Contemporary Clinical Practice in Electrophysiology

Focus on complications and post-discharge e-Health

John de Heide

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Hedendaagse klinische praktijk in de elektrofysiologie:

Focus op complicaties en e-Health na ontslag

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COLOFON

ISBN	978-94-6506-734-6
Design / layout	John de Heide
Printing	Ridderprint, www.ridderprint.nl

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Hedendaagse klinische praktijk in de elektrofysiologie:

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Proefschrift

ter verkrijging van de graad van doctor aan de

Erasmus Universiteit Rotterdam

op gezag van de

rector magnificus

Prof. dr. ir. A.J. Schuit

volgens besluit van het College voor Promoties.

De openbare verdediging zal plaatsvinden op

op woensdag 5 februari 2025 om 15.30 uur

door

John de Heide

geboren te Vlaardingen.

Erasmus University Rotterdam

PROMOTIECOMMISSIE

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

Financial support by the Dutch Society of Cardiovascular Nursing (NVHVV) for the publication of this thesis is gratefully acknowledged.

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CHAPTER 1

General introduction

Cardiac electrophysiology is a rapidly evolving subspecialty of cardiology. Its main focus is to treat cardiac arrhythmias and prevent sudden cardiac death. Within the Erasmus MC there is a dedicated team of cardiac electrophysiologists, fellows, nurse practitioners, nurses, technicians and researchers who are actively involved in the care and cure of patients with a heart rhythm disorder.

Over the last decades the treatment of heart rhythm disorders has evolved from exclusive anti-arrhythmic drug therapy to a broad spectrum of invasive and non-invasive therapies. The invasive treatment arsenal includes pacemakers, implantable cardioverter-defibrillators (ICDs), and catheter ablation of cardiac arrhythmias (1). Furthermore, patient centred care with emphasis on shared decision making has entered the clinical arena. Currently, there is an enhanced emphasis on risk factor management, which inherently optimizes therapy outcomes and as such is the underlying principle of this thesis.

1.1 Evaluation of complications in atrial fibrillation

Atrial fibrillation (AF) is a supraventricular tachyarrhythmia with uncoordinated atrial electrical activation (2). It is the most common cardiac arrhythmia in adults and constitutes a significant burden to patients, communal health and health economy. The lifetime risk of AF in Europe is as high as 40% (2). In 2021 approximately 123,400 newly diagnosed AF cases were documented in the Netherlands (3).

In recent years a paradigm shift in the management of AF was observed with a change from prescribing anti-arrhythmic drugs and electrical cardioversions (ECVs) to comprehensive AF care (1). Comprehensive AF care includes a focus on patient engagement, participation, and shared decision making in a treatment plan and involves a combination of lifestyle management, risk factor management, anti-arrhythmic drugs, ECV and AF catheter ablation (1). Currently, the first aim is to improve lifestyle management and initiate a more aggressive risk factor management. Secondly, a choice will be made between rate or rhythm control depending on patient preferences, symptoms, comorbidity, and anticipated benefits and risks of invasive catheter ablation. Rate control is achieved using atrioventricular blocking agents (i.e., betablockers, digoxin, verapamil) or a “pace and ablate” strategy. Rhythm control is achieved using a combination of anti-arrhythmic drugs, ECVs, and AF catheter ablation. Inherent to every medical procedure, there are

certain risks associated with electrophysiology procedures. Both ECVs and AF catheter ablation can be associated with the risk of bleeding and thrombo-embolic events (2, 4, 5). For example, AF catheter ablation requires the introduction of catheters in the left atrium. This introduces the risk of air emboli or blood clots resulting in cerebral lesions. Furthermore, vascular access complications and cardiac perforation can occur in patients who are fully anticoagulated.

In addition, AF in itself is associated with an elevated risk of ischemic stroke. Preventing the risk of an ischemic stroke usually implies the use of oral anticoagulation, which in turn induces a higher risk of bleeding. In recent years, the use of anticoagulation has shifted from the use of vitamin K anticoagulants (VKAs) to direct oral anticoagulants (DOACs). Several large randomized studies (RE-LY, ROCKET-AF, ARISTOTLE and ENGAGE AF-TIMI) have demonstrated that DOACs have a more favourable risk-benefit profile regarding stroke, intracranial haemorrhage, and mortality (6). Consequently, the use of DOACs has increased considerably over recent years. In the Netherlands there was a slow uptake of its use before 2016, due to limited clinical experience and data on peri-procedural efficacy and safety, lack of an antidote, combined with a lack of reimbursement for patients with AF (7, 8). Since 2016 there was a clear shift from the use of VKA to DOAC in AF patients. This was also observed in the patients who presented for an ECV or AF ablation. In this thesis we evaluated the impact of the increased use of DOACs in our AF population.

To improve the outcome of AF ablation, there should not only be a focus on improved technologies. Addressing modifiable risk factors is equally important. A potentially modifiable risk factor for AF is sleep apnoea, and shares the same risk factors, such as overweight and hypertension (1, 9, 10). This may be mitigated by lifestyle management such as losing weight and exercise. Preferably lifestyle management and treatment of sleep apnoea should be initiated before catheter ablation, as it can improve outcome (2). Importantly, sleep apnoea is not easily recognized and may thus be undertreated. In this thesis we evaluated the effect of undiagnosed sleep apnoea on the outcome of AF ablation.

1.2 Evaluation of complication rates in device therapy

Cardiac implantable electronic devices (CIED) are used to treat impulse and conduction abnormalities, ventricular arrhythmias and heart failure. CIEDs include pacemakers, ICDs, cardiac resynchronization therapy (CRT). Furthermore, diagnostic CIEDs like implantable loop recorders are used to detect the cause of unexplained syncope. Many new innovations have been introduced in the past decade and include subcutaneous ICDs, leadless pacemakers, and conduction system pacing to achieve CRT (11, 12).

Growing numbers of pacemaker and ICD implantations can be observed due to increasing life expectancy and growing age of the population (11, 12). This can also be observed in the Netherlands, with 14,570 pacemaker interventions in 2022. However, the number of ICD interventions has remained stable with 5,664 ICD interventions in 2022, with up to 40% for secondary prevention (13). The indications for a pacemaker most commonly are sinus node dysfunction and high-degree atrioventricular block. Over 80% of implanted pacemakers are in patients >65 years of age. An ICD is usually indicated in patients for secondary prevention of sudden cardiac death, or for primary prevention in heart failure patients with a left ventricular ejection fraction of ≤35% (12). Finally, CRT therapy is indicated in patients with chronic heart failure with severe LV dysfunction and left bundle branch block (LBBB). By correcting the electromechanical desynchrony caused by LBBB, positive LV remodelling is possible. This has resulted in significant improvement in morbidity and mortality in patients with heart failure and LBBB (11).

Both pacemakers and ICDs are considered low-risk procedures, but unfortunately are still associated with complications such as bleeding, infection and lead dislocation (11, 12). To minimize risks, preventive measures such as antibiotics prophylaxis, experienced and certified staff, sterile environment, periprocedural haemostatic agents, antibacterial envelopes and post-procedural pressure bandages are essential (14). Prevention of pocket hematoma is important and this also requires meticulous attention to modifiable risk factors, including older age, renal failure, congestive heart failure, low operator experience, concomitant antiplatelet therapy, device replacement, lead revision, and heparin bridging (15, 16). Periprocedural oral anticoagulation is associated with a higher likelihood for pocket hematoma (17).

Discontinuing DOACs 24–48 h before surgery depending on their renal function, or targeting an international normalized ratio of 2.0 to 2.5, and avoiding heparin bridging were important changes in anticoagulation regimen over the last decade (2013-2023) (18). The increased use of DOACs may have further influenced the risk profile in CIED procedures in our center. In this thesis we evaluated this change in anticoagulation regimen for CIED related surgery in our patient population.

Another key complication is the risk of a pocket infection. It is associated with increased mortality risk and substantial morbidity (19, 20). A pocket infection may necessitate device and lead extraction to prevent endocarditis, which leads to higher costs, a higher risk profile and a significant burden to the patient. In reducing the risk of infections the use of antibiotic prophylaxis, chlorhexidine skin preparation, delaying the procedure in case of fever, avoidance of heparin bridging, avoidance of pocket hematoma, the use of strict sterile techniques, and having experienced operators are important preventive measures (21). Antibacterial envelopes may be used in high-risk patients. However, they are associated with high costs (22). Currently, there is no reimbursement for the antibacterial envelope in the Netherlands. Risk stratification with risk score calculators can be useful in identifying these high-risk patients (23-25). The identification of patients may be aided using risk calculators such as the PADIT (*Prevention of Arrhythmia Device Infection Trial*)-score (26, 27). In this thesis we evaluated the usefulness of the PADIT score in clinical practice.

1.3 Patient empowerment: Use of eHealth as discharge aid

Finally, in this thesis we would like to address the importance of involving the patient in his or her treatment strategy. Patient centred care models encourage shared decision-making between patients and healthcare providers (1, 28). Patient empowerment may be impacted by knowledge about early recognition of possible complications. Patients who are engaged in their care are more likely to adhere therapy, helping identification of irregularities or complications promptly (28). Health literacy and disease self-management can benefit from eHealth applications (29, 30). In this thesis we evaluated a computer generated personalized discharge letter as a discharge aid in comparison to the standard discharge information.

As a result of advances in therapy and changes in care pathways a reduction in (re)hospitalizations was observed in the Erasmus MC. The Erasmus MC, being a

tertiary referral hospital, has a wider adherence area than other hospitals and referred patients are at risk for a gap in their follow-up. Use of eHealth may facilitate a reduction of patient time spent in clinical assessments, and reduced travel times (31). Early recognition of complications may also be possible using telemedicine. In our clinical practice we offer teleconsultation for our patients until their first outpatient clinic visit. In this thesis we evaluated the feasibility of patient initiated mobile phone photography in assessing a possible complication.

1.4 Aims and outline of this thesis

This thesis has two aims: First, to focus on various strategies on reducing complication rates in electrophysiology procedures (part I and II). Secondly, to improve patient empowerment via the use of eHealth innovations with a focus on prevention, identifying and early reduction of complications (part III).

In the first part of this thesis (**chapters 2 - 4**) the focus will be on evaluating the complication rates in ECV and catheter ablation of AF in the Erasmus MC after changes in anticoagulant regimen, but also identifying the proportion of patients with sleep apnoea after catheter ablation of AF.

The second part of this thesis (**chapters 5 - 7**) focuses on evaluating the complication rates in device therapy. We focused on identifying complication rates in CIED therapy. We explored thromboembolic and bleeding complications in CIED related surgery procedures, being implantation, device change or upgrade, but also in a novel lead extraction technique. Furthermore, we evaluated the use of the PADIT score in identifying patients at risk for infection.

In the third part of this thesis **(chapters 8 and 9)**, the development of an eHealth and mHealth intervention by the nurse practitioner as a discharge aid in our center is being explored. Both interventions may have furthered patient participation and empowerment.

Finally, in **chapter 10**, the main results of the previous chapters are integrated and interpreted in the summary and final discussion focusing on the clinical implications of the presented studies and directions for future research.

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Part I

Evaluation of complications in atrial fibrillation management

Part I **Evaluation of complications in atrial fibrillation**

Efficacy and safety of direct oral anticoagulants in patients undergoing elective electrical cardioversion: A real-world patient population

Anticoagulant	DOAC		VKA
Use in AF patients	↑		↓
Major bleeding event	0.41%	n.s.	0.11%
Trombo-embolism	0.41%	n.s.	0.64%

Figure 2. Type of periprocedural oral anticoagulant during the study period

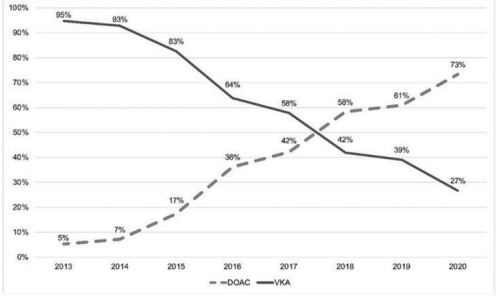

Table 2. Study outcomes <60 days after ECV

	Total n=1,431	VKA group n=943	DOAC group n=488	p-value
Primary efficacy endpoint				
Stroke, TIA and SEE	8 (0.56)	6 (0.64)	2 (0.41)	0.72
Primary safety endpoint				
Major bleeding	3 (0.21)	1 (0.11)	2 (0.41)	0.27
Secondary endpoints				
All-cause death	8 (0.56)	5 (0.53)	3 (0.61)	1.00
Stroke	3 (0.21)	2 (0.21)	1 (0.20)	1.00
TIA	5 (0.35)	4 (0.42)	1 (0.20)	0.67
SEE	-	-	-	-
Stroke and SEE	3 (0.21)	2 (0.21)	1 (0.20)	1.00

AF=atrial fibrillation; DOAC=direct oral anticoagulant; ECV=electrocardioversion; n.s.=non significant; SEE= systemic embolic event; TEE=trans oesophageal echogram; TIA=transient ischemic attack; VKA=vitamin K antagonist

CHAPTER 2

Efficacy and safety of direct oral anticoagulants in patients undergoing elective electrical cardioversion: A real-world patient population

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International Journal of Cardiology, March 2021, Volume 326, p. 98–102, https://doi.org/10.1016/j.ijcard.2020.10.070

Abstract

Background: Direct oral anticoagulants (DOACs) have emerged as the preferred choice of oral anticoagulation in patients with atrial fibrillation. Randomized trials have demonstrated the efficacy and safety of DOAC in patients undergoing electrical cardioversion (ECV); however, there is limited real-world data.

Objective: To evaluate the outcome of patients undergoing an elective ECV for atrial tachyarrhythmia in a tertiary referral center who were treated with DOAC or vitamin K antagonist (VKA) without routine trans oesophageal echocardiography (TEE).

Methods: This was a retrospective single-center cohort study of consecutive patients undergoing an elective ECV for atrial tachyarrhythmia from January 2013 to February 2020. The primary endpoints were thromboembolism (composite of stroke, transient ischemic attack or systemic embolism) and major bleeding events within 60 days.

Results: A total of 1431 ECV procedures were performed in 920 patients. One-third of the procedures were performed under DOAC (N=488, 34%) and the remainder of the procedures was performed under VKA (N=943, 66%). There were no differences between groups with regard to demographic variables (mean age 62.4±11.7, 72% men) and mean CHA_2DS_2-VASc score (2.3±1.6); however, the VKA group had a higher proportion of patients with co-morbidity. Thromboembolism occurred in 0.41% in the DOAC group versus 0.64% in the VKA group (P=0.72). Major bleeding events occurred in 0.41% in the DOAC group versus 0.11% in the VKA group (P=0.27).

Conclusion: In a real-world population, the rates of thromboembolism and major bleeding events were low after elective ECV in patients using DOAC or VKA, even without routine TEE.

1. Introduction

Direct oral anticoagulants (DOACs) are currently the preferred choice of oral anticoagulation in patients with atrial fibrillation (AF) for long-term stroke prevention (1). Electrical cardioversion (ECV) play an important role in a rhythm control strategy, therefore it is not surprising that many patients undergoing ECV are treated with a DOAC. For patients with AF of >48 hours duration, it is recommended to use therapeutic oral anticoagulation at least 3 weeks before and 4 weeks after ECV (2). An advantage of DOAC is that therapeutic oral anticoagulation can be achieved rapidly, which is especially relevant for anticoagulation naïve patients. However, it is important to ensure adherence to the DOAC intake, as there is no coagulation assay available providing information on effective anticoagulation over the past 3 weeks.

Post-hoc subgroup analysis from large phase 3 stroke prevention trials have shown a good safety profile of DOACs pericardioversion with a thromboembolic risk of <1% (3-6). Furthermore, prospective randomized controlled trials (RCTs) in patients requiring elective ECV demonstrated low and similar thromboembolic and bleeding rates when comparing factor Xa inhibitors to vitamin K antagonists (VKA) (7-9). It is important to note that all RCTs were not powered to demonstrate noninferiority. In addition, the majority (>50%) of patients in the RCTs underwent transoesophageal echocardiography (TEE) to guide cardioversion, which is not routine practice in many centers.

There is limited real-world data of DOACs in patients undergoing elective ECV outside the scope of highly controlled RCT (10-18). The availability of real-world data is important as it reflects actual clinical practice. For example, in many centers it is not common practice to have a preprocedural TEE before an elective ECV. We evaluated the efficacy and safety of DOACs versus VKA in patients undergoing elective ECV for atrial tachyarrhythmia in a large tertiary referral center without routine preprocedural TEE.

2. Methods

2.1 Study cohort

We retrospectively evaluated all consecutive adult patients who underwent an elective ECV for sustained atrial tachyarrhythmia (>48 hours) from January 2013 to February 2020 at the department of Cardiology of the Erasmus MC, University Medical Center Rotterdam, the Netherlands. Atrial tachyarrhythmias comprised atrial fibrillation, atrial flutter and atrial tachycardia. Patients who had an emergency ECV or received an ECV for an atrial tachyarrhythmia with a duration <48 hours were not included in the study. Patients were identified by screening all scheduled ECV procedures in the study period. If the patient did not undergo an ECV for any reason, then this patient was excluded from the final analysis. Furthermore, patients who had <60 days of follow-up after the procedure, except when death occurred, were excluded. Data were collected from the electronic medical records.

2.2 Anticoagulation regimen

All patients required therapeutic oral anticoagulation for at least 3 weeks prior to ECV. In patients using VKA, the International Normalized Ratio (INR) level had to be in the therapeutic range (≥2.0) in the 3 weeks prior to the procedure. The INR was rechecked on the day of the procedure. Patients using DOAC had to use them continuously for at least 3 weeks. Compliance was evaluated by asking the patient whether they did not miss a dose in the previous 3 weeks. If abovementioned conditions were not met, we usually postponed the procedure. If required (e.g., inadequate INR, doubt about DOAC adherence, symptom-driven), a TEE-guided ECV was performed. Thus, not all patients with an inadequate oral anticoagulation received a TEE. Patients continued their oral anticoagulation for a minimum of 4 weeks after the ECV procedure. Continuation of oral anticoagulation after this 4-week period was based on the CHADS-VASc score or other indication for oral anticoagulation (e.g., mechanical heart valves).

2.3 Electrical cardioversion

Electrical cardioversion was performed in the holding area or on the ward under the supervision of a nurse practitioner or cardiologist. The procedures were performed under monitored anaesthesia care. The placement of the external patches was usually posterior-anterior. For patients in atrial fibrillation a synchronized ECV was

performed with a biphasic shock of 200 Joules. For patients in atrial flutter a lower dose was used (usually 100 Joules). A cardioversion was repeated when necessary.

2.4 Study endpoints

The primary efficacy endpoint was a composite of stroke, transient ischemic attack (TIA), and systemic embolic event (SEE) within 60 days. The primary safety endpoint was major bleeding within 60 days. Major bleeding was defined according to the International Society of Thrombosis and Haemostasis (ISTH) criteria and included clinically overt bleeding accompanied by a decrease in the haemoglobin level of at least 20 g/L (1.24 mmol/L) or transfusion of at least 2 units of packed red cells, occurring at a critical site, or resulting in death (19). TIA and stroke were diagnosed by a neurologist. The secondary efficacy endpoints were death from any cause, stroke, TIA, SEE, and a composite of stroke and SEE (excluding TIA).

2.5 Statistical analysis

Continuous parameters were tested for normality before analysis and are expressed as mean ± standard deviation (SD) or median [interquartile range], as appropriate. Categorical data are presented as frequencies and percentages. Comparisons between groups were performed with an independent Student t test, chi-square tests, Fisher exact test, or a Mann-Whitney U test, as appropriate. All analyses were two-tailed; a p-value<0.05 was considered statistically significant. Statistical analyses were performed using SPSS software (SPSS, version 25; IBM, Chicago, Illinois).

2.6 Ethics

The Medical Ethics Committee reviewed the study (MEC-2019-0405), and this retrospective single-center study was not subjected to the Dutch Medical Research Involving Human Subjects Act. The study was carried out according to the ethical principles for medical research involving human subjects established by Declaration of Helsinki, protecting the privacy of all the participants and the confidentiality of their personal information.

3. Results

3.1 Patient population and cardioversion

A total 1570 elective ECV procedures were scheduled in the study period. In 94 cases (6.0%) no ECV was performed and 45 cases (2.9%) had insufficient follow-up after an ECV (Fig. 1). Preprocedural TEE was performed in 23 patients (1.5%) and a left atrial thrombus was suspected in 5 cases resulting in postponement of the procedure (Appendix A). Final analysis was performed in the remaining 1431 ECV procedures among 920 patients. Almost two-third of the patients received one ECV procedure during the study period (n=610), while the remaining one-third received ≥2 ECV procedures (n=310). These 310 patients with multiple ECV procedures had a total of 511 repeat ECV procedures. Repeat ECV procedures were performed more often in the VKA group in comparison to the DOAC group (39% versus 28%, P<0.001). The reason for a repeat ECV was recurrence of atrial tachyarrhythmia (n=450, 88%) or a prior not successful ECV (n=61, 12%), this was similar for both groups.

Periprocedural DOAC was used in 488 (34%) procedures, while in the remainder of the procedures (n=943, 66%) periprocedural VKA was used. Of the 488 cardioversions performed on DOAC, dabigatran was used in 225 of 488 procedures (46%); apixaban in 114 procedures (23%); rivaroxaban in 81 procedures (17%); and edoxaban in 68 procedures (14%). Periprocedural VKAs used were acenocoumarol (n=846) or phenprocoumon (n=97). The use of DOAC increased steadily over the years during the study period, increasing from 5% in 2013 to 73% in 2020 (Fig. 2). Since 2018, DOAC was used in more than half of the procedures.

There were differences in baseline characteristics between the VKA and DOAC group (Table 1). The VKA group comprised a more complex patient population with a higher proportion of patients with congenital heart disease, congestive heart failure, coronary heart disease, diabetes mellitus, LV dysfunction and renal insufficiency. This is also reflected by a higher proportion of patients with a HAS-BLED bleeding score ≥3 and American Society of Anaesthesiologists (ASA) physical status classification system score ≥3. However, the thromboembolic risk as reflected by the mean CHA_2DS_2-VASc score was similar between groups. The acute cardioversion success was similar between groups (92% for both groups, P=0.70).

3.2 Primary endpoints

In total, 8 patients (0.56%) had a thromboembolic event and 3 patients (0.21%) had an ISTH major bleeding event during the 60-day follow-up period. There were no differences in the primary efficacy and safety endpoints between both groups (Table 2). A detailed overview of endpoints is presented in Appendix B. A thromboembolic event occurred in 6 (0.64%) and 2 (0.41%) patients in the VKA and DOAC group, respectively (P=0.72). The timing of thromboembolic events was similar between groups (VKA: median 19 [10, 25] days; DOAC: 13 [4, 22] days, P=0.64). In the 8 patients with a thromboembolic event, 5 patients (63%) had a medical history of prior stroke or TIA (Appendix B). All patients with a TIA after ECV had an uneventful recovery. The patients who had experienced a stroke had a modified Rankin scale (20) ranging from 0 to 2. No SEE occurred in the study population.

Major bleeding occurred in 1 (0.11%) and 2 (0.41%) patients in the VKA and DOAC group, respectively (P=0.27) (Table 2, Appendix B). One patient had a trauma-related subdural hematoma and had a modified Rankin scale of 4. The two other patients experienced a gastro-intestinal bleeding requiring blood transfusion and had an uneventful recovery.

3.3 Secondary endpoints

In total, 8 patients (0.56%) died within 60 days after the ECV procedure. There were no differences in the all-cause mortality rate between both groups (Table 2, Appendix B). Also, when looking at the individual endpoints there was no difference between groups with regard to stroke, TIA or SEE. For comparison with RCTs, the composite endpoint of stroke and SEE was also presented. The 30-day rate of the composite endpoint of stroke and SEE and major bleeding after ECV was comparable to the results of the 3 RCTs focusing on the efficacy and safety of pericardioversion DOAC (Appendix C).

4. Discussion

The present study demonstrates that DOACs are associated with low thromboembolic and bleeding rates (both <0.5%) in patients undergoing elective ECV for atrial tachyarrhythmia in the setting of a tertiary referral center. Furthermore, the study period was a transition time in our center where DOAC use pericardioversion increased from 5% in 2013 to 73% in 2020.

In non-anticoagulated patients, ECV is associated with an increased risk of stroke (5-7%) (21). This risk is mitigated (<1%) if patients use oral anticoagulation. The 2016 ESC AF guidelines recommends the use of therapeutic oral anticoagulation at least 3 weeks before and 4 weeks after ECV (2). The use of VKA has its limitations, the most important being its narrow therapeutic window requiring regular INR assessments, delayed onset of action and certain drug-drug interactions (11, 22). Considering these limitations, DOACs has become an attractive alternative for VKA (1). In the Netherlands, there was initially a conservative policy with regard to DOAC mainly due to concerns about the lack of an antidote, patient adherence, lack of monitoring and increased health care costs (23). In the Netherlands there was a slower uptake of DOAC use in comparison to other Western European countries (24). Since 2016 there is a steady increase in the use of DOAC in the Netherlands and this is reflected in a higher proportion of patients with DOAC undergoing an elective ECV in our center in the second half of the study period. Nowadays, DOAC is the most commonly used oral anticoagulant pericardioversion. An advantage of the use of DOAC in the setting of ECV is that it can avoid delays or postponement of ECV due to inadequate INR levels with VKA (9, 11). Avoiding postponement and rescheduling of ECV procedures by using DOAC has been shown to be cost-effective in comparison to VKA (25).

RCTs and meta-analysis have demonstrated the safety and efficacy of DOAC in patients undergoing ECV (7-9, 26-28). Our results are in line with the outcome of the 3 RCTs focusing on pericardioversion DOAC (Appendix C). The mean CHA_2DS_2-VASc score and the proportion of patients with moderate to high thromboembolic risk (CHA_2DS_2-VASc score ≥2) in our study population was comparable to the RCTs (Appendix C). These randomized trials are important, but the study populations and pre-procedural work-up do not always reflect clinical practice. For example, the EMANATE trial only included anticoagulation naïve patients (<48 hours of anticoagulation before randomization) (8). Furthermore, >50% of patients in the RCTs underwent cardiac imaging to rule out thrombus in the left atrial appendage before ECV. Previous observational studies have shown that in 1.4-3.6% of therapeutically anticoagulated patients a TEE prior to ECV or AF ablation revealed a LAA thrombus (29, 30). The incidence of LAA thrombus seems to correlate with the CHADS-VASc score (29). In many centers, however, preprocedural imaging is not standard practice. Therefore, availability of real-world studies of pericardioversion

DOAC is important (10-18). Of these real-world studies, 2 single-center studies had a larger sample size than our study, however, in both studies approximately one-fifth of procedures were guided by TEE (11, 17). Coleman et al. retrospectively evaluated 4,647 cardioversions in the Cleveland Clinic (USA) in the period 2009 to 2013, of which only 20% were performed under DOAC (17). The thromboembolic event rate under DOAC was relatively high, 1.62% within 8 weeks of follow-up, but this was similar to the VKA group (0.97%, P=0.16). Frederiksen et al. retrospectively evaluated 2,150 cardioversions from the Regional Hospital Central Jutland (Denmark) in the period 2011 to 2016 (11). This study showed a low thromboembolic event rate within 60 days with either DOAC or VKA (0.15% versus 0.14%). Our study also demonstrates a low thromboembolic event rate in procedures performed under DOAC and VKA in a routinely non-TEE-guided strategy.

5. Study limitations

The present study has the known limitations inherent to an observational study. Selection bias may play a role, as DOAC are not used in patients with severe renal dysfunction or mechanical valves. This is partly reflected by a higher proportion of patients with comorbidity in the VKA group. Furthermore, the low event rates precluded a thorough statistical analysis between groups.

6. Conclusions

During the past years, DOAC has replaced VKA as the most commonly used oral anticoagulant in patients undergoing elective ECV for atrial tachyarrhythmias. The use of pericardioversion DOAC was associated with low rates of thromboembolic and bleeding complications (both <0.5%) and was comparable to the use of VKA in a real-world population without routine TEE.

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Tables

Table 1. Baseline characteristics

Characteristic	Total n=1,431	VKA group n=943	DOAC group n=488	p-value
Age (years), mean ± SD	62.4 ± 11.7	62.1 ± 11.6	62.8 ± 12.0	0.32
Male gender	1032 (72.1)	669 (70.9)	363 (74.4)	0.17
BMI, mean ± SD	28.3 ± 5.4	28.3 ± 5.5	28.3 ± 5.1	0.98
TEE	18 (1.3)	13 (1.4)	5 (1.0)	0.80
Medical history				
Prior TIA	111 (7.8)	71 (7.5)	40 (8.2)	0.65
Prior stroke	106 (7.4)	72 (7.6)	34 (7.0)	0.65
Prior intracranial bleeding	17 (1.2)	15 (1.6)	2 (0.4)	0.069
Prior extracranial bleeding	64 (4.5)	48 (5.1)	16 (3.3)	0.14
Arterial hypertension	612 (42.8)	402 (42.6)	210 (43.0)	0.88
Renal insufficiency*	342 (23.9)	266 (28.2)	76 (15.6)	<0.001
Congestive heart failure	333 (23.3)	250 (26.5)	83 (17.0)	<0.001
Coronary artery disease	323 (22.6)	239 (25.3)	84 (17.2)	<0.001
LVEF ≤40%	304 (21.3)	227 (24.1)	77 (15.8)	<0.001
Diabetes mellitus	209 (14.6)	151 (16.0)	58 (11.9)	0.036
Vascular disease	175 (12.2)	119 (12.6)	56 (11.5)	0.53
Congenital heart disease	114 (8.0)	90 (9.5)	24 (4.9)	0.002
Type of atrial tachyarrhythmia				
Atrial fibrillation	1094 (77.2)	724 (77.7)	370 (76.3)	0.55
Atrial flutter	262 (18.5)	163 (17.5)	99 (20.4)	0.18
Atrial tachycardia	61 (4.3)	45 (4.8)	16 (3.3)	0.22
Scores				
ASA ≥3	774 (56.3)	543 (59.2)	231 (50.4)	0.002
CHA_2DS_2-VASc, mean ± SD	2.3 ± 1.6	2.4 ± 1.7	2.2 ± 1.6	<0.001
CHA_2DS_2-VASc ≥2	935 (65.3)	625 (66.3)	310 (63.5)	0.30
HAS-BLED, mean ± SD	1.3 ± 1.1	1.4 ± 1.1	1.1 ± 1.0	<0.001
HAS-BLED ≥3	176 (12.3)	132 (14.0)	44 (9.0)	0.007
Antiplatelet therapy				
Acetylsalicylic acid	105 (7.3)	81 (8.6)	24 (4.9)	0.12
Clopidogrel	53 (3.7)	35 (3.7)	18 (3.7)	0.98
Persantin	2 (0.1)	2 (0.2)	-	0.55
Ticagrelor	1 (0.1)	1 (0.1)	-	1.00
Triple therapy	14 (1.0)	10 (1.1)	4 (0.8)	0.78
Antiarrhythmic therapy				
Amiodaron	356 (24.9)	271 (28.7)	85 (17.4)	<0.001
Sotalol	335 (23.4)	208 (22.1)	127 (26.0)	0.093
Digoxin	286 (20.0)	210 (22.3)	76 (15.6)	0.003
Flecainide	95 (6.6)	53 (5.6)	42 (8.6)	0.031
Verapamil	30 (2.1)	24 (2.5)	6 (1.2)	0.10
Diltiazem	15 (1.0)	9 (1.0)	6 (1.2)	0.63
Propafenone	3 (0.2)	3 (0.3)	-	0.56

All data depicted as n (%) unless stated otherwise. * eGFR <60 ml/min/m^2. Abbreviations: ASA= American Society of Anaesthesiologists physical status classification system, DOAC = direct-acting oral anticoagulation; LVEF= left ventricular ejection fraction, TEE = transesophageal echocardiogram; VKA= vitamin K antagonist

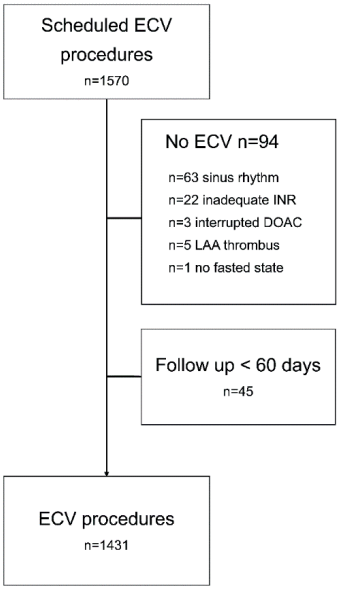
Table 2. Study outcomes <60 days after ECV

	Total n=1,431	VKA group n=943	DOAC group n=488	p-value
Primary efficacy endpoint				
Stroke, TIA and SEE	8 (0.56)	6 (0.64)	2 (0.41)	0.72
Primary safety endpoint				
Major bleeding	3 (0.21)	1 (0.11)	2 (0.41)	0.27
Secondary endpoints				
All-cause death	8 (0.56)	5 (0.53)	3 (0.61)	1.00
Stroke	3 (0.21)	2 (0.21)	1 (0.20)	1.00
TIA	5 (0.35)	4 (0.42)	1 (0.20)	0.67
SEE	-	-	-	-
Stroke and SEE	3 (0.21)	2 (0.21)	1 (0.20)	1.00

All data depicted as n (%) unless stated otherwise. DOAC = direct-acting oral anticoagulant; ECV = electrical cardioversion; SEE = systemic embolic event; TIA = transient ischemic attack; VKA = vitamin K antagonist.

Figure legends

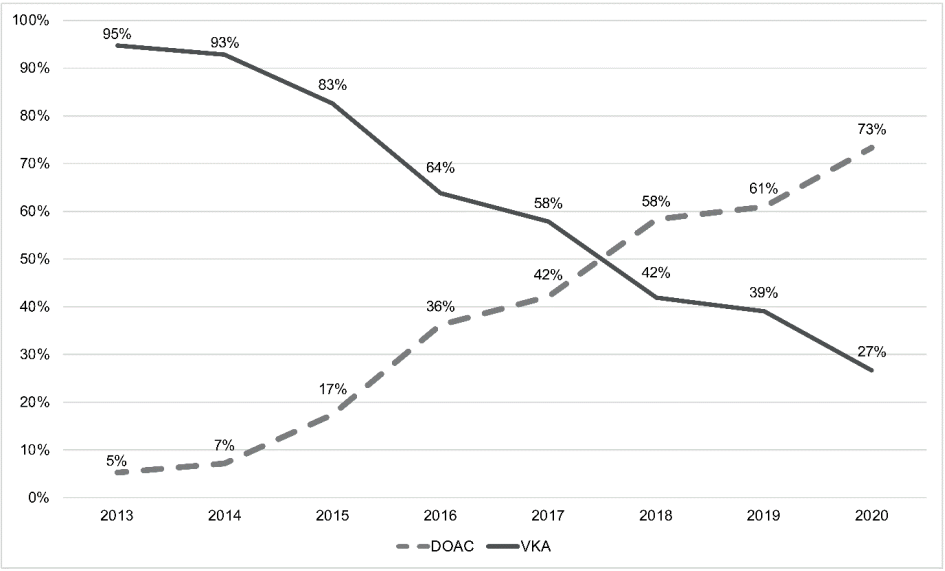
Figure 1. Flowchart study population



Abbreviations: DOAC = direct oral anticoagulant, ECV= electrical cardioversion, INR= International Normalized Ratio, LAA= left atrial appendage.

Figure 2. Type of periprocedural oral anticoagulation during the study period.

Figure 2. Type of periprocedural oral anticoagulation during the study period.



Abbreviations: DOAC=direct oral anticoagulant, VKA=vitamin K antagonist

Appendix A. Detailed overview of patients with left atrial appendage thrombus

Patient	Indication TEE	Findings TEE	Type of oral anticoagulation	Age (years)/ sex	CHA_2DS_2-VASc score	Management
1	INR 1.7 at day of admission	Thrombus	Acenocoumarol	70/M	4	Increase lower rate biventricular ICD to improve biventricular pacing, AF accepted.
2	INR 1.3 at day of admission	Possible thrombus	Acenocoumarol	62/M	3	Postponement ECV, 1 month later successful ECV. No complications within 60 days after ECV.
3	Inadequate INR in past 3 weeks	Thrombus	Acenocoumarol	65/M	3	Postponement ECV, increase target INR to 2.5-3.5. 2 months later successful TEE-guided ECV. No complications within 60 days after ECV.
4	Inadequate INR in past 3 weeks	Possible thrombus	Fenprocoumon	63/M	2	Postponement ECV, CT scan 1 month later demonstrated no LAA thrombus. Successful non-TEE-guided ECV. No complications within 60 days after ECV.
5	Interrupted DOAC in past 3 weeks	Thrombus	Apixaban	62/M	2	Postponement ECV, CT scan 1 month later demonstrated no LAA thrombus. Successful non-TEE-guided ECV. No complications within 60 days after ECV.

Abbreviations: CT= computerized tomography, DOAC = direct oral anticoagulant, ECV = electrical cardioversion, INR = International Normalized Ratio, TEE= transoesophageal echocardiogram.

Appendix B. Detailed overview of study endpoints

Patient	Event	Days after procedure	OAC	Age (years)/ sex	Prior stroke or TIA	CHA_2DS_2-VASc score	HAS-BLED score	Details event
1	TIA	2	Acenocoumarol	60/ F	Yes	4	1	-
2	TIA	10	Acenocoumarol	63/ M	No	3	2	-
3	TIA	22	Dabigatran	69/ F	No	2	3	-
4	TIA	25	Acenocoumarol	82/ F	Yes	7	4	-
5	TIA	39	Acenocoumarol	61/ M	Yes	4	2	-
6	Stroke	4	Rivaroxaban	55/ M	Yes	2	1	Thrombectomy, MRS 0
7	Stroke	16	Acenocoumarol	54/ M	Yes	3	2	Failed thrombectomy, MRS 2
8	Stroke	22	Acenocoumarol	84/ M	No	2	4	Switch to DOAC, MRS 1
9	Major bleed	2	Dabigatran	60/ M	No	1	0	GI bleeding, blood transfusion and idarucizumab
10	Major bleed	12	Acenocoumarol	77/ M	No	6	1	Subdural hematoma after fall, MRS 4
11	Major bleed	54	Edoxaban	75/ M	No	4	2	Stoma bleeding, blood transfusion, prothrombin complex
12	Death	2	Acenocoumarol	66/ M	Yes	5	4	SCD, ischemic cardiomyopathy
13	Death	3	Rivaroxaban	33/ M	No	1	0	SCD, complex congenital heart disease
14	Death	4	Acenocoumarol	70/ M	No	2	1	SCD
15	Death	8	Acenocoumarol	68/ M	No	5	3	Death due to MI
16	Death	18	Edoxaban	85/ M	No	5	2	Death due to heart failure
17	Death	24	Acenocoumarol	54/ F	Yes	5	2	SCD, dilated cardiomyopathy
18	Death	31	Rivaroxaban	75/ F	No	5	2	Death due to heart failure
19	Death	35	Acenocoumarol	68/ M	No	5	3	Death due to MI

Abbreviations: DOAC= direct oral anticoagulant, GI = gastro-intestinal; MI = myocardial infarction; MRS = modified Rankin scale, OAC= oral anticoagulant, SCD = sudden cardiac death, TIA=transient ischemic attack.

Appendix C. Comparison of outcomes <30 days post-cardioversion in present study to randomized controlled trials focusing on DOAC and elective cardioversion

Study	OAC group	Patients (n)	Mean CHA_2DS_2-VASc score	CHA_2DS_2-VASc score ≥2	Stroke/ SEE*	ISTH major bleeding*	Death*
Present study	DOAC	488	2.2 ± 1.6	64%	1 (0.20)	1 (0.20)	2 (0.41)
X-VeRT (7)	Rivaroxaban	978	NA	64%	2 (0.20)	6 (0.61)	5 (0.51)
ENSURE-AF (9)	Edoxaban	1095	2.6 ± 1.4	77%	3 (0.27)	3 (0.27)	1 (0.09)
EMANATE (8)	Apixaban	753	2.4 ± 1.7	NA	0 (0)	3 (0.41)	2 (0.27)
Present study	VKA	943	2.4 ± 1.7	66%	2 (0.21)	1 (0.11)	4 (0.42)
X-VeRT (7)	VKA	492	NA	63%	3 (0.61)	4 (0.80)	3 (0.61)
ENSURE-AF (9)	VKA	1104	2.6 ± 1.4	78%	4 (0.36)	5 (0.45)	6 (0.54)
EMANATE (8)	VKA	747	2.4 ± 1.7	NA	6 (0.80)	6 (0.83)	1 (0.13)

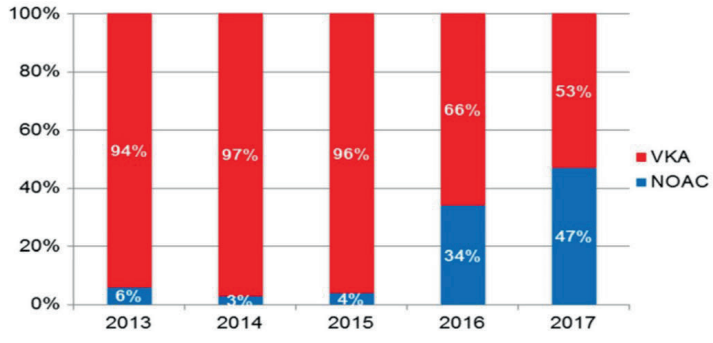
Data are presented as number (percentages), unless stated otherwise. *The endpoints given in this table are based on a follow-up of 30 days. Abbreviations: DOAC = direct acting oral anticoagulation; ISTH = International Society of Thrombosis and Haemostasis; NA = not available; OAC = oral anticoagulation; SEE = systemic embolic event; VKA = vitamin K antagonist.

Part I **Evaluation of complications in atrial fibrillation**

Minimally interrupted novel oral anticoagulant versus uninterrupted vitamin K antagonist during atrial fibrillation ablation

	DOAC interrupted		VKA continued
Anticoagulant			
Use in AF patients	↑		↓
Non major bleeding event (BARC/ISTH)	2.6% / 0%	p=0.03	8.3% / 3.8%
Major bleeding event (BARC/ISTH)	3.4% / 6.0%	n.s.	4.2% / 8.7%
Trombo-embolism	0%	n.s.	0.6%

Figure 1. Proportion of periprocedural NOAC and VKA use over the years in Erasmus MC



DOAC=direct oral anticoagulant; VKA=vitamin K antagonist

CHAPTER 3

Minimally interrupted novel oral anticoagulant versus uninterrupted vitamin K antagonist during atrial fibrillation ablation

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Journal of Interventional Cardiac Electrophysiology, Aug 2018, 53, p. 341–346, https://doi.org/10.1007/s10840-018-0417-0

Abstract

Purpose The safety and efficacy of a minimally interrupted novel oral anticoagulant (NOAC) strategy at the time of atrial fibrillation (AF) ablation is uncertain. The purpose of this study was to compare rates of bleeding and thromboembolic events between minimally interrupted NOAC and uninterrupted vitamin K antagonist (VKA) in patients undergoing AF ablation.

