Novel oral anticoagulants at the time of cardiac rhythm device surgery: a systematic review and meta-analysis

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Abstract

Introduction: Between 14% and 35% of the patients requiring cardiac implantable electronic device (CIED) surgery are on chronic oral anticoagulant therapy. Novel oral anticoagulants (NOACs) have emerged as a valid and more practical alternative to warfarin, and their widespread use has rapidly increased worldwide. We aimed to systematically assess the available evidence regarding the safety and efficacy of NOACs in patients undergoing CIEDs surgery.

Methods: We performed a systematic literature search of PubMed, EMBASE and Cochrane Controlled Register of Trials (from inception to March 2019). Eligible randomised controlled trials and cohort studies were included. The primary outcome measures were clinically significant device-pocket haematoma and thromboembolic events.

Results: A total of 12 studies were included, equating to a population of 2120 patients. All but 2 studies reported the incidence of clinically significant device-pocket haematoma, which occurred in 17 out of 1687 patients (1%;$CI_{95\%}$0.6-1.6). Any device-pocket haematoma occurred in 68 out of 2120 individuals (3.2%;$CI_{95\%}$2.5-4.0). A total of 8 thromboembolic events (0.4%;$CI_{95\%}$0.2-0.8) were reported during the follow-up. From a meta-analysis of 3 studies (equating to 773 subjects) allowing for a comparison of continued versus interrupted NOAC, we found no significant difference between the 2 strategies in terms of clinically significant pocket haematoma (1.14;CI95%0.43-3.06, p=0.79), thromboembolic complications (1.03;CI95%0.06-16.37, p=0.98), and any pocket haematoma (1.19;CI95%0.65-2.20, p=0.57).

Conclusion: Use of NOACs at the time of CIEDs surgery is safe, and either strategy of peri-procedure continuation or interruption appears to be reasonable.

Key words: novel oral anticoagulants; pacemaker; defibrillator; haematoma; bleeding.

Introduction

Each year, more than one million pacemakers and 400,000 implantable cardioverters defibrillators (ICDs) are implanted worldwide [1]. Between 14% and 35% of the patients requiring pacemaker or ICD surgery are on chronic oral anticoagulant therapy, most of them for prevention against thromboembolic complications of atrial fibrillation (AF) [2].

Prospective and randomised data have demonstrated the superiority of an uninterrupted vitamin K antagonists (VKAs) strategy compared to VKA interruption and heparin bridging [3], and the former has now become part of routine clinical practice.

More recently, novel oral anticoagulants (NOACs) have emerged as a valid and more practical alternative to VKA [4]. There is an increasing body of evidence suggesting that an uninterrupted or minimally interrupted anticoagulant strategy, with no bridging, might be adopted for NOAC-treated patients undergoing cardiovascular implantable electronic devices (CIEDs) implantation [5, 6]. Furthermore, the use of NOACs might reduce the risk of device-pocket haematoma compared to VKA [7].

We aimed to systematically assess the available evidence in the literature regarding the safety and efficacy of NOACs in patients undergoing CIEDs surgery.

Methods

Study Selection

A systematic electronic search was performed on PubMed, EMBASE and Cochrane Controlled Register of Trials (from inception to March 2019) with no language limitations, using the following search string: “novel oral anticoagulant” OR “NOAC” OR “rivaroxaban” OR “apixaban” OR “dabigatran” OR “edoxaban” AND (“cardiac electronic device” OR “pacemaker” OR “defibrillator”).

The population, intervention, comparison and outcome (PICO) approach was used [8]: the population of interest was patients on long-term NOAC therapy; the intervention was CIEDs surgery, which was defined as implantation, generator replacement, or upgrade of either permanent pacemaker, ICD or cardiac resynchronization device (CRT); the comparison was continued versus interrupted anticoagulation, and the outcomes are specified below.

All published randomised and non-randomised controlled trials, as well as prospective or retrospective case series were collected. Eligibility criteria for inclusion were: 1) clear definition of the peri-procedure NOAC management (either continuation or interruption); 2) explicit definition of the end-points according to the peri-procedure NOAC strategy, namely device-pocket haematoma which was considered mandatory. Observational non-controlled case series required a minimum of ten patients to be considered eligible. Controlled studies comparing continued versus interrupted NOAC strategy were included in the meta-analysis part of the present article. Reviews, editorials and case reports were not considered eligible. Reference lists of all accessed full-text articles were further searched for sources of potentially relevant information.

