

# Peri-interventional management of novel oral anticoagulants in daily care: results from the prospective Dresden NOAC registry

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## Aims

Patients receiving novel oral anticoagulants (NOACs) frequently undergo interventional procedures. Short half-lives and rapid onset of action allow for short periods of NOAC interruption without heparin bridging. However, outcome data for this approach are lacking. We evaluated the peri-interventional NOAC management in unselected patients from daily care.

## Methods and results

Effectiveness and safety data were collected from an ongoing, prospective, non-interventional registry of >2100 NOAC patients. Outcome events were adjudicated using standard event definitions. Of 2179 registered patients, 595 (27.3%) underwent 863 procedures (15.6% minimal, 74.3% minor, and 10.1% major procedures). Until Day 30 ± 5 post-procedure, major cardiovascular events occurred in 1.0% of patients [95% confidence interval (95% CI) 0.5–2.0] and major bleeding complications in 1.2% (95% CI 0.6–2.1). Cardiovascular and major bleeding complications were highest after major procedures (4.6 and 8.0%, respectively). Heparin bridging did not reduce cardiovascular events, but led to significantly higher rates of major bleeding complications (2.7%; 95% CI 1.1–5.5) compared with no bridging (0.5%; 0.1–1.4; *P* = 0.010). Multivariate analysis demonstrated diabetes [odds ratio (OR) 13.2] and major procedures (OR 7.3) as independent risk factors for cardiovascular events. Major procedures (OR 16.8) were an independent risk factor for major bleeding complications. However, if major and non-major procedures were separately assessed, heparin bridging was not an independent risk factor for major bleeding.

## Conclusion

Continuation or short-term interruption of NOAC is safe strategies for most invasive procedures. Patients at cardiovascular risk undergoing major procedures may benefit from heparin bridging, but bleeding risks need to be considered.

## Keywords

Oral anticoagulants • Apixaban • Dabigatran • Rivaroxaban • Bridging • Invasive procedures

## Introduction

For more than five decades, vitamin-K antagonists (VKAs) were the standard in the long-term anticoagulation for stroke prevention in atrial fibrillation (SPAF), for the treatment of venous thromboembolism (VTE), and for other indications. Many VKA patients need to undergo surgical or interventional procedures,<sup>1</sup> and most interventions require temporary interruption of VKA therapy. VKA therapy is usually discontinued 5–7 days before the procedure.<sup>2</sup> After

re-initiation of VKA anticoagulation, the therapeutic international normalized ratio range will be achieved only after another 5–7 days. As a consequence, many patients receive bridging therapy with low-molecular-weight heparin (LMWH) during this time.<sup>2–4</sup> However, a recent meta-analysis of bridging studies demonstrated that LMWH bridging, although effective in preventing thromboembolic complications, increases the risk of peri-procedural bleeding complications.<sup>3</sup> Large prospective trials are investigating the risk:benefit ratio of bridging VKA patients to LMWH in more detail.<sup>4</sup>

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Over the past 2 years, novel oral anticoagulants (NOACs) such as apixaban, dabigatran, and rivaroxaban have become approved for long-term oral anticoagulation and, consequently, there are more cardiovascular risk patients who are receiving these agents. Large Phase III trials in SPAF and VTE treatments compared different NOACs against VKAs and consistently demonstrated high efficacy and safety for the novel drugs.<sup>5–8</sup> In a *post hoc* analysis of the peri-procedural management of patients on either dabigatran or warfarin in the open-label RE-LY trial, patients on dabigatran had similar rates of cardiovascular or major bleeding events as for those on warfarin.<sup>9</sup> However, the authors found that pre-procedural interruption of anticoagulation was significantly shorter for dabigatran (49 h) than for warfarin (114 h), and that the use of heparin bridging was less frequent (~16% of dabigatran patients vs. 28% of warfarin patients).

These observations reflect the specific pharmacological profile of all NOACs. Short half-lives reduce the interval of pre-procedural interruption down to 1 or 2 days, and a fast onset of action achieves rapid restitution of anticoagulant activity after the procedure. Therefore, for NOAC patients undergoing invasive procedures, anticoagulant-free time intervals are expected to be shorter than for patients on VKAs. Expert opinions thus recommend against heparin bridging therapy for NOAC patients undergoing procedures.<sup>10–12</sup> However, these recommendations currently lack scientific evidence. Therefore, data on the management and safety of surgical or interventional procedures in the daily care of unselected NOAC patients are scarce and urgently needed.<sup>4</sup> Using data from a large, regional, prospective NOAC registry, we evaluated the management and safety of peri-interventional NOAC use in a large cohort of patients from daily care.

## Methods

### Patients

The Dresden NOAC registry (NCT01588119) is a large prospective registry in the administrative district of Dresden (Saxony), Germany. In this ongoing project, a network of >230 physicians from private practices and hospitals enrol NOAC patients, who are prospectively followed up by the central registry office. Patients are eligible if the following inclusion criteria are met:

- Planned NOAC anticoagulation for at least 3 months.
- Therapeutic NOAC indication including SPAF, deep vein thrombosis (DVT), pulmonary embolism (PE), and other indications.
- Age > 18 years.
- Written informed consent.
- Availability for follow-up by telephone visits.

