

Novel Anticoagulants: How to Manage Patients Who Need a Procedure

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Financial Disclosure Information

Novel Anticoagulants: How to Manage
Patients Who Need a Procedure

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None

Learning objectives: Oral Direct Factor Inhibitors

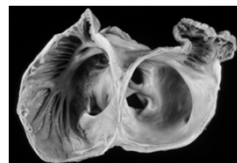
To appreciate:

1. The nature of the problem
2. The published bleeding and thromboembolic event rates
3. Our general approach to peri-procedural AC management

How Many Americans are taking Anticoagulants?



> 6,000,000



Atrial Fibrillation ~ 4 M

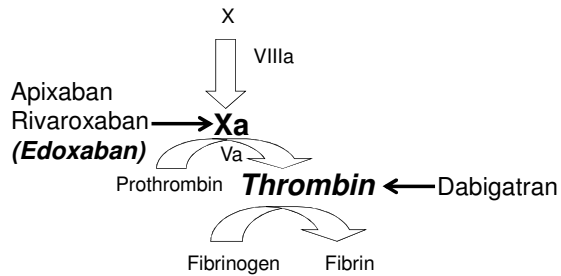


Mechanical Valve
~ 0.5 M



Venous
Thromboembolism
~ 2 M

Oral Direct Factor Inhibitors



Direct Factor Inhibitors

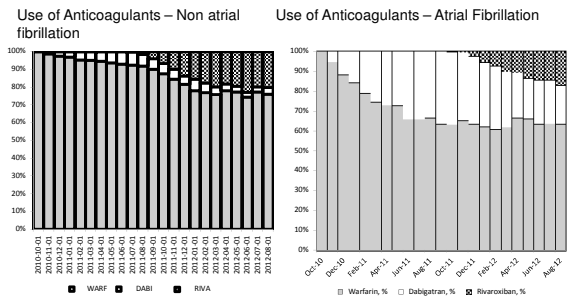
	Dabigatran	Rivaroxaban	Apixaban
Factor Target	Thrombin	Xa	Xa
T _{1/2} (hrs)	12-17	7-11	7-11
Elimination	Renal	Renal Hepatic	Renal Hepatic Enteric

Oral Direct Factor Inhibitors

Advantages:

- Few drug interactions
- No food interactions
- No monitoring
- No continuous dose adjustments

Increased Use of Novel Anticoagulants



Use of Novel Anticoagulants Real World Experience: ORBIT AF

AF patients : New onset
50% started on a NoAC

AF patients: Chronic on warfarin
25% transitioned to a NoAC

Circ Cardiovasc Qual Outc. 2014; 7: A336

Anticoagulant Prescribing Patterns



Warfarin

Novel Anticoagulants

Direct Factor Inhibitor Use



~3 Million Patients in USA

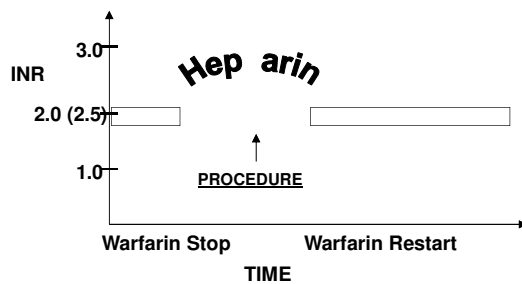
Periprocedural Management: Novel Anticoagulants

- ~ **10% annually** require an invasive procedure.
- **300,000 patients** will require periprocedural management of a direct factor inhibitor in 2014.

Bayer, Johnson & Johnson, Pfizer 2013

Bridging Therapy

Heparin substitution during **warfarin** interruption



Circulation

Periprocedural Heparin Bridging in Patients Receiving Low-Dose Warfarin: A Systematic Review and Meta-Analysis of Bleeding and Thromboembolic Events
Delfino, Sergio; Garcia, Victor; Scott, David; Hayes, D; Dunbar, Timothy; et al. 2012

Circulation. 2012;126:1630-1638. doi:10.1161/CIRCULATION.111.211111
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The online version of this article, along with updated information and services, is located on the World Wide Web at:

<http://circ.ahajournals.org/content/126/16/1630>

DOI: 10.1161/CIRCULATION.111.211111

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Warfarin Bridging

Metaanalysis

- 34 studies, **1 RCT**.
- 2004 forward
- Event Rates:
 - Thromboembolism 0.9%.
 - Major bleeding 4%.
- “Bridging” Heparin
 - Increased major bleeding 3.6 fold.
 - No obvious impact on thromboembolism rates.

