Direct Oral Anticoagulants versus Vitamin-K Antagonists during Cardiac Rhythm Device Surgery: A Multicentre Propensity-matched Study

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Abstract

Introduction: There is a paucity of data comparing vitamin-K antagonists (VKAs) to non-vitamin K anticoagulants (NOACs) at the time of cardiac implantable electronic devices (CIEDs) surgery. Furthermore, the best management of NOACs (interruption vs. continuation) is yet to be determined.

Objective: This study aimed to compare the incidence of device-related bleeds and thrombotic events based on anticoagulant type (NOAC vs. VKA) and regimen (interrupted vs. uninterrupted).

Methods: Observational multicentre study. We included patients on chronic oral anticoagulation undergoing CIEDs surgery. Patients were matched using propensity scoring.

Results: We included 1975 patients (age 73.8±12.4). Among 1326 patients on NOAC, this was interrupted pre-surgery in 78.2% (1039) and continued in 21.8% (287). There were 649 patients on continued VKA. The matched population included 861 patients. The rate of any major bleeding was higher with continued NOAC (5.2%) compared to interrupted NOAC (1.7%) and continued VKA (2.1%) – p=0.03. The rate of perioperative thromboembolism was 1.4% with interrupted NOAC, while no thromboembolic events occurred with NOAC or VKA continuation (p=0.04). Use of dual antiplatelet therapy, NOAC continuation and male gender were independent predictor of major bleedings on a multivariable analysis.

Conclusion: In this large real-world cohort, a continued NOAC strategy was associated with a higher bleeding risk compared to NOAC interruption or VKA continuation in patients undergoing CIEDs surgery. However, NOAC interruption was associated with non-negligible thromboembolic risk. Concomitant dual antiplatelet therapy should be avoided whenever clinically possible. A bespoke approach is necessary, with a strategy of minimal NOAC interruption likely to represent the best compromise.

Key words: pacemaker; implantable defibrillator; anticoagulation; haematoma; warfarin; non-vitamin K oral anticoagulants.

Introduction

Many patients undergoing pacemaker or defibrillator surgery are on chronic oral anticoagulant therapy [1]. Several studies have explored different strategies to minimise bleeding risk in this clinical scenario. After the publication of the BRUISE CONTROL-1 (BC-1) trial, a strategy of uninterrupted vitamin K antagonists (VKAs) has become part of the routine clinical practice during cardiac implantable electronic devices (CIEDs) procedures, given its superiority compared to VKAs interruption and heparin bridging [1] in reducing clinically significant device-pocket haematoma. More recently, non-vitamin K oral anticoagulants (NOACs) have emerged as a valid and more practical alternative to warfarin, and their widespread use has rapidly increased worldwide. The BRUISE CONTROL-2 (BC-2) trial has suggested that a strategy of continuing NOACs at the time of device surgery might be comparable to NOACs interruption [2] in terms of risk of clinically significant haematoma. However, no definite conclusion could be drawn as the trial was stopped prematurely due to a lower event rate than anticipated. A recent meta-analysis has suggested that NOAC continuation may be associated with an increased risk of bleeding at the time of CIEDs surgery [3]. However, data on this topic remain sparse. Furthermore, there is a paucity of data and no randomised trials comparing NOAC vs. VKA in this population. NOACs have been shown to be not only at least effective as VKAs in thromboembolic prophylaxis, but also to have a better safety profile in terms of bleeding [4]; whether this applies to patients undergoing CIEDs surgery is yet to be determined. The aim of this study was to compare the incidence of device-related bleeds and thrombotic events based on anticoagulant type (NOAC vs. VKA) and regimen (interrupted vs. uninterrupted).

Methods

In this observational non-randomised study, consecutive patients on chronic oral anticoagulation undergoing cardiac rhythm device surgery were included in two centres (Barts Heart Centre, London, UK; Campus Bio-Medico University of Rome, Rome, Italy), between January 2018 and February 2021. Inclusion criteria were age > 18 years, de novo implantation, generator replacement or upgrade/revision of pacemaker (PPM), implantable cardioverter defibrillator (ICD) or cardiac resynchronisation therapy (CRT), and chronic treatment with either a VKA or NOAC agent. Patients with mechanical prosthetic valve or heparin bridging were excluded. The study complied with the Declaration of Helsinki and the protocol was approved and endorsed by the Barts Health Clinical Effectiveness Unit.

