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Leading Our Community to Outstanding Health

Clinical Conundrums with Anticoagulation: Periprocedural anticoagulation and restarting therapeutic anticoagulation after a bleed

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Disclosure Statement

Lucy Stanke declares no conflicts of interest, real or apparent, and no financial interests in any company, product, or service mentioned in this program, including grants, employment, stockholdings, and honoraria.

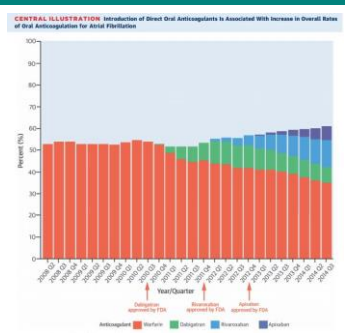
Objectives

- Assess a patient's periprocedural thromboembolism and bleed risk
- Recommend to hold or bridge oral anticoagulation with parenteral anticoagulation
- Create a plan to re-initiate anticoagulant therapy after reversal of an oral anticoagulant related bleed

Oral Anticoagulants (OACs)

- Vitamin K antagonist (VKA)
  - Warfarin (Coumadin®) 1954
- Direct thrombin inhibitor
  - Dabigatran (Pradaxa®) 2010
- Factor Xa inhibitors
  - Rivaroxaban (Xarelto®) 2011
  - Apixaban (Eliquis®) 2012
  - Edoxaban (Savaysa®) 2015
  - Betrixaban (Bevyxxa®) 2017

Oral Anticoagulant Use

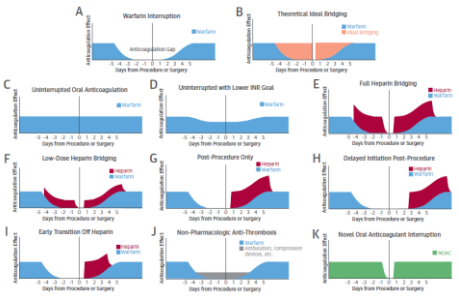


Marzec L et al. J Am Coll Cardiol 2017;69:2475-84

Periprocedural Anticoagulation Interruption

Bridging	• Use of short-acting anticoagulants (heparin or LMWH) for ~10-12 days during interruption of warfarin therapy when INR is not within a therapeutic range
Therapeutic Intent	• Aims to minimize risk for arterial thromboembolism in patients with mechanical heart valve or atrial fibrillation • Aims to minimize risk for recurrent thrombosis in patients with prior VTE

Bridging the Gap



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Rechenmacher and Fang. JACC 2015;12(66):1392-403

2017 ACC Expert Consensus Decision Pathway for Periprocedural Management of Anticoagulation in Patients With Nonvalvular Atrial Fibrillation

EXPERT CONSENSUS DECISION PATHWAY

A Report of the American College of Cardiology Clinical Expert Consensus Document Task Force

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Whether to interrupt
When to interrupt
Whether to bridge
How to bridge
How to restart oral anticoagulation

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Whether to Interrupt: Patient Thromboembolism Risk

	Indication for Anticoagulation		
Risk Group	**Mechanical Heart Valve**	**Atrial Fibrillation**	**VTE**
High	• Mitral valve prosthesis • Cage-ball or tilting disc aortic valve prosthesis • CVA/TIA <6 months prior	• CHADS2 score 5 or 6 • CVA/TIA <3 months prior • Rheumatic valvular heart disease	• VTE <3 months prior • Severe thrombophilia†
Moderate	• Bileaflet aortic valve and other risk factors‡	• CHADS2 score 3 or 4	• VTE 3-12 months prior • Nonsevere thrombophilia§ • Recurrent VTE • Active Cancer
Low	• Bileaflet aortic valve without other risk factors	• CHADS2 score 2 or less without prior CVA/TIA	• VTE >12 months prior without other risk factors

†Deficiency of protein C , protein S, or antithrombin; antiphospholipid antibodies; multiple abnormalities
‡CVA risk factors include: atrial fibrillation, prior CVA/TIA, hypertension, diabetes, congestive heart failure, age >75 years
§ Heterozygous factor V Leiden or prothrombin gene mutation