Circulation. 2012;126:1630



Interpreting the “Peri-procedure” Literature

Acknowledge:

- Anticipated annual bleeding and thrombosis rates **without** a procedure

Anticipated Annual Event Rates *Apart from a Procedure*

	Dabigatran	Rivaroxaban	Apixaban
Stroke/Embolism	1.1%	1.7%	1.3%
Major Bleed	3.1%	3.6%	1.0%

N Engl J Med 2009;361:1139
N Engl J Med 2011;365:981
N Engl J Med 2011;365:883

Interpreting the “Peri-procedure” Literature

Acknowledge:

- Annual bleeding and thrombosis rates **without** a procedure
- Procedure-specific bleeding and thrombosis rates **without** a chronic anticoagulation.

Surgical Bypass Grafting

Complications within 30 days

- MI 5.0%
- Stroke 0.5%
- **Bleeding 20.8 %**
- Mortality 2.0%

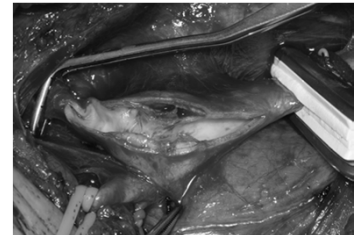


Ann Vasc Surg. 2010 Apr 1 N Engl J Med 2004;351:2795

Carotid Endarterectomy

Complications within 30 days

- MI 5.0%
- Stroke 1.0%
- **Bleeding 1.1 %**
- Mortality 0.0%



Diagnostic Endoscopy

Including biopsy

- **Bleeding <1.0 %**



Polypectomy

Including biopsy

- **Bleeding 1.0 – 5.0%**




Interpreting the “Peri-procedure” Literature

Acknowledge:

- Annual bleeding and thrombosis rates **without** a procedure
- Procedure-specific bleeding and thrombosis rates **without** a chronic anticoagulation.
- Event rates must be interpreted in the context of **duration of follow up**.

Time Frame varies by Study

Author	n	Follow up
Douketis (04)	215	2 weeks
Pengo (09)	190	1 month
Kovacs (04)	112	3 months
Hammerstingl (07)	116	1 month
Daniels (2007)	556	3 months



ISTH Guideline: Reporting Standards

- Risk stratification
- Procedure description
- Major event definition
- Time-frame for events

“Harmonized reporting would facilitate across-study comparisons, enable meta-analysis, allow robust assessments of benefits and risks of different periprocedural antithrombotic strategies.”

J Thromb Haemost 2012;10:692

Bleeding Definitions*

Major bleeding

- Hemoglobin drop ≥ 2 g/dL
- Transfusion ≥ 2 units pRBCs
- Intraocular, intracerebral, or retroperitoneal bleed
- Fatal

Non-major clinically relevant

- Medical intervention required
- Unscheduled physician contact
- Drug discontinuation
- Pain or impairment of daily activities


J Thromb Haemost. 2005;3:692-694.

What are the published **peri-procedural** event rates for patients taking a **oral direct factor inhibitor**?

ROCKET AF Trial: Temporary Anticoagulant Interruption

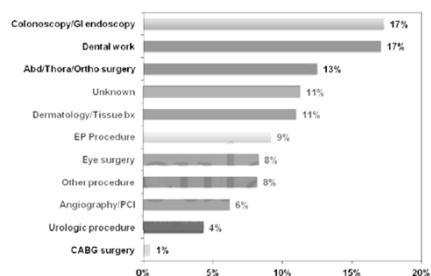
4,692 Patients

- 7555 Interruptions
- 40% underwent an invasive procedure
- Median interruption: 5 days
- Majority stopped ≥ 3 days prior to procedure.
- Bridging therapy used in 9% (left to investigator discretion)



Circulation. 2014;129:1850-9

Rivaroxaban Interruption: Procedure Type



~ 18% would be considered "major procedures"

Circulation. 2014;129:1850-9

Rivaroxaban Interruption: Bridging

Characteristic	Bridging therapy		P
	Yes (n=431)	No (n=4261)	
CHADS2 Score, MN %	3.52	3.40	0.0094
Percent	1	0	<0.1
	2	9.5	16.4
	3	47.1	42.9
	4	27.1	27.3
	5	13.9	11.5
	6	2.3	1.9
History of stroke/TIA/TE	52.4	50.0	0.34

Circulation. 2014;129:1850-9

No Difference by Treatment Allocation (Outcomes for Surgical/Invasive Procedures)