Aim

We aimed to compare the efficacy and safety of 1) NOAC vs. continued VKA; 2) interrupted vs. continued NOAC strategy.

Management of oral anticoagulation peri-procedure

In the VKA group, anticoagulation was continued peri-surgery as per usual regimen and INR was checked out before surgery. In the NOAC group, oral anticoagulation was interrupted or uninterrupted based on operator discretion (Figure 1). In the interrupted NOAC group, rivaroxaban, apixaban or edoxaban were held for 12-48 hours pre-procedure, while dabigatran was held for 24-48 hours based on glomerular filtration rate. All NOACs were restarted at least 12 hours post procedure. In the uninterrupted group, NOACs were continued as per usual regimen and administered on the day of the procedure.

Procedure details

The procedures were performed under local anaesthesia and sedation or general anaesthesia. Diathermy was routinely used. Venous access was obtained via cephalic, subclavian or axillary vein, based on operator preference. Use of pressure dressing postoperatively was at operator discretion.

Bleeding and thromboembolic events

The following endpoints were assessed:

1. *Major bleeding,* which was defined as combination of clinically significant device-pocket haematoma, and/or cardiac tamponade, and/or haemothorax, and/or any other bleeding requiring surgical intervention or blood transfusion.
2. *Device-pocket haematoma*, which was defined as any palpable swelling anteriorly or laterally to the pulse generator
3. *Clinically significant device-pocket haematoma,* which was defined as any hematoma requiring further surgery, and/or resulting in prolongation of hospitalization or requiring rehospitalization for at least 24 hours after index surgery and/or requiring interruption of the anticoagulant therapy for at least 24 hours. A hematoma requiring further surgery was defined as a hematoma continuing to expand or causing imminent skin necrosis/perforation [1, 2, 5]
4. *Cardiac tamponade,* which was defined as any new pericardial effusion requiring pericardiocentesis within 30-day post procedure
5. *Haemothorax or any other bleeding* requiring surgical intervention or blood transfusion within 30-day post procedure [1, 2, 5]
6. *Pericardial effusion,* which was defined as any new pericardial effusion (> 0.5 cm) not requiring pericardiocentesis within 30-day post procedure

7. *Thromboembolism*, which was defined as a composite of stroke, transient ischemic attack (TIA), myocardial infarction, pulmonary embolism, peripheral embolism, or deep vein thrombosis in the 30-day period post procedure [1, 2, 5]

The definition of major bleeding was largely based on the recommendation from the *International Society on Thrombosis and Haemostasis* [9] but adapted for CIEDs surgery.

Statistical analysis

The chi-square and one-way ANOVA test were used for categorical and continuous variables, respectively. Fisher's exact test was adopted instead of chi-square when the number of observations was < 5 for more than 20% of the cells. Levene's test was used to check the homogeneity of variance and in the absence of normal distribution Kruskal-Wallis H Test was used instead of one-way ANOVA. Independent predictors of any major bleeding were assessed with binary logistic regression Variables with $p < 0.10$ in the unadjusted analysis were included in the multivariable model. Patients in the VKA and interrupted NOAC group were matched 1:1 with those on continued NOAC using propensity score. A nearest neighbour matching with replacement was adopted. The following independent variables were included in the propensity score: age, gender, type of device (PPM vs ICD, and CRT), type of procedure (new implant/upgrade vs. generator replacement), hypertension, single or dual antiplatelet therapy, chronic kidney disease, and congestive heart failure.

The results with $p < 0.05$ were regarded as significant. SPSS version 27.0 was used for statistical analysis.

Results

We included a total of 1975 unmatched patients (mean age 76.0±9.0, 68% male), of whom 95.0% (1877) were on oral anticoagulation for atrial fibrillation/atrial flutter, 2.7% (53) for left ventricular thrombus and 2.3% (45) for deep vein thrombosis (Supplementary Table 1).

As many as 649 patients were on uninterrupted VKA, with a mean INR at the time of surgery of 2.4±0.5 (median 2.4, interquartile range 2.0-2.7). Among 1326 patients on NOAC, this was interrupted pre-surgery in 78.4% (1039) and uninterrupted in the remaining 21.6% (287). In the interrupted NOAC group, the median time from last pre-operative NOAC dose to surgery and from surgery to NOAC resumption were 24 and 48 hours (interquartile range 20.5-48 and 24-72), respectively; the median time from last pre-operative dose to first post-operative dose was 96 hours (interquartile range 48-120). A total of 8.8% (175) and 2.0% (39) of the participants were on single or dual antiplatelet therapy, respectively. Pressure dressing was used post procedure in 59.9% of the participants (1183) with no significant difference among the anticoagulation regimens ($p = 0.24$). Baseline population characteristics in the unmatched cohort are reported in Table 1. Figure 2 and Supplementary Table 2 show the distribution of anticoagulation type and regimen.