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Douketis JD et al. Chest. 2012;141:e326S-50S

Thromboembolism Risk: Atrial Fibrillation

Risk Factor	Score	CHA_2DS_2-VASc Total	1-yr risk of ischemic stroke(%)
Congestive heart failure / LV dysfunction*	1	0	0
Hypertension┼	1	1	1.3
Age ≥75 years	2	2	2.2
Diabetes mellitus	1	3	3.2
Stroke, TIA or thromboembolism	2	4	4.0
Vascular Disease∫	1	5	6.7
Age 65-74	1	6	9.8
Sex (female)	1	7	9.6
		8	9.7
Total		9	15.2

*Not clear whether history of or current heart failure; ┼History of hypertension not specifically defined; ∫prior MI, PAD or aortic plaque

CHADS-VASc = 0: no therapy rather than antithrombotic therapy; suggest aspirin
CHADS-VASc = 1: no antithrombotic therapy or oral antithrombotic therapy
CHADS-VASc ≥2 (men) or ≥3 (women): recommend oral antithrombotic therapy

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You J et al. CHEST 2012;141:e531S-e575S
Lane D et al. Circulation 2012;126:860-5
Medi C et al. Stroke 2010;41:2705-2713

Whether to Interrupt: Patient Bleed Risk

H	A	S	B	L	E	D
HTN†	Abnormal Renal Function‡ Abnormal liver function§	Prior Stroke	History of or risk for major bleeding	Labile INR‖	Elderly (>65 years)	Concomitant antiplatelet or NSAID Alcohol or drug use¶

†Systolic blood pressure >160 mmHg; ‡Chronic dialysis, renal transplantation, or serum creatinine >200 mcmmol/L; § Chronic hepatic disease or laboratory evidence of hepatic derangement (ex bilirubin >2x ULN, AST or ALT >3x ULN); ‖Time in the therapeutic range <60%; ¶ >8 uses/week

- Scores ≥3 predictive of bleeding events
- Predictive accuracy of 0.72 in original study
- Not endorsed by current guidelines

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Whether to Interrupt: Surgical Bleed Risk

Peri-Procedural Bleeding Risk		
Low	**Moderate**	**High**
Minor dental	SVT ablation	Cardiovascular/Thoracic surgery
Minor dermatologic	ICD implant	Intra-abdominal/Pelvic surgery
Ophthalmologic	Endoscopy with biopsy	Major orthopedic surgery
Endoscopy without biopsy	Prostate biopsy	Neurosurgery
	Cardiac catheterization via radial artery	Cardiac catheterization via femoral artery

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American College of Cardiology. Common procedures and associated procedural bleed risk. http://jaccjacc.acc.org/Clinical_Document/PMAC_Online_Appendix.pdf

Whether to Interrupt: Anticoagulant Specific

Circulation

ORIGINAL RESEARCH ARTICLE

Periprocedural Outcomes of Direct Oral Anticoagulants Versus Warfarin in Nonvalvular Atrial Fibrillation

Meta-Analysis of Phase III Trials

- **4 Phase III randomized controlled trials**
  - RE-LY
  - ROCKET AF
  - ARISTOTLE
  - ENGAGE_AF
- **Primary outcomes (30-day pooled):**
  - Stroke/systemic embolism (SSE)
  - Major bleed (MB)
  - Death (all cause)
- **Results**
  - 24024 procedures from 19353 patients

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Nazha B et al. Circulation. 2018;138:1402-11

Pooled incidence rates of SSE, MB, and Death under an uninterrupted periprocedural anticoagulation strategy

	Pooled Risk, % (95% CI), Events/Patients at risk		Relative Risk
	DOAC	Warfarin	
Stroke / Systemic Embolism	0.6 (0.4-0.8) 29/4519	1.1 (0.7-1.4) 31/2971	0.7 (0.41-1.18)
Major bleed	2 (1.6-2.4) 97/4540	3.3 (2.7-4) 98/2985	0.62 (0.47-0.82)
Death	1.4 (1-1.7) 62/4457	1.8 (1.3-2.3) 54/2971	0.77 (0.53-1.12)

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Pooled incidence rates of SSE, MB, and Death under an interrupted periprocedural anticoagulation strategy

