Navigating Complexities in Implantable Cardioverter-Defibrillator Therapy

Insights, Challenges, and Patient-Centred Approaches

Dilek Yilmaz

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Chapter 1

General introduction and outline of the thesis

List of abbreviations

SCD	Sudden Cardiac Death
ICD	Implantable Cardioverter-Defibrillator
CVD	Cardiovascular Disease
ZIN	Dutch Healthcare Institution
EHRA	European Heart Rhythm Association
HRS	Heart Rhythm Association
PG	Pulse Generator
SDM	Shared Decision Making
DA	Decision Aid
CRT-D	Cardiac Resynchronization Therapy with Defibrillation

Sudden Cardiac Death and Implantable Cardioverter-Defibrillators

Cardiovascular diseases pose a significant global health challenge. Cardiovascular disease (CVD) remains the most common cause of death in Europe(1). More than 60 million potential years of life are lost to CVD in Europe annually(1). Moreover, it has been previously estimated that Sudden cardiac death (SCD) from cardiac arrest is a major global health problem accounting for an estimated 15%–20% of all deaths(2). Individuals at risk include those with a history of heart disease, heart attack survivors, or those with specific structural or genetic abnormalities of the heart (2). Therefore, several decades ago, the Implantable Cardioverter-Defibrillators (ICD) was developed to prevent sudden cardiac death in patients at risk. ICD therapy has been shown to be effective in reducing sudden cardiac death and all-cause mortality in selected patient groups (3). These devices have become a cornerstone in both primary and secondary prevention strategies against SCD. In the Netherlands, 6000 ICDs are implanted annually in patients at risk of SCD (4). It is estimated that 83% of these patients, will never experience a life threatening arrhythmia after ICD implantation (4). Considering the rising health care costs in general, and substantial part of patients that never receive ICD tachytherapy, The Dutch Healthcare Institution (ZIN) has published a report, encouraging more stringent patient selection. They estimated that improvements in patient selection, may result in an annual cost reduction of 19,8 million euros per year (4).

Primary Prevention

Primary prevention ICDs are implanted in individuals at high risk of developing malignant ventricular arrhythmias (5). This proactive approach aims to prevent death from life-threatening arrhythmias through ICD tachytherapy. The majority of this population at risk of ventricular arrythmias consists of patients with structural, mainly ischemic heart disease either or not with symptoms of heart failure with reduced ejection fraction (5).

Secondary Prevention

Secondary prevention strategies involve the use of ICDs in individuals who have already experienced life-threatening arrhythmias and/or are survivors of a cardiac arrest attributed to a ventricular tachyarrhythmia. This application serves to mitigate the risk of death due to recurrent events, offering a lifeline to those with a history of severe cardiac arrhythmias that remain at risk (5).

Concerns of ICD therapy

Despite technological advances, challenges persist in identifying individuals at risk, understanding the complex underlying causes of SCD, and identifying potential risks. While ICDs have revolutionized the management of the risk for SCD, they are not without limitations and potential drawbacks. Understanding of their impact on patient care is important for the recognition of these drawbacks for thorough patient selection and counselling. Drawbacks to be taken into account during patient selection for ICD therapy, are:

1. Peri- and post-procedural complications
   The surgical implantation of ICDs carries inherent risks, including the possibility of infection at the device site. Additionally, patients may experience complications related to lead placement, such as lead dislodgement or venous thrombosis (6-8). Even though rates of severe complications are low, less severe complications still occur rather frequently: procedure-related mortality 0-0.1%, pneumothorax 0.4%-2.8%, pericardial effusion 1.3%, clinical tamponade 0.5-1.5%, pocket hematoma 0.2%-16%, infection 0.6-3.4%, lead dislodgement 1.2%-3.3% (9).
2. Inappropriate shocks
   ICDs are designed to deliver shocks when necessary, but at times, they may misinterpret non-lethal arrhythmias or noise as life-threatening events, leading to inappropriate shocks. These shocks can be painful and distressing for patients (11). Technological advancements continually address these concerns, but malfunctions still occur (7).
3. Psychological Impact
   Living with an ICD can have profound psychological implications for patients. The awareness of having a device that intervenes during life-threatening situations can lead to anxiety, depression, or a reduced quality of life (12, 13). On the other hand, people may feel safe due the the presence of the device.
4. Cost and Resource Utilization
   The initial cost of implanting an ICD, along with ongoing monitoring and potential device replacements, contributes to the economic burden of healthcare. This cost factor necessitates careful consideration of healthcare resource allocation and patient selection (14, 15).
5. Limited Benefit in Certain Populations
   While ICD therapy significantly reduce the risk of sudden cardiac death in specific patient groups, their benefits might be limited in certain populations, such as those with significant comorbidities or a limited life expectancy (16, 17).

6. Battery Depletion
   ICDs are powered by batteries that have a finite lifespan. Regular device check-ups are necessary to monitor battery status. When the battery nears depletion, the device requires replacement through an additional surgical procedure (10). Fortunately, battery life has increased during the past decade, e.g. for a single lead ICD's from approximately 7 to 15 years.
7. Ethical Considerations
   Decision-making regarding ICD implantation involves ethical considerations, especially in patients with advanced illnesses or limited life expectancy. Shared decision-making becomes crucial in balancing potential benefits and drawbacks (17–19).

End-of-life issues

Position papers by international societies such as the European Heart Rhythm Association (EHRA) and Heart Rhythm Association (HRS) encourage that end-of-life issues should be a part of pre-procedural counselling (20–23). The urgency of this recommendation is substantiated by the fact that up to half of all patients in a European ICD cohort do not have tachytherapy functions disabled at the time of death (24), leaving them prone for painful shocks in the last week of their life (20, 21, 23, 25).

Patient's clinical situations as well as their preferences may change over time. Although in the first decades, it used to be common practice to continue ICD therapy until death, perceptions have changed. Physicians are increasingly aware that ICD therapy is not a lifelong commitment. As time passes, patients can be withdrawn from ICD therapy if they choose - or if the clinical benefit of continuing ICD therapy is considered absent. Moreover, patient preferences can change with the progression of age and the involvement of a new comorbidity. Considering ICD pulse-generator will last for only 5 to 10 years, the moment for pulse-generator exchange due to battery depletion, provides an excellent moment for discussing continuation of ICD therapy.

Whereas doctors may reconsider the indication and appropriateness of the ICD with certain patients, it has been shown previously that more than half of the patients who had already an ICD replacement. at time of battery depletion, were not aware that they had a choice (26). Only a minority of patients have been reported to consider non-replacement under certain circumstances, such as serious illness and/or advanced age (26). This illustrates the importance of shared decision-making, also when a patient is up for an ICD replacement.

In summary, unlike in the past when it was thought that an ICD indication was fixed, we now think of ICD therapy as more fluid in terms of indication and appropriateness. Patient preferences with respect to continuation of discontinuation of ICD therapy should be discussed.

Importance of Shared Decision-Making in Implantable Cardioverter-Defibrillator (ICD) Patients

Shared decision-making (SDM) plays a pivotal role in the care of patients (and their relatives) considering or receiving ICDs. This collaborative approach involves active participation and communication between healthcare providers and patients, considering individual values, preferences, and clinical evidence (29). There are many aspects to the process of SDM in the context of ICDs:

1. Informed Choices
   ICD therapy involves decisions, such as whether to undergo the implantation of an ICD for primary or secondary prevention indication and/ or whether to undergo a pulse generator exchange at time of battery depletion. SDM ensures that patients receive comprehensive information about their condition, treatment options, potential risks, and expected benefits. This empowers patients to make informed choices aligned with their individual values and preferences.
2. Quality of Life Considerations
   The psychological and lifestyle impact of living with an ICD is substantial. Some patient even choose not to have an ICD, due to the potential impact on their quality of life. In contrast, other patients, e.g. in whom an ICD is no longer indicated, have a hard time with withdrawing from ICD therapy because of the of the secure feeling it provides them.Engaging in SDM allows patients to discuss their concerns, fears, and expectations. Healthcare providers can offer insights into how ICD therapy might influence a patient's quality of life, helping individuals weigh the potential benefits against the drawbacks.
3. Patient-Centered Care
   SDM places patients at the center of the decision-making process. It acknowledges their autonomy and engages them as active and central participants in determining their healthcare pathway. This patient-centered approach fosters a sense of control and ownership, which positively impacts patient satisfaction and adherence to treatment plans.

4. Addressing Ethical Dilemmas
   Decisions about ICD implantation often involve ethical considerations, especially in cases of advanced disease or limited life expectancy. Shared decision-making provides a platform to openly discuss these ethical dilemmas. Patients can express their values and preferences and healthcare providers can offer guidance, fostering a collaborative resolution.
5. Reducing Decisional Conflict
   The complexity of decisions on ICD implantation can lead to a decisional conflict, with patients feeling uncertain or struggling with their choices. SDM helps clarify expectations, understand possible outcomes, and reduce decisional conflict. This contributes to a more confident and satisfied patient population.
6. Enhancing Adherence
   Patients who actively participate in decision-making processes are more likely to adhere to treatment plans. Understanding the rationale behind ICD therapy and feeling involved in the decision promotes a sense of commitment to the prescribed care (both pharmacological and life-style measures), potentially improving long-term adherence.
7. Tailoring Care to Individual Needs
   Each patient's situation is unique, and SDM enables customized care plans. By understanding the patient's values, lifestyle, and expectations, healthcare providers can tailor recommendations for ICD therapy and optimize the match between medical interventions and individual needs.
8. Improved Communication
   SDM enhances communication between patients and healthcare providers. This transparent and open dialogue builds trust, addresses misconceptions, and facilitates shared responsibility for health outcomes. Effective communication is particularly crucial in managing expectations and addressing concerns related to ICD therapy.

Overall, shared decision-making is an integral part of the ethical, patient-centered, and personalized care of individuals considering or receiving ICD therapy. It is consistent with the principles of autonomy, beneficence, and respect for persons, and contributes to a collaborative healthcare environment that prioritizes the well-being and values of each patient (29).

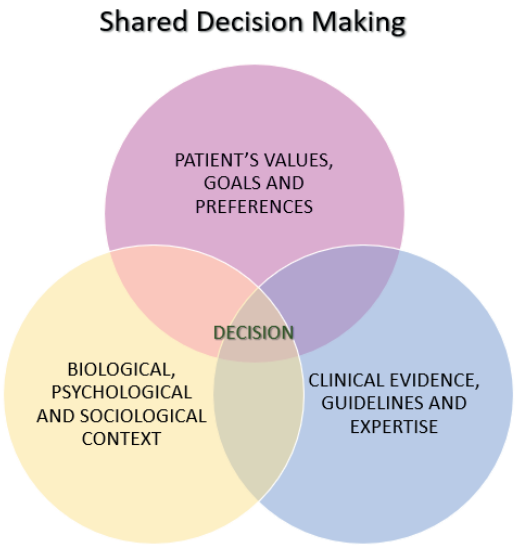

Figure: Key factors contributing to the shared decision-making process.
Image adapted from colitisconversations.org/Benefits_to_care

Role of Decision Aids in Shared Decision-Making for ICD patients

Decision aids (DAs) are valuable tools in the shared decision-making process (30), especially for patients facing complex choices such as whether to undergo an ICD implantation. These aids facilitate communication between healthcare providers and patients, providing structured information to support informed decisions aligned with individual values (29, 30).

1. Clarification of Information
   Decision aids can present comprehensive, evidence-based information about ICDs, including their purpose, benefits, and potential risks. They clarify technical details in a patient-friendly manner, ensuring that patients have a solid understanding of the intervention.
2. Visual Representation
   Visual aids, such as diagrams or videos, help convey complex concepts related to ICDs. These aids enhance patient understanding and serve as visual reinforcement during discussions about device operation and the implantation procedure.

3. Clarification of Values
   DAs guide patients in clarifying their values and preferences regarding ICD therapy. Interactive exercises and prompts help people think about what is most important to them, and facilitate conversation about how ICD treatment aligns with their personal goals.
4. Risk-Benefit Assessment
   DAs provide balanced information about the potential benefits and risks of ICD therapy. This supports patients in weighing the pros and cons based on their individual health status, lifestyle, and values.
5. Facilitating Communication
   By fostering understanding and clarification of personal values, DAs contribute to more meaningful discussions between patients and healthcare providers. Patients can express their concerns, ask questions, and actively participate in the decision-making process.

In conclusion, decision aids are crucial tools in shared decision-making for ICD patients by providing accessible information, promoting the clarification of values, and facilitating informed discussions. Their integration into clinical practice enhances the collaborative decision-making process, empowering patients to actively participate in decisions about their healthcare.

Outline of the thesis

The thesis explores technical and decision-making aspects of ICD therapy in patients with heart disease. It examines the clinical outcomes of subcutaneous versus transvenous implantable defibrillator therapy, the impact of chronic total coronary occlusion on ventricular arrhythmias and mortality, and shared decision-making around ICD therapy. The thesis also evaluates the clinical practice of ICD therapy in end-of-life scenarios.

Chapter 2 of the thesis focuses on the technical aspects of ICD therapy, comparing the long-term clinical outcomes of subcutaneous versus transvenous ICD therapy. The chapter also discusses the practical considerations of device selection, including patient characteristics, indication for therapy, and the potential risks and benefits of each device type. **Chapter 3** evaluates the impact of a chronic total coronary occlusion on ventricular arrhythmias and long-term mortality in patients with ischemic cardiomyopathy and an ICD. **Chapter 4A** examines the risk of painful shocks in the last moments of life in patients with an ICD. **Chapter 4B** investigates the causes of death in patients who had their tachytherapy deactivated in a large

population over a 10-year period. **Chapter 5** examines the use of ICD therapy in elderly patients in Dutch clinical practice. **Chapter 6** describes the development of a decision aid for shared decision-making in the Dutch ICD patient population. The chapter discusses the effectiveness of the decision aid in improving patient knowledge and satisfaction with the decision-making process. Finally, **chapter 7** reports on the randomized controlled trial that aimed to evaluate the use of a decision aid for patients undergoing an elective pulse generator exchange for their implantable cardioverter-defibrillator and assessed shared decision-making levels, decisional conflict, and knowledge before and after the intervention.

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Part I

Exploring ICD Therapies:
Comparative Clinical Investigations

Chapter 2

A Comparison of Long-term Clinical Outcomes of Subcutaneous and Transvenous Implantable Defibrillator Therapy

Yilmaz D*, Brouwer TF,* Lindeboom R, Buiten MS, Olde Nordkamp LR, Schalij MJ, Wilde AA, van Erven L, Knops RE.

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*shared first authorship

Abstract

Background

Transvenous implantable cardioverter-defibrillators (TV-ICD) improve survival in patients at risk for sudden cardiac death, but (lead-related) complications remain an important drawback. The subcutaneous ICD (S-ICD) was developed to overcome lead-related complications. Comparison of clinical outcomes of both device types in previous studies is hampered by dissimilar patient characteristics.

Objective

This retrospective study compares long-term clinical outcomes of S-ICD and TV-ICD therapy in a propensity matched cohort.

Methods

Analysis of 1160 patients who underwent S-ICD or TV-ICD implantation in two high-volume hospitals in The Netherlands. Propensity matching for 16 baseline characteristics, including diagnosis, yielded 140 matched pairs. Clinical outcomes were device-related complications requiring surgical intervention, appropriate and inappropriate ICD therapy and were reported as five-year Kaplan-Meier rate estimates.

Results

All 16 baseline characteristics were balanced in the matched cohort of 140 patients with S-ICDs and 140 patients with TV-ICDs (median age 41 (IQR 30, 52)years and 40% females). The complication rate was 13.7% in the S-ICD group versus 18.0% in the TV-ICD group (p=0.80). The infection rate was 4.1% for S-ICDs versus 3.6% for TV-ICDs (p=0.36). Lead complications were lower in the S-ICD arm as compared to the TV-ICD arm, 0.8% versus 11.5% respectively (p=0.03). S-ICD patients had more non-lead related complications than TV-ICD patients, 9.9% versus 2.2% respectively (p=0.047). Appropriate ICD intervention (ATP and shocks) occurred more often in the TV-ICD group (HR 2.42, p=0.01). Incidence of appropriate shocks (TV-ICD HR 1.46, p=0.36) and inappropriate shocks (TV-ICD HR 0.85, p=0.64) were similar.

Conclusions

In this matched cohort of S-ICD and TV-ICD patients the complication rate was similar, but their nature differed. The S-ICD reduced lead-related complications significantly at the cost of non-lead-related complications. Both appropriate and inappropriate shock rates were similar between the two groups. Consideration of these differences in patients eligible for both devices is essential.

Introduction

Implantable cardioverter-defibrillators (ICD) improve survival of patients at increased risk of sudden cardiac death.[1,2] Advances in ICD programming have reduced the burden of shocks, but device-related complications remain an important drawback of transvenous ICD (TV-ICD) therapy, resulting in significant morbidity.[3] Transvenous sensing and defibrillation leads are associated with both infective and mechanical complications, such as lead endocarditis, pneumothorax, venous occlusion and cardiac perforation.[4,5] Lead failure may cause inappropriate shocks and impede delivery of appropriate therapy for ventricular arrhythmias.[6–8]

The subcutaneous ICD (S-ICD) was designed to eliminate complications related to transvenous leads, but lacks pacing capabilities and can therefore only be used in patients without a need for pacing.[9] Studies of the S-ICD have demonstrated clinical efficacy, but reported also a 13.1% inappropriate shock rate at three-years follow-up, that was significantly reduced with dual zone programming.[10–12] However, direct comparison of clinical outcomes of the available S-ICD cohorts to TV-ICD cohorts is limited by varying patient characteristics, follow-up durations and definition of complications.

The objective of the current retrospective study is to compare long-term clinical outcomes of S-ICD and TV-ICD therapy in a propensity score balanced cohort.

Methods

Study Setting

Patients with ICDs implanted in two hospitals in the Netherlands, Academic Medical Center (AMC) and Leiden University Medical Center (LUMC), were included. For this analysis, patients implanted with transvenous single- and dual-chamber ICDs between 2005 and 2014 at the LUMC and S-ICDs between 2009 and 2015 at the AMC were selected. During this period of time, LUMC had not adopted the S-ICD into their clinical practice, and therefore this variation in practice between AMC and LUMC was used to compare the two types of ICD therapy. Patients included in the ongoing PRAETORIAN trial were excluded from this analysis.[13] The need for informed consent was waived in both centers due to the observational nature of the study.

Study population

At the LUMC 1312 patients received a TV-ICD between 2005 and 2014. In the AMC 148 patients were implanted with an S-ICD between 2009 and 2015. As baseline characteristics were significantly different, we used propensity score matching as the primary analysis. The type of devices used were S-ICDs (Boston Scientific) and TV-ICDs (Biotronik, Boston Scientific, Medtronic and St. Jude Medical). The majority of both S-ICD and TV-ICD patients were implanted under local anesthesia, according to the prevailing local hospital protocol.[14] LUMC is an experienced implantation center for TV-ICDs, as is AMC for S-ICDs and TV-ICDs.

Data Collection

Data collection in both centers was performed at regular intervals by reviewing medical records for baseline characteristics, implantation data and follow-up data on clinical outcomes, complications and therapy delivery. The survival status of patients was retrieved from municipal civil registries.

Definition of outcomes

Complications were defined as all device related complications requiring surgical intervention. Lead complications were defined as complications requiring replacement or repositioning of the lead, without elective pulse generator replacement. In addition, lead survival was defined as the time between lead implantation and lead failure, with or without elective pulse generator replacement. Appropriate therapy consists of antitachycardia pacing (ATP) only and shocks (preceded by ATP or not) for ventricular tachycardia (VT) or ventricular fibrillation (VF). Inappropriate therapy consists of ATP and shocks for heart rhythms other than VT or VF. All arrhythmia episodes were adjudicated by the local electrophysiologists.

Statistical Analysis

Entire cohort

Categorical variables were presented as numbers and percentages and were compared for the entire cohort with Fisher's exact test. Based on their distributions, continuous variables are presented as mean ± standard deviation or median with interquartile ranges (25^{th}, 75^{th}) and compared with student's t- or Wilcoxon rank-sum test.

Propensity score matching

Propensity score matching was performed with patients for whom complete baseline variables were available (total n=1154). Analysis of excluded patients due to missing baseline data did not suggest selection bias. We used logistic multivariable regression with device type (S-ICD or TV-ICD) as dependent variable and 16 baseline variables as independent predictors to calculate the propensity score (Table 1). The Harrell's C-statistic for the propensity score logistic regression model was 0.89. Patients were 1-to-1 greedy matched using the nearest-neighbor method. There was sufficient overlap in the propensity scores to individually match each S-ICD case to a TV-ICD control (supplemental figure 1).

Analysis of the matched cohort

Baseline variables of the matched cohort were compared with paired tests, McNemar and Wilcoxon signed-rank tests and standardized mean differences were calculated. We used the Kaplan-Meier method to correct for difference in follow-up and estimate the cumulative incidence of outcomes at five-year follow-up. P-values and hazard ratios were calculated using conditional proportional hazards (CPH) models with adjustment for ICD programming. CPH assumptions were visually inspected by plotting Schoenfeld residuals.

Sensitivity analyses

A sensitivity analysis was performed excluding patients exposed to transient external factors: patients implanted with advisory leads, i.e. *Medtronic Sprint Fidelis* and *St. Jude Medical Riata* (n=20) in the TV-ICD group, and an equal number of patients exposed to the operators' learning curve in the S-ICD group. [15,16] Additionally, a sensitivity analysis for patients with a left ventricular ejection fraction ≤35% was performed.

All statistical analyses were conducted in R Studio and R version 3.2.2 and the package MatchIt for propensity matching.[17,18] All reported p-values were 2 tailed, and p-values <0.05 were considered statistically significant.

Results

Entire cohort

In the entire cohort, before matching, most baseline variables were significantly different between the two groups (Table 1, left columns). The characteristics of the TV-ICD group represent a typical ICD cohort, with the predominant diagnosis

ischemic cardiomyopathy (64%), significant cardiovascular comorbidity and a median left ventricular ejection fraction of 34%. The S-ICD group is younger with fewer comorbidity, higher left ventricular ejection fraction (50%) and genetic arrhythmia syndromes as the main diagnosis (53%).

Propensity matched cohort

In the propensity matched cohort S-ICD cases (n=140) were similar to their TV-ICD controls (n=140), with no significant differences in any baseline characteristic (Table 1, right columns). Compared to the entire cohort, the matched cohort was younger with a median age of 41 (30, 52) years and had a higher left ventricular ejection fraction. In the TV-ICD group 124 (88.6%) devices were dual- and 16 (11.4%) were single-chamber. The median follow-up duration was longer in the TV-ICD group than in the S-ICD group: 5 years versus 3 years respectively (p<0.001).

ICD programming

The conditional zones in S-ICDs and the fast VT zones in TV-ICDs were similar with a median of 190 (180, 200) beats per minute (BPM) and 188 (188, 200) BPM respectively, p=0.77. The unconditional zone in the S-ICD and VF zone in the TV-ICD differed with median 250 (250, 250) BPM and 231 (230, 231) BPM respectively, p<0.001. Defibrillation testing was performed in 92% of S-ICD and 97% of TV-ICD patients. There were 13 (9.3%) patients in the TV-ICD group with >5% bradycardia pacing (atrial or ventricular) in the first year. In the S-ICD group six (4.3%) patients had a concomitant transvenous pacemaker.

Clinical outcomes

Complications

The complication rate at five years follow-up was 13.7% (95%CI 6.4-20.3%) in the S-ICD group versus 18.0% (95%CI 10.5-24.8%) in the TV-ICD group, p=0.80 (Figure 1). Table 2 presents the crude number of patients, the type of complications and the Kaplan Meier complication rate, corrected for follow-up duration. Lead complications necessitating surgical intervention that were not performed during elective pulse generator replacement occurred more often in the TV-ICD group (11.5%, 95%CI 5.3-17.2%) compared to the S-ICD group (0.8%, 95%CI 0.0-2.2%), p=0.03 (Figure 2A). Infections occurred in the S-ICD group in 4.1% (95%CI 0.5-7.7%) and in the TV-ICD group in 3.6% (95%CI 0.0-7.1%), p=0.36 (Figure 2B). There were two patients with bacteremia in the TV-ICD group and one in the S-ICD

group, who also had a concomitant transvenous pacemaker. S-ICD patients had more non-lead-related complications (pocket erosion, defibrillation threshold testing failure and device failure) than TV-ICD patients, 9.9% (95%CI 2.0-15.4%) and 2.2% (95%CI 0.0-4.6%) respectively, p=0.047 (Figure 2C). Lead survival was significantly longer in the S-ICD group 99.2% (95%CI 0.0-2.2%) compared to the TV-ICD group 85.9% (95%CI 92.7-78.46%), p=0.02 (Figure 2D).

Appropriate ICD interventions

Appropriate ICD intervention rates (shocks and ATP) were lower in the S-ICD group 17.0% (95%CI 6.3%-26.4%) versus 31.3% (95%CI 22.6%- 39.7%) (Figure 3A). In the Cox-proportional hazards model adjusted for ICD programming, the HR for appropriate intervention for the TV-ICD group was 2.42, p=0.01. Appropriate shock rates was 17% (95%CI 6.3%-26.4%) in the S-ICD and 21.3%(95%CI 12.6%-27.3%) in the TV-ICD group (Figure 3B). In the Cox-proportional hazards model with adjustment for ICD programming this difference was not significant, TV-ICD HR 1.46, p=0.36.

Inappropriate ICD interventions

Inappropriate ICD interventions (shocks and ATP) were 20.5% (95%CI 11.5-28.6%) in the S-ICD group versus 29.7% (95%CI 19.7-37.6%) in the TV-ICD group (Figure 3C). The HR for inappropriate therapy, adjusted for ICD programming, in the TV-ICD group was 1.29, p=0.42. The percentage of patients who experienced inappropriate shocks was 20.5% (95%CI 11.5-28.6%) in the S-ICD group and 19.1% (95%CI 11.6-26.0%) in the TV-ICD group (Figure 3D). This difference was not significantly different after adjustment for programming: HR 0.85 for TV-ICD group, p=0.64. In 94%, inappropriate shocks from TV-ICDs were for supraventricular tachycardia (atrial fibrillation, atrial flutter and sinus tachycardia). In 85%, S-ICD inappropriate shocks were for oversensing and in 15% for supraventricular tachycardia.

Follow-up

Five year patient survival was 96.0% (95%CI 90.1-100.0%) in the S-ICD arm and 94.8% (95%CI 90.7-99.0%) in the TV-ICD arm, p=0.42. Pulse generator replacement due to battery depletion did not differ at five-year follow-up, p=0.18. Of S-ICD patients, 1.3% (95%CI 0.0-3.7%) was upgraded to a TV-ICD or cardiac synchronization therapy device (CRT) versus 4.6% (95%CI 0.5-8.5%) in the TV-ICD group to CRT, p=0.26.

Sensitivity analyses

The first sensitivity analysis that excluded 20 patients implanted with advisory leads (Medtronic Sprint Fidelis and St. Jude Medical Riata) and the 20 chronologic first S-ICD implants to account for the learning curve, did not show difference in clinical outcomes compared to the primary analysis (supplementary tables and figures). The complication rate at five-year follow-up was 14.0% (95%CI 5.4-21.8%) in the S-ICD group versus 13.8% (95%CI 6.3-20.7%) in the TV-ICD group, p=0.36. Of the 20 TV-ICD patients implanted with advisory leads, 8 (41%, 95%CI 14.6-59.7%) leads failed at 5 years. In the chronologic first 20 S-ICD implants there were 3 (15%, 95%CI 0.0-29.3%) complications at five-year follow-up.

The second sensitivity analysis that included patient with a left ventricular ejection fraction of ≤ 35% yielded 38 S-ICD and 51 TV-ICD patients with a median ejection fraction of 25% and 28%, respectively. None of the comparisons for clinical outcomes demonstrated a significant difference between the S-ICD and TV-ICD patients and trends were similar, except for a non-significant trend towards more inappropriate shocks in the S-ICD arm.

Discussion

Main findings

The current study provides the first balanced comparison of S-ICD and TV-ICD therapy for clinical outcomes during long-term follow-up. The main findings of this study are as follows: the complication rate was similar, but the nature of the complications differed significantly. Appropriate and inappropriate shocks were delivered at equal rates in both groups. TV-ICD patients received more appropriate and inappropriate therapy when ATP was also taken into account.

Complications

The complication rate in both groups was similar, but the nature of complications differed significantly as can be expected by the different design of the devices. The weakest link of the TV-ICD system is the lead, which remained true after exclusion of advisory leads. In the S-ICD group, inappropriate sensing resulted in explanation of the device in one patient and in the need for lead repositioning in another. Improvements of the S-ICD algorithm may avoid sensing issues. The observed complication rate at five year follow-up is similar to the SCD-HeFT trial (9% acute and 5% long-term complications during 3.8 years follow-up) and previous reports on complications in younger patients (22% during 4.5 years follow-up).[2,19]

Therapy

The difference in appropriate therapy may be explained by the ability of TV-ICDs to deliver ATP instantly after VT detection, whereas the S-ICD has a longer charging time that allows non-sustained VTs to terminate. Although ATP has been demonstrated to successfully terminate approximately 70% of VT episodes, it did not result in fewer appropriate shocks in this cohort.[20–23] This may be explained by the fact that patients with ischemic scars represented a minority in this study. The incidences of inappropriate therapy and inappropriate shocks were high in both groups, but are in line with previous publication on young ICD patients.[19] The reasons for inappropriate shocks differed between the two groups: the majority of inappropriate shocks by TV-ICDs were for supraventricular tachycardia and by S-ICDs for cardiac oversensing.

