-up period was 2.1 years (IQR, 1.1-3.7), with no significant differences among all groups. In the adjudication of 1,045 intracardiac electrogram recordings, unanimity was achieved in 92.9% with a between-adjudicators concordance coefficient of 0.54. After exclusion of inappropriate episodes, SVA occurrence was confirmed in 123 women (25.2%), 748 men (31.6%), and in 174 PS-matched men (35.6%). The product-limit estimate of 3-year SVA-free rate was 72.4% (CI, 67.5%-77.5%) in women, 61.9% (CI, 59.3%-64.7%) in the unmatched men group, and 57.8% (CI, 52.5%-63.7%) in the PS-matched men group. Adjusted HRs of SVA occurrence in women were 0.68 (CI, 0.53-0.86, p=0.0018) versus unmatched men, and 0.65 (CI, 0.51-0.81; p=0.0002) versus the PS-matched men group. Individual contribution of adjusting covariates is reported in Table 4.2. Kaplan-Meier plots for the primary endpoint in women and men are shown in Figure 4.3, panel A.

Table 4.2: Hazard ratios with 95% confidence intervals from univariable and multivariable Cox proportional hazard models fitted for the different endpoints in the entire cohort and in the propensity score-matched subgroup.

	Women vs. unmatched men		**Women vs. PS-matched men**	
Cox model	**Univariable**	**Multivariable**	**Univariable**	**Multivariable**
Sustained ventricular arrhythmia (primary endpoint)				
Female sex	0.75 (0.61-0.90), p=0.0029	0.68 (0.53-0.86), p=0.0018	0.65 (0.51-0.81), p=0.0002	0.65 (0.51-0.81), p = 0.0002
Adjusting variables				
Age	-	1.00 (0.99-1.01), p=0.69	-	1.00 (0.99-1.01), p=0.82

Secondary prevention	-	2.08 (1.70-2.56), p<0.0001	-	1.55 (1.14-2.09), p=0.004
Ischemic etiology	-	0.96 (0.80-1.16), p=0.71	-	1.10 (0.86-1.40), p=0.45
CRT-D	-	0.96 (0.79-1.16), p=0.66	-	0.82 (0.64-1.06), p=0.13
LVEF%	-	0.98 (0.97-0.99), p=0.0017	-	0.98 (0.97-1.00), p=0.055
Appropriate device therapy				
Female sex	0.66 (0.53-0.82), p=0.0002	0.59 (0.45-0.78), p=0.0002	0.58 (0.45-0.75), p<0.0001	0.59 (0.45-0.76), p<0.0001
Adjusting covariates				
Age	-	1.00 (0.99-1.01), p=0.33	-	1.00 (0.99-1.01), p=0.48
Secondary prevention	-	2.03 (1.63-2.53), p<0.0001	-	1.68 (1.22-2.33), p=0.001
Ischemic etiology	-	0.88 (0.72-1.07), p=0.19	-	0.98 (0.75-1.29), p=0.92
CRT-D	-	0.95 (0.77-1.17), p=0.65	-	0.75 (0.57-0.99), p=0.041
LVEF%	-	0.98 (0.97-0.99), p=0.005	-	0.98 (0.97-0.99), p=0.014
Appropriate shock				
Female sex	0.73 (0.54-0.98), p=0.035	0.62 (0.43-0.91), p=0.014	0.65 (0.46-0.92), p=0.015	0.66 (0.47-0.94), p=0.021
Adjusting covariates				
Age		0.99 (0.98-1.01), p=0.88	-	1.00 (0.99-1.02), p=0.56
Secondary prevention		2.37 (1.78-3.16), p<0.0001	-	1.72 (1.12-2.65), p=0.013
Ischemic etiology		0.93 (0.71-1.22), p=0.61	-	1.04 (0.73-1.50), p=0.82
CRT-D		0.99 (0.74-1.31), p=0.93	-	0.79 (0.54-1.15), p=0.22
LVEF%		0.98 (0.96-0.99), p=0.003	-	0.98 (0.96-0.99), p=0.043

Abbreviations: CRT-D, cardiac resynchronization therapy defibrillator; LVEF, left ventricular ejection fraction; PS, propensity score.

Appropriate device therapies occurred in 96 women (21.4%), in 566 men (27.7%), and in 152 PS-matched men (31.1%). Appropriate shocks were delivered in 52 women (11.6%), 296 men (14.5%), and 79 PS-matched men (16.2%).

The adjusted HR estimates of therapy delivery in women were 0.59 (CI, 0.45 - 0.78; p=0.0002) versus unmatched men, and 0.59 (CI, 0.45-0.76; p<0.0001) versus PS-matched men. Estimates for shock HRs in women versus unmatched men were 0.62 (CI, 0.43 - 0.91; p=0.014), 0.66 (CI, 0.47-0.94; p=0.021) versus PS-matched men. More details about the univariable and multivariable models and contributions of individual covariates are provided in Table 4.2. Figures 4.3, panel B and C, shows the Kaplan-Meier curves for the secondary endpoints in women and men groups.

