Perioperative Management of Dabigatran
A Prospective Cohort Study

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Background—The perioperative management of dabigatran in clinical practice is heterogeneous. We performed this study to evaluate the safety of perioperative management of dabigatran using a specified protocol.

Methods and Results—Patients treated with dabigatran and planned for an invasive procedure were eligible for inclusion. The timing of the last dose of dabigatran before the procedure was based on the creatinine clearance and procedure-related bleeding risk. Resumption of dabigatran was prespecified according to the complexity of the surgery and consequences of a bleeding complication. Patients were followed up for 30 days for major bleeding (primary outcome), minor bleeding, arterial thromboembolism, and death. We included 541 cases: 324 procedures (60%) with standard risk of bleeding and 217 procedures (40%) with increased risk of bleeding. The last dose of dabigatran was at 24, 48, or 96 hours before surgery according to the protocol in 46%, 37%, and 6%, respectively, of the patients. Resumption was timed according to protocol in 77% with 75 mg as the first dose on the day of procedure in 40% of the patients. Ten patients (1.8%; 95% confidence interval, 0.7–3.0) had major bleeding, and 28 patients (5.2%; 95% confidence interval, 3.3–7.0) had minor bleeding events. The only thromboembolic complication was transient ischemic attack in 1 patient (0.2%; 95% confidence interval, 0–0.5), and there were 4 deaths unrelated to bleeding or thrombosis. Bridging was not used preoperatively but was administered in 9 patients (1.7%) postoperatively.

Conclusion—Our protocol for perioperative management of dabigatran appears to be effective and feasible. **(*Circulation*. 2015;132:167-173. DOI: 10.1161/CIRCULATIONAHA.115.015688.)**

Key Words: dabigatran ■ hemorrhage ■ medication adherence ■ surgery

Anticoagulants are used to prevent new or recurrent venous or arterial thrombotic events, and the majority of patients are treated for stroke prevention in atrial fibrillation. Until recently, warfarin was virtually the only oral anticoagulant used in North America and the most commonly used anticoagulant worldwide. Warfarin has been used in clinical practice for 60 years, and there is abundant documentation about the drug, including many studies assessing its perioperative interruption.[1] Nevertheless, there is uncertainty about the optimal perioperative management, particularly in terms of the need for the intermediate use of a parenteral, short-acting anticoagulant.[2] A few large, ongoing, randomized trials such as the Effectiveness of Bridging Anticoagulation for Surgery trial (BRIDGE; http://www.clinicaltrials.gov, NCT00786474) and A Safety and Effectiveness Study of LMWH Bridging Therapy Versus Placebo Bridging Therapy for Patients on Long Term Warfarin and Require Temporary Interruption of Their Warfarin (PERIOP 2; http://www.clinicaltrials.gov, NCT00432796) are addressing this problem.

Clinical Perspective on p 173

For the non–vitamin K antagonist oral anticoagulants, even less is known about optimal perioperative management.[3,4] For the oral thrombin inhibitor dabigatran, a retrospective analysis of data derived from a phase III trial in patients with atrial fibrillation[5]

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demonstrated that the risk of bleeding complications was similar to that of the comparator, warfarin, for both elective and emergency surgery and invasive procedures.[6] Recommendations on when to stop dabigatran before surgery were provided only halfway through the trial, and there were no instructions about the timing of resumption of dabigatran. There are currently no evidence-based practice guidelines for the perioperative management of dabigatran-treated patients. The lack of such guidelines is likely to lead to considerable variability in clinical practice, as has occurred with the perioperative management of warfarin-treated patients.[2] Thus, if perioperative management is too aggressive, for example, allowing too little time before surgery for dabigatran interruption[7] or premature resumption of dabigatran after surgery, excessive perioperative bleeding may occur. On the other hand, allowing too much time between dabigatran interruption and resumption may expose patients to an increased risk for arterial thrombosis and venous thromboembolism.

We therefore performed a prospective cohort study to evaluate the safety of a prespecified protocol for the timing of interruption and resumption of dabigatran for surgery or invasive procedures. The primary objective was to determine the risk of major bleeding complications. The time points were determined by the renal function and bleeding risk of the procedure for stopping and the actual bleeding and bleeding risk for resuming dabigatran.

Methods

Study Design

This was a Canadian multicenter, prospective cohort study. It was funded by the Heart and Stroke Foundation of Canada. The manufacturer of dabigatran, Boehringer Ingelheim, had no involvement in the main study described here, although the company funded a substudy on the laboratory assessment of the residual anticoagulation effect of dabigatran on the day of surgery. The protocol was approved by the institutional review board of each participating center. All patients provided written informed consent.

The study was managed by the McMaster Transfusion Research Program. An independent event adjudication committee, the members of which were not otherwise involved in the study, classified all suspected thromboembolic and bleeding events and the cause of any deaths. An external data and safety monitoring board reviewed the safety outcomes periodically.

Study Patients

Patients at least 18 years of age and on long-term anticoagulation with dabigatran for any indication were eligible for the study. In addition, they had to be scheduled for elective surgery or an invasive procedure that required interruption of dabigatran treatment. Exclusion criteria were any condition precluding collection of follow-up information, inability to obtain informed consent, and previous participation in this study for the same procedure. Halfway through the study, we introduced an exclusion criterion for patients planned for cardiac catheterization or electrophysiological study with ablation therapy to avoid dilution of the study population by too many low-risk procedures. Participating study sites were hospital-based anticoagulation clinics that routinely receive referrals for perioperative management of anticoagulation.