No exclusion criteria apply. Patients are followed up by telephone visits at 30 days after enrolment and quarterly thereafter to collect data on the effectiveness, safety, and management of NOAC therapy in daily care.

For all patients with a reported surgical or interventional procedure during follow-up, contact to the family physician, interventionalist, or surgeon was established. Reports, hospital charts, laboratory test results, death certificates, and any other documentation relating to the invasive procedure were collected as applicable.

### Surgical or interventional procedures

Based on the bleeding risk categories provided in the chapter 'Perioperative Management of Antithrombotic Therapy' of the 9th ACCP consensus

document<sup>1</sup> and the 'European Heart Rhythm Association Practical Guide on the use of new oral anticoagulants',<sup>12</sup> we defined three categories of procedures (minimal, minor, and major procedures), according to the severity of tissue trauma and the risk of peri-procedural bleeding.

*Minimal* procedures were procedures with little tissue trauma, such as:

- Superficial skin and oral mucosal surgery, including skin biopsies.
- Wound revisions.
- Non-extraction dental treatment.

*Minor* procedures were procedures with little tissue trauma, but relevant bleeding risk, such as:

- Transluminal cardiac, arterial, and venous interventions.
- Pacemaker-related surgery.
- Pleura and ascites puncture.
- Cataract surgery.
- Arthroscopy, endoscopy, laparoscopy.
- Organ biopsies.
- Dental extraction.
- Hernia repair.
- Intramuscular and paravertebral injections.

*Major* procedures were procedures with relevant tissue trauma and high bleeding risk, such as:

- Open pelvic, abdominal and thoracic surgery.
- Brain surgery.
- Major orthopaedic and trauma surgery.
- Vascular surgery.

### Data collection

Among other variables, the following data were collected:

- Type, day, and time of last intake of NOAC before procedure.
- Type, date, and outcome of procedure.
- Peri-procedural type of anticoagulation and dosage (in the case of heparin bridging).
- Exact day and time of NOAC restart (in the case of NOAC interruption).
- Rates, severity, and management of major cardiovascular events and peri-procedural bleeding complications until Day 30 ± 5.

### Outcome parameters

Rates of outcome events were evaluated until Day 30 ± 5 after procedure. Repeated interventions in the same patient were separately evaluated. Statistical analyses were performed for all procedures and also for subtypes of minimal, minor, or major procedures.

The primary effectiveness outcome was a composite endpoint of fatal or non-fatal major cardiovascular events consisting of centrally adjudicated:

- Acute coronary syndrome, including unstable angina, non-ST-elevation infarction, and ST-elevation infarction.
- Stroke or transient ischaemic attack or systemic embolism.
- DVT or PE.

Secondary effectiveness outcomes were non-major cardiovascular events and death from cardiovascular disease.

The primary safety outcome was the rate of major bleeding using the International Society of Thrombosis and Haemostasis (ISTH) definition.<sup>13</sup> The outcome of major bleeding was defined as overt bleeding with any of the following:

- Documented transfusion of at least two units of red blood cells.
- Drop in haemoglobin > 2 g/L.

- Surgical revision due to bleeding.
- Bleeding into critical sites (intracranial, intraocular, intra-articular, retroperitoneal, and overt gastrointestinal bleeding).
- Fatal bleeding.

Further safety outcomes were the rates of any bleeding, non-major, clinically relevant (NMCR) bleeding, minor bleeding, or death from any cause.

For all patients with suspected major cardiovascular or bleeding events, results of imaging, laboratory tests, patient charts, discharge letters, autopsy reports, and death certificates were reviewed and categorized using standard definitions.

## Statistics

Differences in baseline variables or outcome event rates were compared using the Student's *t*-test, Mann–Whitney *U*-test, Fisher's exact test, or  $\chi^2$  test, as appropriate. Uni- and multivariate analyses were performed using a logistic regression model. All items with significant results in univariate analysis were included in multivariate analysis, followed by a stepwise backward elimination.

95% confidence intervals (95% CIs) for proportions are given according to Clopper–Pearson. Data are shown as absolute values, percentage, standard deviation, and 95% CI, or median with 25th and 75th percentiles, as appropriate. A *P*-value of <0.05 was regarded to be significant.

All statistical analyses were carried out using the IBM® SPSS® Statistics Version 21 and R (Comprehensive R Archive Network).

## Ethics

The study protocol of the Dresden NOAC registry was approved by the local ethics committee at the Technical University Dresden (AZ EK 349092011) and registered at ClinicalTrials.gov (NCT01588119). All patients provided written informed consent, including a data protection waiver before enrolment.

## Results

### Cohort characteristics

Between 1 October 2011 and 15 May 2013, 2179 patients were enrolled into the registry. Of these, 595 (27.3%) patients underwent a total of 863 surgical or interventional procedures, which were classified as minimal in 135 (15.6%) cases, minor in 641 (74.3%), and major in 87 (10.1%) (Table 1, detailed descriptions of procedures provided in Supplementary material online, Appendix 1). Patient characteristics were comparable between the subgroups of procedures; however, patients undergoing major procedures were significantly more likely to have a history of coronary artery disease and to have received concomitant antiplatelet therapy compared with those undergoing minimal or minor procedures.

