Perioperative Management of Patients With Atrial Fibrillation Receiving a Direct Oral Anticoagulant

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藥物資訊系列(PDF)

手術暨侵入性處置抗血栓藥物使用建議

請先評估「手術或侵入性處置之出血風險」及「未服用抗血栓藥物之栓塞風險」。臨床科可依病人個別臨床狀況，給予個別臨床建議。

口服抗凝血藥品(Oral anticoagulant drugs)

學名	檢驗數值	手術出血風險		手術後
		低	中/高	
Warfarin	• 請於手術當天或前一天監測 INR。 • 若術前 **INR >1.5**，給予 vitamin K。	無需停藥	停藥 **5** 天	若停藥，於術後 **12-24** 小時內及適當止血後重新使用。
Dabigatran	CrCl ≧80 ml/min	停藥≧**24** 小時	停藥≧**48** 小時	若停藥，於術後 **24-72** 小時內及適當止血後重新使用。
	CrCl 50-79 ml/min	停藥≧**36** 小時	停藥≧**72** 小時	
	CrCl 30-49 ml/min	停藥≧**48** 小時	停藥≧**96** 小時	
Rivaroxaban	CrCl ≧50 ml/min	停藥≧**24** 小時	停藥≧**48** 小時	若停藥，於術後 **24-72** 小時內及適當止血後重新使用。
	CrCl 30-49 ml/min	停藥≧**24** 小時	停藥≧**48** 小時	
	CrCl 15-29 ml/min	停藥≧**36** 小時	停藥≧**48** 小時	
Edoxaban	CrCl ≧50 ml/min	停藥≧**24** 小時	停藥≧**48** 小時	若停藥，於術後 **24-72** 小時內及適當止血後重新使用。
	CrCl 30-49 ml/min	停藥≧**24** 小時	停藥≧**48** 小時	
	CrCl 15-29 ml/min	停藥≧**36** 小時	停藥≧**48** 小時	

管灌病人使用口服抗癌藥品之使用方式
顯影劑保存方式與使用期限一覽表
高警訊藥品清單
手術暨侵入性處置抗血栓藥物使用建議
給藥途徑縮寫對照表
病房藥物辨識

Background

- **The perioperative management are uncertain**.
- **No studies** had been conducted to inform
  - **Timing of perioperative DOAC therapy interruption and resumption**
  - Whether **heparin bridging** should be given
  - Whether **preoperative coagulation function testing** was needed.
- The perioperative management of DOAC regimens **varies widely in clinical practice**, and practice guidelines provide **weak and inconsistent management recommendations**.

Background

- We designed the **Perioperative Anticoagulation Use for Surgery Evaluation(PAUSE)** protocol

Thromb Haemost. 2017

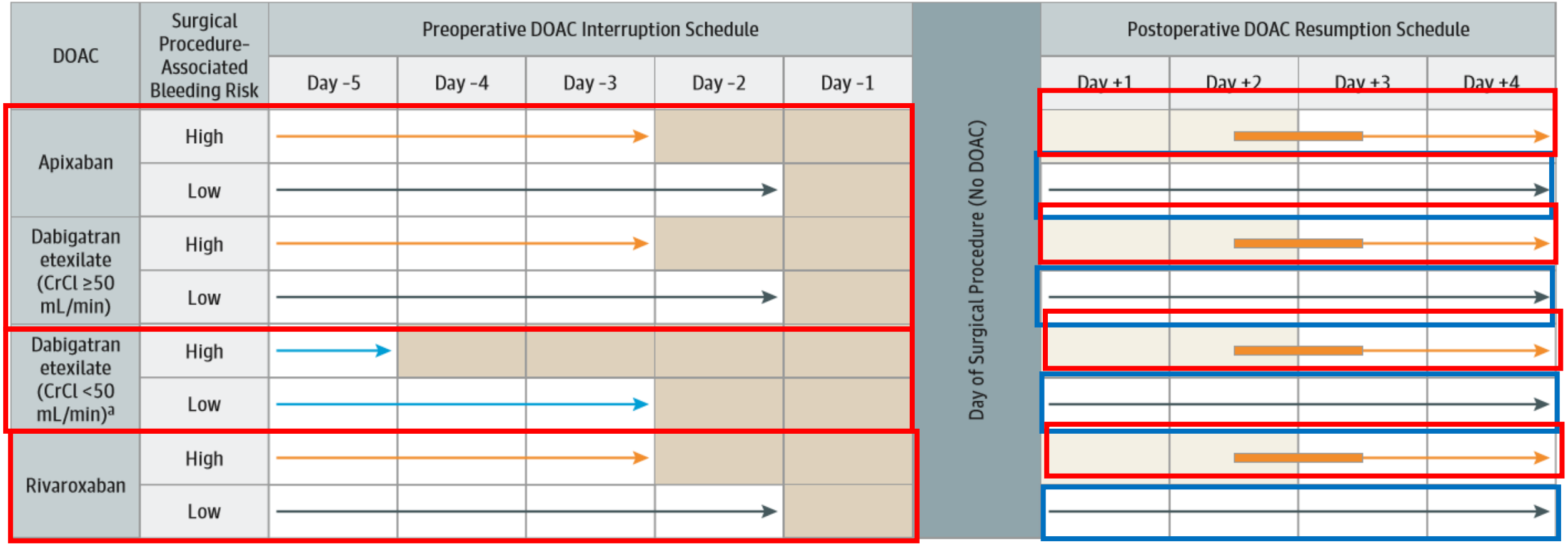
- To assess the safety of a standardized perioperative management strategy for a DOAC regimen.
  - Excluded 30 day perioperative rates of major bleeding of 2% and arterial thromboembolism of 1.5%.
  - High proportion of patients(>90%) with an undetectable or minimal residual anticoagulant level at the time of the procedure.