	Pooled Risk, % (95% CI), Events/Patients at risk		Relative Risk
	DOAC	Warfarin	
Stroke / Systemic Embolism	0.4 (0.3-0.6) 41/9260	0.5 (0.3-0.6) 31/7168	0.95 (0.59-1.55)
Major Bleed	2.1 (1.8-2.4) 218/9175	2 (1.7-2.3) 136/7078	1.05 (0.85-1.3)
Death	0.7 (0.5-0.8) 69/9260	0.6 (0.4-0.8) 38/7168	1.24 (0.76-2.04)

Timing of Interruption
- *Same day*: Lower rate MB between DOAC vs warfarin (RR, 0.45; 95% CI, 0.28-0.71)
- *1 day before*: lower rate MB between DOAC vs warfarin (RR, 0.43; 95% CI, 0.23-0.82)
- *2 days before*: no differences MB between DOAC vs warfarin (RR, 0.91; 95% CI, 0.46-1.8)
- *≥3 days before*: Higher rate MB between DOAC vs warfarin (RR, 1.39; 95% CI, 1.05-1.85)

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Nazha B et al. Circulation. 2018;138:1402-11

Whether to interrupt

	BRUISE CONTROL
	Uninterrupted warfarin vs heparin bridge
Inclusion	Nonemergent pacemaker or ICD surgery At least 5% annual stroke or SE risk
Methods	Warfarin discontinued 5 days pre-procedure and heparin started 3 days pre-procedure. Heparin restarted 24 hours post-procedure and continued until INR therapeutic.
	Primary Outcome
Clinically Significant Hematoma	
Prolonging hospitalization	
Anticoagulation Interruption	
Requiring evacuation	

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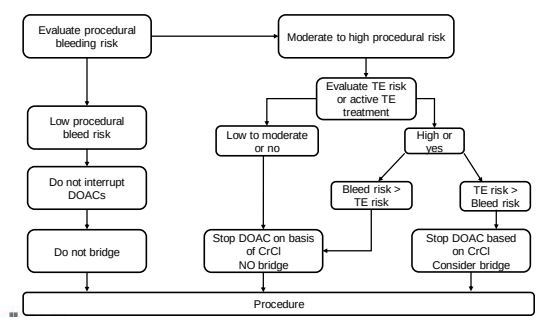
Birnie D et al. N Engl J Med 2013; 368:2084-93
Birnie D et al. Eur Heart J 2018;39:3973-9

Whether to Interrupt: DOACs



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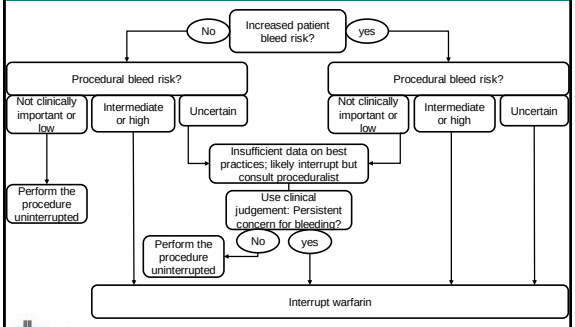
Raval A et al. Circulation. 2017;135:e604-33

Whether to Interrupt: Warfarin



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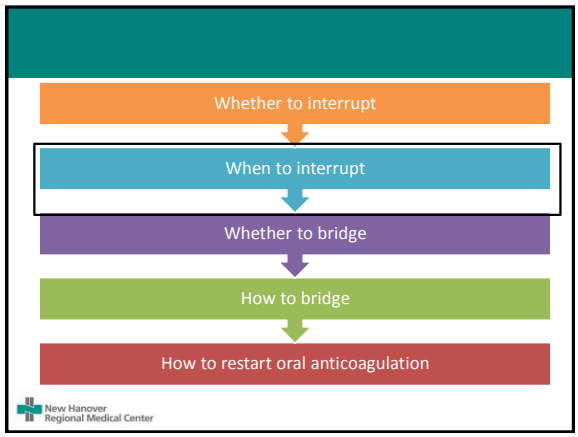
Doherty et al. JACC. 2017; DOI: 10.1016/j.jacc.2016.11.024



