Supplementary material

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ORIGINAL STUDY PROTOCOL (FINAL VERSION DATED 30th June 2015)

„Incidence and associated risk factors of serious bleeding complications after cardiac electronic device surgery in patients on anticoagulation or antiplatelet therapy"

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Study description:

1. The need for a study

1.1. What is the problem to be addressed?

The number of cardiac implantable electronic device (CIED) implantations in patients with different cardiac rhythm disorders or heart failure has significantly increased worldwide over last decades and has been continuing to expand with the growing indications for CIED and population ageing. It is estimated, that up to 45% of patients undergoing CIED surgery receive oral anticoagulation (AC) in order to reduce the risk of thromboembolic event, with the two major indications being atrial fibrillation and the presence of mechanical cardiac valve prosthesis [1]. Moreover, many of these patients have also indications for antiplatelet therapy (APT) due to coexistence of coronary artery disease and related percutaneous interventions.

Discontinuation of drugs affecting the hemostasis due to the planned invasive procedure is associated with an increased risk of thromboembolic events, but invasive procedure alone may also increase the risk of thromboembolic events. However, continuation of therapy carries the risk of bleeding complications.

In the avaible literature, there are many discrepancies regarding the risk of bleeding during implantation of CIED. According to the so-called EHRA "Practical Guidelines"

pacemaker (PM) or implantable cardioverter-defibrillator (ICD) surgery is a procedure with a low risk of bleeding, unless difficult anatomical conditions such as congenital heart disease are present [2]. The position of the American College of Chest Surgeons (ACCP) is quite different. According to ACCP, PM or ICD implantation is associated with a high risk of bleeding if AC or APT is used during the perioperative period [3]. This approach seems to be right, due to the often observed in this group of patients, increased risk of bleeding due to damage to the vessels of the inter-fascial layer during tissue preparation for the pocket, the inability to attach a suture to opposite tissue layers, or the inability to coagulate the vessels inside the pocket.

Bleeding complications and strategies of periprocedural management of patients on antiplatelet or anticoagulation therapy presents a dilemma to physicians, with increasing importance. This is of particularly significance in patients with moderate to high risk (≥5% per year) of thromboembolic events.

The model of AC management during the perioperative period of CIED implantation has undergone a significant transformation in the last years. Previous EHRA guidelines recommended the interruption of AC and the introduction of bridging therapy (BDT) with unfractionated heparin (UHF) or low molecular weight heparin (LMWH) in the periprocedural period in patients with moderate to high risk of thromboembolic events (≥5% per year) [4]. However, both the effectiveness and safety of this procedure have been widely discussed and questioned.

The results of subsequent clinical studies reported that BDT significantly increases the risk of bleeding complications, particularly the incidence of pocket hematoma [5]. In addition, data from clinical trials supported the lack of heparin effect used as a bridge in the reduction of thromboembolic events, regardless of the patient's clinical condition, duration of the procedure or type of implanted device [6]. A breakthrough was the publication in 2013.

results of a large randomized clinical trial BRUISE CONTROL assessing the safety of uninterrupted perioperative vitamin K antagonist therapy compared to perioperative heparin bridging in patients with an estimated annual risk of thromboembolism of at least 5% [7]. Birnie et al. proved that uninterrupted warfarin treatment is associated with a significantly lower risk of significant pocket hematoma as compared BDT, with a comparatively low risk of episodes thromboembolism in both groups of patients [7].

Based on the results of the BRUISE CONTROL study, EHRA recently (updated this year) has changed the position regarding perioperative management of patients on chronic AC with moderate to high risk of thromboembolic events. According to the new position, in these group VKA therapy should be continued with maintenance of international normalized ratio (INR) $\leq$3.0, and $\leq$ 3.5 in patients with prosthetic valve. In contrast, in patients with a thromboembolic risk assessed as low, VKA should be discontinued for 3-4 days without BTD in the periprocedural period [8].