Methods_Study Design

- Inclusion:
  - Adults (aged≥18 yo) with AF who were long-term users of apixaban (5mg or 2.5mg BID), dabigatran (150mg or 110mg BID), or rivaroxaban (**20mg or 15mg** QD)
  - Scheduled to have an elective surgery or procedure that required interruption of the anticoagulant regimen
  - Were able to adhere to the PAUSE protocol at the time of enrollment.
- Exclusion:
  - CrCl <25ml/min for apixaban or CrCl<30ml/min for dabigatran or rivaroxaban
  - Cognitive impairment or psychiatric illness
  - Did not consent to participate
  - Previous study participation
  - More than1 procedure planned within 30 days.

Method_ Procedure

Figure. Perioperative Direct Oral Anticoagulant (DOAC) Management Protocol



Classification Bleeding Risk of Surgery/Procedure

High Bleed Risk Surgery/Procedures

1) any surgery requiring neuraxial anesthesia
   - neuraxial anesthesia/injection
   - epidural anesthesia/injection
2) major intracranial or neuraxial surgery
   - brain cancer resection
   - laminectomy or neuraxial tumour resection
   - intracranial (subdural, epidural) bleed evacuation
3) major thoracic surgery
   - lobectomy, pneumonectomy
   - esophagectomy
4) major cardiac surgery
   - coronary artery bypass
   - valve replacement or repair
5) major vascular surgery
   - aortic aneurysm repair
   - aortobifemoral bypass, popliteal bypass
   - carotid endarterectomy
6) major abdominopelvic surgery
   - hepatobiliary cancer resection
   - pancreatic cancer or pseudocyst resection
   - colorectal and gastric cancer resection
   - diverticular disease resection
   - inflammatory bowel disease resection
   - renal cancer resection
   - bladder cancer resection
   - endometrial cancer resection
   - ovarian cancer resection
   - radical prostatectomy
7) major orthopedic surgery
   - hip arthroplasty or hip fracture repair
   - knee arthroplasty or tibial osteotomy
   - shoulder arthroplasty
   - metatarsal osteotomy
8) other major cancer or reconstructive surgery
   - head and neck cancer surgery
   - reconstructive facial, abdominal, limb surgery

Low Bleeding Risk Surgery/Procedures

1) gastrointestinal procedures
   - colonoscopy
   - gastroscopy
   - sigmoidoscopy
   - endoscopic retrograde pancreaticocholangiography (ERCP)
   - capsule endoscopy
   - push enteroscopy
   - Barrett's esophagus ablation
2) cardiac procedures
   - permanent pacemaker implantation or battery change
   - internal cardiac defibrillator implantation or battery change
   - arterioventricular node ablation
   - coronary artery angiography (radial approach)
3) dental procedures
   - tooth extraction (up to two extractions)
   - endodontic (root canal) procedure
4) skin procedures
   - skin biopsy
5) eye procedures
   - phacoemulsification (cataract)

2018 ESC Practical Guide on the use NOAC in patients with AF
- Classification of elective surgical interventions according to bleeding risk

Interventions with high bleeding risk (i.e. frequent and/or with high impact)
Complex endoscopy (e.g. polypectomy, ERCP with sphincterotomy etc.)
Spinal or epidural anaesthesia; lumbar diagnostic puncture
Thoracic surgery
Abdominal surgery
Major orthopaedic surgery
Liver biopsy
Transurethral prostate resection
Kidney biopsy
Extracorporeal shockwave lithotripsy (ESWL)
Interventions with high bleeding risk AND increased thromboembolic risk
Complex left-sided ablation (pulmonary vein isolation; some VT ablations)