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When to Interrupt: DOACs

	Rivaroxaban	Apixaban	Edoxaban	Dabigatran
Protein binding	92%-95%	~87%	55%	35%
Half life	**5-9 h** **Elderly 11-13 h**	**~12 h (8-15 h)**	**10-14 h**	**12-17 h**
Metabolism	Hepatic: oxidation by CYP3A4/5, CYP2J2 Hydrolysis (51%)	Hepatic: CYP3A4/5 (25%)	Minimal CYP3A4 hydrolysis, conjugation, oxidation	Esterase-catalyzed hydrolysis
	No active circulating metabolites	No active circulating metabolites	Active metabolite (M-4, <10% of parent)	
	P-gp and ABCG2 (BCPR) substrate	CYP3A4, P-gp, BCRP substrate	P-gp substrate	Not a substrate, inhibitor or inducer of CYP450 enzymes
Elimination	**Renal (66%):** 36% active, 30% inactive	**Renal (27%)**	**Renal (~50%):** primarily unchanged	**Renal**
	Feces (28%): 7% active, 21% inactive	Biliary and direct intestinal excretion	Metabolism and biliary / intestinal excretion	Feces

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Raval A et al. Circulation. 2017;135:ahead of print

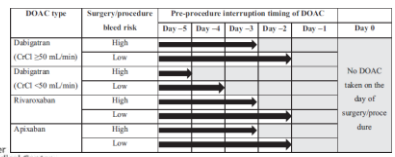
Perioperative Anticoagulant Use for Surgery Evaluation (PAUSE) Study: A Perioperative Management Plan for Patients with Atrial Fibrillation Who Are Receiving a Direct Oral Anticoagulant

Hypothesis

- A standardized perioperative management strategy based on DOAC-specific interruption and resumption intervals without heparin bridging is safe

Methods

- Inclusion criteria
  - Patients taking apixaban, dabigatran or rivaroxaban for atrial fibrillation and requiring interruption for elective surgery/procedure
- Protocol
  - No heparin bridge



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Douketis J et al. Blood 2018;132:LBA-5

The PAUSE Trial

Results

- 23 sites in Canada, US and Europe
- Mean age 72.5 years
- 33.5% high bleeding surgery/procedure

	Apixaban N=1257	Dabigatran N=668	Rivaroxaban N=1082
30-day post-op major bleed	1.35% (95% CI 0-2)	0.9% (95% CI 0-1.33)	1.85% (95% CI 0-2.65)
Arterial thromboembolism	0.16% (95% CI 0-0.48)	0.6% (95% CI 0-1.33)	0.37% (95% CI 0-0.82)
Preoperative DOAC level <50 ng/mL	90.5%	95.1%	96.8%

- A standardized DOAC-specific perioperative protocol was safe and associated with low rate of perioperative MB and ATE
- High percentage of patients had low residual DOAC level at time of procedure

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Douketis J et al. Blood 2018;132:LBA-5

When to Interrupt: DOAC

Low bleed risk				High bleed risk			
Dabigatran		Fxa Inhibitor		Dabigatran		Fxa inhibitor	
CrCl	**Discontinue**	**CrCl**	**Discontinue**	**CrCl**	**Discontinue**	**CrCl**	**Discontinue**
<15	No data; consider dTT and/or ≥96 hrs	<15	No data; consider anti Xa level and/or ≥48 hrs	<15	No data; consider dTT	<30	No data; consider anti Xa level an/or ≥72 hrs
15-29	≥72 hrs	15-29	≥36 hrs	15-29	≥120 hrs	≥30	≥48 hrs
30-49	≥48 hrs	≥30	≥24 hrs	30-49	≥96 hrs		
50-79	≥36 hrs			50-79	≥72 hrs		
≥80	≥24 hrs			≥80	≥48 hrs		

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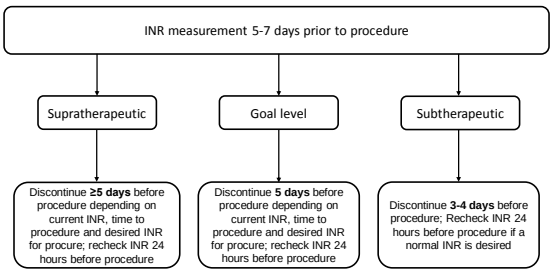
Doherty et al. JACC. 2017; DOI: 10.1016/j.jacc.2016.11.024