The matched population included a total of 861 patients (287 patients per group; mean age 74.8±12.1, 64.7% male). There were no significant differences across the three groups. Baseline population characteristics in the matched population are reported in Table 2. Group comparison before and after propensity score matching is reported in Supplementary Table 3.

Bleeding events in the matched cohort

A total of 26 patients (3.0%) met the endpoint of major bleeding events, with 23 patients (2.7%) experiencing a clinically significant haematoma, 2 (0.2%) cardiac tamponade and one (0.1%) haemothorax requiring surgery. The incidence of major bleeding was significantly higher in

the continued NOAC group (5.2%; n = 15) compared to interrupted NOAC (1.7%, n = 5) and VKA (2.1%; n = 6) (p = 0.03). This difference was mainly driven by a higher rate of clinically significant haematoma with continued NOAC (4.5%; n = 13) vs. interrupted NOAC and continued VKA (1.7%; n= 5 in both groups; p=0.06). These results are shown in Table 2.

Of the 26 major bleeding events in the matched cohort, 3 (11.5%) occurred in patients on antiplatelet therapy. None of the major bleeds in the continued NOAC group occurred in subjects on concomitant antiplatelet therapy.

Thromboembolic events

As many as 11 thromboembolic events (0.6%) occurred in the overall unmatched population, including 6 strokes, 2 TIAs, 1 acute spinal infarction and 2 deep vein thromboses (Table 4). One patient with acute spinal infarction and one patient with stroke died within few days after the procedure. All the thromboembolic events occurred in the interrupted NOAC cohorts. There were 4 thromboembolic events in the matched interrupted NOAC cohort (0.5%) and the difference was statistically significant compared to VKA and continued NOAC (p = 0.04). The rate of thromboembolic event in the matched population was 1.4%.

Subgroup analysis: NOAC regimen

On a subgroup analysis of matched patients on NOAC, there was no significant difference in the rate of any major bleeding between once-daily (rivaroxaban and edoxaban) vs. twice-daily (apixaban and dabigatran) NOAC in both interruption (1.6% vs. 1.9%, respectively; p = 1.0) or continuation regimen (5.9% vs. 4.6%, p = 0.64). The rate of thromboembolic events was also comparable (0.4% for twice-daily vs. 0.9% for once-daily NOACs, p = 0.63).

Subgroup analysis: patients on anticoagulation for deep vein thrombosis/pulmonary embolism or left ventricular thrombus

We conducted a subgroup analysis including 99 unmatched patients (5.0%) with no history of atrial arrhythmias. Among 45 participants on anticoagulation due to DVT/pulmonary embolism, 19 (40.4%) underwent CIED procedure on interrupted NOAC, 13 (27.6%) on continued NOAC and the remaining 13 (29.8%) on continued VKA. Of the 53 patients on anticoagulation due to left ventricular thrombus, 9 (17.0%) were on interrupted NOAC, 10 (18.9%) on continued NOAC and 34 (64.1%) on continued VKA. One patient was on continued VKA due to previous endocardial left ventricular lead implant. Baseline population characteristics of this subgroup are reported in Supplementary Table 4. Patients on VKA underwent more frequently generator replacement compared to interrupted and continued NOAC (25.0% vs. 0% vs. 8.7%, respectively; p = 0.003) and also had more frequently ICD implantation (83.3% vs. 57.1% vs. 43.4%; p = 0.02). Furthermore, use of SAPT was more frequent with VKA (31.2%) compared to interrupted NOAC (0%) and continued NOAC (13%) - p = 0.02. Overall, four patients (4%) in this subgroup met the endpoint of any major bleeding. The rate of major bleeds was significantly higher with a continued NOAC regimen (13.0%) compared to interrupted NOAC (3.6%) and warfarin (0%) – p = 0.03. There were no thromboembolic events.