Other endpoints

This study did not find a difference in patient survival rate, but may be underpowered to detect such a difference. None of the patients died of sudden cardiac death and all spontaneous ventricular arrhythmia were successfully treated in both groups. The number of patients that required upgrade to a CRT device was low, but similar to what has previously been reported.[24] The shorter battery longevity of the S-ICD as projected by the manufacturer was not detected in this analysis, but is likely to be demonstrated with longer follow-up.

Sensitivity analyses

The first analysis excluded patients that were implanted with advisory leads in the TV-ICD group and during the S-ICD implanter's learning curve. The second analysis only included patients with a left ventricular ejection fraction ≤35%. Both sensitivity analyses yielded results similar to the primary analysis with the complete matched cohort.

Clinical implications

This study demonstrates that the S-ICD has a significant benefit over TV-ICDs with respect to lead-related complications. This benefit may be greater with longer follow-up. The rate of non-lead-related complications in the S-ICD group may decrease when the technology is fully matured.

Therefore, in the choice of device type, the risk of lead-related complications versus non-lead-related complications needs to be taken into account as well as specific limitations of the S-ICD including the lack of pacing capabilities and the larger pulse generator size. The consideration also needs to include recommended

defibrillation testing in S-ICD implants, which may be omitted in TV-ICDs.[25,26] It is likely that shorter battery longevity of the S-ICD will require more frequent replacements, which are associated with specific risks.[27]

Limitations

This study has some limitations. First, patients included in the primary analysis represent a category of young ICD patients with little comorbidity from two centers, which may limit the generalizability to the broader ICD population. Also, approximately 15% of all TV-ICD patients from LUMC were included in the analysis. Second, although there were no differences in baseline characteristics in the matched cohort, we cannot exclude residual confounding of unmeasured variables, such as pacing indication at time of implant, due to the non-randomized character of the study. Third, the match between S-ICD and TV-ICD patients would have been more optimal with a higher rate of single-chamber ICDs, as single-chamber ICDs are associated with an approximately one percent lower rate of major complications compared to dual-chamber ICDs during short-term follow-up.[3,28] The observed rate of dual-chamber ICDs was caused by the implanter's preference as opposed to need for chronic bradycardia pacing, a tendency that has been reported in another large cohort as well.[28] Fourth, there may be hospital bias present, which was explored by comparison of dual-chamber ICD complications in both centers and did not reveal a difference.

Conclusion

In this matched cohort of S-ICD and mostly dual-chamber TV-ICD patients the complication rate was similar, although their nature differed. The S-ICD effectively reduced lead-related complications at the cost of non-lead-related complications. Both appropriate and inappropriate shock rates were similar. Consideration of these differences in patients eligible for both devices is needed.

Perspectives

Clinical competencies

The S-ICD is a new and safe treatment modality that reduces lead-related complications, but does not reduce the total complication rate compared to TV-ICDs. The difference in the nature of complications and inappropriate shocks should be considered when selecting the optimal device for a patient.

Translational outlook

Future randomized studies with more patients and longer follow-up in a broader ICD population (older and more comorbidities) will lead to better understanding of the comparative benefit of the S-ICD with regards to complications, appropriate and inappropriate therapy.

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Tables

Table 1: baseline characteristics of the unmatched and matched cohort

Variable	Entire cohort				Complete cases propensity-score matched cohort			
	S-ICD group N=148	TV-ICD group N=1312	Standardized mean difference[1]	P Value	S-ICD group N=140	TV-ICD group N=140	Standardized mean difference[1]	P Value
Age, yrs (IQR)	41 (26, 52)	62 (52, 70)	1.303	<0.001	41 (26, 52)	42 (32, 50)	0.119	0.33
Female	60 (41)	276 (21)	0.431	<0.001	56 (40)	53 (38)	0.044	0.71
Height, cm (IQR)	176 (168, 186)	176 (170, 182)	0.072	0.52	176 (168, 185)	178 (170, 185)	0.129	0.30
Weight, kg (IQR)	78 (65, 90)	80 (72, 90)	0.235	0.01	78 (65, 90)	79 (68, 90)	0.174	0.31
Diagnosis			0.715	<0.001			0.061	0.66
Ischemic Cardiomyopathy	27 (18)	841 (64)			26 (19)	41 (29)		
Genetic Arrhythmia Syndrome	79 (53)	240 (18)			75 (54)	54 (39)		
Non-ischemic Cardiomyopathy	30 (20)	179 (14)			28 (20)	30 (21)		
Congenital Heart disease	5 (3)	49 (4)			5 (4)	12 (9)		
Fam history of SCD	7 (5)	3 (0)			6 (4)	3 (2)		
QRS duration in ms (IQR)	98 (90, 108)	104 (90, 120)	0.373	<0.001	98 (88, 108)	100 (90, 113)	0.135	0.22
Hypertension	30 (20)	503 (42)	0.488	<0.001	30 (21)	34 (24)	0.069	0.56
Primary prevention	97 (66)	820 (63)	0.063	0.53	93 (66)	86 (61)	0.105	0.38
Left ventricular ejection fraction	50%	34%	0.381	<0.001	50%	49%	0.031	0.91
De novo implant	128 (87)	1261 (96)	0.346	<0.001	121 (86)	125 (89)	0.083	0.47
Coronary Artery Bypass Graft	3 (2)	317 (24)	0.649	<0.001	3 (2)	3 (2)	0.000	1
Myocardial infarction	34 (23)	695 (53)	0.649	<0.001	33 (24)	38 (27)	0.084	0.48

Variable	Entire cohort				Complete cases propensity-score matched cohort			
	S-ICD group N=148	TV-ICD group N=1312	Standardized mean difference[1]	P Value	S-ICD group N=140	TV-ICD group N=140	Standardized mean difference[1]	P Value
Diabetes	8 (5)	233 (19)	0.413	<0.001	8 (6)	5 (4)	0.092	0.62
Atrial Fibrillation	14 (10)	320 (24)	0.407	<0.001	13 (9)	21 (15)	0.0196	0.14
Renal function			0.280	0.002			0.000	1
Good (eGFR >60ml/min)	134 (91)	1024 (81)			128 (91)	129 (92)		
Moderate (eGFR 60-30ml/min)	11 (8)	214 (17)			10 (7)	8 (6)		
Poor (eGFR <30ml/min)	2 (1)	31 (2)			2 (1)	3 (2)		
New York Heart Association Functional Class			0.529	0.005			0.013	0.92
NYHA I	109 (74)	643 (49)			103 (74)	102 (73)		
NYHA II	31 (21)	489 (38)			30 (21)	31 (22)		
NYHA III	7 (5)	162 (12)			7 (5)	7 (5)		
NYHA IV	0 (0)	11 (1)			0 (0)	0 (0)		

[1]Standardized mean difference is the difference in group means divided by the control standard deviation. Absolute values less than 0.2 suggest balance between propensity matched groups.
NYHA- New York Heart Association Classification, eGFR – Estimated Glomerulofiltration Rate, IQR – Interquartile range, S-ICD – Subcutaneous Implantable Cardioverter-defibrillator, SCD – Sudden Cardiac Death, TV-ICD – Transvenous Implantable Cardioverter-defibrillator.

Table 2: Clinical endpoints*

Complications	**S-ICD**	**KM-rate**	**TV-ICD**	**KM-rate**
Total	14	13.7%	21	18.0%
Lead (total)	1		17	
Atrial lead failure			3	2.9%
Defibrillation lead failure	0	0%	10	8.5%
Atrial and defibrillation lead failure			3	2.9%
Displacement	1	0.8%	1	0.7%
Infection	5	4.1%	4	3.6%
Erosion	3	3.0%	2	1.5%
DFT failure	1	0.7%	0	0%
Inappropriate sensing	2	3.2%	0	0%
Twiddler Syndrome	1	1.1%	1	0.8%
Device failure	1	1.1%	0	0%
Pneumothorax	0	0%	0	0%
Appropriate Therapy	12	17.0%	39	31.3%
ATP			28	21.8%
Shock	12	17.0%	24	21.3%
Inappropriate shocks	20		22	
Oversensing	17	17.1%	1	1.2%
Supraventricular tachycardia	3	4.2%	21	17.6%
Deceased	2		6	
Non cardiac	1	2.0%	3	2.6%
Cardiac	1	2.0%	2	1.7%
Unknown	0	0%	1	0.9%

*Crude number of patients in the first five years and the for follow-up duration adjusted Kaplan Meier rate.
ATP – Antitachycardia pacing, DFT- Defibrillation Threshold Testing, S-ICD – Subcutaneous Implantable Cardioverter-defibrillator, TV-ICD – Transvenous Implantable Cardioverter-defibrillator.

Figures

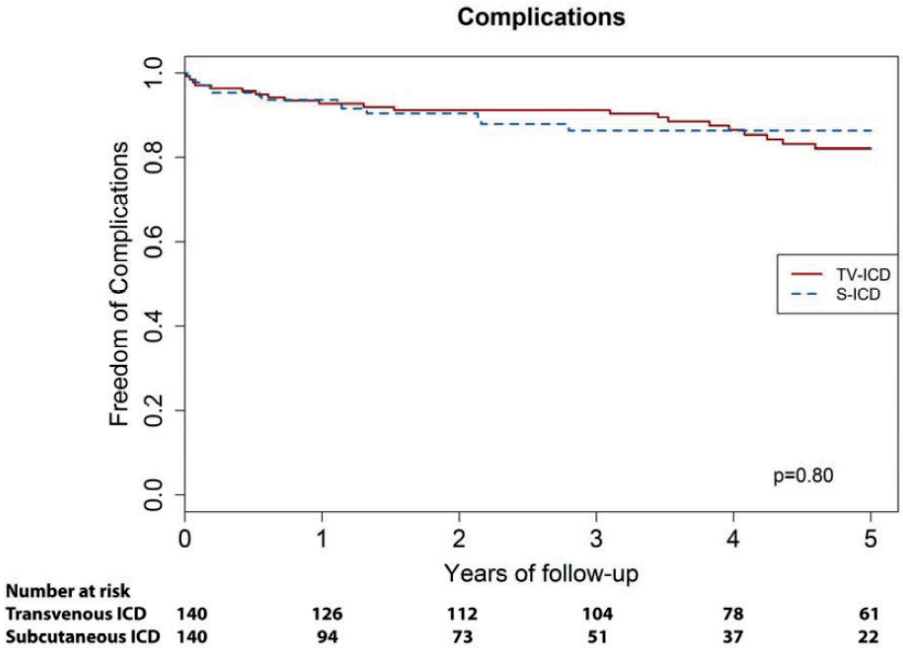

Figure 1 and Central Illustration: Kaplan Meier plot of device-related complications in the subcutaneous and transvenous ICD patients in the propensity matched cohort.

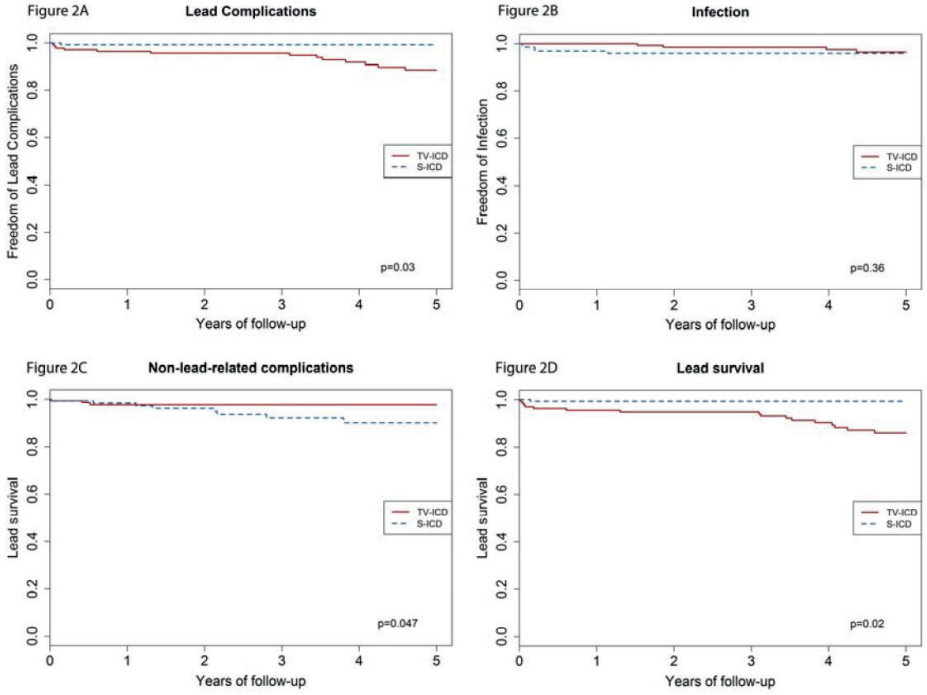

Figure 2: Kaplan Meier plot per type of complications: 2A lead related complications, 2B device infections, 2C non-lead-related complications (pocket erosion, defibrillation threshold failure, Twiddler Syndrome, device failure and inappropriate shocks) and 2D lead survival.

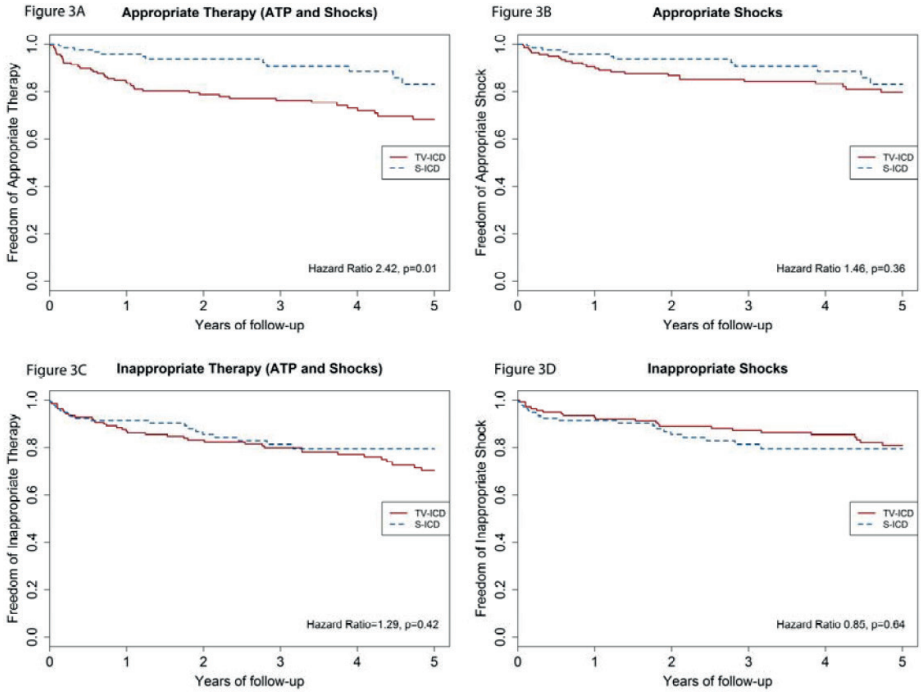

Figure 3: Kaplan Meier plot of: 3A appropriate therapy (antitachycardia pacing and shocks), 3B Appropriate shocks, 3C Inappropriate therapy (antitachycardia pacing and shocks) and 3D inappropriate shocks. Hazard Ratio's (HR) are adjusted for ICD programming.

Chapter 3

Evaluation of the Impact of a Chronic Total Coronary Occlusion on Ventricular Arrhythmias and Long-Term Mortality in Patients With Ischemic Cardiomyopathy and an Implantable Cardioverter-Defibrillator (the eCTOpy-in-ICD Study).

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Abstract

Background

Previous studies report conflicting results about a higher incidence of ventricular arrhythmias (VA) in patients with a chronic total coronary occlusion (CTO). We aimed to investigate this association in a large cohort of implantable cardioverter defibrillator (ICD) patients with long-term follow-up.

Methods and Results

All consecutive patients from 1992 onwards who underwent ICD implantation for ischemic cardiomyopathy (ICM) at the Leiden University Medical Center were evaluated. Coronary angiograms were reviewed for the presence of a CTO. The occurrence of VA and survival status at follow-up were compared between patients with and patients without a CTO. A total of 722 patients constitute the study cohort (age 66 ± 11 years; 84% males; 74% primary prevention, median left ventricular ejection fraction (LVEF) 30% [1st-3rd quartile: 25-37], 44% received a cardiac resynchronization therapy defibrillator. At baseline, 240 patients (33%) had a CTO, and the CTOs were present for at least 44 [2-127] months. The median follow-up duration was 4 [2–6] years. On long-term follow-up, CTO patients had a higher crude appropriate device therapy rate (37% vs. 27%, p=0.010) and a lower crude survival rate (51% vs. 67%, p<0.001) compared to patients without a CTO. Corrected for baseline characteristics including LVEF, the presence of a CTO was an independent predictor for appropriate device therapy.

Conclusions

The presence of a CTO in ICD patients was associated with more appropriate device therapy and worse prognosis at long-term follow-up. Further investigation is warranted into a potential beneficial effect of CTO revascularization on the incidence of VA.

Clinical Perspective

What Is New?

- In a large cohort of patients with an implantable cardioverter defibrillator for ischemic cardiomyopathy, the presence of a chronic total coronary occlusion is associated with higher mortality and more appropriate device therapy rates, and chronic total coronary occlusion revascularization may influence this association positively.

What Are the Clinical Implications?

- When clinicians encounter a patient with a chronic total coronary occlusion, with or without an implantable cardioverter defibrillator, they should be aware of a potentially higher ventricular arrhythmia occurrence in these patients, and chronic total coronary occlusion revascularization and/or implantable cardioverter defibrillator therapy should be considered carefully for improving survival and patient burden.

The presence of a chronic total coronary occlusion (CTO) has been associated with a worse prognosis compared with patients with multivessel disease (MVD) without a CTO or single-vessel disease (SVD).[1] This has been reported both in the setting of stable coronary artery disease and in ST-segment elevation myocardial infarction patients, with or without cardiogenic shock.[2, 3, 4] The underlying mechanism for this poorer prognosis is currently incompletely understood. Additionally, sudden cardiac death appears to occur more frequently in the long term in patients with a nonrevascularized CTO compared with patients with a revascularized CTO.[5] Furthermore, in patients with ischemic systolic heart failure (ejection fraction ≤35%), the presence of a CTO has been associated with an increased 2-year mortality.[6]

One of the hypotheses is that a CTO has a malicious influence on cardiac electrical stability, which makes patients with a CTO more prone to ventricular arrhythmias (VA),[1, 7] leading to a higher mortality rate. There are limited data on the presence of a CTO and a higher incidence of VA in small implantable cardioverter-defibrillator (ICD) patient populations, and reports are limited to short-term follow-up.[8, 9, 10] The aim of the current eCTOpy-in-ICD (evaluation of the impact of a Chronic Total coronary Occlusion on ventricular arrhythmias and long-term mortality in patients with ischemic cardiomyopathy and an Implantable Cardioverter-Defibrillator) study was to investigate this association in a larger cohort of ICD patients with long-term follow-up, and to find variables associated with the occurrence of higher VA rates in CTO patients compared with patients without a CTO.

Methods

The data, analytic methods, and study materials will not be made available to other researchers for purposes of reproducing the results or replicating the procedure.

Patient Population

All consecutive patients from the year 1992 onward who underwent ICD implantation for primary or secondary prevention at the Leiden University Medical Center and had known ischemic heart disease were evaluated. Patient baseline characteristics, ICD-related and clinical follow-up were prospectively collected in the departmental Cardiology Information System (EPD-vision®; Leiden University Medical Center, Leiden, The Netherlands). Indications for the ICD implantations were at the treating physician's discretion according to international guidelines.[11] All data for this study have been collected during routine clinical practice. Therefore, the institutional review board approved all data collection and informed consent was waived by the Leiden University Medical Center ethics committee.

Coronary Artery Disease Assessment

Coronary angiograms of all ICD patients were retrospectively analyzed to identify patients with 1 or more CTOs. All angiograms before the ICD implantation were considered eligible as well as all angiograms performed within the first year after the ICD implantation, unless any coronary event occurred from ICD implantation to angiogram. Preferably, the most recent coronary angiogram before the ICD implantation was used. A CTO was defined as a total coronary artery occlusion of 1 of the main arteries or large side-branches, with thrombolysis in myocardial infarction (TIMI) 0 flow and an assumed duration of ≥3 months (based on prior angiograms/prior documented myocardial infarction in the area of the CTO). In case of the presence of a CTO, the location of the CTO was recorded in a database following a 16-segment subdivision of the coronary artery tree.[12] Any additional lesions were also recorded in the database, and MVD was defined as a lesion >50% in, or previous percutaneous coronary intervention (PCI) of, or coronary artery bypass grafting (CABG) of 2 or more main coronary arteries or large side-branches (ie, diagonal branch or obtuse marginal branch).

Additionally, the quality of collaterals to the CTO was assessed using the Rentrop grade system.[13] Of the CTO patients who underwent revascularization (either PCI or CABG), surgery reports and PCI angiograms were assessed to investigate whether or not the CTO lesion was successfully revascularized. In case of successful CTO revascularization before the ICD implantation, the patient was allocated to the

non-CTO group. In case of (re)occlusion of the CTO lesion or bypass, the patient was placed in the CTO group.

Device Implantation, Programming, and Device Interrogation

All devices that were used were manufactured by Biotronik (Berlin, Germany), Boston Scientific (Natick, MA), Medtronic (Minneapolis, MN), or St. Jude Medical (St Paul, MN). A single-chamber ICD, or a dual-chamber ICD, or a Cardiac Resynchronization Therapy Defibrillator (CRT-D) was implanted.[14] Following implantation, sensing and pacing thresholds were tested, and a defibrillation threshold test was performed. At the start of the data collection for the registry, up until the year 2000, most devices were programmed with a single zone in which shocks were programmed to terminate VA >185 beats/min. From 2004 onward, the devices were programmed with 3 zones: VA with a frequency from 150 to 188/190 were detected in a monitoring zone and no therapy was programmed (30–32 intervals were needed for detection [NID] or 8/10 with a 2.5-s initial delay, depending on the manufacturer).[14] VA with a frequency >188/190 per minute were detected in the ventricular tachycardia (VT) zone, programmed with 2 to 4 bursts of antitachycardia pacing to terminate the VA, followed by shock if the VA persists (22–30 intervals needed for detection or 8/10 with a 2.5-s initial delay, depending on the manufacturer). The final zone was programmed to detect VA >220 to 231 beats/min, in which shock was the first therapy (12–30 intervals needed for detection or 8/10 with a 1.0-s initial delay, depending on the manufacturer).[14] From 2008 to 2009 onward, antitachycardia pacing was programmed during charging in the last zone, depending on the manufacturer. Furthermore, supraventricular tachycardia discriminators were enabled, and atrial arrhythmia detection was set to >170 beats/min.[14]

Follow-Up

Periodic follow-up visits were performed every 3 to 6 months. During follow-up visits, patients were clinically assessed, and devices were interrogated. During this device interrogation, stored episodes were analyzed and defibrillator interventions were registered. Device therapy was classified on the basis of intracardiac electrograms and was considered appropriate only when occurring in response to VT or ventricular fibrillation (VF). All other triggers for therapy were considered inappropriate.

In the case of emigration or transmigration resulting in referral to centers far from the primary center, or when follow-up visits were not performed for ≥12 months, follow-up was considered incomplete. These patients were censored in the analysis at last known date of contact. In the case of heart transplantation or premature termination of ICD treatment, follow-up was ended at the time of intervention.

Patients who did not reach any end point remained at risk until the end of the study. Survival status was retrieved from regularly updated municipal civil registries. In all deceased patients, the cause of death was retrieved from hospital letters or follow-up reports if present, and otherwise from the general practitioner.

End Points and Definitions

The end points of interest for this study were the occurrence of appropriate device therapy (as a substitute for VA occurrence) and all-cause mortality, hypothesizing that in the CTO group these end points would occur more often. Appropriate device therapy was defined as shock or antitachycardia pacing for VF/VT. Therapy delivered for anything other than VT or VF was defined as inappropriate. Additionally, (patient and coronary) variables associated with the occurrence of appropriate device therapy and all-cause mortality were identified. Furthermore, we investigated the impact of a CTO on end points in patients with an ICD for primary as compared with secondary prevention, the role of collateral vessels to the CTO, and the influence of SVD and MVD with or without a CTO on outcomes. At baseline, we calculated an adjusted MADITII (Multicenter Automatic Defibrillator Implantation Trial II) risk score for all patients. The previously published MADITII risk score[15] entails presence of New York Heart Association functional class >II, atrial fibrillation at baseline, a QRS duration of >120 ms, age >70 years, and blood urea nitrogen >26 mg/dL. Presence of any of these variables was scored as 1, and per patient a total risk score was calculated (with a maximum score of 5). Since blood urea nitrogen is not used regularly in the clinical setting in The Netherlands, we used creatinine level >1.3 µmol/L instead, which does not influence the sensitivity of the risk score as assessed by the developers of the risk score.[15]

Statistical Analysis

Continuous variables are depicted as mean (±SD) or median (interquartile range), and comparisons between groups were made using independent *t* test or nonparametric tests, respectively. Categorical variables are depicted as frequencies (percentage of total), and comparisons between groups were made with the Fisher exact test or χ^2 test when applicable. All-cause mortality event rates within groups are depicted with Kaplan–Meier curves, and were compared using the log-rank test. Kaplan–Meier estimates for 10-year follow-up were derived from the analyses, and depicted as the estimate rates with SE. Cox proportional hazards regression was used to assess the predictive value of variables on outcomes, after visual verification of the proportionality assumption. Appropriate variables were included after backward stepwise selection, excluding variables with a $P>0.10$.

For appropriate device therapy, the left ventricular ejection fraction (LVEF) was forced into the multivariate model since it is a known strong predictor for device therapy. Overall, a *P* value of <0.05 was considered statistically significant. All analyses were performed using SPSS (Version 24; IBM Corp., Armonk, NY).

Results

Inclusion and Patient Population

In total, the cohort consisted of 722 patients with an ICD for ischemic cardiomyopathy (ICM) for whom an angiography was available (see Figure 1 for the flow diagram). Of these 722 patients, 275 (38%) had a CTO before the ICD implantation and 35 (13%) of these patients underwent CTO treatment (either PCI or CABG) before the ICD implantation, resulting in a total number of 240 patients (33%) with a confirmed CTO at the time of ICD implantation. Fifty-nine of these patients (25%) had >1 CTO at baseline. The median time between date of the angiography used for CTO identification and date of ICD implantation was 1 (0.4–15) week. The median documented duration of the CTOs (age of the CTOs) was 44 (2–127) months.

Long-Term Outcomes

On long-term follow-up, with a median duration of 4 (2–6) years, the overall crude cumulative event rates in this ICD population were 30% for appropriate device therapy and 39% for all-cause mortality. Both appropriate device therapy and all-cause mortality occurred more frequently in the CTO group, compared with the non-CTO group (37% versus 27%, *P*=0.010, and 49% versus 33%, *P*<0.001, respectively) (Table 3).

Figure 2 shows the Kaplan–Meier curves for appropriate device therapy and survival, comparing patients with and without a CTO. The 10-year appropriate device therapy Kaplan–Meier estimates were 55 (SE 5)% for patients with a CTO and 43 (SE 4)% for patients without a CTO. The Kaplan–Meier estimates for 10-year survival were 26 (SE 5)% for patients with a CTO and 42 (SE 4)% for patients without a CTO, and the Kaplan–Meier estimates for other time points are shown in Table 4.

On long-term follow-up, corrected for baseline patient and angiographic characteristics such as LVEF, the presence of a CTO was an independent predictor for appropriate device therapy (hazard ratio 1.394; 95% confidence interval, 1.060–

1.832; 0.018) and there was a trend for higher all-cause mortality (hazard ratio 1.269; 95% confidence interval, 0.996–1.616; *P*=0.054) (Tables 5 and 6).

Influence of Primary Prevention Versus Secondary Prevention

Irrespective of whether the ICD was implanted for primary or secondary prevention, CTO patients had worse survival compared with non-CTO peers. Primary prevention patients without a CTO experienced the lowest appropriate device therapy rate, compared with primary prevention patients with a CTO and secondary prevention patients (Figure 3).

Current Available Data

In Figure 4A and 4B, an overview of the available event rates for all-cause death and appropriate device therapy of all studies on this subject is depicted.[8, 9, 10] Event rates were numerically higher in CTO patients with an ICD for ICM, compared with patients without a CTO.

Influence of SVD, MVD, and CTO

Patients with SVD without a CTO experienced the lowest rate of appropriate device therapy over time, followed by patients with MVD without a CTO, compared with patients with a CTO (Figure 5). Furthermore, patients with SVD with or without a CTO had the highest survival rate compared with patients with MVD and a CTO (Figure 5).

Influence of Collaterals

In patients with a CTO, the presence of well-developed collaterals did not seem to influence long-term survival nor appropriate device therapy compared with patients with poorly developed collaterals (Figure 6).

CTO Revascularization

A small proportion of the CTO patients in this cohort was revascularized before the ICD implantation (n=35), mainly because of myocardial viability, inducible arrhythmias in the CTO territory, or severe CAD for which CABG was indicated. Patients with a revascularized CTO had similar appropriate device therapy rates compared with patients without a CTO (n=447) (Figure 7). Regarding long-term survival, patients with a revascularized CTO had similar survival rates compared with patients with a CTO (Figure 7).