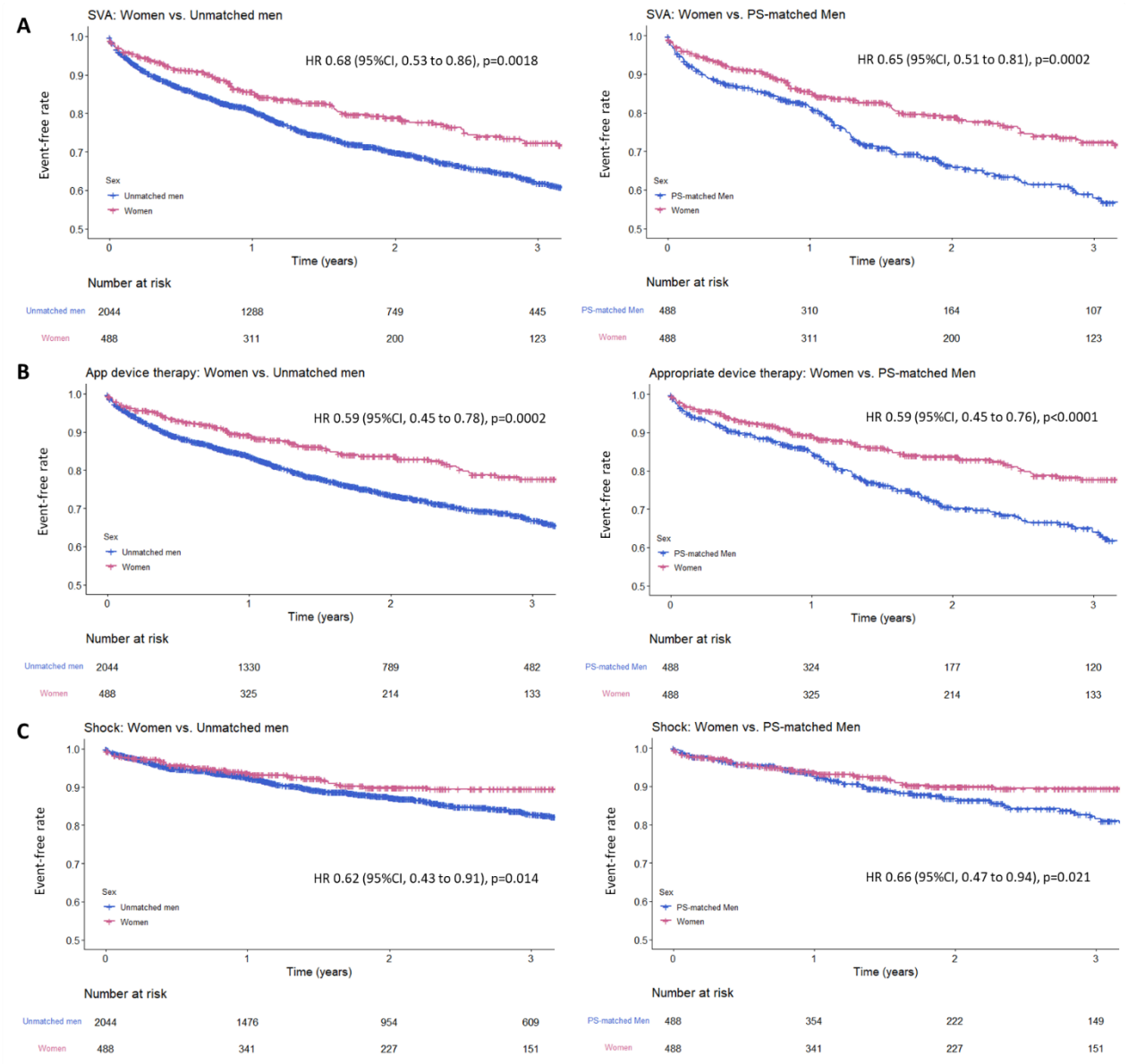

Figure 4.3: Kaplan-Meier curves comparing proportions of patients free from sustained ventricular arrhythmia (A), appropriate device therapy (B), and appropriate shock (C). HR, hazard ratio; PS, propensity score; SVA, sustained ventricular arrhythmia.

4.3.3 Subgroup analysis

The analysis primary endpoints in ICD/CRT-D and ≥/<30% LVEF subgroups revealed some differences in sex-specific SVA incidence (Figure 4.4).

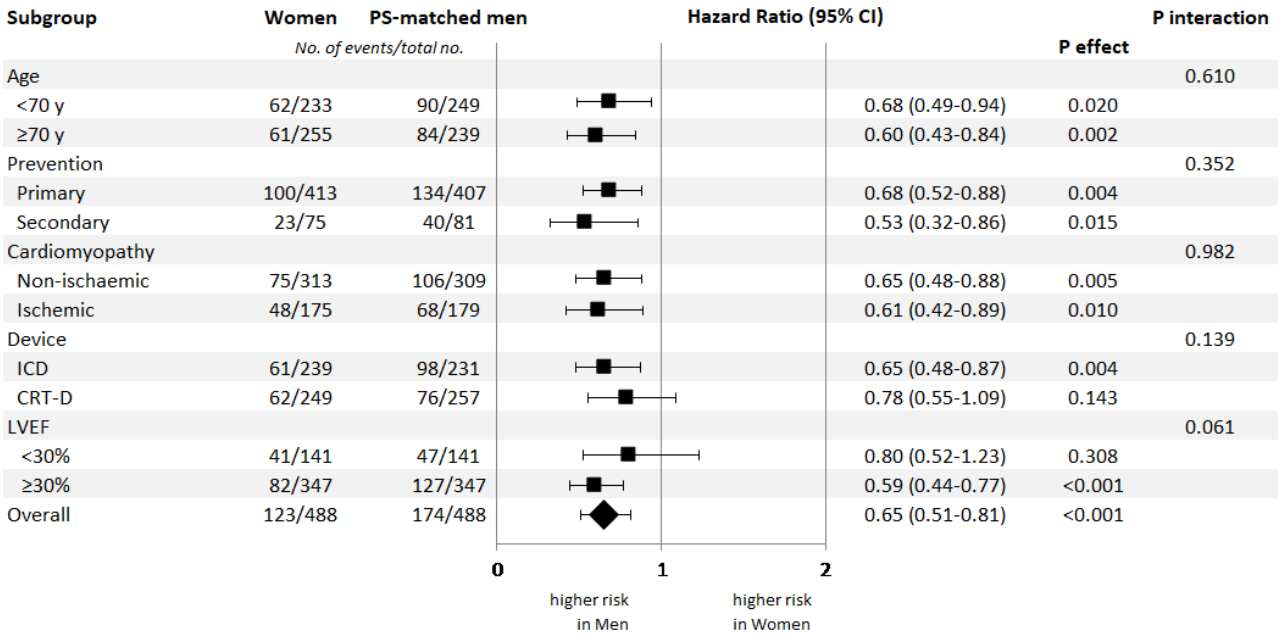

Figure 4.4: Subgroup analyses of the primary endpoint (Forest plot). Hazard ratios are based on Cox proportional hazard model and propensity score-matched analysis. CRT-D, cardiac resynchronization therapy defibrillator; ICD, implantable cardioverter-defibrillator; LVEF, left ventricular ejection fraction; PS, propensity score; SVA, sustained ventricular arrhythmia.

Indeed, by comparing women with the PS-matched men group, a lower risk of SVA for women was confirmed in the ICD subgroup (HR, 0.65; CI, 0.48-0.87; p=0.004), but not in the CRT-D subgroup (HR, 0.78; CI, 0.55-1.09; p=0.143). Indeed, the Kaplan-Meier curves of CRT-D women (Figure 4.5, upper panel) start diverging PS-matched men curves only after 1 year of follow-up.

Similarly, the risk of SVA was significantly lower in women with LVEF ≥30% (HR 0.59; CI, 0.44-0.77; p<0.001), but not in women with LVEF <30% (HR, 0.80; CI, 0.52-1.23; p=0.308). The survival Kaplan-Meier curves for the LVEF subgroups are shown in Figure 4.5 (bottom panel).