Predictors of bleeding events

On a multivariable analysis, male gender (OR 2.3, 90% CI 1.19-4.44, p=0.04), NOAC continuation (OR 2.32, 90% CI 1.33-4.03, p = 0.001) and dual antiplatelet therapy (OR 3.76, 90% CI; 1.13-10.77; p = 0.04) were the only independent predictors of major bleeding events. These results are shown in Table 5.

Discussion

In this multicentre study, we present a large cohort of patients undergoing CIEDs surgery on chronic oral anticoagulation. The main findings are: (i) NOAC continuation is associated with a significantly higher rate of bleeds, whereas NOAC interruption is associated with a non-negligible rate of thromboembolism; (ii) NOAC interruption and VKA continuation have a similar safety profile in terms of bleeding; and (iii) NOAC continuation along with dual antiplatelet therapy and male gender are independent predictors of major bleeding.

In the last decade, NOACs have been increasingly used as alternative to VKAs. However, the optimal management of NOACs in patients undergoing CIEDs surgery is yet to be determined. Recent guidelines from the European Society of Cardiology do not provide specific recommendation on this regard, leaving at operator discretion the decision to continue or interrupt NOAC [7]. The 2017 Expert Consensus of the American College of Cardiology suggests interrupting NOAC for low-bleed risk procedures [8]. According to the 2021 European Heart Rhythm Association practical guide on use of NOACs [9], PPM or ICD implantation (excluding complex procedures) are considered minor risk procedures which can be performed with NOAC "at trough level (i.e., 12 or 24 hours after last intake)". Evidences behind such recommendations are mainly based on the BC-2 trial [2], which randomised 662 patients to either withhold or continue NOAC at the time of CIEDs surgery; no difference was found between the two cohorts, with clinically significant haematoma occurring in only 2.1% of the population in both arms. However, due to a much lower event rate than originally expected the trial was interrupted prematurely and as such it remains largely underpowered. A recent metanalysis of randomised and non-randomised studies has shown that NOAC continuation during CIEDs surgery may be associated with increased bleeding risk compared to interruption, although the certainty of the evidence was low due to inclusion of several small observational single-centre studies [3]. In keeping with this finding, the present study shows in

a large “real-world” cohort that NOAC continuation is associated with a higher bleeding risk - particularly development of device-pocket haematoma - compared to NOAC interruption. To the best of our knowledge, this is the largest cohort of patients undergoing CIEDs surgery on NOAC. Interestingly, in our series the rate of clinically significant haematoma was similar to the previous literature for interrupted NOAC [2, 3], while it was more than double for continued NOAC. This difference was also confirmed after adjusting for the baseline population characteristics (including use of antiplatelet therapy) with propensity matching.

An important factor which may have contributed to the high rate of bleeds in our continued NOAC cohort is that patients were allowed to take the morning dose of once-daily regimen NOACs (rivaroxaban or edoxaban) on the day of procedure, while for example in the BC-2 trial [2] patients on rivaroxaban (edoxaban was not evaluated) were asked to take the dose in the evening; as such, while most of the patients on rivaroxaban in the BC-2 trial underwent their procedure at trough level (median time from last dose to surgery was 16 hours), in our series it is likely that a proportion of the participants on rivaroxaban or edoxaban had their surgery at a peak level. Nonetheless, on a subgroup analysis we did not identify any significant difference in the rate of bleeding between patients on once-daily vs. twice-daily NOAC regimen. It should also be highlighted that CIEDs surgery in the BC-2, compared to our study, involved more generator replacements (35.4% vs. 24.7%) and fewer ICDs implants (18.8% vs. 25.8%). Risk of haematoma is lower in patients undergoing generator replacements vs. new implants/upgrades [10], as well as in those receiving PPMs vs. ICDs [11].

Another important finding of this study is that the bleeding risk with continued NOAC was higher compared to continued VKA, while we found no significant difference between interrupted NOAC and continued VKA regimens. These results are of interest given the paucity of data comparing NOAC vs. VKA during CIEDs surgery. To the best of our knowledge, the only large study exploring this topic is a combined post-hoc analysis of the BC-1 and BC-2