Study Procedures

The baseline visit occurred ≈1 week before the planned procedure. At this visit, data on patient characteristics, current antithrombotic treatment, and type of planned surgery or procedure were collected. Blood was obtained for analysis of complete blood count and creatinine, and creatinine clearance was estimated with the Cockcroft-Gault formula.[8]

We gave oral and written instructions to the patient, with a copy to the referring physician and to the unit where the procedure would take place, concerning the interruption and resumption of dabigatran. The timing of interruption was a refined version of the protocol amendment issued in 2008, halfway through the phase III trials with dabigatran in atrial fibrillation and in the treatment of venous thromboembolism that were subsequently published.[9] Rather than time ranges, we stipulated specific time points, still based on the creatinine clearance and the corresponding estimated half-life of dabigatran[10] and on the surgery or procedure having standard or high risk of bleeding (Table 1). Procedures with an increased risk of bleeding were listed in the protocol (Table I in the online-only Data Supplement), but this classification was ultimately left to the discretion of the responsible physician or surgeon because individual anatomic or pathological circumstances may alter the risk. There was no preoperative bridging with any parenteral anticoagulant, and interrupting or continuing aspirin was left to the discretion of the local study site.

On the day of surgery, we asked the investigator, whenever feasible, to obtain a blood sample, preferably before the procedure. For patients with minor procedures performed early in the day, sampling could alternatively be performed after the procedure, provided that heparin had not been given. Samples were analyzed to measure the activated partial thromboplastin time (aPTT) according to local routine. The results were not made available to the surgical team and were not intended to influence the management.

Table 1. Timing of the Last Dose of Dabigatran Before the Surgery or Invasive Procedure

		Timing of Last Dose of Dabigatran Before Surgery	
Renal Function, CL_{CR}, mL/min	Estimated Half-Life, h*	Standard Risk of Bleeding	High Risk of Bleeding†
>80	13 (11–22)	24 h=morning of day –1	2 d=morning of day –2
>50 to ≤80	15 (12–34)	24 h=morning of day –1	2 d=morning of day –2
>30 to ≤50	18 (13–23)	2 d=morning of day –2	4 d=morning of day –4
≤30‡	27 (22–35)	4 d=morning of day –4	6 d=morning of day –6

CL_{CR} indicates calculated creatinine clearance.

*Data from renal impairment study in healthy volunteers,[10] geometric mean (range).

†Types of surgery associated with a high risk of bleeding (or in major surgery in which complete hemostasis may be required) include but are not limited to cardiac surgery, neurosurgery, abdominal surgery, or surgeries involving a major organ. Other procedures such as spinal anesthesia may also require complete hemostatic function. Other important determinants of bleeding risk include advancing age, comorbidities (eg, major cardiac, respiratory, or liver disease), and concomitant use of antiplatelet therapy. See the online-only Data Supplement for details.

‡Dabigatran etexilate is contraindicated for use in these patients, but if a patient was found to have CL_{CR} <30 mL/min at the baseline visit, we did not exclude the patient from the study.

Dabigatran was resumed only after hemostasis had been secured, that is, when there was no ongoing bleeding. In addition, the protocol provided a list of surgical procedures with recommended resumption time and dose. For minor procedures, resumption was in the evening of the procedure at a reduced dose of 75 mg, increasing to the regular dose (110 or 150 mg twice daily) the following morning. With increased risk of bleeding, the resumption time was delayed to 48 or 72 hours after surgery, starting with the regular dose (Table II in the online-only Data Supplement). In case of an in-dwelling catheter for neuraxial anesthesia, the first dose of dabigatran could be given only ≥4 hours after removal of the catheter, as practiced in the phase III clinical trials with dabigatran in major orthopedic surgery.[11]

For patients with bowel paralysis after major abdominal surgery or a "no oral medications" order for any other reason, the resumption of dabigatran was delayed until intake of oral medications became possible. For such patients, bridging with low-molecular-weight heparin was recommended at doses decided on by the local physician.

Patients were contacted after 1 week and 1 month (or visited if still in the hospital), and medical records were reviewed for any outcomes. The follow-up ended at 1 month in accordance with recommendations of the International Society on Thrombosis and Haemostasis.[12]

Outcomes

The primary outcome was major bleeding according to the International Society on Thrombosis and Haemostasis definition for surgical studies (bleeding that is fatal or in a critical organ; extrasurgical site bleeding with a decrease in hemoglobin of ≥20 g/L or requiring transfusion of ≥2 U blood; surgical site bleeding that requires second intervention or causes hemarthrosis with delayed mobilization or wound healing, prolonged hospitalization, or deep wound infection or that is unexpected and prolonged and causes hemodynamic instability).[13] Adhering to the intention of this definition, we also sought the surgeon's assessment of whether the bleeding was considered unexpected and prolonged.

Secondary outcomes were arterial thromboembolic events, characterized as major (ischemic stroke or systemic embolism) or minor (transient ischemic attack). Minor bleeding, defined as any bleeding not fulfilling the criteria for major bleeding, was another secondary outcome. In addition, deaths were classified as caused by bleeding or thromboembolism or unrelated to any of those. A laboratory outcome was the aPTT on the day of procedure.