Most procedures were performed in patients receiving rivaroxaban (*n* = 656; 76%), followed by patients on dabigatran (*n* = 203; 23.5%) and apixaban (*n* = 4; 0.5%). Stroke prevention in atrial fibrillation (*n* = 700, 81.1%) was the most common indication for NOAC therapy, followed by VTE (*n* = 148; 17.1%) and others (*n* = 15; 1.7%).

### Efficacy and safety endpoints at Day 30 after surgical or interventional procedure

The results for effectiveness and safety endpoints are listed in Table 2. In a total of 863 surgical or interventional procedures in NOAC patients, nine major cardiovascular events occurred until Day 30 ± 5

**Table 1** Patient characteristics, NOAC type, and NOAC indication of patients undergoing 863 surgical or interventional procedures

	All procedures	Minimal procedures	Minor procedures	Major procedures	P-value minimal vs. major	P-value minor vs. major
N (%)	863	135 (15.6)	641 (74.3)	87 (10.1)	135 vs. 641	641 vs. 87
Male, <i>n</i> (%)	478 (55.4)	81 (60.0)	355 (55.4)	42 (48.3)	0.172	0.424
Age, median (range)	74 (19–100)	73 (44–92)	75 (34–100)	74 (19–91)	>0.999	>0.999
NOAC indication SPAF/VTE, <i>n</i> (%)	700 (81.1)/148 (17.1)	119 (88.1)/15 (11.1)	514 (80.2)/116 (18.1)	67 (77.0)/17 (19.5)	0.132	>0.999
Mean BMI ± SD, kg/m <sup>2</sup>	28.6 ± 4.8	29.3 ± 4.8	28.4 ± 4.7	29.1 ± 5.2	>0.999	0.532
Coronary artery disease, <i>n</i> (%)	175 (20.3)	13 (9.6)	134 (20.9)	28 (32.2)	<0.001	<b>0.036</b>
Prior stroke or systemic embolism, <i>n</i> (%)	119 (13.8)	18 (13.3)	89 (13.9)	12 (13.8)	>0.999	>0.999
Malignant disease, <i>n</i> (%)	187 (21.7)	32 (23.7)	139 (21.7)	16 (18.4)	0.696	0.962
Concomitant antiplatelet therapy, <i>n</i> (%)	37 (4.3)	3 (2.2)	25 (3.9)	9 (10.3)	<b>0.026</b>	<b>0.028</b>
HAS-BLED score, median (IQR)	2 (1)	2 (2)	2 (1)	2 (2)	0.770	0.810
Impaired renal function <sup>a</sup> , <i>n</i> (%)	125 (14.5)	15 (11.1)	100 (15.6)	10 (11.5)	>0.999	0.632

Bold indicates statistical significance (*P* < 0.05).

SPAF, stroke prevention in atrial fibrillation; VTE, venous thromboembolism; NOAC, novel oral anticoagulants; BMI, body mass index; SD, standard deviation; IQR, inter-quartile range; GFR, glomerular filtration rate.

<sup>a</sup>Impaired renal function was defined as current or history of GFR of <50 mL/min.

**Table 2** Effectiveness and safety outcomes of 863 interventional or surgical procedures in NOAC patients at Day 30 ± 5 post-procedure, according to procedures

Outcome at Day 30 ± 5 after procedure	All procedures (N = 863)	Minimal procedures (N = 135)	Minor procedures (N = 641)	Major procedures (N = 87)	P-value minimal vs. major	P-value minor vs. major	P-value minimal + minor vs. major
Major CV events, n (%; 95% CI)	9 (1.0%; 0.5–2.0)	0 (0%; 0.0–2.7)	5 (0.8%; 0.3–1.8)	4 (4.6%; 1.3–11.4)	<b>0.046</b>	<b>0.030</b>	<b>0.008</b>
CV death, n (%; 95% CI)	3 (0.3%; 0.1–1.0)	0 (0%; 0.0–2.7)	1 (0.2%; 0.0–0.9)	2 (2.3%; 0.3–8.1)	0.306	0.078	<b>0.028</b>
Major bleeding, n (%; 95% CI)	10 (1.2%; 0.6–2.1)	0 (0%; 0.0–2.7)	3 (0.5%; 0.0–1.4)	7 (8.0%; 3.3–15.9)	<b>0.002</b>	<b>&lt;0.001</b>	<b>&lt;0.001</b>
NMCR bleeding, n (%; 95% CI)	29 (3.4%; 2.3–4.8)	2 (1.5%; 0.2–5.2)	20 (3.1%; 1.9–4.8)	7 (8.0%; 3.3–15.9)	0.060	0.066	<b>0.020</b>
Minor bleeding, n (%; 95% CI)	7 (0.8%; 0.3–1.7)	1 (0.7%; 0.0–4.1)	6 (0.9%; 0.3–2.0)	0 (0%; 0.0–4.2)	>0.999	>0.999	>0.999
Any bleeding, n (%; 95% CI)	46 (5.3%; 3.9–12.8)	3 (2.2%; 0.5–6.4)	29 (4.5%; 3.1–6.4)	14 (16.1%; 9.1–25.5)	<b>&lt;0.001</b>	<b>&lt;0.001</b>	<b>&lt;0.001</b>

Bold indicates statistical significance ( $P < 0.05$ ).