In last years, with the increasing use of direct oral anticoagulants (DOACs), the number of patients undergoing CIED implantation who are chronically on DOACs is also growing. However, the patients' preparation for surgery requires special attention from clinicians due to the pharmacokinetic profile of DOACs. DOACs are characterized by a rapid onset of action, with a peak in activity between 1-3 hours after intake and a relatively short half-life of 9-17 hours [9-10].

There is a lack of clearly established guidelines for the management of patients on DOACs in CIED surgery perioperative period due to scarce literature data.AS a general recommendation, discontinuation of DOAC for a period of 2-3 half-lives may be used. According to the recently updated EHRA statement, in preparation for the implantation of CIEDs in patients with normal renal function, it is recommended to discontinue DOAC 24

hours before the procedure [8]. For patients receiving dabigatran who have estimated glomerular filtration rate (GFR) less than 80 ml /min, the DOAC therapy should be discontinued earlier. For patients receiving an active factor X inhibitor who has a GFR between 15-29 ml / min, the last dose of DOAC should be given at least 36 hours before surgery. In patients who are also on amiodarone or verapamil, an additional 24 hours extension may be indicated, especially if the risk of a thromboembolic event has been assessed as low (CHA2DS2-VASc ≤ 3 points). Return to DOAC indicated 24-48 hours after the procedure [8]. Nevertheless, recent studies showed a similar safety profile for DOAC and VKA [11-12].

APT similarly to AC, particularly dual antiplatelet therapy (DAPT) poses a significant clinical challenge in management of patients during CIED periprocedural period. Data from recent observational studies indicated that DAPT significantly increases the risk of bleeding compared to single antiplatelet therapy (SAPT) [13].

According to the EHRA position, it is advisable to postpone the implantation of CIEDs until the use of DAPT is not necessary. However, if is not possible to delay the procedure, clopidogrel should be discontinued 5 days before the procedure and re-start as soon as possible. Exceptionally, CIEDs implantation during DAPT therapy should be performed, if the patient has undergone bare metal stent (BMS) implantation in the last 30 days preceding the CIED procedure or angioplasty with implantation of a drug eluting stent (DES) in the last 3 months [8]. Unfortunately, the recommendations do not apply to the increasingly used new P2Y12 receptor inhibitors - prasugrel and ticagrelor, due to a lack of literature data on the safety and risk of bleeding in patients using these drugs and undergoing the CIEDs procedure.

1.2. Why is a study needed now?

A study is needed now because current clinical practice in Europe and Poland varies widely, and there is a need to clearly define optimal strategy for AC and APT management in preparation for CIED surgery.

Furthermore, to date, there is no existing bleeding score dedicated for patients undergoing CIED surgery which would would help clinicians to optimize perioperative management. Therefore, there remains a need for a simple, accurate risk score that uses readily available clinical information to predict the occurrence of serious bleeding complications (SBC) in patients after CIED procedures, especially in those, who receive drugs affecting hemostasis.

1.3 Study aims

1. The assessment of of significant SBCs rate in patients on APT, AC, or APT+AC concomitantly undergoing CIEDs surgery.
2. The identification of risk factors for SBc related to CIED procedures and development a new scoring system for predicting SBC after CIEDs surgery.
3. The assessment of the correlation between SBCs and the risk of late infectious complications.

2. THE STUDY DESIGN

2.1 Type of the study

Prospective single-center observational cohort study.

2.2 Inclusion/exclusion criteria

Inclusion Criteria

1. Any patient undergoing elective device surgery (i.e. de novo device [pacemaker, implantable cardioverter-defibrillator or cardiac resynchronization therapy device] implantation or pulse generator change or system up-grade)