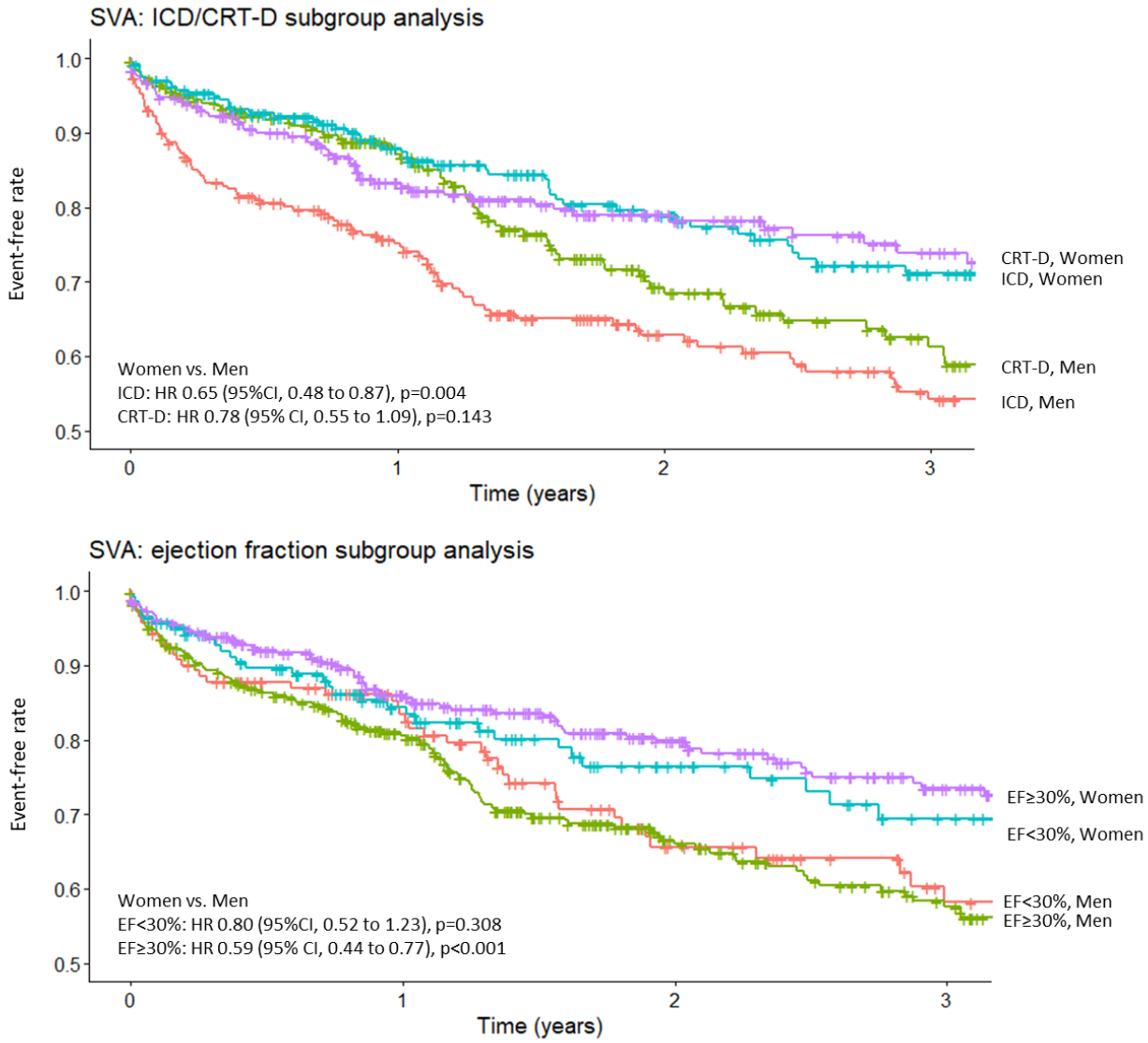

Figure 4.5: Kaplan-Meier curves comparing proportions of patients free from sustained ventricular arrhythmia in women and PS-matched men by device (ICD or CRT-D) and left ventricle ejection fraction (<30% or ≥30%). CRT-D, cardiac resynchronization therapy defibrillator; EF, left ventricular ejection fraction; HR, hazard ratio; ICD, implantable cardioverter-defibrillator; PS, propensity score; SVA, sustained ventricular arrhythmia.

4.4 Discussion

In our analysis of multicenter RM data, women still exhibited a 35% lower risk of ventricular arrhythmias and a 41% lower risk of appropriate ICD therapies than their male counterparts after balancing study groups by major baseline variables relative to demographics, device indication, comorbidities, and therapy, with the PS method. By direct comparison with results of unmatched analyses, these variables may only account for up to 4% of the effect on SVA, therapy, and shock incidence to be ascribed to sex difference.

Conflicting results have been published on the role of sex in the risk of ventricular arrhythmias and ICD therapies, with some studies reporting non-significant differences [102,103] and others showing a sex-specific risk stratification [104-106]. A possible reason for heterogeneity of results could be differences in clinical profile between women and men, which could have caused biased estimates even in large observational studies. Subanalyses of the DEFINITE [107], SCD-HeFT [108], and MADIT CRT [109] randomized clinical trials only showed a trend to less appropriate shocks in women. Again, the underrepresentation of women in those cohorts (with proportions ranging from 16% to 29%) and substantial differences in baseline characteristics may have reduced available statistical power for such analysis. In fact, in a MADIT II subanalysis [110], the incidence of appropriate device therapies was lower in women after adjusting for clinical covariates.

Consistently with previous reports, we observed different baseline characteristics between women and men undergoing device implantation. First, women represented only a marked minority of device recipients also in our cohort (about 20%), to be suspected of some unrevealed sex disparity in implantation rates in ordinary practice [104]. Second, women had a lower prevalence of ischemic cardiomyopathy (31% versus 53%) which may be partly related to differences in underlying substrate, knowing that men generally present with more extensive scar formation [111]. Finally, women showed higher prevalence of CRT-D implantations (51% versus 40%) and more advanced heart failure, which may be consistent with delayed referral to heart failure specialists and device implantation at a more severe disease stage when an ICD is not sufficient [112]. Nevertheless, our results are less prone to limitations relative to imbalances in sample size and uncontrolled confounders, as PS matching allowed reducing percent bias of 19 pre-specified variables by 70% on average and to less than 9% individually (Figure 4.2).

We can only speculate on the mechanisms underlying sex specific differences observed in the arrhythmic risk profile. A lower inducibility of SVA during electrophysiological study has been previously observed in women who survived cardiac arrest or had a history of coronary artery disease, suggesting lower susceptibility to SVA regardless of ischemic cardiomyopathy [113,114]. Consistently, we did not observe sex-specific different SVA risk in ischemic versus non-ischemic cardiomyopathy subgroups, and in primary versus secondary prevention subgroups (Figure 4.4). Potential explanations may be related to cardiac electrophysiological properties, autonomic tone, response to stress, and hormonal regulation that may differently affect arrhythmic vulnerability in women and men [115]. Also, anatomical differences between women and men are well known at cardiac level. The left ventricular size is significantly smaller in women, with a reduced number of reentrant propagating electrical waves and a less susceptible substrate [116]. Finally, other less quantifiable factors, including adherence to a low-risk lifestyle, psychological factors, and patient

care decisions may also play a role. Any study design should ensure that these and other potential factors are sufficiently controlled during data collection. Also, measures to mitigate risk of women under-representation in study cohorts should be pre-specified, including efforts to recruit women researchers among study staff.

Identifying women at high risk for malignant arrythmias remains challenging but is of great importance. Our findings showed that arrhythmia risk reduction in women was significant in the ICD group, but not in the CRT-D group, in whom the Kaplan-Meier curves started diverging 1 year after implantation. This may be related to the antiarrhythmic contribution of left ventricular reverse remodeling induced by cardiac resynchronization [117], more frequently seen in women [118] and typically achieved in months after implant.

In our cohort, the lower incidence of all study endpoints in women was primarily driven by the group of patients with ≥30% baseline LVEF. In patients with a LVEF <30%, the risk of SVA did not differ between men and women, as the dominant effect of severely reduced LVEF may have overshadowed sex-related differences. This further emphasizes the importance of adequate risk-stratification when investigating sex-related differences and supports the recommendations to represent women more extensively in future clinical trials [100].