NMCR, non-major clinically relevant bleeding; CI, confidence interval; CV, cardiovascular; NOACs, novel oral anticoagulants.

post-procedure (1.0%; 95% CI 0.5–2.0), which consisted of four ischaemic strokes, one transient ischaemic attack, two PEs, one upper extremity DVT (all in SPAF patients), and one sudden death of unknown cause in a VTE patient (rated as a fatal cardiovascular event in central adjudication). Five of the major cardiovascular events occurred in patients undergoing minor procedures; the remaining four events occurred after major procedures. Detailed descriptions of the major outcome events are listed in Supplementary material online, Appendix 2. Major cardiovascular events occurred significantly more often in patients undergoing major procedures (4.6%; 95% CI 1.3–11.4%) compared with those after minimal (0%; 95% CI 0.0–2.7%;  $P = 0.046$ ) or minor procedures (0.8%; 95% CI 0.3–1.8%;  $P = 0.030$ ). No minor cardiovascular events were observed.

Up to Day 30 ± 5 post-procedure, major bleeding complications occurred in 10 of 863 procedures (1.2%; 95% CI 0.6–2.1) and were associated with minor surgery in three cases and with major surgery in seven cases. Major bleeding was seen significantly more often in patients after major procedures (8.0%; 95% CI 3.3–15.9%) compared with minimal (0%; 95% CI 0.0–2.7%;  $P = 0.002$ ) or minor procedures (0.5%; 95% CI 0.0–1.4%;  $P < 0.001$ ).

In total, 46 bleeding complications were observed (5.3%; 95% CI 3.9–12.8); of which, 14 occurred after major surgery, 29 after minor surgery, and the remaining three after minimal surgery. In addition, major procedures resulted in higher rates of overall bleeding complications (16.1%; 95% CI 9.1–25.5) compared with minimal (2.2%; 95% CI 0.5–6.4;  $P < 0.001$ ) or minor procedures (4.5%; 95% CI 3.1–6.4;  $P < 0.001$ ).

Six (0.7%) patients died within 30 ± 5 days after the procedure. Of these, three cases were ruled as cardiovascular death (0.3%; 95% CI 0.1–1.0), consisting of one fatal PE during orthopaedic hip surgery, one aspiration pneumonia occurring after stroke related to carotid stenting, and one sudden death of unknown cause in a VTE patient, rated as a fatal cardiovascular event in central adjudication (Table 2). The remaining three deaths were associated with terminal malignant disease in two cases and a pneumonia post-hip fracture surgery.

Differences in cardiovascular death were not statistically significant between the separate subgroups of procedures. However, when data from minimal and minor procedures were pooled, cardiovascular death occurred significantly more often after major surgery compared with non-major surgery (2.3 vs. 0.13%;  $P = 0.028$ ).

Between cohorts of SPAF and VTE patients, no statistically significant differences with regard to cardiovascular events, bleeding complications, or fatal outcomes were detected (see Supplementary material online, Appendix 3).

Furthermore, no significant differences for effectiveness or safety outcomes were observed between patients receiving dabigatran or rivaroxaban (see Supplementary material online, Appendix 4) and those with cancer (see Supplementary material online, Appendix 5).

### Effects of heparin bridging therapy

During 863 procedures, NOAC was continued in 187 (21.7%) cases, temporarily interrupted without heparin bridging in 419 (48.6%) cases or interrupted with heparin bridging using prophylactic or therapeutic dosages in 63 (7.3%) and 194 (22.5%) cases, respectively (Table 3). In cases of NOAC interruption, the median duration of NOAC-free intervals was 2 [inter-quartile range (IQR) 2] days

**Table 3** Effectiveness and safety outcomes of 707 interventional or surgical procedures in NOAC patients at Day 30 ± 5 post-procedure, according to heparin bridging