The primary outcome measures were: 1) clinically significant device-pocket haematoma; 2) thromboembolic events. Any device-pocket haematoma was an additional outcome. A device-pocket hematoma was defined as any palpable mass that protruded >1 cm anteriorly or laterally to the pulse generator. A clinically-significant haematoma 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. Other major bleeding events were defined as any bleeding complications requiring pericardiocentesis or surgical intervention (e.g., cardiac tamponade or haemothorax), a newly diagnosed pericardial effusion (>1 cm) not causing tamponade or any bleeding requiring a blood transfusion [5, 6]. Thrombotic events were defined as stroke, transient

ischemic attack, systemic embolism, myocardial infarction, pulmonary embolism, or deep vein thrombosis [5, 6]. Included articles were searched for other procedural complications, and these were extracted and added to this review when identified.

Two independent reviewers (AC and RP) screened all abstracts and titles to identify potentially eligible studies, and the full text of was subsequently interrogated. Agreement of the two reviewers was required for studies to be considered eligible for analysis. Study quality was formally evaluated by two reviewers (AC, MA) using the *National Heart, Lung, and Blood Institute Quality Assessment Tool* for either *Controlled Intervention* or *Case Series Studies* [9], when appropriate; quality assessment of controlled randomised trials used for the meta-analysis was performed using Cochrane GRADEpro GDT: GRADEpro Guideline Development Tool [Software], McMaster University, 2015 (developed by Evidence Prime, Inc.) [10]. An agreement between the two reviewers was mandatory for the final classification of studies. A third author (RP) intervened to resolve disputes whenever the two reviewers were in disagreement regarding the inclusion or classification of a study.

Data extraction and presentation for the preparation of this manuscript followed the recommendations of the PRISMA group [11]. Where available the following data were extracted from the selected studies: study design, study population characteristics (age and sex), follow-up duration. Patient-level data were obtained whenever these were available in the manuscripts, or provided by authors after contact.

Statistical analysis

Data were pooled using random effects, according to the Mantel–Haenszel model, through Review Manager (RevMan), V.5.3. (Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2014). The measurement of treatment effect was performed using risk ratios (RR) and 95% CIs. Pairwise comparisons were performed for all end points between patients

treated with continued or interrupted NOAC. Statistical heterogeneity on each outcome of interest was quantified using the I^2 statistic. Sensitivity analysis was performed for higher quality studies/randomised controlled studies.

Results

Study selection, quality of evidence, and patient characteristics

A total of 12 studies meeting the inclusion criteria were identified. The selection process is illustrated in Figure 1 (PRISMA) and a total population of 2120 patients was included. The mean age of the patients was 73.6±4.5 years; 68% were male.

There was a perfect agreement between investigators on the inclusion of the selected studies. Baseline data and the design of selected trials are summarized in Table 1.

The studies used for the analysis included one prospective randomised trial [5], one prospective randomised pilot trial [6], four prospective observational studies [12-15], two post-hoc analysis of prospective randomised trials [16, 17], and four retrospective studies [18-21]. Only three studies allowing for the comparison of continued versus interrupted NOAC strategy were identified [5-6, 15]. All but three studies [5, 16-17] were single-centre. According to the *National Heart, Lung, and Blood Institute Quality Assessment Tool for Case Series Studies* [9], a maximum of nine criteria apply for case series as shown in Table S-1. One study fulfilled nine criteria [15], four studies eight criteria [13-14, 19, 21], two studies seven criteria [12, 16], and three studies six criteria [17-18, 20]. Summary of quality assessment for randomised controlled trials is provided on Figure S-1. Both authors (AC and RP) were in agreement regarding study classification.

Among 2120 patients, 551 (26%) underwent CIEDs surgery on continued NOAC versus 1569 (74%) on interrupted NOAC. Time of NOAC interruption was reported in all but three studies, and was at least 24 hours. Median follow-up was 30 days post-procedure. Detailed data

regarding concomitant antiplatelet therapy were available for all but three studies; 30.6% of the patients (115 out of 2012) were on aspirin, and 4.9% (24 out of 2012) on other antiplatelet medications. Only two studies [6, 21], equating to 149 patients, reported the use of dual antiplatelet therapy. Clinical reason for anticoagulation was specified in all but one study [20], and was prevention against thromboembolic complications of AF/atrial flutter for all the participants.