Statistical Analyses

The sample size calculation took into account the best available data at the time of planning with respect to the risk for major bleeding in patients with interrupted warfarin therapy and perioperative bridging anticoagulation. This was obtained from a systematic review from 2005 in which the overall major bleed rate was 2.94% (95% confidence interval [CI], 2.28–3.74).[14] In this first prospective study, we wanted to exclude a doubling of the risk of major bleeding compared with that of the historical control. With a 1-sided α of 2.5%, a power of 80%, and an expected loss to follow-up of 10%, our cohort study required a sample size of 283 patients. The funding period for this study was 2 years. Because recruitment had reached the target already after 1 year, the Steering Committee decided to increase the sample size to improve the precision of the risk estimate and to increase the number of patients with different common invasive procedures.

We analyzed data according to the intention-to-treat principle for the population who had the invasive procedure or surgery performed. Patients who were switched to another anticoagulant after surgery were still followed up for 1 month.

Data are described with mean and standard deviation or, in the case of skewed distribution, with median and interquartile range (IQR). Outcome rates are described as percent and 95% CI. In addition, the event rate is compared with data from the above-mentioned systematic review[14] and with data from a more recent systematic review.[1]

Results

Between May 2012 and April 2014, we recruited 552 patients at 7 centers to the study. Eleven patients had their surgery canceled. The remaining 541 patients had an invasive procedure or surgery and are included in the analysis (Figure). Their characteristics are shown in Table 2. Nine patients (1.7%) were lost to the 1-month follow-up.

The types of invasive procedures and surgeries performed are summarized in Table 3. Investigators considered 60% of the procedures as standard bleeding risk and 40% as high bleeding risk. The timing of last dose before and first dose after the procedures, both planned and actual, is shown in Table 4. For 89% of the patients, dabigatran was stopped according to protocol, that is, 24 hours (in 46%), 48 hours (in 37%), and 96 hours (in 6%) before surgery. For 5%, it was stopped a median of 2 days (IQR, 1–3 days) earlier than planned; for 4%, it was stopped a median of 1 day (IQR, 1–1 day) later than planned (missing data on timing in 2%). Dabigatran was resumed a median of 1 day (IQR, 0–2 days) after the procedure. For 77% of the patients, dabigatran was resumed at the time provided by the protocol; for 3%, it was resumed a median of 2 days (IQR, 1–3 days) earlier than planned; and for 14%, it was resumed a median of 1 day (IQR, 1–3 days) later than planned (missing data on timing in 5%). In 219 patients (40%), dabigatran was resumed with the first dose, which was 75 mg, in the evening of the day of procedure.

Preoperative bridging with a parenteral anticoagulant was not used at all, but 9 patients (1.7%) received postoperative heparin or low-molecular-weight heparin, mainly after bowel resection or major vascular surgery.

There were 10 patients (1.8%; 95% CI, 0.7–3.0) with 1 major bleeding event each and 28 patients (5.2%; 95% CI, 3.3–7.0) with 35 minor bleeding events during the 30-day follow-up. Nine of the patients with major bleeding events were male; the mean age of the 10 patients was 78 years; 9 patients had no risk factors for bleeding at inclusion, but 8 had a procedure considered high risk for bleeding (Table III in

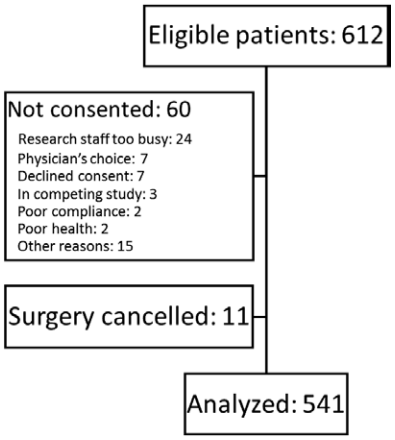

Figure. Eligible, excluded, and analyzed patients.

Table 2. Characteristics of the Patients Included

Characteristic	Patients Included (n=541)
Age, mean (SD), y	72.2 (10.8)
Male sex, n (%)	379 (70)
Body weight, mean (SD), kg	87.3 (20.8)
Creatinine clearance, n (%)	
≤30 mL/min	4 (0.7)
>30–≤50 mL/min	86 (16)
>50–≤80 mL/min	213 (39)
>80 mL/min	238 (44)
Indication for anticoagulation, n (%)	
Atrial fibrillation	524 (97)
Venous thromboembolism	10 (1.8)
Stroke or TIA*	4 (0.7)
Other	3 (0.6)
Maintenance dose of dabigatran, n (%)	
75 mg twice daily	1 (0.2)
110 mg twice daily	229 (42)
150 mg twice daily	311 (57)
Risk factors for bleeding, n (%)†	
None	482 (89)
Bleeding with hospitalization	24 (4.4)
Gastrointestinal bleeding	22 (4.1)
Gastrointestinal, nonbleeding ulcer	18 (3.3)
Thrombocytopenia	1 (0.2)
Bleeding risk of the planned procedure, n (%)	
Standard bleeding risk	324 (60)
High bleeding risk	217 (40)

TIA indicates transient ischemic attack.
*Stroke with no available documentation on atrial fibrillation.
†Risk factors were not mutually exclusive.

Table 3. Number of Invasive Procedures and Surgeries by Bleeding Risk.

