



# Managing Anticoagulation in the Hospitalized Patient

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# Conflicts of Interest



- I have no actual or potential conflicts of interest in relation to this program or presentation to disclose.

# Objectives

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- Summarize management of bleeding on DOAC
- Review available reversal agents
- Outline perioperative management of DOACs
- Antithrombotic therapy for AFIB with stable CAD

## Case



75 yo man with HTN, remote CAD s/p PCI/DES in 2015, NVAF on metoprolol, rivaroxaban 20 mg QD and ASA 81 mg daily presents with syncope. He was in his usual state of health until the morning of admission when he suddenly fainted on his way from the kitchen to the bathroom. He recalls feeling urgency to move his bowels then woke up on the floor. He was able to get himself to the bathroom where he had black tarry stools. His wife called 911 and he is brought to the ED.

1. This is a fascinating case. I have never heard of anything like this.
2. Do we have to talk about melena so early in the morning?
3. Exactly how old is Bob?

## Case



In the ED his BP is 110/70, HR 110, O<sub>2</sub> sat 99%

On exam his lungs are clear, heart is tachy irregular rhythm without murmur; abdomen is soft and non tender, he has no peripheral edema, rectal exam show melena

His HGB/HCT is 7.5 g/dL/24 %. his baseline is 12g/dL/36 %.

Creatinine is 1.3 mg/dL, baseline 0.8 mg/dL, LFTS are normal

INR 1.9 PT 18.7

# Guidance on DOAC Bleeding Management/Reversal

EXPERT CONSENSUS DECISION PATHWAY

## 2017 ACC Expert Consensus Decision ing



Received: 17 February 2019 | Revised: 22 March 2019 | Accepted: 25 March 2019  
DOI: 10.1002/ajh.25475

**CRITICAL REVIEW**



### Reversal of direct oral anticoagulants: Guidance from the Anticoagulation Forum

Adam Cuker<sup>1</sup> | Allison Burnett<sup>2</sup>  
Jack Ansell<sup>5</sup> | Elizabeth M. Van C...

CLINICAL GUIDELINES

blood advances

American Society of Hematology 2018 guidelines for management of  
venous thromboembolism: optimal management of  
anticoagulation therapy

### Antithrombotic Therapy for Atrial Fibrillation

CHEST Guideline and Expert Panel Report



Nadine Shehab,<sup>7</sup> Juliet Mock,<sup>8</sup> Tarra Myers,<sup>9</sup>  
John J. Riva,<sup>2,14</sup> Yuan Zhang,<sup>2</sup> and

Gregory Y. H. Lip, MD; Amitava Banerjee, MD, DPhil; Giuseppe Boriani, MD, PhD; Chern en Chiang, MD, PhD;  
Ramiz Fargo, MD, FCCP; Ben Freedman, MD, PhD; Deirdre A. Lane, PhD; Christian T. Ruff, MD, MPH;  
Mintu Turakhia, MD; David Werring, PhD; Sheena Patel, MPH; and Lisa Moores, MD, FCCP

# The Joint Commission Has Revised Anticoagulation-Related National Patient Safety Goals-JULY 2019

- 8 new or revised Elements of Performance (EP) include DOACs and are applicable to:
  - Acute Care Hospitals
  - Critical Access Hospitals
  - Nursing Care Centers
  - Medical Centers (accredited under Ambulatory Health Care Programs)

# Why did JC Update the NPSGs for Anticoagulation?



- DOACs already among top 10 drugs contributing to ER visits and hospitalization<sup>1</sup>
- Evidence of ADEs and suboptimal quality across care settings<sup>2,3</sup>
- Under-utilization in AF population persists<sup>4</sup>
- “Off-label” dosing of DOACs is common<sup>5,6,7,8</sup>
- 1 in 8 anticoagulated patients undergo invasive procedures requiring interruption each year<sup>9</sup>
- Long-term patient adherence inadequate<sup>10</sup>



# NPSG.03.05.01:



## New or Amended Elements of Performance:\*

- EP-1: Initiation and maintenance of anticoagulants
- EP-2: Reversal and bleeding events
- EP-3: Perioperative management
- EP-4: Laboratory monitoring to monitor and adjust
- EP-5: Identify, respond to, and report ADEs
- EP-6: Patient and family education

\*Including DOACs

**EXPERT CONSENSUS DECISION PATHWAY**

# 2017 ACC Expert Consensus Decision Pathway on Management of Bleeding in Patients on Oral Anticoagulants

A Report of the American College of Cardiology Task Force on  
Expert Consensus Decision Pathways

Assess severity of bleed

DOES  $\geq 1$  OF THE FOLLOWING FACTORS APPLY?

- Bleeding at a critical site (See Table 1)
- Hemodynamic instability
- Clinically overt bleeding with hemoglobin decrease  $\geq 2$  g/dL or administration of  $\geq 2$  units RBCs

YES

NO

Is the bleed at a critical site or life threatening?

Bleed is considered major



Bleed is considered non-major

### • Critical Site Bleeds

- Intracranial hemorrhage
- Other CNS bleeding
- Pericardial tamponade
- Airway (including posterior epistaxis)
- Hemothorax, intra-abdominal bleeding, retroperitoneal hematoma
- Extremity bleeds

Provide supportive care

## Case



In the ED his BP is 110/70, HR 110, O2 sat 99%

On exam his lungs are clear, heart is tachy irregular rhythm without murmur; abdomen is soft and non tender, he has no peripheral edema, rectal exam show melena

His HGB/HCT is 7.5 g/dL/24 %. his baseline is 12g/dL/36 %.

Creatinine is 1.3 mg/dL, baseline 0.8 mg/dL. LETS are normal

INR 1.9 PT 18.7

Major bleeding if  $\geq 1$  of factors apply

- Bleeding in critical site
- Hemodynamic instability
- Overt bleeding with HGB drop  $\geq 2$ g/dL or admin  $\geq 2$  u PRBCs

# Critical Steps in Anticoagulant Related Bleeding



- Stop oral anticoagulation
- If on a VKA, consider 5-10 mg IV Vitamin K
- Provide local therapy/manual compression
- Provide supportive care (e.g. transfusion, antifibrinolytics)
- Consider holding antiplatelet agents-manage contributors to PLTS (uremia/liver disease)
- Consider surgical/procedural management of bleeding sites

## Case



IN ED his BP drifts to 100/60. He receives 3 u lactated ringers and 2 u PRBCs. He continues to have melena. GI is called for urgent evaluation and he is transferred to the ICU. His last dose of rivaroxaban was at 6 am this morning with breakfast. It is now 11 am. Should he receive a reversal agent?

- 1) Yes
- 2) No
- 3) Do we have one of those?

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**CRITICAL REVIEW**



## Reversal of direct oral anticoagulants: Guidance from the Anticoagulation Forum

Adam Cuker<sup>1</sup> | Allison Burnett<sup>2</sup> | Darren Trill  
Jack Ansell<sup>5</sup> | Elizabeth M. Van Cott<sup>6</sup> | Diane W



Cuker A, et al. Am J Hematol 20

### DOAC Reversal Guidance Statements 1,2,3: IF, WHEN, and WHAT to give for Bleeding

**TABLE 1** Prioritized questions and guidance statements on DOAC reversal

Question	Guidance statement
(1) When should reversal agents be used to manage DOAC-associated bleeding?	In all patients with DOAC-associated major bleeding, we suggest treatment with supportive measures and suggest administration of a reversal agent only if bleeding is life-threatening, into a critical organ, or if the patient is uncontrolled with maximal supportive measures and there is demonstration or reasonable expectation that the patient has clinically relevant plasma DOAC levels.
(2) How should reversal agents be used to manage dabigatran-associated bleeding?	In patients with dabigatran-associated major bleeding in whom a reversal agent is warranted, we suggest treatment with idarucizumab 5 g IV. If idarucizumab is not available, we suggest treatment with

# Bleeding on DOAC



- Is drug still present?
  - *What is the  $t_{1/2}$  of the agent*
  - *When was last dose of drug?*
  - *What is patient's renal function?*
  - *Will laboratory data help?*