Efficacy and safety of NOACs

All but two studies [17, 20] reported the incidence of clinically significant device-pocket haematoma, which occurred in 17 out of 1687 patients (1.0%;$CI_{95\%}$0.6-1.6). As most included studies did not allow for direct comparison, the separate pooling of rate of events showed a low and comparable incidence in those on continued NOAC (1.5%;$CI_{95\%}$0.8-3.0) and interrupted NOAC (0.8%;$CI_{95\%}$0.4-1.5).

All the studies reported the incidence of any device-pocket haematoma. This occurred in 68 out of 2120 patients (3.2%;$CI_{95\%}$2.5-4.0) and was numerically higher in those on continued NOAC (5.4%;$CI_{95\%}$3.8-7.7) compared to interrupted NOAC (2.4%;$CI_{95\%}$1.8-3.3).

A total of five patients (0.2%;$CI_{95\%}$0.1-0.5) suffered from peri-procedure pericardial effusion requiring pericardiocentesis, with a comparable incidence on continued versus interrupted NOAC group (0.5%;$CI_{95\%}$0.2-1.5 versus 0.1%;$CI_{95\%}$0.1-0.5, respectively). Eight patients (0.4%;$CI_{95\%}$0.2-0.7) had a drop of haemoglobin >2 gr/dl, not requiring any intervention (0.5%$CI_{95\%}$0.2-1.5 on continued NOAC versus 0.1%CI95%0.1-0.5 on interrupted NOAC).

A total of eight thromboembolic events (0.4%;$CI_{95\%}$0.2-0.8) occurred during the follow-up. Six patients (0.3%;$CI_{95\%}$0.1-0.6) suffered from stroke/TIA, with a comparable incidence among those on continued versus interrupted NOAC (0.2%$CI_{95\%}$0-1.0 versus 0.3%;$CI_{95\%}$0.1-

0.7). Two patients on interrupted NOAC had a myocardial infarction (0.1%;$CI_{95\%}$0.1-0.3). Results are summarised in Table 2.

Continued versus interrupted NOAC strategy: meta-analysis

From a meta-analysis of three studies [5, 6, 15] equating to 773 patients, we found no significant difference between continued versus interrupted NOAC strategy in terms of clinically significant pocket haematoma (2.1% versus 1.8%, respectively; RR1.14, CI95%0.43-3.06, p=0.79, I^2 0%), and any pocket haematoma (5.5% versus 4.6%, respectively; RR1.19, CI95%0.65-2.20, p=0.57, I^2 0%). Similar findings were observed for thromboembolic complications (0.3% for both continued and interrupted NOAC; RR1.03, CI95%0.06-16.37, p=0.98, I^2 0%). These results were confirmed after sensitivity analysis, which was performed only for the end-point any haematoma (RR1.14, CI95%0.61-2.12, p=0.68, I^2 0%), as the only non-randomised controlled study considered [15] did not include enough events for the other end-points, and hence did not contribute for those pooled analyses. These findings are shown in Figure 2.

Discussion

The present study shows that use of NOACs at the time of CIEDs surgery is safe, with very low rates of bleeding and thrombotic complications, and either strategy of peri-procedure continuation or interruption appears to be reasonable. No differences in the rate of clinically significant device-pocket hematoma were observed between the two strategies. However, comparison data between continuation or interruption of NOAC are still scarce, and resulting mainly from low quality case series or underpowered trials, with no effect size to show any minor differences. Notably, a 14% relative risk reduction of significant haematoma (as

suggested in our forest-plot; Figure 2-A) would require a sample size of more than 60.000 patients for showing a significant difference with an alpha of 0.05 and 80% of power.

We have found no difference between the two treatment strategies with regards of thromboembolic risk, which appears to be very low.

The optimal management of NOACs at the time of CIEDs surgery is currently unclear. To date, there are only three studies [5, 6, 15] specifically designed to compare continuation versus interruption of NOAC during pacemaker or ICD surgery. The BRUISE CONTROL-2 is the largest of these, having enrolled 662 patients [5]. This was designed as a superiority trial; however, given a much lower incidence of pocket haematoma than originally hypothesized, the trial was actually underpowered in detecting bleeding differences between continued or interrupted NOAC strategy. Another limitation was the lack of operator blinding to the treatment, which could explain the more frequent use of intra-pocket haemostatic agent and/or pressure dressing in the continued NOAC group.