2. Age 18 years or older

3. Signed informed consent

Exclusion Criteria

1. Unable or unwilling to provide informed consent

2. History of noncompliance of medical therapy

3. Diagnosed thrombocytopenia or thrombophilia

4. Active device infection

5. Lead and/or device extraction surgery,

6. Geographic inaccessibility for the follow-ups

7. Included in another clinical trial

8. Pregnancy

2.3 Study population description

Before the device procedure, the thromboembolic risk will be assessed according to European Society of Cardiology (ESC) and ACCP recommendations [2, 3]. Patients on APT will continue their therapy during the perioperative period, including DAPT. In patients receiving AC treatment, therapy will be continued or discontinued in accordance with the current EHRA recommendations [8]. VKA will be discontinued in patients with low thromboembolic risk. Patients with a moderate or high risk of thromboembolic incidents will continue VKA therapy and maintenance of therapeutic INR level. In patients on DOAC, treatment will be discontinued for a period dependent on the renal function. If the GFR will be above 60 ml / min, DOAC will be discontinued 24 hours prior to surgery. If the GFR will be between 15-29 ml / min, DOAC will be discontinued at least for 36 hours. If no bleeding complication occurs, DOAC will be restarted 24-48 hours after the procedure. If the need of BDT with LMWH exists or patient receives LMWHS chronically, the LMWH will be discontinued 24 hours prior device surgery and reintroduce 24-48 hours after surgery. Patients who do not use

any drugs affecting the hemostasis will be included in the study as a control group selected in terms of gender and age.

2.4 Patient groups

The entire patient population will be divided depending on the type of therapy affecting the hemostasis taking during the perioperative period:

1) Antiplatelet therapy (APT):

a) Single antiplatelet therapy (SAPT)

- Acetylsalicylic acid (ASA; dose: 75-150 mg daily)
- Clopidogrel (dose: 75 mg daily)
- Ticagrelor (dose: 180 mg daily)
- Prasugrel (dose: 10 mg daily)

b) Double antiplatelet therapy (DAPT)

- ASA 75-150 mg daily in combination with clopidogrel 75 mg daily or ticagrelor 180 mg daily or prasugrel 10 mg daily)

2) Anticoagulation therapy (AC)

a) vitamin K antagonist VKA

- Warfarin in dose dependent on INR
- Acenocumarol in dose dependent on INR

I) VKA continued periprocedurally with INR on the day of surgery ≥ 2.0 (VKA I)

II) VKA interrupted periprocedurally with INR on the day of surgery ≤ 2.0 (VKA II)

b) periprocedural bridging therapy (BD) or chronic low molecular weight heparin (LMWH) therapy

- noxaparin/ dalteparin or nadroparin in weight-based dosing - last dose 24 hours before surgery

c) direct oral anticoagulant (DOAC) discontinued for 24-36 hours prior device surgery dependent on GFR

- Rivaroxaban 15-20 mg daily
- Dabigatran at a dose of 220-300 mg per day
- Apixaban 5-10 mg daily

3) Patients on triple antithrombotic therapy (TAT)

- DAPT (ASA 75-150 mg daily and clopidogrel 75 mg daily) in combination with VKA (warfarin or acenocoumarol)
- DAPT (ASA 75-150mg daily and clopidogrel 75mg daily) in combination with DOAC (rivaroxaban 15mg daily or dabigatran 220mg daily or apixaban 5mg daily)

4) Control group - patients not taking any drugs affecting the hemostasis

2.5 Device surgery

All patients will undergo procedures with the standard techniques for a pectoral subfascial pocket formation and transvenous lead placement via the subclavian vein using tined or screw-in leads. All right atrial and right ventricular leads will be positioned in the right auricular appendage and the right ventricular apex, respectively. The left ventricular leads will be positioned in the lateral, posterolateral, or anterior cardiac vein.