Event Rates @ 30 days	Rivaroxaban (n=968)	Warfarin (n=1162)	HR (CI) for Riva vs. Warfarin
Stroke/TE	0.27%	0.42%	0.65 (0.2, 2.13)
Death	0.07%	0.16%	0.44 (0.05, 4.25)
Major Bleed	0.99%	0.97%	1.02 (0.5, 2.06)

Circulation. 2014;129:1850-9

No Difference by Bridging Strategy

Event Rates @ 30 days	Bridging (n=483)	No Bridging (n=7072)
Stroke/TE	0.17%	0.32%
Death	0.33%	0.17%
Major Bleed	0.91%	0.88%

Circulation. 2014;129:1850-9

Rivaroxaban Interruption: Bottom Line

For NVAf Patients from ROCKET-AF Trial undergoing temporary AC interruption:

- Event rates are very low with no clear difference compared to warfarin
- Context of primarily "minor procedures"
- No clear benefit to "bridging LMWH"

Periprocedural Bleeding and Thrombotic Events (RE-LY Trial)

4591 patients

Dasigatran

- 2005 - 08: stop 24 hrs prior
- 2008 - 09: stop 24 hrs for minor
stop 2-5 days for major
- Restart once hemostasis assured

Warfarin

Management left to local provider

Circulation 2012;126:343-48

Periprocedural Bleeding and Thrombotic Events with Dabigatran vs. Warfarin (RE-LY Trial)

- Procedures:
 - PM/defib insertion (10.3%)
 - Dental procedures (10%)
 - Diagnostic (10%)
 - Cataract (9.3%)
 - Colonoscopy (8.6%)
 - Joint replacement (6.2%)

~ 18% of procedures would be considered "major"

Circulation 2012;126:343-48

Periprocedural Bleeding and Thrombotic Outcomes at 30 days

30 day Outcomes	Dabigatran* (n=1546)	Warfarin (n=1558)	p
Major Bleed	5.1%	4.6%	NS
Fatal Bleed	0.1%	0.1%	NS
Bleed requiring reoperation	1.4%	1.0%	NS
Thrombotic event	1.5%	1.2%	NS

*Dabigatran 150 mg

Circulation 2012;126:343-48

Non-Valvular Atrial Fibrillation

Author	n	Clot	Bleed
Douketis (2004)	346	1.2%	0.9%
Pengo (2009)	653	0.2%	1.2%
Kovacs (2004)	112	2.7%	6.3%
Dunn (2007)	76	2.3%	3.5%
Wysokinski (2008)	345	1.1%	2.7%
Total	1532	0.9%	2.0%
RE-LY	1546	1.5%	5.1%

> 50% of procedures would be considered "major"

Urgent Surgery and Risk for Events

	D150 % (n/N)	Warfarin % (n/N)	D150 vs Warfarin RR (95% CI, P Value)	P-Inter
Urgent surgery	17.7 (25/141)	21.6 (24/111)	0.82 (0.50–1.35, 0.43)	
Elective surgery	3.8 (53/1405)	3.3 (48/1447)	1.14 (0.77–1.67, 0.51)	0.31
Major surgery	6.5 (33/511)	7.8 (39/498)	0.82 (0.53–1.29, 0.40)	
Minor surgery	3.2 (14/435)	1.8 (8/436)	1.75 (0.74–4.14, 0.19)	0.13
Original dabigatran protocol	4.9 (66/1346)	4.6 (60/1319)	1.08 (0.77–1.52, 0.67)	
Amended dabigatran protocol	6.0 (12/200)	5.0 (12/239)	1.20 (0.55–2.60, 0.65)	0.81

Major bleeding 5 – 6 fold higher
Stroke/TE 4 fold higher

Circulation. 2012;126:343-348

Dabigatran Interruption: Bottom Line

For NVAf Patients from RE-LY Trial undergoing temporary AC interruption:

- Thromboembolic event rates are low and similar to warfarin
- Major bleeding rates are high
- Context of primarily "minor procedures"
- Event rates are greatly increased with urgent/emergent surgery

What is the structured approach to peri-procedural anticoagulant management for patients taking direct factor inhibitors?

Management Decisions

Does procedure require anticoagulant discontinuation?