Our analysis was retrospective. To minimize inherent limitations, we used RM data to exclude underreporting of endpoint events related to missing device interrogation and storage capacity. To efficiently mitigate cohort heterogeneity and biases from confounding factors, we used the PS method, which is particularly convenient in investigations on sex-specific effects, when ethical and practical concerns hinder randomized study designs. Our findings may be somewhat limited by the relatively short follow-up duration (median 2.1 years) and even affected by sex-specific differences in overall survival. However, analysis of residuals in our models did not reveal any suspected trend of time-dependent differences in arrhythmic risk between women and men. All results were obtained with devices of a single manufacturer which helped reduce some heterogeneities in our analysis, but it is in itself a limitation. Future prospective or retrospective studies should include all available device manufacturers and programming variabilities. Finally, scar evaluation by magnetic resonance imaging was not systematically available in our cohort, although it could have provided important insights for risk stratification [119].

In conclusion, this multicenter retrospective analysis of a large RM dataset from ICDs and CRT-Ds confirmed that women still represents a marked minority of device recipients. Significantly lower risks of SVAs, appropriate device therapies, and shocks were observed in women as compared to men, after controlling for major demographics, device indication, comorbidities, and concomitant

therapies with the PS method. Difference in SVA risks did not reach statistical significance in the subgroup of patients with CRT-D devices and/or severely reduced LVEF. Our findings warrant further investigations to identify mechanisms underlying sex-specific differences in arrhythmic risk profiles and highlight the importance of more accurate methods to control sex disparities in study design and conduct.

CHAPTER 5

MACHINE LEARNING TECHNIQUES: IMPLEMENTATION OF A CLASSIFICATION AND REGRESSION TREE (CART)

Summary

Background: In the PARTITA trial ATP predicted the occurrence of appropriate ICD shocks and catheter ablation of VT after the first shock reduced the risk of death or wHF. However, a threshold of ATP treatments and specific clinical features that might warrant an ablation procedure before ICD shocks are unknown. We aimed to identify a threshold of ATPs and clinical features to predict the occurrence of shocks and major CV events.

Methods: We analyzed data from 517 patients enrolled in phase A of the PARTITA study, from ICD implantation to the first appropriate shock for VT. We used classification and regression tree (CART) analysis to develop and test a risk stratification model based on the natural history of arrhythmias and clinical data to predict the likelihood of ICD shocks. Secondary endpoints were wHF leading to hospitalization and any CV hospitalization.

Results: The final CART classified patients into six leaves characterized by increasing shock probability. We have identified that patients who were treated with ≥5 ATPs in 6 months, defined as the 'active arrhythmia pattern' group, had the highest risk of experiencing an appropriate ICD shock (93% and 86% in the training and testing sample, respectively). Conversely, patients without any appropriate ATP had the lowest risk (1% and 2%). The other predictors were related to clinical variables, including left LVEF <35%, an age <60 years and a body mass index ≥30. The survival analysis revealed a significantly higher risk of both wHF (HR 5.45, 95% CI 1.62-18.4, p=0.006) and CV hospitalization (HR 7.29, 95% CI 3.66-14.5, p<0.001) for patients with an active arrhythmic pattern compared to those with no ATPs.

Conclusions: Patients with an active arrhythmia pattern (≥5ATPs in 6 months) have an increased risk of ICD shocks, wHF hospitalization and CV hospitalization. Catheter ablation could be proposed to this highrisk group as a preventive strategy to reduce the incidence of major events. Other risk factors such as low LVEF, younger age and obesity should also be accounted for when considering catheter ablation.

This chapter is under review in an international peer-reviewed journal:

Radinovic A, Giacopelli D, Bisceglia C, Paglino G, Gargaro A, Della Bella P. Active arrhythmia pattern: a novel predictor of ICD shocks. A sub analysis from the PARTITA study. [Under review]

5.1 Introduction

ICD shocks are associated with an increased risk of mortality [120-123] and progression in heart failure [120, 124]. The PARTITA trial [125] investigated the prognostic impact of catheter ablation after the first ICD shock in patients with ischemic and non-ischemic cardiomyopathy. Randomization of patients to catheter ablation was associated with a reduction of recurrent VTs requiring shock treatment and a subsequent reduction of mortality or wHF that led to hospitalization. The occurrence of appropriate ICD shocks was predicted by VT episodes treated by ATP. However, a threshold of ATP treatments and specific clinical features that might warrant an ablation procedure before ICD shocks are unknown. In this PARTITA sub study, we used machine learning algorithms, based on the natural history of arrhythmias and clinical data, to develop a risk stratification model to predict the occurrence of shock, wHF and CV hospitalization. We aimed to identify specific patterns that could indicate an early catheter ablation strategy to prevent major cardiovascular events.

5.2 Methods

5.2.1 Objective and study end points

We analyzed data only from phase A of the PARTITA study. The primary end point was the first appropriate shock delivered for VT. Our objective was to develop and test a straightforward and easily interpretable risk stratification model using CART analysis to predict the likelihood of shock occurrence in ICD recipients. Secondary end points were worsening HF leading to hospitalization and any CV hospitalization.

5.2.2 Risk Model and Statistics

Tree-based methods are powerful and robust machine learning algorithms that can identify clinically important factors associated with the outcome of interest [14]. To identify subgroups at risk for VT treated with shock, and determine the cut-off values for significant risk predictors, we used CART analysis. This method has a user-friendly way of showing findings that can be easily applied to routine practice.

The original dataset was randomly divided into two parts: the training sample (70% of the study cohort), used to construct the CART, and the test sample (30% of the study cohort), used to provide an unbiased estimate of the model's predictive performance. We analyzed a large number of variables to construct the predictive model using CART, including age, sex, hypertension, diabetes, chronic

renal failure, obesity (body mass index >30 Kg/m2), drug therapy, secondary prevention indication, ischemic cardiomyopathy, ischemic cardiomyopathy with infarction, left ventricle ejection fraction. Among the relevant arrhythmic features we evaluated: CRT, history of AF, number of non-sustained VT episodes before shock, and 6-month rate of VT episodes treated with ATP before shock. At each node, the algorithm selected the variable with the greatest discriminatory power between the two outcome groups (first appropriate shock delivered or not delivered). The CART algorithm adds nodes until they are homogenous or contain few observations (leaves). In the training sample, the pruning of the tree was achieved by identifying the complexity parameter that minimized the misclassification error of the predictive model estimated by tenfold cross-validation approach. The model's predictive performance was evaluated by calculating overall accuracy, sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) in the training and test samples. The receiver operating characteristic curve was then plotted, reporting the area under the curve (AUC). We generated Kaplan-Meier survival curves for the secondary end points by the risk groups identified by the leaves of the model and reported HRs and 95% CIs using leaf 1 as reference.

Continuous variables are presented as mean ± standard deviation or median (interquartile range [IQR]) and compared using the Mann-Whitney U test. Categorical variables are presented by absolute and relative frequencies and compared with the $\chi 2$ test or Fisher exact test. We also generated univariable Cox proportional hazard models for the occurrence of shock for the independent variables included in the CART analysis.

All analyses were performed with STATA 17SE software version (StataCorp LP, TX, USA) and R version 4.0.3, and CART analysis was implemented using the R packages 'rpart' and 'caret'.

5.3 Results

5.3.1 Study Population and Primary End point incidence

The study enrolled 517 patients who were followed in phase A for a median of 2.4 years (IQR, 1.4, 4.4). The patients had a mean age was 67.3±10 years, and 87% of them were men. During study follow-up, 145 patients (28.0%) had non-sustained VT episodes, and 112 (21.7%) received ATP therapy for sustained VT. The mean ATP event rate in these patients was 0.8 (0.4-4.2) per patient-year. The primary end point of first appropriate shock delivered for VT, occurred in 56 patients (10.8%). The product-limit survival estimate from shock was 92% (95% CI, 90%-95%) at 2 years and 87% (84%-91%) at 4 years (Figure 5.1).