2.6 Primary and secondary outcomes measures

The primary outcome is "**significant bleeding complication (SBC)**" defined as:

1. **Significant pocket hematoma (SPH)**

A) SPH requiring surgical intervention – defined as a hematoma that continues to expand despite all appropriate non-operative measures, or is producing impending or actual wound breakdown or skin necrosis

B) SPH prolonging hospitalization for at least 24 hours after the CIED procedure due to interruption of the anticoagulant/antiplatelet treatment for >24 hours. If the patient is

taking VKA subtherapeutic AC will be defined as two consecutive daily INRs < the lower limit of the prescribed therapeutic range for the patient (usually <2; <2.5 for prosthetic valve patients)

2. **Significant bleeding (SB)**– defined according to International Society on Thrombosis and Hemostasis (ISTH) criteria as fatal or symptomatic bleeding in a critical area (e.g., pericardial or gastrointestinal), or any bleeding causing a decrease in hemoglobin concentration of more than 1.24 mmol/L, or leading to transfusion of two or more units of red cells [14].

Considerations in choosing and defining the primary outcome

There is no agreed definition of SBC and investigators have used various definitions [5-7]. In selecting our definition, we took the following into consideration: what has been previously used; that the hematoma leads to sequelae, i.e. is truly clinically significant; and that the definition is as objective as possible.

Secondary Outcomes

1. Each of the components of the primary outcome

2. Thromboembolic events defined as follows:

A) Transient ischemic attack (TIA): presence of a new focal neurologic deficit thought to be vascular in origin, with signs or symptoms lasting <24 hours diagnosed by imaging studies

B) Stroke: presence of a new focal neurologic deficit thought to be vascular in origin, with signs or symptoms lasting >24 24 hours diagnosed by imaging studies

C) Deep venous thrombosis diagnosed by ultrasound

D) Pulmonary embolism diagnosed by imaging studies

E) Peripheral embolus to limb(s) or other major organ diagnosed by imaging studies

F) Valve thrombosis confirmed in imaging studies (echocardiography)

3. All-cause mortality

4. Proven device site infection

5. Proven cardiac device-related endocarditis

2.7 Significant complications treatment

SPHs requiring evacuation will be treated with standard approach in aseptic conditions in the operating room. SPHs leading to discontinuation of ACT/APT will be treated conservatively with prolonged pressure dressing consisting of several layers of rolled bandage applied for 24 hours. SB will be treated conservatively with blood products transfusion or if interventional treatment be required, an adequate technique will be attempted.

2.8 Duration of treatment period

The treatment period is periprocedural. According to estimated risk of thromboembolic event patients on AC with VKA will continue or discontinue VKA within 3-4 prior CIEDs surgery and restart 24 hours after procedure. Patients on AC with DOAC will discontinue DOAC 24-36 prior CIEDs surgery and restart 24-48 hours after procedure. APT, either DAPT or SAPT will be continued periprocedurally.

2.9 Frequency and duration of follow up

All follow-up will be performed by two members of the research team. Patients will be seen post-op on the day of their surgery for assessment of the surgical site and each day throughout their hospital. All patients will have ambulatory follow-up 1-month and 12-months after CIED procedure. They will be examined if they have developed any pocket swelling or

hematoma over their device or bleeding. Patients developing significant hematoma will be followed until resolution of their hematoma. This includes follow-up of any additional complications related to the hematoma (e.g late infection) or procedures required for the management of the hematoma. Final follow up will occur once all device site complications are completely resolved and patient has resumed therapeutic anticoagulation.

2.10 Planned recruitment rate

We plan to complete the study in four years and enroll total 1100 patients.

2.11 Study duration

Patient enrollment time June 2015- June 2018.

2.12 Planned analyses

Descriptive statistics including 95% confidence intervals will be calculated for all baseline variables using means, medians, standard deviations and interquartile ranges for continuous outcomes, and rates and proportions for outcomes for each treatment subgroups. Baseline characteristics of the treatment subgroups will be compared with proper parametric or nonparametric test. A logistic regression analysis will be conducted to evaluate the magnitude of association between potential risk factors and SCs

Receiver operating characteristic (ROC) curve analysis will performed to determine the cut-off values for the predictive level of SBC development and for the evaluation of the models. Independent predictors will be summed for a total scoring system for each patient. The performance of the score in terms of SBCs prediction will be evaluated by ROC curve analysis, and its predictive ability will be determined using c-statistics.

3.1 Funding

Department's statutory funds.

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