Methods This was a retrospective single-center cohort study of consecutive patients who underwent AF catheter ablation between January 2013 and April 2017. Endpoints included major bleeding, clinically relevant non-major bleeding and systemic thromboembolic event from the time of ablation through 30 days. Bleeding events were defined by the Bleeding Academic Research Consortium (BARC) and International Society on Thrombosis and Haemostasis (ISTH).

Results A total of 637 patients were included in the analysis, 520 patients used uninterrupted VKA and 117 patients minimally interrupted NOAC (dabigatran: n = 68; apixaban: n = 30; rivaroxaban, n = 14; edoxaban, n = 5). The rate of clinically relevant non-major bleeding was lower in the NOAC group in comparison to the VKA group (BARC type 2: 2.6% versus 8.3%, P = 0.03; ISTH: 0% versus 3.8%, P = 0.03). Rates of major bleeding were similar between groups (BARC type 3 to 5: 3.4% versus 4.2%, P = NS; ISTH: 6.0% versus 8.7%, P = NS; for NOAC and VKA groups, respectively). Rates of systemic embolism were 0% with minimally interrupted NOAC, and 0.6% with uninterrupted VKA (P=NS).

Conclusions In patients undergoing AF ablation, anticoagulation with minimally interrupted NOAC was associated with fewer clinically relevant non-major bleeding events in comparison with uninterrupted VKA without compromising thromboembolic safety.

1. Introduction

Catheter ablation is increasingly used for the treatment of symptomatic atrial fibrillation (AF). Although catheter ablation of AF is considered safe, it may be associated with a low risk of stroke. One of the strategies to reduce this risk is to perform AF ablation with continuous oral anticoagulation. This strategy has been shown to be safe and effective with vitamin K antagonists (VKAs) (1). However, there is an increased use of novel oral anticoagulants (NOACs) in the current AF population undergoing catheter ablation. NOACs have several advantages, including a rapid onset of therapeutic range of anticoagulation, predictability of the anticoagulant effect, and relatively short time to reversal of anticoagulation when the medication is withheld (2). Several observational and randomized controlled trials (RCTs) have demonstrated that uninterrupted NOAC is as safe and effective in comparison to uninterrupted VKA in patients undergoing AF ablation (3–13). A recent meta-analysis demonstrated that NOAC was even associated with less major bleeding compared with VKA in pooled RCTs (14). The 2016 ESC guidelines give a class IIa indication to perform AF ablation with continuous oral anticoagulation with either VKA or NOAC (15). However, the uninterrupted NOAC strategy does not reflect current clinical practice as most centers still use a minimally interrupted NOAC strategy (16). There is limited data demonstrating the safety and efficacy of a minimally interrupted NOAC strategy. The aim of the present study was to compare the incidence of bleeding and thromboembolic complications of minimally interrupted NOAC versus uninterrupted VKA in patients undergoing catheter ablation of AF.

2. Methods

2.1 Study population

We evaluated consecutive patients who underwent catheter ablation of AF from January 2013 to April 2017 in the Erasmus Medical Center, Rotterdam, the Netherlands. We included patients with 2 specific anticoagulation regimens. The first group included patients who used periprocedural uninterrupted VKA (either acenocoumarol or marcoumar). The strategy of uninterrupted VKA was introduced in our institution at the end of 2012. The second group included patients who used periprocedural minimally interrupted NOAC (1 or 2 doses withheld). In February 2013, our first patient underwent catheter ablation using a minimally interrupted

NOAC strategy. Patients who did not use oral anticoagulation and were accepted for catheter ablation of AF usually received a NOAC.

2.2 Pre- and periprocedural protocol

All patients received therapeutic oral anticoagulation for at least 3 weeks prior to ablation. In patients using VKA the target INR level at the day of the procedure was 2.0 to 2.5. In patients using NOACs, anticoagulation was withheld for 24 h before the procedure (1 or 2 doses withheld). A cardiac CT was routinely performed weeks to months prior to ablation. CT imaging was mainly used to assess PV anatomy. Rarely, a left atrial thrombus could be found as an incidental finding. A preprocedural transoesophageal echocardiogram was routinely performed on the same day or 1 day prior to ablation to exclude left atrial appendage (LAA) thrombus. In the case of LAA thrombus the procedure was cancelled or postponed. During the procedure, a bolus of heparin was administered after sheath placement. Furthermore, immediately after transseptal puncture another bolus of heparin was given and a continuous heparin pump was started and adjusted to maintain an ACT of at least 300 s. We did not administer protamine routinely at the end of the procedure.

2.3 Postprocedural protocol

VKA patients, who had an INR 2.0 or greater at the day of the procedure, continued their anticoagulation regimen with a target INR level of 2.0–3.0. VKA patients who had an INR below 2.0 at the day of the procedure were bridged with intravenous UFH for 24 h (starting 2 h after removal of sheaths). After these 24 h they received low molecular weight heparin until their INR level was equal or above 2.0. NOAC patients restarted NOAC in the evening of the procedure. Patients continued their oral anticoagulation for at least 3 months after the procedure.

2.4 Study endpoints

Primary bleeding endpoints were major bleeding (within 30 days) as defined by the Bleeding Academic Research Consortium (BARC) and International Society on Thrombosis and Haemostasis (ISTH) (17, 18). The reason to choose both classifications is that clinical trials reporting major bleeding either use ISTH and/or BARC classification. In our study, BARC types 3 to 5 were considered a major bleeding. Secondary bleeding endpoints were the individual BARC bleeding types

(types 2, 3a, 3b, 3c, 5), clinically relevant nonmajor bleeding (CRNMB) according to ISTH (19), and any clinically relevant bleeding (BARC types 2 to 5; ISTH major bleeding and CRNMB). BARC type 2 bleeding most closely aligns with the ISTH CRNMB (19). The primary thromboembolic endpoint was a composite of stroke, transient ischemic attack (TIA), or other systemic embolism within 30 days.

2.5 Statistical analysis

Continuous parameters are presented as the mean ± SD as they were normally distributed. Categorical data are presented as frequencies and percentages. Comparisons between groups were performed with an independent Student t test, chi-square tests, or Fisher exact test. A P-value < 0.05 was considered statistically significant. Statistical analyses were performed using SPSS software (SPSS, version 21; IBM, Chicago, Illinois).

3. Results

A total of 637 patients (mean age 60 ± 9 years, 69% male) were included in the analysis, 520 patients (82%) used uninterrupted VKAs and 117 patients (18%) had a minimally interrupted NOAC strategy. In the NOAC group, the following NOACs were used: dabigatran (n = 68), apixaban (n = 30), rivaroxaban (n = 14), and edoxaban (n = 5). The NOAC group comprised more patients with long-standing persistent AF and a lower proportion of patients with a CHA_2DS_2-VASc ≥ 2 (Table 1). All other baseline variables were similar between groups. Figure 1 demonstrates the increased use of NOAC over the years in our AF ablation population.

3.1 Bleeding complications

The rates of major bleeding, either by BARC or ISTH criteria, were similar between groups (Table 2). The rate of any clinically relevant bleeding (BARC types 2–5; composite of ISTH major bleeding and CRNMB) was lower with NOACs compared with VKAs. This difference was mainly due to a difference in clinically relevant non-major bleeding (CRNMB or BARC type 2) (Table 2). No patient in either group had a BARC type 3c (i.e., intracranial bleeding) or type 5 bleeding (i.e., fatal bleeding). Cardiac tamponade occurred in 4 patients (0.8%) of the VKA group and in 1 patient (0.9%) of the NOAC group (P = 1.00).

3.2 Thromboembolic complications

There were no differences in the systemic thromboembolic event rates between both groups (0.6% versus 0%, P = 1.00) (Table 2). In the VKA group, 1 patient (0.2%) experienced a vertebrobasilar stroke 3 days after the procedure. Three months after the procedure, this patient had a modified Rankin score of 1. Furthermore, 2 patients (0.4%) in the VKA group experienced a TIA 1 day after the procedure. They had an uneventful recovery. No patient in the NOAC group experienced a systemic thromboembolic event. No deaths occurred.

4. Discussion

The main findings of our study are that (1) the rate of clinically relevant non-major bleeding was lower in patients with a minimally interrupted NOAC strategy compared with those with an uninterrupted VKA strategy, and (2) the rates of major bleeding and thromboembolic events were similar between groups.

Uninterrupted use of vitamin K antagonists (VKA) as periprocedural anticoagulant is currently widely accepted for patients undergoing catheter ablation of AF who are using VKA. However, there is an increased use of NOACs in the current AF ablation population. Despite initial concerns on the safety of using periprocedural NOAC (20), nowadays, several large RCTs have demonstrated the safety and efficacy of uninterrupted use of NOACs (i.e., dabigatran, rivaroxaban, apixaban) during AF ablation (5, 6, 12) (Table 3).

In clinical practice, however, most centers still use a minimally interrupted NOAC strategy (16). The European Snapshot Survey on Procedural Routines in Atrial Fibrillation Ablation (ESS-PRAFA) in 2015 demonstrated that AF ablations were performed with a minimally interrupted NOAC strategy (1–2 doses withheld) in 53% of procedures, interrupted NOAC ≥2 days in 34%, and an uninterrupted NOAC strategy in 14% (16). The Ablation peRIoperative DabiGatran in use Envisioning in Japan (ABRIDGE-J) randomized trial demonstrated that anticoagulation with minimally interrupted dabigatran (1 or 2 doses withheld) was associated with fewer ISTH major bleeding complications than uninterrupted VKA with no increase in thromboembolic events (Table 3) (13). In addition, the Apixaban Evaluation of Interrupted Or Uninterrupted anticoagulation for ablation of atrial fibrillation (AEIOU)

randomized trial showed no difference between continuous apixaban compared with minimally interrupted apixaban (1 dose withheld) with regard to major bleeding (BARC 3–5) or thromboembolic events (Table 3) (21). Finally, a recent meta-analysis of 4 randomized and 9 prospective observational studies (N = 5463) found that minimally interrupted and continuous NOAC strategy were both safe and non-inferior strategies compared with uninterrupted VKA (14). Our study extends on these results demonstrating less clinically relevant non-major bleeding events with minimally interrupted NOAC in comparison with uninterrupted VKA without compromising thromboembolic safety.

One of the reasons to choose an uninterrupted NOAC strategy instead of a minimally interrupted NOAC strategy is to maximally reduce the incidence of thromboembolic events. However, the risk of a systemic thromboembolic event using a minimally interrupted NOAC strategy is already low (<0.7%) (13, 14, 21). Furthermore, continuous anticoagulation does not prevent all acute brain lesions, which can be caused by debris from ablation lesions, air emboli, or small thrombi (22). This was demonstrated by the MRI substudy of the AXAFA trial in which acute brain lesions occurred in 27% of patients despite uninterrupted apixaban (12). Further research is required to establish the optimal NOAC dosing strategy (minimally interrupted or uninterrupted) with regard to both bleeding and thromboembolic risk. Another question is whether every NOAC is effective in preventing periprocedural thromboembolic complications. RCTs with dabigatran (RE-CIRCUIT) and rivaroxaban (VENTUREAF) did not show any thromboembolic events (5, 6), while RCTs with apixaban (AXAFA, AEIOU) showed a low thromboembolic event rate (12, 21).

5. Study limitations

There were differences in baseline characteristics between the study groups. The VKA group had a higher proportion of patients with a CHA_2DS_2-VASc ≥2 in comparison to the NOAC group (47% versus 34%). This difference can be explained by the fact that in patients who did not use an oral anticoagulant (low CHA_2DS_2-VASc score) and were accepted for catheter ablation, a NOAC was preferentially started as periprocedural anticoagulation regime. This difference in CHA_2DS_2-VASc score could potentially lower the risk of thromboembolic and bleeding events in the NOAC group.

Furthermore, patients used different NOACs in the present study. The limited number of NOAC patients precluded further subanalysis for the different NOACs.

6. Conclusions

In patients undergoing catheter ablation of AF, a minimally interrupted NOAC strategy was associated with fewer clinically relevant non-major bleeding compared with uninterrupted VKA. The risk of major bleeding and thromboembolic events was similar between both strategies. Our study reinforces the safety and efficacy of a minimally interrupted NOAC strategy as periprocedural anticoagulant in patients undergoing catheter ablation of AF.

7. Compliance with ethical standards

The Medical Ethics Committee of the Erasmus Medical Center reviewed the study (MEC-2015-073), and this retrospective study was not subjected to the Dutch Medical Research Involving Human Subjects Act. The study was carried out according to the ethical principles for medical research involving human subjects established by Declaration of Helsinki, protecting the privacy of all the participants and the confidentiality of their personal information.

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Tables

Table 1. Baseline characteristics

Characteristic	Uninterrupted VKA N=520	Interrupted NOAC N=117	P-value
Age (years), mean ± SD	60 ± 10	60 ± 9	0.55
Male sex, n (%)	354 (68)	84 (72)	0.43
Atrial fibrillation, n (%):			0.048
Paroxysmal	392 (76)	86 (74)	
Persistent	116 (22)	24 (20)	
Long-standing persistent	10 (2)	7 (6)	
Hypertension	217 (42)	44 (38)	0.41
Diabetes mellitus	52 (10)	5 (4)	0.05
Coronary artery disease	62 (12)	7 (6)	0.06
Congestive heart failure	20 (4)	2 (2)	0.25
Left ventricular dysfunction	18 (3)	5 (4)	0.58
LA diameter (mm), mean ± SD	42 ± 6	43 ± 7	0.56
CHA_2DS_2-VASc score ≥ 2, n (%)	245 (47)	40 (34)	0.02
HAS-BLED score ≥ 3, n (%)	31 (6)	4 (3)	0.30
Body mass index, mean ± SD (kg/m^2)	27.7 ± 4.1	27.2 ± 3.3	0.23
Technique of catheter ablation, n (%):			0.09
Cryoballoon	100 (19)	33 (28)	
Radiofrequency	402 (78)	83 (71)	
Laser	18 (3)	1 (1)	

LA = left atrium, NOAC = novel oral anticoagulant, VKA = vitamin K antagonist

Table 2. Primary and secondary end points

	Uninterrupted VKA N=520	Interrupted NOAC N=117	P-value
Primary bleeding endpoints			
BARC 3–5 bleeding, n (%)	22 (4.2)	4 (3.4)	0.70
ISTH major bleeding, n (%)	45 (8.7)	7 (6.0)	0.34
Secondary bleeding endpoints			
Bleeding requiring medical attention that does not fit the criteria for types 3–5 (BARC 2), n (%)	43 (8.3)	3 (2.6)	0.03
Bleeding with hemoglobin drop of 30 to < 50 g/L or requiring transfusion (BARC 3a), n (%)	10 (1.9)	3 (2.6)	0.72
Bleeding with hemoglobin drop of ≥ 50 g/L, or requiring surgery or iv vasoactive agents, or cardiac tamponade (BARC 3b), n (%)	12 (2.3)	1 (0.9)	0.48
BARC 2–5 bleeding, n (%)	65 (12.5)	7 (6.0)	0.04
CRNMB, n (%)	20 (3.8)	-	0.03
ISTH major bleeding and CRNMB, n (%)	65 (12.5)	7 (6.0)	0.04
Primary thromboembolic endpoint			
Stroke, TIA, or other systemic embolism, n (%)	3 (0.6)	-	1.00

BARC = Bleeding Academic Research Consortium, CRNMB = clinically relevant non-major bleeding, ISTH = International Society on Thrombosis and Haemostasis, NOAC= novel oral anticoagulant, TIA = transient ischemic attack, VKA = vitamin K antagonist

Table 3. Overview of major bleeding and thromboembolic events in large randomized controlled trials comparing periprocedural NOAC and VKA in patients undergoing catheter ablation of AF

Trial	BARC 3–5 bleedings	ISTH major bleeding	Thrombo-embolic events
RE-CIRCUIT (5) – VKA, N = 318	NA	6.9%	0.3%
RE-CIRCUIT (5) – uninterrupted dabigatran, N = 317	NA	1.6%*	0.0%
VENTURE-AF (6) – VKA, N = 124	NA	0.8%	0.8%
VENTURE-AF (6) – uninterrupted rivaroxaban, N = 124	NA	0.0%	0.0%
AXAFA (12) – VKA, N = 315	4.1%	4.4%	0.0%
AXAFA (12) – uninterrupted apixaban, N = 318	2.5%	3.1%	0.6%
ABRIDGE-J (13) – VKA, N = 222	NA	5.0%	0.5%
ABRIDGE-J (13) – interrupted dabigatran, N = 220	NA	1.4%*	0.0%
AEIOU (21) – uninterrupted apixaban, N = 150	1.3%	NA	0.7%
AEIOU (21) – interrupted apixaban, N = 145	2.1%	NA	0.7%

*Statistically significant difference in comparison to the VKA group. BARC = Bleeding Academic Research Consortium, ISTH = International Society on Thrombosis and Haemostasis, NA = not available, NOAC = novel oral anticoagulant, TIA = transient ischemic attack, VKA= vitamin K antagonist

Figures

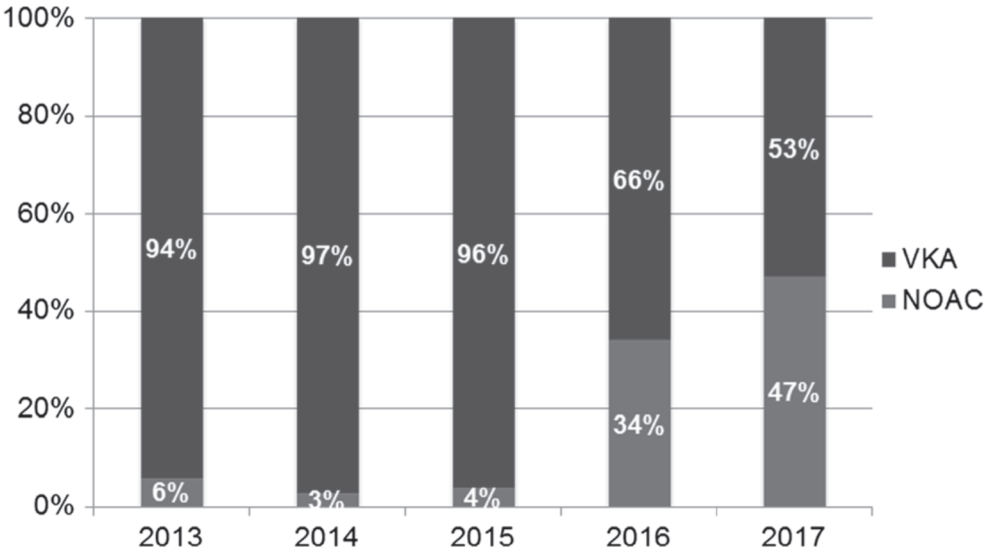


Figure 1. Proportion of periprocedural NOAC and VKA use over the years

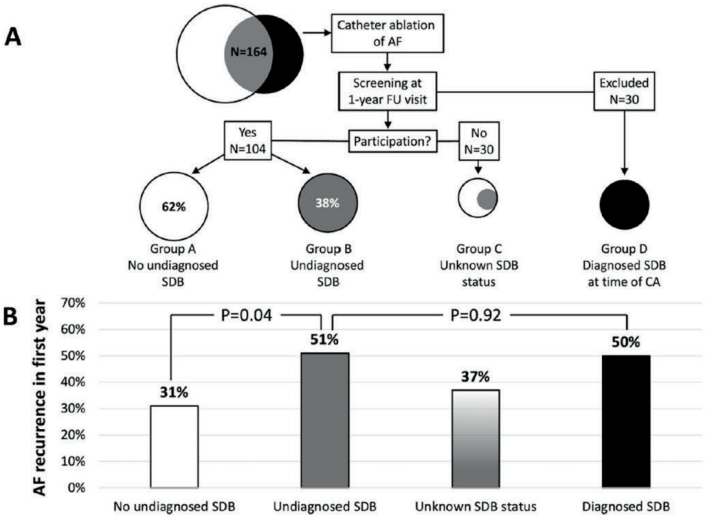
Part I **Evaluation of complications in atrial fibrillation**

Impact of undiagnosed obstructive sleep apnea on atrial fibrillation recurrence following catheter ablation (OSA-AF study)

Undiagnosed sleep disordered breathing (SDB) is common in patients undergoing AF catheter ablation

Two-fold increased risk of AF recurrence

Poor performance of STOP-Bang and ESS questionnaires



AF=atrial fibrillation; CA = catheter ablation; FU = follow-up; SDB = sleep-disordered breathing

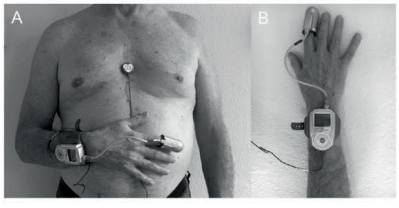


Fig. 1. WatchPAT-200U system: position of snoring and body position sensor on sternum (A) and position of WatchPAT wrist unit and finger probe

CHAPTER 4

Impact of undiagnosed obstructive sleep apnea on atrial fibrillation recurrence following catheter ablation (OSA-AF study)

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https://doi.org/10.1016/j.ijcha.2022.101014

Abstract

Background: Sleep-disordered breathing (SDB) may hamper the outcome of catheter ablation of atrial fibrillation (AF). However, SDB is underdiagnosed in clinical practice and the relevancy of undiagnosed SDB on the outcome of catheter ablation is unclear.

Objective: To evaluate if undiagnosed SDB has an impact on AF recurrence after catheter ablation.

Methods: In this single-center cohort study we enrolled patients who had a catheter ablation of AF 12 to 18 months prior to enrolment. Patients with diagnosed SDB at the time of catheter ablation were excluded. Enrolled patients underwent screening using WatchPAT (WP). SDB was defined as an apnea-hypopnea index (AHI) ≥ 15.

Results: A total of 164 patients were screened for eligibility. After exclusion of patients with previously diagnosed SDB (n = 30), 104 of 134 eligible patients were enrolled and underwent SDB screening. The median AHI was 11.5 (interquartile range 6.8–21.9) and 39 patients (38%) had SDB which was undiagnosed during the first year after ablation. AF recurrence in the first year after catheter ablation occurred in 40 patients (38%). The risk of AF recurrence was higher in the group with undiagnosed SDB in comparison to those without SDB (51% versus 31%, P = 0.04). Interestingly, the prevalence of AF recurrence was similar between patients with previously diagnosed and undiagnosed SDB (51% versus 50%, P = 0.92).

Conclusion: A significant proportion of patients undergoing catheter ablation of AF have undiagnosed SDB which is associated with a twofold higher risk of AF recurrence. SDB screening may improve patient counselling regarding the efficacy of catheter ablation.

1. Introduction

There is an association between sleep-disordered breathing (SDB) and atrial fibrillation (AF). The putative mechanisms for AF vulnerability in SDB patients seem to be a combination of left atrial (LA) dilatation, altered autonomic nerve activity, neuro-humoral activation and electrical atrial remodelling (e.g., atrial conduction slowing, reduction of atrial effective refractory period) (1). Observational studies and meta-analyses have shown a negative impact of SDB on the efficacy of catheter ablation of AF, with a 25% increased risk of AF recurrence (2–6). This lower efficacy may be partly explained by an increased incidence of non-pulmonary vein triggers (7). Treatment of SDB with continuous positive airway pressure (CPAP) improves arrhythmia-free survival after catheter ablation in observational studies, with a 42% risk reduction of AF recurrence (8–10). The 2020 European Society of Cardiology (ESC) guidelines recommend that SDB treatment should be optimized to improve AF treatment results (11–12). The clinical challenge, however, is that many patients with SDB have limited symptoms such as daytime sleepiness or feelings of fatigue which results in underdiagnosis of SDB (13–15). At present, the role of opportunistic screening for SDB before catheter ablation of AF is unclear. The aim of the current study is to evaluate if undiagnosed, thus untreated, SDB was associated with AF recurrence within the first year after initial catheter ablation of AF. To prevent bias due to SDB treatment, we evaluated the presence or absence of SDB, as measured with a dedicated sleep apnea testing device, at least one year after the initial catheter ablation. In addition, we also tested the utility of commonly used SDB screening questionnaires such as STOP-BANG and the Epworth Sleepiness Scale (ESS) to predict SDB in this specific patient population.

2. Methods

2.1. Study population

The Effect of undiagnosed Obstructive Sleep Apnea in patients undergoing Atrial Fibrillation catheter ablation (OSA-AF) study was a cross-sectional single-center cohort study. We included consecutive patients after a first catheter ablation of AF in the Erasmus MC, University Medical Center Rotterdam, the Netherlands from December 2018 to February 2020. Eligible patients were adults who had a first

catheter ablation of AF 12 to 18 months prior to screening for SDB. Thus, SDB status was determined at least 12 months after catheter ablation. We used the assumption that SDB status determined between 12 and 18 months after catheter ablation would reflect the SDB status at the time of catheter ablation. Using this unique study design we prevented treatment bias, which can occur when SDB status was determined at the time of catheter ablation. Consecutive patients were approached during their regular follow-up at the outpatient clinic. We excluded patients who had previously diagnosed SDB at the time of the catheter ablation.

2.2. Assessment of AF recurrence

After a catheter ablation of AF, patients had a routine follow-up at 3, 6 and 12 months after their ablation. Routinely, a 24-hour Holter monitoring was performed at 3 and 6 months, and a 7-day Holter monitoring was performed at 12 months after ablation. Additional Holter monitoring was performed when necessary. AF recurrence was defined as documented AF > 30 s at Holter monitoring or documented AF on a standard 12-lead ECG, after a blanking period of 3 months, irrespective of the use of antiarrhythmic drugs.

2.3. Screening for SDB

Screening for SDB was performed using the WatchPAT-200U (WP) (Itamar Medical, Caesarea, Israel). The WP system is a home sleep apnea testing (HSAT) device which has been shown to be accurate for diagnosing SDB, also in patients with AF (16). It consists of a wrist-worn device with a finger probe that obtains peripheral arterial tonometry (PAT) signals and oxygen saturation levels, a snoring and body position sensor that is positioned under the sternal notch and accelerometer that is embedded in the wrist unit (Fig. 1). The WP finger probe measures changes in the vascular tone at the fingertip which is a measure of sympathetic nervous system activity. Respiratory events are typically terminated by sympathetic activation and this is reflected by transient vasoconstriction events and increased pulse rate (17). The WP algorithm detects respiratory (apnea/hypopnea) events, sleep/wake status, and determines sleep stages. Patients were instructed in the use of the device and used the WP device overnight. If patients had questions on the use of the WP system, they could easily contact us by phone or email. For this study, SDB was defined as an apnea-hypopnea index (AHI) ≥ 15. If the proportion of central apneas over the total

number of apneas was ≥ 50%, these patients were considered to have predominant central sleep apnea; otherwise, they had predominant obstructive sleep apnea.

2.4. SDB screening questionnaires

Enrolled patients were requested to complete two questionnaires: the STOP-BANG and ESS questionnaire. The STOP-BANG questionnaire is specifically developed as a screening tool for SDB (18). It consists of 8 dichotomous items related to the clinical features of SDB, with a total score ranging from 0 to 8. Intermediate risk is defined as 3–4 points, and high risk is defined as ≥ 5 points or as 2 points in the first 4 questions in combination with male sex, obesity (BMI > 35 kg/m^2) or wide neck circumference (>40 cm females, >42 cm males). An intermediate or high-risk STOP-BANG score was considered abnormal in this study. The ESS is a validated questionnaire to screen for excessive daytime sleepiness, which is an important symptom to refer patients for SDB screening (19). It consists of 8 questions related to falling asleep in several common situations, each scored with a degree of severity ranging from 0 to 3. Scores range from 0 (least sleepy) to 24 (sleepiest). Excessive daytime sleepiness was defined in this study as an ESS ≥ 11.

2.5. Statistical analysis

Continuous parameters are presented as mean ± standard deviation (SD) or as median and interquartile range (IQR), as appropriate. Categorical data are presented as frequencies and percentages. Comparisons between groups were performed with an independent Student t-test, Mann-Whitney U test, chi-square test, or Fisher exact test, where appropriate. In case of comparing>2 groups, one-way ANOVA or Kruskal-Wallis test was used to compare continuous variables, where appropriate. Outcomes of logistic regression analysis are presented as odds ratios (OR) and 95% confidence intervals (CI). A P-value < 0.05 was considered statistically significant. Statistical analyses were performed using SPSS software (SPSS, version 25; IBM, Chicago, Illinois).

2.6. Ethics

The Medical Ethics Committee reviewed the study (MEC-2018–1503), and this single-center cohort study was not subjected to the Dutch Medical Research Involving Human Subjects Act. All participants undergoing SDB screening provided

written informed consent. There was a waiver for the use of retrospective data. The study was carried out according to the ethical principles for medical research involving human subjects established by Declaration of Helsinki, protecting the privacy of all the participants and the confidentiality of their personal information.

3. Results

3.1. Patient population

A total of 164 consecutive patients were scheduled for a 1-year follow-up visit at the outpatient clinic after their first catheter ablation of AF (Supplemental Table 1). After exclusion of 30 patients with diagnosed SDB at the time of catheter ablation, 104 of 134 patients (participation rate 78%) were enrolled and comprised the final study population (Fig. 2A). Patient characteristics of the study population are presented in Table 1. In the final study population, there were 40 patients (38%) with AF recurrence in the first year after catheter ablation. All patients could successfully use the WatchPAT, there were no dropouts.

3.2. SDB status and risk of AF recurrence

The median WP-derived AHI for the total study population was 11.5 (IQR, 6.8–21.9) and 39 patients (38%) had undiagnosed SDB with an AHI ≥ 15. All patients with undiagnosed SDB (AHI ≥ 15) had predominant obstructive sleep apnea (no patient had predominant central sleep apnea), with a very low median central AHI of 1.9 (IQR, 0.6–4.4). The patient characteristics between patients with and without undiagnosed SDB is presented in Table 1. In comparison with patients with no SDB, patients with undiagnosed SDB were older, were more often female, more often had diabetes and hypertension, higher CHA_2DS_2-VASc score, higher body mass index and more often used antiarrhythmic drugs (Table 1). The risk of AF recurrence was higher in patients with undiagnosed SDB in comparison to patients without undiagnosed SDB (51% versus 31%, OR 2.37, 95% CI 1.04–5.38, P = 0.04) (Fig. 2B). Vice versa, patients with AF recurrence showed a trend towards a higher median AHI value, 14.7 (IQR, 7.5–28.0) versus 10.6 (IQR, 6.6–16.5), P = 0.09 (Fig. 3). The risk of AF recurrence was similar between patients with undiagnosed and previously diagnosed SDB (51% versus 50%, OR 1.05, 95% CI 0.41–2.73, P = 0.92) (Fig. 2B). Patient characteristics between patients with undiagnosed and previously

diagnosed SDB were similar, except patients with previously diagnosed SDB more often used amiodarone (Supplemental table 1).

3.3. Performance of SDB screening questionnaires

In total, 95 (91%) and 102 (98%) patients completed the STOPBANG questionnaire and the ESS questionnaire, respectively. An abnormal STOP-BANG score (intermediate or high-risk score) was present in 61 patients (64%). A higher proportion of patients with SDB had an abnormal STOP-BANG score in comparison to patients without SDB (79% versus 56%, P = 0.02). An abnormal STOP-Bang score had a sensitivity of 79% and specificity of 44% for the detection of SDB (AHI ≥ 15) with a positive predictive value (PPV) of 44% and negative predictive value (NPV) of 79%. The diagnostic accuracy of the test was 57%. The area under the receiver operating characteristic curve (AUC) was 0.62 denoting a poor diagnostic discrimination. When using only the high-risk STOP-BANG score, the sensitivity, specificity, PPV, NPV and diagnostic accuracy were 35%, 76%, 44%, 68%, and 61%, respectively. Thus, specificity improved at the expense of sensitivity. Fig. 4 provides a comparison of the AHI values for the different STOP-BANG classifications. The median AHI values were statistically different between STOP-BANG groups: patients with low, intermediate, and high-risk STOP-BANG score had a median AHI of 8.7 (IQR, 4.1–14.3), 10.9 (IQR, 6.0–22.8), and 14.9 (IQR, 9.1–24.5), respectively (P = 0.03). The mean ESS score was 4.0 ± 3.6. Excessive daytime sleepiness (ESS ≥ 11) was present in 7 patients (7%). There was no difference in excessive daytime sleepiness between patients with and without SDB (8% versus 6%, P = 0.75). Using an ESS score ≥ 11, the sensitivity was 8% and the specificity was 94% for detecting SDB (AHI ≥ 15), with a PPV of 43% and NPV of 63%. The diagnostic accuracy of an ESS score ≥11 was 62%. The AUC was 0.51 denoting a poor diagnostic discrimination.

4. Discussion

The present study demonstrates that a large proportion of patients undergoing catheter ablation of AF have undiagnosed SDB. In this specific population, the STOP-Bang and ESS questionnaires do not accurately predict the presence of SDB. Importantly, undiagnosed SDB was associated with a two-fold higher risk of AF recurrence in the first year after catheter ablation.

SDB is considered a modifiable risk factor for AF (1). The combination of LA remodelling and deranged neurohumoral and autonomic nervous activity seems to be responsible for the increased vulnerability for AF in SDB patients. Adequate treatment of SDB may reduce the development of AF and reduce AF burden. Randomized controlled trials have shown that aggressive treatment of modifiable risk factors for AF, including SDB, successfully reverses early onset AF (20–22). As SDB shares the same modifiable risk factors as AF, being hypertension, smoking, diabetes, hyperlipidaemia, alcohol, obesity, and physical inactivity (20), aggressive risk factor management may have a positive influence on both entities.

In the clinical context of catheter ablation, the presence of SDB may also be important. Previous studies have shown a negative impact of SDB on the efficacy of catheter ablation of AF, with a 25% increased risk of AF recurrence (2–6). Interestingly, a meta-analysis demonstrated that SDB diagnosed by polysomnography (PSG) was a strong predictor of AF recurrence after catheter ablation, but not when SDB was diagnosed by the Berlin questionnaire (6). This suggests that the method of SDB screening is relevant to predict AF recurrence. Furthermore, treatment of appropriately diagnosed SDB with CPAP improves arrhythmia-free survival after catheter ablation in observational studies (8–10).

The challenge is that screening for SDB is suboptimal in clinical practice. A large majority of patients with SDB remain undiagnosed as demonstrated by our study and others (13–15). Screening for SDB can be done with questionnaires (e.g., Berlin, STOP-BANG, ESS) but the accuracy of these questionnaires is limited, especially in patients with cardiovascular disease (13,23–24). Kadhim et al. previously demonstrated that excessive daytime sleepiness (ESS ≥ 11) was present in only 22 of 149 ambulatory patients (15%) with AF and moderate-to-severe SDB (AHI ≥ 15, assessed by PSG) (13). This low prevalence of excessive daytime sleepiness is also seen in our population and thus daytime sleepiness should not be used in clinical practice to select patients for SDB screening. Even more dedicated questionnaires such as STOP-BANG do not accurately predict SDB although patients with SDB did more often had an abnormal STOP-BANG score (24). Further research is needed before deciding on the most optimal screening method and the role of questionnaires. Currently, it is not clear whether it is cost-effective to perform SBD testing in every patient who is eligible for catheter ablation. Maybe it is more cost-

effective to perform SBD testing only in patients with an intermediate to high probability based on questionnaires.

Opportunistic screening for SDB of eligible patients for catheter ablation of AF with PSG does not seem realistic in clinical practice. In this respect, HSAT seems to be easier to implement as part of the diagnostic work-up for a catheter ablation. Respiratory indexes calculated using PAT-based HSAT devices, such as the WatchPAT, correlate positively with PSG (25). In our study of patients undergoing catheter ablation of AF, 38% of patients had newly diagnosed SDB. This prevalence is higher than a previously reported study where the prevalence of SDB was 18% when diagnosed by PSG (26). However, a recent study by Verhaert et al., which also used WatchPAT for SDB screening, demonstrated that 55% of patients scheduled for catheter ablation had moderate-to-severe SDB (AHI ≥ 15) (27). Furthermore, this study demonstrated that WatchPAT allows easy implementation of sleep apnea management in an AF outpatient clinic.

Before starting opportunistic screening for SDB in patients undergoing catheter ablation of AF, we first wanted to evaluate the impact of undiagnosed SDB on the outcome of catheter ablation. Our study demonstrates that undiagnosed SDB was associated with a two-fold increased risk of AF recurrence after catheter ablation of AF. These data are important for patient counselling regarding the efficacy of catheter ablation of AF. Based on the current study, we cannot rule out that SDB is merely a risk marker than a risk factor. A risk marker can be considered a risk factor if intervention (e.g., CPAP) to modulate this factor results in parallel modulation of risk (i.e., reduction of AF recurrence). A recent randomized controlled trial by Traaen et al. demonstrated that treatment with CPAP for 5 months did not reduce AF burden in patients with paroxysmal AF and moderate to severe SDB (AHI ≥ 15) (28). Currently, there is no randomized controlled trial which has demonstrated the effect of CPAP use on AF recurrence after catheter ablation in SDB patients. Interestingly, in our study the risk of AF recurrence in the group with undiagnosed SDB was as high as those with previously diagnosed SDB (Fig. 2B). It may be presumed that patients with previously diagnosed SDB received appropriate SDB treatment, but we have no data on the type of treatment these patients received.

4.1. Study limitations

We did not determine SDB at the time of the index procedure to prevent treatment bias (i.e., CPAP treatment may influence the rate of AF recurrence). However, there are inherent limitations to our study design. There is a potential influence of catheter ablation on the prevalence and severity of SDB. Naruse et al. demonstrated that successful catheter ablation of AF reduced AHI one week after ablation (29). It was hypothesized that reduced airway congestion due to restoration of sinus rhythm would decrease AHI. In contrast, Hoyer et al. demonstrated that catheter ablation had no influence on the prevalence and severity of SDB 6 months after the procedure (30). We determined AHI 12 to 18 months after catheter ablation, and it is unknown how good this correlates with AHI at the index procedure. An alternative would have been to screen for SDB at the time of the index procedure in a double-blind fashion (patients and physicians unaware of SDB status) for the first year after ablation. Finally, an important limitation is that we used the WatchPAT and not PSG as the gold standard to diagnose SDB. Despite the good correlation between WatchPAT and PSG, this may have influenced the results of our study.

5. Conclusions

Undiagnosed SDB is common in patients undergoing catheter ablation of AF and is associated with a two-fold increased risk of AF recurrence. Screening for SDB in patients eligible for catheter ablation of AF may improve patient counselling with respect to the efficacy of catheter ablation. A HSAT-device may be a useful and easy to implement tool to screen for SDB.

Funding

None.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgements

None

Appendix A. Supplementary material

Supplementary data to this article https://doi.org/10.1016/j.ijcha.2022.101014.

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Figures and tables

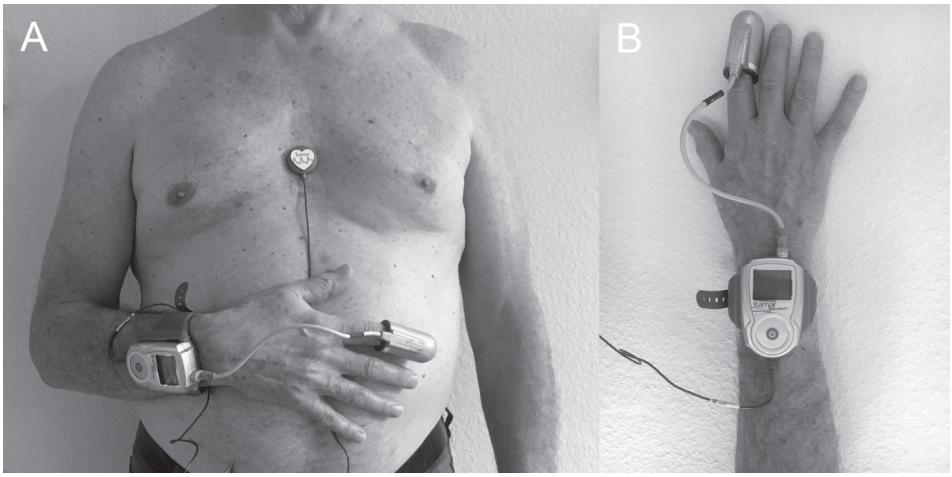

Figure 1. WatchPAT-200U system: position of snoring and body position sensor on sternum (A) and position of WatchPAT wrist unit and finger probe (B).

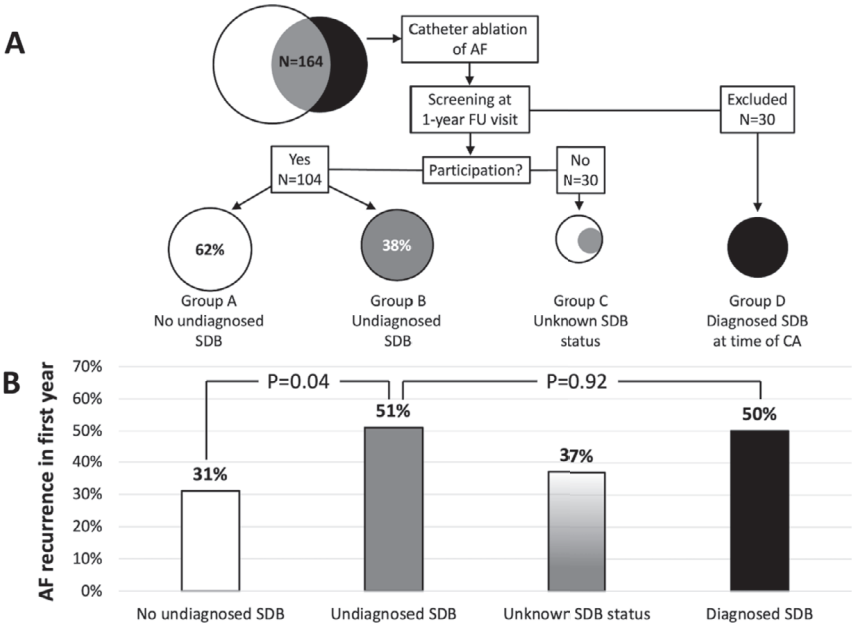

Figure 2. Study flow chart (A) and AF recurrence rate in the first year after catheter ablation per group (B). CA = catheter ablation; FU = follow-up; SDB = sleep-disordered breathing.