# Assessing Residual DOAC Effect



Property	Dabigatran <sup>1</sup>	Rivaroxaban <sup>2</sup>	Apixaban <sup>3</sup>	Edoxaban <sup>4</sup>
Est t $\frac{1}{2}$ hrs				
Crcl > 80	14	8	7-8	8-9
CrCl 30-79	17-19	9	17-18	9-10
CrCl 15-30	28	10		17
Renal clearance of absorbed dose	80%	35%	27%	50%
Approximate anticoagulation resolution <sup>a</sup> (nml renal fxn)	Day 2.5–3.5 after last dose	Day 1.5–3.5 after last dose	Day 1–2 after last dose	Day 1.3–2 after last dose

<sup>a</sup>Estimated as the time it takes for 5 half-lives to elapse since the last dose

# When specialized assays are available

DRUG	CLINICAL OBJECTIVE		
	Exclude Clinically Relevant Drug Level		Measure Therapeutic Drug Levels
	<i>Test</i>	<i>Interpretation</i>	<i>Suggested Test</i>
Dabigatran	Dilute Thrombin Time	Normal probably excludes clinically relevant levels	Dilute Thrombin Time
	Ecarin Clotting Time		Ecarin Clotting Time
	Ecarin Chromogenic Assay		Ecarin Chromogenic Assay
Apixaban, edoxaban, and rivaroxaban	Anti-Xa	Absent chromogenic anti-Xa assay activity probably excludes clinically relevant levels	Anti-Xa (with calibrated reagents)

# When specialized assays not available

DRUG	CLINICAL OBJECTIVE		
	Exclude Clinically Relevant Drug Level		Suggests Clinically Relevant Drug Level Therapeutic Drug Levels
	<i>Test</i>	<i>Interpretation</i>	<i>Suggested Test</i>
Dabigatran	Normal aPTT	Normal does NOT exclude clinically relevant levels	Elevated a PTT
Apixaban, edoxaban, and rivaroxaban	Anti-Xa (LMWH)	Absent chromogenic anti-Xa assay activity probably excludes clinically relevant levels	Elevated Anti-Xa (with calibrated reagents)
	PT/INR	Normal PT/INR does NOT exclude clinically relevant levels	Elevated PT/INR



# Assessing Residual Effect of DOAC in Lab

## No clinically relevant drug if:

- On dabigatran and dilute thrombin time normal
- On anti Xa and drug specific anti Xa level (riva, apix, betrix or edox) negative
- Negative LMWH anti-Xa level and on riva, apix, edox
- Normal PT, INR, PTT DOES NOT exclude residual apixaban, edoxaban, rivaroxaban

## Residual DOAC Present if:

- PTT elevated-dabigatran
- INR/PT elevated-apix, riva, edox, betrix

INITIAL LABS  
PT/INR  
PTT  
CBC  
Specialized assays  
Cr/LFTs

# Dosing of Reversal Agents for DOAC-Induced Major Bleeding

	Idarucizumab	Andexanet Alfa	APCC	4-factor PCC
Dabigatran-induced bleeding	5 g IV	n/a	50 units/kg	n/a
Rivaroxaban- or Apixaban-induced bleeding	n/a	See table	n/a	2000 units
Edoxaban- or Betrixaban-induced bleeding*	n/a	High-dose		2000 units

**TABLE 2** Dosing and administration of andexanet alfa according to the United States Food and Drug Administration package insert

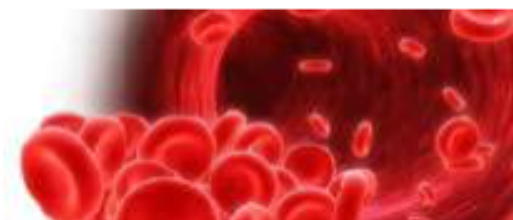
Drug	Last Dose	Time from last dose	
		<8 h or unknown	≥8 h
Rivaroxaban	≤10 mg	Low dose <sup>a</sup>	Low dose <sup>a</sup>
	>10 mg or unknown	High dose <sup>b</sup>	
Apixaban	≤5 mg	Low dose <sup>a</sup>	
	>5 mg or unknown	High dose <sup>b</sup>	

<sup>a</sup>Initial 400 mg IV bolus at target rate of 30 mg/min followed by continuous infusion at 4 mg/min for up to 120 min.

<sup>b</sup>Initial 800 mg IV bolus at target rate of 30 mg/min followed by continuous infusion at 8 mg/min for up to 120 min.



Anticoagulation  
FORUM



# DOAC Reversal Guidance Statements 4,5,6: IF, WHEN, and WHAT to give for Urgent Procedures

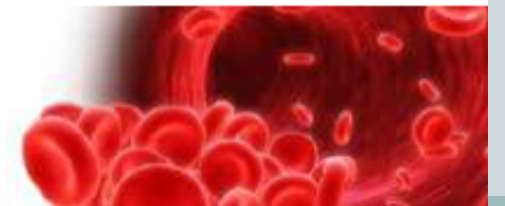
(4) When should reversal agents be used before an invasive procedure?

In DOAC-treated patients who require an invasive procedure, we suggest that a reversal agent be administered only if the procedure cannot be safely performed while the patient is anticoagulated, cannot be delayed, and there is demonstration or reasonable expectation that the patient has clinically relevant plasma DOAC levels.

(5) How should reversal agents be used in dabigatran-treated patients who require an urgent procedure and in whom a reversal agent is warranted, up to and including the use of idarucizumab?

In dabigatran-treated patients who require an urgent procedure and in whom a reversal agent is warranted, up to and including the use of idarucizumab, we suggest that idarucizumab be administered only if the procedure cannot be safely performed while the patient is anticoagulated, cannot be delayed, and there is demonstration or reasonable expectation that the patient has clinically relevant plasma DOAC levels.