Location of the CTO Lesion

Appropriate device therapy rates were similar between patients with a CTO in the right coronary artery, left anterior descending coronary artery, or ramus circumflexus coronary artery (Figure 8). Survival was highest in patients with a CTO in the ramus circumflexus coronary artery (Figure 8).

Discussion

The current study showed that on long-term follow-up, patients with an ICD for ischemic heart disease who also have a CTO (1) received more appropriate device therapy and (2) had a higher all-cause mortality, compared with ICD patients with ICM but without a CTO; (3) corrected for several baseline characteristics (including age, LVEF, and QRS duration). The presence of a CTO was an independent predictor for more appropriate device therapy in this specific patient population.

Currently Available Data

Previous published studies[8, 9, 10, 16, 17] have shown a trend towards higher appropriate device therapy and all-cause mortality rates in ICD patients with a CTO. Also, the presence of a CTO has proven to be associated with a worse survival compared with patients with SVD or MVD without a CTO.[3, 4] The current, substantially larger, study confirms this observation. Regarding appropriate device therapy, Nombela-Franco et al found that patients with an ICD for ICM and a CTO experience more device therapy both in primary (n=162) and secondary (n=425) prevention.[9, 10] We have also observed this in our cohort, suggesting that the presence of a CTO has more impact on the myocardium than 1 or more narrowed coronary arteries.

In the COMMIT-HF (Contemporary Modalities in Treatment of Heart Failure) substudy with patients with ischemic systolic heart failure (n=675), the presence of a CTO (n=278) was associated with an increased 2-year all-cause mortality compared with patients without a CTO (n=397). Also, 1-year cardiovascular mortality and 1-year major adverse cardiovascular event rates were significantly higher in the group of patients with a CTO,[6] and (corrected for LVEF) the presence of a CTO was independently associated with a higher 1-year mortality.

The cause of the high death rate in CTO patients, despite the presence of an ICD, remains unclear. In our cohort this does not appear to be driven by a higher occurrence of, for example, untreatable VAs in the patients with a CTO. It could be postulated that an ICD does decrease mortality from VAs, but that CTO patients have a higher mortality because of the presence of other comorbidities, such as

diabetes mellitus. In addition, when looking at the MADITII risk score (which was developed in a primary prevention population post myocardial infarction) in our population,[15] a trend towards less CTO patients with risk score 0 and more CTO patients with risk scores of 1 and 2 can be appreciated. In the MADITII population,[15] these risk score groups were at lower risk for mortality. Furthermore, in a large portion of all deaths in our cohort, the exact cause was unknown. Hypothetically, these CTO patients could have died more frequently from arrhythmic causes untreatable by an ICD, which would be unknown since their deaths would most likely have been ruled as from natural causes and the ICD would not have been read out postmortem.

The pathophysiology of VAs is important and accordingly, the cause of the CTO could be just as important. Di Marco et al have shown that the presence of a CTO in a previous infarcted area (infarct-related artery [IRA]-CTO) is associated with the occurrence of more VA (especially fast VT/VF) and more ICD therapy.[18, 19] VT ablation could be an appropriate treatment option in these patients. Nevertheless, Di Marco et al have also shown that the presence of an infarct-related artery–CTO is an independent predictor of VT recurrence after VT ablation, compared with patients with prior myocardial infarction without an infarct-related artery–CTO.[20]

Most CTOs are infarct-related artery–CTOs,[1] so this could mean that in CTO patients most likely a larger infarct zone is present, leading to more VTs. Combined with a reduced ischemia reserve (during stress, exercise), leading to more VF, the CTO could be a strong substrate for more arrhythmias. In the eCTOpy-in-ICD population more appropriate therapy was observed in the CTO group, because of both more VT and more VF, compared with the non-CTO group.

Collaterals

The influence of collateral vessels to a CTO has been investigated sparsely. One registry showed that the presence of well-developed collaterals to a concomitant CTO in ST-segment elevation myocardial infarction patients was associated with better long-term survival.[21] In our cohort of stable ICD patients, we found no clear effect of the quality of collateral vessels on survival or on appropriate device therapy, although appropriate device therapy appeared to occur more frequently in patients with well-developed collaterals. In the VACTO secondary (impact of chronic total coronary occlusion on recurrence of ventricular arrhythmias in ischemic secondary prevention implantable cardioverter-defibrillator recipients) study, a trend towards more appropriate therapy was observed in patients with Rentrop 3 collaterals.[9] The authors hypothesize that

hibernating myocardium may explain this finding.[9] In patients with good collateral filling of the CTO vessel, more viability could be present, especially in a border zone around the necrotic core of the area affected by the CTO.[9] This hypothesis has been underscored in a cardiac magnetic resonance imaging study of patients in the EXPLORE (Evaluating xience and left ventricular function in PCI on occlusions after STEMI) trial (ST-segment elevation myocardial infarction patients with a concurrent CTO [n=302]). Patients with well-developed collaterals showed an improved restoration of dysfunctional segments in the CTO territory, compared with patients with poorly developed collaterals.[22] In addition, Werner et al showed that few patients with well-developed collaterals show a normal coronary flow reserve, which suggests that even in these patients episodes of ischemia can occur, which would be a trigger for VA.[9, 23]

Primary Versus Secondary Prevention in Combination With a CTO

The presence of a CTO results in higher all-cause mortality rates in patients with an ICD for ICM for both primary and secondary prevention. The presence of a CTO has, however, a less abundant effect on appropriate device therapy in secondary prevention patients in the long term. However, the relatively lower number of secondary prevention patients in our cohort (n=191) could have played a role in this observed difference. On the Kaplan–Meier curve, at 2-year follow-up a clear divergence of the appropriate therapy rates in the secondary prevention patients with a CTO can be observed. This coincides with the observations made in the VACTO secondary study. In their population (n=425) of secondary prevention patients, the presence of a CTO was associated with, and was an independent predictor for, both decreased survival and more appropriate therapy.[9]

Treatment of a CTO

Since it has been established that patients with a CTO experience more VAs and have a lower life expectancy, one of the most significant questions is whether CTO revascularization can improve outcomes. In general registry populations of patients with a CTO, CTO revascularization seems to improve outcomes.[1, 24] Regarding patients with an ICD for ICM and a CTO, little is known about the effect of revascularization. Raja et al compared patient groups without a CTO, with a CTO, and with a revascularized CTO. Their analyses did not show any statistical differences between the 3 groups.[16] Yap et al looked at outcomes in a small subgroup (n=25) of out of hospital cardiac arrest patients with a CTO, and found that compared with patients with an unrevascularized CTO, event rates were similar. The current study showed that appropriate device therapy rates in patients undergoing CTO revascularization (n=35) before ICD implantation were

similar to the rates found in the non-CTO group (n=447). The currently limited available data is thus conflicting with regard to the question of whether CTO revascularization influences the increased occurrence of VAs in CTO patients, but our data might suggest that CTO revascularization could improve electrical stability and reduce appropriate device therapy, which is a heavy burden for ICD patients. In addition, one could question the need for an ICD in patients with a successfully revascularized CTO.

In a systematic review and meta-analysis of studies investigating the effect of CTO revascularization on ECG parameters, we found that directly after successful revascularization, several ECG parameters improved compared with before CTO revascularization.[7] However, in most of the included studies in this review, no clinical follow-up data were available.[7] Therefore, whether CTO revascularization truly ameliorates ventricular arrhythmogenicity remains unclear. Furthermore, what type of CTO revascularization should be preferred (CTO, PCI, or CABG) is also unknown.

Limitations

This study has several limitations that should be taken into account when interpreting the data. First, this study is a registry study, with all associated limitations. Importantly, because of the retrospective nature of this study, there is a lack of insight into reasons whether or not to revascularize the diagnosed CTOs. Also, in some of the patients the exact cause of death could no longer be determined, and since in The Netherlands it is not customary to read out the ICD postmortem, no information on arrhythmias premortem was available. Second, for some subanalyses the numbers are low, so these analyses should be considered purely as hypothesis generating.

Conclusion

The current study shows that in a large cohort of patients with an ICD for ICM, the presence of a CTO is associated with more appropriate device therapy and worse survival at long-term follow-up, compared with patients without a CTO. Moreover, the presence of a CTO in patients with an ICD is an independent predictor for the occurrence of VAs leading to more appropriate device therapy. CTO revascularization might ameliorate this negative effect of a CTO on the myocardium.

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Table 1. Patient baseline characteristics.

	Overall (n=722)	CTO (n=240)	Non-CTO (n=482)	p-value
Age (year)	66±11	67±10	65±11	0.019
Male	605 (84%)	208 (87%)	397 (82%)	0.163
Diabetes Mellitus	194 (27%)	75 (31%)	119 (25%)	0.009
Hypertension	334 (46%)	115 (51%)	219 (48%)	0.466
Hypercholesterolemia	327 (45%)	133 (55%)	194 (40%)	0.001
Family history of CVD	270 (37%)	90 (38%)	180 (37%)	0.295
Family history of SCD	37 (5%)	11 (5%)	26 (5%)	0.568
Creatinine clearance	73 [52-99]	70 [50-95]	76 [55-100]	0.019
History of CABG	268 (37%)	86 (36%)	182 (38%)	0.424
ICD indication				0.031
- Primary prevention	531 (74%)	164 (68%)	367 (76%)	
- Secondary prevention	191 (27%)	76 (32%)	115 (24%)	
ICD type				0.383
- Single- or dual chamber	402 (56%)	128 (53%)	274 (57%)	
- CRT-D	320 (44%)	112 (47%)	208 (43%)	
AFl/AF	218 (30%)	67 (28%)	151 (31%)	0.390
LVEF	30% [25-37]	30% [22-35]	31% [26-38]	0.001
QRS duration (ms)	120 [100-150]	120 [104-156]	117 [100-150]	0.029
Medication use				
- Beta-blocker	504 (70%)	158 (66%)	346 (72%)	0.103
- Sotalol	79 (11%)	21 (9%)	58 (12%)	0.207
- Calcium antagonist	77 (11%)	30 (13%)	47 (10%)	0.306
- Amiodarone	111 (15%)	45 (19%)	66 (14%)	0.080
- Digoxin	55 (8%)	17 (7%)	38 (8%)	0.767
Documented age CTO (months)	-	43.7 [2.1-127.3]	-	-
MADITII risk score*				0.070
0	157 (22%)	40 (17%)	117 (24%)	
1	178 (25%)	54 (23%)	124 (26%)	
2	167 (23%)	69 (29%)	98 (20%)	
3	128 (18%)	45 (19%)	83 (17%)	
4	65 (9%)	23 (10%)	42 (9%)	
5	27 (4%)	9 (4%)	18 (4%)	

CVD = cardiovascular disease; SCD = sudden cardiac death; ICD = implantable cardioverter defibrillator; AFl = atrial flutter; AF = atrial fibrillation; LVEF = left ventricular ejection fraction; CTO = chronic total coronary occlusion. *adjusted: creatinine level >1.3umol/L instead of blood urea nitrogen level >26mg/dL.

Table 2. Angiographic baseline characteristics.

	Overall (n=722)	CTO (n=240)	Non-CTO (n=482)	p-value
CTO vessel				-
• **LAD**	-	68 (28%)	-	
• **RCx**	-	48 (20%)	-	
• **RCA**	-	124 (52%)	-	
Proximal location CTO	-	133 (55%)	-	-
Max collateral Rentrop				-
• **Grade 0**	-	37 (15%)	-	
• **Grade 1**	-	101 (42%)	-	
• **Grade 2**	-	60 (25%)	-	
• **Grade 3**	-	33 (14%)	-	
• **Unknown**	-	9 (4%)		
Type of collateral filling				-
• **Bridge**	-	28 (12%)	-	
• **Retrograde**	-	145 (60%)	-	
• **Both**	-	21 (9%)	-	
Vessel disease (VD)				<0.001
• **1VD**	187 (26%)	34 (14%)	153 (32%)	
• **2VD**	205 (28%)	62 (26%)	143 (30%)	
• **3VD**	330 (46%)	144 (60%)	186 (39%)	

CTO = chronic coronary total occlusion; LAD = left anterior descending coronary artery; RCx = ramus circumflexus coronary artery; RCA = right coronary artery

Table 3. Cumulative crude long-term event rates.

	Overall (n=722)	CTO (n=240)	Non-CTO (n=482)	p-value
All-cause mortality	279 (39%)	118 (49%)	161 (33%)	<0.001
Cause of death (n, % of observed deaths)				0.538
• **Tachy-arrhythmic**	8 (2.9%)	3 (3%)	5 (3%)	
• **Brady-arrhythmic**	2 (1%)	1 (1%)	1 (1%)	
• **Heart failure**	73 (26%)	26 (22%)	47 (29%)	
• **SCD**	6 (2%)	1 (1%)	5 (3%)	
• **Cardiovascular**	28 (10%)	13 (11%)	15 (9%)	
Appropriate device therapy	219 (30%)	88 (37%)	131 (27%)	0.010
• **ATP**	155 (71%)	64 (73%)	91 (70%)	0.651
• **Shock**	132 (60%)	53 (60%)	79 (60%)	1.000
Time-to-first appropriate device therapy in years	2.8 [1.0-5.2]	2.3 [0.9-4.4]	3.1 [1.1-5.6]	0.019
VT ablation	12 (2%)	5 (2%)	7 (2%)	0.555

SCD=sudden cardiac death, miscellaneous consists of malignancy, infectious disease, pulmonary disease etc. Appropriate device therapy consists of ATP and/or shock for ventricular arrhythmia. ATP=anti-tachypacing, VT=ventricular tachycardia, CTO=chronic total coronary occlusion.

Table 4. Kaplan-Meier estimates for appropriate device therapy and all-cause mortality rates at several time-points.

	Appropriate device therapy			All-cause mortality		
	CTO (n=240)	No-CTO (n=482)	p-value	CTO (n=240)	No-CTO (n=482)	p-value
1 year follow-up	15.8%	11.2%	0.103	7.4%	7.3%	0.982
3 year follow-up	36.0%	22.6%	0.003	25.1%	16.5%	0.020
5 year follow-up	46.8%	32.8%	0.002	41.9%	27.8%	0.001

CTO=chronic total coronary occlusion

Table 5. Influence of patient and angiographic characteristics on all-cause mortality.

	Univariate			Multivariate		
Characteristic	**HR**	**95% CI**	**p-value**	**HR**	**95% CI**	**p-value**
Age	1.052	1.038-1.065	<0.001	1.050	1.036-1.064	<0.001
Male sex	0.878	0.634-1.215	0.433	-		
Hypertension	1.124	0.883-1.429	0.342	-		
Hypercholesterolemia	1.126	0.871-1.454	0.365	-		
Diabetes mellitus	1.682	1.309-2.162	<0.001	1.573	1.222-2.025	<0.001
Creatinine clearance	1.000	1.000-1.000	0.794	-		
QRS duration	1.001	1.000-1.001	<0.001	1.001	1.000-1.001	<0.001
LVEF	0.980	0.970-0.989	<0.001	0.982	0.972-0.991	<0.001
CTO	1.544	1.217-1.958	<0.001	1.269	0.996-1.616	0.054
Primary prevention	0.853	0.662-1.099	0.218	-		
MVD	1.899	1.395-2.586	<0.001	1.562	1.145-2.131	0.005

LVEF = left ventricular ejection fraction; CTO = chronic coronary total occlusion; MVD = multi-vessel disease

Table 6. Influence of patient and angiographic characteristics on appropriate device therapy.

	Univariate			Multivariate		
Characteristic	**HR**	**95% CI**	**p-value**	**HR**	**95% CI**	**p-value**
Age	1.017	1.004-1.030	0.013	1.013	1.00-1.026	0.055
Male sex	1.901	1.200-3.011	0.006	1.757	1.107-2.787	0.017
Hypertension	1.051	0.800-1.380	0.723	-		
Hypercholesterolemia	0.930	0.701-1.234	0.616	-		
Diabetes mellitus	0.845	0.614-1.163	0.302	-		
Creatinine clearance	1.000	1.000-1.000	0.224	-		
QRS duration	1.000	1.000-1.001	0.302	-		
LVEF	1.000	0.997-1.002	0.750	0.999	0.989-1.008	0.801
CTO	1.529	1.166-2.005	0.002	1.394	1.060-1.832	0.018
Primary prevention	0.516	0.393-0.679	<0.001	0.548	0.416-0.723	<0.001
MVD	1.273	0.931-1.743	0.131	-		

LVEF = left ventricular ejection fraction; CTO = chronic coronary total occlusion; MVD = multi-vessel disease

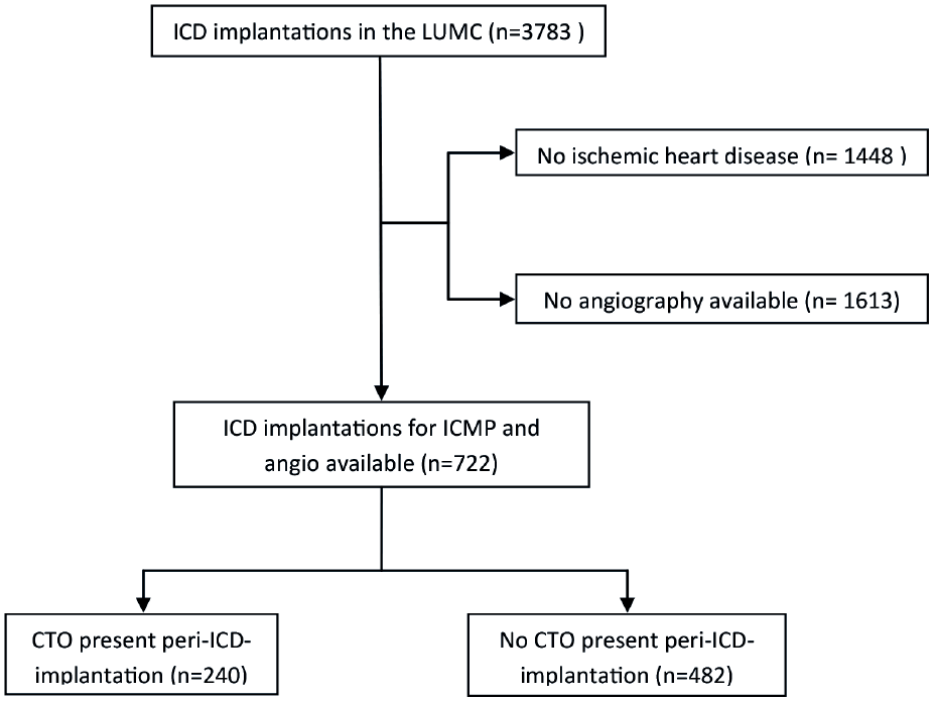


Figure 1. Flow-diagram of patient inclusion.
ICD: implantable cardioverter defibrillator; CTO: chronic total coronary occlusion.

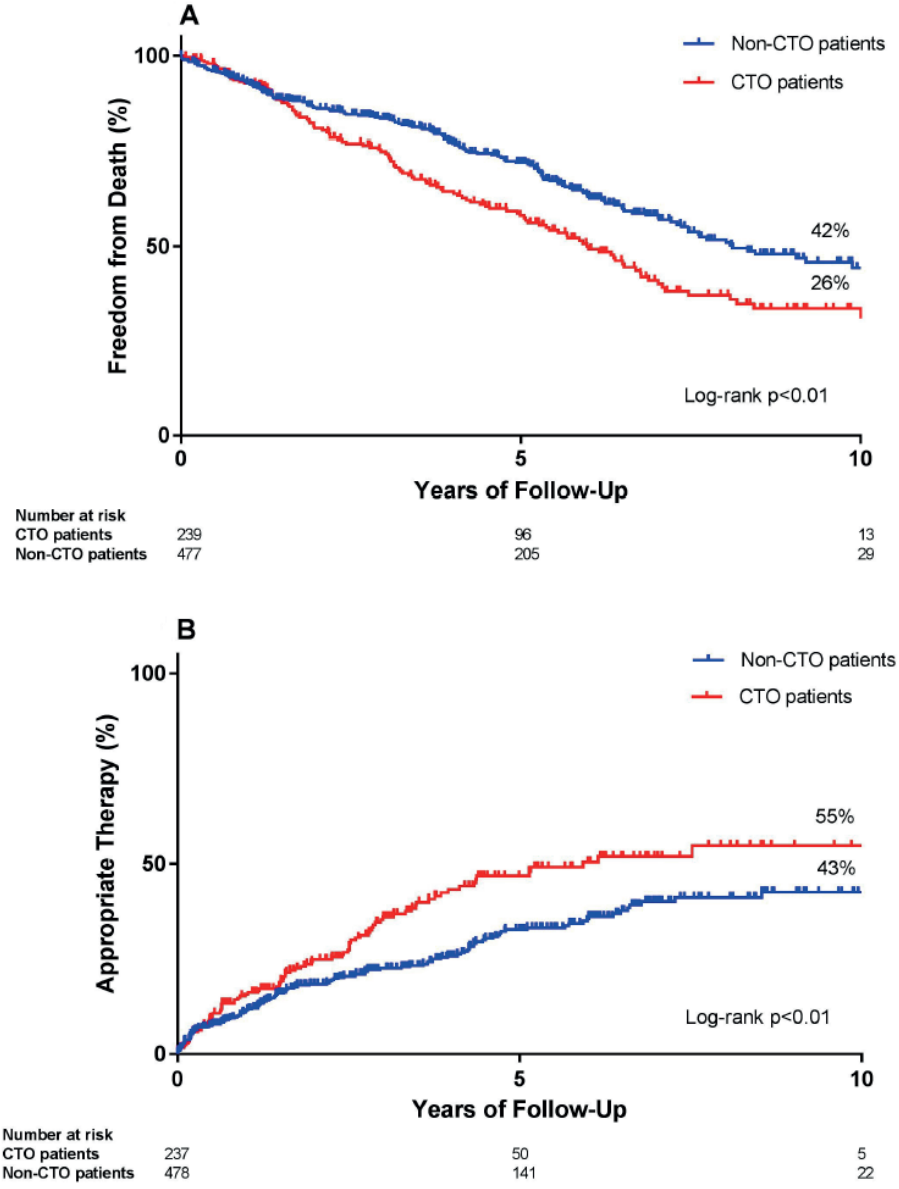
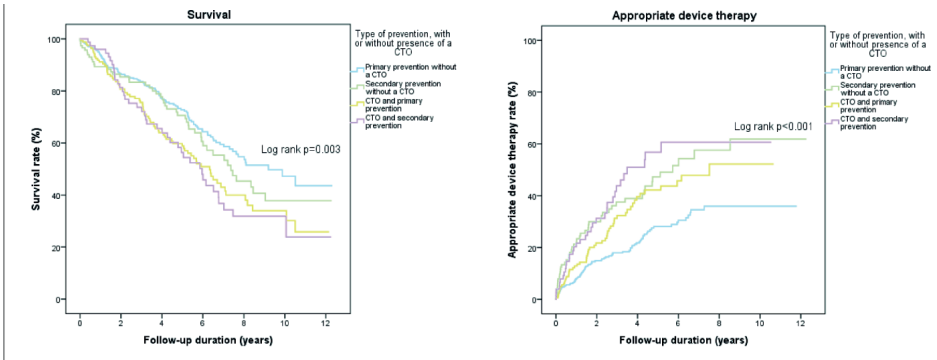


Figure 2. Kaplan–Meier curves for freedom of death (A) and appropriate device therapy (B), comparing patients with and without a CTO. CTO: chronic total coronary occlusion.



No at risk	0	2	4	6	8	10	12
Prim. prev. + CTO	164	114	78	46	21	9	1
Prim. prev. – CTO	366	263	183	111	51	18	1
Sec. prev. + CTO	76	55	38	22	13	4	1
Sec. prev. - CTO	115	86	67	36	20	10	1

No at risk	0	2	4	6	8	10	12
Prim. prev. + CTO	164	90	48	27	9	3	0
Prim. prev. - CTO	366	233	150	87	38	15	0
Sec. prev. + CTO	76	39	19	9	5	2	0
Sec. prev. - CTO	115	59	39	18	11	6	1

Figure 3. Influence on long-term outcomes of the presence of a CTO in primary and secondary prevention. CTO: chronic total coronary occlusion.

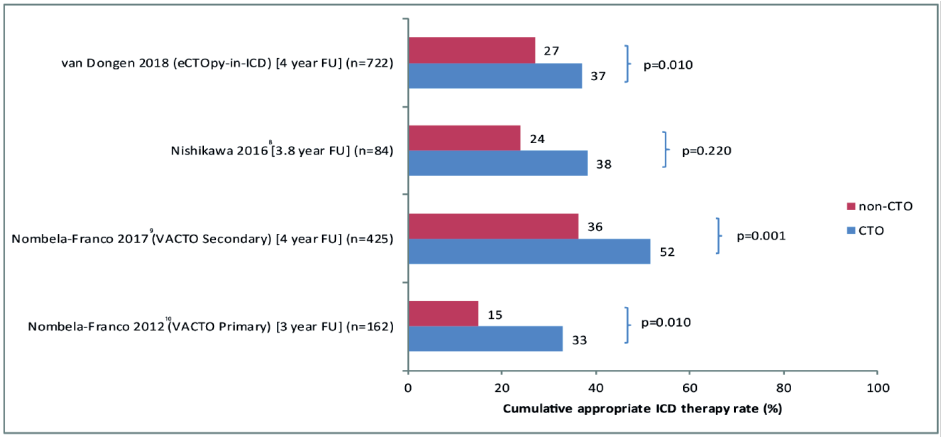


Figure 4. A. Overview of all-cause mortality rates (%) per study. B. Overview of cumulative appropriate ICD therapy rates (%) per study. ICD: implantable cardioverter defibrillator.

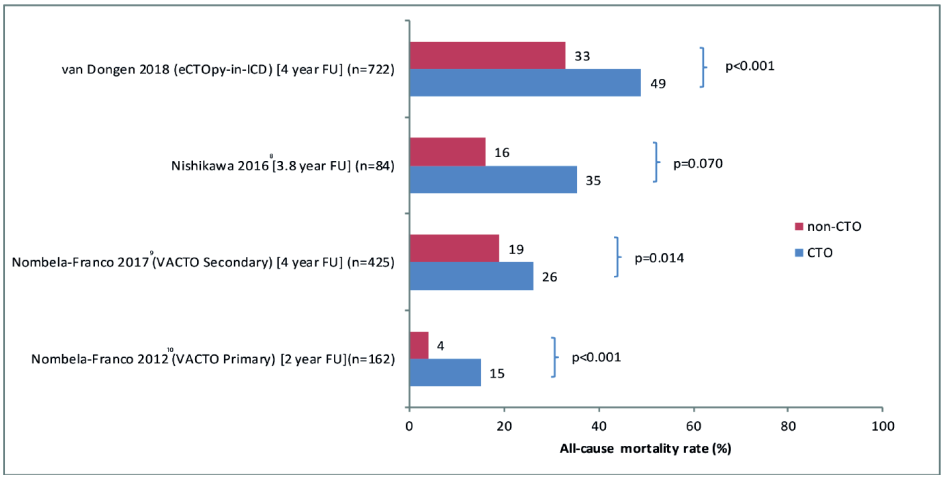
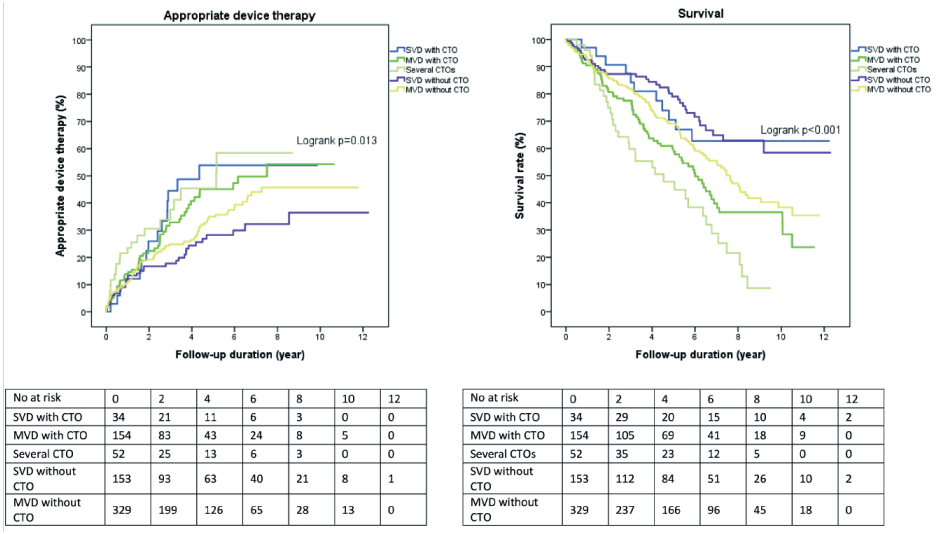


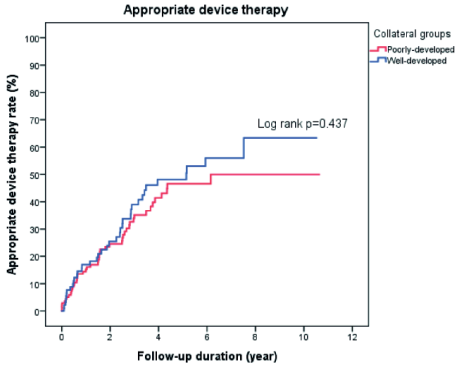
Figure 5. Influence on long-term outcomes of single-vessel disease, multi-vessel disease and presence of a CTO. CTO: chronic total coronary occlusion. SVD: single-vessel disease; MVD: multi-vessel disease.