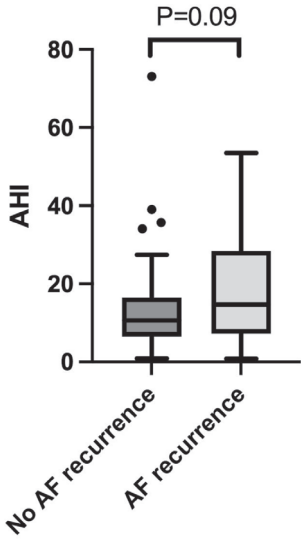

Figure 3. Tukey box plots demonstrating the apnea-hypopnea index (AHI) for patients with and without AF recurrence. The whiskers are defined as 1.5 * interquartile range. Outliers are denoted by the dots. AF = atrial fibrillation; AHI = apnea-hypopnea index.

Table 1 Patient characteristics

Characteristic	Total N = 104	Group A No SDB N=65	Group B Undiagnosed SDB N=39	P-value
Demographic data				
Age, years	59 ± 10	57 ± 9	62 ± 9	0.01
Female sex	34 (33)	15 (23)	19 (49)	0.01
Type of AF				
Paroxysmal AF	77 (74)	52 (80)	25 (64)	0.07
Nonparoxysmal AF	27 (26)	13 (20)	14 (36)	0.07
LA size				
LAVI, ml/m^2	38 ± 14	36 ± 14	41 ± 14	0.07
Scores				
CHA_2DS_2-VASc	1.4 ± 1.3	1.0 ± 1.0	2.1 ± 1.3	<0.001
CHA_2DS_2-VASc ≥2	44 (42)	18 (28)	26 (67)	<0.001
Modifiable risk factors				
Obesity, BMI ≥30 kg/m^2	20 (19)	9 (14)	11 (28)	0.07
BMI	26.5 (24.4-29.2)	25.7 (24.2-28.8)	27.8 (26.4-31.1)	0.02
Diabetes	7 (7)	1 (2)	6 (15)	0.01
Hyperlipidaemia	12 (12)	7 (11)	5 (13)	0.76
Hypertension	42 (40)	15 (23)	27 (69)	<0.001
Smoking	6 (6)	3 (5)	3 (8)	0.67
Alcohol use*	9 (9)	3 (5)	6 (15)	0.08
Type of procedure				
PVI only	96 (92)	60 (92)	36 (92)	1.00
PVI and substrate ablation	8 (8)	5 (8)	3 (8)	1.00
Antiarrhythmic drugs				
None	34 (33)	28 (43)	6 (15)	0.004
Flecainide	21 (20)	13 (20)	8 (21)	0.95
Betablockers	34 (33)	18 (28)	16 (41)	0.16
Sotalol	25 (24)	12 (19)	13 (33)	0.09
Amiodaron	2 (2)	1 (2)	1 (3)	0.71
Verapamil	4 (4)	2 (3)	2 (5)	0.58
Digoxin	3 (3)	1 (2)	2 (5)	0.28

Data are presented as mean ± SD, median (IQR) or as n (%). AF = atrial fibrillation; AHI = apnea-hypopnea index; BMI = body mass index, LA = left atrial, LAVI = left atrial volume index, PVI = pulmonary vein isolation, SDB = sleep-disordered breathing.

*Alcohol use was defined as >1 standard drink per day.

EDITORIAL

Undiagnosed sleep apnea in patients with atrial fibrillation: an underutilized opportunity for antiarrhythmic management

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IJC Heart&Vasculature 2022;40:101050. https://doi.org/10.1016/j.ijcha.2022.101050

Sleep-disordered breathing (SDB), of which obstructive sleep apnea is the most common subtype, has been shown to be highly prevalent in patients with atrial fibrillation (AF) (1). The arrhythmogenic mechanisms of SDB facilitating AF include nocturnal high-frequency desaturation and reoxygenation, intrathoracic pressure changes and sympathovagal activation (2). This provokes progressive structural atrial remodelling in long-term SDB, creating a complex and dynamic substrate for AF. Therefore, concomitant SDB and AF is associated with lower success rates of anti-arrhythmic therapy with increased risk of AF recurrence (3). Sleep apnea in patients scheduled for AF ablation is highly underdiagnosed. The OSA-AF study, published in the current edition of the IJC Heart & Vasculature, focused on the association of undiagnosed SDB on the outcome of AF catheter ablation in 164 patients (4). After exclusion of patients with previously diagnosed SDB (n = 30), 104 of 134 eligible patients were enrolled and underwent SDB screening. The median AHI was 11.5 (interquartile range 6.8–21.9) and 39 patients (38%) had SDB which was undiagnosed during the first year after ablation. AF recurrence in the first year after catheter ablation occurred in 40 patients (38%). The risk of AF recurrence was higher in the group with undiagnosed SDB in comparison to those without SDB (51% versus 31%, P = 0.04). Interestingly, the prevalence of AF recurrence was similar between patients with previously diagnosed and undiagnosed SDB (51% versus 50%, P = 0.92). This study shows that a significant proportion of patients undergoing catheter ablation of AF have undiagnosed SDB which is associated with a twofold higher risk of AF recurrence. Given the high prevalence and negative prognostic factor on AF outcomes, undiagnosed SDB is an underutilized modifiable AF risk factor and component of antiarrhythmic management. However, identifying SDB is difficult as most patients with AF do not report typical SDB-related symptoms as daytime sleepiness (5). Self-reported questionnaires on SDB-related symptoms, even if combined with basic clinical characteristics, seem insufficient in detecting SDB in AF patients (5). Additionally, a joint survey by the European Heart Rhythm Association (EHRA) and the Association of Cardiovascular Nurses and Allied Professions (ACNAP) recently identified a number of challenges occur in SDB management in patients with AF. A majority of health care professionals reported a missing collaboration between cardiology and sleep clinic as well as lack of financial and personnel related resources as major barriers in a systematical SDB screening (6). Further, access to polysomnography (PSG) based SDB screening, the current gold-standard, is limited due to various reasons. Polygraphy based home sleep testing may be a solution, as recent studies showed a high to fair sensitivity in detecting SDB when compared to PSG (7). Remote home SDB testing can herein provide accessible and reliable results with lower costs compared with conventional polysomnography (8). This can promote early detection and treatment of SDB in patients with AF. The relative cost of this approach could be justified by the benefits of improved treatment efficacy, which reduces medical and economic burden (see Fig. 1). The clinical challenge that remains is, however, identifying which patients need to be selected for SDB-screening. Current international AF management guidelines recommend identification and treatment of OSA in confirmed cases to help

maintain sinus rhythm. However, specific recommendations concerning when and how to test for SDB, remain uncertain. A systematic testing by home sleep test or respiratory polygraphy as well as structured SDB management pathways are often not established (6). The high prevalence and the negative prognostic effect of undiagnosed SDB on treatment efficacy in AF patients indicates a potentially high number of patients for SDB screening. Even with more cost effective and accessible SDB screening solutions, as for example home sleep tests, a pre-selection might therefore be necessary. We propose the assessment of pre-test probability of SDB based on SDB- related and clinical characteristics to further guide patient selection for SDB screening (2). However, evidence is needed for which patient characteristics or reported symptoms SDB screening is indicated in patients with AF. SDB screening can be reasonable in every patient who is experiencing SDB related symptoms. However, patients with difficult to treat hypertension or high AF symptom burden/AF recurrence can also benefit from SDB screening, as these conditions can be symptoms or consequences of SDB (9). Within AF patients, these might more often be patients who are scheduled for AF ablation or other rhythm control strategies, as investigated by the authors of the OSA-AF study, published in the current issue (4). However, the authors did not investigate consecutive AF patients and no prospective data was collected yet. Also, recent studies have demonstrated that OSA-severity exhibits considerable night-to-night variability, particularly in patients with cardiovascular disease, which cannot be detected by one overnight sleep assessment (10). The implementation of SDB screening and management in AF clinics requires a close interdisciplinary collaboration between the cardiologist and sleep specialists, ideally within an integrated care approach. Examples of integrated, multidisciplinary pathways for detection and treatment of SDB in patients with AF are slowly emerging. Previously, a virtual remote management pathway incorporating an mobile-health based overnight home sleep test was introduced in two AF outpatient clinics in the Netherlands (8). Integrated care pathways in this case can enable an interactive structured follow-up to assess AF burden, disease progression, and treatment efficacy. Simultaneously, the interactive feedback between patient and clinician may induce treatment success by empowering patient self-management through education. The majority of patients is not aware of the negative prognostic effects of SDB on AF (8). Educating and engaging patients supports informed decision making and adherence to treatment. Lifestyle intervention programs, such as sleep hygiene, alcohol abstinence and weight loss, could also be implemented as a component of the structured follow-up. Collectively, AF-SDB digital and remote monitoring tools may allow patient-tailored management decisions. Although the required technologies are available, implementation of SDB screening in AF clinics is complicated by lack of infrastructure and inflexible reimbursement models. SDB can probably be considered the most expensive cardiovascular risk factor in terms of its assessment. Management trials justifying SDB-screening and consecutive management are required to firmly establish the role of SDB treatment in AF management guidelines and thereby promote implementation in AF clinics. A systematical SDB screening approach can be considered relevant for patients with

high AF symptom burden or patients who report SDB related symptoms. However, until certain clinical and economic barriers in establishing a systematical SDB screening can be overcome, pre-selection models should be investigated and improved. Declaration of Competing Interest The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Part II

Evaluation of complications in device therapy

Part II **Evaluation of complications in device therapy**

Pocket hematoma after pacemaker or defibrillator surgery: Direct oral anticoagulants versus vitamin K antagonists

	DOAC interrupted		VKA continued
Anticoagulant			
Use in AF patients	↑		↓
Clinically significant pocket hematoma	0%	n.s.	2.5%
Trombo-embolism		none	

Figure 1. Flow chart study population

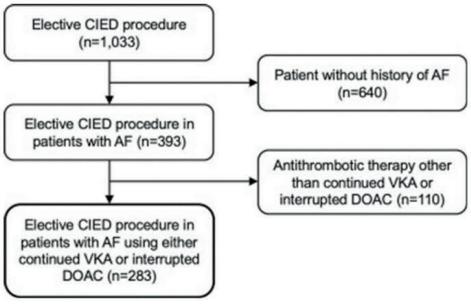
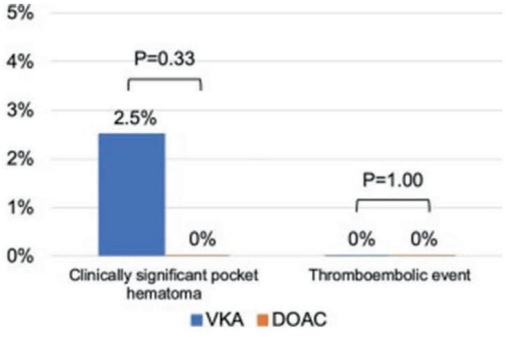


Figure 2. Primary and secondary outcomes



Abbreviations: AF = atrial fibrillation, CIED = cardiac implantable electronic device; DOAC = direct oral anticoagulant; VKA = vitamin K antagonist.

CHAPTER 5

Pocket hematoma after pacemaker or defibrillator surgery: Direct oral anticoagulants versus vitamin K antagonists

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IJC Heart & Vasculature, 2022 April, volume 39, 101005, https://doi.org/10.1016/j.ijcha.2022.101005

Abstract

Background: Direct oral anticoagulants (DOACs) are the preferred choice of oral anticoagulation in patients with atrial fibrillation (AF). Randomized trials have demonstrated the efficacy and safety of DOAC in patients undergoing a cardiac implantable electronic device procedure (CIED); however, there is limited real-world data.

Objective: To evaluate the outcome of patients undergoing an elective CIED procedure in a tertiary referral center with an interrupted DOAC or continued vitamin K antagonist (VKA) regimen.

Methods: This was a retrospective single-center study of consecutive patients with AF undergoing an elective CIED procedure between January 2016 and June 2019. The primary endpoint was a clinically significant pocket hematoma < 30 days after surgery. The secondary endpoint was any systemic thromboembolic complication < 30 days after surgery.

Results: Of a total of 1,033 elective CIED procedures, 283 procedures were performed in patients with AF using oral anticoagulation. One-third of the procedures were performed under DOAC (N = 81, 29%) and the remainder under VKA (N = 202, 71%). The DOAC group was younger, had less chronic renal disease, more paroxysmal AF and a lower HAS-BLED score. The VKA group more often underwent a generator change only in comparison to the DOAC group. Clinically significant pocket hematoma occurred in 5 patients (2.5%) in the VKA group and did not occur in the DOAC group (P = 0.33). There were no thromboembolic events reported.

Conclusion: In patients with AF undergoing an elective CIED procedure, the risk of a pocket hematoma and a systemic thromboembolic event is comparably low when using either continued VKA or interrupted DOAC.

1. Introduction

In patients with atrial fibrillation (AF) direct oral anticoagulants (DOACs) are currently the preferred choice of oral anticoagulation for long-term stroke prevention (1,2). A cardiac implantable electronic device (CIED) procedure is generally considered a procedure with a low bleeding risk (2). However, device-pocket hematoma is a common complication with an incidence ranging from 0.2% up to 16%, depending on definition and antithrombotic regimen (3-7). A pocket hematoma is associated with local discomfort, increased risk of infection, prolongation of hospitalization and may require surgical intervention in some cases (8-11).

Previous studies have shown that periprocedural oral anticoagulation is associated with a higher likelihood for pocket hematoma (5,12,13). The current guidelines recommend continuation of vitamin K antagonists (VKAs) during CIED procedures as bridging therapy with heparin is associated with a five-fold higher risk of bleeding compared with continued VKA (2,4,7). With regard to periprocedural DOAC use, the BRUISE CONTROL-2 trial, published in 2018, demonstrated that continued and interrupted DOAC had a similar low incidence of clinically significant pocket hematoma.(3) However, a meta-analysis in 2020 demonstrated a numerically higher incidence of bleeding complications in patients who continued DOAC (14). Furthermore, a large European survey demonstrated that in the majority of patients (89%) an interrupted DOAC strategy was used (15). The ESC guidelines and a EHRA expert consensus statement did not suggest a preference for either continued or interrupted DOAC during CIED surgery (6,7). Currently, there is little real-world data comparing the safety and efficacy of continued VKA versus interrupted DOAC in patients undergoing CIED surgery. The aim of the present study is to evaluate the incidence of clinically significant device pocket hematoma between both periprocedural anticoagulation regimens in patients with AF undergoing an elective CIED procedure in an academic center.

2. Methods

2.1. Study cohort

We retrospectively evaluated all consecutive adult patients who underwent an elective pacemaker or defibrillator surgery between January 2016 and June 2019. This population did not include patients with a recent (<3 months) transvenous lead extraction, patients who received a device during unplanned hospitalization, and patients who received a leadless pacemaker. The only inclusion criterion was a history of AF. Exclusion criteria were the use of concomitant antiplatelet therapy (i.e., aspirin, clopidogrel, ticagrelor or prasugrel) and any other regimen than continued VKA or interrupted DOAC. Thus, patients with bridging therapy, interrupted VKA or no oral anticoagulation use were excluded. No patient in our center continued DOAC during an elective CIED procedure. Data were collected from the electronic medical records.

2.2. Anticoagulation regimen and discharge

Patients using DOAC discontinued their drug 24–48 h before surgery depending on their renal function. All DOACs were restarted 24 h after end of surgery, unless stated otherwise by the operator. In patients using acenocoumarol or fenprocoumon, the target international normalized ratio (INR) was 2.0 to 2.5 in the morning of the procedure. Patients with continued VKA usually attained to their regular dosing schedule.

Patients undergoing a device implantation were discharged the day after the procedure. At the day of discharge, these patients underwent a physical examination of their device pocket, had a device interrogation and a chest X-ray. Patients undergoing a generator replacement only were discharged on the same day of the procedure after clinically significant pocket hematoma had been ruled out.

2.3. Study endpoints

The primary endpoint was clinically significant device pocket hematoma < 30 days after surgery. A clinically significant hematoma was defined as a hematoma resulting in either re-operation, prolongation of hospitalization (>24 h after index surgery) or interruption of oral anticoagulation. This definition of clinically significant hematoma is

in accordance with the landmark BRUISE CONTROL trials.(4,16) The secondary endpoint was any systemic thromboembolic complication (i.e., transient ischemic attack, stroke) < 30 days after surgery.

2.4. Statistical analysis

Continuous parameters were tested for normality before analysis and are expressed as mean ± standard deviation (SD) or median (interquartile range), as appropriate. Categorical data are presented as frequencies and percentages. Comparisons between groups were performed with an independent Student t-test, chi-square tests, Fisher exact test, or a Mann-Whitney U test, as appropriate. All analyses were two-tailed; a p-value < 0.05 was considered statistically significant. Statistical analyses were performed using SPSS software (SPSS, version 25; IBM, Chicago, Illinois).

2.5. Ethics

The Medical Ethics Committee reviewed the study (MEC-2020–0299), and this study was not subjected to the Dutch Medical Research Involving Human Subjects Act. The study was carried out according to the ethical principles for medical research involving human subjects established by Declaration of Helsinki, protecting the privacy of all the participants and the confidentiality of their personal information.

3. Results

3.1. Study population

A total of 1,033 elective CIED procedures were performed during the study period. After exclusion of patients who did not fulfil the criteria, the final study population consisted of 283 patients (Fig. 1). The VKA group comprised 202 patients (71%) and the DOAC group comprised 81 patients (29%). In the VKA group, most patients used acenocoumarol (Fig. 2A). In the DOAC group, most patients used dabigatran (43%) or apixaban (24%) (Fig. 2B). Patients who used a lower dose of DOAC had a lower mean eGFR in comparison to those with a normal dose of DOAC (50 ± 23 mL/min vs 74 ± 18 mL/min, p= < 0.001). The use of DOAC in the study population increased over the years, increasing from 15% in 2016 to 42% in 2019 (Fig. 3).

Baseline patient characteristics are depicted in Table 1. In comparison to the VKA group, patients using DOACs were younger, had a lower median HAS-BLED score,

were more likely to have paroxysmal AF and to use class I antiarrhythmic drugs, but less likely to have chronic renal disease and to use digoxin and diuretics. Patients with mechanical heart valves were only present in the VKA group. In the VKA group, the median INR at the day of surgery was 2.1 (IQR 1.8–2.4). In the DOAC group, the rhythm at the day of the procedure was sinus rhythm (57%), AF (38%), atrial flutter (3%) and atrioventricular sequential pacing (3%).

Besides differences in patient characteristics, there were also differences in surgical characteristics (Table 2). The DOAC group more often underwent a de novo dual chamber device implantation, while the VKA group more often had a pulse generator replacement procedure only. The median procedure duration was longer in the DOAC group in comparison to the VKA group.

3.2. Study endpoints

The primary endpoint occurred only in the VKA group. Although, there was a numerically higher incidence of clinically significant pocket hematoma in the VKA group (2.5%, 95% confidence interval [CI] 0.8%–5.7%) in comparison to the DOAC group (0%, 95% CI 0%–4.5%), this was not statistically different (P = 0.33) (Fig. 4). Of the 5 patients with clinically significant pocket hematoma, 4 patients (80%) had a device replacement or revision as the index procedure, 3 patients (60%) had an impaired renal function (eGFR < 60 mL/min) at baseline and 3 of 5 patients (60%) were > 70 years of age at the time of surgery (Table 3). Only 1 patient with a clinically significant pocket hematoma required a reoperation. Regarding the secondary endpoint, no systemic thrombotic event occurred (Fig. 4).

4. Discussion

The present study demonstrates that continued VKA and interrupted DOAC were associated with a comparable low risk of clinically significant pocket hematoma in patients with AF undergoing CIED surgery in a tertiary referral center. Furthermore, no systemic thromboembolic events were observed in both groups in the first month after surgery.

4.1. Pocket hematoma and periprocedural anticoagulation

Pocket hematoma is one of the most common complications following CIED surgery.(6) A pocket hematoma is not always benign and can be associated with prolongation of hospitalization, an increased risk of reoperation, and serious device-related infection (8,10,11,17). Therefore, prevention of pocket hematoma is important and this requires meticulous attention to modifiable risk factors, good operative skills and proper patient preparation. Risk factors for device pocket hematoma includes older age, renal failure, congestive heart failure, low operator experience, concomitant antiplatelet therapy, device replacement, lead revision, and heparin bridging (4,15,17-23). In patients using VKA, continued VKA is preferred over heparin bridging as the last is associated with a higher risk of pocket hematoma and prolonged hospital stay (4,6,19). Currently, most centers prefer either a continued VKA regimen or interrupt VKA without heparin bridging in case of a low CHA_2DS_2-VASc score (<3) in patients with AF (15).

With regard to periprocedural DOAC, the 2021 ESC guidelines on Cardiac Pacing and Cardiac Resynchronization Therapy and a 2021 EHRA expert consensus statement have no specific preference for either continued or interrupted DOAC in patients undergoing CIED surgery (6,7). The BRUISE CONTROL-2 trial demonstrated a similar low risk for clinically significant pocket hematoma in patients using either continued or interrupted DOAC (2.1% in both groups).(3) Several single-center studies have demonstrated a similar low risk of clinically significant pocket hematoma when using continued DOAC,(24,25) however, a recent meta-analysis demonstrated a numerically higher incidence of bleeding complications in patients who continued DOAC (14). Furthermore, many centers still prefer a interrupted DOAC regimen (15).

Therefore, it is interesting to know in a real-world population how an interrupted DOAC regimen would compare to the widely accepted continued VKA regimen regarding the incidence of pocket hematoma. It should be noted that we excluded patients who used concomitant antiplatelet therapy to prevent bias, as it is well-established that concomitant antiplatelet therapy in anticoagulated patients is associated with a two-fold higher risk of clinically significant pocket hematoma (23). We observed a low incidence of clinically significant pocket hematoma; this was

2.5% in patients using continued VKA and 0% in patients with interrupted DOAC. Our results are in line with both BRUISE CONTROL trials, which showed an incidence of 3.5% and 2.1% in the continued VKA arm and interrupted DOAC arm, respectively (3,4). Using patient level data from both BRUISE CONTROL trials, Essebag et al. also showed no difference in clinically significant pocket hematoma between DOAC use (either continued or interrupted) and continued VKA after adjusting for concomitant antiplatelet use (odds ratio 0.86, 95% CI 0.38–1.96, P = 0.72) (23).

4.2. Trend in DOAC use

In the Netherlands, there was initially a conservative policy with regard to DOAC use, mainly due to concerns about the lack of an antidote, patient adherence, lack of monitoring and increased health care cost (26). Therefore, there was a slower uptake of DOAC use in the Netherlands in comparison to other Western European countries (27). Since 2016 there has been a steady increase in the use of DOAC in the Netherlands. This is reflected by the steady increase in the relative proportion of patients with periprocedural DOAC in our study population, from 15% in 2016 to 42% in 2019. This also explains why patients in the DOAC group were more likely to undergo a de novo implantation and less likely to undergo a device replacement in comparison to the VKA group. Because a device replacement is associated with a higher likelihood of pocket hematoma (21), this may result in bias towards a more favourable outcome for the DOAC group in comparison to the VKA group in the present study.

It is expected that in the future the majority of patients will undergo CIED surgery with periprocedural DOACs as these are the preferred agents for stroke prevention in patients with AF (1). Also, the potential treatment of device-detected AF with DOAC, depending on the outcome of NOAH-AFNET 6 and ARTESiA (28,29), will result in more CIED patients being treated with a DOAC. Our real-world data is reassuring that an interrupted DOAC regimen is associated with a low risk of clinically significant pocket hematoma and no thromboembolic events in patients undergoing elective CIED surgery.

4.3. Study limitations

This was a retrospective observational single-center study with its inherent limitations. Selection bias may play a role as DOAC are less often used in patients with renal dysfunction which is a known risk factor for pocket hematoma. Furthermore, we were unable to statistically correct for differences in baseline variables between groups due to the low number of events.

5. Conclusions

In patients with AF undergoing an elective CIED procedure, the risk of a clinically significant pocket hematoma and a systemic thromboembolic event is comparably low when using either continued VKA or interrupted DOAC.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgements

None.

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Figures and Tables

Table 1. Baseline characteristics

Characteristic	VKA group (n=202)	DOAC group (n=81)	P-value
Age (years)	71 (63-77)	68 (62-73)	0.04
Male sex	144 (71.3%)	52 (64.2%)	0.24
Body mass index	26.0 (23.7-30.1)	27.3 (23.9-30.0)	0.27
Medical history			
- Chronic heart failure	134 (66.3%)	49 (60.5%)	0.35
- Hypertension	79 (39.1%)	34 (42.0%)	0.66
- Diabetes mellitus	32 (15.8%)	13 (16.0%)	0.97
- Stroke	22 (10.9%)	4 (49%)	0.12
- Transient ischemic attack	26 (12.9%)	5 (6.2%)	0.10
- Coronary artery disease	69 (34.2%)	25 (30.9%)	0.59
- Peripheral artery disease	14 (6.9%)	7 (8.6%)	0.62
- Chronic renal disease*	105 (52.0%)	29 (35.8%)	0.01
- eGFR (mL/min)	56 ± 22	68 ± 22	<0.001
- Dilated cardiomyopathy	61 (30.2%)	28 (34.6%)	0.47
- Ischemic cardiomyopathy	53 (26.2%)	16 (19.8%)	0.25
- COPD	42 (20.8%)	13 (16.0%)	0.36
- Mechanical heart valve	23 (11.4%)	-	0.002
- History of bleeding	15 (7.4%)	4 (4.9%)	0.45
Type of AF:			0.034
- Paroxysmal AF	98 (48.5)	53 (65.4)	
- Persistent AF	30 (14.9)	9 (11.1)	
- Permanent AF	74 (36.6)	19 (23.5)	
CHA_2DS_2-VASc score	3 (2-5)	3 (2-4)	0.07
HAS-BLED score	2 (1-3)	1 (1-2)	<0.001
Cardiac medication:			
- ACEI	88 (43.6%)	26 (32.1%)	0.08
- ARB	56 (27.7%)	18 (22.2%)	0.34
- Aldosterone inhibitor	81 (40.1%)	23 (28.4%)	0.07
- Digoxin	56 (27.7%)	13 (16.0%)	0.04
- Class I AAD	6 (3.0%)	8 (9.9%)	0.03
- Beta-blocker	141 (69.8%)	53 (65.4%)	0.47
- Amiodarone	48 (23.8%)	18 (22.2%)	0.78
- Sotalol	15 (7.4%)	4 (4.9%)	0.45
- Calcium antagonist	26 (12.9%)	8 (9.9%)	0.48
- Diuretics	138 (68.3%)	35 (43.2%)	<0.001
- Statin	111 (55.0%)	36 (44.4%)	0.11

Data are presented as n (%), median (25^{th}, 75^{th} percentile) or mean ± standard deviation. * eGFR <60 mL/min. Abbreviations: AAD= antiarrhythmic drug; ACEI= angiotensin-converting-enzyme inhibitor; AF= atrial fibrillation; ARB= angiotensin receptor blocker; COPD= chronic obstructive pulmonary disease; DOAC = direct oral anticoagulant; eGFR= estimated glomerular filtration rate; VKA= vitamin-K antagonist.

Table 2. Operative details.

Characteristic	VKA group (n=202)	DOAC group (n=81)	P-value
New implant of a pacemaker			
- Single	6 (3.0)	4 (4.9)	0.42
- Dual	16 (7.9)	19 (23.5)	<0.001
- Cardiac resynchronization	9 (4.5)	4 (4.9)	0.86
New implant of an ICD			
- Single	9 (4.5)	6 (7.4)	0.32
- Dual	3 (1.5)	5 (6.2)	0.03
- Cardiac resynchronization	11 (5.4)	3 (3.7)	0.54
- Subcutaneous ICD	4 (2.0)	4 (4.9)	0.17
Device replacement or revision			
- Pulse generator change only	115 (56.9)	21 (25.9)	<0.001
- Pulse generator change with additional	25 (12.4)	12 (14.8)	0.58
- Other	4 (2.0)	3 (3.7)	0.40
Subpectoral pocket	15 (7.4)	5 (6.2)	0.71
Participation of fellow in procedure	123 (60.9)	57 (70.4)	0.13
INR at day of procedure	2.1 (1.8-2.4)	-	
Duration of procedure (min)	50 (32-75)	69 (45-91)	0.003

Data are presented as n (%) or as median (25^{th}, 75^{th} percentile). Abbreviations: DOAC= direct oral anticoagulant; ICD= implantable cardioverter-defibrillator; INR= international normalized ratio; VKA = vitamin K antagonist.

Table 3. Detailed overview of clinically significant hematoma.

Case no.	Type VKA	Sex	Age	Cardiomyopathy	eGFR (mL/min)	Type of procedure	HAS-BLED	Intervention
1	Acenocoumarol	M	64	Ischemic	67	Generator change and RV shock lead implantation	2	Prolongation of hospital stay & interruption of VKA
2	Acenocoumarol	M	66	Non-ischemic	5	CRT-D implantation	3	Interruption of VKA
3	Acenocoumarol	F	72	none	60	RV pacing lead change	2	Prolongation of hospital stay
4	Acenocoumarol	M	81	Ischemic	56	ICD generator change	3	Prolongation of hospital stay
5	Acenocoumarol	M	88	none	34	ICD generator change	2	Interruption of VKA & reoperation

Data are presented as n (%). Abbreviations: CRT-D= cardiac resynchronization therapy defibrillator; eGFR= estimated glomerular filtration rate; F= female; ICD= implantable cardioverter-defibrillator; M= male; RV= Right Ventricle; VKA= vitamin K antagonist.

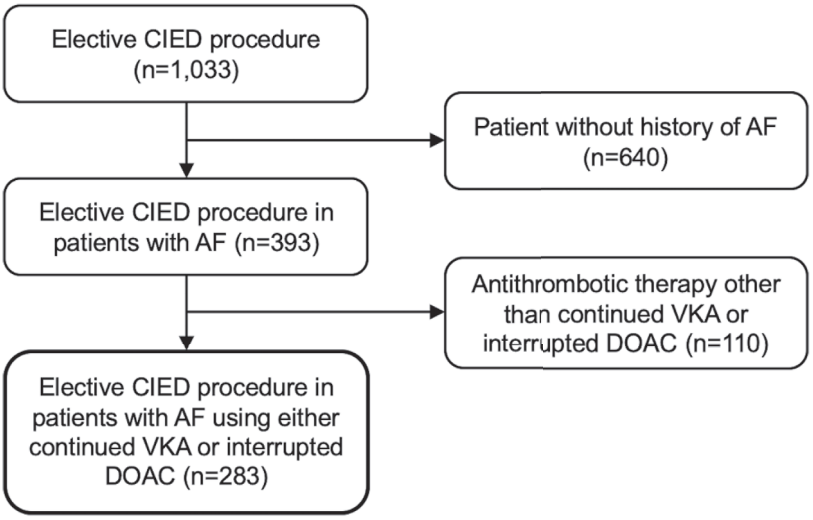


Fig. 1. Flow chart study population. Abbreviations: AF = atrial fibrillation, CIED = cardiac implantable electronic device; DOAC = direct oral anticoagulant; VKA = vitamin K antagonist.

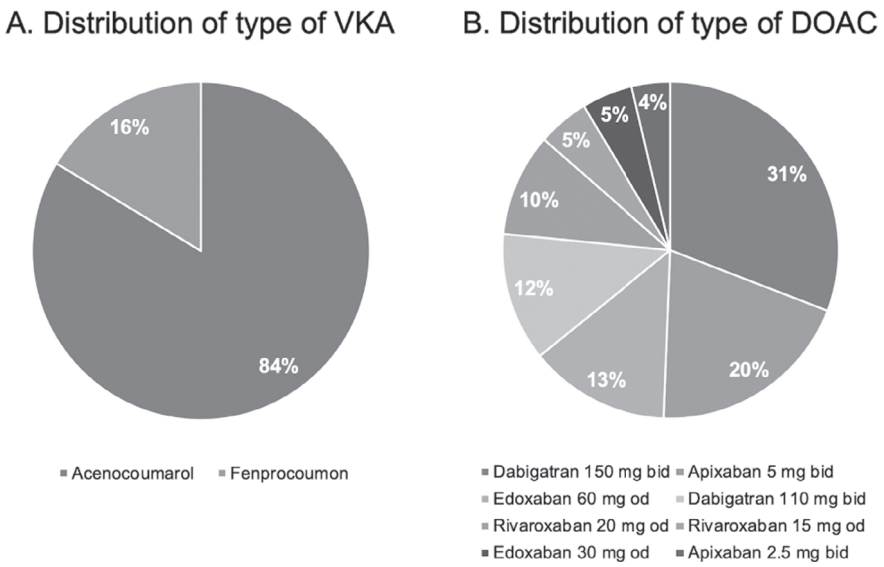


Fig. 2. Distribution of type and dose of periprocedural oral anticoagulation. Abbreviations: DOAC = direct oral anticoagulant; VKA = vitamin K antagonist.

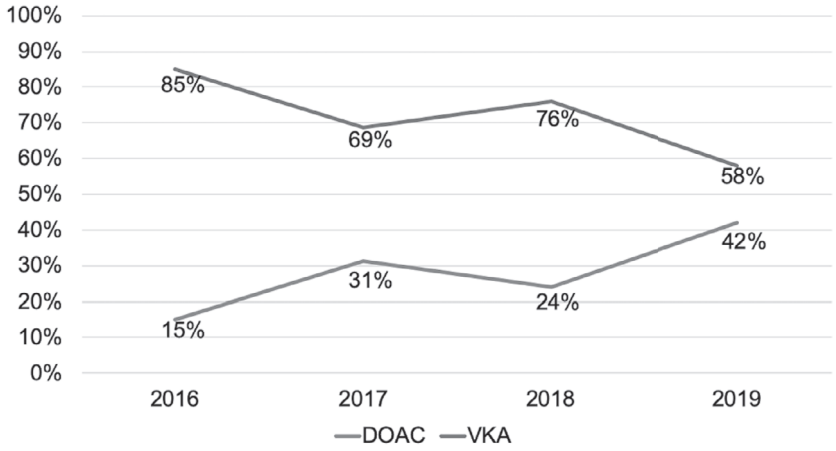


Fig. 3. Temporal trend in the type of periprocedural oral anticoagulation. Abbreviations: DOAC = direct oral anticoagulant; VKA = vitamin K antagonist.

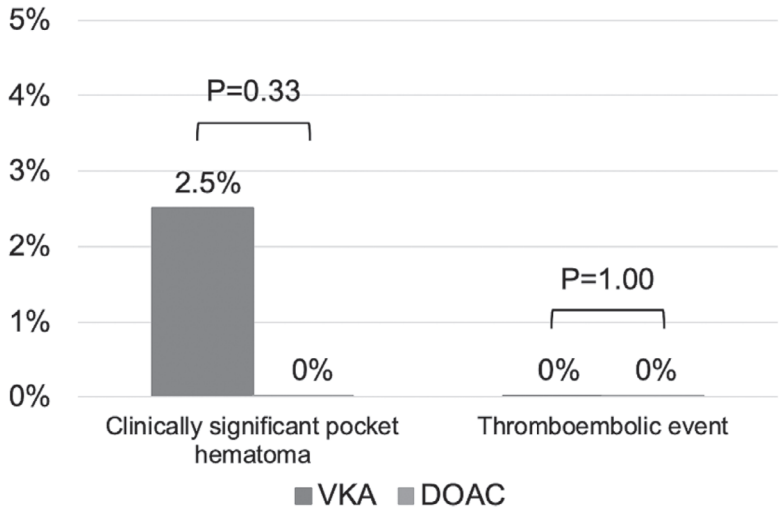


Fig. 4. Primary and secondary outcomes. Abbreviations: DOAC = direct oral anticoagulant; VKA = vitamin K antagonist.

Part II **Evaluation of complications in device therapy**

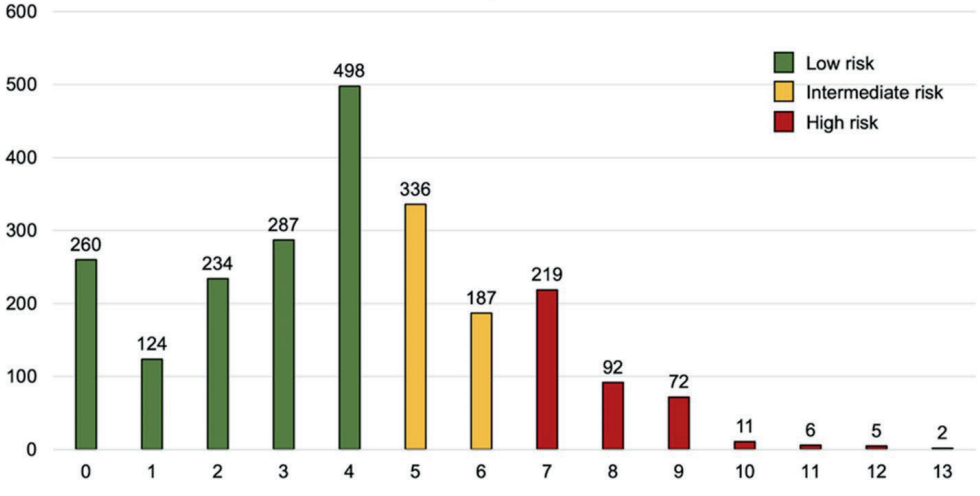
Device infection in patients undergoing pacemaker or defibrillator surgery: risk stratification using the PADIT-score

Risk of device infection was low (0.43%)

The median PADIT-score was 6 (IQR, 4 – 8)

In a real-world all-comers cohort, a PADIT-score of ≥7 identified a high-risk population (C-statistic 0.70; 95% CI 0.54-0.86, P=0.03)

Figure 1. Distribution of PADIT score in the study population.



PADIT-score classified as low (≤4), intermediate (5-6), or high risk (≥7) in accordance with the original paper by Birnie et al. J Am Coll Cardiol. 2019;74(23):2845-54

CHAPTER 6

Device infection in patients undergoing pacemaker or defibrillator surgery: risk stratification using the PADIT-score

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Journal of Interventional Cardiac Electrophysiology, Jan 2024, DOI: 10.1007/s10840-024-01759-1

Abstract

Background: The use of an antibacterial envelope is cost-effective for patients at high risk of developing cardiac implantable electronic device (CIED) infection. The identification of these high-risk patients may be facilitated using a clinical risk score. The aim of the current study is to evaluate the PADIT score for identifying high-risk patients in patients undergoing a CIED procedure in a tertiary academic center.

Methods: This was a retrospective single-center study of consecutive patients undergoing a CIED procedure between January 2016 and November 2021. Patients who received an antibacterial envelope were excluded from this study. The primary endpoint was hospitalization for a CIED infection in the first year after the procedure.

Results: A total of 2333 CIED procedures were performed in the study period (mean age 61.6 ± 16.3 years, male sex 64.5%, previous CIED infection 1.7%, immunocompromised 5.4%). The median PADIT score was 4 (interquartile range, 2–6). CIED infection occurred in 10 patients (0.43%). The PADIT score had good discrimination in predicting major CIED infection (C-statistic 0.70; 95% confidence interval [CI] 0.54 to 0.86, P = 0.03). Using an optimal PADIT score cut-off value of 7, the risk of CIED infection was higher in the patients with a PADIT score of ≥ 7 in comparison to those with a lower PADIT score (1.23% vs. 0.26%, P = 0.02; odds ratio 4.8, 95% CI 1.4 to 16.6, P = 0.01).

Conclusion: The PADIT score is a clinically useful score for identifying patients at high risk of developing CIED infection. The use of an antibacterial envelope in these high-risk patients may be cost-effective.

1. Introduction

The risk of device infection is approximately 1% in the first year after cardiac implantable electronic device (CIED) implantation (1-4). CIED infection is associated with substantial morbidity and increased mortality risk. Patients with CIED infection often require hospitalization, prolonged antibiotic treatment, timely removal of their CIED system, and often CIED reimplantation (5,6). Management of CIED infection is therefore associated with a high financial health care burden (7). Mitigation of the risk of CIED infection is crucial and preventive measures include among others preoperative antibiotics, chlorhexidine skin preparation, and avoidance of heparin bridging (8,9,10). In 2019, the WRAP-IT (World-wide Randomized Antibiotic Envelope Infection Prevention) trial demonstrated that an absorbable antibacterial envelope reduced the risk of major CIED infection by 40% in patients undergoing CIED reoperations and initial cardiac resynchronization therapy defibrillator (CRT-D) implantation (11). Cost-effectiveness studies demonstrated that an antibacterial envelope had the most favorable cost-effectiveness profile in high-risk patients (7,12). An antibacterial envelope is thus recommended by the European Heart Rhythm Association (EHRA) in high-risk patients (13). The identification of high-risk patients may be aided using risk calculators such as the PADIT (Prevention of Arrhythmia Device Infection Trial) score which uses five independent clinical and procedural predictors of CIED infection (14,15). The aim of the present study is to evaluate the usefulness of the PADIT score in identifying patients at high risk for CIED infection in a tertiary academic center.

2. Methods

2.1. Study cohort

We retrospectively evaluated all consecutive adult patients who underwent a pacemaker or defibrillator surgery between January 2016 and November 2021 in our academic center. Exclusion criteria were a recent (< 3 months) transvenous lead extraction, implantation of a leadless pacemaker, and use of an anti-bacterial envelope. The antibacterial envelope is only sparsely used in the Netherlands considering the lack of reimbursement. Data were collected from the electronic medical records. Our center is a high-volume tertiary center with approximately 430 implants annually and is a referral center for heart transplantation, left ventricular

assist devices, adult congenital heart disease, lead extraction, inherited cardiac disease, and pediatric cardiac surgery.

2.2. Anticoagulation regimen

Patients using direct oral anticoagulants (DOACs) discontinued their drug 24–48 h before surgery depending on their renal function. All DOACs were restarted 24 h after the end of surgery, unless stated otherwise by the operator. In patients using vitamin K antagonists (VKA), the target international normalized ratio was 2.0 to 2.5 in the morning of the procedure. Patients with continued VKA usually attained to their regular dosing schedule. Heparin bridging was avoided if possible.

2.3. Antibiotic treatment regimen

All patients received systemic antibiotic prophylaxis within 1 h of the procedure. This was either a single dose of intravenous cefazolin (2 g) or intravenous clindamycin (600–900 mg depending on weight) if patients were allergic to beta-lactam antibiotics (i.e., penicillin, cephalosporins). Vancomycin was reserved for patients with an allergy to both cefazoline and clindamycin. This local antibiotic regimen was based on the national guidelines for antibiotic use in the Netherlands. We postponed CIED procedures in patients who had a fever or high C-reactive protein at the day of their surgery. No postoperative antibiotic therapy was routinely given.