Interventions with minor bleeding risk
Dental interventions
Extraction of 1–3 teeth
Paradontal surgery
Incision of abscess
Implant positioning
Cataract or glaucoma intervention
Endoscopy without biopsy or resection
Superficial surgery (e.g. abscess incision; small dermatologic excisions; . . .)
Interventions with low bleeding risk (i.e. infrequent or with low clinical impact)
Endoscopy with biopsy
Prostate or bladder biopsy
Electrophysiological study or catheter ablation (except complex procedures, see below)
Non-coronary angiography (for coronary angiography and ACS: see Patients undergoing a planned invasive procedure, surgery or ablation section)
Pacemaker or ICD implantation (unless complex anatomical setting, e.g. congenital heart disease)

Method_Outcomes

- Outcomes were assessed from the time **the first DOAC dose was interrupted until 30 days after the operation.**
  - Primary outcomes:
    - **Major bleeding**
    - **Arterial thromboembolism (ischemic stroke, transient ischemic attack, and systemic embolism)**.
  - Secondary outcomes:
    - Clinically relevant non major bleeding
    - Minor bleeding
    - Death
    - Myocardial infarction
    - Deep vein thrombosis
    - Pulmonary embolism
    - Catheter-associated venous or arterial thrombosis.
  - The residual anticoagulant level just before the procedure
    - Anti–factor X aassays for apixaban and rivaroxaban
    - Dilute thrombin time for dabigatran.

Method_Statistical Analysis

- Primary outcomes:
  - 1-sided $P < 0.05$ was considered statistically significant (with the 1-sided 95% CI, the true incidence of major bleeding was lower than 2% and arterial thromboembolism was lower than 1.5%)
- Secondary outcomes:
  - 2- sided 95%CIs.
- The preoperative residual anticoagulant level:
  - The proportion of patients with an level less than 50ng/mL (30-49.9ng/mL and<30ng/mL) or 50ng/mL or greater.
- Required sample size was 987 patients per DOAC cohort
  - 80% power.

Results_Baselines

Table 1. Baseline Patients Characteristics

Variable	No. (%)		
	Apixaban Cohort (n = 1257)	Dabigatran Cohort (n = 668)	Rivaroxaban Cohort (n = 1082)
Age, mean (SD), y	73.1 (9.15)	72.4 (9.9)	72.0 (9.3)
Male	805 (64.0)	458 (68.6)	725 (67.0)
BMI, mean (SD)	29.49 (6.2)	30.24 (6.8)	29.8 (6.5)
Race/ethnicity			
White	1204 (95.8)	654 (97.9)	1045 (96.6)
Non-white	43 (3.4)	12 (1.8)	25 (2.3)
Unknown	10 (0.8)	2 (0.3)	12 (1.1)
Risk stratification scores, mean (SD)			
$CHADS_2$[a]	2.1 (1.3)	2.2 (1.3)	2.0 (1.3)
$CHADS_2$-VA_2Sc[b]	3.5 (1.7)	3.5 (1.6)	3.3 (1.6)
Modified HAS-BLED[c]	2.0 (0.9)	1.9 (0.9)	1.8 (0.9)
Medical condition			
Congestive heart failure	243 (19.3)	111 (16.6)	140 (12.9)
Hypertension	933 (74.2)	504 (75.4)	784 (72.5)
Diabetes	337 (26.8)	185 (27.7)	273 (25.2)
Stroke	98 (7.8)	64 (9.6)	77 (7.1)
Transient ischemic attack	117 (9.3)	93 (13.9)	99 (9.1)
Coronary artery disease	232 (18.5)	113 (16.9)	177 (16.4)
Peripheral arterial disease	8 (0.6)	6 (0.9)	13 (1.2)
Bioprosthetic heart valve	35 (2.8)	10 (1.5)	20 (1.8)
Mitral valve disease	125 (9.9)	51 (7.6)	86 (7.9)
Venous thromboembolism	77 (6.1)	40 (6.0)	85 (7.9)
Active cancer[d]	105 (8.3)	57 (8.5)	107 (9.9)

Screened 3640 patients from August, 2014, through July, 2018, and 3007 (82.6%) were included.
Patients had a mean age of 72.5 years and were predominantly male (1988 [66.1%]).

Variable	No. (%)		
	Apixaban Cohort (n = 1257)	Dabigatran Cohort (n = 668)	Rivaroxaban Cohort (n = 1082)
Laboratory values, mean (SD)			
Hemoglobin, g/L	134.4 (17.8)	140.1 (50.0)	136.8 (31.6)
Platelets <100 × 10^6/L	8 (0.6)	2 (0.3)	3 (0.3)
Serum creatinine, µmol/L	94.1 (28.8)	87.7 (21.6)	90.3 (22.5)
Creatinine clearance, ml/min[e]	77.9 (32.0)	85.9 (35.7)	82.2 (32.8)
Medication use			
Lower-dose DOAC regimen[f]	252 (20.0)	248 (37.1)	181 (16.7)
Aspirin	156 (12.4)	98 (14.7)	99 (9.1)
$P2Y_{12}$ inhibitor[g]	12 (0.9)	7 (1.0)	11 (1.0)
P-glycoprotein or cytochrome P450 3A4 inhibitor or inducer[h]	76 (6.0)	53 (7.9)	55 (5.1)
Elective surgery or procedure type			
High bleeding risk	406 (32.3)	228 (34.1)	373 (34.5)
Low bleeding risk	851 (67.7)	440 (65.9)	709 (65.5)
Anesthesia type			
General	410 (32.6)	193 (28.9)	384 (35.5)
Neuraxial	103 (8.2)	57 (8.5)	70 (6.5)
Other	689 (54.8)	369 (55.2)	584 (54.0)