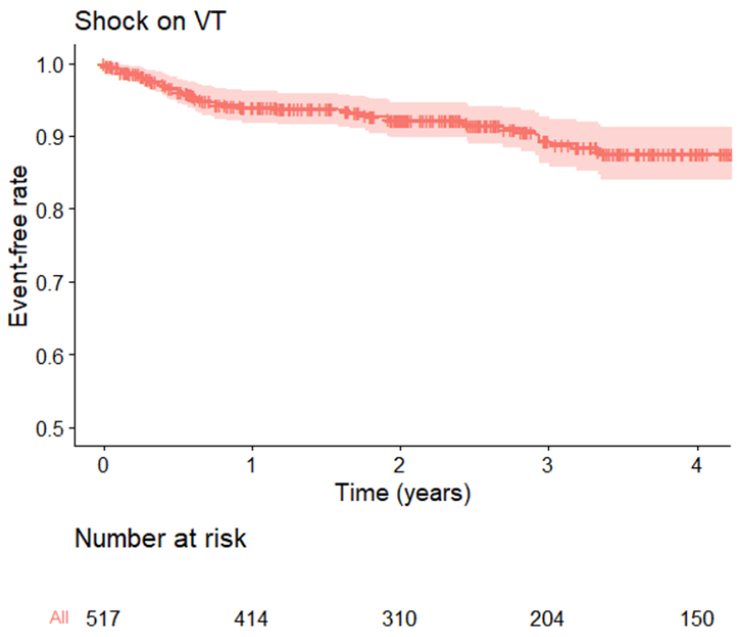

Figure 5.1: Kaplan-Meier survival curve of shock on ventricular tachycardia (VT) in the overall study cohort with 95% confidence interval.

Table 5.1 reports the patients' characteristics by the occurrence of shock. No significant differences were observed except for a tendency of lower left ventricle ejection fraction in patients with shock (31.6%±8.3% vs. 34.3%±9.6%, p = 0.073).

Table 5.1: Baseline patients' characteristics by occurrence of appropriate shock on ventricular tachycardia.

	Overall (N=517)	**First appropriate shock delivered (N=56)**	**First appropriate shock not delivered (N=461)**	**p-value***
Male	449 (87%)	48 (86%)	401 (87%)	0.8
Age (years)	67.3 (10.7)	67.2 (10.9)	67.6 (9.6)	>0.9
NYHA				0.8
Class I	95 (20%)	9 (17%)	86 (21%)	
Class II	291 (62%)	36 (68%)	255 (61%)	
Class III	82 (17%)	8 (15%)	74 (18%)	
Class IV	1 (0.2%)	0 (0%)	1 (0.2%)	
LV Ejection Fraction (%)	34.0 (9.5)	31.6 (8.3)	34.3 (9.6)	0.073
QRS duration (ms)	120.8 (31.1)	122.3 (29.4)	120.6 (31.3)	0.8
Device				0.5
Single-chamber ICD	177 (35%)	19 (34%)	158 (35%)	
Dual-chamber ICD	209 (41%)	20 (36%)	189 (42%)	
CRT-D	123 (24%)	17 (30%)	106 (23%)	
ICD Indication				0.4
Primary prevention	403 (79%)	42 (75%)	361 (80%)	
Secondary prevention	107 (21%)	14 (25%)	93 (20%)	
Cardiomyopathy				0.4
Ischemic with Infarction	351 (69%)	44 (79%)	307 (67%)	
Ischemic without Infarction	46 (9.0%)	2 (3.6%)	44 (9.6%)	
Idiopathic dilated	114 (22%)	10 (18%)	104 (23%)	
Comorbidities				
Hypertension	355 (77%)	39 (76%)	316 (77%)	>0.9
Diabetes	165 (36%)	16 (31%)	149 (36%)	0.5

Obesity	90 (20%)	13 (25%)	77 (19%)	0.3
Chronic renal failure	66 (14%)	9 (18%)	57 (14%)	0.5
COPD	50 (11%)	8 (16%)	42 (10%)	0.2
Stroke/TIA	37 (8.1%)	3 (5.9%)	34 (8.3%)	0.8
Liver disease	28 (6.1%)	4 (7.8%)	24 (5.9%)	0.5
History of atrial fibrillation	144 (29%)	21 (37%)	123 (27%)	0.112
Drug therapy				
ACE inhibitors	327 (67%)	37 (66%)	290 (67%)	>0.9
Anticoagulants	154 (31%)	25 (45%)	129 (30%)	0.024
ARBs	79 (16%)	8 (14%)	71 (16%)	0.7
Aspirin	326 (67%)	36 (64%)	290 (67%)	0.7
Betablockers	423 (97%)	48 (100%)	375 (96%)	0.4
Diuretics	381 (78%)	48 (86%)	333 (77%)	0.13
Statins	343 (70%)	42 (75%)	301 (69%)	0.4
Amiodarone	56 (13%)	7 (15%)	49 (13%)	0.7

Values are mean (standard deviation) or n (%). ACE indicates angiotensin-converting enzyme; ARB, angiotensin receptor blocker; COPD, chronic obstructive pulmonary disease; CRT-D, cardiac resynchronization therapy defibrillator; ICD, implantable cardioverter defibrillator; LV, left ventricle; NYHA, New York Heart Association; and TIA, transient ischemic attack.
*Wilcoxon rank sum test, Pearson $\chi 2$ test, or Fisher exact test.

At univariable Cox regression analysis (Table 5.2), none of patient or disease-related variables predicted appropriate shock delivery for VT (except for LVEF <35%), whereas each ATP delivery were associated with 5% increased risk of subsequent appropriate shock.

Table 5.2: Cox proportional hazard model for occurrence of appropriate shock on ventricular tachycardia.

Variables	**HR**	**95% CI**	**P value**
Patient-dependent			
Age (years)	1.01	0.99-1.04	0.330
Male	0.84	0.39-1.81	0.650
Diabetes	0.89	0.49-1.60	0.688
Chronic renal failure	1.45	0.66-3.19	0.342
Amiodarone intake	1.14	0.49-2.66	0.761
Disease-dependent			
Secondary prevention	1.14	0.61-2.11	0.683
Previous infarction	1.70	0.89-3.28	0.107
LV injection fraction (%) <35%	1.77	1.00-3.14	**0.049**
QRS duration >120 ms	0.91	0.47-1.79	0.782
CRT-D	1.53	0.85-2.74	0.153
History of AF	1.18	0.54-2.58	0.652
Arrhythmic findings			
Number of NSVTs	1.00	0.99-1.01	0.612
Number of VT episodes treated with ATP	1.05	1.04-1.07	**<0.001**

AF indicates atrial fibrillation; ATP, antitachycardia pacing; CRT-D, cardiac resynchronization therapy defibrillator; HR, hazard ratio; LV, left ventricular; and NSVT, nonsustained ventricular tachycardia.