2.4. Peri-procedural setting

CIED procedures were performed in a catheterization lab which is a sterile environment which complies with the requirements of an operating room Class 2 according to the Dutch Infection Prevention Taskforce guidelines. This includes the use of two semi-restricted zones and tightly controlled ranges for temperature, pressure (i.e., positive pressure of at least 5 Pa from zone A to B), relative humidity, and ventilation rates (i.e., minimum of 10 total air exchanges per hour, use of air filter using HEPA). The number of staff was kept to a minimum and usually consisted of a physician, scrub nurse, circulating nurse, and a CIED technician. All procedures were performed or supervised by an EHRA-certified cardiac device specialist with a large experience in CIED implantations. CIED procedures were also performed by fellows. After a surgical scrub, the operator(s) and scrub nurse wore a sterile gown, cap, mask, and non-powdered double gloves. The scrub nurse performed the prepping

and draping. The skin was prepared with antiseptic formulated with 0.5% chlorhexidine digluconate and 70% alcohol and sufficient time was given to allow the antiseptic preparation to dry. After the application of sterile drapes, the operating field was covered by an adhesive iodophor-impregnated incise drape, except in patients who were allergic to iodine. For transvenous lead implantation, the primary choice for venous access was the cephalic vein. For generator replacements and upgrade/revision procedures, we used a pulsed electron avalanche knife (PEAK) PlasmaBlade™ (Medtronic, Minneapolis, MN, USA). This is an electrocautery device which uses pulses of radiofrequency energy to cut and coagulate soft tissue without the thermal damage to surrounding tissues normally seen with traditional electrosurgery. Meticulous attention was paid to hemostasis before wound closure in several layers. The final skin closure was performed with an absorbable suture. A sterile dressing was applied to the wound for a minimum of 4 days. Pressure dressing was only applied in selected patients (e.g., oozing of wound). Patients were instructed to keep the wound dry for a minimum of 4 days. The peri-procedural measures are largely in line with the current EHRA consensus document (16).

2.5. Discharge and follow-up

Patients undergoing a generator replacement only were discharged on the same day of the procedure after clinically significant pocket hematoma had been ruled out. Patients undergoing a de novo device implantation, upgrade, or revision were discharged the day after the procedure. On the day of discharge, these patients underwent a physical examination of their device pocket, a device interrogation, a chest X-ray (to rule out pneumothorax and lead dislodgement), and a bed-side echocardiogram (to rule out pericardial effusion). Two weeks after discharge the patients were seen at the outpatient clinic for wound inspection and device interrogation. Thereafter, device interrogation was performed every 6 months with or without remote monitoring. Every 3 months a CIED complication meeting was organized in which all CIED-related complications, including infections, are discussed by the operators. Furthermore, our center organizes a weekly regional multidisciplinary Endocarditis Heart Team in which patients with suspected endocarditis, including CIED-related infections, are discussed. Finally, our center is the only center in the region which performs transvenous lead extractions and is a

high-volume center for transvenous lead extractions (approximately 50 cases annually).

2.6. PADIT-score

The PADIT score was developed to predict the risk of hospitalization for device infection within 1 year (14). A correction was published to the original risk score and this modified score was used (15). This model includes 5 independent predictors of CIED infection including number of Prior procedures, Age, Depressed renal function (estimated glomerular filtration rate [GFR] < 30 mL/min), being Immunocompromised, and procedure Type. Immunocompromised was defined in the PADIT trial as receiving therapy that suppresses resistance to infection (e.g., immunosuppression, chemotherapy, radiation, long-term, or recent high-dose steroids) or having a disease that is sufficiently advanced to suppress resistance to infection (e.g., leukemia, lymphoma, HIV infection). The minimum risk score is 0 and the maximum is 13 (Supplemental Table 1). The PADIT score was calculated using the online calculator (https://padit-calculator.ca) which used the corrected version of the PADIT score. Based on the PADIT score, 3 risk categories could be identified according to the original publication: low risk (≤ 4), intermediate risk (5,6), and high risk (≥ 7) (14).

2.7. Study endpoint

The primary endpoint was a CIED infection requiring hospitalization within 1 year of the procedure. This definition was also used in the original PADIT trial (2). The diagnosis of CIED or pocket infection followed the 2019 International CIED Infection criteria (16).

2.8. Statistical analysis

Continuous parameters were tested for normality before analysis and are expressed as mean ± standard deviation (SD) or median (interquartile range [IQR]), as appropriate. Categorical data are presented as frequencies and percentages. Comparisons between groups were performed with an independent Student t-test, chi-square test, Fisher exact test, or a Mann–Whitney U test, as appropriate. We used the receiver operating characteristic (ROC) curve to evaluate the performance of the PADIT score to predict the 1-year risk of device infection. Discrimination was assessed by using the Harrell's C-statistic. Model discrimination was deemed poor if

the C-statistic was between 0.50 and 0.70, good between 0.70 and 0.80, and excellent if > 0.80. Binary logistic regression analysis was performed to test the diagnostic properties of the optimal PADIT score threshold. Odds ratios will be presented with their corresponding 95% confidence intervals (CI). All analyses were two-tailed; a P-value < 0.05 was considered statistically significant. Statistical analyses were performed using SPSS software (SPSS, version 28.0.1.0; IBM, Chicago, IL).

3. Results

3.1 Study population

A total of 2511 CIED procedures were performed during the study period. After the exclusion of patients who did not fulfil the eligibility criteria, the final study population consisted of 2333 CIED procedures in 2105 patients (Fig. 1). Baseline characteristics of the study population are presented in Table 1. The mean age at the time of the procedure was 61.6 ± 16.3 years and 64.5% were male. A previous CIED infection was present in 1.7%, and chronic kidney disease stage IV to V (eGFR < 30 ml/min) was present in 5.4%. One hundred twenty-seven patients (5.4%) were immunocompromised. The most common procedure was an ICD procedure (new or generator replacement, 42.6%), followed by a pacemaker procedure (new or generator replacement, 29.3%), CRT procedure (new or generator replacement, 16.6%), and revision and/or upgrade procedure (11.5%). A total of 1117 patients (47.9%) would be considered potential WRAP-IT patients (i.e., CIED reoperations and initial CRT-D implantation).

The median PADIT score was 4 (IQR, 2–6). Figure 2 shows the distribution of the PADIT score in the study population. The proportion of patients with low (≤ 4 points), intermediate (5–6 points), and high-risk PADIT score (≥ 7 points) was 1403 (60.1%), 523 (22.4%), and 407 (17.4%), respectively.

3.2 Primary endpoint and PADIT-score

Within 1 year of follow-up, hospitalization for CIED infection occurred in 10 patients (0.43%, 95% CI 0.21–0.79%). Details regarding the CIED infections are summarized in Table 2. Most cases occurred within the first 5 weeks after the procedure (80%)

and Staphylococcus aureus was the most frequently isolated pathogen (40%). Almost all patients had complete removal of their CIED system (90%).

The median PADIT score in patients with a CIED infection in the first year after the procedure was 6 (IQR, 4–8). The PADIT score showed good discrimination in predicting CIED infection requiring hospitalization within the first year (C-statistic 0.70; 95% CI 0.54–0.86, P = 0.03). The optimal cut-off was a PADIT score of ≥ 7 resulting in a sensitivity of 50% and a specificity of 83% for predicting CIED infection. Patients with a PADIT score ≥ 7 had a higher risk of hospitalization for CIED infection within the first year than patients with a lower PADIT score (1.23% vs. 0.26%, P = 0.02; odds ratio 4.8, 95% CI 1.4–16.6, P = 0.01).

In the 1117 patients who can be considered potential WRAP-IT candidates (i.e., CIED reoperations and initial CRT-D implantation) the incidence of CIED infection within the first year after the procedure was 0.45% (95% CI 0.15–1.04%).

Of the study population, a total of 130 patients (5.6%) died within 1 year of the procedure (cardiovascular death 32%, non-cardiovascular death 25%, unknown cause 44%). None of these 130 patients had a hospitalization for CIED infection.

4. Discussion

The present study demonstrates that the risk of device infection can be low (0.43%) when strict adherence to preventive measures for CIED infections is used. The PADIT score was useful in identifying patients at high risk of CIED infection. For our tertiary referral center, a PADIT score ≥ 7 had the highest sensitivity and specificity for predicting CIED infection requiring hospitalization with a 1-year risk of 1.23%. Identification of this high-risk population for CIED infection is useful because they can potentially benefit from adjunctive preventive measures like an antibiotic envelope.

4.1. Risk of CIED infection

CIED infection is associated with significant morbidity, increased hospitalizations, reduced survival, and financial health care burden (12). The large prospective PADIT trial (n = 19,603) demonstrated a 1-year infection rate of 0.9% (2). It is important to note that most patients in the PADIT trial were high-risk patients (66%) who

underwent either CIED reoperation or a CRT procedure. Infection risk is dependent on several patient-related, procedure-related, and device-related factors (17). Important preventive measures to reduce the risk of CIED infections are the use of antibiotic prophylaxis, chlorhexidine skin preparation, delaying the procedure in case of fever, avoidance of heparin bridging, avoidance of pocket hematoma, the use of strict sterile techniques, and having experienced operators. These preventive measures are summarized in the 2019 EHRA international consensus document (16). In comparison to the PADIT study population, our study population was younger (61 vs. 72 years), had a higher proportion of immunocompromised patients (5.4% vs. 1.6%), and had relatively more ICD implantation/replacement (42.6% vs. 21.6%). All these factors are independent predictors of a higher risk of CIED infection. However, the 1-year risk of CIED infection was low (0.43%, 95% CI 0.21–0.79%). Our results agree with a recent prospective single-center study using a real-world cohort (median age 77 years, median PADIT score 2 [IQR, 2–4]) which demonstrated a 1-year risk of CIED infection requiring hospitalization of 0.36% (18). Thus, it seems that strict adherence to preventive measures may result in CIED infection rates well below 1% in an all-comer population.

4.2. Identification of the high-risk patient

The WRAP-IT study demonstrated that an absorbable antibiotic envelope (TYRX™, Medtronic, MN, USA) reduced the risk of major CIED infection by 40% in high-risk patients (11). It is important to realize that immunocompromised patients, patients with previous CIED infection, and hemodialysis patients were excluded in WRAP-IT. Cost-effectiveness studies in the USA and European health care systems demonstrated that the antibiotic envelope was cost-effective when the standard-of-care infection risk was ≥ 1.0% (12) or when the PADIT score was ≥ 6 (7). The 2019 EHRA international consensus document recommends an antibiotic envelope in patients aligned with the WRAP-IT study population or other high-risk factors, in the context of the local incidence of CIED infections (16). This last aspect is important to note because different centers have different standard-of-care infection rates depending on their patient populations and local preventive measures. Risk stratification with risk score calculators could play a useful role by providing an objective way to identify high-risk patients (14,19,20). Such a calculator should be easy to use and be readily available for widespread adoption in clinical practice. We

chose the PADIT score calculator (14), as this score has been validated in several independent cohorts supporting the generalizability of its use with a C-statistic ranging between 0.63 and 0.76 (3,21,22). Besides the US Health claims database study, the number of patients in these validation cohorts ranged from 1000 to 2675 patients. In our study population (n = 2333), the PADIT score also provided good discriminative ability with a C-statistic of 0.70. Patients with a PADIT score of ≥ 7 comprised 17.4% of our study population and had a 1-year standard-of-care infection rate of 1.23%. This infection rate (≥ 1%) seems to justify an antibiotic envelope based on cost-effectiveness studies (12).

4.3. Clinical implications

The different cost-effectiveness studies evaluating incremental cost-effectiveness ratios of the TYRX™ envelope used different costs of the antibacterial envelope depending on the specific country (USA, $669; Germany, €945; Italy, €945; England, £800) (7,12). Currently, there is no reimbursement for the antibacterial envelope in the Netherlands. Almost half of our study population fulfilled the inclusion criteria for WRAP-IT; however, the 1-year standard-of-care infection rate was < 0.5% in this specific cohort. This renders the use of an antibacterial envelope less cost-effective for our patient population based on WRAP-IT inclusion criteria. Restricting the use of antibacterial envelopes to high-risk patients according to the PADIT score (≥ 7) will be more cost-effective in our tertiary center because less than 20% of the patients will require an antibacterial envelope. Prospective randomized data should evaluate whether patient selection for an antibacterial envelope based on a high PADIT score (including clinical and procedural factors) is more cost-effective in comparison to using the eligibility criteria for WRAP-IT (mainly based on type of procedure).

4.4. Study limitations

The present study has the known limitations inherent to a retrospective study design. Despite the retrospective study design, the variables needed for the PADIT calculator were readily available from the medical records. Furthermore, the primary endpoint comprised hospitalization for CIED infection which is an event that is usually well documented. The fact that our center is a regional endocarditis and lead extraction tertiary referral center reduces the risk of missing a clinically relevant endpoint. We did not focus on minor CIED infections not requiring hospitalization; this may explain

the discrepancy in infection rates with other studies. Considering the single-center design and low number of events, the results of our study should be interpreted with caution, and larger prospective studies are warranted.

5. Conclusions

When using strict preventive measures, the risk of CIED infection can be relatively low. The PADIT-score had a good discriminative value in our study population for identifying patients at high risk for CIED infections. In our real-world all-comers cohort, a PADIT-score of ≥7 identified a high-risk population in which an antibacterial envelope may be cost-effective considering a standard-of-care infection rate of >1%. However, randomized trials are needed to evaluate whether the strategy of using an antibacterial envelope only in patients with a high PADIT score is beneficial and cost-effective.

Funding

None.

Ethics declarations

The Medical Ethics Committee reviewed the study (MEC-2020–0299), and this retrospective single-center study was not subjected to the Dutch Medical Research Involving Human Subjects Act. The study was carried out according to the ethical principles for medical research involving human subjects established by Declaration of Helsinki, protecting the privacy of all the participants and the confidentiality of their personal information.

Conflicts of interest

SCY is a consultant for Boston Scientific and has received institutional research grants and speaker fees from Medtronic, Boston Scientific and Biotronik. TST has received institutional research grants from Abbott, Biosense Webster, Acutus Medical, Stereotaxis and Catheter Precision. TST had received consultancy and speaker fees from Ablacon, Acutus Medical and Stereotaxis until 2022. The other authors report no conflicts of interest related to the subject of this manuscript.

Acknowledgements

None.

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Tables

Table 1 – Patient and procedural characteristics

Characteristic	Total (n=2333)
Age (years)	61.6 ± 16.3
Male sex	1505 (64.5)
Body mass index	23.4 ± 4.5
PADIT score	4 (2 – 6)
Medical history	
- Chronic heart failure	1028 (44.1)
- Non-ischemic cardiomyopathy	680 (29.1)
- Ischemic cardiomyopathy	497 (21.3)
- History of atrial fibrillation	819 (35.1)
- Coronary artery disease	847 (36.3)
- CKD stage III to V (eGFR <60 mL/min)	714 (30.6)
- CKD stage IV to V (eGFR <30 mL/min)	126 (5.4)
- eGFR (mL/min)	69 ± 24
- Hypertension	773 (33.1)
- Diabetes mellitus	415 (17.8)
- COPD	211 (9.0)
- History of stroke	196 (8.4)
- History of transient ischemic attack	171 (7.3)
- Peripheral artery disease	155 (6.6)
- History of bleeding	119 (5.1)
- Mechanical heart valve	113 (4.8)
- History of CIED infection	40 (1.7)
- Immunocompromised	127 (5.4)
Antithrombotic therapy	
- Vitamin K antagonist	871 (37.3)
- Antiplatelet agent	729 (31.2)
- Direct acting oral anticoagulant	355 (15.2)
Type of procedure	
- New pacemaker (excluding CRT)	548 (23.5)
- New transvenous ICD (excluding CRT)	436 (18.7)
- New subcutaneous ICD	178 (7.6)
- New CRT pacemaker	54 (2.3)
- New CRT defibrillator*	136 (5.8)
- Pacemaker generator replacement (excluding CRT)*	135 (5.8)
- ICD generator replacement (excluding CRT)*	380 (16.3)
- CRT generator replacement*	198 (8.5)
- Revision or upgrade procedure*	268 (11.5)
- Subpectoral position	148 (6.3)
Fellow participation in procedure	1238 (53.1)
Procedure duration (min), median (IQR)	60 (40 - 84)

Data depicted as (n, %), mean ± standard deviation, or median (IQR). Abbreviations: ACEI = angiotensin converting enzyme inhibitor; ARB = angiotensin receptor blocker; CIED = cardiac implantable electronic device; CKD = chronic kidney disease; COPD = chronic obstructive pulmonary disease; CRT = cardiac resynchronization therapy; eGFR = estimated glomerular filtration rate; ICD = implantable cardioverter-defibrillator. * Potential WRAP-IT candidate.

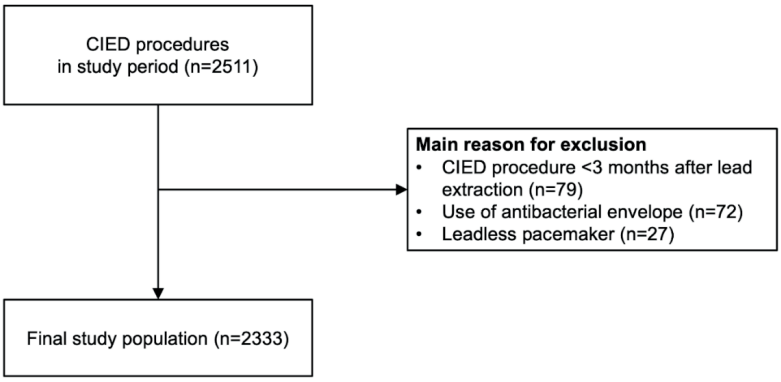
Table 2 – Details of CIED infection requiring hospitalization.

Case	Age/ sex	PADIT-score	Index procedure	CIED infection	Timing (days after procedure)	Causative pathogen	Management
1	45/ F	5	Pacemaker implantation	Pocket infection	4	-	Complete system removal, cefuroxime iv, reimplantation single chamber pacemaker contralateral side
2	34 / F	7	ICD generator change (no CRT)	Pocket infection	13	*CNS*	Complete system removal with TLE, flucloxacillin iv, reimplantation subcutaneous ICD
3	65 / F	4	ICD implantation	Pocket infection	20	*S. aureus*	Clindamycin oral, pocket revision with Tyrx envelope
4	69/ M	9	CRT-D generator change	Pocket infection	21	*S. epidermidis*	Complete system removal with TLE, no antibiotics, no reimplantation due to LVEF 49%
5	55/ M	4	ICD implantation	Systemic CIED infection	24	*S. aureus*	Complete system removal, flucloxacillin iv, reimplantation dual chamber ICD after antibiotic treatment
6	42 / F	2	Pacemaker implantation	Systemic CIED infection	29	*S. aureus*	Complete system removal, flucloxacillin iv, reimplantation dual chamber pacemaker contralateral side
7	72/ M	8	CRT-D generator change	Pocket infection	31	*S. aureus*	Complete system removal with TLE, flucloxacillin oral, reimplantation CRT-D with antibiotic envelope contralateral side
8	19/ M	4	ICD implantation	Pocket infection	33	*K. variicola*	Complete system removal, no antibiotics, reimplantation dual chamber ICD contralateral side
9	65 / F	7	ICD generator change (no CRT)	Systemic CIED infection	146	*E. faecalis*	Complete system removal with TLE, amoxicillin iv, ceftriaxone iv, reimplantation subcutaneous ICD
10	65/ M	9	Upgrade to ICD	Systemic CIED infection	260	*E. faecalis*	Complete system removal with TLE, vancomycin iv, no reimplantation due to improved systolic left ventricular function

Cases are ordered based on timing of hospitalization for CIED infection. *Abbreviations*: AB = antibiotic therapy; CIED = cardiac implantable electronic device; CNS = coagulase-negative staphylococci; TLE = transvenous lead extraction.

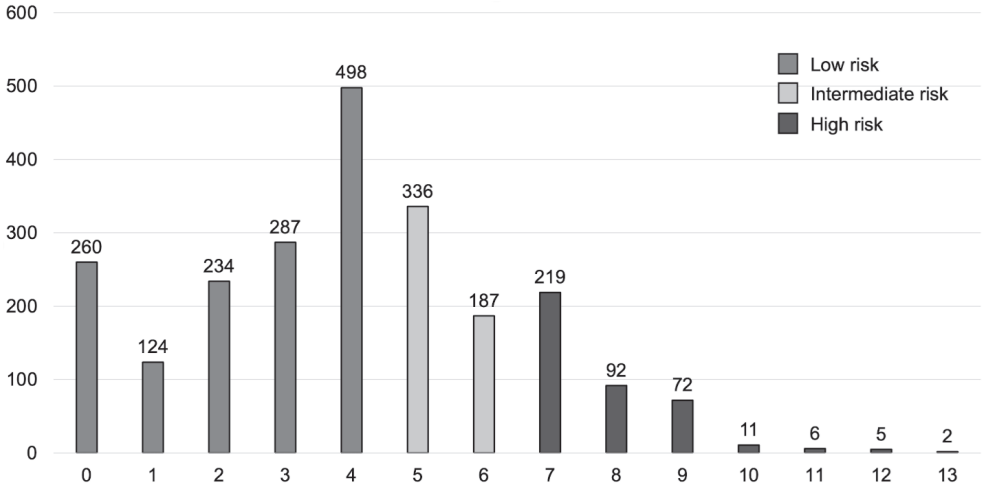
Figures

Figure 1. Flow chart study population



Abbreviations: CIED= cardiac implantable electronic device.

Figure 2. Distribution of PADIT score in the study population.



PADIT-score classified as low (≤4), intermediate (5-6), or high risk (≥7) in accordance with the original paper by Birnie et al. (14).

Part II Evaluation of complications in device therapy

Efficacy and safety of transvenous lead extraction using a liberal combined superior and femoral approach

The main indications for TLE were lead malfunction (67.0%), isolated pocket infection (17.0%) and systemic infection (11.7%)

The major and minor procedure-related complication rates were 1.1% and 10.2%

An effective and safe TLE procedure can be achieved by using both a superior and femoral approach

Fig. 1 Schematic overview of the combined lead vein entry site and femoral approach

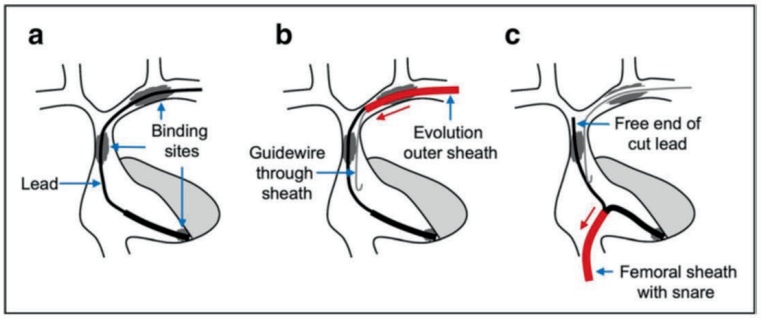
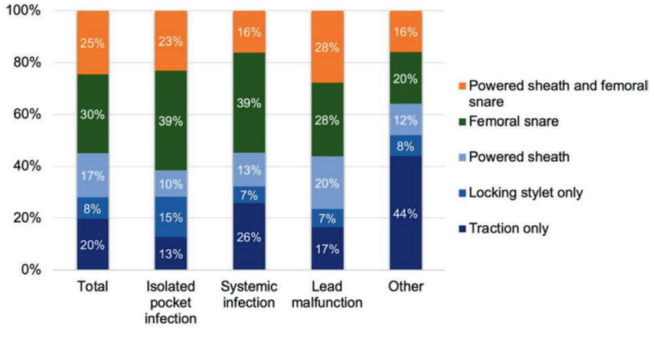


Fig. 2 Technique of lead removal for the total group and per indication group



CHAPTER 7

Efficacy and safety of transvenous lead extraction using a liberal combined superior and femoral approach

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J Interv Card Electrophysiol. 2021 Nov, 62(2), p. 239-248, doi: 10.1007/s10840-020-00889-6

Abstract

Purpose: During transvenous lead extraction (TLE), the femoral snare has mainly been used as a bail-out procedure. The purpose of the present study is to evaluate the efficacy and safety of a TLE approach with a low threshold to use a combined superior and femoral approach.

Methods: This is a single-center observational study including all TLE procedures between 2012 till 2019.

Results: A total of 264 procedures (median age 63 (51–71) years, 67.0% male) were performed in the study period. The main indications for TLE were lead malfunction (67.0%), isolated pocket infection (17.0%) and systemic infection (11.7%). The median dwelling time of the oldest targeted lead was 6.8 (4.0–9.7) years. The techniques used to perform the procedure were the use of a femoral snare only (30%), combined rotational powered sheath and femoral snare (25%), manual traction only (20%), rotational powered sheath only (17%) and locking stylet only (8%). The complete and clinical procedural success rate was 90.2% and 97.7%, respectively, and complete lead removal rate was 94.1%of all targeted leads. The major and minor procedure-related complication rates were 1.1% and 10.2%, respectively. There was one case (0.4%) of emergent sternotomy for management of cardiac avulsion. Furthermore, there were 5 in-hospital non-procedure-related deaths (1.9%), of whom 4 were related to septic shock due to a Staphylococcus aureus endocarditis after an uncomplicated TLE with complete removal of all leads.

Conclusion: An effective and safe TLE procedure can be achieved by using the synergy between a superior and femoral approach.

1. Introduction

Transvenous lead extraction (TLE) is a technically complex procedure for the removal of indwelling leads and may be associated with serious complications including venous or cardiac perforation requiring emergency surgery. Cardiac implantable electronic device (CIED)-related infections and lead failures are important reasons for TLE. Despite the complexity of the procedure, TLE can be performed successfully using several approaches and tools, including simple manual traction, locking stylets, telescopic sheaths, femoral snares, mechanical powered sheaths and laser sheaths (1–4). Previous studies have shown that adding femoral snaring (bail-out) to a superior approach increases the complete procedural success rate (5–8). Some centers prefer femoral snaring as the primary approach with a complete procedural success rate of 94% in experienced centers (9, 10). However, the femoral approach has been associated with a higher complication and failure rate in comparison to other techniques in the ELECTRa prospective registry (11). The higher failure rate with the femoral approach in this registry may be biased as the femoral approach is usually used after failure of a superior approach in difficult cases.

Instead of using the femoral snare tool as a bail-out procedure or as a primary approach, we adopted an approach where we used a low threshold to use a femoral snare or a combined superior and femoral approach in order to maximize the complete procedural success rate and to minimize complications. The rational of this approach is to free the lead from encapsulating fibrous or calcified tissue in the axillary-subclavian-brachiocephalic veins with a powered sheath (if necessary); to avoid mechanical dissection with the powered sheath in the superior vena cava (SVC) area to prevent SVC laceration; and to use the benefits of indirect traction (traction applied from an inferior approach) with the femoral snare. The aim of the current study was to assess the efficacy and safety of our approach.

2. Methods

2.1 Study population

Using our prospective registry, all TLE procedures in the Erasmus MC (Rotterdam, the Netherlands) between January 2012 till Dec 2019 were evaluated. In the case of CIED related infection, there was a strong recommendation for early complete device and lead removal. In other cases, the decision to perform a TLE was made on a case-by-case basis after careful discussion with the patient integrating lead (e.g. recall lead, dwell time), procedural (e.g. risk of lead abandonment versus lead extraction) and patient characteristics (e.g. age, comorbidities, pacemaker [PM] dependency, patient preference). The institutional review board of the Erasmus MC approved this study.

2.2 Patient preparation

All TLE procedures were performed in a cardiac catheterization laboratory or hybrid operating room by an experienced lead extraction team, consisting of at least 2 cardiologists, with immediate availability of cardiothoracic surgical backup. Most procedures took place under general anesthesia, unless the operator decided otherwise based on the anticipated procedural complexity considering the lead dwell time, lead characteristics (e.g. dual-coil ICD lead) and patient characteristics. Anticoagulation was interrupted to minimize the risk of bleeding. A preprocedural venography was performed to identify regions of severe venous stenosis or occlusion and adhesion sites. In patients under general anesthesia, a preprocedural transesophageal echocardiogram was performed to gain information on lead adhesions, vegetations and pre-existing pericardial effusion. The transesophageal echocardiography probe was left in situ to monitor the presence of pericardial effusion during the procedure. Sterile drapings were applied considering the possibility for access for contralateral implantation, emergent pericardiocentesis, thoracentesis, thoracotomy, sternotomy or cardiopulmonary bypass. All patients received invasive hemodynamic monitoring with a radial arterial line. Four units of packed red blood cells were readily available. A “time-out” procedure was performed to prepare the team for the approach of TLE, need for reimplant at the time of extraction, plans for retaining vascular access in case of reimplant and occluded

veins and need for temporary pacing. In pacing-dependent patients, a temporary pacing wire was inserted from the femoral or jugular vein.

2.3 Lead extraction approach

In general, we used a stepwise approach for TLE. A horizontal incision was made to permit easy access to the venous entry site. Tissue debridement was performed, especially in patients with pocket infection, and leads were dissected free to their venous entry site with removal of the anchor sleeves. If reimplantation was planned, then ipsilateral venous access was gained and guidewire(s) passed into the SVC if the vein was not occluded. If present, the active-fixation mechanism was retracted, and manual traction was attempted with a standard stylet in place. If lead removal with manual traction was unsuccessful, the lead was cut and a Liberator Beacon tip locking stylet (Cook Medical, Bloomington, IN, USA) and One-Tie Compression Coil (Cook Medical) were placed. The Liberator locking stylet provides focal traction at the tip of the lead and stabilizes the lead. The One-Tie device binds the proximal lead components and locking stylet together.

When lead removal with a locking stylet was still unsuccessful, we either proceeded with a mechanical powered sheath or a femoral snare. If resistance was encountered in the superior veins, a mechanical powered sheath was used to dissect the lead from encapsulating fibrous tissue at proximal binding sites (Fig. 1). If no superior binding sites were encountered and venous access could be established in the case of a reimplantation, then a femoral snare was directly used (without the need for a powered sheath).

The rotational mechanism of the hand-powered sheath (11F/13F Evolution and 9F/11F Evolution Shortie, from 2013: Evolution RL and Evolution Shortie RL, Cook Medical) permits movement along the lead body by cutting fibrous or even calcified tissue using the stainless-steel spiral cut dissection tip. The outer telescoping polymer sheath protects the venous wall from the metal cutting tip while advancing over the lead in tracts free from adhesions. In case of occluded superior veins and the need for reimplantation, we placed a guidewire through the outer sheath after creating a path through the adhesions in the superior veins (Fig. 1b). We avoided mechanical dissection in the area of the SVC to prevent SVC laceration, unless there was a dual-coil shock lead with dense fibrotic adhesions.

If careful continuous steady direct traction fails to extract the lead from the lead vein entry site after freeing the lead from superior binding sites, a Needle's Eye snare (Cook Medical) was used to extract the lead (Fig. 1c). Thus, we usually do not advance the Evolution sheath up to the tip of the lead. The Needle's Eye snare has a double loop design which can be used to grasp free-floating lead extremities or the lead body. The 16F Introducer Sheath may not be large enough to accommodate a doubled-up ICD lead, depending on the location of snaring. When necessary, the proximal end of the lead was pulled down to the IVC and the free-floating end was grasped to avoid this issue. Sometimes a simultaneous hybrid superior and femoral approach was used to facilitate extraction and maintenance of vascular access where femoral snaring of the lead stabilizes the lead in order to perform mechanical powered dissection to free the lead and gain vascular access (12).

The timing of device re-implantation, if needed, depended on the indication for TLE, need for ongoing CIED therapy and the complexity of the TLE procedure. Usually, if TLE was performed for lead malfunction, CIED re-implantation was performed during the same procedure. In patients with TLE for CIED-related infection, device re-implantation on the contralateral side was postponed until blood cultures were negative for at least 72 h. In PM-dependent patients with CIED infection, a temporary right ventricular bipolar active fixation lead was implanted through the right jugular vein. The lead was sutured to the patient's skin with non-resorbable sutures and the lead was connected to a PM generator.

2.4 Definitions

Definitions for procedural approach, techniques, outcomes and complications follow current expert consensus statements (1–3). Most definitions were initially based on the 2009 HRS expert consensus document on TLE (3); later expert consensus documents refined the definition of the size of portion of the lead that could be retained to be considered a clinical success (1, 2). Complete procedural success was defined as removal of all targeted leads and all lead material from the vascular space, with the absence of any permanently disabling complication or procedure-related death. Clinical success was defined as removal of all targeted leads and lead material from the vascular space or retention of a small portion of the lead (<4 cm) that does not negatively impact the outcome goals of the procedure. A TLE

procedure was considered a failure if complete procedural success or clinical success could not be achieved, or if any permanently disabling complication or procedure-related death occurred.

A major complication was defined as any outcome related to the procedure which is life-threatening or results in death. In addition, any unexpected event that causes persistent or significant disability, or any event that requires significant surgical intervention to prevent any of the outcomes listed above is regarded as a major complication. Minor complications are defined as any undesired event related to the procedure that requires medical intervention or minor procedural intervention to remedy, and does not limit persistently or significantly the patient's function, nor does it threaten life or cause death.

2.5 Statistical analysis

Continuous data are presented as mean ± standard deviation if the data were normally distributed, or as median with interquartile range (25th and 75th percentile) otherwise. Categorical variables are presented by frequencies and percentages. Differences of continuous variables between two groups were analyzed with the unpaired Student's t test or the Mann-Whitney U test, as appropriate. Differences between categorical variables were evaluated using the Chi-square test or the Fisher's exact test in case of small expected cell frequencies. Statistical analyses were performed using SPSS V.25.0. All statistical tests were two-sided. P values <0.05 were considered statistically significant.

3. Results

3.1 Study population

A total of 264 TLE procedures were performed in the study period. Baseline patient characteristics are presented in Table 1. The median age was 63 (51–71) years and the majority were men (67.0%). Approximately one-fifth (20.8%) of the population had a previous cardiac surgery. The main indications for TLE were lead malfunction (67.0%), isolated pocket infection/erosion (17.0%) and CIED-related systemic infection (11.7%). The median dwelling time of the oldest targeted lead was 6.8 (4.0–9.7) years.

In case of lead malfunction, the dysfunctional lead usually comprised an ICD lead (62.1%), followed by an atrial lead (18.6%), right ventricular lead (13.6%) and coronary sinus lead (5.6%). Among 110 dysfunctional ICD leads, the three most common types were Biotronik Linox leads (33.6%), St. Jude Medical Riata leads (30.0%) and St. Jude Medical Durata leads (10.9%).

In 31 patients with CIED-related systemic infection, the most common isolated pathogen was Staphylococcus aureus (48.4%). Other pathogens were coagulase-negative staphylococci (12.9%), aerobic Gram-positive non-staphylococci (12.9%), Gram-negative bacilli (12.9%), anaerobes (3.2%) and Mycobacterium species (3.2%). Two patients with a CIED-related systemic infection had negative blood cultures.

3.2 Procedural outcome

An overview of procedural details is presented in Table 2. Most procedures were performed under general anesthesia. The three most common techniques used to perform the procedure were the use of a femoral snare as a primary tool (30%), combined powered sheath and femoral snare (25%) and traction only (20%) (Fig. 2). Thus, in the majority of the cases (54.5%), a femoral snare was used. The median number of targeted leads were 2 (1–2). The complete procedural success rate and clinical success rate was 90.2% and 97.7%, respectively. Complete lead removal rate was 94.1% of all targeted leads. A detailed overview of the 6 procedural failures is presented in Table 3. An overview of the procedural characteristics and outcome per indication group is presented in Fig. 3.

Patients who underwent TLE with traction only had a higher complete procedural success rate than patients who required an extraction tool (98.1% versus 88.2%, P = 0.03). In contrast, the clinical success rate was similar between patients who underwent TLE with or without extraction tools (97.2% versus 98.1%, respectively, P = 1.00). The median dwelling time of the oldest targeted lead was shorter in patients who underwent TLE with traction only (3.3 [1.6–5.2] versus 7.9 [5.1–10.8] years, P < 0.001). General anesthesia was less often used in procedures were TLE was performed with manual traction only (42.3% versus 88.7%, P < 0.001).

3.3 Complications

An overview of in-hospital complications is presented in Table 4. The major and minor procedure-related complication rates were 1.1% and 10.2%, respectively. There was one case (0.4%) of emergent sternotomy for cardiac avulsion due to TLE. This was a 57-year-old woman with a dual-chamber ICD who had externalization of her Riata 1580 dual-coil shock lead which was in situ for 8 years. An Evolution RL sheath was used to free the lead up to the tricuspid annulus. After this maneuver, the patient became hemodynamic unstable and pericardial effusion was drained percutaneously. After complete removal of the ICD lead using the femoral snare, the patient deteriorated despite the drain and an emergent sternotomy was performed demonstrating laceration of the right atrial wall. She recovered clinically and at her last follow-up 5 years later, she is doing well. An overview of the complication rate per indication group is presented in Fig. 3.

There were no procedure-related deaths; however, there were 5 in-hospital non-procedure-related deaths after TLE (Table 5). Four patients with Staphylococcus aureus CIED related endocarditis died due to septic shock with multi-organ failure after an uncomplicated complete CIED removal. The interval between diagnosis of CIED-related endocarditis and the TLE procedure was 0, 1, 3 and 9 days. The last patient was presented late to our hospital. Patients who required TLE for a systemic infection had a higher risk of in-hospital nonprocedural-related death in comparison to patients with another indication (12.9% versus 0.4%, P = 0.001).

4. Discussion

In this study, we evaluated the efficacy and safety of a liberal combined superior and femoral approach for TLE procedures. This approach was associated with a high complete and clinical success rate and a low major complication rate. There were no procedure-related deaths.

4.1 Individualized approach to TLE

TLE has become an integral part of PM and ICD lead management. The number of TLE procedures has increased over the years as a consequence of an increase in CIED implantations, increasing rate of infections, lead failure, and development of extraction tools (2, 13). An individualized approach is paramount with respect to

indication, TLE technique and peri and post-procedural care for patients undergoing TLE. In clinical practice, a wide spectrum of tools and techniques are used ranging from simple manual traction to combined approaches including powered sheaths and snare tools (11). In general, the goal of TLE is to achieve the highest clinical success rate with a low complication rate. The most important risk of lead removal includes venous or cardiac perforation requiring emergency surgery. This risk depends on multiple patient and lead related factors, including the lead dwelling time, lead properties (presence of defibrillator coils, active or passive leads), lead tip location and the presence of prior sternotomy. Although outcomes of TLE has improved as a result of technological advancements in extraction tools, experienced operators and high-volume centers are essential to achieve an optimal TLE outcome (11, 14, 15).

4.2 Role of femoral snaring

Most centers perform a stepwise TLE approach where femoral snaring is used as a bail-out procedure when previous methods have failed (4, 7, 16). Several single-center studies have shown that adding femoral snaring to a superior approach increases clinical success by approximately 10% (5, 6, 8). Femoral snaring seems especially useful for older leads and leads with passive fixation which are more prone to fracture (5, 6). Instead of using femoral snaring as a bail-out procedure, a few single-center studies have demonstrated a high complete procedural success rate (94%) when femoral snaring is used as the primary approach (9, 10). In these experienced centers, the rate of cardiac tamponade requiring surgical intervention ranged from 0.6 to 0.9%. It is important to note that in these two studies, the proportion of extracted ICD leads was relatively low (0% to 4%) (9, 10), which may positively bias their results as ICD lead removal is known to be associated with a higher risk of major complications (15). In a European multicenter prospective registry (n = 3510), a femoral approach was associated with a higher rate of procedure-related major complications (4.1%), either as primary (9.1%) or secondary (3.5%) approach, compared with other approaches (1.4%) (11). In addition, the femoral approach was associated with a higher clinical failure rate (odds ratio 3.9) (11). The higher clinical failure rate may be biased as the femoral approach is usually used as a bail-out procedure in difficult cases. Thus, there is some discrepancy with regard to the procedural outcome of femoral snaring depending of its use as a bail-out procedure or as a primary approach.

4.3 Liberal combined superior and femoral approach

Instead of using femoral snaring as a primary approach or as a bail-out tool, we adopted a novel approach where we used a liberal combined superior and femoral approach or femoral approach only. Major advantages of this approach are (1) maintaining superior venous access in contrast to a strictly femoral approach in case of occluded veins; (2) reducing the resistance on the proximal lead when pulling the lead down from the femoral workstation after freeing the lead from the superior binding sites; (3) avoiding hemodynamic instability by failure of the lead to return to its original position (slippage of lead body through binding site) after direct traction from the vein entry site; and (4) avoiding risk of SVC laceration in contrast to a strictly superior approach (17, 18). These advantages are especially relevant in case of occluded superior veins. Complete venous occlusion occurs relatively frequently (approximately 10%) after CIED implantation (19), and especially in patients undergoing TLE for device infection (up to 32%) (20). The complete procedural success rate and clinical success rate in our study was 90.2% and 97.7%, respectively, and complete extraction was achieved for 94.1% of leads (complete lead removal rate).

There was one case (0.4%) of cardiac avulsion requiring emergent surgery, highlighting the relative safety of this approach. This cardiac avulsion occurred in a patient where we had to dissect the dual-coil ICD lead from the SVC using the powered sheath. Despite the use of traction from above to provide a tight “rail”, there was probably an unfavourable sheath-SVC wall geometric relationship creating a RA laceration. Freeing dual-coil ICD leads from severe SVC binding sites may be challenging. For these cases, Schaller et al. have described an interesting technique to reduce the risk of SVC injury by using simultaneous lead traction from above and below (with a femoral snare) during advancement of a powered sheath (21). Simultaneous traction results in increased separation and a more parallel alignment of the lead and SVC wall, allowing the sheath to be better oriented in the desired lead-vein cleavage plane.

The results of our liberal combined superior and femoral approach are in agreement with the outcomes of high-volume centers (≥ 30 TLE procedures/year) in the ELECTRa registry (TLE procedures between 2012 and 2014) with regard to clinical

success rate (97.3%, 95% confidence interval [CI] 96.6–97.8%), complete lead removal rate (96.2%, 95% CI 95.6–96.7%), in-hospital procedure-related major complications (1.5%, 95% CI 1.1–2.0%) and in-hospital procedure-related death (0.4%, 95% CI 0.2–0.7%) (11). In contrast, our median procedure time was higher than in the ELECTRa registry (102 versus 83 min). This may be related to the relative higher proportion of patients with lead malfunction as these patients require CIED reimplantation during the same procedure (Fig. 3).

Our TLE outcome was also comparable to a recently published European registry, the PROMET (Patient-Related Outcomes of Mechanical lead Extraction Techniques) study, which was focused on the use of rotational TLE tools in 6 high-volume centers (22). In the PROMET study, clinical success was obtained in 97.0% of procedures (present study 97.7%), and complete lead removal was achieved in 96.5% of targeted leads (present study 94.1%). Whether a liberal combined approach is cost-effective should be further investigated.

Despite similarities in TLE outcomes with 2 large European registries, certain centers have demonstrated a higher complete procedural and clinical success rate (23). We report our single-center experience with TLE tools from Cook Medical. Perhaps the availability of a wider range of TLE tools (e.g. TightRail, laser sheath) may further improve our TLE results but this should be evaluated.