trials [12]; a total of 1343 patients were included, and the authors did not find any difference in the rate of clinically significant haematoma between NOAC (either interrupted or continued) vs. continued VKA. Such discrepancy compared to our results is driven by the fact that in our series the rate of significant haematoma was higher in the continued NOAC group compared to the BC-2 trial (4.9% vs. 2.5%) while it was lower in the continued VKA group compared to the BC-1 (1.7% vs. 3.5%). This difference is interesting and appears to reinforce the concept that a continued NOAC regimen independently increased bleeding events in our population. It may be hypothesised that the pharmacodynamic profile of NOACs – with a maximal anticoagulant effect achieved a few hours post administration [13] – may promote perioperative bleeds when a continued NOAC regimen is adopted. This effect may not be observed with a continued VKA regimen because of a steadier anticoagulant effect. It should be highlighted that the low rate of bleeds in our VKA group may be explained by the fact that we excluded patients with mechanical prosthetic valves; in contrast, almost one third of the participants in the BC-1 had mechanical prostheses. Patients with mechanical valves are likely to have a greater bleeding risk due to the higher INR target.

The rate of thromboembolic events with NOAC interruption was higher in our study compared to previous reports. In the BC-2 trial [2], the rate of thromboembolism was as low as 0.3% in both arms; however, the study had no power to draw any definite conclusion on this regard. In the PAUSE study [14], which included 3007 AF patients undergoing any surgery on interrupted NOAC, the rate of arterial thromboembolism was lower compared to our series (ranging from 0.16% in patients on apixaban to 0.60% in those on dabigatran) despite a similar mean CHA_2DS_2VASC score across the two populations. However, only one third of the participants in the PAUSE study underwent cardiothoracic procedures (such as CIEDs surgery) which are known to involve a higher thromboembolic risk [14]. It should be noted that the median time off anticoagulation in our cohort was higher compared to the BC-2 and PAUSE study (96 vs.

72 and 39.3-64.4 hours, respectively). This was driven by a longer interval from surgery to NOAC resumption in our series, with the first-operative dose being administered after a median of 48 hours vs. 31/24 hours in the BC-2 and PAUSE study. It is conceivable that the longer time to NOAC resumption in the present study may have contributed to the higher rate of thromboembolic events compared to previous reports. Indeed, there is evidence that patients undergoing CIEDs insertion have a particularly increased thromboembolic risk in the post-operative period [15]. The majority of thromboembolic events in our cohort occurred in an early stage after surgery (day 0 or day 1) and this highlights the importance not only of a short interruption pre procedure but also of a rapid reintroduction of NOAC. It is well recognised that intracardiac thrombi can develop in very short period of time during episodes of AF, due to processes promoting local hypercoagulability such as inflammation, endothelial dysfunction, and increased level of haemostatic grow factors [16-18]. Of note, one quarter of the arterial thromboembolic events in our series occurred in patients who were in normal sinus rhythm during the procedure. Overall, our results raise concerns on the practice of routinely interrupting NOAC before PPM/ICD surgery for prolonged periods of time and particularly delaying the resumption of NOAC for more than 24 hours post-surgery.

In accordance with previous literature [12, 20], concomitant dual antiplatelet therapy was independently associated with almost a 4-fold increased risk of bleeds in our series. We also found a significantly increased bleeding risk in patients on single antiplatelet therapy, although the latter was not an independent predictor of bleeds in our multivariable analysis. Overall, one quarter of the major bleeding events in our unmatched cohort occurred in participants on either single or dual antiplatelet therapy. A careful risk-benefit analysis should be made in subjects on dual or triple antithrombotic therapy and deferring non-urgent CIEDs procedures should be considered until antiplatelet therapy can be safely discontinued.

Another interesting finding of the present study is that male gender was an independent predictor of bleeding events in our multivariable analysis. This is in contrast with previous literature suggesting that females have a higher risk of complication after CIEDs surgery [21]. However, to the best of our knowledge there are no studies specifically designed to investigate the impact of gender on bleeding complications in patients on oral anticoagulation undergoing CIEDs surgery. A meta-analysis by Pancholy et al [22] found that male gender was associated with a higher bleeding risk among patients on NOAC for atrial fibrillation. Further studies are required to clarify gender differences in the outcomes of CIEDs surgery, particularly in subjects on chronic oral anticoagulation.

To the best of our knowledge, this is the first study investigating the management of oral anticoagulation at the time CIEDs surgery in patients with DVT/pulmonary embolism or left ventricular thrombus and no history of atrial arrhythmias. There were no thromboembolic events in this subgroup, which also included 29 patients in the interrupted NOAC cohort. These preliminary data are of interest, although further research is required to explore the safety of NOAC interruption at the time of CIEDs procedure in this population.