- ONLY IF PROCEDURE CANNOT BE DONE ON AC
- CANNOT BE DELAYED
- DEMONSTRATION OF CLINICALLY RELEVANT LEVELS OF DOAC





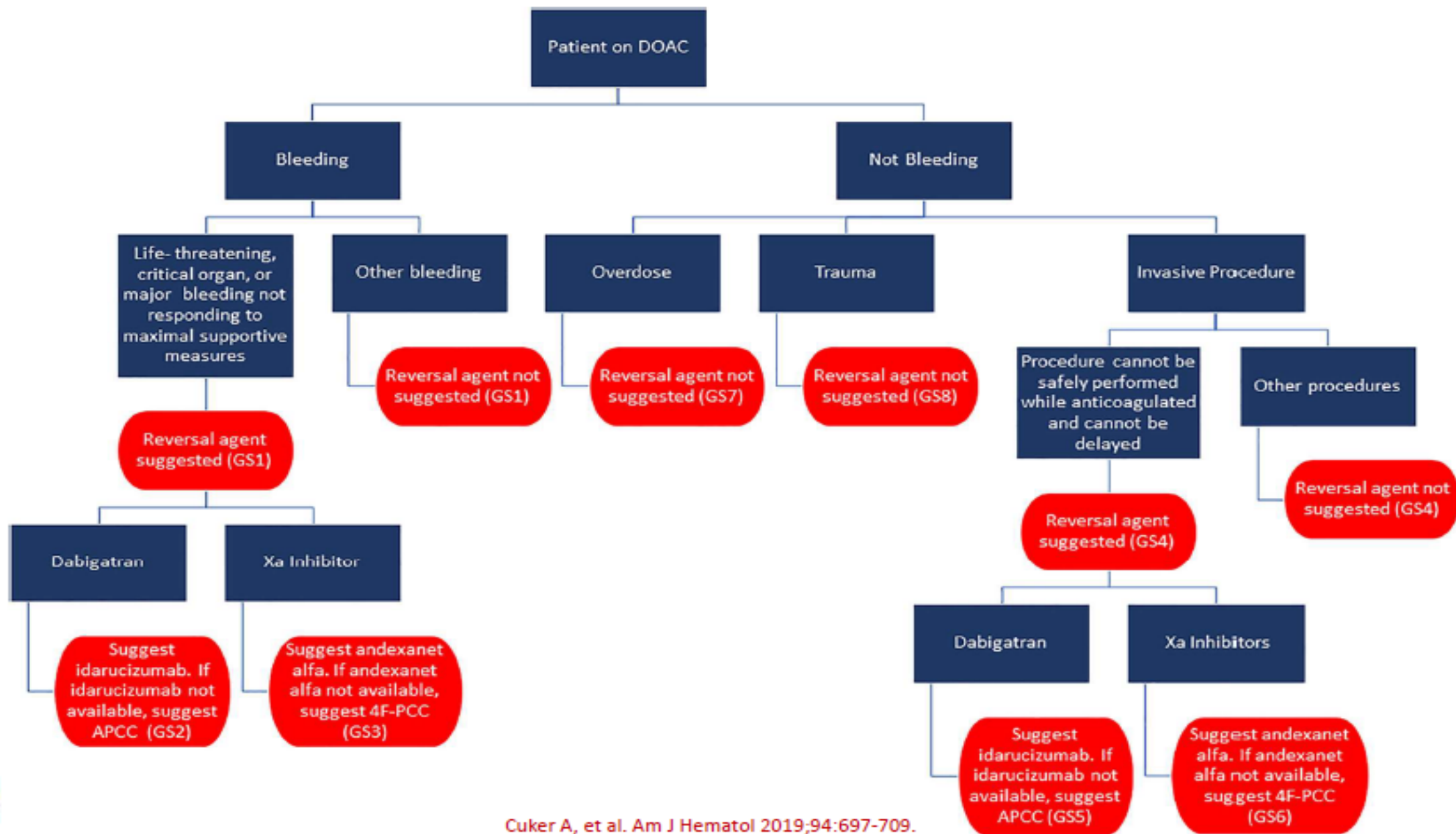
CLINICAL GUIDELINES

 blood advances

## American Society of Hematology 2018 guidelines for management of venous thromboembolism: optimal management of anticoagulation therapy

Daniel M. Witt,<sup>1</sup> Robby Nieuwlaat,<sup>2</sup> Nathan P. Clark,<sup>3</sup> Jack Ansell,<sup>4</sup> Anne Holbrook,<sup>5</sup> Jane Skov,<sup>6</sup> Nadine Shehab,<sup>7</sup> Juliet Mock,<sup>8</sup> Tarra Myers,<sup>9</sup> Francesco Dentali,<sup>10</sup> Mark A. Crowther,<sup>11</sup> Arnav Agarwal,<sup>2,12</sup> Meha Bhatt,<sup>2</sup> Rasha Khatib,<sup>13</sup> John J. Riva,<sup>2,14</sup> Yuan Zhang,<sup>2</sup> and Gordon Guyatt<sup>2</sup>

For life threatening bleeding during oral direct Xa inhibition ASH suggests 4 factor PCC OR andexanet alpha plus cessation of anticoagulant OR cessation alone. no preference for either reversal agent





# Andexanet (ANDEXXA)

- AKA: Coagulation Factor Xa [recombinant], inactivated zhzo
- Recombinant, modified Factor Xa (FXa) decoy molecule that binds and inactivates FXa inhibitors
- Received accelerated FDA approval for the reversal of **apixaban** and **rivaroxaban** in patients with life-threatening or uncontrolled **bleeding**
- High cost: \$27,500 - \$49,500 per patient\*



WAC=wholesale acquisition cost

# Andexanet: BOXED WARNING



## **Andexanet is associated with serious and life-threatening adverse events including:**

- **Arterial and venous thromboembolic events**
- **Ischemic events, including MI, ischemic stroke**
- **Cardiac arrest**
- **Sudden death**
- Monitor patients for s/sx
- Resume anticoagulant therapy as soon as appropriate
- Safety not evaluated in patients who received other reversal agents or with recent thromboembolic event
- Anti-FXa activity returns to placebo levels ~2 hrs after stopping andexanet

# What about 4F-PCC (off-label)?



- Most extensively studied agent for FXa inhibitor reversal
- Evidence limited to:
  - Human volunteer studies– correction of laboratory parameters (not entirely consistent) and bleeding on punch biopsy (variable)
  - Case series
  - Meta-analysis of case series\*
- Cannot conclude whether stopping FXa inhibitor plus 4F-PCC is superior to stopping FXa inhibitor alone without comparator group
- **Reserve for the most severe, life-threatening cases**

\*Blood Adv. 2019;3(2):158-67.

# Summary of Outcomes with Reversal Agents

	Andexanet	Idarucizumab	4F-PCC-OFF LABEL
Study	ANNEXA-4	REVERSE-AD	Meta-analysis
Effective mgmt of bleed	82%	68%	~69-77%
TE events	10%	4.8%	4%
Mortality	14%	13%	16%

- NOTE: For informational purposes only; outcomes cannot be directly compared to each other
- Many differences between studies: population, design, outcomes definitions

# When to consider a reversal agent?



- **Mainstay of managing bleeding in patients on DOACs is temporary discontinuation of DOAC and supportive care**
- Major bleed that is in a critical site (e.g., intracranial) or life-threatening  
**AND**
- Confident that therapeutic anticoagulant is present
  - Often established by patient history, as specific assays are often not rapidly or readily available
- Concerns:
  - Reversal exposes patients to baseline or possibly additional thromboembolic risk
  - Improvement in outcomes is low quality or lacking
  - Some agents are high cost

## Case



IN ED his BP drifts to 100/60. He receives 3 u lactated ringers and 2 u PRBCs. He continues to have melena. GI is called for urgent evaluation and he is transferred to the ICU. His last dose of rivaroxaban was at 6 am this morning with breakfast. It is now 11 am. Should he receive a reversal agent?

- a) Yes
- b) No
- c) Do we have one of those?