Outcome at Day 30 ± 5 after procedure	Type of procedures	NOAC continued (N = 187)	NOAC interrupted, no heparin bridging (N = 419)	NOAC interrupted, prophylactic dose LMWH (N = 63)	NOAC interrupted, intermediate dose LMWH (N = 179)	NOAC interrupted, therapeutic dose LMWH (N = 15)
Major cardiovascular events, n (%; 95% CI)	Minimal procedures	0 (0.0%; 0.0–2.0)	0 (0.0%; 0.0–0.9)	0 (0.0%; 0.0–5.7)	0 (0.0%; 0.0–2.0)	0 (0.0%; 0.0–21.8)
	Minor procedures	0 (0.0%; 0.0–2.0)	4 (1.0%; 0.3–2.4)	0 (0.0%; 0.0–5.7)	0 (0.0%; 0.0–2.0)	1 (6.7%; 0.1–31.9)
	Major procedures	1 (0.5%; 0.0–2.9)	0 (0.0%; 0.0–0.9)	0 (0.0%; 0.0–5.7)	3 (1.7%; 0.0–4.8)	0 (0.0%; 0.0–21.8)
Cardiovascular death, n (%; 95% CI)	Minimal procedures	0 (0.0%; 0.0–2.0)	0 (0.0%; 0.0–0.9)	0 (0.0%; 0.0–5.7)	0 (0.0%; 0.0–2.0)	0 (0.0%; 0.0–21.8)
	Minor procedures	0 (0.0%; 0.0–2.0)	0 (0.0%; 0.0–0.9)	0 (0.0%; 0.0–5.7)	0 (0.0%; 0.0–2.0)	1 (6.7%; 0.1–31.9)
	Major procedures	1 (0.5%; 0.0–2.9)	0 (0.0%; 0.0–0.9)	0 (0.0%; 0.0–5.7)	1 (0.6%; 0.0–3.1)	0 (0.0%; 0.0–21.8)
Major bleeding, n (%; 95% CI)	Minimal procedures	0 (0.0%; 0.0–2.0)	0 (0.0%; 0.0–0.9)	0 (0.0%; 0.0–5.7)	0 (0.0%; 0.0–2.0)	0 (0.0%; 0.0–21.8)
	Minor procedures	0 (0.0%; 0.0–2.0)	2 (0.5%; 0.0–1.7)	1 (1.6%; 0.0–8.5)	0 (0.0%; 0.0–2.0)	0 (0.0%; 0.0–21.8)
	Major procedures	0 (0.0%; 0.0–2.0)	1 (0.2%; 0.0–1.3)	4 (6.3%; 1.8–15.5)	2 (1.1%; 0.1–4.0)	0 (0.0%; 0.0–21.8)
NMCR bleeding, n (%; 95% CI)	Minimal procedures	1 (0.5%; 0.0–2.9)	0 (0.0%; 0.0–0.9)	0 (0.0%; 0.0–5.7)	1 (0.6%; 0.0–3.1)	0 (0.0%; 0.0–21.8)
	Minor procedures	7 (3.7%; 1.5–7.6)	8 (1.9%; 0.8–3.7)	0 (0.0%; 0.0–5.7)	4 (2.2%; 0.6–5.6)	1 (6.7%; 0.1–31.9)
	Major procedures	0 (0.0%; 0.0–2.0)	3 (0.7%; 0.1–2.1)	0 (0.0%; 0.0–5.7)	4 (2.2%; 0.6–5.6)	0 (0.0%; 0.0–21.8)
Minor bleeding, n (%; 95% CI)	Minimal procedures	1 (0.5%; 0.0–2.9)	0 (0.0%; 0.0–0.9)	0 (0.0%; 0.0–5.7)	0 (0.0%; 0.0–2.0)	0 (0.0%; 0.0–21.8)
	Minor procedures	2 (1.1%; 0.1–3.8)	2 (0.5%; 0.0–1.7)	0 (0.0%; 0.0–5.7)	2 (1.1%; 0.1–4.0)	0 (0.0%; 0.0–21.8)
	Major procedures	0 (0.0%; 0.0–2.0)	0 (0.0%; 0.0–0.9)	0 (0.0%; 0.0–5.7)	0 (0.0%; 0.0–2.0)	0 (0.0%; 0.0–21.8)
Any bleeding, n (%; 95% CI)	Minimal procedures	2 (1.1%; 0.1–3.8)	0 (0.0%; 0.0–0.9)	0 (0.0%; 0.0–5.7)	1 (0.6%; 0.0–3.1)	0 (0.0%; 0.0–21.8)
	Minor procedures	9 (4.8%; 2.2–8.9)	12 (2.9%; 1.5–4.9)	1 (1.6%; 0.0–8.5)	6 (3.4%; 1.2–7.2)	1 (6.7%; 0.1–31.9)
	Major procedures	0 (0.0%; 0.0–2.0)	4 (1.0%; 0.3–2.4)	4 (6.3%; 1.8–15.5)	6 (3.4%; 1.2–7.2)	0 (0.0%; 0.0–21.8)

NMCR, non-major clinically relevant bleeding; CI, confidence interval; NOACs, novel oral anticoagulants; LMWH, low-molecular-weight heparin.

before the procedure and 1 (IQR 3) day after the procedure, resulting in a total duration of NOAC interruption of 3 (IQR 6) days.

The use of heparin bridging significantly increased with the severity of the surgical procedure (10.4, 27.8, and 74.7% for minimal, minor, and major surgery, respectively;  $P < 0.001$ ).

Rates of major cardiovascular events were similar for patients without heparin bridging (i.e. NOAC was continued or interrupted without heparin bridging; event rate 0.8%; 95% CI 0.3–1.9%) and for those with heparin bridging (1.6%; 95% CI 0.4–3.9%;  $P = 0.265$ , Table 4).

Rates of minor and NMCR bleedings were similar for patients with or without heparin bridging. In contrast, major bleeding complications were significantly more frequent in patients receiving heparin bridging (2.7%; 95% CI 1.1–5.5%) than in those without heparin bridging (0.5%; 95% CI 0.1–1.4%;  $P = 0.010$ ), which was driven by more major bleeding events after major procedures (Table 4).