All in all, the present study has important clinical implications. Firstly, our findings raise concerns on the routine practice of performing CIEDs procedure on continued NOAC due to a high bleeding risk. On the flip side, the non-negligible rate of thromboembolic events with NOAC interruption highlights the importance of minimising the time off anticoagulation. Future research should investigate whether a personalised approach based not only on individual thromboembolic/bleeding risk but also on pharmacokinetics-pharmacodynamic-guided adjustment of NOAC dose [23] or time of interruption may be helpful in this setting.

Limitations

The main limitation of this study is its non-randomised and retrospective design. Although propensity score matching was used to account for confounding variables, the absence of randomisation should be taken into account in the interpretation of results. Furthermore, operators as well as clinicians who classified the bleeding and thromboembolic events were not blinded to NOAC perioperative strategy. Similarly, the decision of interrupting anticoagulation post procedure or prolonging hospitalisation was performed by clinicians unblinded to the initial NOAC strategy. This should be taken into account as the primary outcome of the study was mainly driven by haematoma requiring interruption of anticoagulation or prolonged hospitalisation. Despite a careful analysis of patients' electronic notes and a systematic and standardised collection of data, the retrospective design remains prone to potential bias due to underestimation of adverse events or misclassification. The probability of rejecting the null hypothesis for the outcome clinically significant haematoma was 5.7% (p=0.057) and as such this can only be interpreted as a trend rather than a statistically significant difference. No data were available regarding the interval time from last pre-operative NOAC dose to surgery in the continued NOAC group; as such, we were unable to ascertain whether procedures were performed with NOAC at the peak level (particularly for once-daily NOACs). In contrast with previous studies, we excluded patients with mechanical valves and as such the rate of bleeding events in the VKA group may not be comparable to previous literature. However, our goal was to compare VKA vs. NOACs and therefore including patients with mechanical valves would have been a major confounding factor as NOACs are contraindicated in this subgroup.

Conclusion

In this large real-world cohort of patients undergoing CIEDs surgery, a continued NOAC strategy was associated with a higher bleeding risk compared to NOAC interruption or VKA continuation. Bleeding complications were similar with an interrupted NOAC or continued VKA strategy. However, NOAC interruption was associated with a non-negligible thromboembolic risk. Concomitant dual antiplatelet therapy and male gender were identified as independent predictors of major bleeding. A bespoke approach for each patient is necessary, with a strategy of minimal NOAC interruption likely to represent the best compromise.

Clinical Perspectives

- Uninterrupted NOAC strategy is associated with an increased risk of bleeding at the time of cardiac rhythm device procedures
- Prolonged peri-procedure interruption of NOAC (> 24 hours) exposes patients to a significant risk of thromboembolic events
- VKA continuation is not associated with a significant increase of bleeding risk compared to NOAC interruption
- A minimally interrupted NOAC strategy is likely to represent the best compromise

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Legend to Figures

Figure 1. Strategies adopted in the study for management of NOAC at the time of cardiac rhythm device surgery.

Figure 2. Distribution of anticoagulation type

Figure 3. Incidence of major bleeding in the matched population

Figure 4. Proposed management of twice-daily (A) and once-daily regimen (B-1 and B-2) NOACs in patients undergoing cardiac rhythm device surgery.

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Table 1. Baseline characteristics in the unmatched population