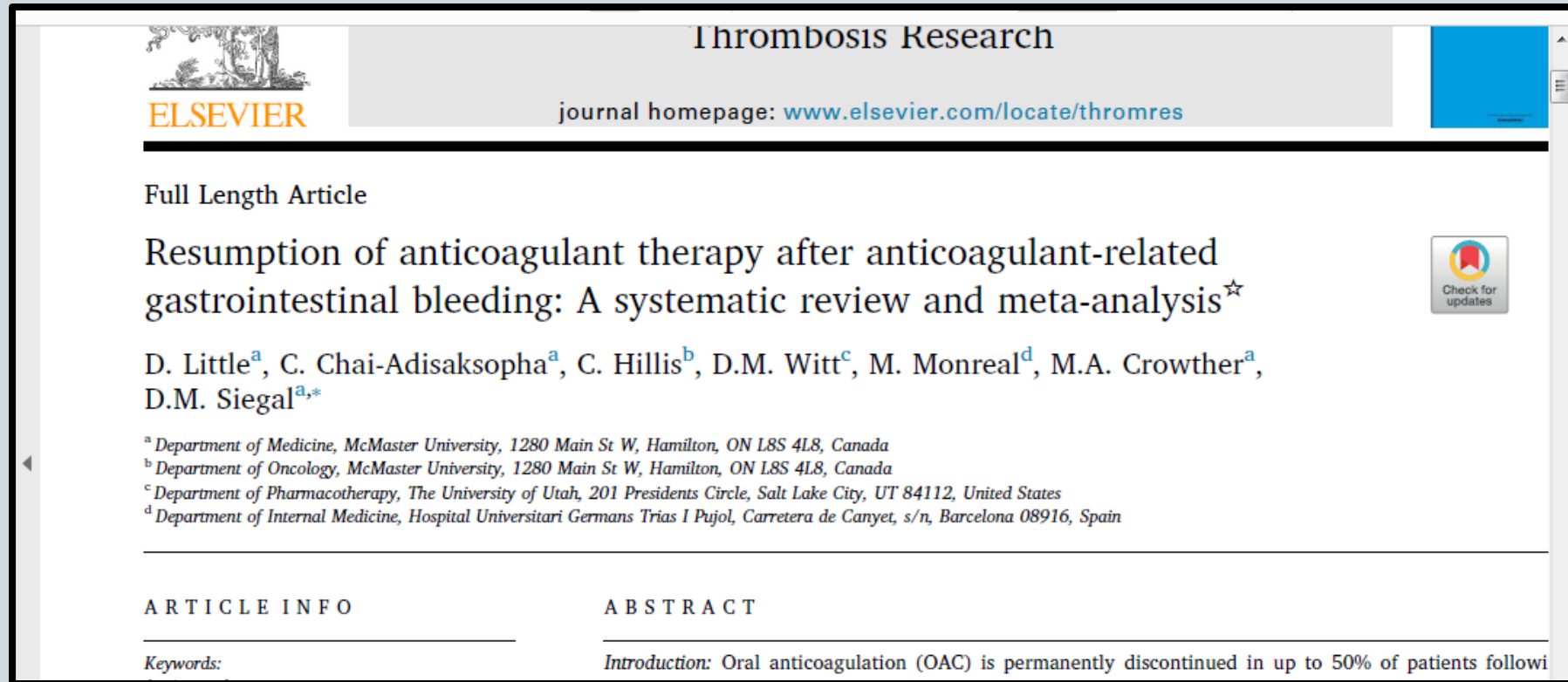
## Case



He has EGD and is found to have peptic ulcer. He is placed on high dose PPI and GI says he can resume anticoagulation in 2 weeks. In two weeks he should

- 1) Resume rivaroxaban and ASA
- 2) Start rivaroxaban only
- 3) Start apixaban only
- 4) Start ASA only
- 5) Talk with his PCP because in two weeks he is no longer on my service

# What To Do After the Bleed



The screenshot shows the journal homepage for Thrombosis Research. At the top left is the Elsevier logo. The journal title "Thrombosis Research" is centered at the top, with the homepage URL "www.elsevier.com/locate/thromres" below it. The article title is "Resumption of anticoagulant therapy after anticoagulant-related gastrointestinal bleeding: A systematic review and meta-analysis" with a star icon. The authors listed are D. Little, C. Chai-Adisaksopha, C. Hillis, D.M. Witt, M. Monreal, M.A. Crowther, and D.M. Siegal. Below the authors are four footnotes (a, b, c, d) providing their respective department and institution information. At the bottom, there are two sections: "ARTICLE INFO" with a "Keywords:" label and "ABSTRACT" with an "Introduction:" label. A "Check for updates" button is visible on the right side of the article title.

**Thrombosis Research**  
journal homepage: [www.elsevier.com/locate/thromres](http://www.elsevier.com/locate/thromres)

Full Length Article

Resumption of anticoagulant therapy after anticoagulant-related gastrointestinal bleeding: A systematic review and meta-analysis<sup>☆</sup>

D. Little<sup>a</sup>, C. Chai-Adisaksopha<sup>a</sup>, C. Hillis<sup>b</sup>, D.M. Witt<sup>c</sup>, M. Monreal<sup>d</sup>, M.A. Crowther<sup>a</sup>, D.M. Siegal<sup>a,\*</sup>

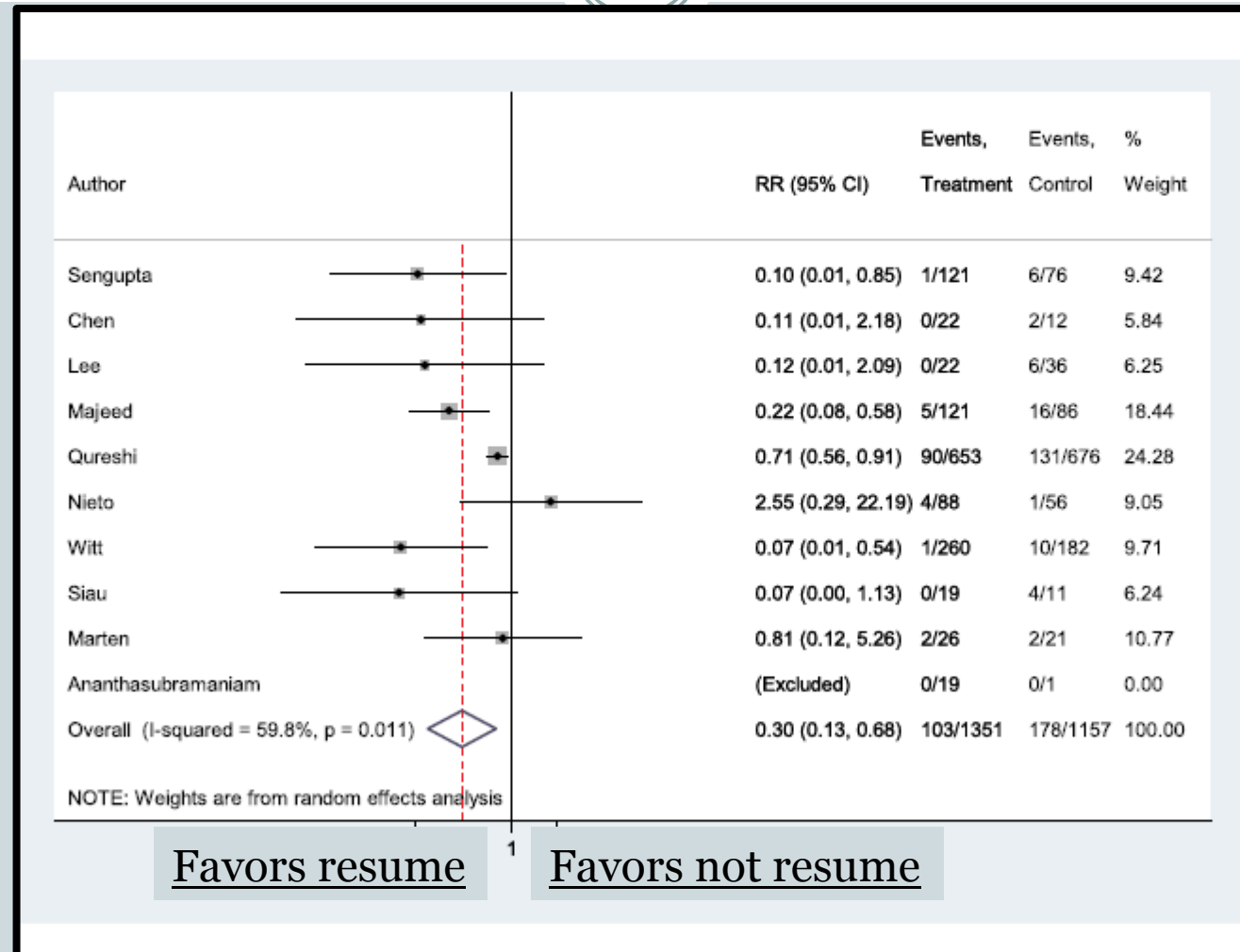
<sup>a</sup> Department of Medicine, McMaster University, 1280 Main St W, Hamilton, ON L8S 4L8, Canada  
<sup>b</sup> Department of Oncology, McMaster University, 1280 Main St W, Hamilton, ON L8S 4L8, Canada  
<sup>c</sup> Department of Pharmacotherapy, The University of Utah, 201 Presidents Circle, Salt Lake City, UT 84112, United States  
<sup>d</sup> Department of Internal Medicine, Hospital Universitari Germans Trias I Pujol, Carretera de Canyet, s/n, Barcelona 08916, Spain