Pocket haematoma represents a serious complication of CIEDs surgery [22]. Reoperation is often required, with subsequent prolonging hospitalisation and increased healthcare costs. In addition, pocket haematoma is associated with a 7-fold higher risk of device infection, and up to 15-fold in case of surgical evacuation [23]. Device infection usually requires explant or extraction, which represents a potentially life-threatening procedure. Reduction of the rate of pocket haematoma represents an important surgical goal, however the risk of bleeds should always be balanced with the risk of thromboembolic complications. Although it might be conceivable that interruption of anticoagulation leads to a higher number of thromboembolic events, this does not seem to be the case in our AF population. Indeed, in this review only 0.4% of patients experienced stroke/TIA/myocardial infarction during follow-up, with no difference between the two peri-procedure NOAC strategies. These findings are consistent with the recent results of the PAUSE trial [24], which enrolled 3007 patients on NOAC for atrial fibrillation

requiring elective surgery/procedure; NOAC was interrupted pre-procedure and restarted afterward, with a timing based on NOAC pharmacokinetic properties, procedure-associated bleeding risk and creatinine clearance, but not on the individual thrombotic risk (i.e., CHA_2DS_2VASc score). In the PAUSE trial, the rate (95%CI) of arterial thromboembolism was as low as 0.16% (0-0.48) in the apixaban cohort, 0.6% (0-1.33) in the dabigatran cohort, and 0.37% (0-0.82) in the rivaroxaban cohort.

The short half-life of NOACs allows interruption with no heparin bridging, and this probably explains the low incidence of bleeding events compared to interrupted warfarin in previous studies, such as the BRUISE-CONTROL trial where the heparin use may have accounted for the high rate of clinically significant device-pocket haematoma (16%) [5]. This review confirms that no bridging with heparin is required in patients with AF undergoing CIED surgery on interrupted NOAC, as the event rate in this group is minor both for bleeding and thromboembolic events.

Limitations

Most of the studies included in this review were single-centre and based on small cohorts, and some of them were retrospective. Only three studies were designed to compare continued versus interrupted NOAC strategy, and none of them was adequately powered to detect small differences between groups. The timing of NOAC interruption and resumption was heterogeneous among the studies included, and these could have influenced the risk of bleeding.

Conclusions

Use of NOACs at the time of CIEDs surgery is safe, and either strategy of peri-procedure continuation or interruption appears to be reasonable.

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Table 1. Baseline characteristics of studies

Study	Design	Multi-Center	Subjects (n)	AF/ flutter	Age (years)	Sex % (female)	Continued NOAC n (%)	Interrupted NOAC n (%)	Timing of NOAC interruption	Timing of NOAC resumption (hours)	SAPT % (n)	DAPT % (n)
Steffel et al 2019C [16]	Post-hoc analysis of randomised trial	Yes	549[A]	100%	74[B]	31%[B]	NA[A]	549[A]	Defined as >3 days of consecutive missed doses of blinded study drug	NA	Aspirin 30% (226) P2Y12 2% (15)	NA
Tsai et al- 2019 [18]	Retrospective	No	100	100%	78.3±10.2	42%	100 (100%)	-	-	-	Aspirin 6% (6) P2Y12 2% (2)	NA
Birnie et al, BRUISE CONTROL 2 trial- 2018 [5]	Prospective randomised trial	Yes	647	100%	74.1±8.9 - 328 73.4±8.9 -334	27.6%	319 (49.3%)	328 (50.7%)	Dabigatran: 24-48 hours (according to GFR) Rivaroxaban/apixaban: 48 hours	≥24	Aspirin 17.4% (115) P2Y12 3.6% (24)	NA
Ricciardi et al- 2018 [6]	Prospective randomised pilot trial	No	101	100%	76.0±8.8	34.6%	50 (49.5%)	51 (50.5%)	Dabigatran: 24-48 hours (according to GFR) Rivaroxaban/apixaban: 24 hours	≥24	Aspirin 15.8% (16) P2Y12 5.9% (6)	3% (3)
Essebag V 2017 [17]	Post-hoc analysis of randomised trial	Yes	410[C]	100%	72.5±8.5	30.5%	0	410[D] (100%)	Dabigatran: 24-96 hours (according to GFR), median 53 hours	22-70 (median 34)	Aspirin 46% (189) P2Y12 8% (33)	NA
Terekhov 2017 [12]	Prospective, observational	No	31[E]	100%	83	74.2%	0	31 (100%)	12 hours	36-48	16% (5)	NA
Madan 2016 [19]	Retrospective	No	47[F]	100%	73.4±11[G]	29.8%	0	47 (100%)	12-91 hours (mean 23.3 hours)	9-54 (mean 21 hours)	Aspirin 50% (23) P2Y12 6.4% (3)	NA
Melton 2015 [20]	Retrospective	No	23[H]	NA	68.4[I]	NA	23[H] (100%)	-	-	-	NA	NA
Kosiuk 2014 (Europace) [13]	Prospective, observational	No	54[JK]	100%	74±9m	31.3%[L]	0	54[JK] (100%)	12 hours	24-48 (median 48)	NA	NA
Kosiuk 2014 (Circ J) [14]	Prospective, observational	No	85[M]	100%	73±11	67.3%	0	85[M] (100%)	24 hours	0-48 (median 24 hours)	Aspirin 20% (17) P2Y12 13% (11)	NA
Jennings et al- 2013 [21]	Retrospective	No	48	100%	66±12.4	27%	48 (100%)	-	-	-	Aspirin 25% (12) P2Y12 6.2% (3)	2.1% (1)
Rowley et al- 2013 [15]	Prospective, observational	No	25	100%	66±11	12%	11 (44%)	14 (56%)	26±16 hours	8±3	Aspirin 48% (12) P2Y12 8% (2)	NA
Total			**2120**		**73.6±4.5**	**32.6%[N]**	**551 (26%)**	**1569 (74%)**			Aspirin 30.6%[O] P2Y12 4.9%[O]	