	Total (n= 1975)	**VKA** (n= 649)	**Interrupted NOAC** (n= 1039)	**Continued NOAC** (n= 287)
Age	73.8±12.4	73.1±12.2	74.1±12.5	74.3±12.6
Female	673 (34.1%)	201 (31.0%)	367 (35.3%)	105 (36.6%)
PPM	1205 (60.8%)	350 (53.6%)	664 (63.9%)	191 (66.6%)
ICD	770 (39.2%)	299 (46.4%)	375 (36.1%)	96 (33.4%)
CRT	590 (29.9%)	234 (35.6%)	289 (27.8%)	67 (23.3%)
New implant/upgrade	1471 (74.7%)	415 (64.8%)	840 (80.8%)	216 (75.3%)
Box change	504 (25.3%)	234 (35.2%)	199 (19.2%)	71 (24.7%)
Subpectoral pocket	58 (3.0%)	21 (3.4%)	31 (3.0%)	6 (2.1%)
Pressure dressing	1183 (59.9%)	393 (59.7%)	607 (58.4%)	183 (63.8%)
SAPT	175 (8.8%)	69 (10.3%)	83 (8.0%)	23 (8.0%)
DAPT	39 (2.0%)	7 (1.1%)	30 (2.9%)	2 (0.7%)
HTN	1189 (59.9%)	354 (54.8%)	655 (63.3%)	170 (59.2%)
Diabetes mellitus	538 (27.3%)	195 (30.1%)	270 (26.1%)	73 (25.4%)
CKD (eGFR<60ml/min)	887 (45.0%)	324 (50.0%)	442 (42.6%)	121 (42.2%)
Anaemia (Hb <13 men, < 12 women)	712 (40.3%)	229 (41.4%)	388 (41.0%)	95 (35.6%)
Previous stroke/TIA/PE	317 (16.1%)	99 (15.3%)	163 (15.8%)	55 (19.2%)
Previous major bleeding	33 (1.7%)	11 (1.7%)	16 (1.5%)	6 (2.1%)
CHF	961 (51.0%)	359 (55.4%)	478 (46.2%)	124 (43.2%)
IHD	620 (31.5%)	211 (32.5%)	320 (30.9%)	89 (31.3%)
CHA2DS2VASc	3.6±1.5	3.5±1.5	3.6±1.5	3.6±1.6
HAS-BLED	1.7±0.9	1.6±1.0	1.7±0.9	1.8±0.9

Table . Baseline characteristics in the matched population

	Total (n= 861)	**VKA** (n=287)	**Interrupted NOAC** (n=287)	**Continued NOAC** (n=287)	**p**
Age	74.8±12.1	75.7±11.3	74.5±12.4	74.3±12.6	0.33
Female	304 (35.3%)	94 (32.8%)	105 (36.6%)	105 (36.6%)	0.54
PPM	594 (69.0%)	203 (70.7%)	200 (69.7%)	191(66.6%)	0.53
ICD	267 (31.0%)	84 (29.3%)	87 (30.3%)	96 (33.4%)	
CRT	188 (21.8%)	64 (22.3%)	57 (19.9%)	67 (23.3%)	0.58
New implant/upgrade	647 (75.1%)	205 (71.4%)	226 (78.7%)	216 (75.3%)	
Box change	214 (24.9%)	82 (28.6%)	61 (21.3%)	71 (24.7%)	0.13
Subpectoral pocket	23 (2.7%)	5 (1.7%)	12 (4.2%)	6 (2.1%)	0.15
Pressure dressing	519 (60.3%)	162 (56.4%)	174 (60.6%)	183 (63.8%)	0.19
SAPT	64 (7.4%)	27 (9.4%)	14 (4.9%)	23 (8.0%)	0.11
DAPT	8 (0.9%)	4 (1.4%)	2 (0.7%)	2 (0.7%)	0.60
HTN	511 (59.3%)	175 (61.0%)	166 (57.8%)	170 (59.2%)	0.75
Diabetes mellitus	224 (26.0%)	81 (28.2%)	70 (24.4%)	73 (25.4%)	0.56
Insulin	29 (3.4%)	15 (5.2%)	8 (2.8%)	6 (2.1%)	0.09
CKD	371 (43.1%)	128 (44.6%)	122 (42.5%)	121 (42.2%)	0.82
Anaemia (Hb <13 men, < 12 women)	315 (36.6%)	115 (40.1%)	105 (36.6%)	95 (33.1%)	0.22
Previous stroke/TIA/PE	141 (16.4%)	40 (13.9%)	46 (16.0%)	55 (19.2%)	0.23
Previous major bleeding	29 (3.4%)	15 (5.2%)	8 (2.8%)	6 (2.1%)	0.09
CHF	344 (40.0%)	113 (39.4%)	107 (37.3%)	124 (43.2%)	0.34
IHD	238 (27.7%)	71 (24.7%)	78 (27.2%)	89 (31.3%)	0.20
CHA2DS2VASc	3.5±1.5	3.5±1.5	3.4±1.5	3.6±1.6	0.33
HAS-BLED	1.7±0.9	1.8±0.9	1.7±0.9	1.8±0.9	0.23