ARTICLE INFO      ABSTRACT

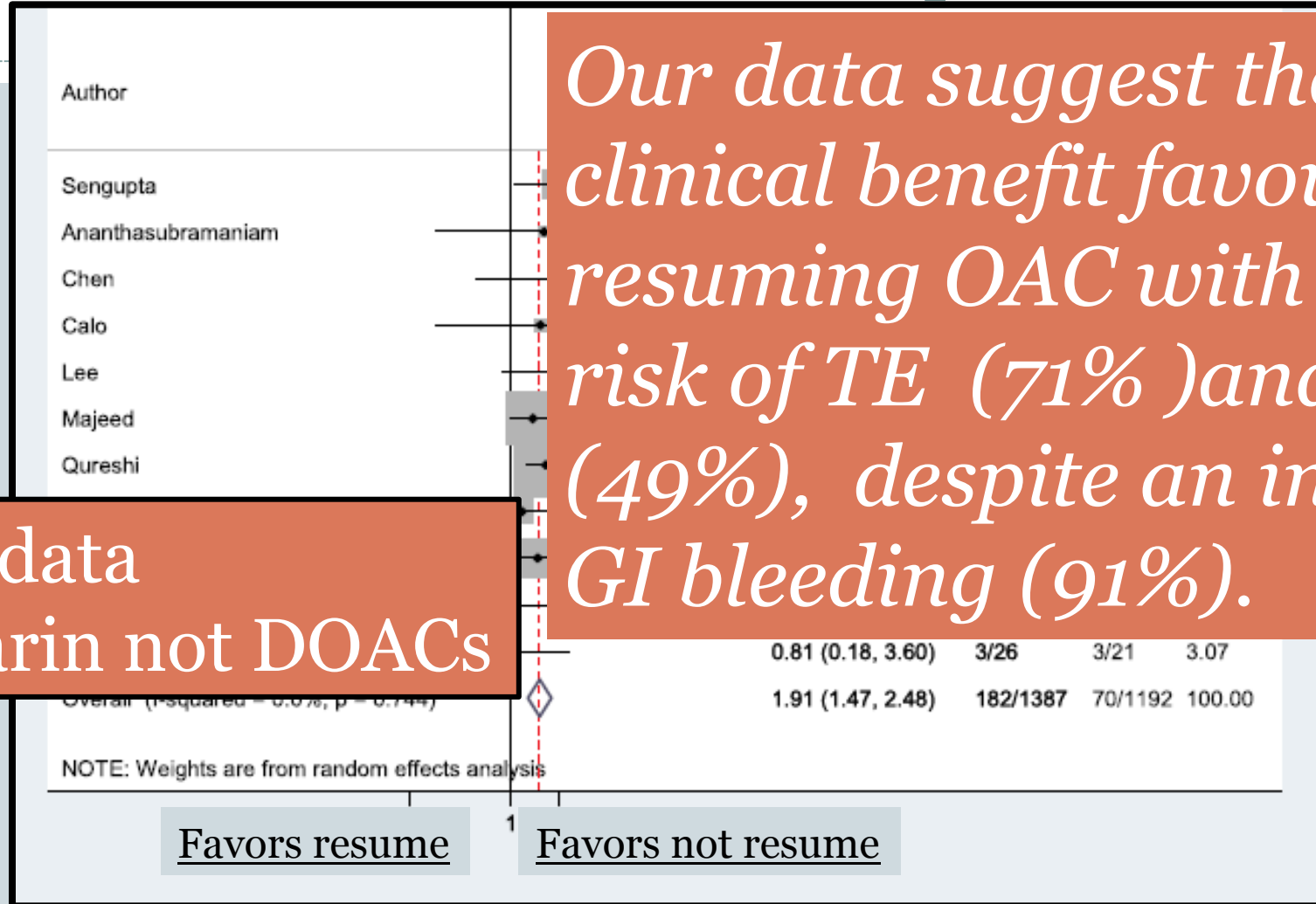
Keywords:      Introduction: Oral anticoagulation (OAC) is permanently discontinued in up to 50% of patients followi



# Thromboembolism After Resumption of AC



# Recurrent GIB After Resumption of AC



Most of this data is with warfarin not DOACs

# CHEST AFIB Guideline 2018



## Antithrombotic Therapy for Atrial Fibrillation

### CHEST Guideline and Expert Panel Report

Check for updates

Gregory Y. H. Lip, MD; Amitava Banerjee, MD, DPhil; Giuseppe Borlani, MD, PhD; Chen en Chiang, MD, PhD; Ramiz Fargo, MD, FCCP; Ben Freedman, MD, PhD; Deirdre A. Lane, PhD; Christian T. Ruff, MD, MPH; Mintu Turakhia, MD; David Werrinq, PhD; Sheena Patel, MPH; and Lisa Moores, MD, FCCP

*After bleeding if you are to resume anticoagulation: apixaban, low dose dabigatran 110 mg or edoxaban*

# Pearls



- Reassess risk benefit of ongoing AC after every bleed
  - Mechanical valve, high risk AFIB, recurrent VTE→yes
  - Low risk AFIB, single remote VTE→maybe not
- Talk directly with GI to get input on rebleed risk
- Reconsider the anticoagulation regimen-if on warfarin or rivaroxaban consider apixaban; if must stay on warfarin—closer monitoring? Add more kale? if on any DOAC was it right dose, is there compromised renal function or DDI resulting in accumulation?
- If on concomitant ASA...is this REALLY necessary? Consult cardiology and ask them to consider THIS case, not give reflexive answer

# This Year in Guidelines...



WHAT ABOUT ASA  
IN ADDITION TO  
ANTICOAGULATION  
IN AFIB + STABLE CAD?

**B-A-POLOOZA**



# This Year in Guidelines...



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[ Evidence-Based Medicine ]