Results_Study Outcomes (1)

- 2624(87.3%) included in the per protocol analysis
  - 159 (5.3%) deviated from the DOAC therapy **interruption protocol**
  - 202 (6.7%) deviated from the DOAC therapy **resumption protocol**
  - 22 (0.7%) were lost to follow-up

Table 2. Preoperative and Postoperative Direct Oral Anticoagulant Interruption and Resumption

	Preoperative Management			Postoperative Management			
Cohort	DOAC Preoperative Omission, No. (IQR), d	Interruption Interval (IQR), h	Patient Adherence to Interruption Protocol, No. (%)	DOAC Postoperative Resumption, No. (IQR), d	Resumption Interval (IQR), h	Patient Adherence to Resumption Protocol, No. (%)	Patient Receipt of Prophylactic-Dose LMWH, No. (%)
Apixaban							
Low bleeding risk (n = 851)	1 (1-1)	39.3 (37.4-41.5)	819 (96.24)	1 (1-1)	22.2 (19.3-31.9)	745 (87.5)	16 (1.9)
High bleeding risk (n = 406)	2 (2-2)	63.8 (61-67	378 (93.1)	3 (2-4)	67.8 (45.1-91.4)	399 (98.3)	133 (32.8)
Dabigatran etexilate, CrCl ≥50 mL/min							
Low bleeding risk (n = 386)	1 (1-1)	39.7 (38-41.9)	368 (95.34)	NA	NA	NA	NA
High bleeding risk (n = 202)	2 (2-2)	63.2 (61.5-67.2)	187 (92.57)	NA	NA	NA	NA
Dabigatran, CrCl <50 mL/min							
Low bleeding risk (n = 54)	2 (2-2)	64.4 (62-66)	50 (92.59)	NA	NA	NA	NA
High bleeding risk (n = 26)	4 (4-4)	110.2 (108.3-112.7)	22 (84.62)	NA	NA	NA	NA
Dabigatran (all patients)[a]							
Low bleeding risk (n = 440)	NA	NA	NA	1 (1-1)	23 (20.5-33.6)	425 (96.6)	7 (1.6)
High bleeding risk (n = 228)	NA	NA	NA	3 (2-3)	66.4 (45.1-81.4)	227 (99.6)	85 (37.3)
Rivaroxiban							
Low bleeding risk (n = 709)	1 (1-1)	48 (40.7-51)	674 (95.06)	1 (1-1)	25 (20.8-33.5)	641 (90.41)	8 (1.13)
High bleeding risk (n = 373)	2 (2-2)	72 (65.6-75)	350 (93.83)	3 (2-4)	69.4 (46.4-94)	370 (99.2)	131 (35.1)

Results_Study Outcomes (2)

eAppendix 6. Study Outcomes in Patients Adhering to DOAC Interruption and Resumption Protocols*

Outcome	DOAC Cohort		
	Apixaban	Dabigatran	Rivaroxaban
	n=1079	n=599	n=946
Primary - number, % (1-sided 95% CI)			
Major bleeding†	13, 1.2 (0-1.89); p=0.031	6, 1.0 (0-1.93); p=0.04	16, 1.69 (0-2.53); p=0.249
Arterial thromboembolism‡§	2, 0.19 (0-0.56); p<0.001	3, 0.50 (0-1.25); p=0.022	4, 0.42 (0-0.94); p=0.003

‡ All episodes of arterial thromboembolism were **ischemic stroke.**

Outcome	DOAC Cohort		
	Apixaban (n = 1257)	Dabigatran Etexilate (n = 668)	Rivaroxaban (n = 1082)
Secondary			
Death			
No. (%)	3 (0.24)	3 (0.45)	3 (0.28)
2-Sided 95% CI	0.08-0.70	0.15-1.31	0.09-0.81
Myocardial infarction			
No. (%)	1 (0.08)	0 (0)	0 (0)
2-Sided 95% CI	0.01-0.45	0-0.57	0-0.35
Deep vein thrombosis			
No. (%)	2 (0.16)	1 (0.15)	0 (0)
2-Sided 95% CI	0.04-0.58	0.03-0.84	0-0.35
Pulmonary embolism			
No. (%)	4 (0.32)	1 (0.15)	1 (0.09)
2-Sided 95% CI	0.12-0.82	0.03-0.84	0.02-0.52
Arterial catheter thrombosis[d]			
No. (%)	1 (0.08)	1 (0.15)	0 (0)
2-Sided 95% CI	0.01-0.45	0.03-0.84	0-0.35
Clinically relevant nonmajor bleeding			
No. (%)	21 (1.67)	13 (1.95)	26 (2.4)
2-Sided 95% CI	1.10-2.54	1.14-3.30	1.65-3.50
Minor bleeding			
No. (%)	54 (4.3)	38 (5.69)	62 (5.73)
2-Sided 95% CI	3.31-5.56	4.17-7.71	4.5-7.28