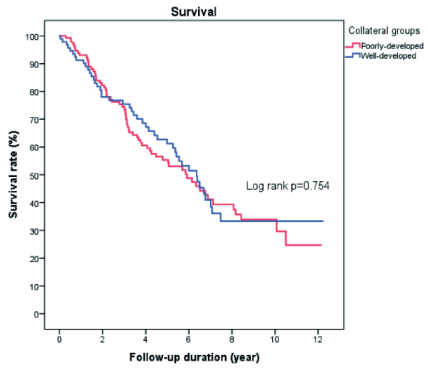
No at risk	0	2	4	6	8	10	12
SVD with CTO	34	21	11	6	3	0	0
MVD with CTO	154	83	43	24	8	5	0
Several CTO	52	25	13	6	3	0	0
SVD without CTO	153	93	63	40	21	8	1
MVD without CTO	329	199	126	65	28	13	0

No at risk	0	2	4	6	8	10	12
SVD with CTO	34	29	20	15	10	4	2
MVD with CTO	154	105	69	41	18	9	0
Several CTOs	52	35	23	12	5	0	0
SVD without CTO	153	112	84	51	26	10	2
MVD without CTO	329	237	166	96	45	18	0

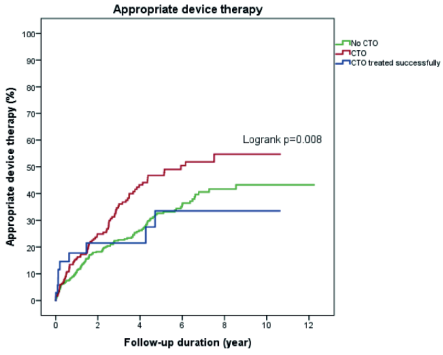
Figure 6. Influence on long-term outcomes of poorly-developed versus well-developed collaterals



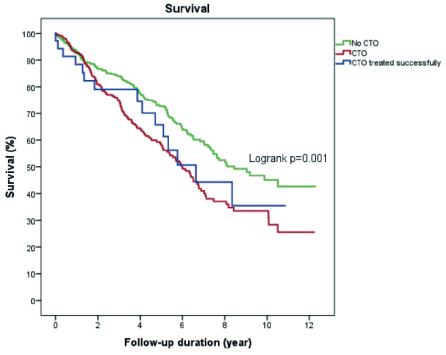
No at risk	0	2	4	6	8	10	12
Poorly-developed	138	75	36	17	9	3	0
Well-developed	93	48	26	15	4	1	0



No at risk	0	2	4	6	8	10	12
Poorly-developed	138	98	62	34	22	8	1
Well-developed	93	63	47	30	11	4	1

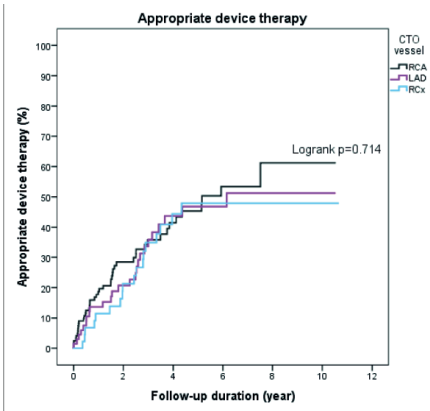


No at risk	0	2	4	6	8	10	12
No-CTO	447	272	175	99	46	20	1
CTO	240	129	67	36	14	5	0
CTO treated successfully	35	20	14	6	3	1	0

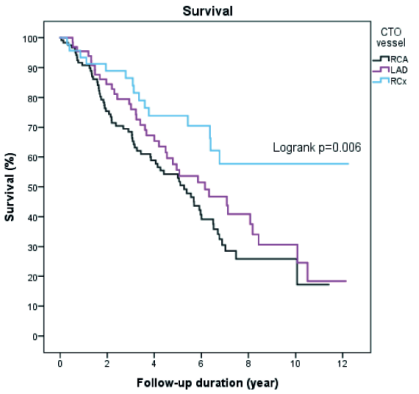


No at risk	0	2	4	6	8	10	12
No-CTO	447	325	233	138	66	26	2
CTO	240	169	116	68	34	13	2
CTO treated successfully	35	24	17	9	5	1	0

Figure 7. Influence on long-term outcomes of CTO revascularization. CTO: chronic total coronary occlusion.



No at risk	0	2	4	6	8	10	12
RCA	124	55	31	15	5	2	0
LAD	68	42	20	13	5	1	0
RCx	48	32	16	8	4	2	0



No at risk	0	2	4	6	8	10	12
RCA	124	77	53	38	10	3	0
LAD	68	53	36	23	12	5	1
RCx	48	39	27	18	12	5	1

Figure 8. Influence of location of the CTO lesion. CTO indicates chronic total coronary occlusion; LAD, left anterior descending coronary artery; RCA, right coronary artery; RCx, ramus circumflexus coronary artery.

Part II

Implantable Cardioverter Defibrillator therapy
in the last moments of life

Chapter 4A

Patients With an Implantable Cardioverter Defibrillator therapy in the last moments of life Remain at Risk for Painful Shocks in Last Moments of Life.

Yilmaz D, van der Heijden AC, Thijssen J, Schalij MJ, van Erven L.

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Patients with an Implantable Cardioverter Defibrillator (ICD) are at risk of unnecessary painful shocks at the end of life when tachytherapy is still active. In 2010, the European Heart Rhythm Associations and the American Heart Rhythm Society published statements on ICD-therapy in patients nearing end of life (1,2). Subsequently, the Netherlands Association for Cardiology (NVVC) released the national guideline "ICD/pacemakers in the last phase of life" in 2013. The current study was performed to evaluate the practice of ICD tachytherapy deactivation prior to death over the last 10 years to reveal areas for improvement.

All patients who received an ICD or Cardiac Resynchronization Therapy-Defibrillator at our institution, and who died between 2006 and 2015, were evaluated. Follow-up was recorded in electronic patient files and the survival status of patients was retrieved from municipal civil registries. Patient records were reviewed to identify cause of death, ICD therapy status and type of device at time of death. Causes of death were categorized according to a modified Hinkle-Thaler Classification (3).

Between 2006-2015, 949 ICD patients died (mean age 72±10 years; 734 (77%) males; 577 (61%) primary prevention; median time from first ICD 4.5 (2-7) years). Baseline characteristics of patients withdrawn from tachytherapy prior to death did not differ from those who were not (data not shown). Overall, 321 (34%) devices were deactivated prior to death. A Kruskal-Wallis H test showed that the time from deactivation to death did not significantly differ between the years ($p = 0.12$), with time from deactivation ranging from 1 to 24 days. Time from deactivation was less than 24hrs in 104 (34%) of the patients.

We observed a gradual the proportion of patients withdrawn from tachytherapy over time, to just above 50% in the last 3 years (figure). A logistic regression analysis was performed to evaluate the differences in tachytherapy withdrawal rates over the years, which was statistically significant ($p < 0.0001$). Moreover, the rate of withdrawal doubled within the first four years. Most frequently, tachytherapy deactivation was initiated by the attending physicians in the hospital (n=197, 61%), most often whilst the patient was in a hospitalized setting (n=177, 55%). Most frequent causes of death observed in the 321 patients withdrawn from tachytherapy was terminal heart failure in 38% and malignancy in 24%. Other causes included infectious diseases, renal failure and stroke. This study provides insight in the practice of tachytherapy withdrawal during the last phase of life in a large population of ICD patients throughout the last decade. The gradual increase of tachytherapy deactivation over the last 10 years from 6% to 52% is encouraging.

Nevertheless, a substantial proportion of patients remains at risk for shocks. In addition, time from deactivation to death, has not changed over the years. This allows for the question how further improvement can be achieved. To evaluate whether patients in the last three years had an identifiable terminal stage which could have prompted discussions on tachytherapy withdrawal, all cases of the plateau era were reviewed. Between 2013 and 2015, 141 patients died without prior tachytherapy withdrawal. In retrospect, a terminal stage could be identified in 36 (26%). In 2 of these patients, tachytherapy withdrawal was planned but could not be performed in time. Acute deterioration of the clinical status of a patient appears to prompt ICD deactivation. However, the limited period of time remaining and the subsequent logistical constraints lead to failure of withdrawal. Most important additional improvement is to be expected from recognizing the beginning of the palliative or terminal phase. This stage is easily missed at the biannual (or less in case of remote monitoring) check-ups by ICD caregivers. Early and repetitive discussions, e.g. at first implantation or regular ICD follow-ups, with patient and family on the risks of shocks at the end of life is needed to allow for time to create patient awareness and acceptance of ICD therapy withdrawal.

References

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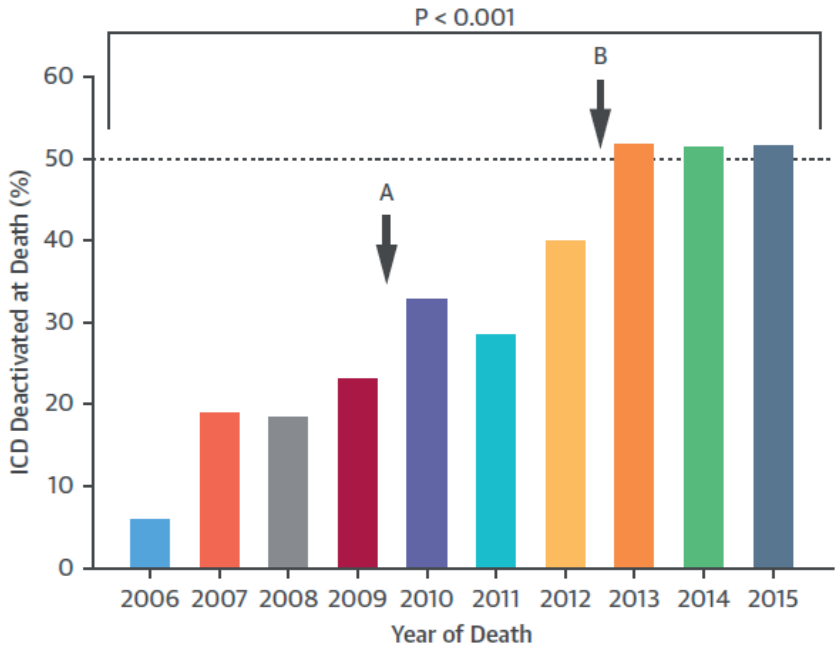
3. Hinkle LE, Jr., Thaler HT. Clinical classification of cardiac deaths. Circulation 1982;65:457-64.

FIGURE 1 **Proportion of Tachytherapy Deactivation in Patients With an ICD Deceased Each Year Between 2006 and 2015**



(A) Indicates 2010 publication of position papers by the European Heart Rhythm Associations and American Heart Rhythm Society. **(B)** Indicates 2013 introduction of the Dutch guideline. ICD = implantable cardioverter-defibrillator.

Figure. Proportion of tachytherapy deactivation in ICD patients deceased each year between 2006–2015. A: 2010, publication position papers European Heart Rhythm Associations and American Heart Rhythm Society. B: 2013, introduction Dutch guideline.

Chapter 4B

Causes of death in patients withdrawn from tachytherapy

Yilmaz D, van der Heijden AC, Thijssen J, Schalij MJ, van Erven L.

Unpublished

Abstract

Background

Implantable Cardioverter-defibrillators (ICDs) have proven effective in preventing sudden cardiac death. However, patients with active ICD devices face the risk of painful shocks during end-of-life care. Despite guidelines, there's variability in ICD-tachytherapy deactivation practices.

Objective

This study aimed to analyze ICD-tachytherapy deactivation trends over a decade and assess the mode of death among patients whose tachytherapy was deactivated.

Methods

The study included patients from the Leiden University Medical Center's ICD registry who died between 2006 and 2015. Data on deactivation, cause of death, and device status were collected. Trends in deactivation practices and causes of death were analyzed.

Results

Of 949 deceased patients, 321 (33.8%) had tachytherapy deactivated before death. The majority were male (75%) with a median age of 73 years. Terminal heart failure (38%) and malignancy (24%) were the primary causes of death among those with tachytherapy deactivated. Over time, there was a shift in causes of death, with increasing numbers of patients with non-cardiac terminal illnesses undergoing tachytherapy deactivation.

Discussion

The study highlights a growing awareness of ICD-tachytherapy implications for end-of-life care. Deactivation practices have diversified beyond cardiac care settings, emphasizing the importance of advanced care planning across medical disciplines.

Conclusion

Increasing awareness has led to improved tachytherapy withdrawal policies. Deactivation rates have risen, encompassing patients with non-cardiac terminal illnesses. Early discussions and open communication are crucial for avoiding unnecessary shocks and stress during patients' final moments.

Introduction

Large randomized trials have demonstrated the beneficial effect of Implantable Cardioverter-defibrillators (ICDs), initially in survivors of life-threatening ventricular arrhythmias (secondary prevention) and subsequently, also in patients at high risk of sudden cardiac death (primary prevention).(1-7) As expected, along with the adoption of the international guidelines incorporating these results, a progressive decrease in the annual number of people dying of sudden cardiac death was observed in developed countries such as the Netherlands.(8) While heart disease was the leading cause of death for decades, as of 2009, death by cancer has exceeded the number of cardiac deaths in the Netherlands. (9, 10) The majority of causes of death leave time for advance care planning. For ICD patients, this is important since, in case of an active ICD-device, they are at risk of painful tachytherapy shocks in the last hour of life and first moments of death, imposing great morbidity on patients and next-of-kin.(11) Attention has been drawn towards the subject by several reports on repetitive, unwanted and unnecessary shock therapy in dying patients(12-16). The International and national position papers (17, 18) and guidelines (19) have been published to provide physicians with recommendations on tachytherapy management in the ICD patients when the end of life is in sight. However, considering the implications of an ICD at the last moment of life, it is important not only for cardiac care givers, but for all medical disciplines to be aware of the possible deactivation of ICD-tachytherapy in the last moments of life.

The current study was performed to examine the practice of ICD-tachytherapy deactivation over the last 10 years, thereby assessing the mode of death amongst patients who have died after their ICD's tachytherapy was deactivated.

Methods

Study population

Since 1996, all patients who received an ICD or CRT-D at the Leiden University Medical Center (LUMC), the Netherlands, are registered in the departmental Cardiology Information System (EPD-Vision®; Leiden University Medical Center, Leiden, The Netherlands) and followed up on prospectively. This registry has been described in previous studies.(20-24) Characteristics at baseline, data of the implant procedure, and pacemaker/ICD data were recorded. Data of clinical follow-up visits and consultations are best available digitally from 2006 onwards. Eligibility implantation in this population was according to the prevailing

international guidelines.(7, 25-30) For the current analysis, patients deceased between January 1, 2006 and December 31, 2015 whilst still under follow-up for their ICD-care at the LUMC, were selected from our registry. Patients who emigrated or transmigrated and were referred to other centers, or when follow-up visits were not performed for >12 months, were considered incomplete. These patients were excluded from this study. The institutional review board of the LUMC waived the need for informed consent for this study.

Data Collection

After implantation, technical follow-up was performed in all patients at regular intervals of 6 months and clinical follow-up at least once a year. Some patients had a cardiologist at an affiliated center as primary caregiver. All device related follow-up was however performed at the LUMC. Data on ICD interrogations and patient survival recorded in EPD-Vision were checked for delivery ICD-therapy and survival status. The survival status of patients was retrieved from municipal civil registries, enabling identification of also deaths occurring outside our center. Patient records were reviewed in order to identify date of death, cause of death, ICD-therapy status and type of device at time of death. In case of ICD-deactivation prior to death, initiator of the deactivation (i.e. physician, family doctor, patient or family) was noted, including location of the actual deactivation, e.g. hospital ward or patient's (nursing)home.

Logistics of deactivation

Depending on the timing and initiator of tachytherapy deactivation, tachytherapy deactivation was performed by ICD technician or knowledgeable physician, after consultation with the cardiologist in charge. In all cases, the patient and next a kin were informed prior to deactivation. The initiator of deactivation was recorded in the electronic patient file. When patients were unable to visit the hospital for the deactivation, a technician was sent out to perform the task on location. As a result, all deactivations were coordinated by the hospital and recorded in patient files accordingly.

Definition of clinical outcomes and assessment

Deactivation of an ICD-tachytherapy prior to death was defined as deactivation of tachytherapy because of the terminal nature of the patient's disease state or condition. Devices deactivated due to malfunction, improved left ventricle ejection fraction, battery depletion and the decision of not replacing the device, or a patient's specific request due to personal preferences other than life expectancy,

were viewed as tachytherapy withdrawal for other reasons than assessed in this study and excluded.

Appropriate therapy consists of both anti-tachycardia pacing (ATP) and shocks for ventricular tachycardia (VT) or ventricular fibrillation (VF). Appropriate shocks are shocks for VT or VF. Inappropriate therapy consists of both ATP and shocks for heart rhythms other than VT or VF. Inappropriate shocks are those delivered not for VT or VF.

Causes of death were categorized according to a modified Hinkle-Thaler Classification and categorized in three groups: cardiac death, non-cardiac death and sudden death.(31) Cause of death for patients dying while hospitalized was, in absence of an autopsy, based on hospital records. In all other cases without autopsy, the cause of death was determined by the expertise of the contacted general practitioners (i.e. family doctors).

For the purpose of this study, cardiac death was further categorized into tachyarrhythmic death, heart failure death and death due to other cardiac causes. The non-cardiac deaths were divided into death due to malignancy and death due to other non-cardiac causes. Patients who died in their sleep or died unexpectedly without worsening of their clinical situation, were categorized as sudden death cases. Patients who died suddenly but with clear alternative mode of death were categorized as non-sudden cases and allocated to the alternative mode of death's category. Death due to heart failure was defined as patients dying of terminal heart failure, progressive failure of cardiac pump function, or cardiac asthma under maximal inotropic drug support. All other causes were categorized as 'other non-cardiac causes'. In all cases, the mechanism underlying the immediate demise, was selected as the mode of death. In case of palliative sedation and euthanasia, mode of death was categorized according to the underlying illness, e.g. malignancy.

Statistical analysis

Based on their distributions, continuous variables are presented as mean ± standard deviation or median with interquartile ranges (25^{th}, 75^{th} percentile). Dichotomous and categorical data are expressed as numbers and percentages. Deceased patients were divided into two groups: patients with tachytherapy deactivated prior to death and patients with active tachytherapy functions during death.

RESULTS

Patients

A total of 3998 consecutive patients have been enrolled to the Leiden ICD registry between 1996 to December 2015. Of these patients, 1005 deceased between 2006 and 2015. Twenty-eight (2.8%) of these 1005 patients were lost to follow-up. In 28 (2.8%) patients, tachytherapy function of the device was readily deactivated for other reasons or explanted because of expiration of ICD-indication (e.g. heart transplantation or improvement of LVEF). Of the remaining of 949 deceased patients, 321 (33.8%) were withdrawn from tachytherapy prior to their death. Mean age at death was 73±9 years, 241 (75%) patients were male and 201 (63%) patients had a primary ICD-indication. Median time from first ICD-implantation to death was 4.6 (2.7, 7.5) years. Baseline characteristics at primary implantation are summarized in table 1. In table 2 patient characteristics at death are summarized.

Mode of death

In the majority of the 321 patients withdrawn from tachytherapy, death was due to terminal heart failure or malignancy (38% and 24% respectively). Other frequent causes of death included terminal kidney insufficiency, infectious diseases and other non-cardiac causes. Sudden death occurred in only 3 (0.9%) patients with a deactivated device.

Terminal heart failure lead to the death of 186 (30%) patients not withdrawn from tachytherapy. In this latter group, 70 (11%) patients deceased from malignancies and sudden death was identified in 52 (8%) patients as the cause of death.

A gradual change over time in causes of death was observed. Initially, In 2006, all causes of death for patients withdrawn from tachytherapy were cardiac causes. The distribution shifted over time. In 2015 cardiac causes accounted for 64% of all deaths and malignancies alone for 24%. Initially, terminal heart failure patients were the only few patients composing the population in which tachytherapy was timely deactivated. However, a gradual emergence and increase of number of patients and other causes of death can be observed throughout the years, with an uprising of malignancies and other types of non-cardiac terminal illnesses (e.g. terminal kidney failure and refractory infectious diseases) (figure 1).

Tachytherapy withdrawal

In a total of 116 (36%) devices, tachytherapy was deactivated in the last 24 hours of patients' lives. Ninety-nine (31%) devices were deactivated at patients' homes

and nursing homes in case of patients' conditions impeding them from visiting the outpatient clinic in person. Median time from deactivation to death was 96 (24, 480) hours. Most frequently, tachytherapy deactivation was initially proposed by the attending physicians in the hospital (n=197, 61%) most often whilst the patient was in a hospitalized setting (n=177, 55%). In a minority of cases, patients were recognized to be moribund outside of clinical settings and tachytherapy withdrawal was requested by the patient or patient's family (n=59, 18%)(Table 3).

DISCUSSION

This study provides insight in the practice of tachytherapy withdrawal during the last phase of life in a large population throughout a recent decade. The most important findings is the diversification over time of the cause of death in patients with tachytherapy deactivation, indicating an increase of awareness of ICD tachytherapy implications for the last moments of life. Deactivating ICD-tachytherapy is no longer limited to the cardiac care ward. However, although the observed trends are favorable, patients in whom tachytherapy deactivation was not performed, remain to exist in all disciplines. This study's findings press the need for advanced care planning in order to avoid painful shocks and stress in the last moments of patients' lives.

Diversification in cause of death

Causes of death for patients included in the Leiden ICD registry have been previously described.(20) Most patients died from end-stage heart failure (32.6%) or other non-cardiac terminal illnesses such as neoplasms, end-stage renal failure, infectious causes or pulmonary diseases. The number of unknown causes of death is relatively low, with only 11.6% of our registered patients dying from unknown causes. When observed separately for patients withdrawn from tachytherapy prior to death, a diversification throughout the years can be noted. In 2006, the majority of the (few) patients undergoing tachytherapy deactivation were those with terminal heart failure. With the increased awareness of the issue over the recent years, numbers of patients diagnosed with also other terminal illnesses than cardiac causes have risen as well. In the recent years, withdrawal from tachytherapy is no longer limited to patients moribund from cardiac causes. Moreover, it is performed increasingly in patients with terminal malignant disease and other non-cardiac causes.

International scope

With elaborate numbers on end-of-life care practice in other countries being unavailable, it is difficult to put our findings in an international perspective. Colleagues from Northern Ireland observed that in ICD patients deceased in 2012-2013, end of life discussions were performed in up to 52% of their patients, resulting in a deactivation rate of 36.4% overall.(32) It would be interesting to assess the level of end of life discussions in other clinics and countries and deactivation rates throughout the years other than our own to provide more insight in the awareness on this topic internationally. Recent data for other centers over multiple years is unfortunately currently unavailable.

The Netherlands is a relatively small country in which deactivation at patient homes or nursing homes can be arranged on short notice. In larger countries however, this might be more complicated and take longer. In the latter case, there is a risk of being too late to withdraw tachytherapy in patients for whom this is requested in the last moments of life. Early discussions of the topic can therefore be even more valuable to clinics servicing large (rural) areas.

Clinical implications

This is large-scaled study evaluating the practice of tachytherapy withdrawal structurally over multiple years. This study confirms that there has been an increasing awareness for the risk of painful ICD shocks at the last moments of life for patients. The need for tachytherapy deactivation is not limited to patients dying under the care of a cardiologist. Considering the fact that many patients die at home or nursing homes, awareness amongst primary care providers on tachytherapy withdrawal remains necessary.

It is unclear what the exact burden of shocks in patients dying from other causes is. Similar to previous studies, we were unable to assess the true burden of shocks in the last moments of life (other than the estimated cumulative incidence of therapy in the last 30-days of life). Post-mortem read-outs of devices are not a standard part of clinical practice and data is frequently unavailable due patients dying outside the hospital. The only structural study in which devices of deceased patients at one Swedish center were explanted and structurally and consecutively, revealed that 35% of the patients experienced a ventricular tachycardia episode in the last hour of their lives.(11) Secondary prevention was however the case in 82% of the included patients. These results are therefore possibly not applicable to the currently investigated patients and the majority of patients in general clinical practice who mostly have an ICD as primary prevention.

Limitations

This study is an observational cohort study to assess the practice of tachytherapy withdrawal over the past decade in clinical practice. Patients were collected and enrolled to our ICD registry over a long period of time and evolvement of guidelines could have created a heterogeneous population influencing also the development over time. In addition, some patients can also have died whilst under the care of a different caregiver than our hospital with possible tachytherapy withdrawal without our knowledge, leading to an underestimation of tachytherapy deactivation rates. Even though the retrospective non-randomized nature of this study prevents the demonstration of a causal association, the trend over the years is clear and both the trend as the position papers and guideline are a result of an increasing awareness for the issue.

CONCLUSIONS

Increasing awareness of the issue of ICD and tachytherapy in end-of-life care has led to an improvement of tachytherapy withdrawal policies over the recent years. Deactivation numbers have gradually increased, also for patients dying from non-cardiac causes. Identification of a terminal stage of illness is complex and not possible in all patients. Early and open discussions on this issue with also non-moribund patients are an essential part of advanced care planning in order to avoid painful shocks and stress in the last moments of patients' lives.

Tables

Table 1: Baseline characteristics at ICD implantation.

Baseline characteristic	All patients (n=321)
Age at implant (y),	68 ± 9
Sex: male	241 (75)
ICD-indication: primary	201 (63)
CRT-D	159 (49.5)
BMI (kg/m^2)	26 ± 3.9
LVEF (%)	30 ± 12
Creatinin (mmol/L)	104 (86, 130)
Ischemic heart disease	221 (69)
Congenital heart disease	5 (1.6)
Hypertension	144 (45)
Diabetes mellitus	77 (24)
NYHA	
• I	78 (24)
• II	86 (27)
• III	134 (42)
• IV	15 (4.7)
• Unknown	8 (2.5)

Categorical variables are expressed by n (%), and continuous variables are expressed by mean ± standard deviation or median (interquartile range). ICD: Implantable cardioverter-defibrillator. CRT-D: Cardiac Resynchronization Therapy-defibrillator. BMI: body mass index. LVEF: left Ventricle Ejection Fraction. NYHA: New York Heart Association classification of dyspnoea.

Table 2. Patient characteristics at time of death.

Patient characteristic	ICD deactivated (n=321)
Age at death (y)	73 ± 9
Median ICD-therapy duration (y)	4.6 (2.7, 7.5)
CRT-D	307 (96)

Categorical variables are expressed by n (%), and continuous variables are expressed by mean ± SD or median (interquartile range). ICD: Implantable cardioverter-defibrillator. CRT-D: Cardiac Resynchronization Therapy-defibrillator.

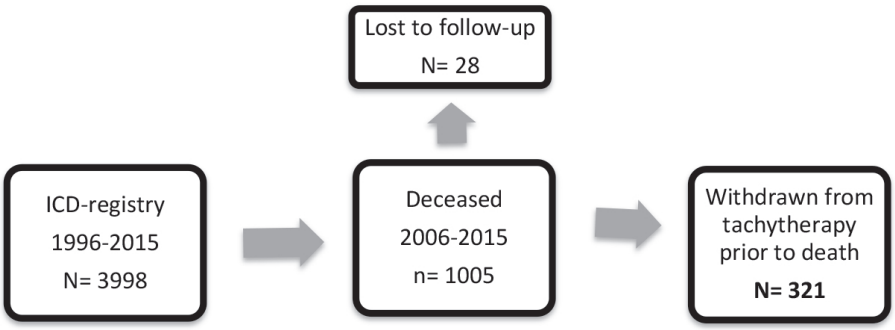
Table 3. Overall results of tachytherapy deactivation

	Therapy deactivated patients (n=321)
Tachytherapy deactivation in last 24hs of life	104 (32)
Location of deactivation	
- Hospital ward	58 (18)
- ICU/CCU	53 (17)
- Outpatient clinic	45 (14)
- (Nursing)home	99 (31)
- Other hospital	66 (21)
Initiator of deactivation	
- Hospital physician	197 (61)
- General Practitioner/primary care physician	65 (20)
- Patient and/or family	59 (18)

Variables are expressed by n (%). ICU: Intensive Care Unit. CCU: Cardiac Care Unit.

Figures

Flow-chart total number of patients included in study:



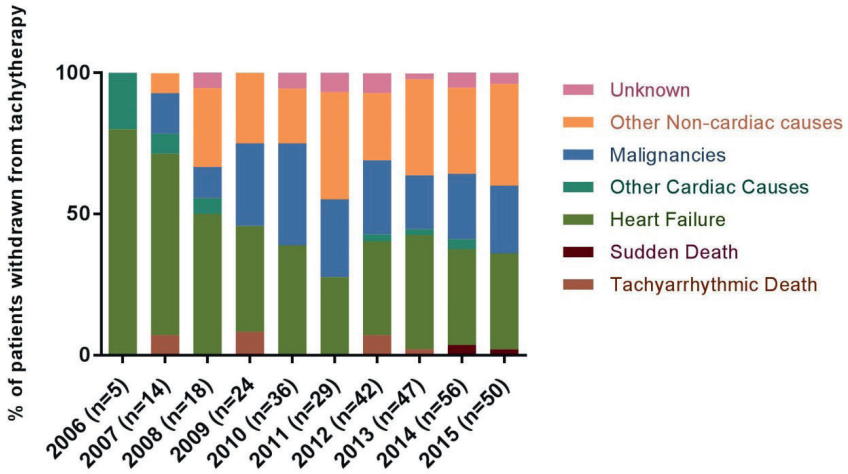


Figure. Distribution of mode of death over the studied decade. Total n=321.