4.4 Study limitations

This was an observational study without a control group. Therefore, it is difficult to draw firm conclusions whether this approach is better than other techniques. Considering the stepwise approach, selection bias is an issue when comparing the different techniques (superior of femoral approach only versus combined approach) in our study population. In the field of TLE, there is a paucity of randomized controlled trials with regard to comparison between different techniques. Nevertheless, the use of standard definitions of TLE outcome and complications ensures reliable comparison to TLE studies. Finally, the single-center design impacts the generalizability of the data.

5. Conclusions

An effective and safe TLE procedure can be achieved by using a stepwise approach with a low threshold to use a combined superior and femoral approach. Thus, instead of using the femoral snare as a last resort, the use of the synergy between a superior and femoral approach may optimize the results of TLE.

Compliance with ethical standards

Conflicts of interest The authors declare that they have no conflicts of interest.

Ethics approval The Medical Ethics Committee of the Erasmus MC reviewed the study (MEC-2018-1152), and this study was not subjected to the Dutch Medical Research Involving Human Subjects Act. The study was carried out according to the ethical principles for medical research involving human subjects established by Declaration of Helsinki, protecting the privacy of all the participants and the confidentiality of their personal information.

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Tables and Figures

Table 1 Baseline characteristics

	N=264
Demographics	
- Age (years), median (IQR)	63 (51–71)
- Male gender	177 (67.0%)
Medical history	
- Coronary artery disease	87 (33.0%)
- Hypertension	65 (24.6%)
- Prior cardiac surgery	55 (20.8%)
- Diabetes mellitus	49 (18.6%)
- Chronic kidney disease (GFR < 45 ml/min)	42 (15.9%)
- Peripheral artery disease	5 (1.9%)
Antithrombotic agents	
- Vitamin K antagonist	108 (40.9%)
- Antiplatelet agent	73 (27.7%)
- NOAC	20 (7.6%)
Device type	
- PM	106 (40.2%)
○ Single-chamber PM[a]	15 (5.7%)
○ Dual-chamber PM	85 (32.2%)
○ Biventricular PM	6 (2.3%)
- ICD	158 (59.8%)
○ Single-chamber ICD[b]	60 (22.7%)
○ Dual-chamber ICD	45 (17.0%)
○ Biventricular ICD	53 (20.1%)
Indications	
- CIED-related infection	70 (26.5%)
○ Isolated pocket infection/erosion	39 (14.8%)
○ Systemic infection	31 (11.7%)
- No CIED-related infection	194 (73.5%)
○ Lead malfunction	169 (64.0%)
○ Other indication[c]	25 (9.5%)
Dwelling time oldest targeted lead (years), median (IQR)	6.8 (4.0–9.7)

Data are presented as number (percentages), unless stated otherwise. CIED cardiac implantable electronic device, ICD implantable cardioverter defibrillator, NOAC non-vitamin K oral anticoagulation, PM pacemaker, TLE transvenous lead extraction

[a] Including 3 VDD pacemakers
[b] Including 2 VDD ICDs
[c] Including 18 upgrade procedures

Table 2 Procedural details and outcome

	N=264
General anesthesia	210 (79.5%)
Extraction tool used:[a]	
- Locking stylet	156 (59.1%)
- Powered sheath	112 (42.4%)
- Femoral snare	144 (54.5%)
Procedure time (min), median (IQR)	102 (70–140)
Fluoroscopy time (min), median (IQR)	12 (7–22)
Leads extracted per case, median (IQR)	2 (1–2)
Procedural outcome	
- Complete procedural success	238 (90.2%)
- Clinical success	258 (97.7%)
- Failure	6 (2.3%)
Reimplantation CIED during same hospital admission	193 (73.1%)
Duration of hospital stay (days), median (IQR)	4 (3–5)
Radiological lead outcome[b]	
- All leads (N = 477)	94.1%/4.8%/1.0%
- RA lead (N = 158)	96.8%/2.5%/0.6%
- RV lead (N = 101)	92.1%/6.9%/1.0%
- CS lead (N = 42)	90.5%/9.5%/0%
- ICD lead (N = 152)	94.7%/3.9%/1.3%
○ Single coil lead (N = 111)[c]	93.7%/5.4%/0.9%
○ Dual coil lead (N = 41)[c]	97.6%/0%/2.4%
- Abandoned RA lead (N = 7)	100%/0%/0%
- Abandoned RV lead (N = 10)	100%/0%/0%
- Abandoned LV lead (N = 1)	0%/100%/0%
- Abandoned ICD lead (N = 6)	66.7%/16.7%/16.7%

Data are presented as n (%), unless stated otherwise. CIED cardiac implantable electrical device, CS coronary sinus, ICD implantable cardioverter-defibrillator, RA right atrial, RV right ventricular, TLE transvenous lead extraction

[a] Different extraction tools could be used in one procedure

[b] Percentages denote complete radiological success, partial radiological success (< 4 cm residual lead portion), and failure, respectively

[c] There was no difference in radiological outcome between single and dual-coil ICD leads (P = 0.25)

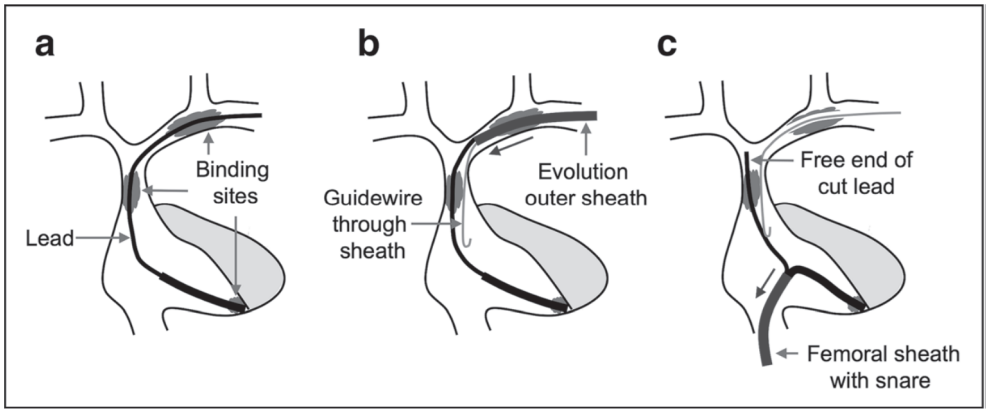

Fig. 1 Schematic overview of the combined lead vein entry site and femoral approach. a The axillary-subclavian-brachiocephalic veins usually contains the most abundant and resistant encapsulating tissue. b In the case of thrombosis of the superior veins or excessive fibrosis, dissection of encapsulating tissue using the Evolution RL or Evolution Shortie RL (CookMedical, Bloomington, IN, USA) was performed. The powered sheath was advanced over the lead body using counterpressure and countertraction. To reinforce the lead and reduce the risk of lead disruption, the lead was prepared with a Liberator locking stylet (Cook Medical, Bloomington, IN, USA) and One-Tie compression coil (Cook Medical, Bloomington, IN, USA). If needed, a guidewire can be placed through the sheath for maintaining venous access. Mechanical dissection in the SVC area was avoided if possible. c Removal of the lead by the femoral work station using a Needle's Eye Snare (Cook Medical, Bloomington, IN, USA). The 16F outer femoral sheath can be used to perform counterpressure and countertraction. The proximal free end of the cut lead can be pulled down through binding sites in the superior vena cava area

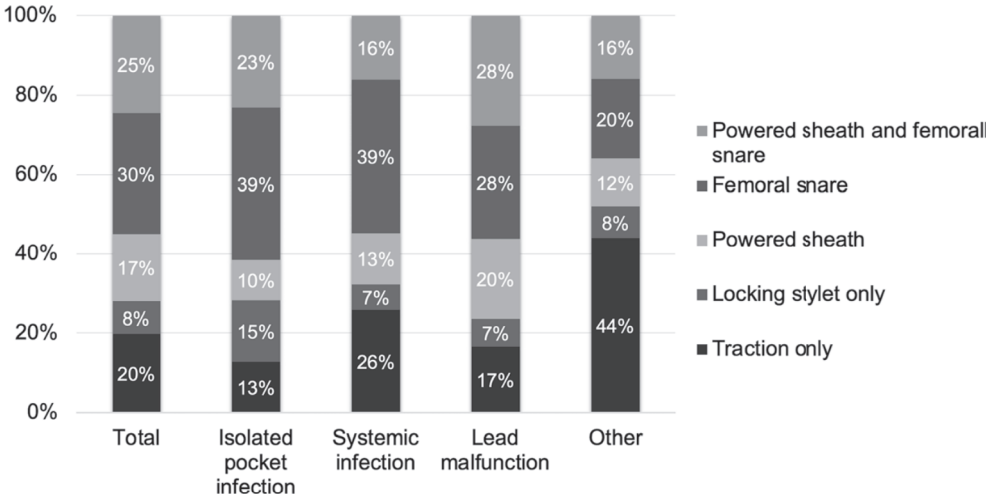

Fig. 2 Technique of lead removal for the total group and per indication group. There was a trend towards a relationship between groups with regard to the TLE technique used (P = 0.06). The use of the combined superior and femoral approach was numerically the highest in the patients undergoing TLE for lead malfunction

Table 3 Detailed overview of procedural failures

Pt.	Age/sex	Indication TLE	Implanted device	Details
1	36/F	VCS syndrome	Biventricular ICD, abandoned ICD lead	Disruption and breakage of abandoned St. Jude Medical Riata 1582 ICD lead (10 years in situ) just proximal to distal coil during indirect traction with snare. Successful SVC stenting.
2	41/M	Upgrade to biventricular ICD	Dual-chamber PM	Wedging and breakage of distal part of Biotronik Solia S ProMRI ventricular lead (2 years in situ) at proximal binding site in subclavian vein during direct traction. No attempt with mechanical sheath as new leads were already in situ.
3	43/M	ICD and LV lead malfunction	Biventricular ICD	Disruption and breakage of Biotronik Linox Smart S65 ICD lead (5 years in situ) just proximal to distal coil during indirect traction with snare.
4	49/F	Fracture of ICD lead	Dual-chamber ICD	Disruption and breakage of Medtronic Sprint Fidelis 6949 ICD lead (10 years in situ) distal to proximal coil during indirect traction with snare (after superior approach with powered mechanical heath failed).
5	62/M	Lead-related endocarditis (S. epidermidis)	Dual-chamber PM	Disruption and breakage of tip (< 1 cm) of atrial lead during countertraction with powered mechanical sheath. Complicated by left-sided ischemic stroke the following day with permanent disability (modified Rankin score 3). Most likely due to paradoxical embolus as the patient was known with patent foramen ovale.
6	70/M	Atrial and LV lead malfunction	Biventricular ICD	Wedging of distal part of Biotronik Setrox S53 atrial lead in subclavian vein. Powered mechanical sheath caused excessive bleeding at venous entry site requiring surgical repair, decided to leave remnant lead in place.

ICD implantable cardioverter-defibrillator, PM pacemaker, SVC superior vena cava, TLE transvenous lead extraction

Table 4 In-hospital complications

	N=264
Procedure-related major complications including deaths	3 (1.1%)
- Stroke[a]	1 (0.4%)
- Cardiac avulsion requiring surgery	1 (0.4%)
- Coronary sinus perforation during reimplantation requiring surgery	1 (0.4%)
Non-procedure-related major complications including deaths	5 (1.9%)
- Death	5 (1.9%)
- Sepsis	4 (1.5%)
- Stroke	1 (0.4%)
Procedure-related minor complications	27 (10.2%)
- Pocket hematoma without intervention	9 (3.4%)
- Pneumothorax requiring a chest tube	3 (1.1%)
- Lead dislocation requiring repositioning	3 (1.1%)
- False aneurysm femoral artery requiring intervention	2 (0.8%)
- Pericardial effusion without intervention	2 (0.8%)
- Pulmonary embolism	2 (0.8%)
- Intra-procedural bleeding requiring blood transfusion	2 (0.8%)
- Migrated lead fragment without sequelae	2 (0.8%)
- Vascular repair at venous entry site	1 (0.4%)
- Pocket hematoma requiring surgical intervention	1 (0.4%)
- Air embolism	1 (0.4%)
- Upper extremity thrombosis	1 (0.4%)
Any procedure-related complication	30 (11.4%)

Data are presented as n (%), unless stated otherwise. Different complications could occur in the same patient. [a] This patient is described in Table 3, patient 5

Table 5 Overview of in-hospital non-procedural related deaths

Pt.	Age/sex	Indication TLE	Outcome TLE	Details death
A	55/F	S. aureus endocarditis	Complete removal single-chamber ICD	Septic shock with multiorgan failure 2 days after TLE
B	58/M	S. aureus endocarditis	Complete removal biventricular ICD	Septic shock with multiorgan failure 1 day after TLE
C	61/M	S. aureus endocarditis	Complete removal biventricular ICD	Septic shock with multiorgan failure 2 days after TLE
D	65/M	S. aureus endocarditis	Complete removal dual-chamber ICD	Septic shock with multiorgan failure 21 days after TLE
E	89/F[a]	Isolated pocket infection	Complete removal dual-chamber PM	Ischemic stroke 3 days after TLE, thrombolysis followed by thrombectomy, died 9 days after stroke

ICD, implantable cardioverter-defibrillator, PM pacemaker, TLE transvenous lead extraction
[a] Patient had a prior history of atrial fibrillation and recurrent transient ischemic attack

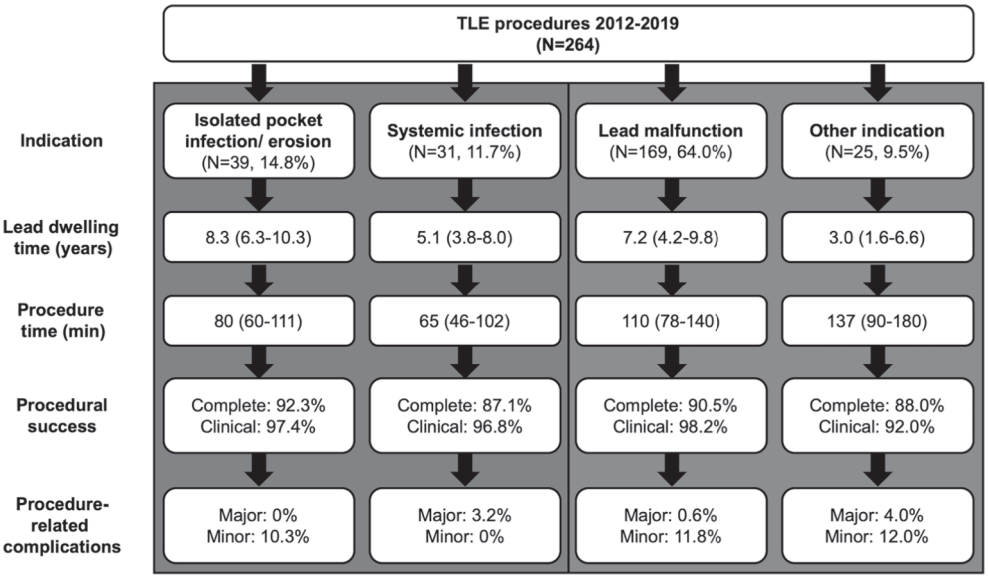

Fig. 3 Detailed overview of outcome per indication. There was a difference between the 4 groups with regard to lead dwelling time ($P < 0.001$) and procedure time ($P < 0.001$). After Bonferroni correction, the lead dwelling time in the group "other indication" was shorter in comparison to both the group "lead malfunction" ($P = 0.002$) and the group "isolated pocket infection/erosion" ($P < 0.001$). After Bonferroni correction, there was a difference in procedure time between all groups except between the groups "isolated pocket infection/erosion" and "systemic infection" ($P = 0.16$), and between the groups "lead malfunction" and "other indication" ($P = 0.08$). There were no statistical differences between groups with regard to procedural success and procedure-related complications

Part III

Patient empowerment:

Use of eHealth as discharge aid

Part III **Patient empowerment:**

Use of eHealth as discharge aid

A quality improvement initiative for patient knowledge comprehension during the discharge procedure using a novel computer-generated patient-tailored discharge document in cardiology

Computer-generated patient-tailored discharge information was equivalent to conventional discharge information

Increased uniformity in discharge information and reduction in preperation time reported

Webtool evaluated as easy to use and time saving

Figure 1 Inclusion strategy

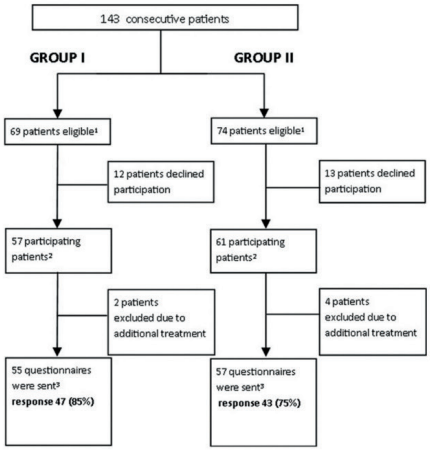

Table 4. Outcome healthcare provider questionnaire.

	Nurses	Nurse practitioners
	n=8	n=3
Overall clarity	8.4 (0.8)	7.7 (0.6)
Time taken		NA
Traditional discharge info		
<5 min	1 (12)	
5–10 min	7 (88)	
>10 min	-	
Personalised discharge info		
<5 min	7 (88)	
5–10 min	1 (12)	
>10 min	-	
Would like to continue personalized discharge info	8 (100)	3 (100)

All data is depicted as mean (SD) or as n (%) where applicable.

CHAPTER 8

A quality improvement initiative for patient knowledge comprehension during the discharge procedure using a novel computer-generated patient-tailored discharge document in cardiology

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Digital Health, 2022 Sept, Volume 8: 1–12,
https://doi.org/10.1177/20552076221129079

Abstract

Objective: The duration of hospital admissions has shortened significantly. This challenges healthcare professionals to provide the necessary information and instructions in a limited time. Patient-tailored discharge information may improve the patient's understanding of the discharge information but may also be time-consuming. The objective of this descriptive quality improvement study was to evaluate patient comprehension of discharge information using a novel computer-generated patient-tailored discharge document.

Methods: A prospective pre-post study comparing patient-tailored discharge information with conventional discharge information, for patients undergoing an electrophysiological procedure during two periods of six weeks between January and March 2016. Group I received conventional discharge information (n = 55). Group II received a computer-generated, patient-tailored discharge document (n = 57). Their comprehension of the discharge information was evaluated using a peer-reviewed questionnaire distributed among patients, comparing groups I and II using Likert scales. Nurses and nurse practitioners evaluated the use of personalized discharge information by means of a short survey.

Results: In terms of discharge information, comprehensibility was equivalent; however, an increase in comprehension was observed in patients seeking a telephone consultation with the cardiology department within one-week post-discharge. A reduction in discharge preparation time and an increased uniformity of discharge information were reported by nurses. Nurse practitioners found the web tool easy to use and time-saving.

Conclusions: In this study, computer-generated patient-tailored discharge information was equivalent to conventional discharge information. A more positive trend was seen for patients who initiated teleconsultation with the hospital within one-week post-discharge. This suggests that for this subgroup the patient-tailored discharge web tool might lead to an improvement in care. However, more research with a larger number of participants is needed to confirm this trend.

1. Introduction and background

Patients require comprehensive information concerning their illness, treatment and daily management, which entails conveying sufficient knowledge to patients by healthcare professionals, with the objective of improving compliance and self-care (1). The current duration of hospital admission has shortened significantly (2), which challenges healthcare professionals to provide the necessary information and instructions. There is only a limited amount of time available to provide instructions, but also the timing is shortly after an invasive procedure in which patients may be less receptive to receiving information (3). The provided instructions should at least cover lifestyle and discharge (aiming at reducing post-procedural complications) since these instructions are important to improve outcomes (4). Poor health literacy can result in delayed treatment of post-procedural complications as the potential postintervention symptoms are not recognized, and thus these patients do not contact a healthcare provider in time (5). Importantly, the older the patient the higher the risk of a knowledge deficit which may consequently result in an increased risk of adverse events (6).

Typically, the essential information is conveyed verbally along with standardized patient discharge information booklets. Although these standardized booklets have been shown to increase patient knowledge retention (7,8), it has been advocated that personalized (patient-tailored) discharge information may further improve patient comprehension (9,10), especially if it is integrated into a patient-tailored discharge procedure (11).

The routine practice for patients undergoing invasive electrophysiological procedures at our center includes a standardized discharge information booklet and nonstructured verbal post-discharge instructions from a healthcare provider (e.g. nurse(-practitioner) and/or medical doctor). In addition, a telephone follow-up, approximately 1-week post-discharge, is included in the clinical practice. During this follow-up, which includes an evaluation of the hospitalization, it was observed that the discharge instructions provided proved unclear for some patients (particularly for adjustment in medication regimen), consequently leading in some cases to increased patient anxiety. This resulted in an initiative to improve the post discharge procedure by providing patient-tailored information in a uniform discharge document created using a dedicated web-based tool.

The aim of this pilot study was to evaluate patient knowledge comprehension prior and post introduction of a novel computer-generated patient-tailored discharge document.

2. Methods

2.1 Study population

The implementation of a novel computer-generated patient-tailored discharge document was evaluated in this prospective pre-post study performed at our center, a tertiary referral University Hospital in an urban area population of 1,015,000 inhabitants. From January to March 2016, all consecutive patients undergoing an invasive percutaneous diagnostic or therapeutic electrophysiological procedure who fulfilled the study criteria were included in this study. Patients were eligible if they were 18 years or older and fluent both in oral and written Dutch. Exclusion criteria were requiring an additional invasive procedure during the same admission or treatment other than a percutaneous electrophysiological procedure. The control group (group I) received standard discharge information and was included during the first six weeks of the study. The study group (group II) received the novel computer generated patient-tailored discharge information and document during the second period of six weeks. In both groups, patient relatives were preferably present when the discharge information was conveyed. One week post-discharge a peer-reviewed questionnaire was sent to both groups to evaluate their retention and comprehension of the provided discharge instructions, the clarity of the medication regimen, the recovery process, and finally the overall evaluation of the discharge procedure. To avoid a potential bias between each group, the usual telephonic follow-up, 1 week after discharge, was not carried out during the timeline of this study. For patients who contacted the cardiology ward seeking aid after the ablation, additional specifics were noted as to the reason for the contact and what was done to assist the patients.

2.2 Discharge information

Group I received the standardized discharge information booklet, as well as general verbal instructions, including the advice to consult the booklet in case of uncertainty concerning possible complications. Group II received the novel patient-tailored discharge information, which included a computer-generated document based on predefined variables (via check-boxes), as illustrated in Figure 1(a). The variables were derived from the analysis of two years of telephone patient follow-up data of 931 patients between 2010 and 2012, including patients discharged after the percutaneous electrophysiological intervention. Also, a small subgroup of 10 patients was surveyed to review an early version of the novel discharge information for lay-out and for the necessity of additional information. Minor alterations were done to the personalized discharge information afterward. The consequences of these various enhancements were that group II received both more specific and for some variables more extensive information than group I.

The variables included clinical and procedural characteristics namely: type of ablation (relevant due to the number and diameter of used catheters), type of percutaneous access (arterial or venous), anticoagulation regimen and postprocedural bleeding or hematoma formation. Additionally, information on discharge medication (and dose), explicitly stating “altered, new or unchanged,” date of the outpatient appointment and whether cardiac rehabilitation is advised, were also provided. If necessary, additional information via free text could be entered. Importantly, a dedicated and secure server within the hospital IT structure was adopted to host the web-based tool. Based on this information, patient-tailored discharge information and instructions, consisting of one or two pages following a predefined format were printed (Figure 1(b)/1(c)). This document was dispensed to patients and used by healthcare providers to convey the discharge information uniformly and clearly, in addition to serving as a reference document for the guidance of patients after discharge.

2.3 Questionnaire

The peer-reviewed questionnaire was based on the analysis of two years of telephone patient follow-up data of 931 patients between 2010 and 2012, including patients discharged after percutaneous electrophysiological intervention. This analysis revealed poor health literacy, poor retention of (provided) information and

associated increased levels of uncertainty among patients. Consequently, a panel of three nurse practitioners, an interventional cardiologist (electrophysiologist) and an epidemiologist developed a questionnaire consisting of 10 questions using a Likert scale from 1 to 10 as depicted in Figure 2. The questionnaire measured the comprehensibility of the given information by reviewing the responses provided. Patients unable to comprehend the written documents were excluded from the study. Therefore, no levels of comprehension are reported.

As well as sending questionnaires to participants, nurses and nurse practitioners received a short questionnaire to evaluate their experiences with the computer-generated patient tailored discharge document. This questionnaire consisted of one Likert scale question, one categorized question, two yes/no questions and three open questions as outlined in Figure 3.

The Medical Ethics Committee of our center reviewed the study and deemed the study was not subject to the Dutch Medical Research Involving Human Subjects Act and hence no formal approval was required. The study was conducted in accordance with the Declaration of Helsinki.(12) All participants provided written consent.

2.4 *Study endpoint*

The primary endpoint was an improvement in comprehension of the discharge information. Secondary endpoints were usability and feasibility as reported by the nurses and nurse practitioners.

2.5 Data collection and analysis

Baseline characteristics were collected from the electronic patient record. The comprehension of the discharge information (control group vs study group) was measured using the Likert scales in the questionnaire, completed one-week post-discharge and compared using the Student's t-test, Pearson's chi-squared test or Mann–Whitney U test, as deemed appropriate.

In addition, the use of computer-generated discharge information was evaluated among nurse(-practitioners).

Continuous data are presented as mean ± SD or median with IQRs and compared between the two groups with the Student's t-test or Mann–Whitney U test, as appropriate. Categorical data are presented as frequencies and percentages and compared with chi-square or the Fisher exact test, as appropriate. Statistical analyses were performed using SPSS software (SPSS, version 25; IBM, Chicago, Illinois).

3. Results

A total of 143 patients were eligible for the participation of whom 31 did not fulfil the study criteria (26 patients did not consent, three patients were excluded due to the need for additional pacemaker implantation or implantable cardiac monitor, and in two patients the procedure was cancelled). As a result, the final study cohort consisted of 112 patients (conventional information, n = 55; patient-tailored information, n = 57) as shown in Figure 4. In 100 patients (89%), patient relatives were present during the discharge session. The patient characteristics were comparable between the two groups (Table 1) and ablation for atrial fibrillation (n = 42, 38%) and atrial flutter (n = 17, 15%) were the most prevalent electrophysiological procedures (Table 2). The mean admission time was 1.9 days (± 0.9).

3.1 Discharge information

A total of 90 questionnaires (80% response) assessing the comprehension of discharge information as reviewed by patients were returned. The overall discharge information scored 8.6 (±1.2) for group I (conventional information) and 8.8 (±1.0) for group II (patient-tailored information) on the 10-point Likert scale, with high scores (>8.5) in all subcategories (Table 3).

Of the patients who contacted the cardiology department within one week after discharge (n=12, 11%), 9 patients returned the questionnaire. In this particular subgroup, the differences between the conventional and patient-tailored discharge information (8.0 (±0.9) vs 9.2 (±1.2)) showed a greater improvement in comprehension, favouring group II. The most important reasons for contacting the cardiology department included groin/leg complaints, palpitations, dizziness, or concerns about the prescribed medication. Seven of these patients (n=3, group I;

n=4, group II) were evaluated at the emergency department, none of whom required a re-admission.

3.2 Survey among healthcare professionals

The survey among those who provided the discharge information (registered nurses, n = 8) and those who prepared the discharge information (nurse practitioners, n = 3), expressed a preference for the novel patient-tailored discharge information documents compared to the conventional booklet information. Registered nurses gave the personalized discharge information an 8.1 ± 0.84 on a scale from 0 to 10 and nurse practitioners gave it a 7.7 ± 0.58 (Table 4). Both nurses and nurse practitioners remarked that the personalized discharge information should be extended into daily practice, chiefly because of the personalized nature, improved consistency of the provided information and that all information was consolidated in one document. In addition, it was also reported by nurses that the novel procedure required less time for preparing and providing the actual discharge information. The reason for this improvement in time-saving was that all the information regarding medication changes, outpatient clinic appointments, etc. was easily included in the personalized discharge information document and did not, therefore, need to be extracted from different sources such as the ward secretary or nurse practitioner. The personalized discharge information is created by the nurse practitioner. This requires more time in composition. However, the nurse practitioners noted that this increase is compensated by the convenience of the ICT tool and that the information was already available. Furthermore, improved uniformity was specified as an improvement of the patient-tailored discharge procedure.

4. Discussion

This pilot study evaluated the implementation of a novel discharge procedure, based on a computer-generated patient-tailored document. Importantly, both groups (pre and post-implementation) evaluated the discharge procedure as favourable and comparable, with scores higher than 8.5. Consequently, no further improvement of the provided information may be required. However, a small subgroup of patients, those who initiated teleconsultation with the department after discharge, showed a trend towards increased comprehension of the provided discharge instructions. Although this small group does not reach scientific significance, it is considered by

the authors as a harbinger that personalized discharge information can be an effective solution to increase the quality of post-discharge care. Additionally, healthcare professionals (e.g. nurses involved in the discharge procedure) reported a decrease in time needed for preparing and providing discharge information while maintaining the quality of the delivered information and enhancing uniformity in discharge information.

In contrast to previous literature which reported that patients often feel unprepared for hospital discharge due to a lack of information (5,6). This study demonstrated that the discharge information (before and after the implementation of patient-tailored information) satisfied patient expectations resulting in high evaluation scores. The necessity of personalization and preparation is also shown by Kang (13) and Rushton (14). Both these studies verified a lack of preparedness at discharge but also indicated an increase in preparedness when using personalized information.

Naturally, one can question, aside from socially desirable responses on the part of the patients, whether the applied questionnaires (using a Likert scale from 1 to 10) were the best way to evaluate patient satisfaction and the comprehensibility of the provided discharge information. Moreover, the questions posed were elementary, unambiguous, and based on routine standard follow-up questions. Open-ended questions may have provided more detailed responses concerning information comprehension and could be considered in future studies. Additionally, the conventional discharge information also used some form of written procedural information, which increases patient preparedness (7,8). In contrast to previous reports, in which patient comprehension increased when using patient-tailored discharge information, this could not be replicated in the current pilot study (9,10). One of the reasons might be the difference in comprehension assessment between the studies. While Lin (9) used a telephonic follow-up where a physician scored patient understanding, Bench (10) used a peer-reviewed questionnaire with closed questions. Due to the allotted timeframe of our study, a telephonic follow-up was not possible. After e-mail contact with Bench, their questionnaires were reviewed for our needs but did not include the discharge sections we wanted to address, probably because of the difference in a clinical setting (ICU vs cardiac short stay). For this

reason, we developed and used our own peer-reviewed questionnaire using a Likert scale.

When focusing on the small subgroup of patients who contacted the department for consultation, those who received patient-tailored information conveyed the impression of an improved level of knowledge. This may indicate that patient-tailored discharge information could have resulted in a lower threshold to actively contact the hospital for consultation. It should be noted, however, that this aspect falls out of the scope of this study and could be included in future studies, for instance, with a specific qualitative research design employing interviews to ensure detailed analysis.

Creating personalized discharge information, as reported in the literature,(9) is typically reviewed as too time-consuming for use in a clinical setting, specifically when this is handwritten. The application of this computer tool as evaluated in the current study proved to be both convenient and time-saving, while providing adequate information to patients. Moreover, this procedure has been demonstrated to be a feasible alternative in generating patient-tailored discharge documents and consequently has been now fully implemented in our department.

Limitations of the current study include the single center character of the study, the small sample size, and the use of non-validated questionnaires. Also, one may consider the influence of patient relatives who were present during the discharge sessions, in this study 89%. These effects are not evaluated in this study.

Future research is warranted to optimize the discharge process. The current personalization of discharge information appears to improve the discharge process. More information is however necessary which could not be derived from the current study. A mixed method study using questionnaires, open-ended questions and interviews could provide more insights concerning gaps in information and the reasons why patients act as they do. This information could be used in an early stage to optimize the discharge information (15).

5. Conclusion

In this pilot study a novel discharge procedure, using patient-tailored discharge information, was demonstrated to be equivalent to conventional discharge information, and was evaluated as easier to use. A positive trend was observed for patients who initiated teleconsultation with a healthcare question after discharge. This may suggest that for this subgroup the patient-tailored discharge tool can lead to lowering the threshold to contact healthcare providers and consequently leading to improvements in care. However, further research is warranted to better evaluate this effect.

Acknowledgments: We would like to thank the late R.T. van Domburg for his assistance and guidance in this research. Also, we would like to thank the nurse practitioners and nurses from the ward to cooperate with this research.

Ethical approval: The Medical Ethics Committee of our institution reviewed the study (MEC-2015-744) and deemed this study as not subjected to the Dutch Medical Research Involving Human Subjects Act and hence no formal approval was required.

Guarantor: AW, the first author, takes full responsibility of this article.

Contributorship: This research was part of the nurse practitioner program of AW, therefore AW researched literature and conceived the study with the help of JH, RB and GB. AW, JH, RB and ML were involved in protocol development, gaining ethical approval, patient recruitment and data analysis. AW wrote the first draft of the manuscript. All authors reviewed and edited the manuscript and approved the final version of the manuscript.

Declaration of conflicting interests: The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Funding: The authors received no financial support for the research, authorship, and/or publication of this article.

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Tables and figures

Table 1. Patient characteristics and cardiac risk factors.

	Total n = 112	Conventional information n = 55	Patient-tailored information n = 57	P-value
Age, mean ± SD	57 ± 13	57 ± 14	57 ± 13	0.94
Male	58 (52)	30 (55)	28 (49)	0.57
Smoking current	16 (14)	9 (16)	7 (12)	0.92
BMI				0.30
Low (<18.5)	2 (2)	2 (4)	0 (0)	
Normal (18.5-25)	43 (38)	19 (34)	24 (42)	
High (>25)	67 (60)	34 (62)	33 (58)	
Diabetes	4 (4)	2 (4)	2 (4)	0.35
Dyslipidemia	14 (13)	7 (13)	7 (12)	0.35
Hypertension	23 (21)	9 (16)	14 (25)	0.22
Family history of cardiac disease, Mann–Whitney U test	27 (24)	17 (31)	10 (18)	0.25

All data is depicted as n (%). BMI = body mass index; SD = standard deviation. Significant if P-value≤ 0.05, determined with Pearson's chi-squared test

Table 2. Performed percutaneous electrophysiological procedures.

	Total n = 112	Conventional information n = 55	Patient-tailored information n = 57	P-value
Electrophysiology study (no ablation performed)	11 (10)	6 (11)	5 (9)	0.70
Ablation				
Left-sided accessory pathway	6 (5)	3 (6)	3 (5)	0.96
Right-sided accessory pathway	2 (2)	1 (2)	1 (2)	0.98
Atrial-ventricular re-entry tachycardia	14 (13)	6 (11)	8 (14)	0.62
Atrial tachycardia	1 (1)	0 (0)	1 (2)	0.32
Atrial flutter	17 (15)	9 (16)	8 (14)	0.93
Atrium fibrillation	42 (38)	21 (38)	21 (37)	0.73
Premature ventricular complex	11 (10)	6 (11)	5 (9)	0.71
Ventricular tachycardia	6 (5)	2 (4)	4 (7)	0.42
His bundle	2 (2)	1 (2)	1 (2)	0.98

All data is depicted as n (%). Significant if P-value ≤ 0.05, determined with Pearson's chi-squared test.

Table 3. Outcome patient questionnaire.

	Group I n=47, 85% response	Group II n = 45, 79% response	Absolute difference	P-value
Response on the clarity of the information presented at the discharge talk				
Overall clarity	8.6 (1.2)	8.8 (1.0)	+0.2	0.55
Post discharge instructions	8.8 (1.2)	8.9 (1.0)	+0.1	0.53
Possible complications	8.7 (1.2)	8.9 (1.1)	+0.2	0.43
Expected recovery process	8.6 (1.4)	8.7 (1.2)	+0.1	0.74
New or altered medication	9.0 (1.3)	8.9 (1.1)	-0.1	0.61
Response on the clarity of the way the discharge information was written				
Clearly written	8.8 (1.0)	8.7 (1.0)	-0.1	0.73
Comprehensible	8.9 (1.0)	8.7 (1.0)	-0.2	0.58
Specific for the patient	8.6 (1.3)	8.7 (1.4)	+0.1	0.82
Did discharge information help after discharge	8.4 (1.5)	8.4 (1.3)	0	0.87

Significant if P-value ≤ 0.05, determined with Pearson's chi-squared test.

Table 4. Outcome healthcare provider questionnaire.

	Nurses n=8	Nurse practitioners n=3
Overall clarity	8.4 (0.8)	7.7 (0.6)
Time taken		NA
Traditional discharge info		
<5 min	1 (12)	
5–10 min	7 (88)	
>10 min	-	
Personalised discharge info		
<5 min	7 (88)	
5–10 min	1 (12)	
>10 min	-	
Would like to continue personalized discharge info	8 (100)	3 (100)

All data is depicted as mean (SD) or as n (%) where applicable.

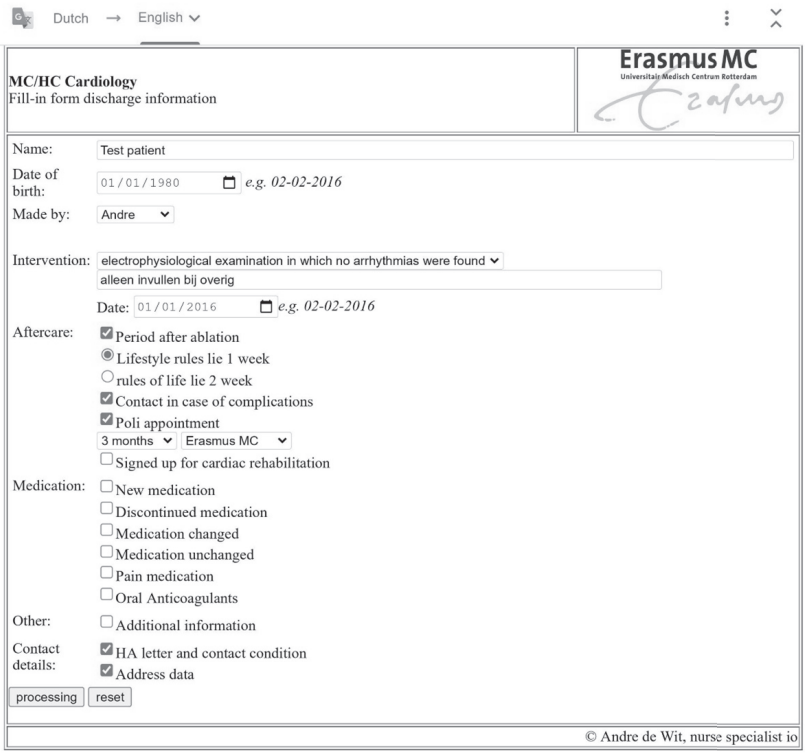


Figure 1a. ICT tool

This personalized dismissal information is intended for:
Name: test patient
Born on: 03071984

Erasmus MC
Universitair Medisch Centrum Rotterdam

MC/HC Cardiology
tel. 4147435349

On 10022016 you had a Flutter ablation.
Below is the information regarding your personal situation.

The period after the treatment:
During the ablation, wounds are made to the heart muscle tissue. The wounds and their healing can cause pain, fatigue, shortness of breath or a burning sensation.
This is not uncommon, these complaints should diminish within a few weeks. The area in the heart where the ablation took place needs a recovery period.
If these complaints worsen or hinder you in your daily life, we ask you to contact the cardiology department until the first outpatient visit.

After 3 months you will come to the cardiology outpatient clinic to further discuss your recovery and medication use with the electrophysiologist.
Sometimes an ablation is successful at first, but the arrhythmia comes back later. In that case, your cardiologist can suggest another treatment.

A nurse from the cardiology department will call you a few days after your discharge with a number of questions about your health and your stay on our ward. Any questions that have arisen after your dismissal can then also be answered. The interview will take no more than 10 minutes.
The purpose of this conversation is to further improve the care for our patients, we thank you in advance for your cooperation.

Precepts to avoid complications of the groin puncture:
Your treatment has taken place through the groin vein. There is a small risk of bleeding during the first days after treatment. To prevent the puncture site in your groin from bleeding again, you should spare the groin for the first time. We advise you to observe the following rules of life.
We recommend that you:
to walk little the day after the procedure. Walking in and around the house is no problem. Avoid longer distances.
Limited climbing stairs at a leisurely pace, step by step is no problem.
do not put too much strain on the groin for the first three days after discharge. Avoid riding a bicycle, driving a car, lifting heavy things and taxing movements. If you have to cough, sneeze or strain, support the wound in the groin by applying light pressure with your hand on the site where you have been punctured.
do not bathe, swim or use the sauna during the first week. You can take a shower.
after 4 days you can resume work, provided that the procedure is uncomplicated and that you have recovered and that you are not (yet) engaged in heavy physical labour.
after 7 days you can slowly build up with sports/more intensive exercise.

What should I do if something happens:
Your groin may still be a bit thick and blue for the foreseeable future. The bruise can spread all over the thigh. This is a normal phenomenon as long as the puncture site does not thicken.

Immediately call the emergency number 112 when:
the puncture site in the groin is pumping or bleeding in waves. This may indicate a possible arterial bleeding. Press with your fingers or fist about 2 cm above the place where the blood flows. The bleeding should then decrease/stop. If this doesn't work, call for help. Don't panic and call emergency services!

there is a sudden increasing swelling at the groin puncture site. Press the resulting bulge with a fist until help arrives.
In the first week after the procedure, contact the short stay cardiology department at:
pain, rash, fever, or numbness occur in and on the leg of the punctured groin.
unexplained shortness of breath.
After the first week after the procedure, contact your doctor if:
symptoms persist or worsen

Outpatient appointment:
An outpatient check-up is planned after about 3 months at the cardiology outpatient clinic of the Havenziekenhuis with one of our cardiologists.
For more information, see the appointment overview, which will be sent to your home address.

Information about your medication use:
Discontinued medication:
Your medication has been discontinued, namely:
metoprolol
Specific medication for anticoagulation: Rivaroxaban
has already been restarted on 10022016.

For a complete overview of your current medication, see the enclosed medication overview.

Do you have any questions:
Your personal discharge information has been created by: A. de Wit, nurse specialist in training. A digital version of the medical discharge letter to the general practitioner and other data can be found at https://zorgportaal.erasmusmc.nl/.

If you have any questions, if a complication arises or if you would like advice, please contact the Short Stay Cardiology Department.

Erasmus MC Department AD3 (short-term stay and day treatment Cardiology)
'sGravendijkwal 230
3015CE Rotterdam
telephone : 010 703 53 49
internet: www.erasmusmc.nl

Figure 1b. Personalized discharge information

Patient questionnaire

One week ago you were discharged from the short stay cardiology ward. With this questionnaire we would like to enquire concerning your thoughts on your experience and opinion relating to our discharge information. Could you please answer the question below.
Thank you for participating in this study!