## Risk factors for major cardiovascular or bleeding events

Uni- and multivariate analyses were performed to evaluate potential risk factors for cardiovascular and major bleeding complications, respectively (Tables 5 and 6). A history of diabetes [odds ratio (OR) 13.2; 95% CI 1.6–107.3;  $P = 0.016$ ] and major procedures (OR 7.3;

95% CI 1.9–28.5;  $P = 0.004$ ) were the only independent risk factor for cardiovascular events. In contrast, heparin bridging did not significantly affect this risk (OR 1.9; 95% CI 0.5–7.1;  $P = 0.341$ ).

For major bleeding, major procedures (OR 16.8; 95% CI 3.8–78.9;  $P < 0.001$ ) and heparin bridging (OR 5.0; 95% CI 1.2–20.4;  $P = 0.023$ ) were the only independent risk factors. Of note, heparin bridging was significantly more used in major procedures. If major and non-major procedures were separately assessed, heparin bridging was not an independent risk factor for major bleeding (univariate for major procedures: OR 2.1; 95% CI 0.2–18.8;  $P = 0.494$ ; univariate for non-major procedures: OR 1.5; 95% CI 0.1–16.9;  $P = 0.732$ ). Furthermore, when NMCR bleeding and major bleeding were used as an endpoint, heparin bridging was also not found to be an independent risk factor (univariate for major procedures: OR 0.8; 95% CI 0.2–2.9;  $P = 0.758$ ; univariate for non-major procedures: OR 1.4; 95% CI 0.6–3.2;  $P = 0.470$ ; Supplementary material online, Appendices 6a and 6b).

## Discussion

To our knowledge, these are the first available results regarding the management and outcome of NOAC patients undergoing surgical

**Table 4** Effectiveness and safety outcomes of 863 interventional or surgical procedures in NOAC patients at Day 30  $\pm$  5 post-procedure, according to heparin bridging

Outcome at Day 30 $\pm$ 5 after procedure	Type of procedures	Procedures without heparin bridging (N = 606)	Procedures with heparin bridging (N = 257)	P-value no bridging vs. bridging
Major cardiovascular events, n (%; 95% CI)	Minimal	0 (0.0%; 0.0–0.6)	0 (0.0%; 0.0–1.4)	>0.999
	Minor	4 (0.7%; 0.2–1.7)	1 (0.4%; 0.0–2.1)	0.830
	Major	1 (0.2%; 0.0–0.9)	3 (1.2%; 0.2–3.4)	0.082
	All	5 (0.8%; 0.3–1.9)	4 (1.6%; 0.4–3.9)	0.265
Cardiovascular death, n (%; 95% CI)	Minimal	0 (0.0%; 0.0–0.6)	0 (0.0%; 0.0–1.4)	>0.999
	Minor	0 (0.0%; 0.0–0.6)	1 (0.4%; 0.0–2.1)	0.298
	Major	1 (0.2%; 0.0–0.9)	1 (0.4%; 0.0–2.1)	0.507
	All	1 (0.2%; 0.0–0.9)	2 (0.8%; 0.1–2.8)	0.213
Major bleeding, n (%; 95% CI)	Minimal	0 (0.0%; 0.0–0.6)	0 (0.0%; 0.0–1.4)	>0.999
	Minor	2 (0.3%; 0.0–1.2)	1 (0.4%; 0.0–2.1)	0.654
	Major	1 (0.2%; 0.0–0.9)	6 (2.3%; 0.9–5.0)	<b>0.004</b>
	All	3 (0.5%; 0.1–1.4)	7 (2.7%; 1.1–5.5)	<b>0.010</b>
NMCR bleeding, n (%; 95% CI)	Minimal	1 (0.2%; 0.0–0.9)	1 (0.4%; 0.0–2.1)	0.507
	Minor	15 (2.5%; 1.4–4.0)	5 (1.9%; 0.6–4.5)	0.759
	Major	3 (0.5%; 0.1–1.4)	4 (1.6%; 0.4–3.9)	0.122
	All	19 (3.1%; 1.9–4.9)	10 (3.9%; 1.9–7.0)	0.352
Minor bleeding, n (%; 95% CI)	Minimal	1 (0.2%; 0.0–0.9)	0 (0.0%; 0.0–1.4)	>0.999
	Minor	4 (0.7%; 0.2–1.7)	2 (0.8%; 0.1–2.8)	0.576
	Major	0 (0.0%; 0.0–0.6)	0 (0.0%; 0.0–1.4)	>0.999
	All	5 (0.8%; 0.3–1.9)	2 (0.8%; 0.1–2.8)	0.667
Any bleeding, n (%; 95% CI)	Minimal	2 (0.3%; 0.0–1.2)	1 (0.4%; 0.0–2.1)	0.654
	Minor	21 (3.5%; 0.2–5.2)	8 (3.1%; 1.3–6.0)	0.673
	Major	4 (0.7%; 0.2–1.7)	10 (3.9%; 1.9–7.0)	<b>0.001</b>
	All	27 (4.5%; 3.0–6.4)	19 (7.4%; 4.5–11.3)	0.059

Bold indicates statistical significance ( $P < 0.05$ ).