## Antithrombotic T Fibrillation

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David

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ELSEVIER

Journ

Practice Guideline: Full Text



Canadian Journal of Cardiology 34 (2018) 1371–1392

### Society Guidelines

## 2018 Focused Update of the Canadian Cardiovascular Society Guidelines for the Management of Atrial Fibrillation

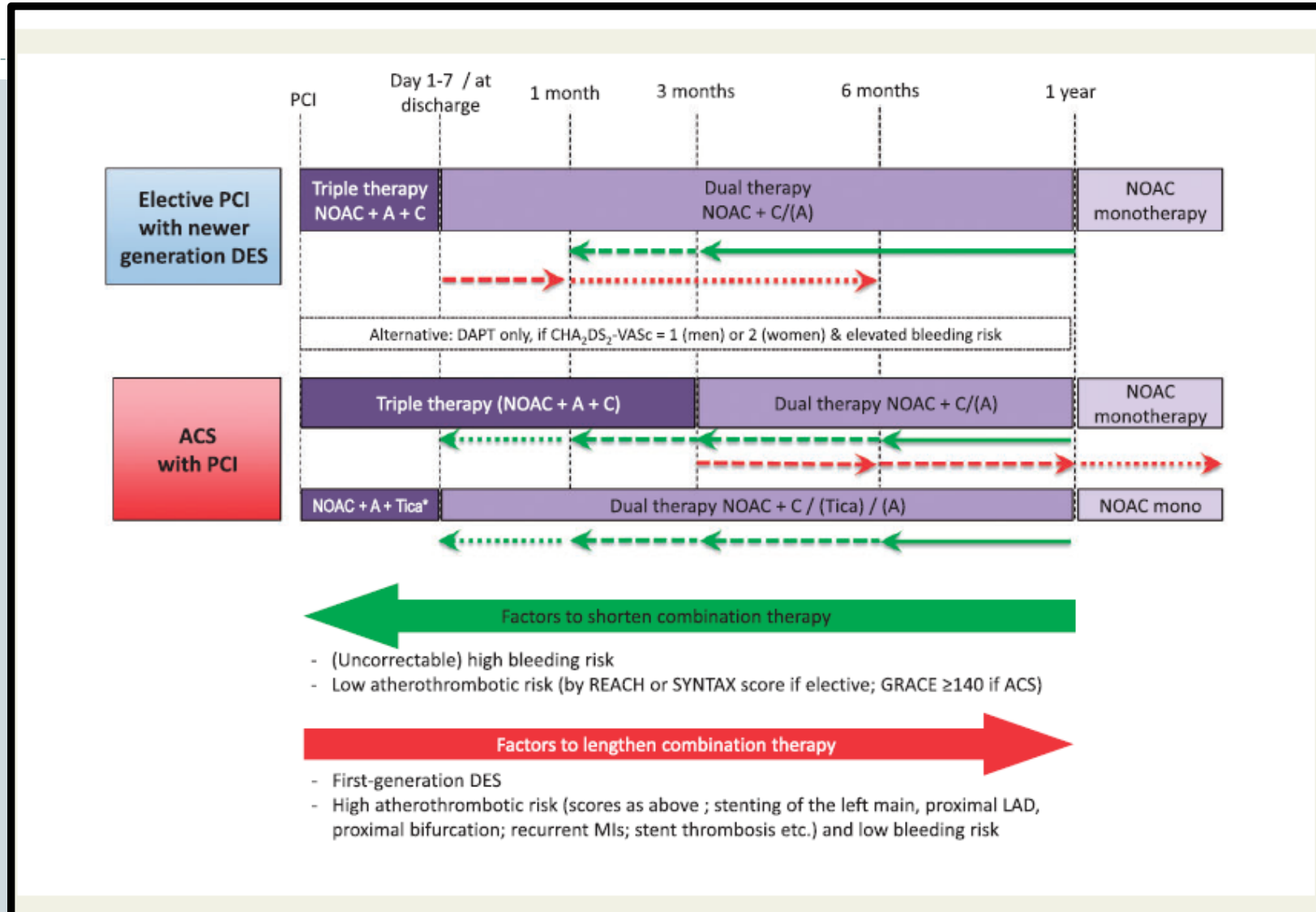
Jason G. Andrade, MD (Co-chair),<sup>a,b</sup> Atul Verma, MD (Co-chair),<sup>c</sup> L. Brent Mitchell, MD,<sup>d</sup> Ratika Parkash, MD,<sup>e</sup> Kori Leblanc, ACPR, PharmD,<sup>f</sup> Clare Atzema, MD,<sup>g,h</sup> Jeff S. Healey, MD,<sup>i,j</sup> Alan Bell, MD,<sup>h</sup> John Cairns, MD,<sup>g</sup> Stuart Connolly, MD,<sup>i,j</sup> Jafna Cox, MD,<sup>c</sup> Paul Dorian, MD,<sup>k</sup> David Gladstone, MD,<sup>g,h</sup> M. Sean McMurtry, MD,<sup>l</sup> Girish M. Nair, MBBS,<sup>m</sup> Louise Pilote, MD,<sup>n</sup> Jean-Francois Sarrazin, MD,<sup>o</sup> Mike Sharma, MD,<sup>i,j</sup> Allan Skanes, MD,<sup>p</sup> Mario Talajic, MD,<sup>b</sup> Teresa Tsang, MD,<sup>a</sup> Subodh Verma, MD,<sup>k</sup> D. George Wyse, MD, PhD,<sup>d</sup> Stanley Nattel, MD,<sup>b</sup> and Laurent Macle, MD (Co-chair),<sup>b</sup> for the CCS Atrial Fibrillation Guidelines Committee\*

\* University of British Columbia, Vancouver, British Columbia, Canada; <sup>b</sup> Montreal Heart Institute, Université de Montréal, Montreal, Quebec, Canada; <sup>c</sup> Southlake Regional Health Centre, Newmarket, Ontario, Canada; <sup>d</sup> Libin Cardiovascular Institute of Alberta, University of Calgary, Calgary, Alberta, Canada; <sup>e</sup> QEII Health Sciences Centre, Dalhousie University, Halifax, Nova Scotia, Canada; <sup>f</sup> University Health Network, University of Toronto, Toronto, Ontario, Canada; <sup>g</sup> Sunnybrook Health Sciences Centre, Toronto, Ontario, Canada; <sup>h</sup> University of Toronto, Toronto, Ontario, Canada; <sup>i</sup> McMaster University, Hamilton, Ontario, Canada; <sup>j</sup> Hamilton General Hospital, Hamilton, Ontario, Canada; <sup>k</sup> St Michael's Hospital, University of Toronto, Toronto, Ontario, Canada; <sup>l</sup> University of Alberta, Mazankowski Alberta Heart Institute, Edmonton, Alberta, Canada; <sup>m</sup> University of Ottawa Heart Institute, Ottawa, Ontario, Canada; <sup>n</sup> McGill University Health Centre, Montreal, Quebec, Canada; <sup>o</sup> Institut universitaire de cardiologie et de pneumologie, Quebec, Quebec, Canada; <sup>p</sup> London Heart Institute, Western University, London, Ontario, Canada

## 2019 AHA/ACC/HRS Focused Update of the 2014 AHA/ACC/HRS Guideline for the Management of Patients With Atrial Fibrillation: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines and the Heart Rhythm Society

Writing Group Members \*, Craig T. January MD, PhD, FACC (Chair), L. Samuel Wann MD, MACC, FAHA (Vice

# EHRA 2018 AFIB DOAC Guidelines

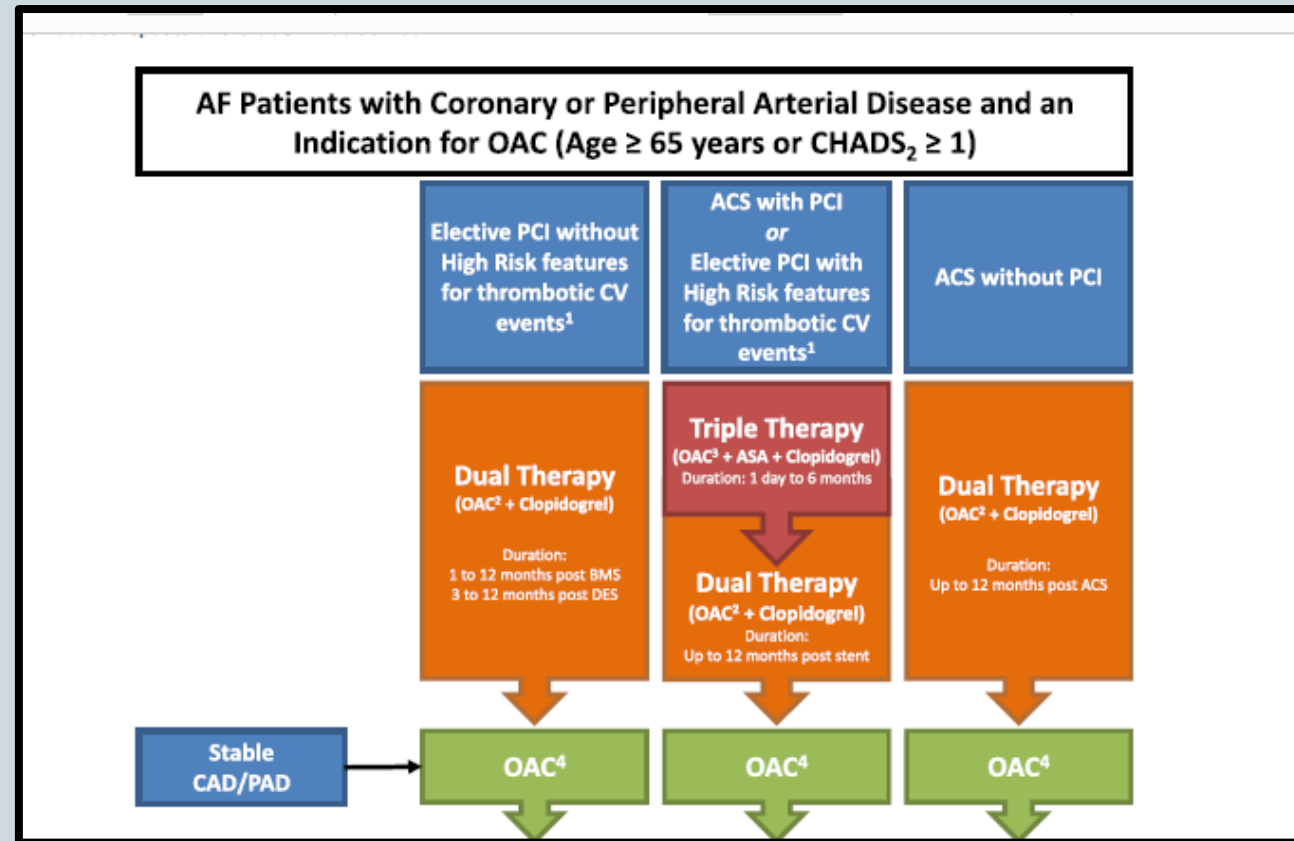


# CHEST 2018 AFIB Guidelines

*In AF patients requiring OAC undergoing elective PCI/stenting, where bleeding risk is high (HASBLED  $\geq$  3), we suggest triple therapy for 1 month, followed by dual therapy with OAC plus single antiplatelet (preferably clopidogrel) for 6 months, following which OAC monotherapy can be used (Weak recommendation, low quality)*