General Questions

1. Did you receive a discharge information leaflet?	Yes	No
2. Did you read the discharge information leaflet?	Yes	No

The following questions relate to the complete discharge information:
Could you rate the discharge information on a scale from 1 (completely unclear) to 10 (completely clear)?

1. In general, is the discharge information understandable ?

1	2	3	4	5	6	7	8	9	10

2. Were the post discharge instructions clear?

1	2	3	4	5	6	7	8	9	10

3. Is it clearly expressed what you should do in the event of complications?

1	2	3	4	5	6	7	8	9	10

4. Is the out-patient follow-up procedure clear?

1	2	3	4	5	6	7	8	9	10

5. Do you know which medication you should use?

1	2	3	4	5	6	7	8	9	10

The following questions regard the WRITTEN discharge information:
Could you rate the discharge information on a scale from 1 (completely unclear) to 10 (completely clear)?

6. Is the discharge information clearly written?

1	2	3	4	5	6	7	8	9	10

7. Is the discharge information comprehensible?

1	2	3	4	5	6	7	8	9	10

8. Is the discharge information adaptable to your personal situation?

1	2	3	4	5	6	7	8	9	10

9. Did the written discharge information support you after discharge?

1	2	3	4	5	6	7	8	9	10

10. How was the length of the written discharge information?

Too short	Good	Too long

Patient sticker

Figure 2. Patient questionnaire

Questionnaire healthcare providers

Please answer the following questions regarding the discharge information given in the past period.

Was the discharge information personalized

Yes	No (only answer 4)

1. How would you overall rate the personalized discharge information

1	2	3	4	5	6	7	8	9	10

2. Could you describe 'Pros' of the personalized discharge information

3. Could you describe 'Cons' of the personalized discharge information

4. How much time did it take to prepare for the discharge session

<5 minutes	5-10 minutes	>10 minutes

5. Would you like to continue the personalized discharge information

Yes	No

Last remarks

Figure 3. Healthcare provider questionnaire

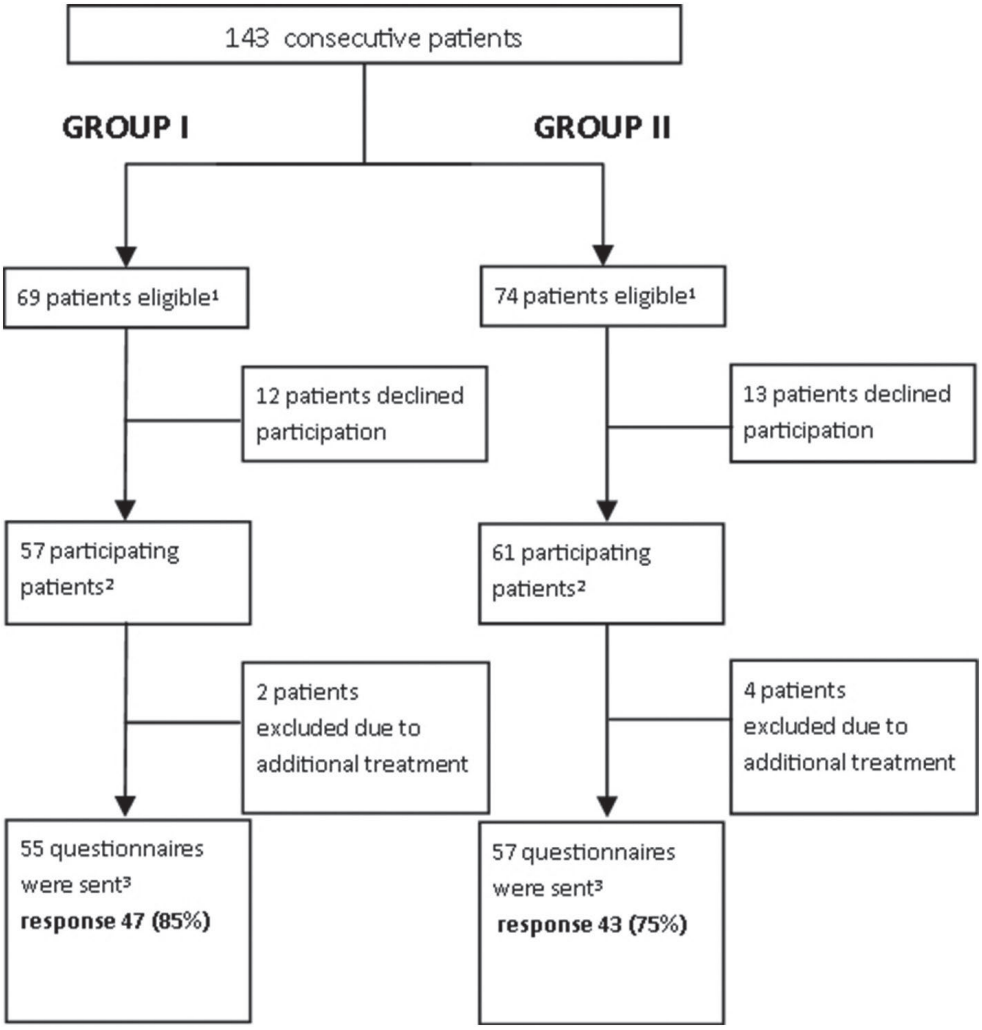


Figure 4. Patient inclusion workflow

Part III **Patient empowerment:**

Use of eHealth as discharge aid

Get the picture: A Pilot Feasibility Study of Telemedical Wound Assessment Using a Mobile Phone in Cardiology Patients

Patients are able to take and upload the mobile clinical photos to the secure email address, and the vast majority was interpretable

Smartphone users were more successful in uploading their pictures compared with feature phone users (93% vs 55%, P <0.01)

The interobserver variability had an agreement between 93% and 97%

Table 1 Demographic Characteristics

Baseline Characteristics	Participants (n = 46)	Nonparticipants (n = 45)	*P-value*
Age, mean (SD), y	53 (13.1)	66 (12.4)	<.01
Male gender, n (%)	25 (54)	24 (53)	.92
Scheduled intervention, n (%)			.62
Change of pacemaker or ICD	14 (30)	18 (40)	
Pacemaker	3	9	
ICD	11	8	
S-ICD	-	1	
Implantation of pacemaker or ICD	18 (39)	16 (36)	
Pacemaker	2	4	
ICD	14	11	
S-ICD	2	1	
PV isolation	14 (30)	11 (24)	
Comorbidity, n (%)			
Diabetes	3 (7)	11 (24)	.02
Rheumatism[a]	0 (0)	4 (9)	.04
Thyroid dysfunction	3 (7)	2 (4)	.66
Adrenal suffering	0(0)	0 (0)	-
Medication, n (%)			
OAC	27 (59)	27 (61)	.80
ASA	9 (20)	12 (27)	.42
ASA and OAC	1 (2)	4 (9)	.16
OAC AND LMWH	13 (28)	9 (20)	.36
Living with partner, n (%)	27 (84)	10 (71)	.31
Education, n (%)			.89
Low	5 (16)	3 (21)	
Middle	12 (38)	5 (36)	
High	15 (47)	6 (43)	

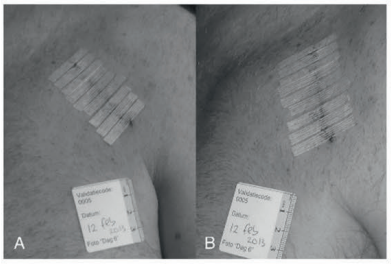
Abbreviations: ASA, acetyl salicylic acid; ICD, implantable cardiac defibrillator; LMWH, low-molecular weight heparin; OAC, oral anti coagulation; PV, pulmonary veins.

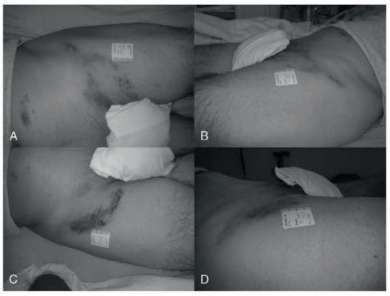
[a] Rheumatism or connective tissue disease (data of 1 patient missing).

Figure 1 Assessment scheme

Quality	O Sufficient	O Insufficient
Erythema	O Clinically relevant	O Clinically irrelevant
Hematoma	O Clinically relevant	O Clinically irrelevant
Conclusion	O Conservative therapy	O Clinical assessment mandatory

Figure 2 Examples of smartphone photographs with frontal and lateral views





CHAPTER 9

Get the picture. A Pilot Feasibility Study of Telemedical Wound Assessment Using a Mobile Phone in Cardiology Patients

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Journal of Cardiovascular Nursing, 2017, Vol.32, No. 2, pp E9-E15,
DOI: 10.1097/JCN.0000000000000377

Abstract

Background: Postprocedural complications after elective cardiac interventions include hematomas and infections. Telemedical wound assessment using mobile phones with integrated cameras may improve quality of care and help reduce costs.

Aims: We aimed to study the feasibility of telemedical wound assessment using a mobile phone. The primary aim was the number of patients who were able to upload their pictures. Secondary aims were image interpretability, agreement between nurse practitioners, and patient evaluation of the intervention.

Methods: This is a prospective study of all consecutive patients who underwent an elective cardiac intervention. Patients were instructed to photograph their wound or puncture site after hospital discharge and upload the pictures to a secure email address 6 days after hospital discharge. Received photos were assessed by 2 nurse practitioners. The intervention was evaluated using a peer-reviewed questionnaire and photo assessment scheme.

Results: In total, 46 eligible patients were included in the study, with 5 screen failures (e.g., clinical stay Q 6 days) and 1 patient lost to follow-up. Thirty-three of 40 patients (83%) were able to upload their pictures. Smartphone users were more successful in uploading their pictures compared with feature phone users (93% vs 55%, P G .01). Eighty-eight percent of the clinical pictures were interpretable. The interobserver variability had an agreement between 93% and 97%.

Conclusions: Patients are able to take and upload the mobile clinical photos to the secure email address, and the vast majority was interpretable. Smartphone users were more successful than feature phone users in uploading their pictures. The interobserver variability was good.

1. Introduction

In the last decades, a decline in hospital length of stay has been observed, including early discharge after percutaneous cardiac intervention. Consequently, patients may face postprocedural complications after hospital discharge. Important complications may include hematoma, bleeding, and infection, which often occur within 4 days after the intervention (1). Most patients, however, are discharged on the day of the procedure or the day after. Early discharge may be accompanied with having a complication in the domestic situation and consequently may need an evaluation by a healthcare professional. It is to be expected that patients who worry about having a complication contact the hospital (ward) that performed the intervention, most often by telephone. One limitation of this remote contact is the lack of visual wound inspection, which may initiate a follow-up visit to reassure patients or confirm and treat a complication. An alternative to clinical assessment may be remote assessment of clinical pictures, which has been implemented successfully by several medical subspecialties and in different clinical situations (2-4). Mobile telemedicine is a recent development in which patients use their mobile phones (3). It can offer a safe and cost-effective form of communication (5). Mobile phones are often personalized, which can reduce the barriers in the use and acceptance of health interventions with it (6). The camera function has become integrated in almost all mobile phones (6). Consequently, we can make use of this integrated function in mobile phones in the context of remote ‘‘monitoring’’ or telecare until the first follow-up visit (range, 10 days to 3 months) after an invasive procedure with early discharge. In this study, we focused on patients who underwent an electrophysiological treatment (e.g., device implantation or treatment of a dysrhythmia).

The aim of this pilot study was to evaluate the feasibility of augmenting post discharge telemedical wound assessment by using a mobile phone for making and sending photos of an intervention-related wound in patients undergoing an elective cardiac intervention.

2. Methods

2.1 Study design

This was a prospective, nonrandomized, single-center pilot study of consecutive patients undergoing an elective cardiac intervention at the Department of Clinical Electrophysiology of the Erasmus Medical Center between January and April 2013. The Erasmus Medical Center is a tertiary referral and teaching hospital in Rotterdam, The Netherlands. Patients had to be at least 18 years old and have had an elective cardiac implantable electrical device implantation or a catheter ablation of atrial fibrillation. Furthermore, they should have a mobile phone with an integrated camera function and be able to send an email by computer or mobile phone. Patients used their own phone. The study was reviewed by the medical ethics committee who approved the noninterventional character of this study (MEC-2012-593). All patients provided written informed consent. The study conforms with the principles outlined in the Declaration of Helsinki.[7] The incentive for participation was a luxury ballpoint for filling out the questionnaire or outlining a hematoma.

2.2 Discharge Information

On discharge, patients received specific instructions on regimens and warning signs regarding their surgical wound or puncture site(s). These written instructions were explained by both the nurse practitioner and staff nurse, including instructions on how to act in case of (possible) complications. Patients after device-related surgery should keep the wound dry until day 5 and remove the bandage on day 5. Regarding the puncture site, patients were asked to remove the adhesive plaster after 1 day if it was dry. Patients were explicitly requested to call the ward for advice in case of (suspected) complications, as is our standard of care, having easy access to a nurse practitioner. This service was available until their first outpatient clinic visit. Furthermore, standard care also incorporates a telephonic follow-up by a staff nurse 1 week after discharge. Patients undergoing device implantation were clinically assessed at day 10 to check their wound and the functioning of their device. Patients undergoing catheter ablation were seen at the outpatient clinic visit 3 months after ablation without having access to specific wound inspection.

2.3 Taking and Uploading Pictures

Patients received specific instructions on how to make and upload lateral and frontal pictures of the intervention related wound at day 6 after hospital discharge. For puncture sites, 1 frontal, 1 lateral right-sided, and 1 lateral left-sided pictures were needed. A feature phone is a mobile phone with basic multimedia capabilities such as an integrated camera, without the ability to install third-party software and limited Internet capabilities. Examples are Nokia 2230, Motorola Razr, or Sony K700i. In contrast, a smartphone can install third-party software (apps) and has seamless integration of multimedia and Internet capabilities. The investigator gave a 10- to 20-minute explanation on the actual device used and provided a detailed written brand- and model-specific protocol for uploading, detailing the steps as practiced. During this training, patients practiced uploading a picture to the laptop of the investigator. Smartphone users could also directly email to the specified address. Furthermore, they were given the chance to practice taking and uploading pictures during their clinical stay. Sending emails was not explicitly practiced. When patients suspected a complication, additional pictures could be sent within the existing telecare. Relatives were also allowed to make pictures. The picture should be taken at a distance of 50 cm, in a room with adequate daylight (no artificial lighting or flash), and include the provided label specifying the date, study number, and a ruler of 37 mm. Patients were instructed to check the quality of the pictures before sending them to the secure email address. All patients received a leaflet with these instructions and the dedicated email address. In addition, patients were asked to complete a questionnaire, which was developed in a focus group of 2 nurse practitioners and 2 epidemiologists and showed good validity. The purpose of the questionnaire was to evaluate the perceived difficulty in using the camera function, feelings toward the intervention, and whether taking photos required help from a caregiver. If no pictures were received at day 7 after discharge, patients received a telephonic reminder. For privacy reasons, patients were asked not to include a name or date of birth on the provided label or sent email and restrict to a header containing the study number. Emails were received on a secure email server.

2.4 Assessment of Pictures

Two independent investigators (nurse practitioners) evaluated all transmitted pictures according to the predefined criteria. To analyze the agreement between these 2 investigators, a simplified assessment scheme with dichotomous variables was used (refer to Figure 1). Assessment was done blindly to medical data after the inclusion period, on a high-resolution screen (1980 x 1080 pixels), paying attention to redness or hematoma. The investigators gave a conclusion on a set of pictures per case being clinically relevant or not. ‘‘Clinically relevant’’ was defined as possibly needing further clinical assessment or medical treatment. Both investigators were experienced in assessing wounds and puncture sites. Conservative therapy was defined as needing no additional clinical assessment or medical treatment. If the wound or puncture site was not visible or if the picture was not sharp or too dark according to the assessing nurse practitioner, the quality was deemed insufficient and should not be assessed further. If so, further data on all subitems were censored.

2.5 Statistical Analysis

Continuous data are presented as means and corresponding standard deviations (SDs) or as median values and corresponding 25th and 75th percentiles. Categorical variables are represented as frequencies and percentages. For a comparison of normally distributed continuous variables between participants who used a smartphone versus those with a feature phone, Student t test was used; in case of skewed distribution, Mann-Whitney U test was used. For comparing frequencies, the χ^2 test or Fisher exact test was used. Statistical analysis was performed using IBM SPPS 21 (IBM Corp, Armonk, New York). A $P < .05$ was considered statistically significant.

3. Results

A total of 91 consecutive patients were screened for participation in the study. Forty-five patients were excluded because of refusing participation (n = 12), the absence of an integrated camera in the mobile phone (n = 23), no mobile phone (n = 6), or no Internet connection (n = 2) or computer (n = 1). Forty-six of the 91 patients (51%) were included in the study. Baseline demographics of the study population are

depicted in Table 1. Patients who participated in the study were younger and had less comorbidity (eg, diabetes, rheumatism) than nonparticipants. Of these 46 patients, 5 were excluded from participation because of a prolonged clinical stay (96 days), miscommunication, or cancellation of their procedure, and 1 patient was lost to follow-up. Consequently, the final study population included 40 patients of whom 29 patients had a smartphone and 11 patients had a feature phone.

Participants expressed a positive attitude regarding the studied intervention, especially smartphone users. Feature phone users, however, were doubtful whether they were able to provide the pictures as requested. In addition, some family members/caregivers of smartphone users offered to help, even if they had to visit the patient extra for it.

Most participants (n = 33, 83%) were able to upload their pictures after hospital discharge. Importantly, patients with a smartphone were more successful in uploading pictures in comparison with patients with a feature phone (93% vs 55%, P < .01). Examples can be seen in Figures 2 and 3.

During this pilot study, a total of 102 pictures were transmitted. Most pictures (88%) were considered to be of sufficient quality for interpretation. According to the predefined criteria, the agreement between the 2 independent investigators in assessment of the pictures was between 93% and 97%. Interobserver agreement was good, as depicted in Table 2.

The results of the questionnaire are presented in Table 3. Overall, 32 patients (80%) returned the questionnaire. More than half of these patients indicated that they made the photo with some help. Importantly, most smartphone users were able to send the photo and indicated this as easy, whereas feature phone users more often experienced technical issues (63% vs 13%, P <.01). Overall, smartphone and feature phone users had a positive attitude toward making pictures as part of post discharge care (88% and 75%, respectively). When focusing on the preferred mode of contact, 71% of the smartphone users preferred a telephonic consultation in combination with uploading photos, as compared with 38% of the feature phone users. Fifty percent of the feature phone users preferred a hospital visit, whereas for smartphone users, this was only 8%.

4. Discussion

This is the first (pilot) study in the field of cardiology to demonstrate the feasibility of using smartphone mobile photography as a practical instrument in post discharge telecare. Where many studies focus on providing a device, we let patients use their own device.(8-10) Importantly, most patients were able to make post discharge photos of sufficient quality for evaluation and sent them to a secure email address.

Our findings are in agreement with Wiseman et al (11) who performed a survey in 2014 among older patients after vascular surgery who were able and willing to use smartphone photography for remote wound management. In addition, patients after an electrophysiological intervention proved to be successful in uploading pictures of their intervention-related wound for clinical assessment. In addition to an increasing ownership of smartphones during recent years (e.g., in the Netherlands from 58% in 2012 to 82% in 2015), even among older patients (12,13), the quality of smartphone cameras has improved considerably. As shown in this study, the quality of most photos was considered good and enabled the investigators to evaluate the wound remotely in addition to the existing care, with good interobserver agreement. Previous studies in dermatology have indicated that telemedicine using pictures from mobile phones was feasible and accurate (2,8). In addition, patients may not be prone to low sustained use of mHealth, as described by Bhavnani et al (14), because this is a 1-time use of the integrated technology in a smartphone. Consequently, the proposed intervention with emailing photographs to a secure email server could be a feasible alternative until secure uploading of pictures by patients themselves in their electronic health record is implemented. It might be a good alternative in reassuring patients when suspecting a complication instead of an extra follow-up visit. This might further bridge the gap between discharge and the first outpatient clinic visit.

Our study clearly indicates that smartphone users experienced fewer problems when uploading pictures in comparison with patients with a feature phone. This suggests that telemedical wound care is better suited for those with a smartphone. This is also reflected by most smartphone users who preferred a telemedical contact with clinical pictures taken with the mobile phone than a clinical visit. In contrast, most feature phone users preferred a clinical visit. Importantly, both groups evaluated teleconsultation with mobile photography as appropriate.

5. Implementation

On the basis of the results of this study, smartphone photography by patients was implemented as an addition to the existing telephonic post discharge care in our clinical practice. It is almost real time with immediate assessment after getting an email notification on our smartphone when receiving the pictures. Usually, a set of 1 lateral and 1 frontal pictures is sufficient for patients after device implantation. After catheter ablation, a set of 3 to 4 pictures is required with 1 or 2 frontal (depending whether both sides of the groin are visible), 1 lateral right-sided, and 1 left-sided views. Most patients, however, send more pictures, enabling us to select which picture will be uploaded to their electronic health record. Importantly, there is a formal backup as colleagues, and a medical supervisor can assist in the evaluation of submitted pictures. Regarding privacy issues, a workaround for keeping the email clear of personal information included clear instructions to patients by asking them to only include a code based on the time stamp of the telephonic consultation, for example, 11.20 hours. This implementation is a subject of future research.

This use of mHealth may be a practical and useful instrument in following patients in rural areas or those who might not be able to reach the clinic or emergency department easily because of their medical condition. The described intervention is cost-effective, especially when sending through existing Wi-Fi networks. Our hospital is a tertiary referral center in an urban setting, but even then, patients may prefer remote follow-up as a feasible alternative to a clinical assessment, which is associated with travel time, travel and parking costs, waiting times, and so forth. The combination of clinical history and pictures proved helpful in deciding whether complications were clinically relevant. Moreover, patients indicated to be satisfied with the option to transmit pictures. When implementing it in a different healthcare and legal system, special attention should be given to the legal consequences on the use of multimedia and the privacy of patient-sensitive data.

Limitations

What's New and Important

- Smartphones may be useful for telemedical wound assessment.
- Uploading pictures is feasible for most patients.
- Interobserver agreement of pictures is good.

This study has certain limitations that should be taken into account when interpreting the results, starting with the low number of participants in this pilot study investigating the use of mobile phones in augmenting telemedical wound care. Importantly, nonparticipants and feature phone users were more often older adults. Despite the expectation that the number of patients who are not able or willing to use their smartphone for mHealth will diminish, a minority of patients will still require the traditional clinical assessment of their complications. Importantly, we did not evaluate patients clinically on the same day as the photos were taken and uploaded. Thus, we could only report on telemedical assessment and evaluation of the intervention by patients. Furthermore, assessment of the clinical pictures was reduced to 2 options: whether the patient had a clinically relevant complication, which is rather subjective. In daily clinical practice, the evaluation of wounds incorporates many different factors. We realize that it would be useful to have an objective measurement, especially for groups other than nurse practitioners or physicians who lack specialized training or experience. This may imply a certain multipoint score to evaluate hematomas and infections, which may be the focus of future research. When all elements that are essential for optimal telemedical wound care are covered (i.e., high success rate of uploading pictures, objective measurements of clinical pictures, clear agreements how to deal with complications), then the next phase would be to investigate whether telemedical wound care reduces healthcare use (eg, reduction in clinical visits). This pilot study is the first step in moving toward this direction.

6. Conclusions

In conclusion, this pilot study indicated the usefulness of smartphone mobile photography as a feasible option in augmenting existing telecare. Smartphone users were able to make and upload pictures. The agreement on assessing clinical images was good between the 2 nurse practitioners. Smartphone mobile photography matched the patients' expectations of providing contemporary care.

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S-ICD	2	1	
PV isolation	14 (30)	11 (24)	
Comorbidity, n (%)			
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Rheumatism[a]	0 (0)	4 (9)	.04
Thyroid dysfunction	3 (7)	2 (4)	.66
Adrenal suffering	0(0)	0 (0)	-
Medication, n (%)			
OAC	27 (59)	27 (61)	.80
ASA	9 (20)	12 (27)	.42
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OAC AND LMWH	13 (28)	9 (20)	.36
Living with partner, n (%)	27 (84)	10 (71)	.31
Education, n (%)			.89
Low	5 (16)	3 (21)	
Middle	12 (38)	5 (36)	
High	15 (47)	6 (43)	

Abbreviations: ASA, acetyl salicylic acid; ICD, implantable cardiac defibrillator; LMWH, low-molecular weight heparin; OAC, oral anti coagulation; PV, pulmonary veins.

[a.] Rheumatism or connective tissue disease (data of 1 patient missing).

Table 2 Interobserver Agreement per Case (N = 33)

	Valued by Nurse Practitioner 1	Valued by Nurse Practitioner 2	Agreement
Quality, n (%)	33	33	
Sufficient	32	29	29 (88)
Insufficient	1	4	1 (3)
Erythema, n (%)	29	29	
Clinically irrelevant	28	27	27 (93)
Clinically relevant	1	2	1 (3)
Hematoma, n (%)	29	29	28 (96)
Clinically irrelevant	29	28	28 (97)
Clinically relevant	-	1	-
Conclusions, n (%)	29	29	
Conservative therapy	28	27	27 (93)
Clinical assessment	1	2	1 (3)

Table 3 Outcomes Questionnaire (N = 32)

	Smartphone (n = 24)	**Feature Phone (n = 8)**	**P-value**
Photos made with aid of another, n (%)	16 (67)	3 (38)	.15
Emailed the photos with the phone, n (%)	20 (83)	1 (13)	<.01
Degree of difficulty in making photos, n (%)			.02
- Very easy	11 (46)	1 (13)	
- Easy	9 (38)	5 (63)	
- Neutral	4 (17)	-	
- Difficult	-	-	
- Very difficult	-	2 (25)	
Degree of difficulty in sending the photos, n (%)			.03
- Very easy	11 (46)	2 (25)	
- Easy	8 (33)	1 (13)	
- Neutral	4 (17)	-	
- Difficult	-	-	
- Very difficult	1 (4)	3 (38)	
- Missing data	-	2 (25)	
Technical problems, n (%)	3 (13)	5 (63)	<.01
Reported time uploading pictures, min			.31
1	10 (42)	-	
2	3 (13)	2 (25)	
3	1 (4)	-	
5	7 (29)	1 (13)	
10	1 (4)	-	
30	2 (8)	-	
Missing data	-	5 (62)	
Identification of technical problems, n (%)			
- Could not transfer	-	2 (25)	
- Could not transfer and send	1 (4)	3 (38)	
- Other technical problems	2 (8)	-	
Considering e-consult with photo as appropriate care, n (%)	21 (88)	6 (75)	.40
Preference mode of consult, n (%)			.08
- Telephone contact with photograph	17 (71)	3 (38)	
- Visit hospital without consultation	2 (8)	4 (50)	
- Only telephone contact	3 (13)	1 (13)	
- Only send in photograph	1 (4)	-	
- Missing data	1 (4)	-	

Quality	O Sufficient	O Insufficient
Erythema	O Clinically relevant	O Clinically irrelevant
Hematoma	O Clinically relevant	O Clinically irrelevant
Conclusion	O Conservative therapy	O Clinical assessment mandatory

Figure 1. *Assessment scheme per case.*

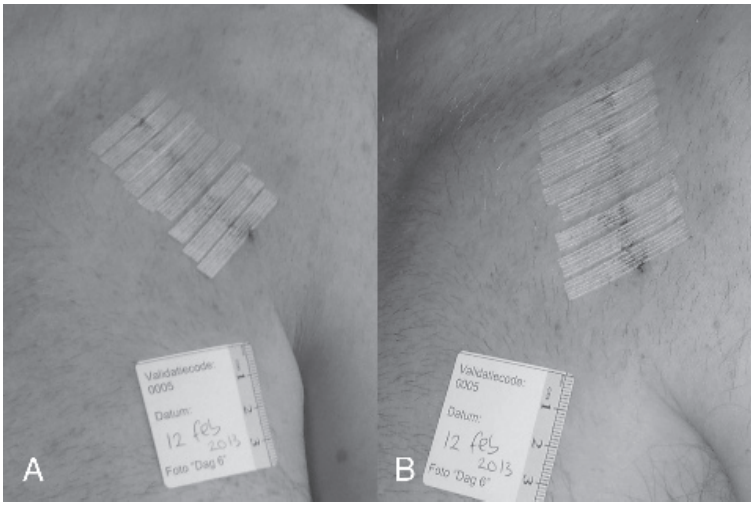

Figure 2. Example of implantable cardiac defibrillator pocket (smartphone). A, Frontal view. B, Lateral view.

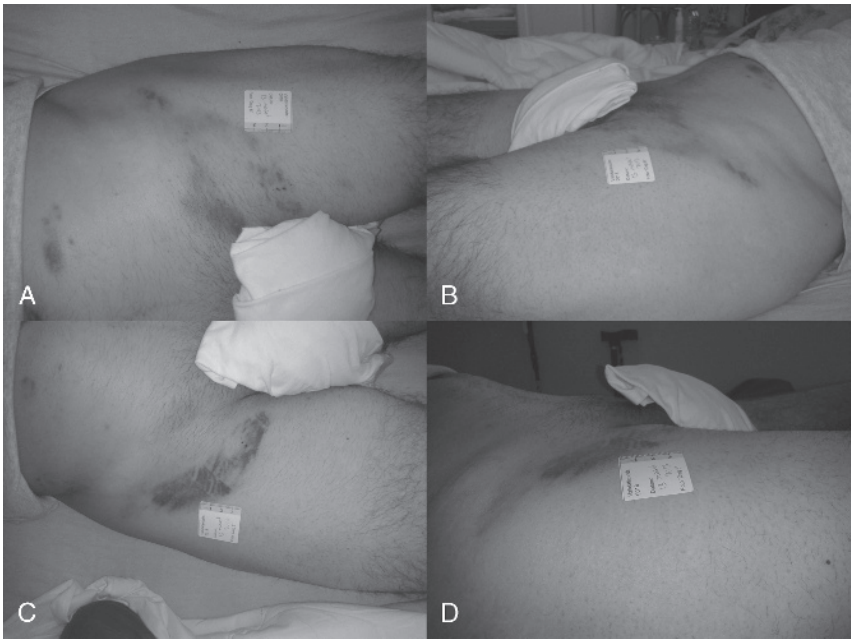

Figure 3. *Example of puncture site (smartphone). A, Frontal view, left. B, Lateral view, left. C, Frontal view, right. D, Lateral view, right.*

Epilogue

CHAPTER 10

SUMMARY AND GENERAL DISCUSSION

Introduction

Cardiac electrophysiology, a subspecialty of cardiology, concentrates on the management of cardiac arrhythmias and the prevention of sudden cardiac death. Within the Erasmus MC a specialised team comprising cardiac electrophysiologists, fellows, nurse practitioners, nursing staff, technicians, and research personnel is committed to the treatment and care of individuals suffering from heart rhythm disorders. The treatment of heart rhythm disorders has evolved over the last decades to a broad spectrum of invasive and non-invasive therapies. The invasive treatment arsenal includes pacemakers, implantable cardioverter-defibrillators (ICDs), cardiac resynchronization therapy (CRT), and catheter ablation of cardiac arrhythmias (1). Both cardiac implantable electronic device (CIED) therapy, and catheter ablation have further progressed in recent years, with associated improvement in effectiveness. Furthermore, patient centred care with an emphasis on shared decision making has entered the clinical arena. Presently, there is an enhanced accent on risk factor management, which may optimise therapy outcomes and as such was the underlying principle of this thesis.

Part I – Evaluation of complications in atrial fibrillation management

Summary

Atrial fibrillation (AF) is a supraventricular tachyarrhythmia with uncoordinated atrial electrical activation (2). It is the most common cardiac arrhythmia in adults and constitutes a significant burden to patients, communal health, and health economy. The lifetime risk of AF in Europe is as high as 40% (2). In 2021 approximately 123,400 newly diagnosed AF cases were documented in the Netherlands (3).

Currently, the first aim is to improve lifestyle management and initiate a more aggressive risk factor management. Secondly, patients with AF are at increased risk of stroke and the use of oral anticoagulation will reduce this risk, but in turn introduces a bleeding risk. Finally, a choice will be made between rate or rhythm control depending on patient preferences, symptoms, comorbidity, and anticipated

benefits and risks of invasive catheter ablation. Rate control is achieved using atrioventricular blocking agents (i.e., betablockers, digoxin, verapamil) or a “pace and ablate” strategy. Rhythm control is achieved using a combination of anti-arrhythmic drugs, electrical cardioversions (ECVs), and AF catheter ablation. Inherent to every medical procedure, there are certain risks associated with electrophysiology procedures. Both ECVs and AF catheter ablation are associated with the risk of bleeding and thrombo-embolic events (2, 4, 5).

In the last decade, the use of anticoagulation in patients with AF has shifted from the use of vitamin K anticoagulants (VKAs) to direct oral anticoagulants (DOACs). Several large, randomised studies (RE-LY, ROCKET-AF, ARISTOTLE and ENGAGE AF-TIMI) have demonstrated that DOACs have a more favourable risk-benefit profile regarding stroke, intracranial haemorrhage, and mortality (6). Consequently, the use of DOACs has increased considerably in patients with AF. In the Netherlands there was a slow uptake of its use before 2016, due to limited data on peri-procedural efficacy and safety, lack of an antidote, and associated increased health care costs (7, 8). Since 2016 there was a clear shift from the use of VKA to DOAC in AF patients, including patients who presented for an ECV and AF catheter ablation.

In chapter 2 we evaluated thromboembolism (composite of stroke, transient ischemic attack, or systemic embolism) and major bleeding events within 60 days after ECV (9). We enrolled 920 consecutive patients undergoing an ECV comparing patients with a direct oral anticoagulants (DOAC) anticoagulation regimen to a vitamin K antagonists (VKA) regimen, without routine trans oesophageal echocardiography (TEE) between January 2013 and February 2020. There were no differences between groups regarding demographic variables and mean CHA_2DS_2-VASc score; however, the VKA group had a higher proportion of patients with co-morbidities. We found that in a real-world population, the rates of thromboembolism and major bleeding events were low after elective ECV in patients using DOAC or VKA and did not differ between both groups.

AF catheter ablation can be associated with bleeding and thromboembolic events. In chapter 3 we evaluated 637 consecutive patients undergoing AF ablation (10). These patients had an AF catheter ablation under a VKA- or DOAC anticoagulation regimen between January 2013 and April 2017. The primary endpoints were clinically relevant

non-major bleeding, major bleeding, and systemic thromboembolic events from the time of ablation through 30 days. Bleeding events were defined by the Bleeding Academic Research Consortium (BARC) and International Society on Thrombosis and Haemostasis (ISTH), as both bleeding scores are commonly used. The rate of clinically relevant non-major bleeding was lower in the DOAC group in comparison to the VKA group. Rates of major bleeding were similar between groups. Rates of systemic embolism were not significantly different, with no events in the minimally interrupted DOAC group, and a few events with uninterrupted VKA. We found that in patients undergoing AF catheter ablation, anticoagulation with minimally interrupted DOAC was associated with fewer clinically relevant non-major bleeding events in comparison with uninterrupted VKA without compromising thromboembolic safety.

To improve the outcome of AF ablation, there should not only be a focus on technology. Addressing modifiable risk factors is equally important. A potentially modifiable risk factor for AF is sleep apnea, which shares the same risk factors as AF, such as obesity and hypertension (1, 11, 12). This may be mitigated by lifestyle management such as losing weight and physical exercise. Preferably lifestyle management and treatment of sleep apnea should be initiated before catheter ablation, as it can improve outcome (2). Sleep disordered breathing (SDB) including sleep apnea may hamper the outcome of catheter ablation of AF. Importantly, SDB is not easily recognised and may thus be undertreated.

In chapter 4 we evaluated if undiagnosed SDB has an impact on AF recurrence after catheter ablation in a single-center prospective cohort study (13). Patients were enrolled 12 to 18 months after AF catheter ablation. One hundred and four eligible patients were enrolled and underwent SDB screening, using WatchPAT (WP), a portable home sleep apnea test device. We demonstrated that the risk of AF recurrence was significantly higher in the group with undiagnosed SDB in the first year after ablation in comparison to those without SDB. A significant proportion of patients undergoing catheter ablation of AF have undiagnosed SDB which is associated with a twofold higher risk of AF recurrence. SDB screening may improve patient counselling regarding the efficacy of catheter ablation. We found that the commonly used Epworth Sleepiness Scale and STOP-Bang questionnaire underperformed in detecting SDB in our cohort of patients.

Discussion

In part I we evaluated the periprocedural use of DOAC on thromboembolism and bleeding events, and if undiagnosed SDB had an impact on AF recurrence after catheter ablation.

The management of AF has evolved significantly over the past decade, in which special attention has been paid to the treatment of modifiable risk factors (e.g., hypertension, obesity, smoking, alcohol, lack of exercise) and the value of having a multidisciplinary team. We also observed a change from a rate control strategy to a rhythm control strategy for symptomatic patients with AF. This is primarily attributed to improved efficacy and safety of AF ablation procedures rather than the development of new antiarrhythmic drugs.

As mentioned earlier, another important development was the introduction of DOAC in 2016 in the Netherlands, including the factor IIa inhibitors (dabigatran) and Xa inhibitors (rivaroxaban, apixaban, edoxaban). Large RCT's have clearly demonstrated a reduction in bleeding events with a similar preventive effect on thromboembolic events in patients with non-valvular AF (6). The safety profile of DOACs have resulted in their widespread acceptance, which has, in turn, led to them largely supplanting VKAs in the treatment of the majority of patients with atrial fibrillation. Notable exceptions are patients with mechanical valves, end-stage renal disease and frail elderly (FRAIL-AF) (14). The increased use of DOAC also had a major impact on the management of patients with AF who presented in hospitals for an electrical cardioversion or AF ablation. After the introduction of DOAC, the lack of an antidote caused hesitation among operators to conduct an invasive AF procedure while the patient was using DOAC. We evaluated a minimally interrupted DOAC strategy (discontinuation 24 hour before procedure) in patients undergoing AF ablation and this was associated with a similar safety profile as uninterrupted VKA. Furthermore, several randomized trials have demonstrated the safety of uninterrupted DOAC, and this is now the standard approach in most EP hospitals, including ours.

Novel oral anticoagulants are being developed, like the factor XIa inhibitors (e.g., asundexian, milvexian), with a presumed better safety profile (less bleeding) than the current DOACs. Unfortunately, clinical trials (e.g., OCEANIC-AF) have shown a

reduced thrombo-embolic protective effect (15). Consequently, we do not expect that factor XIa inhibitors will be introduced for AF management in clinical practice in the short term.

Besides developments in novel oral anticoagulants, a major technological improvement in the past few years is the introduction of pulsed field ablation (PFA). PFA is a non-thermal cardio selective energy source and thus reduces collateral damage (e.g., phrenic nerve palsy, oesophageal damage). The ease of use and increased procedural efficiency has rendered PFA an interesting ablation modality. However, the first large RCT (ADVENT) had only demonstrated that PFA was noninferior to conventional thermal energy sources (cryoablation, radiofrequency) (16). The coming years will determine whether PFA will replace conventional energy sources.

In addition to cardioversion, ablation, anticoagulation, and antiarrhythmic drugs, it is crucial to address underlying modifiable risk factors to improve the outcome of AF management. These risk factors include obesity, hypertension, smoking, excessive alcohol, OSA, and lack of exercise (17). Obesity is a major societal problem with a dire impact on the health system. Weight loss and risk factor management is associated with a significant reduction of AF burden and the maintenance of sinus rhythm (LEGACY, ARREST-AF) (12, 18). Unfortunately, in daily practice it is arduous to establish a sustained change in lifestyle adaptation (RACE-3) (19). Furthermore, many patients and treating caregivers are insufficiently appreciative that certain risk factors, such as OSA are present. We demonstrated that 38% of patients undergoing AF ablation had undiagnosed OSA. To improve the detection, management and treatment of modifiable risk factors in patients with AF, the establishment of integrated AF care initiatives proved to be a valuable strategy (20). To further develop AF care, it is also crucial to implement regional AF care to homogenize the treatment of AF patients. This is also in accordance with the Integral Care Agreement which promotes appropriate care at the right location (21). Since AF ablation is only possible in centers with thoracic surgical backup in the Netherlands, clear indications for invasive rhythm management should be made in this regional collaboration.

Finally, we anticipate that the novel indication of the GLP1 agonists (e.g., semaglutide) in AF patients with obesity promises to play a significant role in their

treatment. The SELECT trial has previously demonstrated that in patients with preexisting cardiovascular disease and obesity, the prescribing of semaglutide improved cardiovascular outcomes (22). The DUTCH-WAIST trial aims to evaluate whether semaglutide reduces AF burden in obese patients (NCT06184633). The future will tell whether GLP1 agonists will become part of the therapeutic arsenal in obese patients with AF.

Part II – Evaluation of complication rates in device therapy

Summary

Cardiac implantable electronic devices (CIED) are used to treat impulse and conduction abnormalities, ventricular arrhythmias, and heart failure. CIEDs include pacemakers, leadless pacemakers, ICDs, and cardiac resynchronization therapy (CRT) using biventricular pacing or conduction system pacing (CSP). Growing numbers of pacemaker and ICD implantations can be observed due to increasing life expectancy and growing age of the population (23, 24). This is also observed in the Netherlands, with 14,570 pacemaker interventions in 2022. However, the number of ICD interventions has remained relatively stable with 5,664 ICD interventions in 2022, with up to 40% for secondary prevention (25). The indications for a pacemaker are most commonly sinus node dysfunction and high-degree atrioventricular block. Over 80% of implanted pacemakers are in patients >65 years. An ICD is usually indicated in patients for secondary prevention of sudden cardiac death, or for primary prevention in heart failure patients with a left ventricular ejection fraction of ≤35% (24). Finally, CRT is indicated in patients with chronic heart failure with severe LV dysfunction and left bundle branch block (LBBB). By correcting the electromechanical desynchrony caused by LBBB, positive LV remodelling is possible. This has resulted in significant improvement in morbidity and mortality in patients with heart failure and LBBB (23).

Both pacemakers and ICDs are considered low-risk procedures, but nonetheless are still associated with complications such as bleeding, infection, pneumothorax, and lead dislocation (23, 24). To minimise the risk of infection, preventive measures such as antibiotics prophylaxis, experienced and certified staff, sterile environment, periprocedural haemostatic agents, antibacterial envelopes and post-procedural pressure bandages are essential (26). Prevention of pocket hematoma is important,

and this also requires meticulous attention to risk factors, including renal failure, congestive heart failure, low operator experience, concomitant antiplatelet therapy, device replacement, lead revision, and heparin bridging (27, 28). Periprocedural oral anticoagulation is associated with a higher likelihood for pocket hematoma (29). Discontinuing DOACs 24–48 hours before surgery depending on renal function status, or targeting an international normalised ratio of 2.0 to 2.5, and avoiding heparin bridging were important changes in anticoagulation regimen over the last decade (30).