Abbreviations: NOAC: novel oral anticoagulant. NA- not available; P2Y12- inhibitors of P2Y12 platelet receptor.
Notes: A: this includes only subjects in whom edoxaban was interrupted > 3 days pre-procedure; patients on "continued" NOAC were excluded from the present review, because actually no information regarding NOAC cessation and resumption ≤ 3 days pre-procedure were available; **B**: this refers to all the population on edoxaban, however only those on interrupted NOAC were included (see note A for details); **C**: this study included 611 patients, but only 410 of them were on NOAC; **D:** heparin bridging pre-procedure in 56 patients (13.7%), post-procedure in 41 (10%); **E**: this study included 126 patients, but only 31 of them were on NOAC; **F**: this study included 133 patients,

but only 47 of them were on NOAC; **G**: this refers to the whole population of the study (see note F); **H**: this study included 380 patients, but only 23 were on NOAC; **I**: this refers to the whole population of the study (see note H); **J**: rivaroxaban-naïve patients excluded as not meeting inclusion criteria of this review; **K**: patients on dabigatran excluded as part of the same population from Kosiuk et al, Circ J 2014; **L**: this include 11 rivaroxaban-naïve patients who were excluded from this review; **M**: 35 dabigatran-naïve patients excluded as not meeting inclusion criteria of this review; N: this refers to a population of 2307 patients; **O**: this refers to a population of 2012 patients, as data were not available for 2 studies.