Table 3. Results in the matched population

	Total (n=861)	VKA (n= 287)	Interrupted NOAC (n= 287)	Continued NOAC (n= 287)	p
Any major bleeding	26 (3.0%)	6 (2.1%)	5 (1.7%)	15 (5.2%)	**0.03**
Any bleeding	67 (7.8%)	16 (5.6%)	18 (6.3%)	33 (11.5%)	**0.01**
Any haematoma	61 (7.1%)	15 (5.2%)	18 (6.3%)	28 (9.8%)	0.09
Clinically significant haematoma	23 (2.7%)	5 (1.7%)	5 (1.7%)	13 (4.5%)	0.057
Haematoma requiring surgery	5 (0.6%)	0 (0%)	3 (1.0%)	2 (0.7%)	0.38*
Haematoma requiring prolonged hospitalisation	12 (1.4%)	1 (0.3%)	4 (1.4%)	7 (2.4%)	0.11*
Haematoma requiring interruption of OAC	18 (2.1%)	4 (1.4%)	4 (1.4%)	10 (3.5%)	0.13
Cardiac tamponade	2 (0.2%)	0 (0%)	0 (0%)	2 (0.7%)	0.33*
Pericardial effusion not requiring drain	4 (0.5%)	0 (0%)	1 (0.3%)	3 (1.0%)	0.33*
Haemothorax	1 (0.1%)	1 (0.3%)	0 (0%)	0 (0.0%)	-
Non-pocket bleed	8 (0.9%)	1 (0.2%)	2 (0.2%)	5 (1.7%)	0.052*
Thromboembolism 30-day	4 (0.5%)	0 (0%)	4 (1.4%)	0 (0%)	**0.04***
Death related to TE 30-day	0 (0%)	0 (0%)	0 (0%)	0 (0%)	-

Table 4. Thromboembolic events

TE event	Timing of TE post procedure	Age	Indication for OAC	CHA_2DS_2VASc	Previous stroke or TIA	Rhythm during procedure	NOAC	Time of interruption	Time of planned resumption
Stroke	Day 2	84	AF	5	1	AF	Apixaban	24	48
Stroke	Day 1	53	AF	2	1	AF	Rivaroxaban	48	72
Stroke	Day 1	76	AF	6	0	AF	Rivaroxaban	48	48
Stroke	Day 2	69	AF	4	1	AF	Dabigatran	48	48
Stroke	Day 1	81	AF	2	0	AF	Apixaban	NA	12
Stroke	Day 3	66	AF	3	0	SR	Apixaban	36	48
Stroke	Day 0	73	AF	2	0	SR	Rivaroxaban	24	12
TIA	Day 1	94	AF	6	0	AF	Apixaban	12	-
TIA	Day 3	81	AF	5	0	AF	Dabigatran	48	24
DVT	Day 1	61	AF	6	1	SR	Rivaroxaban	24	48
DVT	Day 1	61	AF	3	0	SR	Apixaban	24	120

Table 5. Unadjusted and adjusted logistic regression for any major bleeding

Variable						
	OR	90%CI	P	OR	90%CI	P
Age	1.00	0.98-1.02	0.77	-	-	-
Male gender	**1.88**	**1.09-3.23**	**0.05**	**2.30**	**1.19-4.44**	**0.04**
Device type (ICD vs PPM)	1.53	0.97-2.40	0.12	-	-	-
Generator replacement only	0.64	0.36-1.15	0.21	-	-	-
Biventricular device	1.59	1.00-2.51	0.10	-	-	0.27
Subpectoral pocket	1.25	0.38-4.19	0.76	-	-	-
Pressure dressing	1.65	0.92-2.98	0.09	-	-	0.21
Hypertension	1.28	0.73-2.24	0.40	-	-	-
Diabetes mellitus	1.00	0.60-1.66	0.99	-	-	-
Continued vs. interrupted NOAC	**2.15**	**1.25-3.71**	**0.02**	**2.32**	**1.33-4.03**	**0.01**
NOAC vs. VKA	1.45	0.86-2.42	0.24	-	-	-
SAPT	2.36	1.31-4.27	0.02	-	-	0.69
DAPT	**3.02**	**1.09-8.33**	**0.07**	**3.76**	**1.31-10.77**	**0.04**
CKD (eGFR <60ml/min)	1.06	0.67-1.67	0.84	-	-	-
Anaemia	1.09	0.68-1.73	0.77	-	-	-
Prev major bleeding	2.28	0.67-7.74	0.27	-	-	-
CHA2DS2VASC	1.18	1.01-1.36	0.07	-	-	0.27
HASBLED	1.36	1.07-1.72	0.04	-	-	0.47