Randomized trials have demonstrated the efficacy and safety of DOAC in patients undergoing a cardiac implantable electronic device procedure (CIED). However, there is limited real-world data. In chapter 5 we evaluated clinically significant pocket hematoma and any systemic thromboembolic complication < 30 days after surgery of consecutive patients with AF undergoing an elective CIED procedure between January 2016 and June 2019 (31). Two-hundred eighty-three procedures were performed in patients with AF using oral anticoagulation. One-third of the procedures were performed under interrupted DOAC and the remainder under continued VKA. The DOAC group was younger, had less chronic renal disease, more paroxysmal AF, and a lower HAS-BLED score. The VKA group more often underwent a generator change only, in comparison to the DOAC group. There was no significant difference in clinically significant pocket hematoma between the VKA and DOAC groups. No thromboembolic events were reported for both groups. We found that in patients with AF undergoing an elective CIED procedure, the risk of a pocket hematoma and a systemic thromboembolic event is comparably low when using either interrupted DOAC or continued VKA.

Another important complication of a CIED procedure is the risk of a pocket infection. It is associated with increased mortality risk and substantial morbidity (32, 33). A pocket infection may necessitate device and lead extraction to prevent endocarditis, which leads to a significant burden for the patient and high health care costs. In reducing the risk of infections the use of antibiotic prophylaxis, chlorhexidine skin preparation, delaying the procedure in case of fever, avoidance of heparin bridging, avoidance of pocket hematoma, the use of strict sterile techniques, and having experienced operators are important preventive measures (34).

The PADIT (*Prevention of Arrhythmia Device Infection Trial*) score was developed to predict the risk of hospitalisation for device infection within 1 year (35, 36). This model includes 5 independent predictors of CIED infection including number of Prior procedures, Age, Depressed renal function (estimated glomerular filtration rate [GFR] <30 mL/min), being Immunocompromised, and procedure Type. The minimum risk score is 0 and the maximum is 13. Based on the PADIT-score, 3 risk categories can be identified: low risk (≤4), intermediate risk (5-6), and high risk (≥7) of hospitalisation for device infection within 1 year (35). Antibacterial envelopes may cost effectively be used in high-risk patients as the WRAP-IT trial has demonstrated (37). In the Netherlands reimbursement is currently lacking, further underlining the need for properly identifying high risk patients.

To evaluate the risk in every day clinical practice we performed a retrospective single-center study of consecutive patients undergoing a CIED procedure (chapter 6) (38). We evaluated hospitalisation for a CIED infection in the first year after the index procedure between January 2016 and November 2021. Patients who received an antibacterial envelope were excluded from this study. The primary endpoint was hospitalisation for a CIED infection in the first year after the procedure. A total of 2333 CIED procedures were performed in the study period, with a CIED infection occurring in 10 patients (0.43%). In predicting major CIED infection the PADIT-score had a good discrimination. The risk of CIED infection was higher in the patients with a PADIT score of ≥7 compared to those with a lower PADIT-score. Based on these results, we concluded that the PADIT-score is a clinically useful score for identifying patients at risk of developing CIED infection. The use of an antibacterial envelope in these high-risk patients may be cost-effective.

When CIED-related infection occurs, there is a class I indication for transvenous lead extraction (TLE). TLE is also used in case of dysfunctional leads or in upgrade procedures when venous access is limited. TLE tools have evolved, and the most common tools are a mechanical or laser extraction sheath and the use of snares. In general, the femoral snare has mainly been used as a bail-out procedure. In chapter 7 we evaluated the efficacy and safety of a TLE approach with a low threshold to use a combined superior and femoral approach between 2012 till 2019 (39). A total of 264 procedures were performed in the study period. The main indications for TLE were mostly lead malfunction, but also isolated pocket infection and systemic

infection. The complete and clinical procedural success rate, and complete lead removal rate was high of all targeted leads. The major procedure-related complication rate was low. We found that an effective and safe TLE procedure can be achieved by using the synergy between a superior and femoral approach.

Discussion

In part II we focused on the periprocedural and long-term complications associated with CIED therapy, including bleeding complications in patients using oral anticoagulation, the identification of patients at risk of CIED infection and risk of transvenous lead extraction in patients with CIED-related infection or lead dysfunction.

Overall, there is a steady increase in the number of implanted pacemakers, ICDs and CRTs in Europe according to the 2017 EHRA white book (40). This can potentially increase the number of associated complications. To improve patient outcome, various factors should be taken into account, including accurate patient selection, optimal implantation technique, and adequate follow-up to timely detect CIED dysfunction. In the past, pre-procedural information was focused on informing patients what to expect during and after the procedure, including short-term complications (within the first year), rather than on device selection (modality), long-term effects, end-of-life care, inappropriate shocks and psychological burden. This has also been recognised by the Dutch government, the Netherlands Society of Cardiology (NVVC), and Dutch society of Cardiovascular Nursing (NVHVV) (41). Uniform patient information materials, with a focus on shared decision-making, benefits and disadvantages of CIED therapy, and care pathways have a functional role. In this respect it is important to encourage patient participation in shared decision making, not only when selecting the preferred treatment (modality), but also involving the patient actively in the follow-up phase as they themselves can provide essential information concerning both prevention and treatment of potential complications when informed thoroughly.

When both patients and health care provider achieve consensus on CIED implantation, preoperative assessment should aim to optimise the conditions for implantation regarding patient condition (e.g., afebrile status, allergies, fluid status) and perioperative management of anticoagulation/antiplatelet drugs. To achieve an

optimal implantation technique, operator experience and facilities should meet a certain standard.

CIED implantations are considered low bleeding risk procedures with an incidence of bleeding of approximately 2% (30). However, pocket hematoma and CIED-related infections remain a significant concern, as this not only can cause local discomfort or pain but also may result in prolongation of hospitalisation and even re-operation on some occasions (42-44). Furthermore, a pocket hematoma increases the risk of a pocket infection (45), and consequently increased morbidity and mortality (34, 46). Therefore, mitigation of the risk of hematoma is essential and this requires meticulous attention to modifiable risk factors, good operative skills, and proper patient preparation. Modifiable risk factors for pocket hematoma include heparin bridging, concomitant antiplatelet therapy, low operator experience, and the use of a submuscular pocket (27, 47, 48). Non-modifiable risk factors include renal failure, congestive heart failure, device replacement and upgrade or lead revision procedure. In addition to these (non)modifiable risk factors, active preventive measures with gelatine-thrombin matrix sealants, like FloSeal® or Surgiflow®, can be used to effectively aid haemostasis in CIED surgery (49). Postoperative surveillance for signs of hematoma formation is essential for timely intervention. Compression with sandbags, vests or tapes can be effective as an intervention (50).

Risk assessment using risk score calculators serve as a valuable tool by offering an objective means to identify high-risk patients for bleeding and infection (35, 51-53). Furthermore, it enhances communication between healthcare providers by quantifying if the selected patient is at high-risk and consequently taking appropriate preventive measures. Ideally, this is also communicated with the patient as part of the shared decision-making process.

However, risk-scores like the HAS-BLED have shown limited performance in patients under a DOAC anticoagulation regimen in predicting bleeding risk. The novel ‘DOAC Score’ has a stronger predictive performance than the HAS-BLED score in patients with AF and using either apixaban, edoxaban or rivaroxaban (53) and consequently has the potential to better identify patients at risk for a pocket hematoma. This ‘DOAC Score’ assigns points for age, creatinine clearance/glomerular filtration rate, underweight status, stroke/transient ischemic attack/embolism history, diabetes,

hypertension, antiplatelet use, nonsteroidal anti-inflammatory use, liver disease, and bleeding history.

Integration of the PADIT-score into clinical practice and decision support tools enables the planning of proactive measures to mitigate potential infection, such as an antibacterial envelope, meticulous surgical technique, and postoperative surveillance. We demonstrated the usefulness of the PADIT score in the identification of patients at high risk for developing CIED infection, where an antibacterial envelope may have been useful. The 2019 EHRA consensus document recommends using an antibiotic envelope in patients exhibiting characteristics similar to those in the WRAP-IT study or presenting with other high-risk factors, in the context of the local incidence of CIED infections (34). It is important to note this latter aspect, as different centers have different standard-of-care infection rates depending on their patient populations and local preventive measures. The WRAP-IT trial demonstrated the efficacy and cost-effectiveness of antibacterial envelopes in selected CIED populations (i.e., CRT procedures, CIED replacements and upgrades) (54, 55). Regrettably, in the Netherlands, reimbursement is lacking for the utilisation of an antibiotic envelope in CIED surgery, in contrast to other European countries.

Other complications associated with CIED implantations, such as pneumothorax, cardiac perforation, lead dysfunction and lead-related endocarditis, can be related to the implantation of a transvenous lead. Most of these complications can be overcome by using novel devices such as subcutaneous ICDs and leadless pacemakers (34, 56, 57), which currently are used when a lack of a superior access exists (i.e., occluded superior veins). The PRAETORIAN trial has shown that subcutaneous ICDs are noninferior to transvenous ICDs with respect to device-related complications and inappropriate shocks (58). Thus, S-ICDs should be considered as an alternative to transvenous technologies. However, the higher costs of these novel devices require scrutiny to identify the patients who will benefit the most of these devices. Future studies will identify which patient groups are most suitable.

Part III – Patient empowerment: Use of eHealth as discharge aid

Summary

Finally, in this thesis we addressed the importance of involving the patient in his or her treatment strategy. Patient centred care models encourage shared decision-making between patients and healthcare providers (1, 59). Patient empowerment may be impacted by knowledge concerning early recognition of possible complications. Patients who are engaged in their care are more likely to adhere to therapy, helping promptly identify irregularities or complications (59). Health literacy and disease self-management can benefit from eHealth applications (60, 61).

In chapter 8 we compared patient-tailored discharge information with conventional discharge information in a single center prospective study (62). A total of 112 patients undergoing an electrophysiological procedure were enrolled between January and March 2016. The provided discharge information was evaluated using a peer-reviewed questionnaire distributed among patients, nurses, and nurse practitioners. The web tool was found easy to use and time-saving by the nurse practitioners. Patients evaluated the generated discharge information as equal to the standard information. A reduction in discharge preparation time and increased uniformity of provided information were reported by nurses.

As a result of advances in therapy and changes in care pathways a reduction in (re)hospitalisations was observed in the Erasmus MC. The Erasmus MC, being a tertiary referral hospital, has a wider catchment area than other hospitals in the region and referred patients are at risk for a gap in their follow-up. Use of eHealth may facilitate a reduction of patient time spent in clinical assessments, and reduced travel times (63). Early recognition of complications may also be possible using telemedicine. In our clinical practice we offer teleconsultation for patients until their first outpatient clinic visit.

In chapter 9 we studied the feasibility of telemedical wound assessment using a mobile phone (64). In a single center prospective study we compared groups using feature phones with integrated camera (e.g. Nokia 2230 or Sony K700i) with those using smartphones. Typically, older patients used a feature phone. Patients were instructed to photograph their wound or puncture site after hospital discharge and

upload the photographs to a secure email address 6 days after hospital discharge. Received photos were assessed by two nurse practitioners independently on high-resolution screens. The intervention was evaluated using a peer-reviewed questionnaire and a photo assessment scheme. Thirty-three of 40 patients (83%) were able to upload their photographs. However, smartphone users were significantly more successful in uploading their photographs compared with feature phone users (93% vs 55%, P < .01). Eighty-eight percent of the clinical photographs were interpretable. The interobserver variability had an agreement between 93% and 97%.

Discussion

In part III we evaluated the applicability of selected eHealth tools implemented in our clinical practice, specifically for patient discharge and supporting follow-up. Importantly, when developing eHealth tools, we focused on pre-identified gaps in the patient care pathway.

The identified lack of uniformity in the discharge information was approached via a computer-generated discharge letter, merging various elements from diverse information sources. This novel letter enhanced the discharge process in which the nurses were able to inform better the patient. Importantly, with the introduction of a new electronic heath record system (HiX™ by Chipsoft) these gaps were addressed. Consequently, after two years the computer-generated letter program was discontinued. Nonetheless, patients with low or insufficient (health) literacy levels, constituting almost 30% of the Dutch population, experience difficulty in comprehending health related information irrespective of the method in which information is provided (65, 66). The level of literacy or preferences for the form of patient discharge information has not been screened in our clinical practice. It is recommended to assess the level of health literacy prior to providing discharge information, for example via the three question Set of Brief Screening Questions questionnaire (67). Moreover, other forms of media communication, such as illustrations, online animations or videos may be more appropriate for low literacy level patients.

A novel approach in wound assessment has been the confluence of patient empowerment and telemedicine. Previously, wound assessment was the sole domain of healthcare professionals. The adoptability of smartphones has made

patients engagement in their own healthcare more assessable. Patients can take photographs with their smartphone of wounds and/or puncture sites, after discharge, and forward them to a health care professional for assessment. This simplistic approach aligns with the needs of patients and health care professional, and therefore empowers patients in post-discharge treatment (68). Although smartphone photography cannot fully replace clinical appraisal, it can act as a preliminary indicator for consultation.

Importantly, patients need to have sufficient digital literacy. The current level of digital literacy of the Dutch population is approximately 80 percent, with the younger and higher educated cohorts scoring highest (69). Therefore, the challenge may lie in assessing if the patient is capable in using eHealth technologies and introducing it to the standard discharge procedure. In addition, a set of concise instructions should be provided to aid these patients.

Meanwhile, photographic telemedical evaluation of puncture sites and surgical wounds using smartphones has been fully implemented in the short stay cardiology department of our hospital. This innovation has also been established to other subspecialities, including patients treated with a Left Ventricular Assist Device (LVAD). Importantly, the quality of the photographs has increased significantly with the improved camera possibilities of current day smartphones. The next development phase is the opportunity for patients to upload clinical photographs directly into their own electronic health care record. This aspect, avoiding data breaches, adheres therefore with the EU-GDPR (70).

Assessing clinical photographs can be labour intensive for healthcare professionals and novel Artificial Intelligence (AI) initiatives may reduce the assessment workload. In 2024 the Erasmus MC will start a single center feasibility study on the use of AI in smartphone photography telemedical assessment of LVAD wounds/puncture sites.

A topical challenge for the health care system and professionals focusses on reducing the ecological footprint. Using photograph-based telemedicine will substantially reduce visits to outpatient departments. When focusing on discharge letters, these may be forwarded to the patient as a PDF file through a secure email server, instead of handing out a printed version. Both may be small contributions in reducing the ecological footprint but are easily implemented.

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DUTCH SUMMARY | NEDERLANDSE SAMENVATTING

Introductie

Elektrofysiologie, een subspecialisatie van cardiologie, richt zich op de behandeling van hartritmestoornissen en de preventie van plotselinge hartdood. Binnen het Erasmus MC is een gespecialiseerd team, bestaande uit elektrofysiologen, fellows, verpleegkundig specialisten, verpleegkundigen, technici en onderzoekspersoneel, toegewijd aan de behandeling en zorg voor patiënten met hartritmestoornissen. De behandeling van hartritmestoornissen is in de afgelopen decennia geëvolueerd naar een breed spectrum van invasieve en niet-invasieve therapieën. Het invasieve behandelarsenaal omvat pacemakers, implanteerbare cardioverter-defibrillatoren (ICD's), cardiale resynchronisatietherapie (CRT) en katheterablatie van hartritmestoornissen. (1). Zowel therapie met cardiac implantable electronic devices (CIED) als katheterablatie zijn de afgelopen jaren verbeterd, met een bijbehorende toename in effectiviteit. Bovendien is patiëntgerichte zorg, met nadruk op gezamenlijke besluitvorming, onderdeel geworden van de klinische praktijk. Momenteel ligt de nadruk op het beheersen van risicofactoren, wat de therapieresultaten kan optimaliseren, en was zo het onderliggende principe van deze thesis.

Deel I – Evaluatie van complicaties in de behandeling van atriumfibrillatie

Atriumfibrilleren (AF) is een supraventriculaire tachyaritmie met ongecoördineerde elektrische activatie van de atria (2). Het is de meest voorkomende hartritmestoornis bij volwassenen en vormt een aanzienlijke last voor patiënten, de volksgezondheid en de gezondheidszorg. Het levenslange risico op AF in Europa is maar liefst 40% (2). In 2021 werden in Nederland ongeveer 123.400 nieuw gediagnosticeerde gevallen van AF gedocumenteerd (3).

Momenteel is het eerste doel om aanpassing van levensstijl te verbeteren en in te zetten op een agressiever management van risicofactoren. Ten tweede lopen patiënten met AF een verhoogd risico op een beroerte, en het gebruik van orale anticoagulantia zal dit risico verminderen, maar dit brengt op zijn beurt weer een bloedingsrisico met zich mee. Ten slotte zal er een keuze worden gemaakt tussen frequentie- of ritmecontrole, afhankelijk van de voorkeuren van de patiënt,

symptomen, co-morbiditeit en de verwachte voordelen en risico's van invasieve katheterablatie. Frequentiecontrole wordt bereikt met behulp van atrioventriculaire blokkerende geneesmiddelen (zoals bètablokkers, digoxine, verapamil) of een "pace and ablate" strategie. Ritmecontrole wordt bereikt door een combinatie van anti-aritmische geneesmiddelen, elektrische cardioversies (ECV's) en AF katheterablatie. Inherent aan elke medische procedure zijn er bepaalde risico's verbonden aan elektrofysiologische procedures. Zowel ECV's als AF katheterablatie gaan gepaard met het risico op bloedingen en trombo-embolische gebeurtenissen (2, 4, 5).

In het afgelopen decennium is het gebruik van anticoagulantia bij patiënten met AF verschoven van vitamine K-anticoagulantia (VKA's) naar directe orale anticoagulantia (DOAC's). Verschillende grote, gerandomiseerde studies (RE-LY, ROCKET-AF, ARISTOTLE en ENGAGE AF-TIMI) hebben aangetoond dat DOAC's een gunstiger risico-batenprofiel hebben met betrekking tot beroerte, intracraniële bloeding en mortaliteit (6). Als gevolg hiervan is het gebruik van DOAC's aanzienlijk toegenomen bij patiënten met AF. In Nederland was er vóór 2016 een verminderde acceptatie in het gebruik ervan, vanwege beperkte gegevens over de peri-procedurele effectiviteit en veiligheid, het ontbreken van een antidotum en de verhoogde zorgkosten (7, 8). Sinds 2016 is er een duidelijke verschuiving geweest in het gebruik van VKA naar DOAC bij AF-patiënten, inclusief patiënten die zich presenteerden voor een ECV en AF katheterablatie.

In hoofdstuk 2 evalueerden we trombo-embolieën (combinatie van beroerte, voorbijgaande ischemische aanval of systemische embolie) en klinisch significante majeure bloedingen binnen 60 dagen na ECV (9). We includeerden 920 opeenvolgende patiënten die een ECV ondergingen en vergeleken patiënten met een DOAC anticoagulatiebeleid met een VKA beleid, zonder routinematige transoesofageale echocardiografie (TEE), tussen januari 2013 en februari 2020. Er waren geen verschillen tussen de groepen wat betreft demografische variabelen en de gemiddelde CHA_2DS_2-VASc score; echter, de VKA-groep had een hoger aandeel patiënten met co-morbiditeit. We vonden dat in een ‘real-world’ populatie de incidentie van trombo-embolieën en majeure bloedingen laag was na electieve ECV bij patiënten die DOAC of VKA gebruikten en dat er geen verschil was tussen beide groepen.

AF-katheterablatie kan gepaard gaan met bloedingen en trombo-embolische events. In hoofdstuk 3 hebben we 637 opeenvolgende patiënten geëvalueerd die een AF-ablatie ondergingen (10). Deze patiënten hadden een AF-katheterablatie onder een VKA- of DOAC-antistollingsbehandeling tussen januari 2013 en april 2017. De primaire eindpunten waren klinisch relevante niet-majeure bloedingen, majeure bloedingen en systemische trombo-embolische events vanaf het moment van ablatie tot 30 dagen daarna. Bloedingen werden gedefinieerd volgens het Bleeding Academic Research Consortium (BARC) en de International Society on Thrombosis and Haemostasis (ISTH), aangezien beide bloedingsscores veel worden gebruikt. De incidentie van klinisch relevante niet-majeure bloedingen was lager in de DOAC-groep in vergelijking met de VKA-groep. De incidentie van majeure bloedingen was vergelijkbaar tussen de groepen. De incidentie van systemische embolieën was niet significant verschillend, zonder events in de minimaal onderbroken DOAC-groep en enkele events met gecontinueerde VKA. We ontdekten dat bij patiënten die een AF-katheterablatie ondergaan, antistolling met minimaal onderbroken DOAC geassocieerd was met minder klinisch relevante niet-majeure bloedingen in vergelijking met ononderbroken VKA, zonder de trombo-embolische veiligheid in gevaar te brengen.

Om de uitkomst van AF-ablatie te verbeteren, moet er niet alleen gefocust worden op technologie. Het aanpakken van beïnvloedbare risicofactoren is even belangrijk. Een potentieel beïnvloedbare risicofactor voor AF is slaapapneu, die dezelfde risicofactoren deelt als AF, zoals obesitas en hypertensie (1, 11, 12). Dit kan worden verminderd door lifestylemanagement zoals gewichtsverlies en lichamelijke oefening. Bij voorkeur moet lifestylemanagement en de behandeling van slaapapneu worden gestart vóór katheterablatie, omdat dit de uitkomst kan verbeteren (2). Slaapstoornissen zoals slaapapneu kunnen de uitkomst van katheterablatie van AF verminderen. Belangrijk is dat slaapstoornissen niet gemakkelijk worden herkend en dus mogelijk onvoldoende worden behandeld.

In hoofdstuk 4 hebben we geëvalueerd of niet gediagnosticeerde slaapapneu invloed heeft op de recidief AF na katheterablatie in een single-center prospectieve cohortstudie (13). Patiënten werden 12 tot 18 maanden na AF-katheterablatie geïncludeerd. Honderd en vier geschikte patiënten ondergingen een screening op slaapapneu, met behulp van een WatchPAT (WP), een draagbaar thuisslaapapneu-

testapparaat. We hebben aangetoond dat het risico op recidief AF significant hoger was in de groep met niet gediagnosticeerde slaapapneu in het eerste jaar na de ablatie in vergelijking met patiënten zonder slaapapneu. Een significant aantal patiënten dat een katheterablatie van AF onderging, heeft niet gediagnosticeerde slaapapneu, wat geassocieerd is met een tweevoudig hoger risico op recidief AF. Screening op slaapapneu kan de patiëntenvoorlichting over de effectiviteit van katheterablatie verbeteren. We vonden dat de veelgebruikte Epworth Sleepiness Scale en STOP-Bang vragenlijsten onvoldoende presteerden bij het detecteren van slaapapneu in ons cohort.

Deel II – Evaluatie van complicaties in device therapie

CIED's worden gebruikt om impuls- en geleidingsstoornissen, ventriculaire hartritmestoornissen en hartfalen te behandelen. Ze omvatten pacemakers, pacemakers zonder leads, ICD's en cardiale resynchronisatietherapie (CRT) met bi-ventriculaire pacing of conduction system pacing (CSP). Er is sprake van een toenemend aantal pacemaker- en ICD-implantaties als gevolg van een toenemende levensverwachting en vergrijzing van de bevolking (14, 15). Dit wordt ook waargenomen in Nederland, met 14.570 pacemakerinterventies in 2022. Het aantal ICD-interventies is echter relatief stabiel gebleven, met 5.664 ICD-interventies in 2022, waarvan tot 40% voor secundaire preventie (16). De indicaties voor een pacemaker zijn meestal sinusbradycardie en hooggradig atrioventriculair blok. Meer dan 80% van de geïmplanteerde pacemakers vindt plaats bij patiënten ouder dan 65 jaar. Een ICD is meestal geïndiceerd bij patiënten voor secundaire preventie van plotse hartdood, of voor primaire preventie bij patiënten met hartfalen en een linkerventrikelejectiefractie van ≤35% (15). Tot slot is CRT geïndiceerd bij patiënten met chronisch hartfalen met ernstige LV-dysfunctie en een linker bundeltakblok (LBTB). Door de elektromechanische desynchronie veroorzaakt door LBTB te corrigeren, is positieve LV-remodeling mogelijk. Dit heeft geleid tot een significante verbetering van morbiditeit en mortaliteit bij patiënten met hartfalen en LBTB (14).

Zowel pacemakers als ICD's worden beschouwd als ingrepen met een laag risico, maar desondanks zijn ze nog steeds geassocieerd met complicaties zoals bloedingen, infecties, pneumothorax en leaddislocatie (14, 15). Om het risico op infectie te minimaliseren, zijn preventieve maatregelen zoals antibiotische profylaxe,

ervaren en gecertificeerd personeel, een steriele omgeving, peri-procedurele hemostatische geneesmiddelen, antibacteriële enveloppen en drukverbanden na de ingreep essentieel (17). Preventie van pockethematomen is belangrijk, en dit vereist ook nauwgezette aandacht voor risicofactoren, waaronder nierfalen, congestief hartfalen, beperkte ervaring van de operator, adjuvante antiplaatjestherapie, CIED-vervanging, revisie van de lead en heparine-overbrugging (18, 19). Peri-procedurele orale anticoagulatie is geassocieerd met een grotere kans op een pockethematoom (20). Het stopzetten van DOAC's 24-48 uur vóór de operatie, afhankelijk van de nierfunctie, of het streven naar een internationaal genormaliseerde ratio van 2,0 tot 2,5, en het vermijden van heparine-overbrugging waren belangrijke veranderingen in het antistollingsregime in de afgelopen tien jaar (21).

Randomised control trials hebben de werkzaamheid en veiligheid van DOAC's aangetoond bij patiënten die een CIED-procedure ondergaan. Er is echter beperkte real-world data beschikbaar. In hoofdstuk 5 hebben we de klinisch significante pockethematomen en eventuele systemische trombo-embolische complicaties < 30 dagen na de operatie geëvalueerd bij opeenvolgende patiënten met AF die een electieve CIED-procedure ondergingen tussen januari 2016 en juni 2019 (22). Er werden 283 procedures uitgevoerd bij patiënten met AF die orale anticoagulatie kregen. Een derde van de procedures werd uitgevoerd onder onderbroken DOAC en de rest onder gecontinueerde VKA. De DOAC-groep was jonger, had minder chronische nierziekte, meer paroxismale AF en een lagere HAS-BLED-score. In vergelijking met de DOAC-groep onderging de VKA-groep vaker alleen een generatorvervanging. Er was geen significant verschil in klinisch significante pockethematomen tussen de VKA- en DOAC-groepen. Er werden geen trombo-embolische gebeurtenissen gemeld voor beide groepen. We zagen dat bij patiënten met AF die een electieve CIED-procedure ondergingen, het risico op een pockethematoom en een systemische trombo-embolische gebeurtenis vergelijkbaar laag is bij zowel onderbroken DOAC als gecontinueerde VKA.

Een andere belangrijke complicatie van een CIED-procedure is het risico op een pocketinfectie. Dit is geassocieerd met een verhoogd risico op mortaliteit en aanzienlijke morbiditeit (23, 24). Een pocketinfectie kan vereisen dat de CIED en de lead(s) worden verwijderd om endocarditis te voorkomen, wat leidt tot een aanzienlijke belasting voor de patiënt, evenals hoge zorgkosten. Bij het verminderen

van het risico op infecties zijn het gebruik van antibiotische profylaxe, chloorhexidine huiddesinfectie, uitstel van de procedure bij koorts, vermijding van heparine-overbrugging, vermijding van pockethematomen, het gebruik van strikte steriele technieken en het hebben van ervaren operators belangrijke preventieve maatregelen (25).

De PADIT (*Prevention of Arrhythmia Device Infection Trial*) score is ontwikkeld om het risico op ziekenhuisopname voor CIED-infectie binnen 1 jaar te voorspellen (26, 27). Dit model omvat 5 onafhankelijke voorspellers van CIED-infectie, waaronder het aantal voorafgaande procedures, leeftijd, verminderde nierfunctie (geschatte glomerulaire filtratiesnelheid [GFR] <30 ml/min), immuun gecompromitteerd zijn en het type procedure. Het minimum van de risicoscore is 0 en het maximum is 13. Op basis van de PADIT-score kunnen 3 risicocategorieën worden geïdentificeerd: laag risico (≤4), intermediair risico (5-6) en hoog risico (≥7) op ziekenhuisopname voor CIED-infectie binnen 1 jaar (26). Antibacteriële enveloppen kunnen kosteneffectief worden gebruikt bij patiënten met een hoog risico, zoals is aangetoond in de WRAP-IT trial (28). In Nederland ontbreekt momenteel vergoeding, wat de noodzaak benadrukt om hoog-risicopatiënten correct te identificeren.

In hoofdstuk 6 evalueerden we het risico in de dagelijkse klinische praktijk met een retrospectieve single-center studie van opeenvolgende patiënten die een CIED-procedure ondergingen (29). We evalueerden ziekenhuisopname voor een CIED-infectie in het eerste jaar na de indexprocedure tussen januari 2016 en november 2021. Patiënten die een antibacteriële envelop kregen, werden uitgesloten van deze studie. Het primaire eindpunt was ziekenhuisopname voor een CIED-infectie in het eerste jaar na de procedure. In totaal werden 2333 CIED-procedures uitgevoerd in de studieperiode, waarbij een CIED-infectie optrad bij 10 patiënten (0,43%). Bij het voorspellen van een majeure CIED-infectie had de PADIT-score een goed onderscheidend vermogen. Het risico op een CIED-infectie was hoger bij patiënten met een PADIT-score van ≥7 in vergelijking met die met een lagere PADIT-score. Op basis van deze resultaten concludeerden we dat de PADIT-score een klinisch bruikbare score is voor het identificeren van patiënten met een risico op het ontwikkelen van een CIED-infectie. Het gebruik van een antibacteriële envelop bij deze hoog-risicopatiënten kan kosteneffectief zijn.

Wanneer er een CIED-infectie optreedt, is er een indicatie van klasse I voor transveneuze leadextractie (TLE). TLE wordt ook gebruikt in geval van disfunctionele leads of bij upgrade-procedures wanneer de veneuze toegang beperkt is. TLE-hulpmiddelen zijn steeds beter geworden, en de meest voorkomende hulpmiddelen zijn een mechanische of laser-extractieschede en het gebruik van snares. Over het algemeen is de femorale snare voornamelijk in gebruik als een noodprocedure. In hoofdstuk 7 hebben we de werkzaamheid en veiligheid geëvalueerd van een TLE-benadering met een lage drempel om een gecombineerde superieure en femorale benadering te gebruiken tussen 2012 en 2019 (30). Gedurende de studie werden in totaal 264 procedures uitgevoerd. De belangrijkste indicaties voor TLE waren voornamelijk disfunctie van de lead, maar ook geïsoleerde pocketinfectie en systemische infectie. Het percentage volledig en klinisch procedureel succes, en het percentage volledige leadverwijdering was hoog voor alle leads. Het percentage majeure procedure gerelateerde complicaties was laag. We ontdekten dat een effectieve en veilige TLE-procedure kan worden bereikt door de combinatie van een superieure en femorale benadering te gebruiken.

Deel III – Empowerment van patiënten: gebruik van eHealth als ontslaghulp

Tot slot hebben we in dit proefschrift het belang benadrukt van het betrekken van de patiënt bij zijn of haar behandelstrategie. Modellen voor patiëntgerichte zorg stimuleren gedeelde besluitvorming tussen patiënten en zorgverleners (1, 31). Empowerment van patiënten kan worden beïnvloed door kennis over het vroegtijdig herkennen van mogelijke complicaties. Patiënten die betrokken zijn bij hun zorg zullen zich waarschijnlijk beter aan de voorschriften houden, waardoor ze sneller onregelmatigheden of complicaties kunnen identificeren (31). Gezondheids-vaardigheden en zelfmanagement van ziekten kunnen verbeteren door eHealth-toepassingen (32, 33).

In hoofdstuk 8 hebben we patiënt-specifieke ontslaginformatie vergeleken met conventionele ontslaginformatie in een single center prospectieve studie (34). In totaal werden 112 patiënten die een elektrofysiologische procedure ondergingen, geïncludeerd tussen januari en maart 2016. De verstrekte ontslaginformatie werd geëvalueerd met behulp van een peer-reviewed vragenlijst die onder patiënten, verpleegkundigen en verpleegkundig specialisten werd verspreid. De webtool, voor

genereren van patiënt-specifieke ontslaginformatie, werd door de verpleegkundig specialisten als gemakkelijk te gebruiken en tijdbesparend ervaren. Patiënten beoordeelden de gegenereerde ontslaginformatie als gelijkwaardig aan de standaardinformatie. Verpleegkundigen meldden een afname van de voorbereidingstijd voor ontslag en een toename van de uniformiteit van de verstrekte informatie.

Als gevolg van vooruitgang in therapieën en veranderingen in zorgpaden werd een vermindering van (her)opnames waargenomen in het Erasmus MC. Het Erasmus MC heeft, als een tertiair verwijsziekenhuis, een breder verzorgingsgebied dan andere ziekenhuizen in de regio, en verwezen patiënten lopen het risico op een lacune in hun follow-up. Het gebruik van eHealth kan een vermindering van de tijd die patiënten doorbrengen in klinische beoordelingen en verminderde reistijden bewerkstelligen (35). Vroegtijdige herkenning van complicaties is ook mogelijk met behulp van telegeneeskunde. In onze klinische praktijk bieden we teleconsultatie aan voor patiënten tot hun eerste polikliniekbezoek.

In hoofdstuk 9 hebben we de haalbaarheid van telemedische wondbeoordeling met een mobiele telefoon bestudeerd (36). In een single center prospectieve studie vergeleken we groepen die feature phones gebruikten met geïntegreerde camera's (bijv. Nokia 2230 of Sony K700i) met diegenen die smartphones gebruikten. Doorgaans gebruikten oudere patiënten een feature phone. Patiënten kregen de instructie om hun wond of punctieplaats na ontslag uit het ziekenhuis te fotograferen en de foto's 6 dagen na ontslag naar een beveiligd e-mailadres te uploaden. Ontvangen foto's werden onafhankelijk beoordeeld door twee verpleegkundig specialisten op high-resolutieschermen. De interventie werd geëvalueerd met behulp van een peer-reviewed vragenlijst en een fotobeoordelingsschema. Drieëndertig van de 40 patiënten (83%) konden hun foto's uploaden. Smartphonegebruikers waren echter significant succesvoller in het uploaden van hun foto's in vergelijking met feature phonegebruikers (93% vs. 55%, $P < .01$). Achtentachtig procent van de klinische foto's was interpreteerbaar. De interobserver-variabiliteit had een overeenstemming tussen 93% en 97%.

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GERMAN SUMMARY | ZUSAMMENFASSUNG IN DEUTSCH

Einleitung

Die Elektrophysiologie, eine Subspezialisierung der Kardiologie, konzentriert sich auf die Behandlung von Herzrhythmusstörungen und die Prävention des plötzlichen Herztodes. Im Uniklinikum Erasmus Medisch Centrum in Rotterdam ist ein spezialisiertes Team, bestehend aus Elektrophysiologen, Stipendiaten, *Nurse Practitioners*, Krankenpflegepersonal, Technikern und Forschungspersonal, der Behandlung und Pflege von Patienten mit Herzrhythmusstörungen gewidmet. Die Behandlung von Herzrhythmusstörungen hat sich in den letzten Jahrzehnten zu einem breiten Spektrum invasiver und nicht-invasiver Therapien entwickelt. Das invasive Behandlungsspektrum umfasst Herzschrittmacher, implantierbare Kardioverter-Defibrillatoren (ICDs), kardiale Resynchronisationstherapie (CRT) und Katheterablation von Herzrhythmusstörungen. Sowohl die Therapie mit *Cardiac Implantable Electronic Devices* (CIED) als auch die Katheterablation haben sich in den letzten Jahren weiterentwickelt und damit ihre Effektivität verbessert. Darüber hinaus ist die patientenzentrierte Versorgung, mit Schwerpunkt auf gemeinsamer Entscheidungsfindung, ein Teil der klinischen Praxis geworden. Derzeit liegt der Fokus auf der Kontrolle von Risikofaktoren, was die Therapieergebnisse optimieren kann und das zugrundeliegende Prinzip dieser Dissertation war.

Teil I – Bewertung von Komplikationen bei der Behandlung von Vorhofflimmern

Vorhofflimmern (VHF) ist eine supraventrikuläre Tachyarrhythmie mit unkoordinierten elektrischen Aktivierungen der Vorhöfe. Es ist die häufigste Herzrhythmusstörung bei Erwachsenen und stellt eine erhebliche Belastung für Patienten, die öffentliche Gesundheit und das Gesundheitssystem dar. Das lebenslange Risiko für VHF in Europa liegt bei beachtlichen 40%. Im Jahr 2021 wurden in den Niederlanden etwa 123.400 neu diagnostizierte Fälle von VHF dokumentiert.

Derzeit besteht das erste Ziel darin, die Lebensstilanpassung zu verbessern und ein aggressiveres Management der Risikofaktoren einzusetzen. Darüber hinaus haben Patienten mit VHF ein erhöhtes Schlaganfallrisiko, welches durch den Einsatz oraler Antikoagulantien verringert werden kann. Dies bringt jedoch ein Blutungsrisiko mit sich mit. Schließlich wird ein therapeutischer Ansatz zwischen Frequenz- oder

Rhythmuskontrolle getroffen, abhängig von den Vorlieben des Patienten, Symptomen, Komorbiditäten und den erwarteten Vorteilen und Risiken invasiver Katheterablationen. Die Frequenzkontrolle wird durch atrioventrikuläre blockierende Medikamente (wie Betablocker, Digoxin, Verapamil) oder eine *"Pace and Ablate"-Strategie* erreicht. Die Rhythmuskontrolle wird durch eine Kombination von Antiarrhythmika, elektrischen Kardioversionen (EKVs) und VHF-Katheterablationen erreicht. Wie bei jeder medizinischen Prozedur sind auch elektrophysiologische Eingriffe mit bestimmten Risiken verbunden. Sowohl EKVs als auch VHF-Katheterablationen sind mit dem Risiko von Blutungen und thromboembolischen Ereignissen verbunden.

Im letzten Jahrzehnt hat sich der Einsatz von Antikoagulantien bei Patienten mit VHF von Vitamin-K-Antagonisten (VKA) zu direkten oralen Antikoagulantien (DOAC) verschoben. Verschiedene große randomisierte Studien (RE-LY, ROCKET-AF, ARISTOTLE und ENGAGE AF-TIMI) haben gezeigt, dass DOACs ein günstigeres Nutzen-Risiko-Profil in Bezug auf Schlaganfall, intrakranielle Blutungen und Mortalität aufweisen. Infolgedessen hat der Einsatz von DOACs bei Patienten mit VHF erheblich zugenommen. In den Niederlanden gab es vor 2016 eine geringere Akzeptanz für den Einsatz, aufgrund begrenzter Daten zur peri-prozeduralen Effektivität und Sicherheit, des Fehlens eines Antidots und der erhöhten Gesundheitskosten. Seit 2016 hat es eine deutliche Verschiebung im Einsatz von VKA zu DOAC bei VHF-Patienten gegeben, einschließlich Patienten, die sich einer ECV und VHF-Katheterablation unterzogen.

In Kapitel 2 haben wir Thromboembolien (eine Kombination aus Schlaganfall, transitorischer ischämischer Attacke oder systemischer Embolie) und klinisch signifikante größere Blutungen innerhalb von 60 Tagen nach EKV evaluiert. Wir haben 920 aufeinanderfolgende Patienten, die sich einer EKV unterzogen haben, inkludiert und Patienten mit einer DOAC-Antikoagulation oder mit einer VKA-Antikoagulation ohne routinemäßige transösophageale Echokardiographie (TEE) zwischen Januar 2013 und Februar 2020 verglichen. Es gab keine Unterschiede zwischen den Gruppen hinsichtlich demografischer Variablen und dem durchschnittlichen CHA_2DS_2-VASc-Score; jedoch hatte die VKA-Gruppe einen höheren Anteil an Patienten mit Komorbiditäten. Wir fanden heraus, dass in einer *"real-world"*-Population die Inzidenz von Thromboembolien und größeren Blutungen

nach elektiver EKV bei Patienten, die DOAC oder VKA verwendeten, niedrig war und es keinen Unterschied zwischen den Gruppen gab.

Die VHF-Katheterablation kann mit Blutungen und thromboembolischen Ereignissen einhergehen. In Kapitel 3 haben wir 637 aufeinanderfolgende Patienten evaluiert, die sich einer VHF-Ablation unterzogen haben. Diese Patienten hatten eine VHF-Katheterablation unter einer VKA- oder DOAC-Antikoagulationsbehandlung zwischen Januar 2013 und April 2017. Die primären Endpunkte waren klinisch relevante nicht-erhebliche lutungen, erhebliche Blutungen und systemische thromboembolische Ereignisse ab dem Zeitpunkt der Ablation bis 30 Tage danach. Blutungen wurden gemäß dem Bleeding Academic Research Consortium (BARC) und der International Society on Thrombosis and Haemostasis (ISTH) definiert, da beide Blutungsscores weit verbreitet sind. Die Inzidenz klinisch relevanter nicht-erhebliche Blutungen war in der DOAC-Gruppe im Vergleich zur VKA-Gruppe niedriger. Die Inzidenz von größeren Blutungen war zwischen den Gruppen vergleichbar. Die Inzidenz systemischer Embolien war nicht signifikant unterschiedlich, ohne Ereignisse in der minimal unterbrochenen DOAC-Gruppe und einigen Ereignissen mit fortgesetzter VKA. Wir stellten fest, dass bei Patienten, die sich einer VHF-Katheterablation unterzogen, eine Antikoagulation mit minimal unterbrochener DOAC mit weniger klinisch relevanten nicht-erhebliche Blutungen im Vergleich zu ununterbrochenem VKA verbunden war, ohne die thromboembolische Sicherheit zu gefährden.

Um das Ergebnis der VHF-Ablation zu verbessern, muss nicht nur der Fokus auf der Technologie liegen. Die Bekämpfung beeinflussbarer Risikofaktoren ist ebenso von großer Relevanz. Ein potenziell beeinflussbarer Risikofaktor für VHF ist die Schlafapnoe, die dieselben Risikofaktoren wie VHF teilt, wie Adipositas und Bluthochdruck. Dies kann durch Lifestylemanagement wie Gewichtsverlust und körperliche Betätigung reduziert werden. Vorzugsweise sollte Lifestylemanagement und die Behandlung der Schlafapnoe vor der Katheterablation begonnen werden, da dies zu einer Verbesserung des Ergebnisses führen kann. Schlafstörungen wie Schlafapnoe können das Ergebnis der Katheterablation von VHF beeinträchtigen. Wichtig ist, dass Schlafstörungen nicht leicht erkannt werden und daher möglicherweise unzureichend behandelt werden.