# Canadian AFIB Guidelines

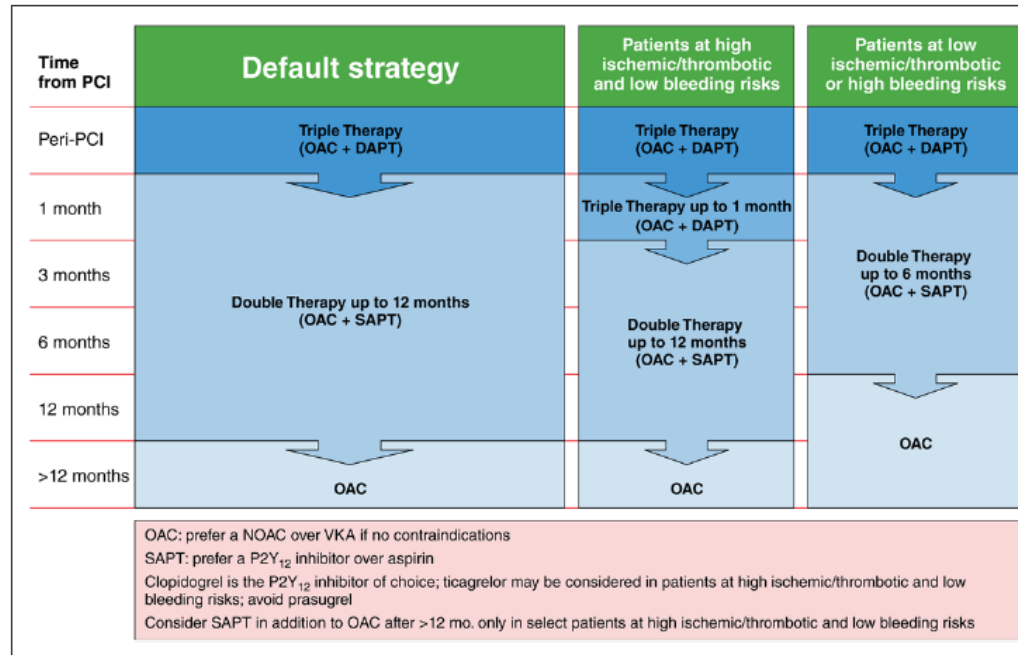


# Antithrombotic Therapy in AFIB on OAC

## WHITE PAPER

### Antithrombotic Therapy in Patients With Atrial Fibrillation Treated With Oral Anticoagulation Undergoing Percutaneous Coronary Intervention A North American Perspective—2018 Update

**ABSTRACT:** The optimal antithrombotic treatment for patients with atrial fibrillation undergoing percutaneous coronary intervention with stent implantation represents a challenge. In 2016, an updated opinion of selected experts from the Canadian Society of Cardiology and the American College of Cardiology on the treatment of patients with atrial fibrillation undergoing percutaneous coronary intervention was reported. This American consensus statement on the management



2. Management of antiplatelet therapy in patients with atrial fibrillation undergoing percutaneous coronary intervention (PCI) treated

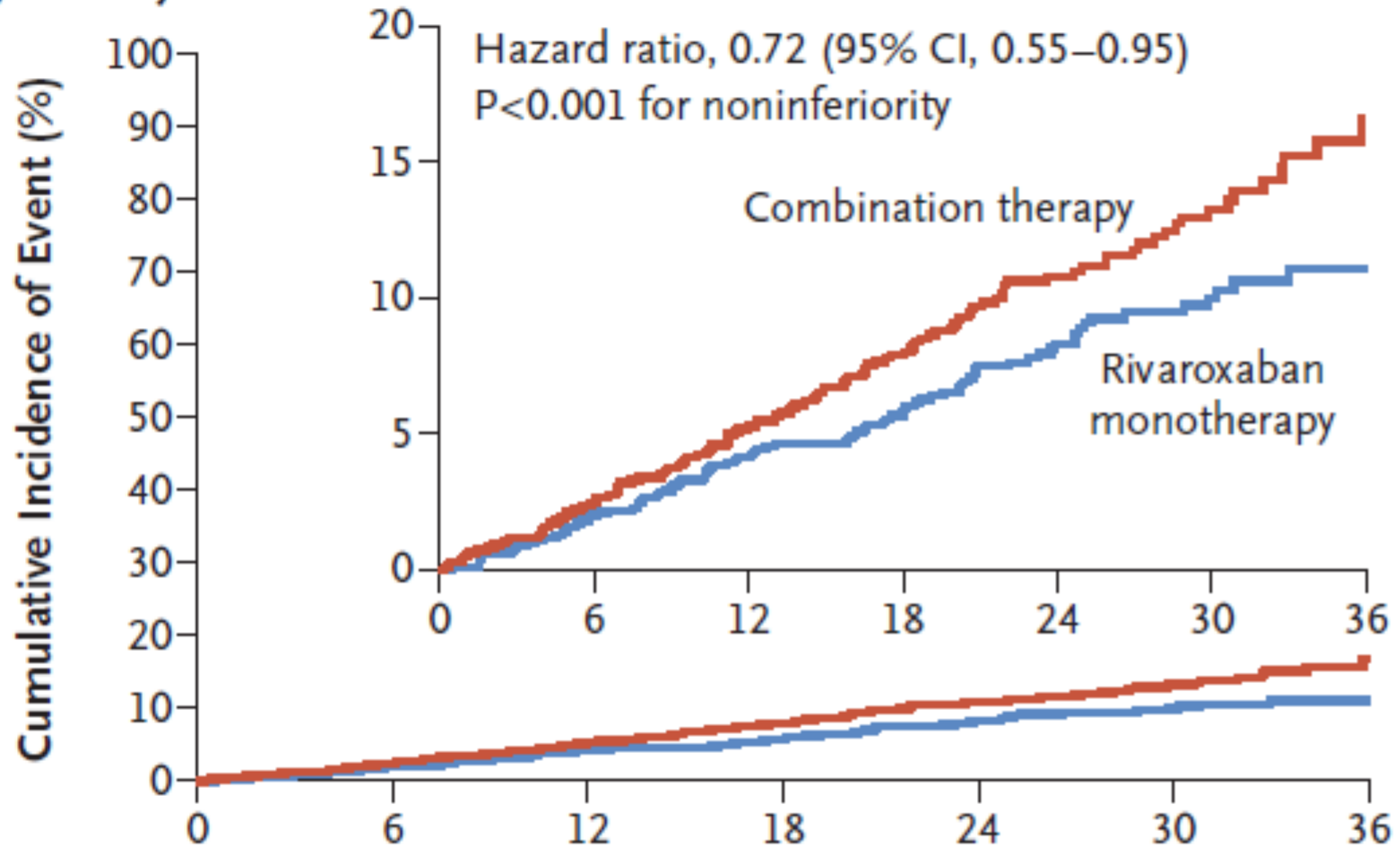
# AFIRE Results



The screenshot shows the top portion of a web page from The New England Journal of Medicine. At the top left, there are links for 'NEJM Group' and 'Follow Us'. At the top right, there are links for 'Sign in' and 'Create Account'. Below these is the NEJM logo and the text 'The NEW ENGLAND JOURNAL of MEDICINE'. A yellow banner contains the text 'This article is available to subscribers. [Subscribe now.](#) Already have an account? [Sign in](#)'. Below the banner, the article title 'Antithrombotic Therapy for Atrial Fibrillation with Stable Coronary Disease' is displayed in a large font. Above the title is the label 'ORIGINAL ARTICLE' and a 'FREE PREVIEW' button. Below the title is the list of authors: 'Satoshi Yasuda, M.D., Ph.D., Koichi Kaikita, M.D., Ph.D., Masaharu Akao, M.D., Ph.D., Junya Ako, M.D., Ph.D., Tetsuya Matoba, M.D., Ph.D., Masato Nakamura, M.D., Ph.D., Katsumi Miyauchi, M.D., Ph.D., Nobuhisa Hagiwara, M.D., Ph.D., Kazuo Kimura, M.D., Ph.D., Atsushi Hirayama, M.D., Ph.D., Kunihiko Matsui, M.D., M.P.H., and Hisao Ogawa, M.D., Ph.D. for the AFIRE Investigators\*'. At the bottom right of the page, the date 'September 2, 2019' is visible.