	Bleeding Risk, n		
Procedure	Standard	High	Total
Abdominal surgery	7	21	28
Ankle/knee/hip/shoulder surgery	10	19	29
Biopsy	8	16	24
Brain surgery	0	3	3
Cardiac catheterization	67	0	67
Dental	7	2	9
EPS and ablation therapy	78	1	79
Ear surgery	4	1	5
Endoscopy, bronchoscopy*	84	34	118
Epidural/spinal injection	1	4	5
Eye surgery	20	1	21
Gynecological surgery	4	2	6
Hand or wrist surgery	6	1	7
ICD or pacemaker insertion†	0	52	52
Kidney surgery	0	5	5
Lung surgery	0	7	7
Neck surgery	1	6	7
Skin surgery	13	3	16
TURP/TURBT	2	15	17
Vascular surgery	6	13	19
Other‡	6	11	16
Total, n (%)	324 (60)	217 (40)	541

EPS indicates electrophysiological study; ICD, implantable cardioverter-defibrillator; and TURP/TURBT, transurethral resection of prostate/transurethral resection of bladder tumor.
*High-risk endoscopy was typically combined with polyp removal or multiple biopsies.
†Considered high risk for pocket hematoma.
‡The standard risk procedures were thoracentesis (2), cyst removal, joint injection, unspecified analgesic injection, and insertion of artificial urinary sphincter. The high-risk procedures were rhizotomy (2), wide resection of myxosarcoma with free flap rotation, lumbar decompression laminectomy, transapical aortic valve replacement, radical prostatectomy, breast lumpectomy, cystoscopy, perineal cancer excision, scapular tumor removal, and amputation of 2 toes.

the online-only Data Supplement). For 21 of the patients with minor bleeds, the bleed was related to the surgical site, either as overt bleeding (15) or wound hematoma (6). Eight of the overt bleeds were after urological procedures. The extrasurgical site minor bleeds were hematochezia (2), hematuria (2), hemoptysis (2), and epistaxis (1).

Eight patients had neuraxial anesthesia for their surgery, and another 5 had epidural injections as the qualifying procedure, all of which were uncomplicated.

There was only 1 thromboembolic event (0.2%; 95% CI, 0–0.5), a transient ischemic attack. Four patients (0.7%; 95% CI, 0–1.5) died of causes unrelated to bleeding or thrombosis, and 12 serious adverse events were reported.

A result for aPTT on the day of the procedure was obtained in 214 patients (40%), and the median was 32 seconds (IQR, 29–36 seconds; Figure I in the online-only Data Supplement). Twenty patients had an aPTT >40 seconds, but they did not experience any bleeding. Of the 10 patients with major bleeding, 6 had aPTT analyzed in the morning of the procedure; their median aPTT was 31 seconds (IQR, 30–31.7 seconds; maximum, 36 seconds) and was always within the normal range of the method used locally. Of the 28 patients with minor bleeding, 14 had aPTT analyzed; their median aPTT was 33 seconds (IQR, 29–36.7 seconds; maximum, 39 seconds), with 9 in the normal range and 5 prolonged by 1 to 3 seconds.

Discussion

This is the first study on perioperative management of dabigatran using a specified protocol for both the interruption and the resumption of the drug. We have shown that a protocol based on pharmacokinetic principles and the estimated bleeding risk is feasible and safe and does not require bridging with heparin. An interval of 24 to 96 hours between the last dose of dabigatran and surgery or an invasive procedure is sufficient for the vast majority of patients. Resumption of dabigatran occurred after 0 to 2 days in 73% of patients.

Table 4. Planned and Actual Discontinuation and Resumption of Dabigatran in Subsets of Patients According to Renal Function and Bleeding Risk

			Last Dose Before Procedure			First Dose After Procedure		
CL_{CR} mL/min	n	Planned Stopping Time, h	As Planned, n (%)*	Earlier, n (%)	Later, n (%)	As Planned, n (%)	Earlier, n (%)	Later, n (%)
Procedures with standard risk of bleeding								
>50	274†	24	249 (91)	15 (5)	2 (0.7)	226 (82)	3 (1)	32 (12)
>30–≤50	47†	48	43 (91)	2 (4)	1 (2)	43 (91)	0	3 (6)
≤30	3	96	3 (100)	0	0	3 (100)	0	0
Procedures with high risk of bleeding								
>50	177†	48	155 (88)	11 (6)	9 (6)	117 (66)	10 (6)	35 (20)
>30–≤50	39†	96	29 (74)	2 (5)	8 (21)	27 (69)	2 (5)	6 (15)
≤30	1	154	0	0	1 (100)	0	1 (100)	0
Overall	541		479 (89)	30 (6)	21 (4)	415 (77)	16 (3)	77 (14)

CL_{CR} indicates calculated creatinine clearance.

*Stopping dabigatran "as planned" was in a minority of patients 1 day before the formal day to avoid a shorter interruption than planned. For example, if the procedure was scheduled for 7 AM on day 0 and the planned stopping time was 24 hours before but the patient normally took the morning dose at 9 AM, then the last dose was to be taken on day –2 instead of day –1.

†The total number per subset exceeds the sum of the cells in the same row because there was no information on timing for stopping dabigatran for 11 patients and for resuming dabigatran for 29 patients, and 4 patients did not restart anticoagulation or were switched to another anticoagulant.