NMCR, non-major clinically relevant bleeding; CI, confidence interval; NOAC, novel oral anticoagulants.

**Table 5** Uni- and multivariate analyses of potential risk factors for cardiovascular events

Risk factor	Univariate analysis			Multivariate analysis		
	OR	95% CI	P-value	OR	95% CI	P-value
Dabigatran vs. rivaroxaban	7.4	0.7–82.2	0.101	–	–	–
Arterial hypertension	n.a.	0–∞	0.996	–	–	–
Diabetes	14.9	1.9–119.9	<b>0.011</b>	13.2	1.6–107.3	<b>0.016</b>
TIA/stroke in history	1.8	0.4–8.8	0.467	–	–	–
Coronary artery disease	2.0	0.5–8.0	0.337	–	–	–
Impaired renal function (GFR < 50 mL/min)	n.a.	0–∞	0.996	–	–	–
Major vs. non-major procedure	7.4	2.0–28.2	<b>0.003</b>	7.3	1.9–28.5	<b>0.004</b>
Age > 65 years vs. < 65 years	1.7	0.2–13.7	0.616	–	–	–
Pre-procedural NOAC interruption > 24 h vs. < 24 h	0.6	0.2–2.7	0.545	–	–	–
Heparin bridging vs. no bridging	1.9	0.5–7.1	0.341	–	–	–

Bold indicates statistical significance ( $P < 0.05$ ).

Of note, some ORs could not be determined (n.a.) due to the low absolute number of events and zero events in some subgroups.

OR, odds ratios; GFR, glomerular filtration rate; NOACs, novel oral anticoagulants; TIA, transient ischaemic attack; CI, confidence interval.

**Table 6** Uni- and multivariate analyses of potential risk factors for major bleeding events

Risk factor	Univariate analysis			Multivariate analysis		
	OR	95% CI	P-value	OR	95% CI	P-value
Arterial hypertension	n.a.	0–∞	0.996	–	–	–
Diabetes	1.2	0.3–4.3	0.763	–	–	–
TIA/stroke in history	0.7	0.1–5.5	0.728	–	–	–
Coronary artery disease	2.7	0.7–9.5	0.133	–	–	–
Impaired renal function (GFR < 50 mL/min)	0.67	0.1–5.2	0.687	–	–	–
Major vs. non-major procedure	22.5	5.7–88.9	<b>&lt;0.001</b>	16.8	3.8–78.9	<b>&lt;0.001</b>
Age > 65 years vs. < 65 years	0.8	0.2–4.0	0.847	–	–	–
Pre-procedural NOAC interruption > 24 h vs. < 24 h	n.a.	0–∞	0.955	–	–	–
Heparin bridging vs. no bridging	5.6	1.4–21.9	<b>0.013</b>	5.0	1.2–20.4	0.023
HAS-BLED $\geq 3$ vs. < 3	1.5	0.4–5.7	0.589	–	–	–

Bold indicates statistical significance ( $P < 0.05$ ).

Of note, some odds ratios (OR) could not be determined (n.a.) due to the low absolute number of events and zero events in some subgroups.

OR, odds ratios; GFR, glomerular filtration rate; NOACs, novel oral anticoagulants; TIA, transient ischaemic attack; CI, confidence interval.

or interventional procedures. Our data indicate that surgical or interventional procedures are common in NOAC patients and mostly consist of minimal or minor procedures. These procedures cause little tissue trauma and only mild-to-moderate bleeding risks. Only 10% of all procedures were classified as major because of relevant tissue trauma and a high bleeding risk.

## Outcome event rates

Rates of major cardiovascular events (1.0%) or cardiovascular death (0.3%) were found to be low during the 30-day follow-up post-procedure. Therefore, our data are in line with the *post hoc* analysis from the RE-LY trial, for which cardiovascular event rates of ~1.2% and cardiovascular death rates of ~0.5% were reported for a similar follow-up period.<sup>9</sup> In contrast to RE-LY, major bleeding complications in our analysis were lower (1.2 vs. 4–5%), despite the fact

that ~30% of patients received heparin bridging compared with 16% in the RE-LY analysis. However, in agreement with the RE-LY analysis, we also found cardiovascular and major bleeding event rates to be significantly higher after major procedures than after non-major procedures.

Interestingly, cohorts of patients undergoing minimal, minor, or major procedures were very similar with regard to age, body mass index, cardiovascular risk factors, or malignant disease. However, patients undergoing major procedures were significantly more likely to have coronary artery disease and, therefore, concomitant antiplatelet medications compared with those undergoing non-major procedures. These differences between cohorts may have contributed to the higher event rates in patients undergoing major procedures. In contrast, these factors were not found to be independent risk factors in uni- and multivariate analyses.