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Chapter 5

Implantable cardioverter-defibrillators and the older patient: the Dutch clinical practice.

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Abstract

Background and objective

Balance between benefit and burden of implantable cardioverter-defibrillator (ICD) therapy is more debatable in older patients, compared to younger patients. Of around 6000 yearly implanted ICDs in the Netherlands, 1:4 is received by patients ≥75 years. We aimed to evaluate the current clinical practice in the Netherlands for ICD implants and generator replacements, with a special focus on the older ICD patients.

Research design and methods

Cardiologists from all Dutch ICD implanting centres (n=28) were interviewed. Questions aimed to evaluate out-patient care, pre-operative patient assessment, end-of-life-care counselling, evaluation of social and cognitive wellbeing, clinical evaluation of all patients prior to ICD replacement and the consideration of the option to downgrade or not replace a device.

Results

Implanting cardiologists from all 28 implanting centres were approached for an interview. Response rate was 86%. Management appeared diverse. Age ≥80 was consistently reported as incentive for more extensive patient evaluation. Patients were invited for counselling prior to device replacements in only the minority (46%) of hospitals. Downgrade or non-replacement was performed in rare cases. End-of-life care discussions were not standard procedure in 67% of the hospitals. Evaluation of social and cognitive wellbeing of patients was based solely on the general clinical impression of the physician in 83%, or not at all assessed in 8% of the centres.

Discussion and implication

A structured framework for care and evaluation of cognitive and/or physical limitations is currently absent in most hospitals. At time of ICD (re-)evaluation, several factors may be considered before deciding on (continuation of) ICD therapy: patient preferences and comorbidity, the need for pacemaker therapy, primary versus secondary prevention, procedural risks and patient preferences.

Background

The perception of 'old age' varies amongst practitioners. The prevailing definition is currently older patients aged >75 with geriatric comorbidity, or simply 80 years of age and older in the general population. [1 2] Over the past decades, Implantable Cardioverter-defibrillators (ICDs) have become the cornerstone in the prevention of sudden cardiac death in selected patient populations, including older patients. In 2019, 6260 ICDs) were implanted in the Netherlands.[3] This included de novo implants and generator exchanges due to battery depletion. It should however be noted that ICD therapy is not without downsides. In a cohort of older patients, up to 1 in 4 patients experienced device-related complications.[4] The European guidelines state multidisciplinary clinical assessment combined with patient preferences should guide the decision making for potential ICD implantation.[5, 6] Moreover, in certain older patients, recent developments have questioned or even disproved the potential benefit of defibrillator therapy. [7-9] In this context, drawbacks and complications of ICD therapy (inappropriate shocks, pocket infections) are more emphasized. These considerations are even more important at the of time of pulse generator replacements, which provide an opportunity to re-evaluate whether it is desired to continue ICD therapy, weighing out ICD benefit, potential harm including higher rates of complications, and patient preferences and quality of life regarding the continuous prevention of sudden cardiac death. [10]

We aimed to evaluate the current clinical practice in the Netherlands for ICD implants and generator replacement, with a special focus on the older ICD patients.

Methods

For this descriptive study, a cross-sectional survey study was performed with representatives from all Dutch ICD implanting centres. In the Netherlands, 28 centres are qualified and certified by the Netherlands Society of Cardiology (NVVC) to perform implantable cardioverter-defibrillator procedures.[11] The responsible representatives from the cardiac devices departments of these centres were contacted through contact information provided by the NVVC. These Cardiologists were interviewed using surveys comprised of open-end questions addressing: the out-patient care for ICD patients, pre-operative patient education on end-of-life-care issues, ICD nurse involvement, social and cognitive evaluation of patients, clinical evaluation of all patients prior to ICD replacement and the consideration of the option to downgrade or not replace a device. In addition, all participants were asked to define what age they perceived to be 'an old patient' and comment. (*See appendix 1 for survey questions, supplementary data).* Questions on the survey

were designed based on clinical experience and outcome of interest. Desired outcome parameters were predefined. Responses were recorded on audiotape with permission from the participants and transcribed as text. Answers were analysed by the primary investigator and matched and scored accordingly to the predefined outcome parameter. Categorical variables were scored binary and are depicted as frequencies (percentage of total). Continuous variables were scored numerically and are presented as mean ± SD or median with interquartile range (IQR) [25th to 75th percentile] based on their distribution. The scientific review board of the Leiden University Medical Center Department of Cardiology and Leiden University Medical Center medical ethics committee approved the study.

Results

Twenty-four cardiologists were interviewed (response rate 86%; 3% female; mean age 49.5 ± 6.5 years, median clinical experience as a cardiologist 14.5 (IQR 11-18) years). Involved centres performed a median number of 237 (IQR 126-365) ICD procedures per year (table 1). Management appeared diverse amongst hospitals. All participant centres reported that they considered the age of 80 or older as a geriatric patient. However, most physicians commented that biological age, defined largely by comorbidity and social and cognitive wellbeing, was of more value in their decision making than the date of birth alone (table 2).

Answers from respondents included "calendar age is important, but there is a shift in what we perceive as old: 75 is the new 60" and "I value the mental and social wellbeing of my patients over their physical age".

Physicians consistently reported to perceive the age ≥80 years as incentive for more extensive patient evaluation and to have had cases in which devices were downgraded to pacemaker if indicated, or not replaced. In addition, evaluation of the social and cognitive wellbeing was solely based on the general clinical impression of the treating cardiologist in 83% of the centres and not addressed at all in 8% of the centres (table 2).

Answers from respondents included "I don't need extra tools to assess my patients. I have an established relationship with my patients for a long time, my clinical judgement allows me to assess whether they are suitable for an ICD" and "Usually my clinical judgement is enough, although in doubt I prefer to consult a geriatrician rather than use time consuming questionnaires that are not in my routine myself".

Patients were invited at the out-patient clinic prior to elective device replacements in 46% of the centres. Twenty-three (96%) of the centres involved an ICD nurse in the care of their patients. The ICD nurse was involved in pre-procedural discussions with patients, as well as their follow-up. In 17% of the centres, replacements as indicated during technical follow up were performed after evaluations based on medical records. End-of-life-care discussions were not part of standard pre-procedural consultation in 67% of the hospitals (table 2).

Discussion

This study shows that the need for ICD generator exchange is currently not rendered as a standard moment for patient counselling and evaluation of continued ICD care. From the point-of-view of device cardiologists, a structured framework for the care and evaluation of older patients or with cognitive and/or other physical limitations is currently absent in most hospitals in the Netherlands. Factors that may be taken into consideration before deciding on ICD therapy include social and cognitive wellbeing and comorbidity, the need for pacemaker therapy, primary or secondary prevention indication, procedural risks and patient preferences.

Patient screening

In this study, respondents defined old patients as 80 years and older. In addition, biological age with regards to comorbidity was more important than calendar age only. Currently, older patients received a quarter of the implanted ICDs in the Netherlands in 2019 according to the Netherlands' Heart Registry. [3] Multidimensional impairment is strongly related to the prognosis of older patients and thus the potential value of an ICD. However, the same factors predispose this group for peri-procedural complications. [12] This increases the demand for thoughtful patient selection and counselling. As is found in this study, a structured framework for this practice is currently absent. Most participating cardiologists rely on their own clinical judgement when evaluating their patients, which has previously been proven to be insufficient to fully comprehend a patient's situation.[13, 14] Standardized tools, including tools such as the Comprehensive geriatric assessment (CGA), were used on indication only in 8%. The CGA has nevertheless throughout the years proven beneficial as the multidimensional and multidisciplinary tool of choice in the holistic evaluation of a patient. [15] However, it is elaborate and time consuming and not currently implemented as a standard of care by the Dutch cardiologists. It can be discussed that it is perhaps more feasible to refer patients to geriatricians for a CGA, which is in line with a statement by one of the respondents in this study.

Pacing and downgrades

The cardiologists involved in the survey represented 24 centres responsible for a median number of 180 [IQR 128-365] ICD procedures per year. One of their centres implanted even up to 550 ICDs per year. All centres had encountered the issue of ICD tachytherapy deactivation or downgrading a device from an ICD to a pacemaker. Deactivating tachytherapy of an ICD is a non-invasive programming procedure. A significant number of the ICD patients, however, receive pacemaker therapy from the same device.[16, 17] When defibrillator therapy is no longer desired, exchanging for a pacemaker pulse generator would be appropriate in such cases. This is mechanically hampered because the ICD lead does not fit in the pulse generator header and may require implantation of a new additional pacing lead, which in turn increases the procedure associated risks. [18,19] This can potentially impede downgrades becoming part of routine clinical practice. More practical solutions such as an adaptor for the lead are yet to become available.[20]

Risks and preferences

Advance care planning and consultations regarding end-of-life issues were scarcely performed by the Dutch hospitals. Only 33% of the centres performed early advanced care planning discussions with all ICD patients. Benefit from ICD therapy in old ICD patients is not simply definable. Death from comorbidity outweighs the likelihood of receiving ICD therapy. Recent clinical trials, including a large European study, illustrated that a significant number of patients ≥75 years old have no benefit from ICD therapy. [4, 7, 21] This decrease however, does not apply to the risk for complciations.[12, 22] Aside from age, indications for ICD implantations are a continuous matter of debate. New trials have led to discussions on ICD benefit in populations included in the guideline. [23] For example the DANISH trial illustrated that in the non-ischemic cardiomyopathy population an ICD for primary prevention did not reduce all-cause mortality. [8]

Considering the drawbacks stated above, patient preferences should be considered when deciding for (continuation of) therapy. These considerations are particularly important at the of time of ICD generator replacements. With increasing battery longevity, patients will be around 10 years older at the moment of pulse-generator exchange compared to the moment of the initial ICD implantation.[24] Substantial clinical and personal changes are likely to have taken place in such a timeframe, rendering this moment favourable for the re-evaluation and possibly reconsideration of ICD therapy.[10] Patients remaining free from tachytherapy by their ICD in the period of their follow-up, may experience ICD benefit differently

from peers who did receive tachytherapy. Furthermore, with every pulse-generator exchanges the risk of a pocket infection increases, a potentially lethal complication requiring a high risk extraction procedure and systemic antibiotic treatment.[25] Only 46% of Dutch centres invited patients to the out-patient clinic as a standard part of care prior to pulse generator exchange procedures. Additionally, there are to date no recommendations or tools for the evaluation of patients at risk of non-benefit or to support the decision making regarding the ICD pulse generator replacement.

ICD nurses and Shared decision making

Shared decision making with decision aids facilitating patient counselling and taking into consideration patient preferences, can help choose the most suitable individual treatment. In the absence of guideline dictated selection criteria and structured framework for the counselling of ICD patients, shared decision making tools can provide an outcome in the future. Moreover, the recently updated European Society of Cardiology guideline on cardiac pacing and cardiac resynchronization therapy emphasizes the need for patient-centred care and shared decision making.[26] Most ICD centres employed a specialized ICD nurse (96%). These nurses were involved in all aspects of the ICD patient care and follow-up, allowing them to build up sustainable relationships with patients and gain insight on patient preferences. Recently, we have developed a Dutch web-based decision aid. The decision aid is aimed to improve patient knowledge and involvement and provide insight in patient preferences to both the caregiver and the patient. This will facilitate shared decision making in the consultation room. Currently, the decision aid is being evaluated in the setting of a multi-centre randomized controlled trial. Participating centres have chosen their ICD nurses as the primary caregiver to hand out decision aids to patients and discuss the results during follow-up out-patient clinic visits.

Study limitations

The study has a small sample size. However, suitable representatives with a clear oversight over their local clinical practice were selected from all Dutch ICD implanting centres. The study is limited to the Netherlands and thereby can potentially introduce bias reflecting the geographical and cultural practice. The interviews were conducted with only one device cardiologist per centre. This could have introduced reporting bias. Sample error cannot be excluded. However, the questions were answered independently with a high level of congruence

between the different centres. In addition, the questions were tailored to the collection of data aimed to evaluate current clinical practice in Dutch ICD centres and thereby answer our research question. We therefore believe the findings of this study reflect the Dutch clinical practice at the time it was conducted.

Implications for practice

- An increasing proportion of ICD patients are of old age.
- Continuing ICD therapy is not a life-time commitment and can be re-evaluated periodically, preferably at time for pulse-generator replacement.
- Patient preferences and social and cognitive wellbeing are important to consider when making a shared decision.
- Decision aids facilitate shared decision making and can help clarify patient preferences.
- Current design of ICD pulse generators and leads impedes downgrades to a pacemaker.

Conclusion

An increasing proportion of ICD patients are of older age. A structured framework for the care and evaluation of older patients is absent in most hospitals in the Netherlands. Shared decision making and the implementation of a decision aid can potentially help improve decision making and management of ICD patients. Such decision aids are aimed to improve patient knowledge and involvement and subsequently decrease decisional conflict.

Disclosures

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TABLES

Table 1. Demographic details of participants.

Responses	**n = 24**
Female respondents, n (%)	3 (13)
Age, mean (SD)	48.5 (6.5)
Years of experience as cardiologist, median (IQR)	14.5 (11-18)
ICD implantations per year (per center), median (IQR)	180 (128-365)

ICD = Implantable cardioverter-defibrillator, IQR = interquartile range

Table 2. Key findings.

Responses	**n = 24**
ICD Nurse involved in patient counselling and follow-up, n (%)	23 (96)
Pre-procedural assessment and counselling of patients at out-patient clinic, n (%)	20 (83)
Pre-procedural information and patient education, n (%)	22 (92)
Patient education on end-of-life issues included in pre-procedural counselling	
• In all patients, n (%)	8 (33)
• In older patients or/and significant comorbidity, n (%)	6 (25)
• Not included, n (%)	10 (42)
Social and cognitive wellbeing evaluation	
• Using standardised tools (when indicated), n (%)	2 (8)
• Solely based on 'clinical impression', n (%)	21 (88)
• None, n (%)	2 (8)
Evaluation when patient is up for pulse-generator exchange due to battery depletion	
• None / based on administrative clinical parameters, n (%)	6 (25)
• Personal discussions with patient at outpatient clinic	
◦ Only in patients selected on old age or increased comorbidity based on clinical parameters, n (%)	7 (29)
◦ All patients, n (%)	11 (46)
One or more downgrades or ICD-deactivations performed in past 5 years, n (%)	24 (100)

ICD = Implantable cardioverter-defibrillator

Part III

Shared decision making in implantable cardioverter defibrillator patients

Chapter 6

The development of a decision aid for shared decision making in the Dutch implantable cardioverter defibrillator patient population: A novel approach to patient education

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Abstract

Background

Counselling of Implantable Cardioverter-defibrillator (ICD) patients with regard to individual risks and benefits is challenging. An evidence-based decision aid tailored to the needs of Dutch ICD patients is not yet available. The objective of this pilot project was to structurally evaluate the current clinical practice in the Netherlands and the ICD patient experience, in order to develop an online decision aid to facilitate shared decision making in ICD procedures.

Methods

Between June 2016 and December 2017 a Dutch web-based decision aid was developed according to the Patient Decision Aid Standards (IPDAS) using the RAND-UCLA/multi-stepped Delphi model. Development process consisted of 5 stages in which the Dutch clinical practice was reviewed (stage 1), patients' needs and their history of decision making was structurally assessed (stages 2A and B) and a modified Delphi consensus process was performed with an expert panel consisting of representatives from different medical fields (stage 3). Results from stages 1 to 3 were used to design and structure the content of an online based decision aid (stage 4) which was finally evaluated in a usability testing by patients in stage 5.

Results and conclusions

This study describes the evidence based approach of the development of the Dutch ICD decision aid. In our population, levels of shared decision-making experience were low. The ICD decision aid was structurally developed for the Dutch ICD patient population. Our upcoming multicenter stepped wedge clustered randomized trial will further evaluate the ICD decision aid in clinical practice.

Introduction

A large body of evidence has shown that Implantable Cardioverter-defibrillators (ICD) play an important role in primary and secondary prevention of sudden cardiac death. For secondary prevention ICD benefit is more clear[1, 2]. Nevertheless, the majority (50-90%) of the ICD patient population receives an ICD for primary prevention[3]. Benefit in terms of appropriate tachytherapy varies widely within the latter population: from 50% at 3 years follow-up to only 2.4% in a recent meta-analysis for non-ischemic cardiomyopathy patients[4]. Despite the increasing number of trials and scientific literature, it remains challenging for individual patients to perceive the impact of an ICD [5] and for medical professionals to appreciate patient's values and to translate scientific data into individually applicable advantages[6]. In addition to potential periprocedural and later complications, ICDs also impose psychological and social consequences on patients and their family[7, 8]. This makes patient counselling challenging. The most recent European guideline (2021) on cardiac pacing and cardiac resynchronization therapy stipulates the importance of patient centered counselling and shared decision making with regards to device implantations[9]. Moreover, the American Medicaid insurance policy has mandated shared decision making in patients undergoing cardiac device implantations with the help of evidence-based decision tools[10]. An evidence-based decision aid tailored to the needs of Dutch ICD patients is not yet available.

The objective of this pilot project was to structurally evaluate current clinical practice in the Netherlands and ICD patient experience, in order to develop an online decision aid that may improve the level of shared decision making in ICD implantations and pulse generator exchanges and to decrease decisional conflict.

Methods

Between June 2016 and December 2017 a Dutch web-based decision aid was developed according to the Patient Decision Aid Standards (IPDAS)[11] using the RAND-UCLA/multi-stepped Delphi model [12, 13]. Development process consisted of 5 stages, illustrated in Figure 1.

Stage 1: Interview-based evaluation of the Dutch Clinical Practice on Implantable Cardioverter-defibrillators.

All centers in the Netherlands qualified to implant ICDs were contacted (n=28). Representative cardiologists of Dutch CIED implanting centers were interviewed. The results of these studies have been recently published[14].

Stage 2A: Assessment of patients' needs.

Ten (10) patients (median age 66 (IQR 52-77) years, 30% female, 50% ICD for primary prevention, 10% previously declined a device, 20% CRT-D and 20% ICD) were interviewed between March and April 2017. Patients were selected at the cardiology outpatient clinic of the Leiden University Medical Center and represented the following categories: patients with an ICD for primary and secondary prevention, patients with a Cardiac Resynchronization Therapy-defibrillator (CRT-D) device and patients who previously declined an ICD implantation. To avoid the potential impact of a medical environment on the in-depth interviews, patients were interviewed at a neutral office outside of the hospital. Semi-structured interviews with questions on their decision making process were performed, inquiring their reasons for choosing or refraining from an ICD, pre-operative counselling by caregivers and current experiences and needs as an ICD patient. Questions on the survey were designed based on clinical experience and outcome of interest. Desired outcome parameters were predefined. Responses were recorded on audiotape with permission from the participants and transcribed as text. Answers were analysed by the primary investigator and matched and scored accordingly to the predefined outcome parameter. Participants were invited to propose topics and items which they considered to be valuable for peers to be included in a decision aid.

Stage 2B: Patient history of shared decision-making.

A cross-sectional assessment of shared decision-making experience levels was performed in ICD patients attending a biannual ICD patient conference in the Leiden area. All the attending patients (n=245) received questionnaires comprising questions based on the Dutch SDM-Q-9[15], (Table 1, questions 5 to 13). In addition, questions regarding patient demographics, together with two statements of interest for patients who previously had undergone a pulse-generator exchange at time of battery depletion were added. Patients indicated their level of agreement on a 5-point Likert Scale. The outcomes were analyzed according to the SDM-Q-9 user manual [15]. Questionnaires missing answers to more than 2 questions were excluded from analysis. In case of 1 or 2 missing values, these were corrected by imputation: the imputed score was the mean score of the present variables[15]. We evaluated the additional questions (questions 1 to 4) as a percentage by grouping the agreement and disagreement answers.

Stage 3: Modified 2-round Delphi Consensus Process.

For determining the content and setting of the Decision Aid, a modification of the RAND Corporation/University of California, Los Angeles consensus methodology on

appropriateness ratings was used as described below [16]. A total of 19 experts from different medical centers over the country were to participate in the expert panel for determining the setting and content of the decision aid. The panel consisted of 7 cardiologists, 1 ICD nurse, 2 general practitioners / family medicine doctors, 1 dedicated MD PhD-fellow focusing on ICD patient care, 3 specialists in elderly care medicine/geriatric specialist, 2 internal medicine physicians specialized in elderly medicine, 1 lawyer specialized in medical ethics, 1 psychologist, the chairman of the ICD patient federation and 1 expert on decision aid development. Statements for the experts to evaluate were formulated to determine the content and setting of the decision aid based on information from literature, guidelines and findings from the previous stages [1, 2, 4, 17-24].

Round 1

Participants received an online questionnaire with 84 items divided into 5 categories (1-target group and setting, 2-content, 3-to be included patient preferences, 4-screening and tools, and 5-format of the decision aid) (Appendix 2). Nineteen (19) items consisted of yes or no questions and 64 items were statements for which the experts indicated their level of agreement on a 10-point Likert scale [12, 13]. Consensus outcomes were classified as median scores. A median score > 7 was considered as positive consensus and the statement was accepted. A median score < 5 was resulted in rejection of the statement. Scores between 5 to 7 were discussed in the second round to seek consensus. Participants also had the opportunity to add on items they felt were missing from the questionnaire, which could be discussed in the second round.

Round 2

All participants from round 1 were invited for a face-to-face meeting. Statements from the previous questionnaire on which no consensus was yet reached and items added on by individual experts, were put up for discussion one by one. At the end of each discussion consensus on agreeing or rejecting the statement was reached by popular vote with a 2/3 majority.

Stage 4: Design and structure of Decision Aid content.

Members for the working group were recruited from the previous expert panel (described in stage 3) in order to form a dedicated team for the materialization of the actual decision aid. Members of the working group consisted of three cardiologists from different hospitals, one decision aid development expert, 1 general practitioner / family medicine physician, one Internist-geriatrician and one dedicated MD PhD-fellow focusing on ICD patient care.

The working group formulated the factual content of the decision aid based on the findings and recommendations from previous stages. Engineers and designers from ZorgKeuzeLab (Delft, The Netherlands) designed a functioning web-based tool encasing the information provided by the working group.

Stage 5: Usability testing of the prototype among patients.

The four patients from the out-patient clinic with an ICD device were randomly selected and invited to undergo in-depth interviews while testing and analyzing the usability of the prototype of the ICD decision aid. These patients were not involved in previous stages of the study. Patients were invited for participation by the device technician during their regular semi-annual check-up. Patients were encouraged to provide live commentary on their experience as they navigated through the decision aid. Patients received open questions addressing whether the decision aid was easy to navigate though, whether they understood the images and animations, whether explanations were clear and easy to read and if they had suggestions for improvement.

Statistics

Categorical variables were presented as numbers and percentages. Based on their distributions, continuous variables are presented as mean ± standard deviation (SD) or median with interquartile range (IQR) [25th to 75th percentile].

Ethics

The scientific review board of the Leiden University Medical Center Department of Cardiology and Leiden University Medical Center medical ethics committee approved the study. All patients and experts involved in panels and interviews for study purposes provided written informed consent.

Results

Stage 1: Interview-based evaluation of the Dutch Clinical Practice on Implantable Cardioverter-defibrillators.

Results have recently been published[14].

Stage 2A: Assessment of patients' needs.

The patients' response rate was 100% (n=10). Mean age was 62±12 years, 90% male, 90% underwent an ICD implantation (70% for primary prevention) and median time from first ICD implantation to interview was 7.5 [7-16] years. One patient

(10%) with an indication for ICD implantation, had declined this. Three (30%) patients experienced appropriate shock therapy and two (20%) had received one or more pulse-generator exchanges for battery depletion. Patients reported shocks as unpleasant and painful, however, also well accepted. One patient (10%) had experienced inappropriate shock therapy. Patients frequently reported that they experienced not to have had a choice or to have trusted their doctor's judgement and (strong) recommendations (50%). In addition, all three patients with an ICD for secondary prevention referred to their choice as "choosing between life or death", whereas primary prevention patients mostly deemed their ICD as an extra insurance (4 out of 7, 57%). One patient (with an ICD for primary prevention) reported to regret the decision, due to limitations in (life-)insurance and travelling opportunities. Furthermore, patients reported implications for their driver's license as an important downside to having an ICD (60%). (Table 2A)

Stage 2B: Patient history of shared decision-making.

A total of 233 patients completed the modified SDM-Q-9 questionnaire (95% response rate). Mean age was 69 ± 10 years, 75% male, median time from first ICD implantation to interview was 5 (IQR 2-10) years and 56% had a CRT-D. Eighty-six respondents (40%) had previously undergone at least once a pulse-generator exchange due to battery depletion. Scores from the modified SDM-Q-9 questionnaires on the level of decision-making could be calculated for 133 respondents (57%). The remaining questionnaires were excluded from analysis due to missing data in accordance with the manual SDM-Q-9 manual[25]. Patients reported to be satisfied with the pre-operative information, however, on a scale of 0 (no shared decision experienced) to 100 (strong shared decision experienced) levels of shared decision were marked at a mean ranked score of 42 (IQR 15.5-78). Furthermore, most of the patients perceived the ICD to be a 'lifelong commitment' (69%). Remarkably, 21 (10%) of the respondents wrote an extra note stating: "I did not have a choice". (Table 2B)

Stage 3: Modified 2-round Delphi Consensus Process.

Round 1

The panel of experts consisted of 7 cardiologists, 1 ICD nurse, 2 general practitioners / family medicine doctors, 1 dedicated MD PhD-fellow focusing on ICD patient care, 3 specialists in elderly care medicine/geriatrics, 2 internal medicine physicians specialized in elderly medicine, 1 lawyer specialized in medical ethics, 1 psychologist, the chairman of the ICD patient federation and 1 expert on decision aid development. Of these experts, 6 were female (32%). Median age was 55 (IQR 43.5 – 59.5) years and median years of clinical experience was

27 (IQR 15.5 – 30) years. Response rate of the experts on the panel was 100% (n= 19). The experts reached consensus on 56 (86%) statements in the first round. Experts decided that the ICD decision aid was not limited to one category of ICD patients, but should be made available to all patients receiving a first ICD device (de novo implants), or who were up for pulse-generator replacement due to battery depletion. In addition, it was agreed that the decision aid would include a tool enabling patients to review their personal preferences. Questions and the corresponding results are found in Table 3a-d and Figure 2.

Round 2

With the exception of 1 expert, all experts from round one were available for participation in round 2. The panelists reviewed all statement and results from round 1 and proceeded in discussions on only the statements on which no consensus had yet been reached. In all cases, this resulted in unanimous rejection of all items that were up for discussion. Rejected statements resulted in the exclusion of content on subcutaneous ICDs, information on resuscitation with an ICD and the risk of anxiety after receiving shock-therapy from the ICD.

Stage 4: Design and structure of Decision Aid content.

The working group of the fourth stage consisted of 7 members recruited from the expert panel: 3 cardiologists from different hospitals, 1 decision aid development expert, 1 general practitioner / family medicine physician, 1 internist-geriatrician and 1 dedicated MD PhD-fellow focused on ICD patient care. Of the working group members, 5 (71%) were female. Median age was 55 (IQR 37 -58) years and median clinical experience was 22 (IQR 6 - 31 years). Working group members together formulated the content of the decision aid, based on current guidelines and literature and tailored it to patient preferences and the Dutch clinical practice based on data gathered in the previous stages.

Stage 5: Usability testing among patients.

Four patients participated in the usability testing, of which three were ≥70 years. All patients completed the decision aid within half an hour. First impressions of the decision aid were stated to be *inviting*, *clear* and of *additional value*. Three patients appreciated that they could have the opportunity to walk through all information in calm home setting. They commented that "it had been impossible to remember all of what the doctor told in the consultation room". One patient admitted to listen to specific advice from the doctor and read as little as possible on potential complications. Nevertheless, also this patient agreed that the opportunity to be informed on all aspects is beneficial for the general patient group.

Discussion

This study was designed in order to create a decision aid for ICD patients. Information was gathered systematically on the Dutch clinical practice in ICD patients, patient preferences and insight in ICD therapy, incorporating expert opinions and levels of shared decision making as experienced by patients. Findings were incorporated into the design of a decision aid to support patients and caregivers to make well informed choices regarding ICD therapy. This evidence-based Decision Aid was developed for all ICD patients facing the choice of receiving a new ICD or replacing one, according to the Patient Decision Aid Standards (IPDAS) [11] using the RAND-UCLA/multi-stepped Delphi model [12, 13]. A previous evidence based developed ICD decision aid was centered around the health care providers. Main findings in the stages of our study are that: [1] patients in retrospect reported they were not aware of having a choice, [2] levels of shared decision making perceived by our ambulatory ICD population was low and [3] the first patient experience with our decision aid was positive and promising.