The incidence of major bleeding of 1.8% (95% CI, 0.7–3.0) in this population indicates that our protocol is unlikely to be associated with a doubling of the rate of major bleeding compared with the patients with vitamin K antagonist interrupted for surgery (rate, 2.94%), according to data from the systematic review with which we initially planned to compare our results (odds ratio, 0.62; 95% CI, 0.30–1.19).[14] During the period of our study, a new systematic review of perioperative management of vitamin K antagonists in which most patients received bridging with therapeutic-dose low-molecular-weight heparin was published. Our results also compare favorably with the rate of 4.3% in that review (odds ratio, 0.43; 95% CI, 0.21–0.78).[1] In a substudy of a randomized trial with dabigatran versus warfarin in atrial fibrillation,[5] the 30-day incidence of major bleeding among 2785 patients treated with dabigatran 110 or 150 mg twice daily and having elective surgery was 2.8% and 3.8%, respectively.[6] In a further analysis of this population, Douketis et al[15] showed that the incidence of major bleeding was significantly higher among the dabigatran-treated patients with than without perioperative bridging (6.5% versus 1.8%). In a registry from Dresden reporting on 863 procedures in patients treated with different non–vitamin K antagonist oral anticoagulants, the 30-day incidence of major bleeding was 1.2%, but 90% of the procedures were minimal or minor.[16]

Our study provides evidence that, during the short interruption of dabigatran with our protocol, there is no need for bridging with heparin unless dabigatran cannot be administered (eg, ileus, nasogastric feeding because dabigatran capsules must not be crushed) or there is a specific indication for heparin (eg, vascular surgery). With a single event of transient ischemic attack (0.2%) and no major arterial thromboembolic events in 541 patients, there is no further efficacy to be gained with routine perioperative bridging. Similarly, in the analysis by Douketis et al,[15] the risk of thromboembolic events in nonbridged dabigatran-treated patients was 0.6%.

The guidelines from the American Society of Regional Anesthesia recommend stopping dabigatran 5 days before surgery with neuraxial block.[17] This is based not on clinical evidence but on concern for the potential risk of epidural hematoma after neuraxial anesthesia. In our population, we had 13 patients with surgery performed under neuraxial anesthesia or with epidural or spinal injection as the main procedure, and no bleeding complications were related to this; the 95% CI for this risk is 0% to 25%. With a reported incidence of hemorrhagic complications resulting in neurological deficit of 1 in 150 000 epidurals and 1 in 220 000 spinal anesthetics, it will not be feasible to perform a study that can exclude the increased risk of such events with perioperative management of any non–vitamin K antagonist oral anticoagulant.[17]

Major bleeding in this study population was managed with conservative measures, including transfusion of red cells for 6 of the 10 patients. For patients with major bleeding in association with emergency surgery or when dabigatran is mistakenly stopped late, more active management may be required, including hemodialysis[7] or possibly infusion of 4-factor or activated prothrombin complex concentrate.[18,19] A specific antidote against dabigatran is currently being evaluated in a clinical trial (Reversal of Dabigatran Anticoagulant Effect With Idarucizumab; http://www.clinicaltrials.gov, NCT02104947) and might be available in the near future.

Adherence, defined as following the protocol to the day, to our recommendation for the timing of the resumption of dabigatran (77%) was lower than the adherence to the stopping

time (89%). This is not surprising because in many patients it is difficult to predict the postoperative course. Assessment of the patient before resumption of any form of therapeutic anticoagulation is therefore warranted after all major procedures.

A limitation of our study is that it did not have a randomized control design. However, we wanted to evaluate a protocol on the basis of our best knowledge of the pharmacokinetics of dabigatran in patients with normal or different degrees of impairment of renal function and on the clinician's assessment of the risk of bleeding combined with the guidance document from the protocol. We felt that a comparison with any other alternative perioperative dabigatran regimen that likely would be inferior was not justified. Another limitation is that the first postoperative dose of 75 mg, administered to 40% of our patients, is not widely available except in the United States (approved for atrial fibrillation) or at hospitals that use dabigatran for prophylaxis against thrombosis after hip or knee replacement. We have therefore initiated another study in which dabigatran is started at the earliest on the first day after surgery and at the regular maintenance dose (http://www.clinicaltrials.gov, NCT02228798).

Conclusions

Our perioperative dabigatran protocol with timing for stopping and resuming anticoagulation based on renal function and procedure-related risk of bleeding appears to be safe and effective. The protocol is feasible, with 89% adherence to the stopping recommendation and 77% adherence to the resumption recommendation. Perioperative management of patients on dabigatran with a protocol similar to ours is probably more likely to keep the risk of bleeding and thromboembolic complications low compared with management according to individual physician preferences and experiences. Routine perioperative bridging with heparin is unlikely to provide any benefit to these patients and has even been reported to cause harm.