When to interrupt: Warfarin



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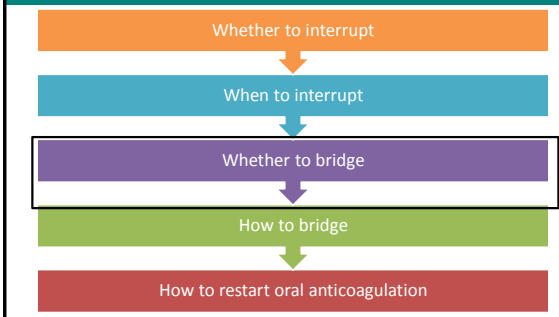

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The Bridge Trial

Hypothesis

- No bridging will be non-inferior to bridging with LMWH on the rate of arterial thromboembolism
- No bridging will be superior to bridging with LMWH on the rate of major bleeding

Methods

- Prospective, randomized, double blind, placebo controlled, multicenter trial in the US and Canada
- Patients on warfarin with elective procedure requiring anticoagulation interruption randomized to dalteparin 100 units/kg SC BID or placebo

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Douketis et al. N Engl J Med 2015;373:823-33

The Bridge Trial - methods

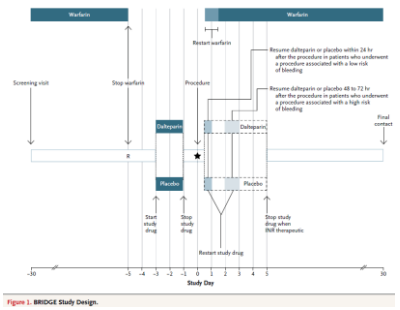

Figure 1. BRIDGE Study Design.

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Douketis et al. N Engl J Med 2015;373:823-33

The Bridge Trial – Results & Conclusions

	No Bridging N=918	Bridging N=895	P-value
Primary Efficacy Endpoint: arterial thromboembolism	4 (0.4)	3 (0.3)	0.01*, 0.73
• Stroke	2 (0.2)	3 (0.3)	-
• TIA	2 (0.2)	0	-
• Systemic embolism	0	0	-
Myocardial infarction	7 (0.8)	14 (1.6)	0.1
Deep Vein Thrombosis	0	1 (0.1)	0.25
Pulmonary embolism	0	1 (0.1)	0.25
Primary Safety Endpoint: Major bleeding	12.1 (1.3)	29 (3.2)	0.005
Fatal bleeding	0	0	-
Minor bleeding	110 (12)	187 (20.9)	<0.001
Death	5 (0.5)	4 (0.4)	0.88

- No bridging is noninferior to bridging for preventing ATE
- Bridging is associated with significantly more major bleeds than no bridging

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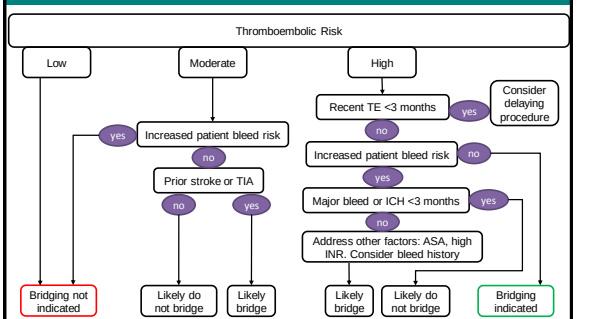
Douketis et al. N Engl J Med 2015;373:823-33

Whether to Bridge: Warfarin



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Doherty et al. JACC. 2017; DOI: 10.1016/j.jacc.2016.11.024

Whether to Bridge: DOAC

Periprocedural Outcomes of Direct Oral Anticoagulants vs Warfarin in NVAF (ARISTOTLE and ENGAGE-AF)	**Heparin bridging** No differences in SSE between DOAC and warfarin (RR, 1.2; 95% CI, 0.28-5.75) No differences in rate of MB between DOAC and warfarin (RR, 0.93; 95% CI, 0.61-1.4)
	Non bridging No differences in SSE between DOAC and warfarin (0.3% in both groups) No differences in rate of MB between DOAC and warfarin (1.6% vs 1.2%)
	3 fold higher rate of MB in DOAC and 5 fold higher rate of MB in Warfarin groups with heparin bridging