Challenges in patient education and counselling

Patients have a right to be well informed on the various aspects of proposed intervention, emphasizing the patient's role in decision making, discussing alternatives and the risks and obtaining the patient's consent. Moreover, proper counseling of patients is a cornerstone of a prosperous patient-caregiver relationship. The recently updated guidelines of the European Society of Cardiology emphasize the need for patient-centered care and shared decision making[26]. Counseling and educating patients on their individual illness and therapeutic options can, however, be challenging. This is particularly true for ICD candidates, as not only is it challenging to predict the benefit from an ICD for and individual patient, but an ICD also has its downsides, such as a lower quality of life after receiving ICD therapy [27, 28]. This is particularly true in those who have received inappropriate therapy[29]. Other important risks include infection, technical failure and receiving shocks in the last moments of life [30-37].

Traditionally, patients are counseled by their caregiver at the outpatient office. These consultations can be supplemented by informative pamphlets filled with information. Or, as a more modern approach, shared decision making with the use of (digital) decision aids can be used.

Consultations with doctors

It has previously been described that doctors have a decisive role in decision making for patients eligible for an ICD[38]. Very strong language emphasizing the benefits of an ICD will lead to patients favoring the device implantation[38, 39]. These findings reaffirm the necessity for an unbiased decision aid. Comprehension by patients of mere percentages has been shown to be overall disappointing [5]. ICD patients overestimate the potential benefit from ICD therapy and are deficient in their comprehension of device function[40-44]. ICD patients have previously reported to have not fully understood the risks and burden of living with an ICD at time of consent for an ICD implantation[38, 40]. In addition, it has appeared that some patients who had previously declined an ICD implantation for primary prevention, in retrospect had not fully understood the benefits for survival. [45]

Print-based educational material

Patients desire to have access to comprehensive information that can help them in deciding. Providing patients with comprehensive information and considering their preferences, is important for sustainable decision making. Interestingly, traditional print-based educational material for ICD patients has previously been proven to be targeted the highly literate population[46]. For this reason, the expert panel decided for the decision aid in this study to be made available online, be interactive and incorporate illustrative educational videos in simple language. To avoid bias towards patients with lower digital literacy, it was nevertheless also decided that the content can be printed out and handed to patients by healthcare providers in selected cases. In addition, all text was reviewed by professional content writers to be comprehendible for the lower-literate population.

Shared decision making

The decision making process for the ICD patient is triggered when risk of sudden cardiac death is discussed[42]. However, these ICD patients have reported that the most important factors influencing their final decision were not the odds and numbers, but trust in the advocacy of their treating physician, social influences and their health state[42]. Likewise, in stage 2 of the process patients also reported to have trusted their doctors' judgement and (strong) recommendations. This illustrates the importance of patient preferences in shared decision making. Moreover, a key factor in shared decision making is helping patients explore preferences and make well thought-out decisions. In clinical practice, shared decision making is, however, still underutilized. Patients in this study reported relatively low experience of shared decision making. Moreover, most interviewed patients admitted not to have been aware they had a choice. Likewise, patients have previously reported not to

recall alternatives for committing to ICD therapy[42]. In addition, in a previous study, clinicians have reported that in order to use shared decision making, they needed a hint or trigger from patients, as it was not part of their standard practice[47].

Shared decision making supplemented by decision aids

Shared decision making can be facilitated by the implementation of decision aids. It has been affirmed that a decision aid results in patients playing a more active role in decision making and accurate risk perception improve patient knowledge and decrease decisional conflict[48]. Patients have reported to feel more knowledgeable, better informed, and clearer about their values with the use of a decision aid[48]. A pilot study with a decision aid for ICD patients showed promising results, with decrease of decisional conflict in patients using the decision aid[49]. Medicare and Medicaid Services in the United States of America, even mandated the use of evidence based decision aids, supporting shared decision making, in patients that were a candidate for cardiovascular device placements, including ICDs[50]. Nevertheless implementation of decision aids in clinical practice is slow[51]. American physicians self-reported to engage in shared decision making when obtaining consent prior to an ICD implantation, however, less than half of these physicians used a decision aid in their clinical practice[52]. Lewis at al., developed a user-centered ICD decision aid to be used for patients facing and ICD replacement, involving key-users in the development in order to encourage utilization of the product in the future. In our study, we proactively involved not only cardiologists, but also experts from relevant medical fields and patients. Moreover, the opinion of 233 ambulatory ICD patients have been taken into account when designing this decision aid (Stage 2B).

Decision making at time of battery depletion

The expert panel in this study decided to target the ICD decision aid at not only patients eligible for a first ICD, but also patients facing an ICD replacement as ICD therapy is not a lifelong commitment. However, as our patients stated, the latter is not always information that is clear to patients. Moreover, as illustrated in our previous study ICD replacement was not always presented as a choice by health care providers[14]. Likewise, it has been previously shown that more than half of the patients who had already undergone an ICD replacement at time of battery depletion, had not been aware that they had a choice [53]. This illustrates that ICD replacement at time of battery depletion goes without saying, whereas patients have been reported to consider non-replacement under certain circumstances such as serious comorbidity and advanced age[53].

Time from first ICD implantation to pulse-generation exchange can easily be longer than 5 years[54]. Discussions with the healthcare provider and information

provided at the commencement of ICD therapy can be forgotten by the patient. Therefore, at time of pulse-generator exchange for battery depletion, there is a need for renewed discussions with the patient before deciding on definitely continuing ICD therapy. This is in contrast of continuing ICD therapy regardless of the costs (risk of complications) or patient preferences (e.g., no longer wanting to prevent a sudden cardiac death).

Moreover, patient preferences can change with the progression of age and the development of comorbidities. In addition, the odd of complications increases with every pocket revision/ redo procedure[54, 55].

An ICD decision aid can facilitate also decision making in these patients, exploring their current individual preferences and weighing them out against expected benefits and downsides from ICD therapy. Especially a decision aid that can be reviewed at home, will provide an opportunity for family members to be involved in the decision making resulting in decisions supported by patients and their doctors as well as their families.

Previous endeavors resulted in an healthcare-provider-centered ICD decision aid to be implemented in patients facing an ICD replacement, in order to help health care providers step away from the automatism of replacing an ICD at battery depletion instead of discussing the options with their patients first[47]. It is expected from the decision aid resulting from this study, to encourage not only healthcare providers but also patients into taking a more active role in the decision making process prior to definitive continuation of ICD therapy.

Future perspective

The ICD Decision Aid Study is currently being conducted in a multicenter stepped wedge clustered randomized trial in 6 Dutch centers. The study will evaluate the decision aid in a clinical setting and its benefit on shared decision making experienced by both doctors as patients. Shared decision-making levels in our population will be reassessed after implementation, to clarify the benefit of the ICD decision aid.

Conclusion

This study describes the evidence based approach of the development of the Dutch ICD Decision Aid. In our population, levels of shared decision-making experience were low. Decision aids have previously proven to improve patients'

decision making and facilitate shared decision making. The ICD Decision Aid was developed for the Dutch ICD patient population according to prevailing decision aid development methods. Results from our multicenter stepped wedge clustered randomized trial will further evaluate the ICD decision aid.

Limitations

This study has several limitations. Most importantly recall bias can be present in the patient groups. Patients reporting experience in Stage 2 are prone for recall bias. However, reported outcomes are accurate for evaluating patient experience as this is what patients eventually actually remember. Moreover, patients from the second round of Stage 2 are a good representation of the average ambulant ICD patients, as hospitalized or patients with end-stage disease would not be able to attend.

With regards to Stage 3, there is a selection bias in patients entering the panel and expert group. Participants have however been carefully selected on their roles in the clinical field and experience with ICDs. Using 2 rounds in this stage allowed elaborate discussions of their points of view and consensus was reached on all items.

In Stage 5 usability of the decision aid was tested amongst a small number of selected patients. The evaluation was however performed carefully and with much attention. Patients were not pre-selected on their computer skills and included patients of old age. It is expected that this patient group is a good representation of the whole population.

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Tables and figures

Table 1: Modified 9-item Shared Decision-Making Questionnaire (SDM-Q-9) with additional questions for regional ICD patient conference. Original statements in Dutch.

Question	*Answer options*
1 I have	*An ICD – a CRT-D – no device*
2 Age	*... years*
3 Gender	*Female - male*
4 I received my device in the year	*.....*
5 Cardiologist made clear I had a choice.	*Strongly disagree – disagree – neutral - agree-strongly agree*
6 Cardiologist wanted to know how much I wanted to be involved in the decision-making.	*Strongly disagree – disagree – neutral - agree-strongly agree*
7 Cardiologist told me there were other options than an ICD.	*Strongly disagree – disagree – neutral - agree-strongly agree*
8 Cardiologist explained pros and cons.	*Strongly disagree – disagree – neutral - agree-strongly agree*
9 Cardiologist helped me understand all the information.	*Strongly disagree – disagree – neutral - agree-strongly agree*
10 Cardiologist asked me if I preferred an ICD.	*Strongly disagree – disagree – neutral - agree-strongly agree*
11 Cardiologist and I thoroughly reconsidered ICD.	*Strongly disagree – disagree – neutral - agree-strongly agree*
12 Cardiologist and I chose an ICD together	*Strongly disagree – disagree – neutral - agree-strongly agree*
13 I felt as if I could choose between an ICD or none	*Strongly disagree – disagree – neutral - agree-strongly agree*
14 My device has been replaced due to battery depletion	*Yes – no, never*
15 I could choose not to replace my ICD at the time of battery depletion	*Strongly disagree – disagree – neutral - agree-strongly agree*
16 An ICD is a life-long commitment/obligation for me	*Strongly disagree – disagree – neutral - agree-strongly agree*

ICD: Implantable Cardioverter-defibrillator. CRT-D: Cardiac Resynchronization Therapy-defibrillator. Original statements in Dutch.

Table 2A
Stage 2A: Assessment of patients' needs.

	N=10
Male (%)	90
Age (mean, SD)	62±12
Time from first ICD implantation (median, IQR)	7.5 [7-16]
ICD indication for primary prevention (%)	70
Declined an ICD *(%)*	10
Underwent ≥1 pulse generator replacement for battery depletion *(%)*	20
Received appropriate ICD (shock) therapy *(%)*	30
Received inappropriate ICD shock therapy *(%)*	10
Perceived not to have a choice regarding ICD implantation *(%)*	50
"The ICD is an extra insurance" *(%)*	30
Regretting the ICD implantation *(%)*	10
Impaired by driver license restrictions *(%)*	60

ICD: Implantable Cardioverter-defibrillator. N: number of total patients that filled in the specific question(s). SD: Standard Deviation. Original statements in Dutch.

Table 2B
Stage 2B: patient history of shared decision making.

		N
Male (%)	75	233
Age (mean, SD)	69 ± 10 years	233
Time from first ICD implantation (median, IQR)	5 (2-10) years	233
SDM Score (mean rank, IQR)	42 (15.5-78)	133
"I could choose not to replace my ICD at the time of battery depletion" (% that disagreed)	50	86
"An ICD is a life-long commitment/obligation for me" (% that agreed)	69	86

SDM score: mean rank calculated score from modified SDM-Q-9 questions reflecting the experienced level of shared decision making (SDM) on a scale from 0 to 100. ICD: Implantable Cardioverter-defibrillator. N: number of total patients that filled in the specific question(s). Original statements in Dutch.

Table 3a: Statements from Delphi round 1 on who should be the target group of the decision aid should be. N=19.

Statements	Yes (%)
The decision aid should be given to …	
… all patients receiving an ICD.	*81*
… all patients receiving an ICD for the first time.	*55*
… all patients who will undergo a pulse-generator replacement due to battery depletion.	*55*
… only patients receiving an ICD for primary prevention of sudden cardiac death.	*36*
… patients concerning secondary prevention of sudden cardiac death.	*18*
… all patients with many comorbidities.	*55*
… patients of high age.	*55*
The decision aid should be handed out by/made available by…	
… the cardiologist	*91*
… the general practitioner / family doctor	*18*
… the ICD-nurse	*72*
… the ICD-technician	*9*
… the patient union	*36*
The decision aid should be handed out per postal mail, *before* the consultation with the cardiologist on ICD therapy	9
The decision aid should be handed out *after* consultation with the cardiologist on ICD therapy	91

ICD: implantable cardioverter-defibrillator. Original statements in Dutch.

Table 3b: Statements from Delphi round 1 on the content of the decision aid.

Statements	Median	Consensus
General explanation about what an ICD does should be included in the decision aid	9.7	Accepted
Discussion on therapeutically benefits of an ICD with primary prevention patients should be separate from secondary prevention patients	7.6	Accepted
The choice for a subcutaneous ICD should be included in the content	6.2	Deferred
Explanation of Cardiac Resynchronization Therapy (CRT) should be included to the content	5.7	Rejected
The added value of an ICD with patients at an older age should be discussed nuanced	9.8	Accepted
The added value of an ICD with patients with unclear life expectancy should be discussed	9.6	Accepted

Statements	Median	Consensus
The most common complications of a procedure should be discussed	9.6	Accepted
Complications of a prolonged hospitalization, such as pneumonia and decubitus in case of immobilization, should be discussed	4.5	Rejected
Risk on advisory leads and recall products should be included in the explanation by default	5.6	Rejected
The role of the ICD at the end of life should be discussed with all patients	8.2	Accepted
The possibility to deactivate tachytherapy at the end of life should be discussed with all patients	7.3	Accepted
All patients should know that an ICD should not be a lifelong commitment	9.3	Accepted
All patients should know that an ICD, if not desired, can be turned off	9.8	Accepted
The role of the ICD at the end of life should be discussed with patients of **old** age	9.3	Accepted
The possibility to deactivate tachytherapy at the end of life should be discussed with patients of **old** age	8.9	Accepted
Patients of **old** age should know that an ICD does not have to be a lifelong commitment	9.4	Accepted
Patients of **old** age should know that an ICD, if not desired, can be turned off	9.4	Accepted
The technical aspects of how an ICD works should be included in the counselling material	6.7	Deferred
The benefits of tachytherapy should be explained	7.5	Accepted
It should be **explained** that ICD therapy protects against sudden cardiac death and not against sudden death in general (because of other causes of death)	9.4	Accepted
It should be **stressed** that ICD therapy protects against sudden cardiac death and not against sudden death in general (because of other causes of death	8.5	Accepted
The psychological impact of tachytherapy (more depressions, traumatic) should be included in the general content	6.9	Deferred
The chance of inappropriate therapy should be included in the content	8.7	Accepted
How you should resuscitate a patient with ICD should be included to the content	5.2	Rejected
Telemonitoring should be explained	6.7	Deferred
The function of various healthcare specialists, cardiologist, EP-cardiologist, ICD-nurse and ICD technician, should be explained in the content	6.4	Deferred

Statements are rated on a scale from 1 to 10. Consensus on acceptance is reached with a median score of ≥7. ICD: implantable cardioverter-defibrillator. EP: electrophysiologist. CRT: cardiac resynchronization therapy. Original statements in Dutch.

Table 3c: Statements in Delphi round 1 on items to be included in rating scales for patients.

Statements	Median	Consensus
In the decision aid, patients should be able to select on a rating scale…		
…how much they tend to an ICD or not.	3.9	Accepted
.. how much they value the advice of their health care provider.	3.9	Accepted
… how much they value the opinion of close ones / relatives.	3.7	Accepted
… how much anxiety they feel for receiving appropriate therapy.	3.6	Accepted
… how much anxiety they feel for receiving inappropriate therapy.	3.7	Accepted
… how self-sustainable they will feel when shock therapy is being felt.	3.6	Accepted
… how self-sustainable they expect to be in showing up on all follow-up appointments.	3.6	Accepted
… how willing they will be to undergo re-inventions for battery replacements.	2.9	Accepted
… how affected they will be by the consequences for their driver's license after implantation.	4.0	Accepted
… how affected they will be by the consequences for their driver's license after receiving shock therapy.	3.9	Accepted
… how willing they are to comply with the necessity for at least semi-annual ICD check-ups	3.7	Accepted
… how much anxiety they feel for potential complications	3.5	Accepted
… their value for philosophical elements, such as the role of ICD at the end of life.	3.8	Accepted
… their value for the psychological aspects of shock therapy, such as the probability of depressions and decrease of quality of life.	3.9	Accepted
… their preference for life extension, such as the role of ICD in the mortal process	4.0	Accepted
… their value for the cosmetic aspects of an ICD, such as the scar and visibility of the contour of the pulse-generator	3.3	Rejected
… their preference for life extension above quality of life (for instance: understanding that preventing sudden cardiac death can lead to a long hospitalization with heart failure)	4.0	Accepted
…their preference for a non-sudden cardiac death with a potential prolonged death bed.	3.9	Accepted

Statements are rated on a scale from 1 to 5. Consensus on acceptance is reached with a median score of ≥3.5. ICD: implantable cardioverter-defibrillator. ICD: implantable cardioverter-defibrillator. Original statements in Dutch.

Table 3d: statements on which patients should be screened on what aspects, by tools integrated into the decision aid.

Statement	Median	Consensus
With a tool incorporated into the decision aid, ...		
... all patients should be screened on frailty.	3.5	Accepted
... all patients should be screened on social-cognitive functions.	3.4	Rejected
... all patients should be screened on dementia.	3.6	Accepted
... all patients should be screened on vitality.	3.7	Accepted
... patients older than **65** years should be screened on **frailty**.	3.6	Accepted
... patients older than **65** years should be screened on **social-cognitive functioning**.	3.7	Accepted
... patients older than **65** years should be screened on **dementia**.	3.7	Accepted
... patients older than **65** years should be screened on **vitality**.	3.9	Accepted
... patients older than **70** years should be screened on **frailty**.	3.6	Accepted
... patients older than **70** years should be screened on **social-cognitive functioning**.	3.7	Accepted
... patients older than **70** years should be screened on **dementia**.	3.8	Accepted
... patients older than **70** years should be screened on **vitality**.	3.9	Accepted
... patients older than **75** years should be screened on **frailty**.	4.0	Accepted
... patients older than **75** years should be screened on **social-cognitive functioning**.	4.1	Accepted
... patients older than **75** years should be screened on **dementia**.	4.2	Accepted
... patients older than **75** years should be screened on **vitality**.	4.2	Accepted
... patients older than **80** years should be screened on **frailty**.	4.5	Accepted
... patients older than **80** years should be screened on **social-cognitive functioning**.	4.3	Accepted
... patients older than **80** years should be screened on **dementia**.	4.5	Accepted
... patients older than **80** years should be screened on **vitality**.	4.5	Accepted

Statements are rated on a scale from 1 to 5. Consensus on acceptance is reached with a median score of ≥3.5. Original statements in Dutch.

Table 3e: Statements in Delphi round 1 on how the decision aid should be made available. N=19.

Statement	Yes (%)
The decision aid should be available in a paper version	100
The decision aid should be available as a downloadable app	56
Only web-access to the decision aid will be sufficient	9
An interactive decision aid, including videos of patient experiences is preferable	72
Videos with experiences of other patients does not belong in a decision aid	9

Original statements in Dutch.

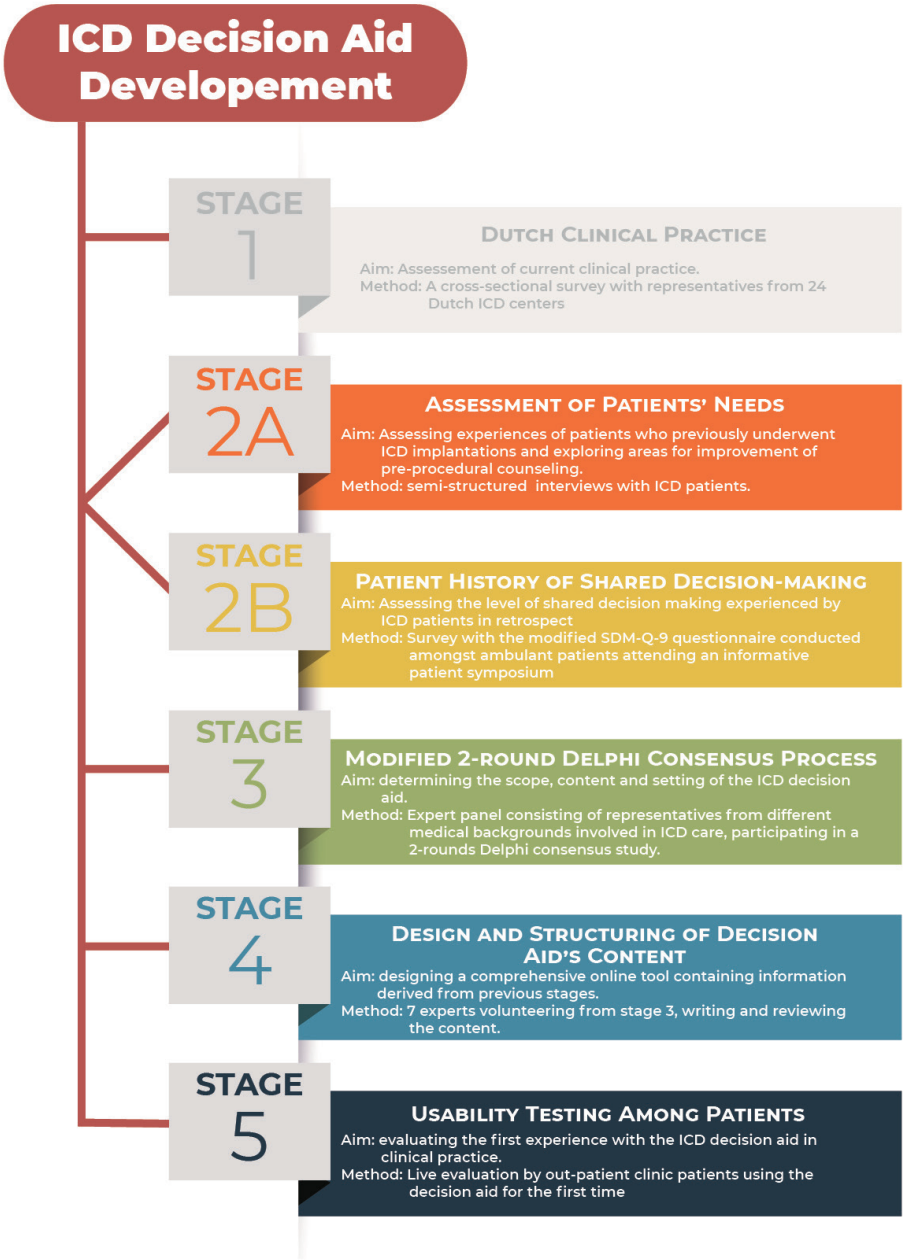

Figure 1: overview of stages in developing the ICD decision aid.

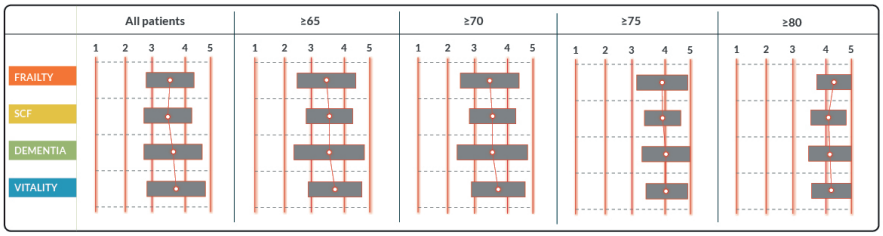

Figure 2: Response to statements on which patients should be screened on what aspects, by tools integrated into the decision aid

Statements are rated on a scale from 1 to 5. Consensus on acceptance is reached with a median score of **≥3.5.** *SCF: social cognitive functioning.*

Appendix 1

Table 1A: List of all ICD Implanting Dutch Centers included in round 1

St. Antonius Ziekenhuis, Nieuwegein
Academic Medical Center, Amsterdam
Leiden University Medical Center, Leiden
Scheper Hospital, Emmen
Medical Spectrum Twente
Radboud Medical Center, Nijmegen
Spaarne Gasthuis, Haarlem
Erasmus MC, Rotterdam
Catharina-hospital, Eindhoven
Nordwest Hospitalgroup, Alkmaar
University Medical Center Groningen, Groningen
FlevoHospital, Almere
Albert Schweitzer Hospital, Dordrecht
Haaglanden Medical Center, The Hague
Medical Center Leeuwarden, Leeuwarden
Rijnstate Hospital, Arnhem
TweeSteden Hospital, Tilburg
Canisius-Wilhelmina Hospital, Nijmegen
Franciscus Gasthuis & Vlietland, Schiedam
Maasstad Hospital, Rotterdam
University Medical Center Utrecht, Utrecht
HagaZiekenhuis, The Hague
Free University Medical Center, Amsterdam
Isala Clinics, Zwolle

Table 1B: "White List 2017": Dutch hospitals licensed to perform ICD procedures

ICD-implementing Centers
Academic Medical Center, Amsterdam
Albert Schweitzer Hospital, location Dordwijk, Dordrecht
Amphia Hospital, location Molengracht, Breda
Canisius-Wilhelmina Ziekenhuis, Nijmegen
Catharina-Hospital, Eindhoven
Erasmus Medical Center, Rotterdam
FlevoHospital, Almere
Franciscus Gasthuis & Vlietland, Schiedam
HagaZiekenhuis, The Hague
Isala Clinics, Zwolle
Leiden University Medical Center, Leiden
Maasstad Hospital, Rotterdam
Maastricht University Medical Center, Maastrisch
Martini Hospital, Groningen
Haaglanden Medical Center, The Hague
Nordwest Hospital Group, Alkmaar
Medical Center Leeuwarden, Leeuwarden
Medical Spectrum Twente, Enschede
Onze Lieve Vrouwen Gasthuis, location Oost, Amsterdam
Onze Lieve Vrouwen Gasthuis, location West, Amsterdam
Radboud University Medical Center, Nijmegen
Rijnstate Hospital Arnhem
Scheper Hospital, Emmen
Spaarne Gasthuis, Haarlem
St. Antonius Hospital, Nieuwegein
TweeSteden Hospital, Tilburg
University Medical Center, Groningen
University Medical Center, Utrecht
Free University Medical Center, Amsterdam

Appendix 2

Table 1a: statements on who should be the target group of the decision aid should be.

Statements
The decision aid should be given to …
… all patients receiving an ICD.
… all patients receiving an ICD for the first time.
… all patients who will undergo a pulse-generator replacement due to battery depletion.
… only patients receiving an ICD for primary prevention of sudden cardiac death.
… patients concerning secondary prevention of sudden cardiac death.
… all patients with many comorbidities.
… patients of high age.
The decision aid should be handed out by/made available by…
… the cardiologist
… the general practitioner / family doctor
… the ICD-nurse
… the ICD-technician
… the patient union
The decision aid should be handed out per postal mail, *before* the consultation with the cardiologist on ICD therapy
The decision aid should be handed out *after* consultation with the cardiologist on ICD therapy
The decision aid should be given to …
… all patients receiving an ICD.
… all patients receiving an ICD for the first time.
… all patients who will undergo a pulse-generator replacement due to battery depletion.
… only patients receiving an ICD for primary prevention of sudden cardiac death.

ICD: implantable cardioverter-defibrillator. Original statements in Dutch.

Table 1b: statements on who should be included to the content of the decision aid.

Statements
General explanation about what an ICD does should be included in the decision aid
Discussion on therapeutically benefits of an ICD with primary prevention patients should be separate from secondary prevention patients
Explanation of Cardiac Resynchronization Therapy (CRT) should be included to the content
The added value of an ICD with patients at an older age should be discussed nuanced
The added value of an ICD with patients with unclear life expectancy should be discussed
The most common complications of a procedure should be discussed
Complications of a prolonged hospitalization, such as pneumonia and decubitus in case of immobilization, should be discussed
Risk on advisory leads and recall products should be included in the explanation by default
The role of the ICD at the end of life should be discussed with all patients
The possibility to deactivate tachytherapy at the end of life should be discussed with all patients
All patients should know that an ICD should not be a lifelong commitment
All patients should know that an ICD, if not desired, can be turned off
The role of the ICD at the end of life should be discussed with patients of old age
The possibility to deactivate tachytherapy at the end of life should be discussed with patients of old age
Patients of old age should know that an ICD does not have to be a lifelong commitment
Patients of old age should know that an ICD, if not desired, can be turned off
The technical aspects of how an ICD works should be included in the counselling material
The benefits of tachytherapy should be explained
It should be **explained** that ICD therapy protects against sudden cardiac death and not against sudden death in general (because of other causes of death)
It should be **stressed** that ICD therapy protects against sudden cardiac death and not against sudden death in general (because of other causes of death
The psychological impact of tachytherapy (more depressions, traumatic) should be included in the general content
The chance of inappropriate therapy should be included in the content
How you should resuscitate a patient with ICD should be included to the content
Telemonitoring should be explained
The function of various healthcare specialists, cardiologist, EP-cardiologist, ICD-nurse and ICD technician, should be explained in the content

ICD: implantable cardioverter-defibrillator. EP: electrophysiologist. CRT: cardiac resynchronization therapy. Original statements in Dutch.

Table 1c: statements on items to be included in rating scales for patients.