5.3.2 Classification Tree Model

The CART model developed in the training sample is presented in Figure 5.2. The best complexity parameter that minimized the misclassification error of model by tenfold cross-validation approach was 0.039 (Figure 5.3). The final CART had five layers and 6 leaves that identified an increasing shock probability ranging from 1% (leaf 1) to 93% (leaf 6). The first two splits were based on the occurrence of VT episodes treated with ATP and on the burden of delivered ATPs, with a cut-off

value of ≥5 episodes in 6 months, which was defined as an active arrhythmic pattern. The following splits were related to clinical variables, including left ventricle ejection fraction, age, and obesity. The highest probability of shock (93%) was observed in Leaf 6, which included patients with an active arrhythmia pattern (≥5ATPs in 6 months) only.

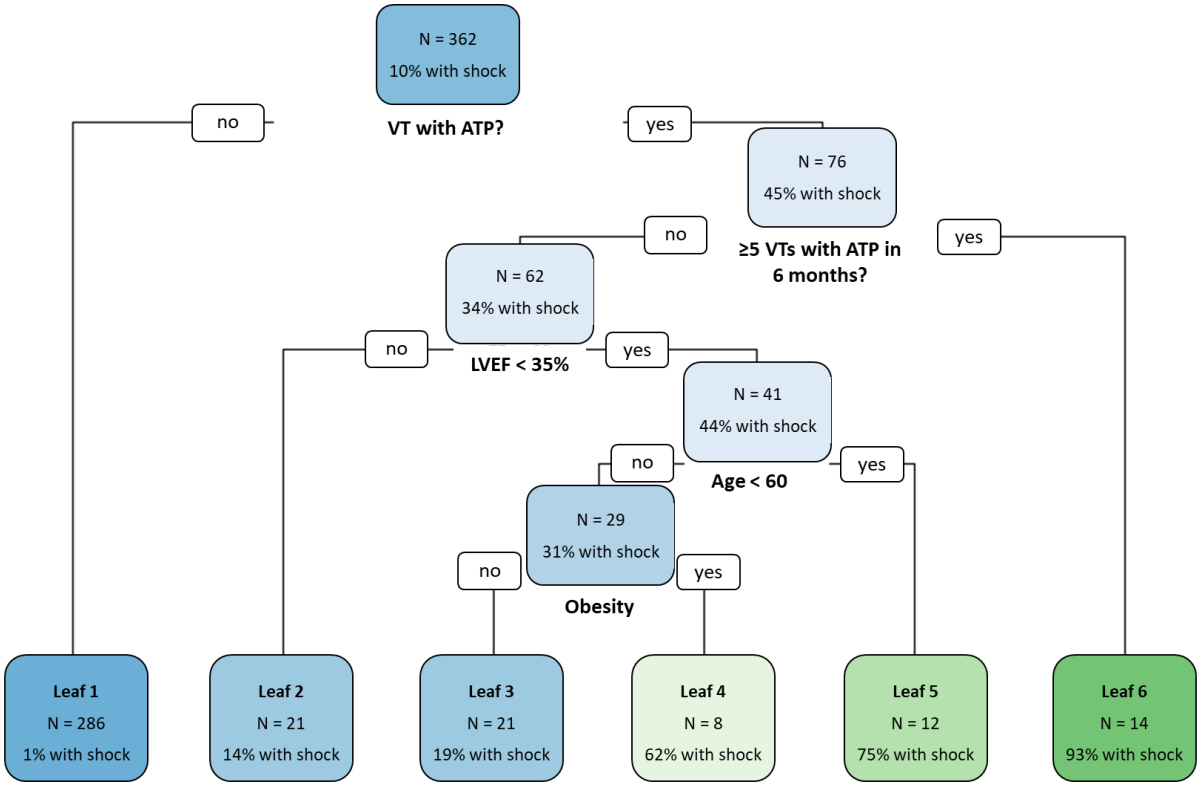

Figure 5.2: Classification tree with 6 leaves for predicting occurrence of appropriate shock for ventricular tachycardia developed in the training sample. The number of patients (N) and the probability of shock are shown at each node.

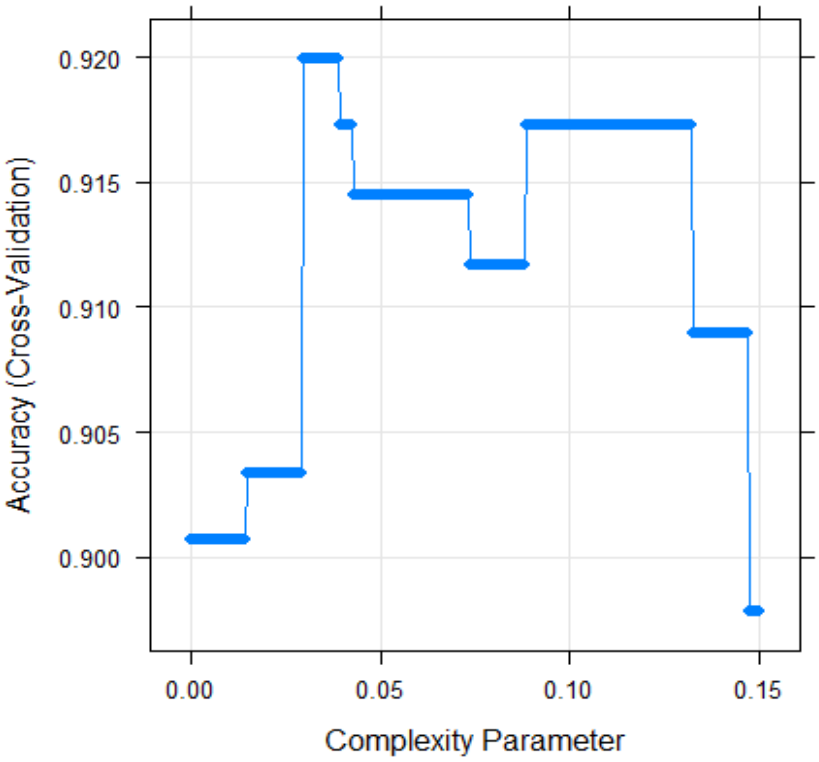

Figure 5.3: Tuning of the complexity parameter of the CART model estimating the tenfold cross-validated accuracy.

In the testing sample, the CART classification confirmed an increase in probability shock with increasing leaves; the lowest values were found in leaf 1 (2%) and the highest in leaf 6 (86%) as shown in Figure 5.4.