Results_Study Outcomes (3)

Table 4. Incidence of Major Bleeding by Elective Surgery or Procedure–Associated Bleeding Risk

Procedure-Associated Bleeding Risk	Apixaban Cohort (n = 1257)	Dabigatran Etexilate Cohort (n = 668)	Rivaroxaban Cohort (n = 1082)
Low bleeding risk			
No. (%)	851 (67.7)	440 (65.9)	709 (65.5)
30-d Postoperative rate of major bleeding, % (95% CI)	0.59 (0-1.20)	0.91 (0-2.01)	1.27 (0-2.17)
High bleeding risk			
No. (%)	406 (32.3)	228 (34.1)	373 (34.5)
30-d Postoperative rate of major bleeding, % (95% CI)	2.96 (0-4.68	0.88 (0-2.62)	2.95 (0-4.76)

Results_Study Outcomes (4)

eAppendix 10. Anticoagulant Level at Time of Surgical Procedure Based on Direct Oral Anticoagulant–Specific Coagulation Tests

Measurement of Anticoagulant Level	DOAC Cohort, No. (%)					
	Apixaban		Dabigatran		Rivaroxaban	
	Low Bleeding Risk (n = 851)	High Bleeding Risk (n = 406)	Low Bleeding Risk (n = 440)	High Bleeding Risk (n = 228)	Low Bleeding Risk (n = 709)	High Bleeding Risk (n = 373)
Samples collected	772 (90.7)	357 (87.9)	367 (83.4)	196 (85.7)	627 (88.4)	338 (90.6)
Samples with residual DOAC values	751 (88.2)	335 (82.5)	352 (80.0)	183 (80.5)	606 (85.5)	314 (84.2)
DOAC-Specific Coagulation Tests						
Anti–Factor Xa Level (Apixaban and Rivaroxaban) or Dilute Thrombin Time (Dabigatran), ng/mL						
>50	96 (12.9)	7 (2.09)	25 (7.1)	1 (0.55)	27 (4.5)	2 (0.64)
30-49.9	134 (17.8)	16 (4.8)	35 (9.9)	1 (0.55)	133 (21.9)	44 (14.0)
<30	521 (69.4)	312 (93.1)	292 (82.9)	181 (98.9)	446 (73.6)	268 (85.3)

The proportion of patients with **a level less than 50ng/mL** :
apixaban: **90.5%**
dabigatran: **95.1%**
rivaroxaban: **96.8%**

Among 832 patients who had a **high–bleeding-risk** procedure and anticoagulant measurements, of whom the proportion with a residual anticoagulant level less than 50ng/mL was **98.8%**

Discussion (1)

- This simple standardized perioperative management strategy **without the use of heparin bridging or preoperative coagulation function testing** was associated with low rates of perioperative major bleeding (<2%) and arterial thromboembolism(<1%).
- Exclude a 2% rate of major bleeding
  - Supported in the dabigatran cohort (0.90%; 95% CI, 0%-1.73%) but not in the apixaban cohort (1.35%; 95% CI, 0%-2.0%) or rivaroxaban cohort (1.85%; 95% CI, 0%-2.65%)
  - Per protocol analysis: supported in the dabigatran cohort (1.0%; 95% CI, 0%-1.93%) and the apixaban cohort (1.2%; 95% CI, 0%-1.89%) but not in the rivaroxaban cohort (1.69%; 95% CI, 0%-2.53%).
- Exclude a 1.5% rate of arterial thromboembolism
  - Supported in all 3 cohorts analysis as well as per protocol analysis.

Discussion (2)

- A high proportion of patients (>90%) would have a preoperative residual anticoagulant level less than 50 ng/mL in all 3 DOAC cohorts. Among patients with a high–bleeding-risk procedure, almost all patients (98.8%) had a level less than 50 ng/mL.
- The rates of **major bleeding appeared to be higher** among patients with a high–bleeding-risk procedure **in the apixaban and rivaroxaban cohorts**.
  - Intrinsically higher rate of bleeding expected with high–bleeding-risk procedure .
  - Further study is needed to assess this strategy in patients with high–bleeding-risk procedures.