- Recommended against bridging DOACs for brief interruptions
- Consider therapeutic bridge if active thromboembolism treatment and procedure cannot be rescheduled

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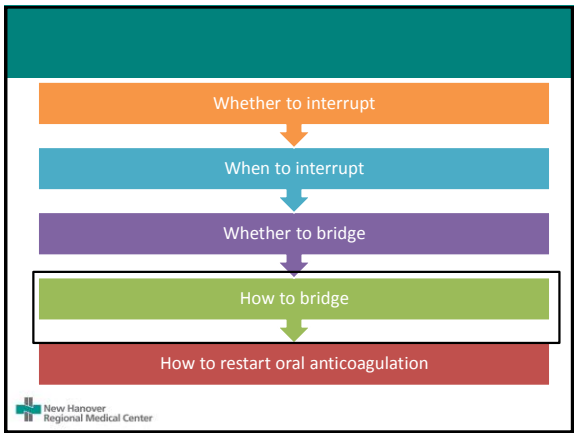
Nazha B et al. Circulation. 2018;138:1402-11



How to Bridge: Therapeutic Dosing

Enoxaparin

- CrCl ≥30 mL/min: 1 mg/kg BID or 1.5 mg/kg daily
- CrCl <30 mL/min: 1 mg/kg daily or consider UFH

Heparin

- IV: per hospital protocol to target aPTT 1.5-2x control
- SubQ: 333 units/kg followed by 250 units/kg q12 hours

Heparin allergy or recent HITT

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How to Bridge: Timing

UFH		LMWH	
Start UFH when the INR is <2 or after omitting 2-3 doses of warfarin is the INR is not measured.	Discontinue >4 hours prior to the procedure and if the aPTT is the normal range.	Start LMWH when the INR is <2 or after omitting 2-3 doses of the OAC if the INR is not measured.	Discontinue >12-24 hours prior to the procedure based on renal function and dosing interval.

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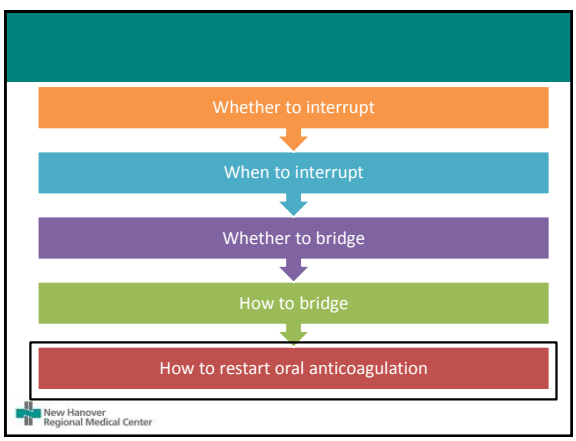
Doherty et al. JACC. 2017; DOI: 10.1016/j.jacc.2016.11.024



Restarting Anticoagulation: DOAC

Complete hemostasis achieved, with no bleeding complications, no high bleed risk features of the patient and absence of a potentially catastrophic bleed location (intracranial, intraspinal)

- no → Use clinical judgement
- yes → Can the patient tolerate oral mediations
  - no
    - High postprocedural bleed risk → Consider parenteral AC until oral medications are possible. Start parenteral agent **48-72 hrs** post-procedure. Convert to DOAC when tolerating oral medications
    - Low postprocedural bleed risk → Consider parenteral AC until oral medications are possible. Start parenteral agent **24 hrs** post-procedure. Convert to DOAC when tolerating oral medications
  - yes
    - High postprocedural bleed risk → Reasonable to reinitiate DOAC **48-72 hrs** after the procedure
    - Low postprocedural bleed risk → Reasonable to reinitiate DOAC within **24 hrs** of procedure