Table 2. Outcomes

Study	Follow-up (days)	Clinically significant haematoma % (n)	Any haematoma % (n)	Other device-related bleeding % (n)	Thromboembolic and other complications % (n)
Steffel 2019	30	Interrupted NOAC: 0.2% (1)	Interrupted NOAC: 0.9% (5)	Interrupted NOAC: minor bleeding at surgical site 0.2% (1)	Interrupted NOAC: stroke 0.2% (1) TIA 0.2% (1) MI 0.2% (1)
Tsai et al- 2019	541	None	Continued NOAC: 1% (1)	Continued NOAC: pericardial effusion[A] 1% (1)	None
Birnie et al, BRUISE CONTROL 2- 2018	7-14	Interrupted NOAC: 2.1% (7) Continued NOAC: 2.1% (7)	Interrupted NOAC: 4.8% (16) Continued NOAC: 5.5% (18)	Interrupted NOAC: pericardial effusion[A] 0.3% (1) Continued NOAC: pericardial effusion[A] 0.3% (1)	Interrupted NOAC: stroke 0.3% (1) Continued NOAC: stroke 0.3% (1)
Ricciardi et al- 2018	60-90	Interrupted NOAC: none Continued NOAC: 2.0% (1)	Interrupted NOAC: 4.0% (2) Continued NOAC: 3.9% (2)	Interrupted NOAC: loss of Hb > 2 gr/dl 6% (3) Continued NOAC: loss of Hb > 2 gr/dl 9.8% (5)	Continued NOAC: pocket infection 1% (1)
Essebag V 2017	30	NA[B]	Interrupted NOAC: 2.2% (9)[C]	None	Interrupted NOAC: stroke: 0.5% (2) MI: 0.2% (1)
Terekhov 2017	90	None	Interrupted NOAC: 6.5% (2)	None	Interrupted NOAC: gastrointestinal bleeding 3.2% (1)
Madan 2016	30	None	None	None	None
Melton 2015	30	NA[B]	Continued NOAC: 35% (8)	None	None
Kosiuk 2014 (Europace)	30	Interrupted NOAC: 1.5% (1)	Interrupted NOAC: 3.1% (2)	Interrupted NOAC: pericardial effusion[A] 1.5% (1)	None
Kosiuk 2014 (Circ J)	30	None	Interrupted NOAC: 2.3% (2)	None	None
Jennings et al- 2013	28-42	None	None	Continued NOAC: pericardial effusion[A] 2.1% (1)	None
Rowley et al- 2013	30	None	Continued NOAC: 7% (1)	None	None
Total NOAC % (n)		**1.0%** (17)[D] Ci95%0.6-1.6	**3.2%** (68) Ci95%2.5-4.0	Pericardial effusion[A] 0.2% (5) CI95% 0.1-0.5 Minor bleeding at surgical site: 0.2% (1) CI95% 0.1-0.3 Loss of Hb >2 gr/dl: 0.4% (8) CI95% 0.2-0.7	All thromboembolism 0.4% (8) CI95% 0.1-0.6 Stroke/TIA 0.3% (6) CI95% 0.1-0.6 MI 0.1% (2) CI95% 0.0-0.4 Other complications Pocket infection 0.2% (1) CI95% 0.1-0.3 Gastrointestinal bleeding % (1) CI95% 0.1-0.3
Total interrupted NOAC % (n)		**0.8%** (9)[E] Ci95%0.4-1.5	**2.4%** (38) Ci95%1.8-3.3	Pericardial effusion[A] 0.1% (2) Ci95%0.1-0.5 Loss of Hb >2 gr/dl 0.2% (3) Ci95%0.1-0.6 Minor bleeding at surgical site 0.2% (1) CI95% 0.1-0.3	All thromboembolism 0.4% (7) CI95% 0.1-0.6 Stroke/TIA 0.3% (5) CI95% 0.1-0.7 MI 0.1% (2) CI95% 0.1-0.3 Other complications Gastrointestinal bleeding % (1) CI95% 0.1-0.3
Total continued NOAC % (n)		**1.5%** (8)[F] Ci95%0.8-3.0	**5.4%** (30) Ci95%3.8-7.7	Pericardial effusion[A] 0.5% (3) Ci95%0.2-1.5 Loss of Hb >2 gr/dl 0.7% (5) Ci95%0.3-1.8	All thromboembolism 0.2% (1) CI95% 0-1.0 Stroke/TIA 0.2% (1) CI95%0-1.0 Other complications Pocket infection 0.2% (1) CI95% 0-1.0

Abbreviations: NOAC- novel oral anticoagulant. NA- not available. Hb- haemoglobin. TIA- transient ischemic attack. MI- myocardial infarction.
Notes: **A**: requiring pericardiocentesis. **B**: data according to anticoagulant treatment not available; **C**: pre-procedure heparin bridging in one patient. **D**: this refers to a population of 1687 patients, as data not available for 2 studies; **E**: this refers to a population of 1159 patients, as data not available for 2 studies; **F**: this refers to a population of 528 patients, as data not available for 2 studies.