Discussion (3)

- Two pertinent studies had similar adverse outcome.
  - In a cohort study of 541 patients receiving **dabigatran**
    - 30-day postoperative rate of major bleeding was 1.8%
    - Arterial thromboembolism rate was 0.2%.
  - In the BRIDGE trial, where patients with AF who had perioperative **warfarin** treatment interruption, patients who were not bridged
    - 30-day postoperative rate of major bleeding of 1.3%, and those who underwent a high–bleeding-risk procedure had a rate of 3.2%.
    - Arterial thromboembolism rate of 0.4%,

Limitations

1. Selection bias due to cohort study design.
   - Unlikely. Because a high proportion (83%) of screened patients participated in this study, and their risk factor was comparable to that of patients with AF included in population-based studies.
2. Although few patients (n = 230) received neuraxial anesthesia
   - The management of such patients was the same as patients undergoing a high–bleeding-risk procedure (n = 1007).
3. The dabigatran cohort (n=668) did not reach the expected sample size
   - The number of patients was sufficient to address the study hypotheses.
4. Patients using edoxaban were not included, and the results are not generalizable to this DOAC.
5. 50 ng/mL cut point used in this study to define a clinically important residual preoperative DOAC level was **not established**, and further study is needed to assess a **correlation** between preoperative DOAC treatment levels and bleeding.
6. Most patients include were white.
7. Patients with venous thromboembolism were not included.

Strengths

- The **generalizability** of the results
  - as a high proportion of screened patients were enrolled (83%) and few were lost to follow-up (<1%).
- The **clinical applicability** of perioperative management strategy
  - as most patients adhered to the interruption (95%) and resumption (93%) management protocol.
- The **simple strategy** of omitting DOAC regimens
  - 1 day before and after a low-bleeding-risk procedure
  - 2 days before and after a high–bleeding-risk procedure

  (except for patients using dabigatran with a CrCl <50 mL/min).

Conclusions

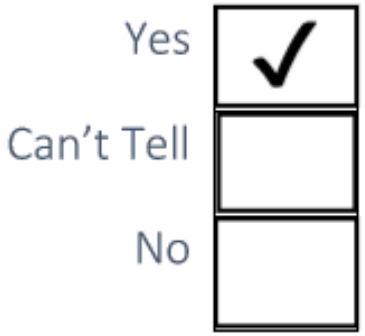
- Patients with AF who had DOAC therapy interruption for elective surgery or procedure, a simple standardized perioperative management strategy **without heparin bridging or measurement of coagulation function was associated with low rates of major bleeding and arterial thromboembolism.**

Paper for appraisal

CASP
Critical Appraisal
Skills Programme

Section A: Are the results of the study valid?

1. Did the study address a clearly focused issue?



HINT: A question can be 'focused' in terms of

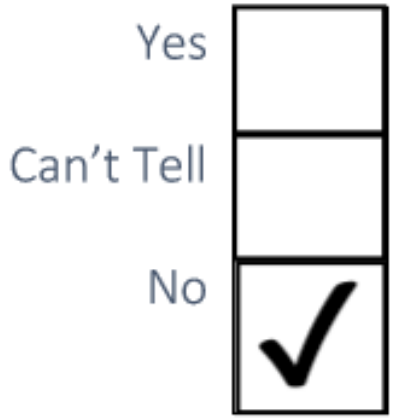
- the population studied
- the risk factors studied
- is it clear whether the study tried to detect a beneficial or harmful effect
- the outcomes considered

To assess the safety of a standardized perioperative management strategy for a DOAC regimen.

CASP
Critical Appraisal Skills Programme

Section A: Are the results of the study valid?

2. Was the cohort recruited in an acceptable way?



HINT: Look for selection bias which might compromise the generalisability of the findings:

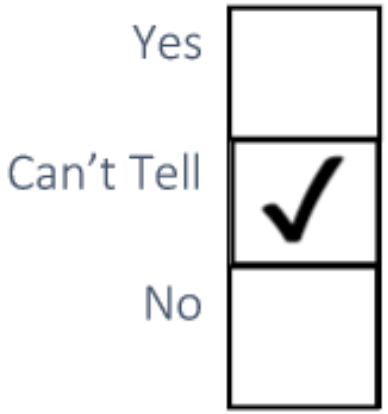
- was the cohort representative of a defined population
- was there something special about the cohort
- was everybody included who should have been

High proportion of screened patients were enrolled (83%) and few were lost to follow-up (<1%).
Exclusion:
- CrCl <25ml/min for apixaban or CrCl<30ml/min for dabigatran or rivaroxaban
- Cognitive impairment or psychiatric illness
- Did not consent to participate
- Previous study participation
- More than1 procedure planned within 30 days.

CASP
Critical Appraisal Skills Programme

Section A: Are the results of the study valid?

3. Was the exposure accurately measured to minimise bias?



HINT: Look for measurement or classification bias:

- did they use subjective or objective measurements
- do the measurements truly reflect what you want them to (have they been validated)
- were all the subjects classified into exposure groups using the same procedure

Long-term users of apixaban, dabigatran, or rivaroxaban... not defined long term and don't know the medication compliance..