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Disclosures

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References

1. Siegal D, Yudin J, Kaatz S, Douketis JD, Lim W, Spyropoulos AC. Periprocedural heparin bridging in patients receiving vitamin K antagonists: systematic review and meta-analysis of bleeding and thromboembolic rates. *Circulation*. 2012;126:1630–1639. doi: 10.1161/CIRCULATIONAHA.112.105221.
2. Douketis JD, Crowther MA, Cherian SS. Perioperative anticoagulation in patients with chronic atrial fibrillation who are undergoing elective surgery: results of a physician survey. *Can J Cardiol*. 2000;16:326–330.
3. Ferrandis R, Castillo J, de Andrés J, Gomar C, Gómez-Luque A, Hidalgo F, Llau JV, Sierra P, Torres LM. The perioperative management of new direct oral anticoagulants: a question without answers. *Thromb Haemost*. 2013;110:515–522. doi: 10.1160/TH12-11-0868.
4. Spyropoulos AC, Douketis JD. How I treat anticoagulated patients undergoing an elective procedure or surgery. *Blood*. 2012;120:2954–2962. doi: 10.1182/blood-2012-06-415943.
5. Connolly SJ, Ezekowitz MD, Yusuf S, Eikelboom J, Oldgren J, Parekh A, Pogue J, Reilly PA, Themeles E, Varrone J, Wang S, Alings M, Xavier D, Zhu J, Diaz R, Lewis BS, Darius H, Diener HC, Joyner CD, Wallentin L; RE-LY Steering Committee and Investigators. Dabigatran versus warfarin in patients with atrial fibrillation. *N Engl J Med*. 2009;361:1139–1151. doi: 10.1056/NEJMoa0905561.
6. Healey JS, Eikelboom J, Douketis J, Wallentin L, Oldgren J, Yang S, Themeles E, Heidbuchel H, Heidbuchle H, Avezum A, Reilly P, Connolly SJ, Yusuf S, Ezekowitz M; RE-LY Investigators. Periprocedural bleeding and thromboembolic events with dabigatran compared with warfarin: results from the Randomized Evaluation of Long-Term Anticoagulation Therapy (RE-LY) randomized trial. *Circulation*. 2012;126:343–348. doi: 10.1161/CIRCULATIONAHA.111.090464.
7. Warkentin TE, Margetts P, Connolly SJ, Lamy A, Ricci C, Eikelboom JW. Recombinant factor VIIa (rFVIIa) and hemodialysis to manage massive dabigatran-associated postcardiac surgery bleeding. *Blood*. 2012;119:2172–2174. doi: 10.1182/blood-2011-11-393587.
8. Cockcroft DW, Gault MH. Prediction of creatinine clearance from serum creatinine. *Nephron*. 1976;16:31–41.
9. van Ryn J, Stangier J, Haertter S, Liesenfeld KH, Wienen W, Feuring M, Clemens A. Dabigatran etexilate: a novel, reversible, oral direct thrombin inhibitor: interpretation of coagulation assays and reversal of anticoagulant activity. *Thromb Haemost*. 2010;103:1116–1127. doi: 10.1160/TH09-11-0758.
10. Stangier J, Rathgen K, Stähle H, Mazur D. Influence of renal impairment on the pharmacokinetics and pharmacodynamics of oral dabigatran etexilate: an open-label, parallel-group, single-centre study. *Clin Pharmacokinet*. 2010;49:259–268. doi: 10.2165/11318170-000000000-00000.
11. Eriksson BI, Dahl OE, Rosencher N, Kurth AA, van Dijk CN, Frostick SP, Prins MH, Hettiarachchi R, Hantel S, Schnee J, Büller HR; RE-NOVATE Study Group. Dabigatran etexilate versus enoxaparin for prevention of venous thromboembolism after total hip replacement: a randomised, double-blind, non-inferiority trial. *Lancet*. 2007;370:949–956. doi: 10.1016/S0140-6736(07)61445-7.
12. Spyropoulos AC, Douketis JD, Gerotziafas G, Kaatz S, Ortel TL, Schulman S; Subcommittee on Control of Anticoagulation of the SSC of the ISTH. Periprocedural antithrombotic and bridging therapy: recommendations for standardized reporting in patients with arterial indications for chronic oral anticoagulant therapy. *J Thromb Haemost*. 2012;10:692–694.
13. Schulman S, Angerås U, Bergqvist D, Eriksson B, Lassen MR, Fisher W; Subcommittee on Control of Anticoagulation of the Scientific and Standardization Committee of the International Society on Thrombosis and Haemostasis. Definition of major bleeding in clinical investigations of antihemostatic medicinal products in surgical patients. *J Thromb Haemost*. 2010;8:202–204. doi: 10.1111/j.1538-7836.2009.03678.x.
14. Spyropoulos AC, Turpie AG. Perioperative bridging interruption with heparin for the patient receiving long-term anticoagulation. *Curr Opin Pulm Med*. 2005;11:373–379.
15. Douketis JD, Healey JS, Brueckmann M, Eikelboom JW, Ezekowitz MD, Fraessdorf M, Noack H, Oldgren J, Reilly P, Spyropoulos AC, Wallentin L, Connolly SJ. Perioperative bridging anticoagulation during dabigatran or warfarin interruption among patients with an elective surgery or procedure: substudy of the RE-LY trial. *Thromb Haemost*. 2015;113:625–632.
16. Beyer-Westendorf J, Gelbricht V, Förster K, Ebertz F, Köhler C, Werth S, Kuhlisch E, Stange T, Thieme C, Daschkow K, Weiss N. Peri-interventional management of novel oral anticoagulants in daily care: results from the prospective Dresden NOAC registry. *Eur Heart J*. 2014;35:1888–1896. doi: 10.1093/eurheartj/eht557.
17. Horlocker TT, Wedel DJ, Rowlingson JC, Enneking FK, Kopp SL, Benzon HT, Brown DL, Heit JA, Mulroy MF, Rosenquist RW, Tryba M, Yuan CS. Regional anesthesia in the patient receiving antithrombotic or

thrombolytic therapy: American Society of Regional Anesthesia and Pain Medicine Evidence-Based Guidelines (Third Edition). *Reg Anesth Pain Med*. 2010;35:64–101.
18. Díaz MQ, Borobia AM, Núñez MA, Virto AM, Fabra S, Casado MS, García-Erce JA, Samama CM. Use of prothrombin complex concentrates for urgent reversal of dabigatran in the emergency department. *Haematologica*. 2013;98:e143–e144. doi: 10.3324/haematol.2013.092767.
19. Schulman S, Ritchie B, Goy JK, Nahirniak S, Almutawa M, Ghanny S. Activated prothrombin complex concentrate for dabigatran-associated bleeding. *Br J Haematol*. 2014;164:308–310. doi: 10.1111/bjh.12620.