Statements
In the decision aid, patients should be able to select on a rating scale...
...how much they tend to an ICD or not.
.. how much they value the advice of their health care provider.
... how much they value the opinion of close ones / relatives.
... how much anxiety they feel for receiving appropriate therapy.
... how much anxiety they feel for receiving inappropriate therapy.
... how self-sustainable they will feel when shock therapy is being felt.
... how self-sustainable they expect to be in showing up on all follow-up appointments.
... how willing they will be to undergo re-inventions for battery replacements.
... how affected they will be by the consequences for their driver's license after implantation.
... how affected they will be by the consequences for their driver's license after receiving shock therapy.
... how willing they are to comply with the necessity for at least two-yearly ICD semi-annual
... how much anxiety they feel for potential complications
... their value for philosophical elements, such as the role of ICD at the end of life.
... their value for the psychological aspects of shock therapy, such as the probability of depressions and decrease of quality of life
... their preference for life extension, such as the role of ICD in the mortal process
... their value for the cosmetic aspects of an ICD, such as the scar and visibility of the contour of the pulse-generator
... their value for psychological aspects of shock therapy, such as the probability of depressions and decrease of quality of life
... their preference for life extension above quality of life (for instance: understanding that preventing sudden cardiac death can lead to a long hospitalization with heart failure)
...their preference for a non-sudden cardiac death with a potential prolonged death bed.

ICD: implantable cardioverter-defibrillator. Original statements in Dutch.

Table 1d: statements on which patients should be screened on what aspects, by tools integrated into the decision aid.

Statement
With a tool incorporated into the decision aid, ...
... all patients should be screened on frailty.
... all patients should be screened on social-cognitive functions.
... all patients should be screened on dementia.
... all patients should be screened on vitality.
... patients older than **65** years should be screened on **frailty**.
... patients older than **65** years should be screened on **social-cognitive functioning**.
... patients older than **65** years should be screened on **dementia**.
... patients older than **65** years should be screened on **vitality**.
... patients older than **70** years should be screened on **frailty**.
... patients older than **70** years should be screened on **social-cognitive functioning**.
... patients older than **70** years should be screened on **dementia**.
... patients older than **70** years should be screened on **vitality**.
... patients older than **75** years should be screened on **frailty**.
... patients older than **75** years should be screened on **social-cognitive functioning**.
... patients older than **75** years should be screened on **dementia**.
... patients older than **75** years should be screened on **vitality**.
... patients older than **80** years should be screened on **frailty**.
... patients older than **80** years should be screened on **social-cognitive functioning**.
... patients older than **80** years should be screened on **dementia**.
... patients older than **80** years should be screened on **vitality**.

Original statements in Dutch.

Table 1e: statements on what kind of medium the decision aid should be available in.

Statement
The decision aid should be available in a paper version
The decision aid should be available as a downloadable app
Only web-access to the decision aid will be sufficient
An interactive decision aid, including videos of patient experiences is preferable
Videos with experiences of other patients does not belong in a decision aid

Original statements in Dutch.

Chapter 7

The Dutch Implantable Cardioverter-defibrillator Decision Aid in Clinical Practice: a Stepped-wedge Randomized Controlled Trial

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Submitted

Abstract

Background

In the ever-evolving landscape of healthcare, the role of shared decision making (SDM) has become increasingly pivotal, particularly in nuanced choices such as those involving implantable cardioverter defibrillator (ICD) therapy. This study evaluates the impact of the Dutch ICD Decision Aid on SDM in patients up for ICD implantation or replacement.

Methods

A stepped-wedge randomized controlled trial was conducted across six Dutch hospitals between February 2018 and September 2019, involving patients eligible for ICD implantation or pulse generator exchange. SDM experiences of the patients and involved medical professionals were assessed using SDM-Q-9 and SDM-Q-Doc questionnaires, respectively. The Decisional Conflict Scale (DCS) scores measured effective decision-making. The intervention group received the decision aid on top of standard care. Both intention-to-treat as treated-as-intended analyses were conducted.

Results

A total of 150 patients and 233 caregivers were included in the study. For caregivers, SDM scores did not differ: the SDM-Q-Doc median score was 36 [28-38] in the control phase and 35 [33-40] in the intervention phase (p= 0.805). Patients in both intervention and control groups demonstrated high SDM scores as well, with SDM-Q-9 scores of 40 [IQR 30-45] in the intervention phase and 39 [IQR 36-45] in the control phase (p= 0.245). Decisional conflict scores were low: DCS score median 12.5 [4.3 – 23.4] in the intervention phase and 16.4 [6.25 – 25.0] in the control phase (p= 0.453). Outcomes did not differ between intention-to-treat and treated-as-intended arms. Patients in the intervention phase accessed the decision aid in 68% of the cases. Patients with a higher education provided more correct answers to the theoretical knowledge questions, both in the control and in the intervention/ decision aid phase (p<0.001). In addition, patients up for a pulse-generator-exchange also had significantly more correct answers, compared to peers up for a first device implantation, both in the control and in the intervention/ decision aid phase (p<0.001)

Conclusions

Although the Dutch ICD Decision Aid did not result in significant differences in SDM scores or levels of decisional conflict between patient groups, both measures remained consistently favourable overall. Despite this, the decision aid still holds

promise as a valuable resource. Moving forward, efforts should focus on refining decision-making tools and improving patient knowledge within the intricate context of ICD therapy to further enhance the quality of patient-centered care.

Introduction

In recent years, shared decision making (SDM) has been established as an essential component of patient education in healthcare related choices (1, 2). Governmental campaigns in Europe and around the world have promoted the use of SDM modalities, with support from various decision aids to enhance the process (3, 4). SDM is of particular value in patients facing treatment choices that require an individualized weighting of several complex factors, and can significantly impact their quality of life.(5)

Implantable cardioverter defibrillator (ICD) patients present a diverse and complex population within cardiology. While current guidelines recommend ICD implantation for selected patient populations, individual nuances related to the patient specific risks, comorbidity, preferences, and life perspectives can significantly impact treatment decisions (6-9). This is especially true for patients who previously underwent an ICD implantation and are now facing battery depletion driven generator replacement. Patients may have developed significant comorbidities and important changes in their life values and preferences may have occurred, which can impact their present day treatment choices (6). Previously, patients have reported not to have been fully involved in the decisional processes preceding the initial ICD implantation (10).

To support patients and their caregivers in the SDM process concerning treatment with ICD's within the Netherlands, the online-based Dutch ICD Decision Aid was developed (11),(10). The current study aims to evaluate the additional value of the Dutch Decision Aid on top of standard care using a multicenter stepped-wedge randomized controlled trial.

Methods

Study design

A stepped wedge randomized controlled trial recruiting participants from six ICD-implanting hospitals in the Netherlands (Leiden University Medical Center, Leiden [1]; Haaglanden Medical Center, the Hague [2]; HagaZiekenhuis, the Hague [3]; St. Franciscus Gasthuis, Schiedam [4]; Albert Schweitzer Hospital, Dordrecht [5]; and Maastricht University Medical Center, Maastricht [6]) was conducted between February 2018 and September 2019.

The trial design was in accordance with the stepped-wedge cluster RCT consensus, the Patient Decision Aid Standards (IPDAS) and using the RAND-UCLA/multi-stepped Delphi model (12-14). The hospitals 1-6 were randomly assigned to either a variable duration of standard of care (control group) or the decision aid implementation on top of standard of care (intervention group). All the centers initially enrolled patients into the control phase and subsequently each of the centers transitioned from the control to the intervention phase at a different point in time, as per study design (Figure 1). The periods of time for each group were 3 months control phase and 9 months intervention phase; 6 months control phase and 6 months intervention phase; and 9 months control phase and 3 months intervention phase, respectively. Figure 2 provides a schematic overview of the study design.

Randomization

Prior to the start of the study, it was determined that a center could enroll in the control phase for 25%, 50% of 75% of the total study enrolling period, after which the intervention phase time period would start. The primary investigator (DY) randomized the centers using an online-based randomization tool to the previously specified enrollment patterns. Due to the nature of the study, blinding of participants and investigators was not possible.

Participants

Patients aged 18 years or older who had an indication for an ICD or implantable cardiac resynchronization therapy-defibrillator (CRT-D) implantation, or pulse generator exchange due to battery depletion according to the ESC guidelines were included (15). Patients with insufficient proficiency in the Dutch language were excluded from participation in the study.

In the standard care phase (control phase), patients were asked to fill out the study questionnaires to assess the consultation with their caregiver in which the ICD/CRT-D was discussed as a treatment option, the level of experienced shared decision making, and their decision-making progress, i.e. the experience, decisional conflict. In addition, three relevant theoretical questions were included to evaluate patient knowledge at the end of the decision-making process. Patients returned the questionnaires by post to the primary investigator (DY). In the phase with the addition of the decision aid (intervention phase), participating hospitals provided all eligible patients with a decision aid as part of their standard practice. Patients in this phase received personal and unique codes from their caregivers to log into the online ICD Decision Aid environment. Patients reviewed the Decision

Aid at home and had a follow-up visit with their caregiver to discuss the outcome and their final decision. Patients were asked for inclusion in the study and received the same questionnaires as the control group.

In the Netherlands, multiple caregivers are involved in ICD-patients' care prior to an ICD implant, including cardiologists and nurse practitioners or physician assistants (PA). In all patients, the indication for an ICD implantation or pulse-generator exchange due to battery depletion was assessed by a cardiologist in accordance with the ESC Guidelines(15). Patients were then individually counseled on their options by either the nurse practitioner/PA or the cardiologist, according to the hospitals' local practice. These caregivers were asked to fill in the caregiver-specific study questionnaires throughout the study (during the control and the intervention phase). Besides their personal demographic characteristics, the caregivers filled out the modified SDM-Q-Doc (16, 17). Based on unique inclusion numbers, caregiver questionnaires could be matched with patient questionnaires. Questionnaires in the first phase were filled out after the standard patient consultation. In the decision aid phase, questionnaires were filled out and returned after evaluating the decision aid with the patient and its outcome.

Questionnaires

To assess the effectiveness of the decision aid, a survey was completed by patients and physicians after the final consultation in which a final decision for therapy was made. Both the patient and the physician questionnaire consisted of the 9-item SDM questionnaire which measures the extent to which patients are involved in the process of decision-making during a consultation from the perspective of the patient (version SDM-Q-9) and the perspective of the physician (SDM-Q-Doc)(16, 17). The SDM-Q, a self-reported survey, consists of nine items that each describe a different step of the SDM process and is the most frequently used instrument for assessing the involvement of the patient in medical decision making (16).

In addition to the SDM-Q-9, the traditional 16- questions Decisional Conflict Scale (DCS) was used for the patients to measure uncertainty in making a health-related decision, factors contributing to uncertainty and perceptions of effective decision-making (18). The DCS expresses the amount of uncertainty within an individual. The DCS assesses aspects of decision-making in 5 different subscales: 1) feeling uncertain about the best course of action, 2) feeling uninformed, 3) feeling unclear about values 4) experienced support during the decision making process and 5) ineffective decision-making. The items are measured on a 5-point

Likert scale (0 strongly agree to 4 strongly disagree), which gives a total score range from 0 (no decisional conflict) to 100 (extremely high decisional conflict). For all subscales, a higher score indicates greater decisional conflict and thus experiencing more uncertainty and less effective choices. The decisional conflict score was determined according to the user manual (18). A total score of 25 or below, is associated with no decisional conflict. A total score above 25 is associated with decisional conflict and scores higher than 37,5 are specifically associated with decision delay or feeling clearly unsure about implementation(18, 19). In addition to the questionnaires, patients' knowledge on the ICD/CRT-D was tested using 4 knowledge questions regarding the ICD/CRT-D implantation and risks. For the analyses, the statements were dichotomized; correct or incorrect answer or missing answer. Data on patients logged on to the online decision aid, including number of logged-in sessions and the duration in time spent online, was collected retrospectively from the online environment log file. For the English translation of the study questionnaires, see Appendix 1 and 2.

Primary Outcomes

The primary outcome of this study was the degree of SDM experienced by patients and caregivers with or without the decision aid implementation (based on the SDM-Q-9 and SDM-Q-doc). Additional primary outcome for patients was the experienced decisional conflict.

Secondary Outcomes

The knowledge, as assessed by the 4 theoretical questionnaires.

Data collection

In case of 1 or 2 missing answers in the SDM-Q-Doc, the mean of the available answers was inputted to the missing answers. Questionnaires missing more than 2 answers were excluded from analysis. All items are scored on a six-point Likert scale. Scores were aggregated to a raw score between 0 and 45; with 0 indication the lowest and 45 the highest level of SDM. Following Kriston et al. the score was transformed by multiplication by 20/9 to get a score range from 0 to 100 as this range is intuitively better interpretable, where 0 represents the lowest level and 100 the highest level of SDM (20). Characteristics of the total score were analyzed and the distributions were checked. Differences in total score between the control group and the decision aid group were analyzed using linear mixed modelling. For the SDM-Q-9 questionnaires for the patients, the same methods were used as for the SDM-Q-Doc questionnaires.

In case of the DCS questionnaires, missing answers to more than 2 questions were excluded from the analysis. In the case of 1 or 2 missing values, these were corrected by imputation: the imputed score was the mean score of the present variables (10, 16). In case of missing answers in the decisional conflict questions, multiple imputation was used. For the 4 questions on patients' theoretical knowledge, all correct answers provided were added up per patient and the score was expressed as a percentage correct answers of the total number of 4 questions (i.e. 0%, 25%, 50% 75% or 100% correct).

Statistical analyses

On the basis of the normality of distribution, continuous variables are presented as mean ± SD or median with interquartile range (IQR) [25th to 75th percentile]. All outcomes were analyzed as intention-to-treat and as-treated (14, 21).The differences between the control and the intervention group in total DSC score patients, SDM scores for patients and caregivers, were evaluated using the linear mixed modelling. The differences in DC subscores were analyzed using linear mixed modelling analysis. Differences in the categorical values were analyzed using Chi2-square test. A p-value of >0.05 was considered statistically significant.

Ethics Statement

The study was conducted in accordance with the Declaration of Helsinki, applicable local laws and regulations and the European directive for data protection (General Data Protection Regulation).

The Medical Ethical Committee of the Leiden University Medical Center approved the study protocol (P16.096). This was endorsed by the local ethical committees of all the individual participating centers. Each patient provided written informed consent for the participation in the study.

Results

A total of 150 patients were included in the study, Figure 3 shows the schematic representation of the study population and inclusions. The control phase included 54 patients and the intervention phase 96 patients. Of all patients, 34 (23%) was female and median age was 68 [59-77] years and 64 (43%) patients were up for a pulse-generator exchange. There was no difference between the study groups for these baseline characteristics. Furthermore, there were no differences in level of education between the groups (i.e. proportions of higher vs. lower education), Table 1. In total, 65 (68%) were confirmed to have logged into the decision aid

online platform. The majority of these patients from the treated-as-intended arm, logged in once (72%) onto the decision aid. Median time spent online on the decision aid was 16 [8.75 – 50.0] minutes, Supplemental Table 5.

The baseline characteristics of the treated-as-intended group did not differ from the controls or intention-to-treat group, except for a difference in number of pulse-generator exchange patients, Table 1. Shared decision making scores were overall high and the experienced decisional conflict was low, Figure 4 and Table 3. The median SDM-Q-9 score for patients was 39 [36-45] in the control phase and 40 [30-45] in the intervention phase (p = 0.245). DC scores were low: median DCS score for patients was 16.4 [6.25 – 25.0] in the control phase and 12.5 [4.3 – 23.4] in the intervention phase (p= 0.453).

A total of 233 caregiver questionnaires were included for analysis, filled out by 26 unique caregivers in the control phase and 29 unique caregivers in the intervention phase. Of these unique caregivers, 9 (69%) were female. The median age was 42 [36-48] years and the median clinical experience was 17 [12-22] years. There were no differences between the groups in baseline characteristics, Table 2. SDM scores were overall high. There was no difference between the two phases for the group of caregivers. The SDM-Q-Doc median score was 36 [28-38] in the control phase and 35 [33-40] in the intervention phase (p= 0.805), Figure 4.

For patients, with both the intention-to-treat and treated-as-intended analyses, there were no differences in decisional conflict or shared decision making experience, also not when corrected for type of caregiver, patient age, patient gender, or patient's level of education, Table 2B.

The theoretical knowledge as assessed by the 4 knowledge questions was overall low. The response rate was 150/150 (100%). Two or more correct answers were provided by 29 (54%) patients in the control group and 58 (60%) patients in the intervention group (p=0.146), Supplemental Table 2. Patients with a higher education provided more correct answers to the theoretical knowledge questions, both in the control and in the intervention/ decision aid phase (p<0.001). In addition, patients up for a pulse-generator-exchange also had significantly more correct answers, compared to peers up for a first device implantation, both in the control and in the intervention/ decision aid phase (p<0.001), Supplemental Table 3.

Discussion

Shared decision making (SDM) has gained prominence in healthcare, emphasizing the importance of involving patients in treatment decisions to align care with their values and preferences. Current study focused on the unique context of implantable cardioverter defibrillator (ICD) patients, a population with complex considerations in treatment choices. It is the largest study on this topic, and the only randomized clinical trial utilizing verified questionnaires for shared decision making and decisional conflict measurement as an end-point.

The main finding of this multicenter stepped-wedge randomized controlled trial is that in the current Dutch practice, patients as well as caregivers experienced high levels of SDM, as reflected by high SDM scores reported by both patients and caregivers, regardless of decision aid implementation and actual utilization. This is Decisional conflict, measured by the DCS, was also low for all patient group. Nevertheless, the theoretical knowledge as assessed by the 4 knowledge questions was overall low. Patients with a higher education and those with experience provided more correct answers to the theoretical knowledge questions.

Although the results reported here are consistent with high-patient satisfaction levels in the Netherlands in general (22), they stand in remarkable contrast to a previous study on Dutch ICD patients, which retrospectively reported low levels of SDM (10). This could have several reasons. First of all, the design of that study was prone for recall bias, as patients were surveyed in a retrospective manner. Additionally, it was reported that only a minority of Dutch clinics invite their patients for a consultation and exploration of options when they are up for a pulse generator exchange at battery depletion (23). In light of the contrast with these previous findings, it can be considered that the adjustments made to patients' education and standard care during or prior to the initiation of the trial may have favorably biased the study outcomes: a phenomenon recognized as the 'Hawthorne Effect' (24, 25).

Furthermore, it has previously been described that doctors have a leading role in decision making for patients eligible for an ICD (26). Strong language emphasizing the benefits of an ICD is likely to lead to patients favoring device implantation or replacement. Previous interviews with patients repeatedly highlighted cognitive biases in ICD patients favoring ICD therapy (27). Also in the aforementioned study, patients reported to be influenced by counselling with favorable framing of the ICD by their physicians. These findings reaffirm the necessity for an unbiased

decision aid, and underlines that the comparable SDM levels in all groups of this study may not be a reliable representation of true clinical practice.

Moreover, in our study, despite high scores on SDM, objective scores on knowledge overall were low, suggesting that patients may in fact be unconsciously uninformed. This highlights the importance of providing patients with adequate information and resources to make well-informed decisions.

In addition, among the study patients provided with log-in codes for the decision aid, only 65% accessed this information. However, even though this participation rate may seem modest, it is comparable to or even exceeds response rates reported in similar studies, such as the one conducted by Etnel et al in patients with congenital aortic and pulmonary valve disease (28),with only 51% of subjects in the intervention group actually visiting the information portal. The challenges associated with online patient engagement are therefore not unique to this specific decision aid.

Misconceptions and information comprehension

Traditionally, pros and cons of treatment options are either summed up or illustrated by percentages. The comprehension of patients of mere percentages has been shown to be disappointing (29). Moreover, it has been previously established that ICD patients overestimate benefit from ICD therapy and are deficient in their comprehension of device function (30-34). Aside from benefit, ICD patients have previously reported to have not understood fully the risks and burden of living with an ICD at time of ICD implantation (26, 30). On the contrary, patients who had previously declined an ICD implantation for primary prevention had not fully understood the benefits for survival (35).

Patients nevertheless desire to have access to comprehensive information that can help them in making a decision. Providing patients with comprehensive information and taking into account their preferences, is important for sustainable decision making. Interestingly, traditional print-based educational material for ICD patients have previously be proven to be targeted at a highly literate population (36). For this reason, the decision aid in this study was available online, interactive and incorporated illustrative educational videos in simple language. Due to the potential limitation of digital illiteracy, content of the decision aid was also available for printing by caregivers for their patients. These patients were, however, not eligible for study inclusion. In addition, all text was reviewed by professional content writers to be comprehendible for the lower-literate population (11).

Previous ICD decision aids

Previously, with 18 participants in total, Lewis et al. developed a user-centered ICD decision aid that was positively evaluated by the participants to the study (37). The evaluation of the decision aid was based on interviews, and no trial for implementation in clinical practice was performed as in this study. Another study by Lewis at al., focused on 30 patients who were randomized to a decision support intervention (ncluded a paper-based PDA and nurse-led coaching) before ICD-battery exchange procedure (38). The authors concluded that the decision support intervention had "the potential to improve ICD replacement decision quality", based on improved knowledge outcomes in this small patient population. No standardized scores were used in the evaluation and patient numbers were small.

In light of these studies, our trial provides insights from a larger study group, with a digital decision aid implemented and evaluated in a RCT setting, using validated questionnaires as a study outcome.

Decision making at time of battery depletion

Interestingly, patients up for a pulse-generator exchange, accessed the decision aid more frequently than their *de novo* peers. This insight was provided by the treated-as-intended analysis of our study, for the baseline of the two groups. Additionally, patients up for a pulse-generator-exchange also provided significantly more correct answers to the theoretical knowledge questions. This potentially illustrates the persistent need of pulse-generator exchange patients for counseling on their options, despite of being 'experienced and knowledgeable patients'. However, in our previous study (23) it had been illustrated that at time of ICD replacement, this was not always considered as a choice by health care providers. Likewise, it has been previously shown that more than half of the patients who had already undergone an ICD replacement at time of battery depletion, were not aware that they had a choice (23, 39). This illustrated that ICD replacement at time of battery depletion in real-life practice often goes without saying, whereas patients have been reported to consider non-replacement under certain circumstances such as serious illness and advanced age (39). Moreover, patient preferences can change with the progression of age and the involvement of new comorbidity. An ICD decision aid can facilitate also decision making in these patients, exploring their current preferences and weighing them out against expected benefits and downsides from ICD therapy.

Limitations

Although this study has the potential to improve the decision-making process for ICD patients, there are several limitations to be acknowledged. First of all, the previously sobering reports of patient involvement and consultations prior to pulse generator exchange procedures might have triggered improvements in the standard of care, resulting in a control group that in fact was better informed. Online decision aids inherently require digital literacy, potentially resulting in selection bias. Patients surveys are prone to recall bias.

Furthermore, the efficiency of the consultations was not measured, and long-term outcomes were not assessed as by study design. Despite these limitations, the current study is the largest study on this topic, and the only randomized clinical trial utilizing verified questionnaires for shared decision making and decisional conflict measurement as an end-point.

Conclusion

In this study, our study assessed the impact of the Dutch ICD Decision Aid on shared decision making in the complex context of implantable cardioverter defibrillator patients facing the decision of a first device implantation, or pulse battery depletion-driven generator replacement. Despite high SDM scores for both patients and caregivers, irrespective of decision aid utilization, knowledge levels remained suboptimal. The decision aid offers a valuable resource but highlights the ongoing need for refining tools to enhance unbiased decision-making and improve patient knowledge in the complex landscape of ICD therapy. Future efforts should focus on addressing these challenges to promote informed and patient-centered decisions.

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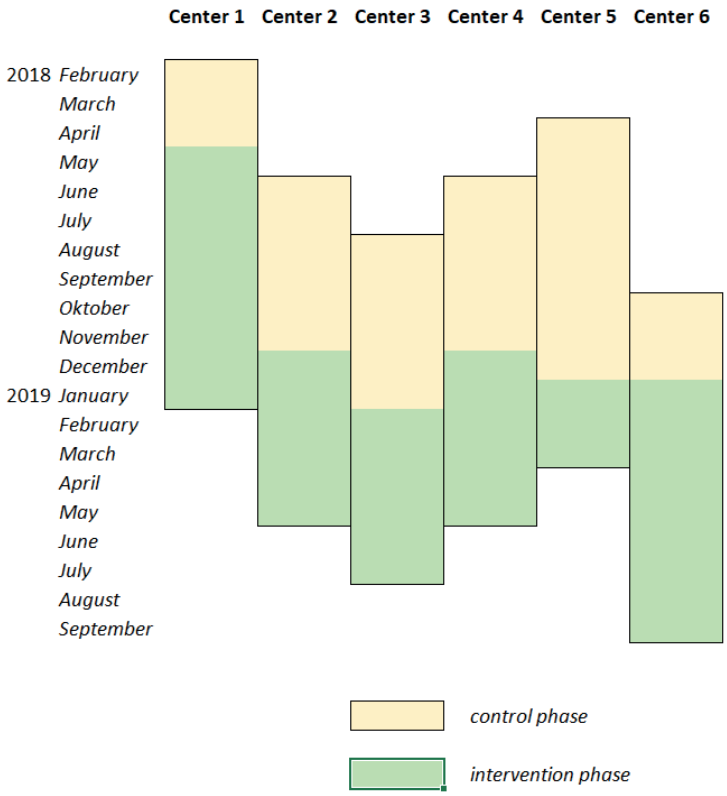

Figure 1. Schematic representation of the stepped-wedge cluster randomized trial design and the study phases distribution for participating hospitals 1 to 6. Control phase in yellow: standard care enrollment period. Intervention phase in green: Decision Aid implementation on top of standard care enrollment period.

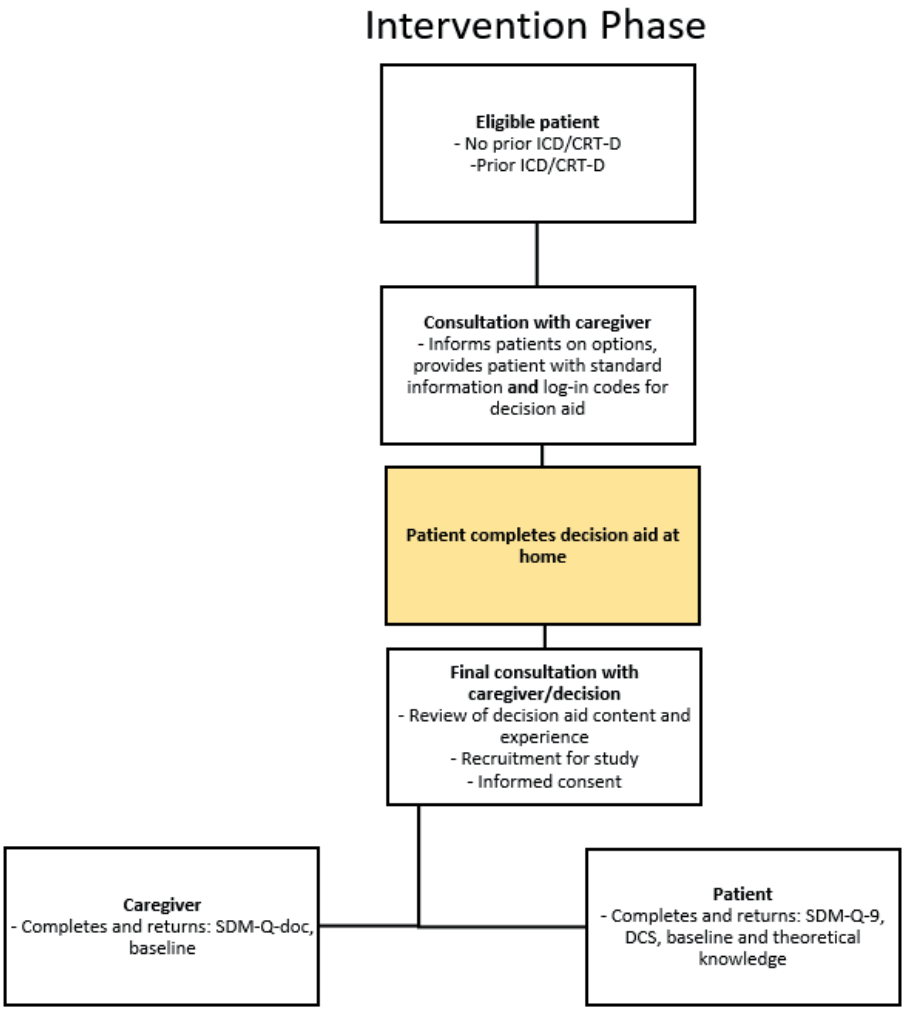

Figure 2. Schematic representation of the study design flow chart.