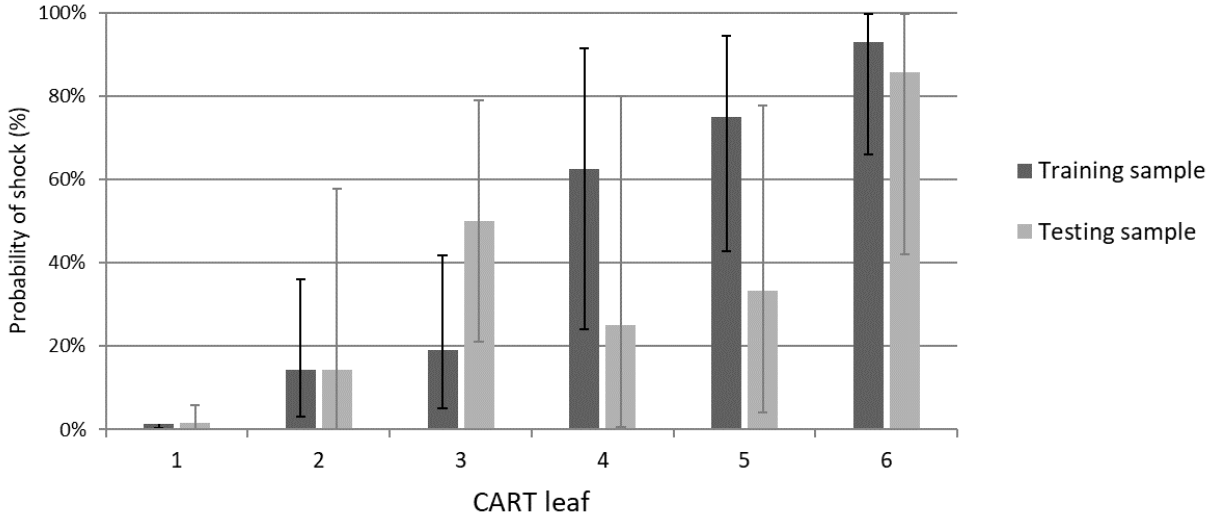

Figure 5.4: Probability of shock in the training and testing samples according to CART leaf. Vertical bars identified 95% confidence interval.

The C-statistics showed similar AUCs in the training and testing sample (AUC training 0.923 vs. AUC testing 0.896, p=0.606; see Figure 5.5).

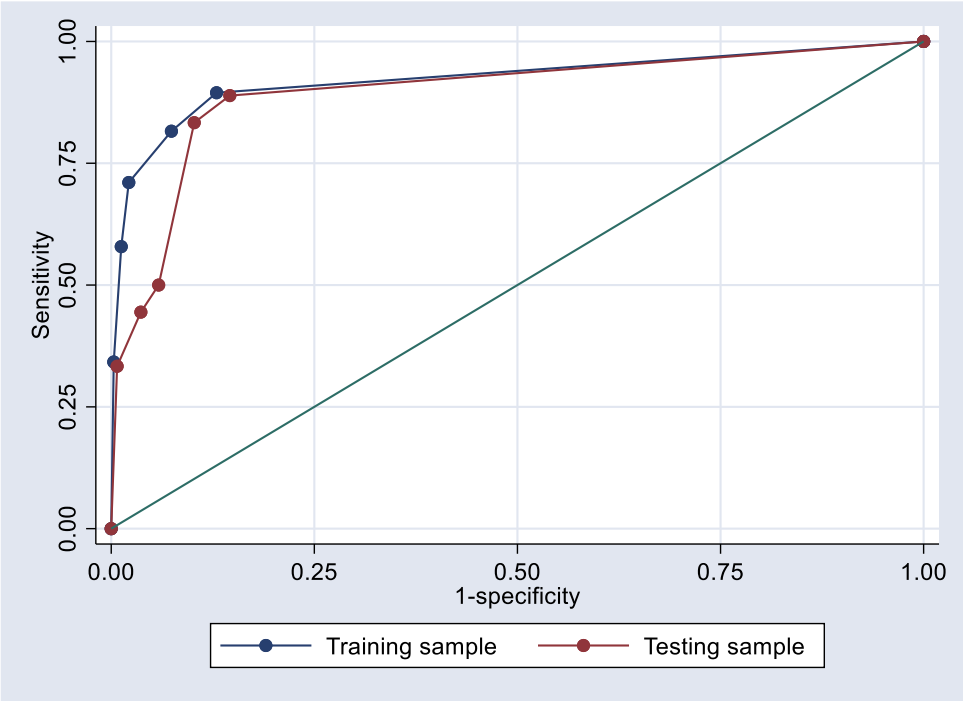

Figure 5.5: The ROC curves showing the sensitivity vs. false positive rate (1-specificity) of the CART leaves in the training and testing samples. ROC, receiver operating characteristic.

Table 5.3 provides information on the predictive performance of the CART model for shock occurrence. Different values of sensitivity, specificity, PPV, and NPV could be obtained by varying the threshold leaf. Considering patients with an active arrhythmic pattern (leaf 6), the overall accuracy was 92% characterized by an 86% PPV and a 92% NPV in the testing sample.

Table 5.3: Accuracy of prediction of CART leaves for shock occurrence in the training and testing sample.

Threshold		**≥ Leaf 2**	**≥ Leaf 3**	**≥ Leaf 4**	**≥ Leaf 5**	**Leaf 6**
Accuracy	Training	87%	91%	95%	95%	93%
	Testing	86%	89%	89%	90%	92%
Sensitivity	Training	89%	82%	71%	58%	34%
	Testing	89%	83%	50%	44%	33%
Specificity	Training	87%	93%	98%	99%	99%
	Testing	85%	90%	94%	96%	99%
PPV	Training	45%	56%	79%	85%	93%
	Testing	44%	52%	53%	62%	86%
NPV	Training	99%	98%	97%	95%	93%
	Testing	98%	98%	93%	93%	92%

PPV, positive predictive value; NPV, negative predictive value.

5.3.3 HF, CV hospitalization by model risk groups

Figure 5.6 depicts the KM survival analysis of the overall population based on the leaves identified by the CART model. During study follow-up, 42 patients (8.1%) experienced worsening HF that required hospitalization and 95 patients (18.4%) had a hospital stay due to CV reasons, including coronary artery disease, HF, acute myocardial infarction, cardiac arrhythmias, and complications related to the cardiac implantable electronic device. The survival analysis revealed a significant higher risk of both HF (HR 5.45, 95% CI 1.62-18.4, p=0.006) and CV hospitalization (HR 7.29, 95% CI 3.66-14.5, p<0.001) for patients included in leaf 6 (active arrhythmic pattern) compared to those in leaf 1.