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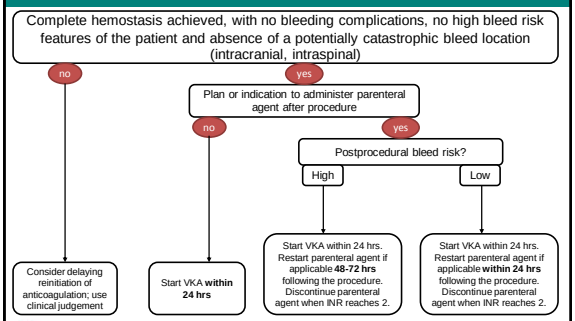
Doherty et al. JACC. 2017; DOI: 10.1016/j.jacc.2016.11.024

Restarting Anticoagulation: Warfarin



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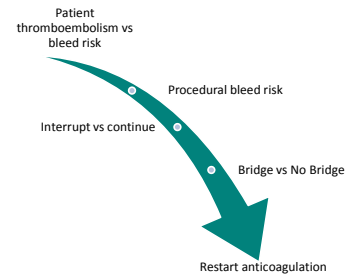
Doherty et al. JACC. 2017; DOI: 10.1016/j.jacc.2016.11.024

Bridging it all together



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Restarting Anticoagulation After Reversal of Oral Anticoagulation

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Bleeding Events with Oral Anticoagulants

- Major bleeding rates 0.6-3.6% with DOACs and warfarin in atrial fibrillation and venous thromboembolisms
- "Real world" data taken from claims assessment and global registries
- At least 8 current global registries evaluating warfarin and DOACs
- "Major bleeding complications with oral anticoagulation in non-valvular atrial fibrillation"
  - Total of 2418 of 54321 patients (4.5%) experienced major bleeding event

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Hellenbart E et al. Vascular Health and Risk Management 2017;13:325-42

Anticoagulation after Bleeds

- Intracranial hemorrhage (ICH)
  - Decreased ischemic stroke/systemic embolism at 1 year
  - Decreased all-cause mortality at 1 year
  - Non-significant risk of re-bleed
- Gastrointestinal bleed (GIB)
  - Decreased thromboembolism rate at 30 and 90 days
  - Decreased overall mortality at 30 and 90 days
  - No study found significant increased risk of recurrent GIB

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Becattini C. Vascular pharmacology 2016;84:15-24
Nielsen P. JAMA Intern Med. 2017;177:563-70
Nielsen P. Circulation 2015. 10.1161/CIRCULATIONAHA.115.015735
Staerk L. BMJ 2015;351:h5876
Qureshi W. Am J Cardiol 2014;113:662-68
Sengupta N. Am J Gastroenterol 2015;110:328-35

Guideline Recommendations for Anticoagulants after ICH

Risk of ICH recurrence vs thrombosis risk	• Risk factors = 1) lobar ICH location, 2) Older age, 3) Presence and number of microbleeds on MRI, 4) Ongoing anticoagulation, 5) Presence of apoliporotein E
Timing	• No randomized trials • Avoiding anticoagulation for 4 weeks might decrease risk of re-bleed
Anticoagulant choice	• Avoiding warfarin after warfarin-associated spontaneous lobar ICH • Uncertain if dabigatran, rivaroxaban or apixaban decrease risk of recurrence
Focus on lifestyle modifications to prevent re-bleed	

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Hemphill J et al. Stroke 2015;46:online

Guideline Recommendations for Anticoagulants after GIB

- American College of Gastroenterology only addresses antiplatelet therapy after lower GIB and peptic ulcer related bleeds
- Recent review in *Annals of Pharmacotherapy*
  - 9 studies identified
  - Lower rate of thromboembolism but non-significant increase in GIB after resuming anticoagulation
  - Timing: 7-15 days after GIB may balance bleeding and thrombotic risks
  - No recommendation on which anticoagulant to use
  - Limitations
    - Optimal timing of restarting still uncertain
    - Few studies evaluating restarting DOACs after GIB
    - Comparisons of GIB risk for DOACs do not represent patients who already experienced GIB