Figure 1. PRISMA

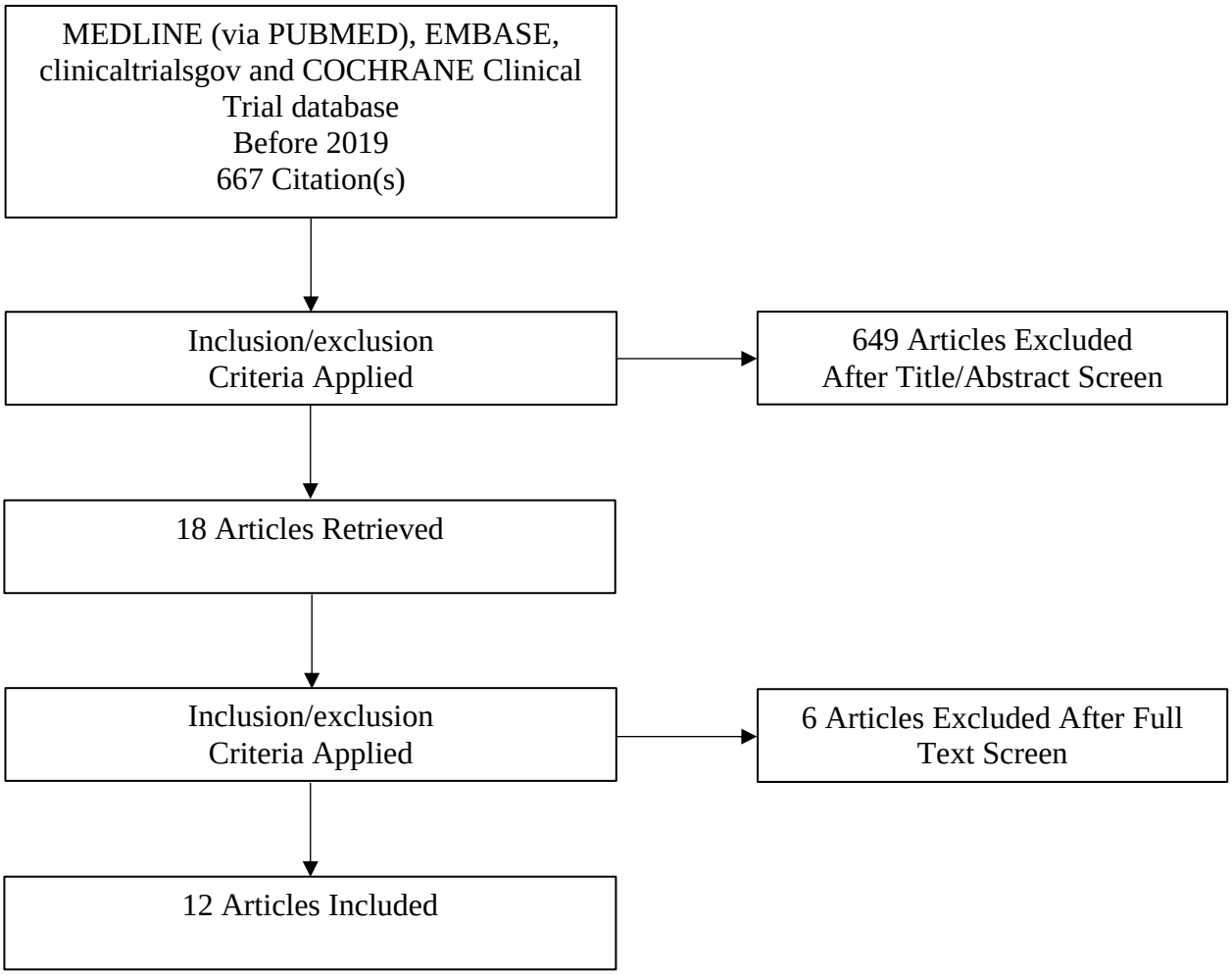


Figure 2-A. Clinically significant device-pocket haematoma

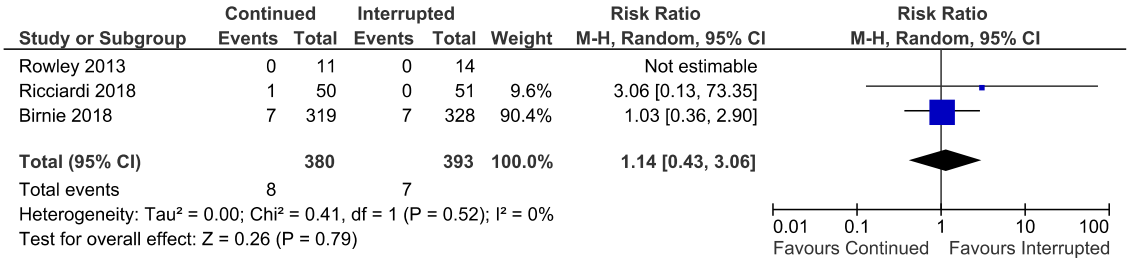


Figure 2-B. Thromboembolic events

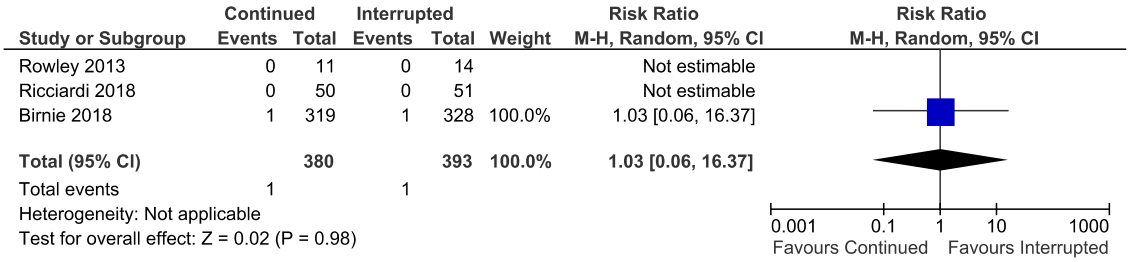
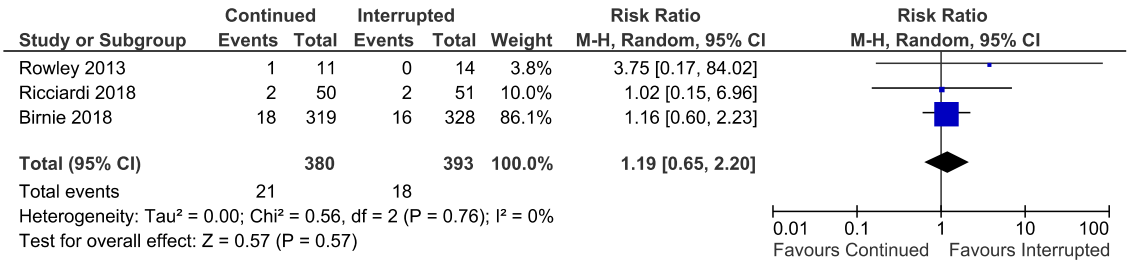


Figure 2-C. Any device-pocket haematoma



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Supplementary materials

S-Table 1. *National Heart, Lung, and Blood Institute Quality Assessment Tool for Case Series Studies*

Criteria	Steffel et al-2019 []	Tsai et al-2019 [18]	Essebag et al-2017 []	Terekhov 2017 [12]	Madan 2016 [19]	Melton 2015 [20]	Kosiuk 2014 (Europace) [13]	Kosiuk 2014 (Circ J) [14]	Jennings et al-2013 [21]	Rowley et al-2013 [15]
1. Was the study question or objective clearly stated?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
2. Was the study population clearly and fully described, including a case definition?	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes
3. Were the cases consecutive?	NA	NR	NA	NR	Yes	Yes	Yes	Yes	Yes	Yes
4. Were the subjects comparable?	Yes	NA	Yes	NA	NA	NA	NA	NA	NA	Yes
5. Was the intervention clearly described?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
6. Were the outcome measures clearly defined, valid, reliable, and implemented consistently across all study participants?	No	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes
7. Was the length of follow-up adequate?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
8. Were the statistical methods well-described?	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
9. Were the results well-described?	Yes	Yes	No	Yes	Yes	No	Yes	Yes	Yes	Yes

S-Figure 1. Cochrane GRADE quality assessment of randomised controlled trials

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	[intervention]	[comparison]	Relative (95% CI)	Absolute (95% CI)		
Primary outcome – Clinically-significant haematoma (follow up: range 30 days to 60 days)												
2	randomised trials	not serious	not serious	not serious	serious[a]	none			not estimable		⨁⨁⨁◯ MODERATE	
Secondary outcome- Non-significant haematoma (follow up: range 30 days to 60 days)												
2	randomised trials	not serious	not serious	not serious	serious[a]	none			not estimable		⨁⨁⨁◯ MODERATE	
Secondary outcome- Thromboembolism (follow up: range 30 to 60)												
2	randomised trials	not serious	not serious	not serious	serious[a]	none			not estimable		⨁⨁⨁◯ MODERATE	

CI: Confidence interval

Explanations

a. Small number of events and patients in study. Follow-up period was different between the two trials.