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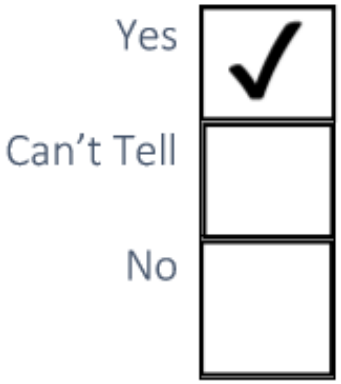
Section A: Are the results of the study valid?

4. Was the outcome accurately measured to minimise bias?



HINT: Look for measurement or classification bias:

- did they use subjective or objective measurements
- do the measurements truly reflect what you want them to (have they been validated)
- has a reliable system been established for detecting all the cases (for measuring disease occurrence)
- were the measurement methods similar in the different groups
- were the subjects and/or the outcome assessor blinded to exposure (does this matter)

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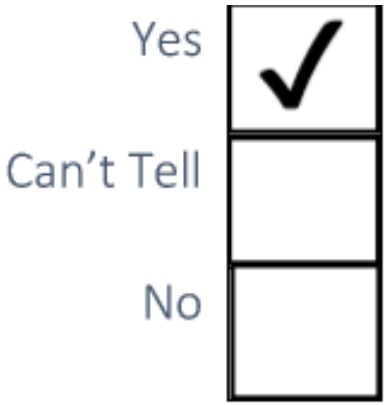
Outcomes measurement

- Major bleeding
  - Fatal bleeding
  - Symptomatic and retroperitoneal, intracranial, intraspinal, intraocular, pericardial, intramuscular with compartment syndrome, or intra-articular
  - Extrasurgical site bleeding causing a drop in hemoglobin ≥2 g/dL (1.24 mmol/L)
  - Extrasurgical site bleeding leading to transfusion ≥2 units whole blood or red cells within 48 hours of the bleed
  - Surgical bleed that leads to intervention (e.g., re-operation) or has one of: interferes with mobilization, leads to delayed wound healing, or leads to deep wound infection
  - Surgical site bleeding requiring intervention (re-operation) resulting in prolonged care or stay
  - Surgical site bleeding that is unexpected or prolonged
  - Surgical site bleeding sufficiently large to cause hemodynamic instability associated with drop in hemoglobin ≥2 g/dL (1.24 mmol/L) within 48 hour of seeking medical help
  - Surgical site bleeding sufficiently large to cause hemodynamic instability associated with transfusion ≥2 units whole blood or red cells within 48 hours of the bleed
- Arterial thromboembolism
  - Ischemic stroke
    - any new focal neurologic deficit that persists for >24 hours or any new focal neurologic deficit of any duration, that occurs with evidence of acute infarction on computed tomography (CT) or magnetic resonance imaging (MRI) of the brain
  - Transient ischemic attack
    - Symptomatic focal neurologic deficit (lasting typically <1 hour and not for >24 hours), that occurs with no evidence of acute infarction on CT or MRI of brain.
  - Systemic embolism
    - Symptomatic embolism to upper or lower extremity or abdominal organ, confirmed intra-operatively or by objective imaging studies (e.g., CT angiography);

Section A: Are the results of the study valid?

5. (a) Have the authors identified all important confounding factors?



HINT:

- list the ones you think might be important, and ones the author missed

Age, gender, race, medical condition (CHF, HTN, DM, stroke, TIA, CAD, PAD, bioprosthetic heart valve, mitral valve disease, VTE, active cancer). lab (Hgb, Platelets, Scr, CrCL), medication use (lower dose DOAC, P2Y12 inhibitor, P-glycoprotein or CYP3A4 inhibitor or inducer), procedure type, anesthesia type.

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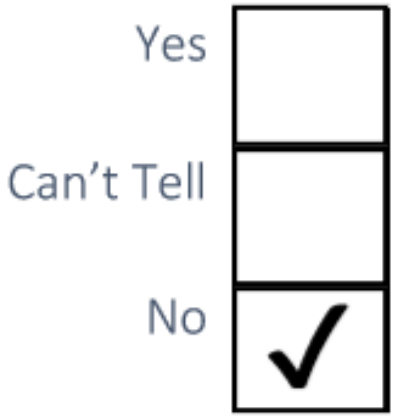
Section A: Are the results of the study valid?

5. (b) Have they taken account of the confounding factors in the design and/or analysis?



HINT:

- look for restriction in design, and techniques e.g. modelling, stratified-, regression-, or sensitivity analysis to correct, control or adjust for confounding factors

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Section A: Are the results of the study valid?

6. (a) Was the follow up of subjects complete enough?

Yes ✓

Can't Tell

No

2624(87.3%) included in the per protocol analysis, and 22 (0.7%) were lost to follow-up.