With **Warfarin**: Many Don't

- **Dental**
 - Extraction
 - Endodontics (root canal)
- **Dermatology**
 - Skin cancer excision
- **Gastroenterology**
 - Endoscopy ± mucosal bx
 - Diagnostic ERCP
 - Cold snare small polyp
- **Gynecology**
 - Diagnostic colposcopy
 - D&C
 - IUD insertion
- **Interventional radiology**
 - Thora/paracentesis
 - Non-tunneled catheters
 - IVC filter placement
- **Ophthalmology**
 - Cataract surgery
 - Intraocular injections
- **Pulmonary**
 - Bronchoscopy ± BAL
 - Endobronchial FNA
- **Urology**
 - Cystoscopy without biopsy

N Engl J Med 2013; 368:2113-2124

Uninterrupted Anticoagulants during Atrial Fibrillation Ablation

	Rivaroxaban (n=157)	Warfarin (n=157)
Major bleeding	1.9%	2.5%
Minor bleeding	7.6%	8.9%
TIA	0.6%	0.6%

Lakkireddy et al. Heart Rhythm Society 2013

Management Decisions

Does procedure require anticoagulant discontinuation?

No

Yes

Mayo Approach:

Until we have more experience, we suggest **discontinuation of direct factor inhibitors** prior to **most invasive procedures**.

Management Decisions

Does procedure require anticoagulant discontinuation?

Yes

Assess overall bleeding risk

- Procedure specific
- Patient specific
- Provider specific

Peri-procedural Risk of Major Bleeding

- “**Low risk**” < 2%
- “**High risk**” ≥ 2%
- Within **2 days** of procedure

J Thromb Haemost 2012;10:692

Surgical Procedures at High Risk for Bleeding

- Open Heart Surgery
- Abdominal Vascular Surgery
- Neurosurgery
- Major Cancer Surgery
- Urologic Procedures
- **Neuraxial anesthesia**

N Engl J Med 2013; 368:2113-2124

Black Box Warnings: Neuraxial Anesthesia

- Dabigatran

(B) SPINAL/EPIDURAL HEMATOMA: Epidural or spinal hematomas may occur in patients treated with PRADAXA who are receiving neuraxial anesthesia or undergoing spinal puncture. These hematomas may result in long-term or permanent paralysis (5.3). Monitor patients frequently for signs and symptoms of neurological impairment and if observed, treat urgently. Consider the benefits and risks before neuraxial intervention in patients who are or who need to be anticoagulated (5.3).

- Rivaroxaban

(B) SPINAL/EPIDURAL HEMATOMA: Epidural or spinal hematomas have occurred in patients treated with XARELTO who are receiving neuraxial anesthesia or undergoing spinal puncture. These hematomas may result in long-term or permanent paralysis (5.2, 5.3, 6.2). Monitor patients frequently for signs and symptoms of neurological impairment and if observed, treat urgently. Consider the benefits and risks before neuraxial intervention in patients who are or who need to be anticoagulated (5.3).

- Apixaban

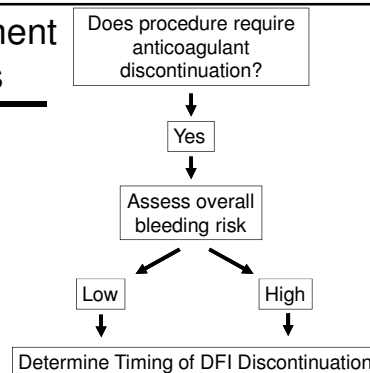
(B) SPINAL/EPIDURAL HEMATOMA: ELIQUIS use in patients undergoing spinal epidural anesthesia or spinal puncture increases the risk of epidural or spinal hematomas which may cause long-term or permanent paralysis. Monitor patients frequently for signs and symptoms of neurologic impairment and if observed, treat urgently. Consider the benefits and risks before neuraxial intervention in patients who are or who need to be anticoagulated. (5.3)

Neuraxial Anesthesia or spinal/epidural catheters*

	Catheter Retrieval	
	Stop Prior	Restart Post
Dabigatran	"Exact timing not known"	
Rivaroxaban	≥ 18 hrs	≥ 6 hrs
Apixaban	≥ 24 hrs	≥ 5 hrs

*If traumatic puncture, delay restarting for > 24 hours

Management Decisions



Direct Factor Inhibitors

	Dabigatran	Rivaroxaban	Apixaban
Target	Thrombin	Factor Xa	Factor Xa
T _{1/2} (hrs)	12-17	7-11	7-11
Elimination	Renal	Renal Hepatic	Renal Hepatic Enteric

Dabigatran: Pre-procedural Discontinuation

Cr Cl	T _{1/2} (hrs)	Minor Procedure	Major Procedure
≥ 50	15	24 hrs	≥ 48 hrs
30 - 50	18	≥ 48 hrs	≥ 96 hrs
< 30	27	≥ 48 hrs	≥ 96 hrs

*Both Cockcroft–Gault and MDRD tend to **over estimate** creatinine clearance!