CLINICAL PERSPECTIVE

The timing of stopping and resuming dabigatran for surgery is heterogeneous, and the role of bridging with heparin is debated. In this prospective cohort study, 541 patients treated with dabigatran for atrial fibrillation were managed for elective invasive procedures or surgery using a specific protocol. The last dose was 24, 48, or 96 hours before the surgery or procedure, depending on renal function and bleeding risk of the procedure. Resumption was timed according to the complexity of the surgery and consequences of a bleeding complication. Despite the absence of heparin bridging unless oral intake postoperatively was delayed, there was only 1 transient ischemic attack and there were no major thromboembolic events. The risk of major bleeding during 30 days of follow-up was 1.8%, which is at the lower end of what previous studies with dabigatran or with warfarin have shown. Our protocol was followed in terms of the correct day of stopping and resuming dabigatran in 89% and 77%, respectively. We recommend that local protocols for perioperative management of dabigatran be established to avoid premature stopping of dabigatran, which may increase the risk of thromboembolism, and to refrain from routine bridging with heparin, which increases the risk of bleeding.

Perioperative Management of Dabigatran: A Prospective Cohort Study

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Supplemental material

Committee Members

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Supplemental Table I. Surgical procedures with high risk of bleeding

Urologic procedures (endogenous urokinase promotes bleed)

- transurethral resection of prostate
- bladder surgery
- kidney biopsy

'No suturing' procedures (healing by secondary intent)

- pacemaker/ICD placement
- bowel polypectomy (especially large polyp stalks)
- facial grafts/reconstructive plastic surgery

'Vascular organ' procedures

- hepatic, thyroid, parathyroid

'Large operative field' procedures (major tissue injury)

Major orthopedic surgery (e.g., total joint replacement)

Major cancer surgery

'Critical site' procedures (site of bleed can be life-threatening)

Cardiac or neurosurgical, as well as when spinal or epidural anesthesia is planned.

Supplemental Table II. Timing and dose of dabigatran resumption after surgery/procedure

Type of surgery/procedure	Time of dabigatran resumption	Dabigatran dose
High risk for bleeding that may be critical		
Major cardiac surgery	evening of POD+1	75 mg first 2 doses
Neurosurgery	no bleed on repeat CT	75 mg first 2 doses
High risk for bleeding		
Large hernia repair	48 hrs or when hemostasis is secured	75 mg first dose
Major cancer surgery	72 hrs or when hemostasis is secured	usual dose
Major urologic surgery (prostate/bladder resection)	when no macroscopic hematuria	usual dose
Major vascular surgery	48 hrs	usual dose
Any other major operation with duration >45 minutes	48 hrs	usual dose
Endoscopic large polyp resection	72 hrs	usual dose
Esophageal variceal treatment, biliary sphincterectomy, pneumatic dilatation	48 hrs	usual dose
Endoscopically-guided fine-needle aspiration; kidney biopsy	48 hrs	usual dose
Pacemaker/ICD insertion*	72 hrs	usual dose
Major dental procedure (multiple extractions)	48 hrs	usual dose
Standard risk for bleeding		
Major orthopedic surgery (joint replacement or laminectomy)[†]	6-10 hrs	75 mg first dose
Coronary angiography /PCI/electrophysiologic testing	same evening	75 mg first dose
Indwelling catheter for neuraxial anesthesia[‡]	4 hrs after removal	75 mg first dose
Cholecystectomy, appendectomy	same evening	75 mg first dose
Abdominal hernia repair	same evening	75 mg first dose
Abdominal hysterectomy	same evening	75 mg first dose
Gastrointestinal endoscopy[§] ±biopsy, enteroscopy, biliary/ pancreatic stent without sphincterotomy,	same evening	75 mg first dose

endosonography without aspiration		
Minor plastic surgery, carpal tunnel repair	same evening	75 mg first dose
Minor orthopedic surgery/ arthroscopy	same evening	75 mg first dose
Minor gynecologic surgery (D&C)	same evening	75 mg first dose
Minor dental procedures (few extractions)	same evening	75 mg first dose
Minor skin procedures (cancer excision)	same evening	75 mg first dose
Minor eye procedures (cataract)	same evening	75 mg first dose

POD = postoperative day; CT = computed tomography; ICD = implantable cardioverter-defibrillator; PCI = percutaneous coronary intervention.

*To reduce risk for pocket hematoma

†In analogy with the trials in orthopedic surgery[1]

‡As practiced in a phase III trial with hip surgery (RE-NOVATE)[1]

§For endoscopy that unexpectedly results in polyp removal the timing of resumption is re-adjusted to 72 hrs.