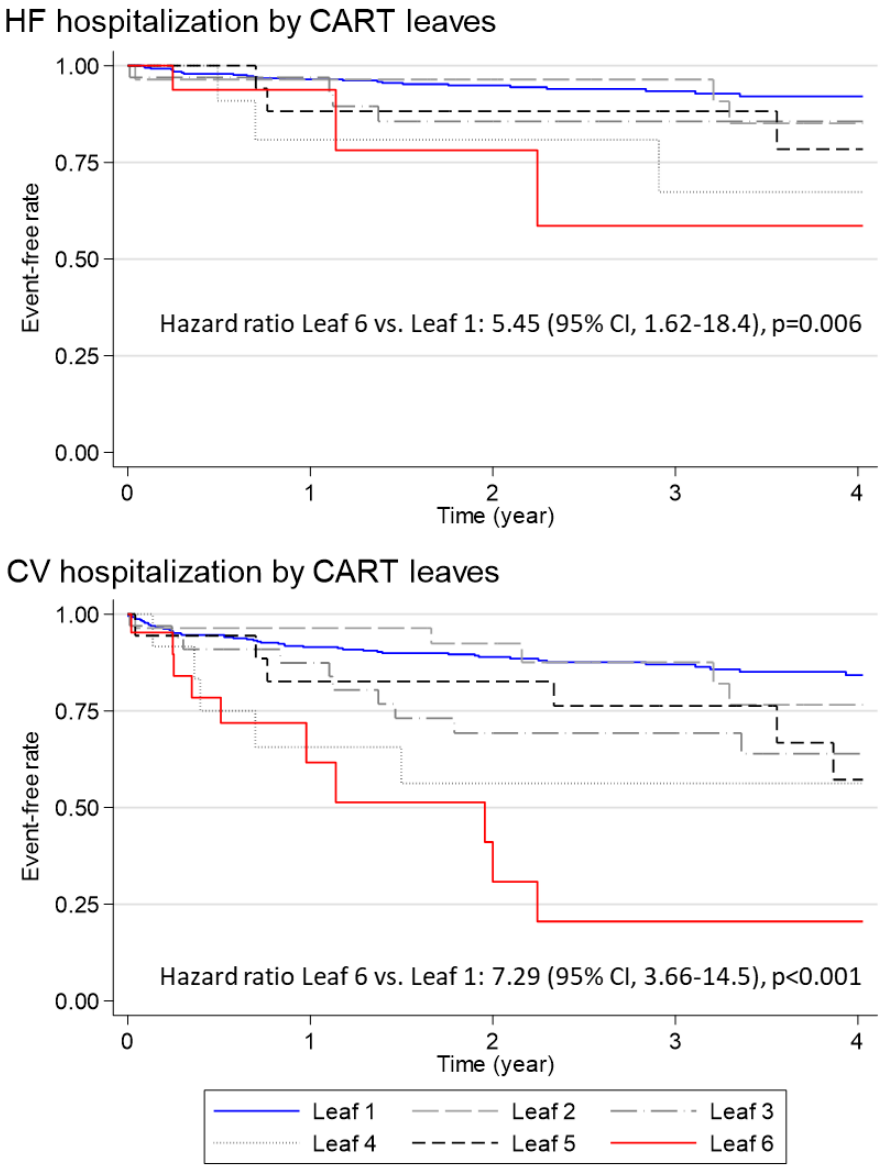

Figure 5.6: Kaplan-Meier survival curves by CART leaves for worsening heart failure (HF) that led to hospitalization and cardiovascular (CV) hospitalization.

5.4 Discussion

In the PARTITA trial, ATPs predicted the occurrence of appropriate ICD shocks, and catheter ablation after the first shock reduced the risk of death or worsening heart failure. In this sub study, we propose for the first time a threshold for ATP rate that is highly predictive of an occurrence of an ICD shock. Using machine learning techniques, we have identified that patients who were treated with five or more appropriate ATPs within six had a very high probability of experiencing an appropriate ICD shock (93% and 86% in the training and testing sample, respectively). This high-risk 'active arrhythmia pattern' group also demonstrated an increased risk of worsening heart failure leading to hospitalization and hospitalization for cardiovascular causes, and could be considered for catheter ablation before a device shock. Furthermore, we profiled a subset of patients, with distinct features, who have an increased risk of ICD shock already after the first appropriate ATP. This group had a LVEF <35%, were younger than years or older but with a BMI ≥30.

The CART model allowed us to stratify the risk of shocks and cardiovascular events in a low-risk and a high-risk group. This classification was confirmed prospectively and, in addition to predicting ICD shocks, allowed to determine a higher probability of both HF and CV hospitalization. In the low-risk groups, the shock probability ranged between 1% and 19%, where patients with no ATPs are the ones with the lowest probability as also confirmed in the testing sample. Subjects who had < 5 ATPs in 6 months, have an LVEF≥35% or an LVEF<35% and are older than 60 years with a normal body weight, should not be considered for catheter ablation due to the low risk of shock and a more benign subsequent clinical course. Optimization of medical therapy is important in this scenario and home monitoring is essential, allowing an earlier detection of ATPs and guiding a prompt titration of beta blockers. Our data confirm the results of the MADIT-CRT trial where patients who had not received ICD shock therapy were older and had a higher LVEF [122]. A low EF is a known risk factor of cardiovascular events and a younger age could be a marker of a more aggressive disease status. In the high-risk group where the risk of shock ranges between 62% and 93% in the training sample and between 25% and 86% in the testing sample, medical therapy alone is less likely to prevent major events and additional actions should be taken. An active arrhythmia pattern (≥5ATPs in 6 months) has the highest risk of major events. Our data suggest that it might not be the shock itself that causes worsening HF, but the combination of an untreated active arrhythmia pattern, that causes an aggravation of the clinical history in patients with an already existing unfavorable clinical profile. In this setting the very likely occurrence of a shock is the marker of a negative combination of arrhythmic events (recurrent VT) on a substrate that is more liable to subsequent deterioration. This might also explain the negative prognostic impact of repeated appropriate shocks. In this setting it is plausible that prevention of recurrences might alleviate the subsequent clinical course. Our findings

suggest a low likelihood of receiving shocks in patients without any previous ATP (1% and 2% in the training and testing sample), indicating limited benefit from prophylactic catheter ablation. However, even in patients with occasional ATPs, a LVEF<35% and obesity, medical therapy and lifestyle changes would seem appropriate before considering catheter ablation. Our analysis links obesity with an increased risk of ICD shocks for the first time. Although the mechanism remains to be determined, obesity could be a surrogate of metabolic disease and an unhealthy lifestyle and its treatment could act on multiple factors and mechanisms.

Randomized controlled trials on the timing of VT ablation focused on prophylactic catheter ablation at the time of ICD implantation (). Results were heterogenous in terms of reduction of VT episodes and mortality. The data from the PARTITA trial have shown that during a mean follow-up of 2.4 years, 52% of patients did not have any VT episodes and only 11% were treated with an ICD shock. Prophylactic ablation studies might include patients who will never have recurrent VTs and ICD shocks, potentially explaining the discordant results. On the other hand, 88% of patients who experienced the first ICD shock had an active arrhythmia pattern with multiple episodes of VT treated by ATP. This sub study allowed us to quantify this burden and identify these patients. Furthermore, all patients of the control group in Phase B (i.e. received an ICD shock and were not treated with catheter ablation) who reached the primary endpoint (death or wHF) had VT recurrences with device therapies confirming the link between ICD shocks mortality and progression of heart failure. Current Guidelines recommend catheter ablation for recurrent VT episodes and VT storm with a Class I indication, whereas an early ablation strategy has a class IIb indication but the timing has not been standardized. The last HRS/EHRA/APHRS/LAHRS expert consensus recommend it in ischemic ICD patients who experienced a first episode of monomorphic VT, while the last ESC Guidelines consider prophylactic ablation in ischemic patients at ICD implantation to reduce VT burden and ICD shocks. However, which patients treated prophylactically will benefit from ablation is unpredictable because their natural history is unknown. Patients with an active arrhythmia pattern would be a subgroup who have an increased risk of ICD shocks, HF and CV hospitalizations and it would seem reasonable to propose an ablation treatment to prevent these events.

The CART analysis provides an assessment tool that can be easily used for clinical insights and decision-making, but it may be affected by high variance across samples compared to ensembles of trees. To address this limitation, we pruned the tree based on misclassification error minimization estimated by tenfold cross-validation approach. Nonetheless, external validation and bedside experience of this risk stratification will need to be assessed.

In conclusion, patients with an active arrhythmia pattern (≥5ATPs in 6 months) have an increased risk of ICD shocks, as well as HF hospitalization and CV hospitalization. Catheter ablation could be proposed as a preventive strategy to this high-risk group to reduce the incidence of major events. Other risk factors such as low ejection fraction, younger age and obesity should also be accounted for when considering an ablation strategy. Further prospective randomized trials are needed to confirm the benefits of early VT ablation.

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