In Kapitel 4 haben wir evaluiert, ob nicht diagnostizierte Schlafapnoe einen Einfluss auf das Wiederauftreten von VHF nach Katheterablation in einer Single-Center prospektiven Kohortenstudie hat. Patienten wurden 12 bis 18 Monate nach VHF-Katheterablation inkludiert. 104 geeignete Patienten unterzogen sich einem Schlafapnoe-Screening mit einem WatchPAT (WP), einem tragbaren Heimschlafapnoe-Testgerät. Wir haben festgestellt, dass das Risiko eines Wiederauftretens von VHF im ersten Jahr nach der Ablation in der Gruppe mit nicht diagnostizierter Schlafapnoe signifikant höher war als bei Patienten ohne Schlafapnoe. Eine signifikante Anzahl von Patienten, die sich einer Katheterablation von VHF unterzogen, hatte nicht diagnostizierte Schlafapnoe, die mit einem doppelt so hohen Risiko eines Wiederauftretens von VHF verbunden war. Das Screening auf Schlafapnoe kann die Patientenaufklärung über die Effektivität der Katheterablation verbessern. Wir fanden heraus, dass die weit verbreitete Epworth Sleepiness Scale und STOP-Bang-Fragebögen in unserem Kollektiv bei der Erkennung von Schlafapnoe unzureichend abschnitten.

Teil II – Evaluierung von Komplikationen bei der CIED-therapie

CIEDs (Cardiac Implantable Electronic Devices) werden zur Behandlung von Impuls- und Leitungsstörungen, ventrikulären Herzrhythmusstörungen und Herzinsuffizienz eingesetzt. Zu diesen Geräten gehören Herzschrittmacher, kabellose Herzschrittmacher, implantierbare Kardioverter-Defibrillatoren (ICDs) und die kardiale Resynchronisationstherapie (CRT) mit biventrikulärem oder Leitungssystempacing (CSP). Aufgrund der steigenden Lebenserwartung und der alternden Bevölkerung nimmt die Zahl der Herzschrittmacher- und ICD-Implantationen zu (14, 15). Dies ist auch in den Niederlanden zu beobachten, wo im Jahr 2022 insgesamt 14.570 Herzschrittmachereingriffe durchgeführt wurden. Die Zahl der ICD-Eingriffe blieb hingegen relativ stabil mit 5.664 Eingriffen im Jahr 2022, von denen bis zu 40% zur sekundären Prävention erfolgten (16). Die Indikationen für einen Herzschrittmacher sind meist Sinusbradykardie und hochgradiger atrioventrikulärer Block. Mehr als 80% der implantierten Herzschrittmacher werden bei Patienten über 65 Jahren eingesetzt. Ein ICD ist in der Regel bei Patienten zur sekundären Prävention eines plötzlichen Herztods oder zur primären Prävention bei Patienten mit Herzinsuffizienz und einer linksventrikulären Ejektionsfraktion von ≤35% indiziert (15). Schließlich ist CRT bei Patienten mit chronischer Herzinsuffizienz, schwerer linksventrikulärer Dysfunktion

und einem linken Schenkelblock (LBTB) indiziert. Durch die Korrektur der elektromechanischen Desynchronie, die durch LBTB verursacht wird, ist ein positives linksventrikuläres Remodeling möglich, was zu einer signifikanten Verbesserung der Morbidität und Mortalität bei Patienten mit Herzinsuffizienz und LBTB geführt hat (14).

Sowohl Herzschrittmacher als auch ICDs gelten als Eingriffe mit geringem Risiko, sind jedoch dennoch mit Komplikationen wie Blutungen, Infektionen, Pneumothorax und Leaddislokation verbunden (14, 15). Um das Infektionsrisiko zu minimieren, sind präventive Maßnahmen wie antibiotische Prophylaxe, erfahrenes und zertifiziertes Personal, eine sterile Umgebung, perioperative hämostatische Medikamente, antibakterielle Hüllen und Druckverbände nach dem Eingriff unerlässlich (17). Die Prävention von Pocket-Hämatomen ist wichtig und erfordert ebenfalls sorgfältige Beachtung von Risikofaktoren wie Niereninsuffizienz, kongestiver Herzinsuffizienz, begrenzter Erfahrung des Operateurs, adjuvanter Thrombozytenaggregationshemmung, CIED-Austausch, Revision der Leitung und Heparin-Bridging (18, 19). Periprozedurale orale Antikoagulation ist mit einem höheren Risiko für ein Pocket-Hämatom verbunden (20). Das Absetzen von DOACs 24-48 Stunden vor der Operation, abhängig von der Nierenfunktion, oder das Anstreben eines internationalen normalisierten Verhältnisses von 2,0 bis 2,5 und das Vermeiden von Heparin-Bridging waren wichtige Änderungen im Antikoagulationsregime in den letzten zehn Jahren (21).

Randomisierte kontrollierte Studien haben die Wirksamkeit und Sicherheit von DOACs bei Patienten, die sich einem CIED-Eingriff unterziehen, nachgewiesen. Es gibt jedoch nur begrenzte *Real-World*-Daten. In Kapitel 5 haben wir klinisch signifikante Pocket-Hämatome und systemische thromboembolische Komplikationen < 30 Tage nach der Operation bei aufeinanderfolgenden Patienten mit VHF, die sich zwischen Januar 2016 und Juni 2019 einem elektiven CIED-Eingriff unterzogen, bewertet (22). Es wurden 283 Eingriffe bei Patienten mit VHF durchgeführt, die orale Antikoagulation erhielten. Ein Drittel der Eingriffe wurde unter unterbrochener DOAC-Therapie durchgeführt, der Rest unter kontinuierlicher VKA-Therapie. Die DOAC-Gruppe war jünger, hatte weniger chronische Nierenerkrankungen, mehr paroxysmale VHF und eine niedrigere HAS-BLED-Punktzahl. Im Vergleich zur DOAC-Gruppe unterzog sich die VKA-Gruppe häufiger nur einem

Generatoraustausch. Es gab keinen signifikanten Unterschied in klinisch signifikanten Pocket-Hämatomen zwischen den VKA- und DOAC-Gruppen. Es wurden keine thromboembolischen Ereignisse für beide Gruppen gemeldet. Wir stellten fest, dass bei Patienten mit VHF, die sich einem elektiven CIED-Eingriff unterzogen, das Risiko für ein Pocket-Hämatom und ein systemisches thromboembolisches Ereignis sowohl bei unterbrochener DOAC- als auch bei kontinuierlicher VKA-Therapie vergleichbar niedrig ist.

Eine weitere wichtige Komplikation eines CIED-Eingriffs ist das Risiko einer Pocket-Infektion. Diese ist mit einem erhöhten Mortalitätsrisiko und erheblicher Morbidität verbunden (23, 24). Eine Pocket-Infektion kann die Entfernung des CIED und der Leitung(en) erfordern, um eine Endokarditis zu verhindern, was eine erhebliche Belastung für den Patienten sowie hohe Pflegekosten bedeutet. Bei der Verringerung des Infektionsrisikos sind die Verwendung von antibiotischer Prophylaxe, Chlorhexidin-Hautdesinfektion, Verschiebung des Eingriffs bei Fieber, Vermeidung von Heparin-Bridging, Vermeidung von Pocket-Hämatomen, die Verwendung strikter steriler Techniken und das Vorhandensein erfahrener Operateure wichtige präventive Maßnahmen (25).

Der PADIT (Prevention of Arrhythmia Device Infection Trial) Score wurde entwickelt, um das Risiko einer Krankenhausaufnahme wegen CIED-Infektion innerhalb eines Jahres vorherzusagen (26, 27). Dieses Modell umfasst fünf unabhängige Prädiktoren für eine CIED-Infektion, darunter die Anzahl der vorhergehenden Eingriffe, das Alter, eingeschränkte Nierenfunktion (geschätzte glomeruläre Filtrationsrate [GFR] <30 ml/min), Immunsuppression und der Typ des Eingriffs. Die Risikoskala reicht von 0 bis 13. Basierend auf dem PADIT-Score können drei Risikokategorien identifiziert werden: niedriges Risiko (≤4), mittleres Risiko (5-6) und hohes Risiko (≥7) für eine Krankenhausaufnahme wegen CIED-Infektion innerhalb eines Jahres (26). Antibakterielle Hüllen können bei Hochrisikopatienten kosteneffektiv eingesetzt werden, wie in der WRAP-IT-Studie gezeigt (28). In den Niederlanden fehlt derzeit die Kostenerstattung, was die Notwendigkeit unterstreicht, Hochrisikopatienten korrekt zu identifizieren.

In Kapitel 6 haben wir das Risiko in der täglichen klinischen Praxis mit einer retrospektiven Single-Center-Studie von aufeinanderfolgenden Patienten, die sich

einem CIED-Eingriff unterzogen, evaluiert (29). Wir bewerteten die Krankenhausaufnahme wegen einer CIED-Infektion im ersten Jahr nach dem Indexeingriff zwischen Januar 2016 und November 2021. Patienten, die eine antibakterielle Hülle erhielten, wurden von dieser Studie ausgeschlossen. Der primäre Endpunkt war die Krankenhausaufnahme wegen einer CIED-Infektion im ersten Jahr nach dem Eingriff. Insgesamt wurden während des Studienzeitraums 2333 CIED-Eingriffe durchgeführt, wobei bei 10 Patienten (0,43%) eine CIED-Infektion auftrat. Bei der Vorhersage einer schweren CIED-Infektion zeigte der PADIT-Score eine gute Unterscheidungskraft. Das Risiko einer CIED-Infektion war höher bei Patienten mit einem PADIT-Score von ≥7 im Vergleich zu denen mit einem niedrigeren PADIT-Score. Basierend auf diesen Ergebnissen kamen wir zu dem Schluss, dass der PADIT-Score eine klinisch brauchbare Methode zur Identifizierung von Patienten mit einem Risiko für die Entwicklung einer CIED-Infektion ist. Der Einsatz einer antibakteriellen Hülle bei diesen Hochrisikopatienten kann kosteneffektiv sein.

Wenn eine CIED-Infektion auftritt, gibt es eine Klasse-I-Indikation für die transvenöse Entfernung der Leitung (TLE). TLE wird auch bei dysfunktionalen Leitungen oder bei Upgrade-Verfahren verwendet, wenn der venöse Zugang eingeschränkt ist. Die TLE-Instrumente haben sich stetig verbessert, und die häufigsten Instrumente sind mechanische oder Laser-Extraktionsscheiden und der Einsatz von Schlingen. Im Allgemeinen wird die femorale Schlinge hauptsächlich als Notfallverfahren eingesetzt. In Kapitel 7 haben wir die Wirksamkeit und Sicherheit eines TLE-Ansatzes mit einer niedrigen Schwelle zur Verwendung einer kombinierten superioren und femoralen Zugangsweise zwischen 2012 und 2019 bewertet (30). Während der Studie wurden insgesamt 264 Eingriffe durchgeführt. Die Hauptindikationen für TLE waren vorwiegend Leitungsdysfunktionen, aber auch isolierte Pocket-Infektionen und systemische Infektionen. Die Rate des vollständigen und klinisch erfolgreichen Eingriffs sowie die Rate der vollständigen Leitungsentfernung waren für alle Leitungen hoch. Der Anteil schwerer prozedurbezogener Komplikationen war gering. Wir stellten fest, dass durch die Kombination von superiorer und femoraler Zugangsweise ein effektives und sicheres TLE-Verfahren erreicht werden kann.

Teil III – Empowerment von Patienten: Nutzung von eHealth zur Unterstützung beim Entlassungsmanagement

Abschließend haben wir in dieser Dissertation die Bedeutung der Einbeziehung des Patienten in seiner oder ihrer Behandlungsstrategie hervorgehoben. Modelle der patientenzentrierten Versorgung fördern die gemeinsame Entscheidungsfindung zwischen Patienten und Gesundheitsdienstleistern (1, 31). Das *Empowerment* der Patienten kann durch Wissen über die frühzeitige Erkennung möglicher Komplikationen beeinflusst werden. Patienten, die in ihre Versorgung eingebunden sind, werden sich wahrscheinlich besser an die Vorschriften halten und Unregelmäßigkeiten oder Komplikationen schneller erkennen (31). Gesundheitskompetenzen und Selbstmanagement von Krankheiten können durch eHealth-Anwendungen verbessert werden (32, 33).

In Kapitel 8 haben wir patientenspezifische Entlassungsinformationen mit herkömmlichen Entlassungsinformationen in einer prospektiven Single-Center-Studie verglichen (34). Insgesamt wurden 112 Patienten, die sich einem elektrophysiologischen Eingriff unterzogen, zwischen Januar und März 2016 inkludiert. Die bereitgestellten Entlassungsinformationen wurden mithilfe eines peer-reviewten Fragebogens bewertet, der unter Patienten, Pflegekräften und *Nurse Practitioners* verteilt wurde. Die Webanwendung zur Erstellung patientenspezifischer Entlassungsinformationen wurde von den *Nurse Practitioners* als benutzerfreundlich und zeitsparend empfunden. Patienten bewerteten die generierten Entlassungsinformationen als gleichwertig mit den Standardinformationen. Pflegekräfte berichteten von einer Verringerung der Vorbereitungszeit für die Entlassung und einer Zunahme der Einheitlichkeit der bereitgestellten Informationen.

Durch Fortschritte in der Therapie und Veränderungen in den Versorgungspfaden wurde im Erasmus MC eine Verringerung der (Wieder-)Aufnahmen beobachtet. Das Erasmus MC hat als tertiäres Überweisungskrankenhaus ein breiteres Einzugsgebiet als umliegende Krankenhäuser in der Region, und überwiesene Patienten haben ein erhöhtes Risiko für Lücken in der Nachsorge. Der Einsatz von eHealth kann zu einer Verringerung der Zeit führen, die Patienten bei klinischen Bewertungen verbringen, und die Reisezeiten verkürzen (35). Eine frühzeitige Erkennung von Komplikationen

ist auch durch Telemedizin möglich. In unserer klinischen Praxis bieten wir Telekonsultationen für Patienten bis zu ihrem ersten ambulanten Besuch an.

In Kapitel 9 haben wir die Machbarkeit der telemedizinischen Wundbeurteilung mit einem Mobiltelefon untersucht (36). In einer prospektiven Single-Center-Studie verglichen wir Gruppen, die Mobiltelefone mit integrierten Kameras (z.B. Nokia 2230 oder Sony K700i) nutzten, mit denen, die Smartphones verwendeten. Ältere Patienten benutzten typischerweise Mobiltelefone ohne Smartphone-Funktionen. Die Patienten wurden angewiesen, ihre Wunde oder Einstichstelle nach der Entlassung aus dem Krankenhaus zu fotografieren und die Bilder sechs Tage nach der Entlassung an eine gesicherte E-Mail-Adresse hochzuladen. Die empfangenen Fotos wurden von zwei *Nurse Practitioners* unabhängig voneinander auf hochauflösenden Bildschirmen bewertet. Die Intervention wurde mithilfe eines peer-reviewten Fragebogens und eines Fotobewertungsschemas bewertet. Dreiunddreißig der 40 Patienten (83%) konnten ihre Fotos hochladen. Smartphone-Nutzer waren jedoch signifikant erfolgreicher beim Hochladen ihrer Fotos im Vergleich zu den Nutzern von einfachen Mobiltelefonen (93% vs. 55%, $P < .01$). Achtundachtzig Prozent der klinischen Fotos waren interpretierbar. Die Inter-Beobachter-Variabilität zeigte eine Übereinstimmung zwischen 93% und 97%.

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CHAPTER 11

LIST OF PUBLICATIONS

1. Efficacy and safety of direct oral anticoagulants in patients undergoing elective electrical cardioversion: A real-world patient population. John de Heide, André de Wit, Rohit E. Bhagwandien, Amira Assaf, Jaleesa Gros-Bisdom, Koen C. van der Meer, Sip A.Wijchers, Felix Zijlstra, Tamas Szili-Torok, Mattie J. Lenzen, Sing-Chien Yap. *International Journal of Cardiology, March 2021, Volume 326, p. 98–102, https://doi.org/10.1016/j.ijcard.2020.10.070*

2. Minimally interrupted novel oral anticoagulant versus uninterrupted vitamin K antagonist during atrial fibrillation ablation. John De Heide; Christiaan J. Vroegh; Rohit E. Bhagwandien; Sip A. Wijchers; Tamas Szili-Torok; Felix Zijlstra; Mattie J. Lenzen & S. C. Yap. *Journal of Interventional Cardiac Electrophysiology, Aug 2018, 53, p. 341–346, https://doi.org/10.1007/s10840-018-0417-0*

3. Impact of undiagnosed obstructive sleep apnea on atrial fibrillation recurrence following catheter ablation (OSA-AF study). John de Heide, Danielle B.M. Kock-Cordeiro, Rohit E. Bhagwandien, Mark G. Hoogendijk, Koen C. van der Meer, Sip A. Wijchers, Tamas Szili-Torok, Felix Zijlstra, Mattie J. Lenzen, Sing-Chien Yap. *IJC Heart & Vasculature, 2022 June, Volume 40, 101014, https://doi.org/10.1016/j.ijcha.2022.101014*

4. Pocket hematoma after pacemaker or defibrillator surgery: Direct oral anticoagulants versus vitamin K antagonists. John de Heide, Marisa van der Graaf, Marijn J. Holl, Rohit E. Bhagwandien, Dominic A.M. J. Theuns, Andre de Wit, Felix Zijlstra, Tamas Szili-Torok, Mattie J. Lenzen, Sing-Chien Yap. *IJC Heart & Vasculature, 2022 April, volume 39, 101005, https://doi.org/10.1016/j.ijcha.2022.101005*

5. Device infection in patients undergoing pacemaker or defibrillator surgery: risk stratification using the PADIT-score. John de Heide, MANP; Marisa van der Graaf, MD; Marijn J. Holl, MD; Mark G. Hoogendijk, MD, PhD; Rohit E. Bhagwandien, MD; Sip A. Wijchers, MD; Dominic A.M.J. Theuns, PhD, Tamas Szili-Torok, MD, PhD; Felix Zijlstra, MD, PhD; Mattie J. Lenzen, PhD; Sing-Chien Yap, MD, PhD. *Journal of*

Interventional Cardiac Electrophysiology, Jan 2024, https://doi.org/10.1007/s10840-024-01759-1

6. Efficacy and safety of transvenous lead extraction using a liberal combined superior and femoral approach. Sing-Chien Yap, Rohit E Bhagwandien, Dominic A M J Theuns, Yunus Emre Yasar, John de Heide, Mark G Hoogendijk, Charles Kik, Tamas Szili-Torok. *J Interv Card Electrophysiol. 2021 Nov, 62(2), p. 239-248, http://dx.doi.org/10.1007/s10840-020-00889-6*

7. A quality improvement initiative for patient knowledge comprehension during the discharge procedure using a novel computer-generated patient-tailored discharge document in cardiology. André de Wit , John de Heide, Paul Cummins, Ada van Bruchem-van de Scheur, Rohit Bhagwandien and Mattie Lenzen. *Digital Health, 2022 Sept, Volume 8: 1–12, https://doi.org/10.1177/20552076221129079*

8. Get the picture. A Pilot Feasibility Study of Telemedical Wound Assessment Using a Mobile Phone in Cardiology Patients John de Heide, MANP; C.J. Vroegh, MANP; T. Szili Torok, MD, PhD; R.J.J. Gobbens, PhD; F. Zijlstra, MD, PhD; M. Takens-Lameijer, MANP; M.J. Lenzen, PhD; S.C. Yap, MD, PhD; W.J.M. Scholte op Reimer, PhD [3]. *Journal of Cardiovascular Nursing, 2017, Vol.32, No. 2, pp E9-E15, https://doi.org/*10.1097/JCN.0000000000000377

CHAPTER 12

PHD-PORTFOLIO

Name Phd-Student	John de Heide
Department	Cardiology
Research School	Cardiovascular Research School Erasmus MC (COEUR)
Phd-period	September 2015 – February 2025
Titel thesis	Contemporary Clinical Practice in Electrophysiology
Subtitle	Focus on complications and post-discharge e-Health
Promotor	Prof. dr. F. Zijlstra
Co promotor	Dr. S.C. Yap Dr. M.J. Lenzen
ORCID	https://orcid.org/0000-0002-6502-1270
Scopus Author ID	57191857621
Date defense	5 February 2025

PhD training	Organizer	EC
Experiences in forming the ANP role (2015)	DNANP	0.30
DNANP München 5 sept 2015 “To be or not to be” (2015)	DNANP	0.30
Posterpresentation Get the Picture (2015)	DNANP	0.30
4e regionale hartfalen bijeenkomst Rotterdam (2015)	Erasmus MC	0.10
Nurse Academy 2015 (2015)	Nurse Academy	1.00
EGSL - Academic Integrity (2016)	Erasmus MC Department of Medical Ethics and Philosophy of Medicine	0.30
Innovatieves Entlassungsconcept in der Kardiologie (2016)	NewNet	0.10
Immediate Life Support course (2016)	Erasmus MC	0.30
Masterclass LVAD (2016)	Erasmus MC	0.10
Erasmus MC - Basic Introduction Course on SPSS (2016)	The Erasmus Postgraduate School Molecular Medicine, Rotterdam	1.00
Nurse Academy 2016 (2016)	Nurse Academy	0.80
Time management (2017)	S Maes Training en Coaching	0.10
Practical considerations regarding supportive compression bandages after percutaneous electrophysiological procedures (2017)	DNANP	0.10
DNANP internationaal congres "Freedom, development and autonomy in practice" (2017)	DNANP	0.30
Getting Better (2017)	EduMedi	0.20
Submittion abstract HRS (2017)	Heart Rhythm Society	0.10
Thesis printing and layouting (2018)	COEUR & Gildeprint	0.10
Submittion abstract EuroHeartCare (2018)	EuroHeartCare	0.10
Posterpresentation HRS 2018 (2018)	Heart Rhythm Society	0.10
HRS 2018 (2018)	Heart Rhythm Society	1.20
Posterpresentation EuroHeartCare (2018)	European Society of Cardiology	0.10
EuroHeartCare 2018 (2018)	European Society of Cardiology	0.90
Hartfalen bijeenkomst 2018 (2018)	Erasmus MC	0.10
CarVasZ 2018 Presentation (2018)	NVHVV	0.10
CarVasZ 2018 (2018)	NVHVV	0.30
Nurse Academy 2018 (2018)	Nurse Academy	2.00

PhD training	Organizer	EC
COEUR cursus "De Patient centraal in onderzoek" (2019)	COEUR Erasmus MC	0.30
DNANP Posterpresentation SCAAF (2019)	DNANP	0.10
DNANP 2019 Posterpresentation Palpitation clinic (2019)	DNANP	0.10
Presentation Implementation of ECV and implantation ILR by NPs (2019)	DNANP	0.10
International congress DNANP (2019)	DNANP	0.60
CarVasZ 2019 (2019)	NVHVV	0.30
Nurse Academy 2019 (2019)	Nurse Academy	2.10
Erasmus MC - Biomedical English Writing (2020)	Molecular Medicine Postgraduate School	2.00
The Photoshop and Illustrator CC 2019 Workshop for PhD-students and other researchers (2020)	Molecular Medicine Postgraduate School	0.30
Nurse Academy 2020 (2020)	Nurse Academy	2.40
The Personal Leadership & Communication for PhD students and Post Docs (2021)	Molecular Medicine Postgraduate School	1.00
Nurse Academy 2021 (2021)	Nurse Academy	1.90
Nurse Academy 2022 (2022)	Nurse Academy	0.60
BDB BKE Certificaat (2023)	NFU	9.00
Nurse Academy (2023)	Nurse Academy (Prelum)	2.90
Total		50.60

CHAPTER 13

ABOUT THE AUTHOR │ CURRICULUM VITAE

John de Heide was born in Vlaardingen, the Netherlands, on November 12, 1972. He completed his pre-university education (VWO) in 1992. After an incomplete propaedeutic year in the Medicine Programme during 1992-1994, he was drafted into military service in 1995, serving as a Corporal ambulance driver. He chose to serve abroad in former Yugoslavia with the UNPROFOR peacekeeping force, earning two service medals.

In late 1996, John began his nursing education at hospital ‘Holy Ziekenhuis’ in Vlaardingen. He graduated in 2000 at the cardiology ward, and pursued further education to become an ICU nurse, graduating in 2002. He continued to work as an intensive and coronary care nurse at 'Holy Ziekenhuis’, which later became ‘Vlietland Ziekenhuis’, until early 2009.

In 2009, John took on a new role as an intensive and coronary care nurse at High Care Detachering, working at the hospital ‘Diakonessen ziekenhuis Leiden’, and in interventional cardiology at the Erasmus Medical Center Rotterdam. In September 2011, he began the Master of Advanced Nursing Practice (MANP) at the University of Applied Sciences Rotterdam, from which he graduated in mid-2013. After graduation he further developed the role of nurse practitioner at the interventional cardiology and electrophysiology ward.

His master’s thesis on smartphone photography by patients was implemented in 2014, earning him the Meyboom Nursing Research Prize at Erasmus Medical Center Rotterdam. He presented his work on this subject in the Netherlands, Germany, the United States, and Finland, winning the poster presentation award at the 2014 International Congress of Nurse Practitioners. This marked the beginning of his scientific career, alongside his full-time role as a nurse practitioner in interventional cardiology and electrophysiology at Erasmus Medical Center Rotterdam. His official promotion began in late 2015. During this period, he had opportunities to present his work at national and international conferences and publish his study results in various international peer-reviewed medical and nursing journals.

As a nurse practitioner in cardiology, he also served as a nursing tutor for eight nurse practitioner students. In early 2022, he began a teaching position at the University of Applied Sciences Rotterdam / Hogeschool Rotterdam (HR) in the Bachelor of Nursing program, focusing on science, nursing, and anatomy/physiology/pathology. Late 2023 he expanded his role to teacher researcher at the Research Center of Innovations in Care at HR.

CHAPTER 14

ACKNOWLEDGEMENT | DANKWOORD

Eindelijk is het mogelijk om het meest gelezen hoofdstuk van elke thesis te schrijven. Toch is dit dan misschien wel weer het moeilijkste hoofdstuk, omdat je promoveren niet alleen doet. Graag wil ik een aantal personen in het bijzonder noemen. In de afgelopen jaren ben ik dank verschuldigd aan zoveel mensen dat het waarachtig lastig is iedereen persoonlijk te benoemen. Ik zal mijn best doen…

Dit proefschrift was nooit mogelijk geweest zonder de duizenden patiënten in de diverse onderzoeken. De meeste patiënten waren onderdeel van retrospectief dossieronderzoek, en het overgrote deel ken ik vanuit de kliniek op de dagbehandeling en short-stay cardiologie. Wat was het mooi om behandelaar en begeleider te mogen zijn als verpleegkundig specialist, en wat bijzonder dat jullie in zulke grote getalen toestemming gaven voor retrospectief onderzoek in het Erasmus MC. De overige patiënten die onderdeel waren van onze prospectieve onderzoeken OSA-AF, Get the Picture en de “digitaal gegenereerde ontslaginformatie/-brief” ben ik tevens uitermate dankbaar. Het was vast niet makkelijk te beslissen om mee te doen aan wetenschappelijk onderzoek als je gedachten liggen bij de geplande elektrofysiologische ingreep of het ontslag. Vaak waren het ook fijne en warme gesprekken die we hadden, en dacht u actief mee bij het wetenschappelijke onderzoek. Weet dat uw bereidheid om mee te doen van onschatbare waarde was voor het medisch/verpleegkundig wetenschappelijk onderzoek. U heeft mijn bewondering.

Met oprechte dankbaarheid wil ik mijn promotor en copromotoren bedanken voor hun steun en toewijding gedurende het promotietraject. Jullie expertise, advies en inspirerende inzichten hebben een belangrijke rol gespeeld in het realiseren van dit werk. De tijd en energie die jullie hebben geïnvesteerd, naast de drukte van het klinische werk, waardeer ik enorm. Dankzij jullie betrokkenheid en kritische blik heb ik dit onderzoek naar een hoger niveau kunnen tillen. Bedankt voor jullie professionaliteit, inspiratie en het vertrouwen dat jullie in mij hebben gesteld.

Beste **prof. dr. F. Zijlstra**, Felix, ik leerde u in 2010 kennen toen ik op de interventiecardiologie werkte als IC-verpleegkundige. Wat was het een genot om met u te mogen samenwerken. De rust en de kunde aan tafel waren ongekend, en ik had het gevoel dat we elkaar snel begrepen tijdens de procedures. Ik leerde door u snel de coronaire anatomie en pathologie verder uit te diepen. In september 2011 werd ik aangenomen op de afdeling cardiologie als verpleegkundig specialist in opleiding, en bleef de interdisciplinaire samenwerking ronduit fantastisch. Over het medisch management van patiënten voor en na een ingreep op de interventiecardiologie leerde ik nu heel veel meer. Uiteraard hadden de overige medici, afdelingsverpleegkundigen en verpleegkundig specialisten Marieke Takens-Lameijer en Paul Musters hier ook hun belangrijke deel in, maar uw kijk op realistisch haalbare therapeutische doelen hebben mij gevormd als behandelaar. In 2013 rondde ik mijn opleiding tot verpleegkundig specialist af. Het masterthese onderzoek werd bekroond met het winnen van een posterpresentatie op het International Congres of Nurse Practitioners in Helsinki en de Erasmus MC Meijboom-prijs voor geïmplementeerd

verpleegkundig wetenschappelijk onderzoek. Ik ben u dankbaar dat het mogelijk was hierna het promotietraject bij u te mogen starten.

Beste **dr. S.C. Yap,** Sing, het lijkt als de dag van gisteren dat ik je op de interventiecardiologie zag. De finesse die je aan tafel liet zien was voor mij ongekend, zonder de patiënt uit het oog te verliezen. Dat zag ik niet vaak zo uitgesproken. Later startte ik de opleiding tot verpleegkundig specialist, en zouden we nog veel intensiever gaan samenwerken. De elektrofysiologie was voor mij nog onbekend, maar door de jaren heen heb je jouw kennis doorgegeven aan mij en mijn collega's. Je had altijd nog wel een volgende laag van kennis paraat. Dank je wel hiervoor. In het promotietraject was je de dagelijkse supervisor, en ook hier presenteerde je de kennis op dezelfde wijze. Ik ben blij dat je mijn copromotor was. Bij het bespreken van researchopzetten was je heel goed in het gezamenlijk reduceren tot de kern van de onderzoeksvraag. Als beginnend wetenschapper had ik de neiging teveel bijzaken mee te willen nemen. Wat ik wel heel grappig vond is dat je niet gewend was aan een promovendus die aangeeft wat hij niet weet, het zelf wil opzoeken en zich nergens doorheen bluft. Weet dat dit geboren is uit de veiligheid en het respect dat ik bij en voor je voel. Dat lukt niet iedereen! Ik wil je bedanken voor je betrokkenheid en vertrouwen (ook tijdens mijn langdurige ziekte). Je hebt een goede balans als leermeester en het was een eer met je samen te mogen werken. Dank je wel.

Beste **dr. M. Lenzen**, Mattie, ik leerde je kennen op de interventiecardiologie, maar nog beter in de opleiding tot verpleegkundig specialist tijdens de wekelijke lessen over wetenschappelijk onderzoek en statistiek. Dit deed je samen met Ron van Domburg, en hebben mij heel veel geholpen om inzicht te krijgen in het opzetten, uitvoeren, en analyseren van data van medisch wetenschappelijk onderzoek. Je had ook altijd een focus op verpleegkundig praktijkgericht onderzoek. Dat heeft mij zeker gevormd. Tijdens het promotieonderzoek heb je me vaak ondersteund als ik weer een verpleegkundig specialistische ingang zocht voor mijn researchvoorstellen. Deze steun was heel erg waardevol voor me, en hierbij wil ik me daarvoor bedanken. Daarnaast heb je geduldig en vriendelijk uitleg gegeven over de statistische analyses. Hier heb ik veel van je geleerd. Ik wil je ook heel erg bedanken dat je geregeld hielp bij de vertaalslag van mijn verpleegkundig gedachtenpatroon naar de methode en belang van medisch wetenschappelijk onderzoek. Niet alleen in schrijven, maar ook in integreren van beide disciplines. Het heeft ook veel bijgedragen aan mijn functioneren als verpleegkundig specialist. Bovendien hadden we altijd een persoonlijke klik en kon ik mijn gedachten vrijelijk met je bespreken. Dank je wel.

Aanvankelijk was in het eerste jaar van mijn promotie mijn tweede promotor **prof. dr. W.J.M. Scholte op Reimer**, Wilma, tevens onderdeel van het team. Door aanpassing van het promotiereglement van de Erasmus Universiteit diende het promotieteam verkleind te worden naar één promotor en maximaal twee copromotoren. Ik heb het altijd een groot gemis gevonden dat we niet samen verder konden werken aan research voor en over de cardiovasculaire patiënten die in mijn werk als verpleegkundig specialist aan mij toevertrouwd waren. Ik voelde een goede klik als we overleg hadden. Bedankt voor je steun in het eerste jaar. Het heeft me gesterkt om de verpleegkundige focus te behouden.

Beste overige commissieleden **prof. dr. J. Roos-Hesselink**, **dr. Olivier Manintveld**, **prof. dr. R.E. Knops**, **prof. dr. T. Jaarsma** en **prof. dr. M. van Dijk**, hierbij wil ik u hartelijk danken voor het beoordelen van het proefschrift en zitting nemen in de kleine en grote commissie. Ik ben dankbaar dat u met uw grote expertise uw tijd heeft vrijgemaakt.

Beste **Paul Cummins**, wat heb ik toch een hoop lol gehad met je. We hebben heel veel gelachen, maar ook veel zaken geregeld voor wetenschappelijk onderzoek op de afdeling. Natuurlijk hebben we het ook heel vaak gehad over musiceren, en die gesprekken waren dan wel weer de lichtpuntjes in een werkdag. Dank je wel. Verder wil ik je bedanken voor het meelezen en corrigeren van de tekst. Als native English speaker heeft dit me heel veel geholpen, ook voor de wetenschappelijke artikelen die ik nog zal schrijven. Uit de grond van mijn hart heel erg bedankt hiervoor.

Beste **C.J. Vroegh**, Chris, we hebben samen de opleiding tot verpleegkundig specialist gedaan. Na diplomering hebben we de zaalfunctie in rap tempo vorm gegeven. Ik heb altijd met heel veel plezier met je samengewerkt, en miste je ook direct toen ik je (tijdelijk) moest missen toen je naar het Haven Ziekenhuis ging. Nadat je een aantal jaar op de thoraxchirurgie gewerkt had, werden we weer directe collega's, maar wel op verschillende werkdagen. We hebben elkaar altijd goed aangevuld en hadden weinig woorden nodig om elkaar te begrijpen. Dank je wel dat we zulke fijne collega's waren.

Met grote dank wil ik ook in het bijzonder mijn overige collega verpleegkundig specialisten, **André**, **Elly**, **Jaleesa**, **Andrea**, **Koen**, **Mandy**, **Merel**, **Teun**, **Chantal**, **Maaike**, **Marleen**, en **Lisette**, en physician assistents in opleiding **Rismy** en **Kevin** noemen, voor de waardevolle steun, inspiratie en teamgeest die we hadden op de cardiologie. De samenwerking met jullie heeft niet alleen bijgedragen aan het slagen van het werk en promotie, maar ook aan mijn persoonlijke groei. Jullie ideeën, feedback en de momenten van humor hebben een positieve impact gehad op mijn motivatie en doorzettingsvermogen. Het is een voorrecht om samen te werken met zo'n toegewijd en warm team. Bedankt voor alles wat jullie hebben bijgedragen en voor de fijne momenten die we samen hebben gedeeld.

Beste **R. van Valen**¸ Richard, we kennen elkaar al voordat ik in het Erasmus MC werkte door de sollicitatie op de thoraxchirurgie. We hebben dan ook weer altijd heel leuk kunnen samenwerken vanaf dat ik verpleegkundig specialist in opleiding werd. Ook hebben we vaak kunnen spreken over hoe het is om te promoveren, en welke uitdagingen daarin zijn. Je advies en luisterend oor waren echt waardevol voor me. Dank je wel. Maar daarnaast konden we ook altijd op persoonlijk vlak met elkaar goed praten. In mijn pioniersrol op de dagbehandeling en short stay cardiologie was jij een voorbeeld hoe je de rol van verpleegkundig specialist kan vormgeven. Jij hebt dit tenslotte gedaan op de thoraxchirurgie voordat ik startte op de cardiologie. Toch bleef je voor iedereen heel benaderbaar, en dat zie je lang niet altijd. Weet dat je een fantastisch mooi mens en een waardevolle vriend bent.

Beste **S.J.F.M. van Gisbergen**, Sander, dank je dat je al die jaren mijn leidinggevende was en dat ik bij jou op de afdeling verpleegkundig specialist heb mogen worden. In de pioniersrol die ik samen met Chris had heb je actief meegedacht hoe dit het beste gefaciliteerd kon worden. Het opleidingsbudget voor

de verpleegkundig specialisten bijvoorbeeld, wat later een organisatiebreed voorbeeld werd, is er mede door jou gekomen. Dit maakte het mogelijk dat de vijfjaarlijkse accreditatie mogelijk werd, en dat uitkomsten van wetenschappelijk onderzoek door verpleegkundig specialisten en physician assistents (inter)nationaal gedeeld kon worden. Ook konden we goed sparren hoe we nu zo efficiënt mogelijk de productie, kwaliteit van zorg en patiënttevredenheid konden verhogen. Het mooie was dat we oor hadden voor elkaars inbreng, en het goede resultaat is er daarom ook gekomen. Voorbeelden genoeg hoe leidinggevende en verpleegkundig specialisten kunnen samenwerken aan verbetering van zorg, efficiëntie en profilering van het verpleegkundig vak. Dank je wel.

Tevens wil ik mijn overige collega's **verpleegkundigen** (op de afdeling en interventiekamers), **elektrofysiologen**, **interventiecardiologen, AOIS, fellows**, **secretaressen** en **medewerkers van het planbureau en het wetenschapsbureau** bedanken voor hun steun, inspiratie en samenwerking. Jullie enthousiasme, betrokkenheid en geduld waren van onschatbare waarde in dit traject. Elk gesprek, elke suggestie en elke kritische blik heeft bijgedragen aan het verbeteren van mijn werk en heeft mij gemotiveerd om steeds een stap verder te gaan. Het is een voorrecht om deel uit te maken van zo'n inspirerend team. Speciaal wil ik hier **Astrid, Mieke, Amira** en **Marco** noemen. Heel veel dank voor jullie steun en vriendschap.

Beste collega's van de Hogeschool Rotterdam, ook richt ik mijn grote dank naar jullie. Naast dat jullie hele fijne, gezellige en topcollega's zijn bij de **HBO Verpleegkunde**, **Master Advanced Nursing Practice** en **Kenniscentrum Innovatie in de Zorg**, hebben jullie ook allemaal intens meegeleefd met de stappen in het promotietraject. Jullie steun, advies en relativerende humor is van onschatbare waarde geweest. Ik ben dankbaar dat ik jullie collega mag zijn. Laten we nog heel veel jaren zorgen voor goed opleiden van onze studenten en tegelijkertijd werken aan verpleegkundig wetenschappelijk onderzoek. Ik zou jullie allemaal niet willen missen.

Hierbij wil ik ook **mijn vrienden** bedanken die altijd een steun waren in de afgelopen jaren. Heel erg bedankt voor jullie luisterend oor, steun en vriendschap in deze periode. Ook al zagen we elkaar veel minder bleef de band toch bestaan. Weet dat ik jullie gemist heb en dat we dat gaan verbeteren! Specifiek wil ik **Maaike** en **Daan** bedanken dat ze paranimf willen zijn. Bedankt voor de feedback en zonder jullie hulp zou de promotiedag niet mogelijk geweest zijn.

Als laatste wil ik mijn familie met diepe dankbaarheid bedanken, en dit zal tweetalig zijn omdat de schoonfamilie Duits is. Ik wil mijn vader **Hans** en zijn vrouw **Hans**, **Sonja, Raymond**, **Martin** en **Noreen** bedanken voor hun steun in de afgelopen jaren. Dit geldt ook voor mijn neven **Colin**, **Mitchel**, **Craig** en **Jens**. Ik hoop dat we elkaar nu weer vaker kunnen zien en veel plezier kunnen hebben. Hier wil ik ook graag mijn moeder **Els** bedanken die altijd zo trots was dat ik aan het promoveren was. Ze vertelde het echt iedereen. Helaas is ze niet meer onder ons.

Anschließend möchte ich ein großes Dankeschön an meine Familie in Deutschland richten. Von Herzen danke ich meiner Schwiegermutter **Bärbel** und meinem leider viel zu früh verstorbenen Schwiegervater **Alfred**. Mein Dank gilt ebenso meiner Schwägerin **Katja**, meinem Schwager **Manfred**, meinem Neffen **Meikel** mit seiner

Freundin **Lea**, meiner Nichte **Charline** und ihrer Freundin **Patricia** sowie meiner Nichte **Elisa**. Eure Unterstützung und eure Nähe waren für mich von unschätzbarem Wert. Ihr wart immer für mich da – in guten wie in schwierigen Zeiten – und habt mich mit eurer Liebe und eurem Glauben an mich gestärkt. Ohne euch wäre dieser Weg nicht möglich gewesen, und ich bin unendlich dankbar, euch an meiner Seite zu haben. Danke für alles!

Mocht ik iemand vergeten zijn in dit dankwoord dan mijn oprechte excuses hiervoor.

In het dankwoord komt de belangrijkste als laatste aan bod, maar voor mij ben je op de eerste plaats. Lieve **Tanja**, liefde van mijn leven, bedankt voor de onvoorwaardelijke steun, liefde en geduld tijdens het promotietraject. Je hebt me door elke fase van dit traject gesteund, zowel op goede als op moeilijke momenten. Ook heb je me vaak moeten missen als ik weer achter mijn computer zat in onze vrije tijd, werkend aan het zoveelste researchvoorstel, METC-aanvraag, dataverzameling of schrijven van een artikel. Maar je was er ook, als ik weer eens gefrustreerd was wanneer iets niet lukte. Zonder je aanmoediging, begrip en het vertrouwen in mijn kunnen was het niet mogelijk geweest. Het heeft mij de kracht gegeven om door te zetten, en daarvoor ben ik je eeuwig dankbaar. Bedankt dat je in mijn leven bent en dat je altijd achter me staat – dit werk draag ik op aan jou. Ik hou heel veel van je.

Cover design was partly generated using Adobe Firefly.

Financial support for the publication of this thesis was generously provided by:
Nederlandse Hartstichting
Dutch Society of Cardiovascular Nursing (NVHVV)