Supplemental Table III. Characteristics of the patients, procedures and events of major bleeding

Case#	Age, y	Sex	Weight, kg	$CHADS_2$ score	CrCl, mL/min	Last dose before, h	Surgery/procedure	High risk	aPTT Day 0, s	Type of bleed	Day of bleed*	Hgb drop, g/L	Transfusion red cells, U
1-065	81	F	48	3	37	96	CABG, mitral valve and ascending aorta replacement	Yes	32	Surgical	0	39	9†
1-102	71	M	91	2	63	24	Ultrasound-guided drainage abdomen	No	D 0: ND D 17: 55	Rectal	17	27	3
1-154	82	M	100	3	69	48	Wide resection myosarcoma	Yes	31	Surgical	0	30	2
4-028	83	M	72	3	53	48	Total knee replacement	Yes	ND	Hemarthrosis in op joint	7‡	ND	0
4-045	66	M	127	0	150	48	Total knee replacement	Yes	30	Surgical, hematoma	1-7	31	0
4-050	78	M	95	4	102	48	Revision hip replacement	Yes	31	Surgical§	0	53	2
4-053	68	M	175	4	123	48	Total hip replacement	Yes	36	Surgical¶	0	21	0
4-069	85	M	81	2	58	3	Colonoscopic polypectomy	No**	ND	From wound	8	39	2
5-011	86	M	84	5	69	48	Revision hip replacement	Yes	ND	Surgical	1	61	2
6-004	84	M	65	3	55	48	AAA endovascular repair	Yes	ND	Hemarth-rosis††	5	ND	0

$CHADS_2$ - risk score for stroke based on Congestive heart failure, Hypertension, Age >75, Diabetes (1 point each) and Stroke/transient ischemic attack (2 points); aPTT – activated partial thromboplastin time; CABG – coronary artery bypass graft; ND – not done; AAA – abdominal aortic aneurysm

*Days after the surgery/invasive procedure, i.e. Day of bleed = 17 means 17 days after surgery

[†]The patient also received 4 units of pooled platelets and 6 units of plasma but no factor concentrates. The surgeon assessed that the bleeding was related to the surgical procedure and not to dabigatran.

[‡]This patient received postoperative bridging with enoxaparin and had not resumed dabigatran yet.

[§]Large bleeding vessel detected during surgery.

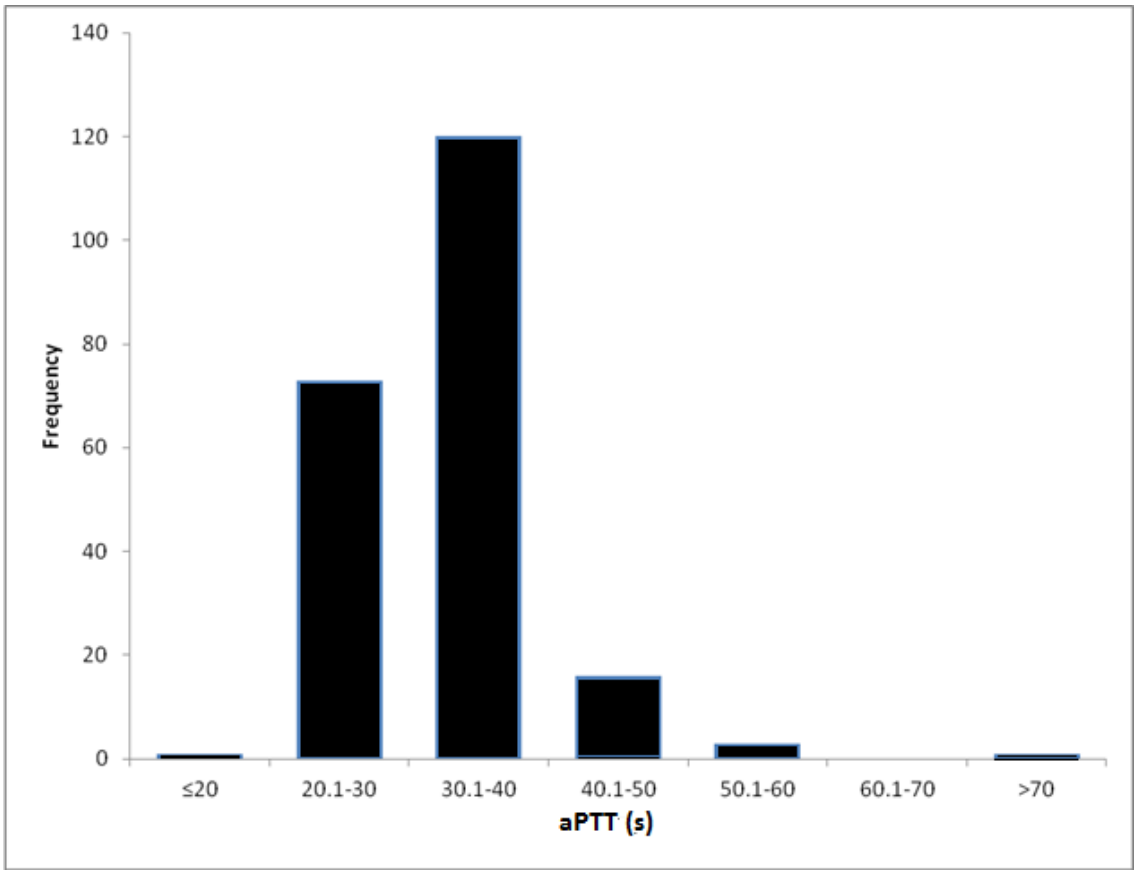
[¶]Complicated by postoperative wound infection.

[**]As classified by investigator, but High risk according to study protocol.

[††]This patient did not resume dabigatran but had been switched to warfarin and was also on enoxaparin and aspirin at the time.

Supplemental Figure 1.

Distribution of activated partial thromboplastin times on the day of procedure



Supplemental Reference

1. Eriksson BI, Dahl OE, Rosencher N, Kurth AA, van Dijk CN, Frostick SP, Prins MH, Hettiarachchi R, Hantel S, Schnee J, Buller HR. Dabigatran etexilate versus enoxaparin for prevention of venous thromboembolism after total hip replacement: a randomised, double-blind, non-inferiority trial. *Lancet.* 2007;370:949-956.