Thromb Haem. 2010; 103:1116

Mayo Prescriber Guidelines: “Dabigatran”

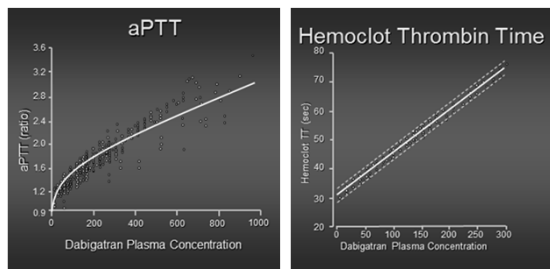
Very Conservative

- Peri-procedural (NVAf) thromboembolism rate ~1%.
- Rapid onset (1 hr) yet long half-life (15 hrs).
- No antidote.

Pre-procedural Recommendations (Dabigatran)

1. Define the surgical date.
2. Define the creatinine clearance*
 - If ≥ 50 , stop 5 days prior
 - If < 50 , stop 7 days prior.
3. If “**high**” bleeding risk, check pre-operative **thrombin time** or **aPTT** to ensure complete elimination.

Pre-procedural Dabigatran Assessment



Thromb Haemst 2010;103:1116

Rivaroxaban: Pre-procedural Discontinuation

Cr Cl	T _{1/2} (hrs)	Minor Procedure	Major Procedure
≥ 50	8	24 hrs	≥ 48 hrs
30 - 49	9	≥ 24 hrs	≥ 48 hrs
15 - 29	9-10	≥ 36 hrs	≥ 48 hrs

Blood 2012;120:2954
Chest 2012;141:e326S

*Respective package inserts

Apixaban: Pre-procedural Discontinuation

Cr Cl	T _{1/2} (hrs)	Minor Procedure	Major Procedure
≥ 50	7.5	24 hrs	≥ 48 hrs
30 - 49	17.5	≥ 24 hrs	≥ 48 hrs
15 - 29	>17.5	≥ 36 hrs	≥ 48 hrs

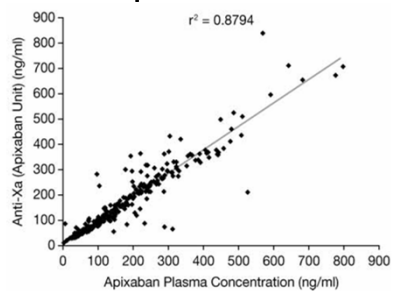
Blood 2012;120:2954
Chest 2012;141:e326S

*Respective package inserts

Mayo Prescriber Guidelines (Rivaroxaban and Apixaban)

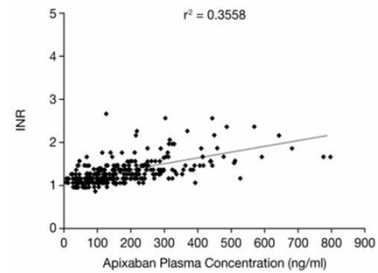
1. Define the surgical date.
2. Define the creatinine clearance*
 - If ≥ 50 , stop **3 days** prior
 - If 30-49, stop **5 days** prior.
 - If 15-30, stop **7 days** prior.
 - If < 15 , postpone surgery and reassess
3. For high bleeding risk procedures, assess preoperative **Anti-Xa** and **Prothrombin Time**.

Anti Xa Activity (Heparin Levels) and Apixaban levels



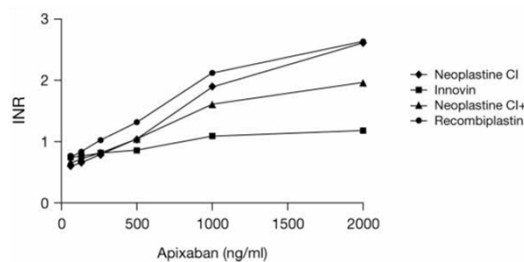
Thromb Haemost. 2010;104:1263-71

Relationship between INR and Plasma Apixaban levels



Thromb Haemost. 2010;104:1263-71

Reagent dependent Variation of INR values



Thromb Haemost. 2010;104:1263-71

Mayo Prescriber Guidelines: Post-procedure Management

1. Deep vein thrombosis prophylaxis.
2. Delay DFI re-initiation **≥ 48 hours** to ensure complete hemostasis.
3. If high risk of bleeding, consider warfarin for one month.

Slow onset (≥ 5 days for full effect)

Reversible with plasma and vitamin K.