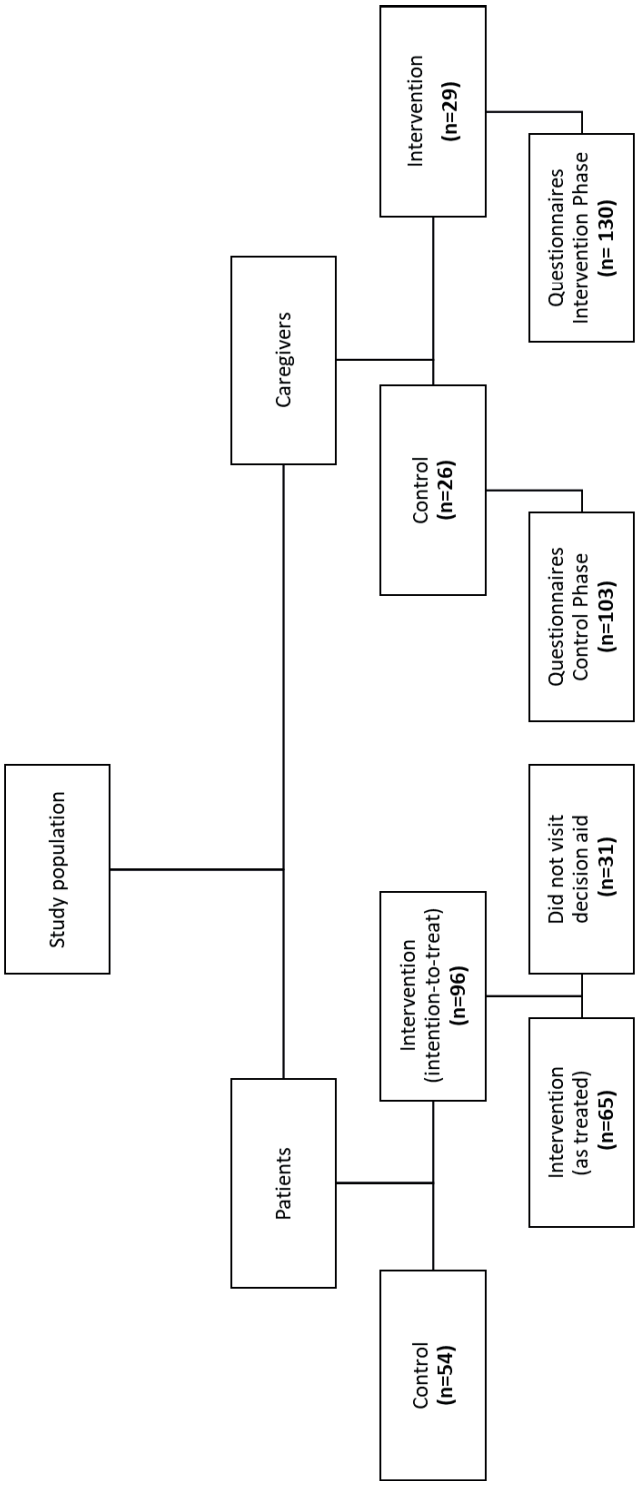

Figure 3. Schematic representation of the study population and inclusions.

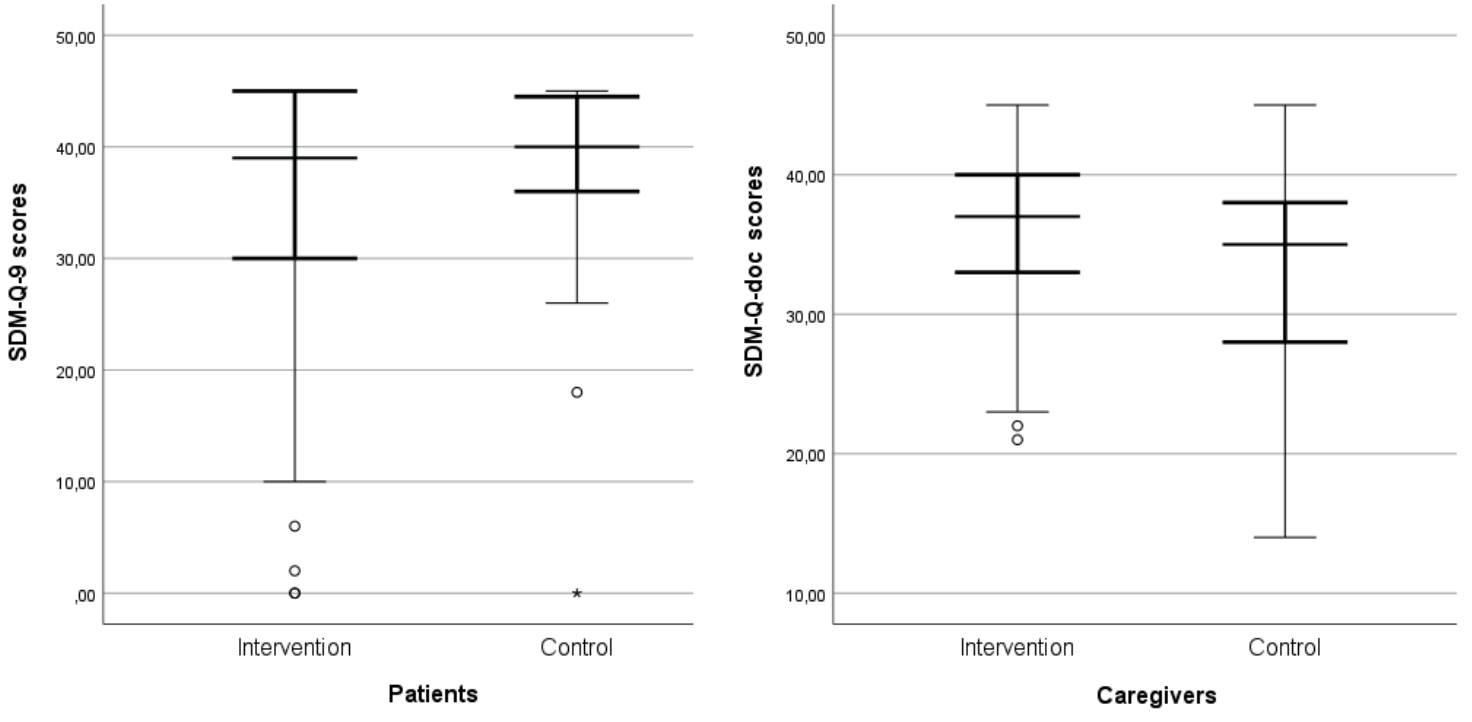

Figure 4: Primary outcome caregivers. SDM-Q-9: shared decision making scores based on the shared decision making 9 questionnaire. SDM-Q-doc: shared decision making scores based on the shared decision making doctor questionnaire. IQR: interquartile range [25th and 75th percentile].

	Control phase	Intervention phase	Treated as intended	Intention to treat vs control *p-value*	Treated as intended vs control *p-value*
	(n= 54)	(n=96)	(n=65)		
Median Age, years [IQR]	69 [60-78]	67 [58 – 75]	69 [63 – 76]	*0.677*	*0.823*
Female sex	15 (18%)	27 (19%)	20 (31%)	*0.735*	*0.924*
Up for pulse-generator exchange	16 (30%)	48 (50%)	30 (46%)	*0.546*	***0.016***
Refrained from ICD implantation/ replacement	2 (0.04%)	0 (0%)	0 (0%)	*0.927*	*0.995*
Educational level				*0.986*	*0.942*
- Elementary school	4 (7%)	9 (9%)	5 (8%)		
- Lower vocational	8 (17%)	12 (13%)	5 (8%)		
- Lower secondary	7 (13%)	11 (11%)	7 (11%)		
- Intermediate vocational	13 (24%)	27 (28%)	19 (29%)		
- Higher secondary	4 (7%)	6 (6%)	6 (9%)		
- Higher vocational	12 (22%)	18 (19%)	14 (22%)		
- University	0 (0%)	9 (9%)	7 (11%)		
- Unknown/other	6 (11%)	2 (2%)	2 (3%)		

Table 1. Baseline patient characteristics.. *IQR: interquartile range [25th-75th percentile]. ICD: implantable cardioverter-defibrillator.*

	Control phase	Intervention phase	*p-value*
Total questionnaires	103	130	
Total unique caregivers	26	29	*0.823*
Cardiologist	8 (31%)	9 (31%)	*0.967*
Nurse practitioner	18 (69%)	20 (69%)	*0.432*
Female sex	19 (73%)	66 (34%)	*0.513*
Age, median years [IQR]	43 [38 - 48]	40 [35 - 48]	*0.538*
Median years of clinical experience [IQR]	18 [15 - 22]	17 [12 - 22]	*0.498*

Table 2: Caregivers' baseline characteristics. IQR: interquartile range (25th and 75th percentile).

	Control phase	Intervention phase	Treated as intended	intention to treat p-value	treated as intended p-value
SDM-Q-9, median *[IQR]*	39 [36-45]	40 [30-45]	39 [30-45]	0.180	0.122
DCS, median *[IQR]*	16.4 [6.25 – 25.0]	12.5 [4.3 – 23.4]	13.3 [4.7-23.4]	0.808	0.726
• *subscore uncertainty*	25 [0 -50]	16.6 [0 -43.75]	16.7 [0-50]	0.543	0.625
• *subscore informed*	8 [0 -25]	0 [0 -16.67]	0 [0-16.7]	0.629	0.604
• *subscore values*	25 [0 -33]	20.8 [0 -33]	16.7 [0-33.3]	0.719	0.794
• *subscore support*	16.6 [0 -27]	16.6 [0 -33]	8.3 [0-33.3]	0.527	0.969
• *subscore effective decision making*	0 [0 -12.5]	0 [0 -6.25]	0 [0-6.25]	0.939	0.726
Chosen for no (longer) ICD therapy	2 (0.04%)	0 (0%)	0 (0%)	0.927	0.995

Table 3: primary outcomes patients. *SDM-Q-9: shared decision making scores based on the shared decision making 9 questionnaire. DCS: decisional conflict scale score. ICD: implantable cardioverter-defibrillator. IQR: interquartile range (25th and 75th percentile).*

Supplementary data

Supplemental table 1: primary outcomes. SDM-Q-9: shared decision making scores based on the shared decision making 9 questionnaire. DCS: decisional conflict scale score. ICD: implantable cardioverter-defibrillator.

	Intervention phase	Treated as intended	*p-value*
SDM-Q-9	40 [IQR 30-45]	39 [30-45]	0.995
DCS	12.5 [4.3 – 23.4]	13.3 [4.7-23.4]	0.256
subscore uncertainty	16.6 [IQR 0 -43.75]	16.7 [0-50]	0.131
subscore informed	0 [IQR 0 -16.67]	0 [0-16.7]	0.956
subscore values	20.8 [IQR 0 -33]	16.7 [0-33.3]	0.334
subscore support	16.6 [IQR 0 -33]	8.3 [0-33.3]	0.285
subscore effective decision making	0 [IQR 0 -6.25]	0 [0-6.25]	0.851
Chosen for no (longer) ICD therapy	0 (0%)	0 (0%)	n/a

	Control phase	Intervention phase	Treated as intended	Intention to treat vs control p-value	Treated as intended p-value vs control
	(n= 54)	(n=96)	(n=65)	0.146	0.199
0% correct	3	4	3		
25% correct	0	6	4		
50% correct	9	17	10		
75% correct	20	21	15		
100% correct	22	47	33		

Supplemental table 2: theoretical knowledge question results.

	Control phase		Intervention phase		Intention to treat vs control
	De novo	Pulse-generator-exchange	*De novo*	Pulse-generator-exchange	p-value
	(n= 38)	(n=16)	(n=48)	(n=48)	<0.001
0% correct	3	1	6	0	
25% correct	8	1	9	3	
50% correct	7	4	9	11	
75% correct	18	8	24	30	
100% correct	2	2	0	4	

Supplemental table 3: theoretical knowledge question results, *de novo* patients versus patients for pulse-generator exchange.

Supplemental table 4: Primary outcome caregivers. SDM-Q-doc: shared decision making scores based on the shared decision making doctor questionnaire. IQR: interquartile range [25th and 75th percentile].

	Control phase	**Intervention phase**	*p-value*
SDM-Q-Doc, median [IQR]	36 [28-38]	35 [33 – 40]	0.805

Supplemental table 5: treated-as intended arm patients logfile data. IQR: interquartile range (25th and 75th percentile)

	Logged-in patients (n=65)
Number of times logged-in	
1	47 (72%)
2	7 (11%)
3	4 (6%)
4	7 (11%)
Median time online in minutes [IQR]	16 [8.75 – 50.0]

Appendix 1

Questionnaire for Caregivers

Name

Position

Age

Sex: male/female

Years of clinical experience in your current position?:

My patient is eligible for:

- First ICD implantation
- ICD pulse generator exchange due to battery depletion

The statements below reflect the conversation you just had with your patient.
Please indicate to what extent this is the case for each individual statement.

	Strongly Disagree	**Disagree**	**Neither Agree nor Disagree**	**Agree**	**Strongly Agree**
1 I have clearly communicated to my patient that a decision needs to be made					
2 I wanted to know how the patient wants to be involved in making the decision					
3 I have informed my patient that 'no ICD' is also an option					
4 I have explained the pros and cons of having / not having an ICD to the patient					
5 I helped my patient understand all the information					
6 I asked my patient if they had a preference for an ICD					
7 My patient and I thoroughly weighed the option of having or not having an ICD					
8 My patient and I jointly decided to proceed/ not proceed with ICD implantation					
9 My patient and I have made plans to follow-up on the decision					

Appendix 2

Patient Questionnaires

1. What is your sex? Male/female
2. What is your highest completed level of education?
    - Elementary school
    - Lower vocational
    - Lower secondary
    - Intermediate vocational
    - Higher secondary
    - Higher vocational
    - University
    - Unknown/other

What is your current situation?

- I do not have an ICD/CRT-D currently and qualify to have one implanted
- I currently have an ICD/CRT-D and qualify for a replacement due to battery depletion.

What decision has been made?

- to have an ICD/CRT-D implanted or replaced
- not to have an ICD/CRT-D implanted or replaced

Knowledge Questions

Below are four statements. Please indicate whether you think the statements are true, false, or if you do not know.

	Ture	False	I don't know
I can choose to have the ICD turned off or removed at any time.			
My heart immediately stops if the ICD is turned off.			
The battery of my ICD can be recharged when it is empty.			
Choosing to have an ICD affects my driver's license.			

Shared decision making

This questionnaire is about how you reflect on the conversation you just had with your healthcare provider. Please indicate to what extent you agree with each statement. We ask you to answer the questionnaire as honestly and accurately as possible. There are no 'right' or 'wrong' answers.

	Strongly Disagree	**Disagree**	**Neither Agree nor Disagree**	**Agree**	**Strongly Agree**
My healthcare provider clearly communicated that a decision needs to be made.					
My healthcare provider wanted to know how I wanted to be involved in the decision-making process.					
My healthcare provider told me that not having an ICD is also an option.					
My healthcare provider explained the pros and cons of having or not having an ICD.					
My healthcare provider helped me understand all the information.					
My healthcare provider asked me if I had a preference for an ICD.					
My healthcare provider and I thoroughly considered the option not having an ICD.					
My healthcare provider and I made the decision together to have or not have an ICD.					
My healthcare provider and I made agreements about the next steps.					

Decisional conflict

	Strongly disagree	Disagree	Neither Agree nor Disagree	Agree	Strongly Agree
I found it difficult to make this decision.					
It was clear to me what the best choice for me is.					
I was unsure about what to decide.					
I was aware of the treatment choices available for my condition.					
I felt that I understood the positive effects of the ICD.					
I felt that I understood the risks and side effects of an ICD.					
I would have wanted to receive more advice and information about the options available.					
I knew how important the benefits of an ICD were to me when making this decision.					
I knew how important the risks and side effects of an ICD were to me when making this decision.					
I found it difficult to decide whether the benefits or the drawbacks were more important to me.					
I felt pressured by others when making this decision.					
I received sufficient support from others in making this decision.					
I feel that I made an informed decision.					
My decision reflects what is most important to me.					
I expect to stick with my decision.					
I am satisfied with my decision.					

Chapter 8

Summary, conclusions and future perspectives

This thesis explores the importance and challenges of patient-centered approaches in ICD therapy. The thesis captures shared decision-making in the contemporary and ageing Dutch ICD patient population, emphasizing the importance of patient-centered care and informed shared decision making of patients and clinicians when it comes to guiding ICD implantation and pulse generator exchange related choices. It addresses barriers to ICD therapy utilization in older patients and advocates for thorough patient selection, taking into account not only the primary cardiac status, but also the growing comorbidities and evolving patient's values. The thesis discusses some of the ethical considerations in end-of-life care of patients with an ICD, advocating for timely advanced care planning discussions and interdisciplinary collaboration to reflect patient preferences. Furthermore, this thesis examines the clinical outcomes of subcutaneous versus transvenous ICD therapy, highlighting some of the advantages of subcutaneous devices in terms of safety and lead related complications. Additionally, it investigates the impact of chronic total coronary occlusion on ventricular arrhythmias and mortality, offering insights into tailored interventions and risk stratification strategies for patients with ischemic heart disease.

Chapter 2 of the thesis focused on the technical aspects of ICD therapy, comparing the long-term clinical outcomes of subcutaneous versus transvenous ICD therapy. The study found that both types of ICDs were effective in reducing the risk of SCD, but that subcutaneous ICD therapy was associated with a lower risk of device-related complications such as infection and lead failure. The chapter also discussed the practical considerations of device selection, including patient and cardiac condition specific characteristics, indication for therapy, expected chance of anti-tachy pacing and the potential risks and benefits of each type of device.

Chapter 3 of the thesis evaluated the impact of a chronic total coronary occlusion on ventricular arrhythmias and long-term mortality in patients with ischemic cardiomyopathy and an ICD. The study found that the presence of a chronic total coronary occlusion was associated with an increased risk of ventricular arrhythmias and long-term mortality in this patient population. The chapter discussed the implications of these findings for the clinical management of patients with ischemic cardiomyopathy and an ICD, including the potential benefits of revascularization in reducing the risk of ventricular arrhythmias .

Chapter 4A of the thesis examined the risk of painful shocks in the last moments of life in patients with an ICD. It reports that patients with an ICD remain at risk for painful shocks in the last moments of life, even when the device is

programmed to minimize the risk of inappropriate shocks. The chapter discusses the ethical implications of ICD therapy in end-of-life care, including the need for careful consideration of patient preferences and values in decision-making and timely tachytherapy deactivation.

Chapter 4B of this thesis investigated the causes of death in patients who had their tachytherapy deactivated in a large population over a decade. The research focused on patients who received an ICD and examined the practice of tachytherapy deactivation, the mode of death, and the diversification of causes of death over time. The study emphasized the need for advanced care planning to avoid painful shocks and stress during patients' last moments of life, highlighting the importance of awareness among (primary) care providers.

Chapter 5 of the thesis investigated the use of ICD therapy in older patients in the Dutch clinical practice. The study found that ICD therapy was underutilized in older patients, despite evidence of its effectiveness in this population. The chapter discussed the factors that may contribute to the restricted use of ICD therapy in older patients, including age bias, competing health risks, and the potential impact on quality of life.

Chapter 6 of the thesis reported on the development of a decision aid for shared decision-making in the Dutch ICD patient population. This novel approach to patient education provided a structured and systematic process for patients and clinicians to discuss the benefits and risks of ICD therapy, including the potential impact on quality of life and the risks of complications such as painful shocks. The decision aid was developed using a patient-centered approach, involving patients, clinicians, and researchers in the development and evaluation process. The chapter discussed the potential of the decision aid in improving patient knowledge and satisfaction with the decision-making process.

Chapter 7 of this thesis reports the results of the randomized controlled trial that aimed to evaluate the use of a decision aid for patients undergoing an elective pulse generator exchange for their ICD and assessed shared decision making levels, decisional conflict, and knowledge before and after the intervention. Experienced shared decision making levels did not differ between the study groups for both patients and caregivers. The degree of decisional conflict was also similar in patient who did and did not use the decision aid. Despite these outcomes, the trial contributed to standardizing care and patient information within the country, with an online accessible platform endorsed by the Dutch Society of Cardiology.

In summary, this thesis contributes to our understanding of ICD therapy and its optimal patient-tailored implementation, emphasizing evidence-based practice, patient-centered care, and interdisciplinary collaboration in optimizing clinical and patient-oriented outcomes.

Future perspectives

Personalized decision-making

Further research is needed to investigate the impact of personalized decision-making tools on patient perceived as well as hard clinical outcomes. By incorporating patient-specific factors such as comorbidities, frailty, and patient values and preferences, decision-making can be tailored to the individual patient's needs and look beyond the primary cardiac indication.

Advancements in technology

As technology continues to evolve, there is an opportunity to improve the technical aspects of ICD therapy. For example, the further development of leadless ICDs may further reduce the risk of complications such as infection and lead failure. Additionally, advancements in remote monitoring technology may improve patient outcomes by allowing for earlier detection of device/ lead malfunctions, arrhythmias and worsening heart failure.

End-of-life care

There is a need for further research into the ethical implications of ICD therapy in end-of-life care. Specifically, there is a need for practical guidelines and decision-making tools to help clinicians and patients navigate the difficult decisions surrounding deactivation of ICD therapy. This is especially the case for the frail and elderly, but also for specific groups such as patients with advance heart failure and those on left ventricular assist device support.

Age selection

The selection approach of ICD therapy in older patients, as highlighted in this thesis, underscores the need to address age bias in clinical decision-making and make a careful weighting against the expected benefit. Holistic patient assessment approaches (e.g. including frailty scores) can help gain thorough understanding of a patient’s both somatic and functional status.

Collaboration between disciplines

The findings of this thesis highlight the importance of a multidisciplinary approach to the management of patients with a high risk of SCD. Collaboration between cardiologists (amongst others rhythm (device) and heart failure specialists), geriatricians, general practitioners and even palliative care specialists can help ensure that patients receive comprehensive, individualized care that addresses their unique needs and preferences.

Patient education and empowerment

This thesis highlights the importance of patient education in improving shared decision-making and reducing decisional conflict. Future research should investigate the most effective methods of patient education and empowerment, including the use of multimedia and interactive (virtual reality) tools.

Revascularization in ischemic cardiomyopathy

The findings suggest that revascularization of a chronic total occlusion may reduce the risk of ventricular arrhythmias and improve long-term outcomes in patients with ischemic cardiomyopathy and an ICD. Further research is needed to investigate the optimal timing and method of revascularization in this patient population.

Chapter 9

Samenvatting en conclusies

Dit proefschrift onderzoekt de meerwaarde en de uitdagingen van patiëntgerichte benaderingen in ICD-therapie. Het proefschrift belicht gedeelde besluitvorming in de hedendaagse en vergrijzende Nederlandse ICD-patiëntpopulatie, met nadruk op het belang van patiëntgerichte zorg en geïnformeerde gedeelde besluitvorming door clinici en patiënten tezamen, bij ICD-implantaties en keuzes met betrekking tot puls-generator vervanging. Het behandelt de barrières voor het gebruik van ICD-therapie bij oudere patiënten en pleit voor zorgvuldige patiëntselectie, waarbij niet alleen de primaire cardiale status, maar ook de toenemende comorbiditeit en veranderende waarden van de patiënt in overweging worden genomen. Het proefschrift bespreekt enkele ethische overwegingen in de zorg aan het einde van het leven van patiënten met een ICD, en pleit voor tijdige gesprekken over palliatie en interdisciplinaire samenwerking om de voorkeuren van de patiënt te weerspiegelen.

Daarnaast onderzoekt dit proefschrift de klinische uitkomsten van subcutane versus transveneuze ICD-therapie, waarbij enkele voordelen van subcutane ICD's in termen van veiligheid en complicaties gerelateerd aan de leads worden belicht. Verder wordt de impact van chronische totale coronaire occlusie op ventriculaire aritmieën en mortaliteit onderzocht, wat inzichten biedt in op maat gemaakte interventies en risicostratificatie strategieën voor patiënten met ischemische hartziekte.

Hoofdstuk 2 van het proefschrift richtte zich op de technische aspecten van ICD-therapie, waarbij de lange termijn klinische uitkomsten van subcutane versus transveneuze ICD-therapie werden vergeleken. De studie vond dat beide typen ICD effectief waren in het verminderen van het risico op plotse (hart)dood, maar dat subcutane ICD-therapie geassocieerd was met een lager risico op apparaat gerelateerde complicaties zoals infectie en lead-falen. Het hoofdstuk besprak ook de praktische overwegingen bij de keuze van het apparaat, inclusief patiënt- en cardiale conditie-specifieke kenmerken, indicatie voor therapie, verwachte kans op anti-tachy pacing en de potentiële risico's en voordelen van elk type apparaat.

Hoofdstuk 3 van het proefschrift evalueerde de impact van een chronische totale coronaire occlusie op ventriculaire aritmieën en langetermijnmortaliteit bij patiënten met ischemische cardiomyopathie en een ICD. De studie vond dat de aanwezigheid van een chronische totale coronaire occlusie geassocieerd was met een verhoogd risico op ventriculaire aritmieën en lange termijn mortaliteit in deze patiëntpopulatie. Het hoofdstuk besprak de implicaties van deze bevindingen voor het klinische management van patiënten met ischemische cardiomyopathie en

een ICD, inclusief de potentiële voordelen van revascularisatie bij het verminderen van het risico op ventriculaire aritmieën.

Hoofdstuk 4A van het proefschrift onderzocht het risico op pijnlijke schokken in de laatste levensmomenten van patiënten met een ICD. Het meldt dat patiënten met een ICD een risico blijven lopen op pijnlijke schokken in hun laatste levensmomenten, zelfs wanneer het apparaat is geprogrammeerd om het risico op ongepaste schokken te minimaliseren. Het hoofdstuk bespreekt de ethische implicaties van ICD-therapie in de zorg aan het einde van het leven, inclusief de noodzaak van zorgvuldige overweging van patiëntvoorkeuren en -waarden bij de besluitvorming en tijdige deactivering van tachytherapie.

Hoofdstuk 4B van dit proefschrift onderzocht de doodsoorzaken bij patiënten bij wie de tachytherapie was gedeactiveerd, over een decennium. Het onderzoek richtte zich op patiënten die een ICD ontvingen en onderzocht de praktijk van tachytherapie-deactivatie, de wijze van overlijden en de diversificatie van doodsoorzaken in de loop van de tijd. De studie benadrukte de noodzaak van geavanceerde zorgplanning om pijnlijke schokken en stress tijdens de laatste levensmomenten van patiënten te voorkomen, en wees op het belang van bewustwording onder zorgverleners.

Hoofdstuk 5 van het proefschrift onderzocht het gebruik van ICD-therapie bij oudere patiënten in de Nederlandse klinische praktijk. De studie vond dat ICD-therapie minder snel benut werd bij oudere patiënten, ondanks bewijs van de effectiviteit ervan in deze populatie. Het hoofdstuk besprak de factoren die kunnen bijdragen aan het beperkte gebruik van ICD-therapie bij oudere patiënten, waaronder leeftijdsvooroordelen, concurrerende gezondheidsrisico's en de mogelijke impact op de kwaliteit van leven.

Hoofdstuk 6 van het proefschrift rapporteerde over de ontwikkeling van een keuzehulp voor gedeelde besluitvorming in de Nederlandse ICD-patiëntenpopulatie. Deze nieuwe benadering van patiënteducatie bood een gestructureerd en systematisch proces voor patiënten en clinici om de voordelen en risico's van ICD-therapie te bespreken, inclusief de mogelijke impact op de kwaliteit van leven en de risico's op complicaties zoals pijnlijke schokken. De keuzehulp werd ontwikkeld met een patiëntgerichte aanpak, waarbij patiënten, clinici en onderzoekers betrokken waren bij het ontwikkelings- en evaluatieproces. Het hoofdstuk besprak het potentieel van de beslissingshulp om de kennis van de patiënt en de tevredenheid met het besluitvormingsproces te verbeteren.

Hoofdstuk 7 van dit proefschrift rapporteert de resultaten van de gerandomiseerde gecontroleerde studie die gericht was op het evalueren van het gebruik van de keuzehulp voor patiënten die een nieuwe ICD implantatie of electieve puls-generatorvervanging voor hun ICD ondergingen en beoordeelde de mate van gedeelde besluitvorming, besluitvormingsconflict en kennis voor en na de interventie. De ervaren niveaus van gedeelde besluitvorming verschilden niet tussen de onderzoeksgroepen voor zowel patiënten als zorgverleners. De mate van besluitvormingsconflict was ook vergelijkbaar tussen patiënten die wel en geen gebruik maakten van de beslissingshulp. Ondanks deze uitkomsten, droeg de studie bij aan het standaardiseren van zorg en patiënte informatie binnen het land, met het opzetten van een online toegankelijke ICD keuzehulp, dat werd ondersteund door de Nederlandse Vereniging voor Cardiologie.

Samenvattend draagt dit proefschrift bij aan ons begrip van ICD-therapie en de optimale patiëntgerichte implementatie ervan, met de nadruk op evidence-based practice, patiëntgerichte zorg en interdisciplinaire samenwerking bij het optimaliseren van klinische en patiëntgerichte uitkomsten.

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The Dutch Implantable Cardioverter-defibrillator Decision Aid in Clinical Practice: a Stepped-wedge Randomized Controlled Trial
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Curriculum vitae

Dilek Yilmaz werd geboren op 2 april 1990 in 's-Gravenhage. In 2008 behaalde zij cum laude haar eindexamen aan het Gymnasium Haganum te 's-Gravenhage. Haar academische reis vervolgde zij aan de Universiteit Leiden met de studie Geneeskunde, waar zij in 2014 haar artsenexamen behaalde. Na haar artsexamen werkte zij als arts niet in opleiding tot specialist op de afdeling Thoraxchirurgie. In 2015 startte zij haar promotieonderzoek aan de afdeling Cardiologie van het Leids Universitair Medisch Centrum (LUMC) in Leiden onder leiding van prof. dr. M.J. Schalij. Haar onderzoek richtte zich specifiek op het gebied van gedeelde besluitvorming bij implanteerbare cardioverter-defibrillatoren, met als doel de kwaliteit van zorg voor patiënten te verbeteren. De resultaten hiervan staan beschreven in dit proefschrift. Per september 2018 is zij begonnen met haar opleiding tot cardioloog vanuit het Leids Universitair Medisch Centrum (opleider initieel prof. dr. M. J. Schalij, heden dr. S.A.I.P Trines. Haar opleiding tot cardioloog rondt zij per 30 december 2024 af, waarna zij zal starten als Fellow Aangeboren Hartafwijkingen aan het ErasmusMC en Radboudmc.