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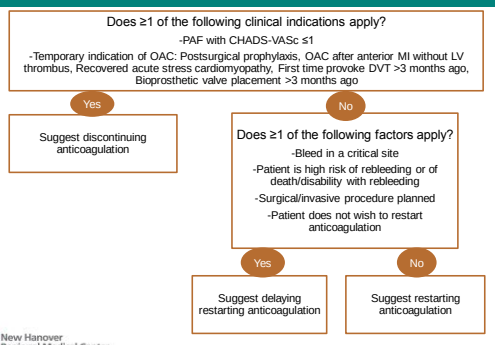
Kido K et al. Annals of Pharmacotherapy 2017;11:1000-7
Strate L et al. Am J gastroenterol 2016; published online
Laine L et al. Am J Gastroenterol 2012;107:345-60

Consideration for Restarting Anticoagulation



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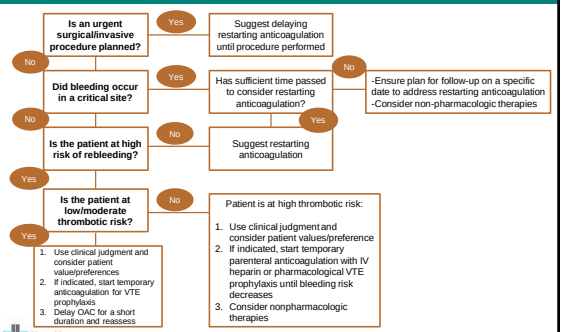
Tomaselli et al. JACC. 2017;70:3042-67

Factors to Consider in Delaying Restart of Anticoagulation



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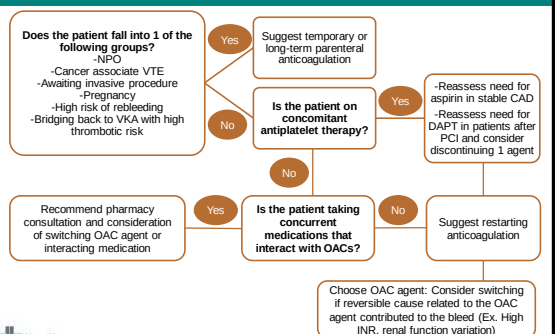
Tomaselli et al. JACC. 2017;70:3042-67

Restarting Anticoagulation



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Tomaselli et al. JACC. 2017;70:3042-67

Minimize Future Bleeds

- Appropriate doses
  - Indication, age, weight, and renal function
- Minimize drug interactions
  - SSRIs, NSAIDs, anti-platelets
  - Fish oil, garlic, gingko
- Proton pump inhibitors after upper GI bleeds
- Blood pressure control after ICH
- Avoid excessive alcohol
- Assess fall risk
- Educate patients on signs and symptoms of bleeding

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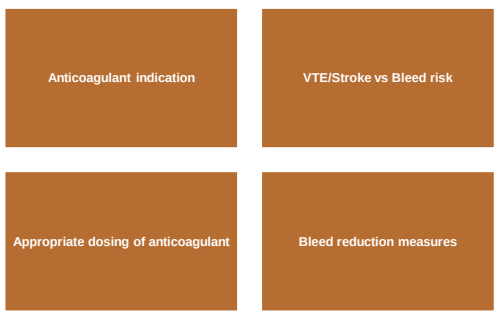
Restart Recap



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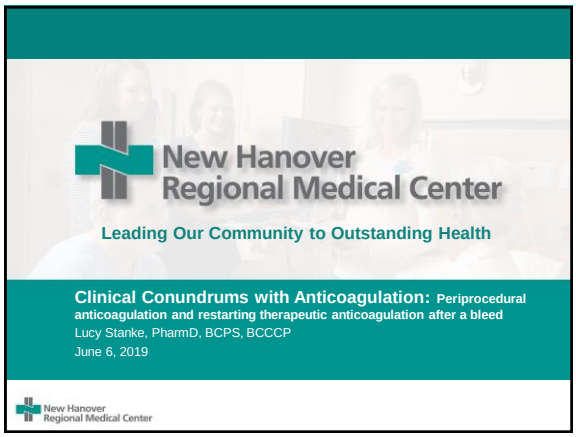
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Leading Our Community to Outstanding Health
Clinical Conundrums with Anticoagulation: Periprocedural anticoagulation and restarting therapeutic anticoagulation after a bleed
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June 6, 2019
New Hanover
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