HINT: Consider

- the good or bad effects should have had long enough to reveal themselves
- the persons that are lost to follow-up may have different outcomes than those available for assessment
- in an open or dynamic cohort, was there anything special about the outcome of the people leaving, or the exposure of the people entering the cohort

6. (b) Was the follow up of subjects **long** enough?

Yes ✓

Can't Tell

No

Follow up was from the time the first DOAC dose was interrupted until 30 days after the operation.

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Section B: What are the results?

7. What are the results of this study?

HINT: Consider

- what are the bottom line results
- have they reported the rate or the proportion between the exposed/unexposed, the ratio/rate difference
- how strong is the association between exposure and outcome (RR)
- what is the absolute risk reduction (ARR)

See slides 13-16

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Section B: What are the results?

8. How precise are the results?

HINT:

- look for the range of the confidence intervals, if given

Considered as precise.

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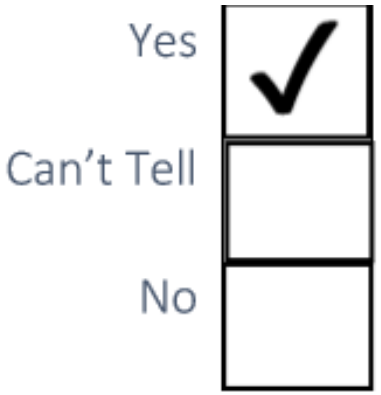
Section B: What are the results?

9. Do you believe the results?



HINT: Consider

- big effect is hard to ignore
- can it be due to bias, chance or confounding
- are the design and methods of this study sufficiently flawed to make the results unreliable
- Bradford Hills criteria (e.g. time sequence, dose-response gradient, biological plausibility, consistency)

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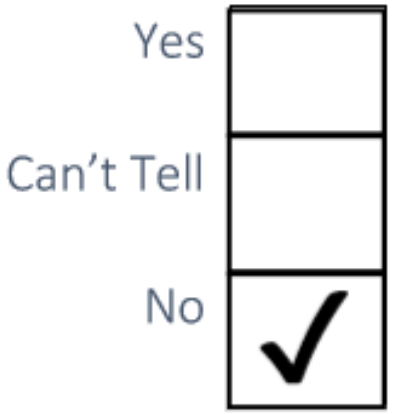
Section C: Will the results help locally?

10. Can the results be applied to the local population?



HINT: Consider whether

- a cohort study was the appropriate method to answer this question
- the subjects covered in this study could be sufficiently different from your population to cause concern
- your local setting is likely to differ much from that of the study
- you can quantify the local benefits and harms

Should exclude patients whose CrCl <25ml/min for apixaban or CrCl<30ml/min for dabigatran or rivaroxaban. No edoxaban.

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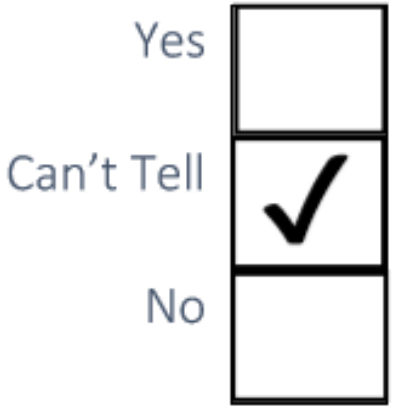
Section C: Will the results help locally?

11. Do the results of this study fit with other available evidence?



Few studies had been conducted to inform the timing of perioperative DOAC therapy interruption and resumption.

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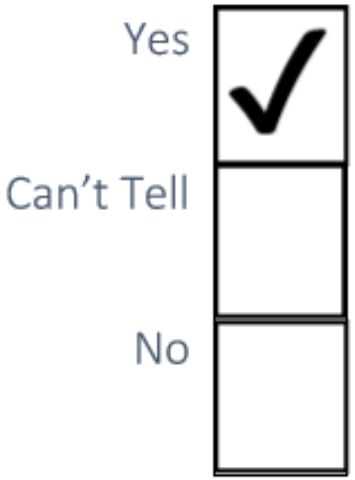
Section C: Will the results help locally?

12. What are the implications of this study for practice?



HINT: Consider

- one observational study rarely provides sufficiently robust evidence to recommend changes to clinical practice or within health policy decision making
- for certain questions, observational studies provide the only evidence
- recommendations from observational studies are always stronger when supported by other evidence

Patients with AF who had DOAC therapy interruption for elective surgery or procedure, a simple standardized perioperative management strategy without heparin bridging or measurement of coagulation function was associated with low rates of major bleeding in dabigatran group and arterial thromboembolism in all three groups.

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Could this perioperative management be used in our hospital?
可以在院內採用這個圍術期管理嗎？

同意(綠牌)：11位
需更多文獻支持(黃牌)：45位
不同意(紅牌)：0位