## Heparin bridging

In our study, although NOAC was not interrupted in 22% of patients undergoing invasive procedures, the majority of procedures were performed with NOAC interruption. This is in agreement with findings from studies in VKA patients, in which 20% of procedures (mainly minor dental, dermatological, or ophthalmological procedures) were also performed without interruption of anticoagulant therapy.<sup>1</sup>

As many as 30% of all procedures in our registry were performed with heparin bridging. Therefore, many physicians do not follow the expert recommendations against bridging therapy for NOAC patients in daily care, which are based on *post hoc* analyses from Phase III trials and pharmacological considerations.<sup>14,15</sup> To our knowledge, our results are the first prospective data to support the concept of short-term interruption without heparin bridging. We did not detect any differences in cardiovascular event rates, but major bleeding complications were significantly more common in patients receiving heparin bridging and were mainly driven by patients undergoing major procedures.

In our observational registry, no specific recommendations for the peri-interventional management of NOAC patients were provided, and all treatment decisions were left to the discretion of the attending physician. Consequently, the decision for or against heparin bridging was subjective and probably influenced by the patient's specific situation. As the use of heparin bridging (and the rates of cardiovascular events) increased with the severity of the procedure, it is reasonable to conclude that most physicians anticipated the increased cardiovascular risk in patients undergoing major procedures—and decided in favour of heparin bridging, with the downside of potentially increasing the bleeding risk. Such a selection bias could explain the fact that both cardiovascular and bleeding events were more common in patients undergoing major procedures, as well as those receiving heparin bridging. Of note, if major and non-major procedures were analysed separately, the risk for major or NMCR bleeding was not independently influenced by heparin bridging in our logistic regression analysis.

Our findings are important with regard to the results of a recent large meta-analysis evaluating the safety of LMWH bridging in VKA-treated patients.<sup>3</sup> In this study, heparin bridging did not affect the rates of cardiovascular events, but significantly increased the risk for any bleeding (OR 5.4) or major bleeding (OR 3.6). The authors concluded 'that bridging anticoagulation, especially in therapeutic-dose regimens and in patients not at high thromboembolic risk undergoing high bleed-risk procedures, should be avoided in the peri-procedural setting'. Consequently, the concept of heparin bridging is no longer undisputed.<sup>16</sup> Despite the fact that heparin bridging was not an independent risk factor for major bleeding in our analysis, absolute rates of bleeding complications were significantly higher in patients receiving heparin bridging. Therefore, our findings also support the recent concerns regarding the necessity and safety of heparin bridging and extend these to the situation of NOAC patients.

## Limitations

There are several limitations to our study. First, the design of our registry introduces the possibility of a selection bias, because local physicians within the network are not instructed which of their patients should receive NOAC or VKA therapy. It is possible that physicians are more likely to use NOAC therapy in VKA-naïve

patients or those who have VKA complications or risk factors for adverse events during VKA therapy. Therefore, our cohort might reflect a selection of patients at high risk of cardiovascular or bleeding complications. However, our results indicate that the peri-interventional management of patients during NOAC therapy is simple, safe, and effective with acceptable rates of cardiovascular and bleeding complications in this cohort.

Owing to the low rate of cardiovascular and major bleeding events until Day 30, uni- and multivariate analyses demonstrated large CIs for a number of potential risk factors, which might have prevented the detection of further significant risk factors for unfavourable outcomes. Although the low event rate in our cohort of patients of high cardiovascular risk is reassuring, data from larger patient cohorts need to be analysed to identify potential risk factors in the future.

Finally, the evaluation of potential outcome measures relied mostly on patient contact and patient-derived information. Although all suspected outcome events were centrally adjudicated based on collected documents from family doctors, specialists in private practices, and hospitals, it is possible that some events remained unreported. However, the high rate of minor events reported in our registry and the low rate of patients lost to follow-up (<1%) indicate that the risk of unreported outcome events is low.

Nevertheless, the size of our cohort and the prospective evaluation of >850 surgical or interventional procedures in unselected NOAC patients from daily care are a significant strength of our study. The use of clinically relevant endpoints (objectively confirmed major cardiovascular events, major bleeding complications, and death of all causes) and a central adjudication process also contribute to the strength and clinical impact of our data.

## Conclusion

We believe that our study is the first to evaluate the effectiveness and safety of the peri-procedural management of NOAC therapy in the daily care of an unselected cohort of patients. Our data indicate that interventional procedures are common in anticoagulated patients and mostly consist of minimal or minor procedures. Rates of complications are low and fatal complications seem to be very rare, indicating that peri-interventional short-term interruption of NOAC in daily care is safe. However, bleeding complications are more common than cardiovascular complications and, in a relevant proportion, related to major procedures or to the peri-procedural heparin bridging (which is similar to VKA patients bridged for invasive procedures).<sup>3</sup> Because heparin bridging did not reduce the risk for cardiovascular events, but correlated with higher rates of major bleeding complications, a careful risk: benefit evaluation is needed. Most patients can safely interrupt NOAC anticoagulation for a short period of time without heparin bridging. However, patients at cardiovascular risk who need to undergo major procedures may benefit from heparin bridging, because their risk for cardiovascular outcomes was increased (major surgery: OR 7; diabetes: OR 13). In contrast, heparin bridging was not an independent risk factor for major bleeding in these patients, whose bleeding risk is mainly defined by the major invasive procedure. Further data are necessary to identify patients at risk for thromboembolic and bleeding complications and to develop preventive measures to avoid these potentially devastating complications.



## Supplementary material

Supplementary material is available at *European Heart Journal* online.

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