3000 patients with AFIB in Japan with stable CAD, > 1 year out from CABG or PCI  
15 mg if CrCl $\geq$  50 ml/min; 10 mg if CrCl < 50 ml/min

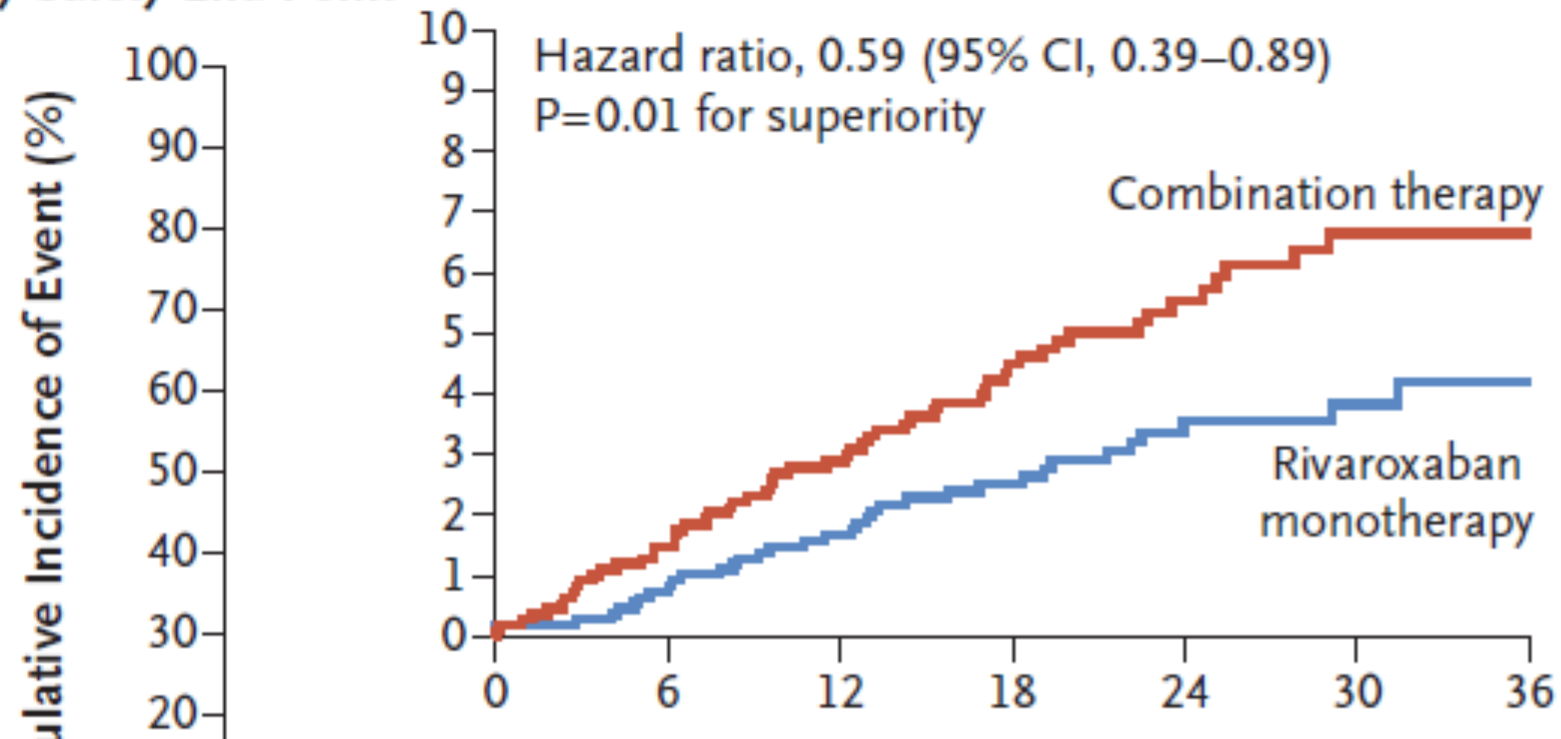
### A Primary Efficacy End Point



Monotherapy non-inferior to dual therapy for combined endpoint (CVA, SE< MI, death) ~4% vs ~6%

Yasuda S. et al NEJM 2019

## B Primary Safety End Point



Major bleeding higher for combined therapy 1.6% vs 2.7%  
Trial stopped early due to higher mortality in combined therapy group  
1.85% vs 3.35%

## Case



He has EGD and is found to have peptic ulcer. He is placed on high dose PPI and GI says he can resume anticoagulation in 2 weeks. In two weeks he should

- 1) Resume rivaroxaban and ASA
- 2) Start apixaban only
- 3) Start ASA only
- 4) Talk with his PCP because in two weeks he is no longer on my service

## Case



A 75 year old man with HTN, PAD, DM and AFIB on rivaroxaban is admitted with recurrent osteomyelitis of the foot. Given his poor perfusion he will need a TMA. How long should you hold his rivaroxaban before going to the OR?

- 1) 5-7 days, seemed to work for warfarin
- 2) Last dose 2 days prior to OR
- 3) Last dose 3 day prior to OR
- 4) no hold required
- 5) I have absolutely no idea but I do know I need more coffee

# NPSG.03.05.01:



## New or Amended Elements of Performance:\*

- EP-1: Initiation and maintenance of anticoagulants
- ~~EP-2: Reversal and bleeding events~~
- EP-3: Perioperative management
- EP-4: Laboratory monitoring to monitor and adjust
- EP-5: Identify, respond to, and report ADEs
- EP-6: Patient and family education

\*Including DOACs





Research

JAMA Internal Medicine | [Original Investigation](#)

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

James D. Douketis, MD; Alex C. Spyropoulos, MD; Joanne Duncan, BSc; Marc Carrier, MD, MSc; Gregoire Le Gal, MD; Alfonso J. Tafur, MD; Thomas Vanassche, MD; Peter Verhamme, MD; Sudeep Shivakumar, MD; Peter L. Gross, MD, MSc; Agnes Y. Y. Lee, MD, MSc; Erik Yeo, MD; Susan Solymoss, MD; Jeannine Kassis, MD; Geneviève Le Templier, MD; Stephen Kowalski, MD; Mark Blostein, MD; Vinay Shah, MD; Elizabeth MacKay, MD; Cynthia Wu, MD; Nathan P. Clark, PharmD; Shannon M. Bates, MDCM, MSc; Frederick A. Spencer, MD; Eleni Arnaoutoglou, MD, PhD; Michiel Coppens, MD, PhD; Donald M. Arnold, MD, MSc; Joseph A. Caprini, MD; Na Li, PhD; Karen A. Moffat, MLT; Summer Syed, MD, MSc; Sam Schulman, MD, PhD

Figure. Perioperative Direct Oral Anticoagulant (DOAC) Management Protocol

DOAC	Surgical Procedure-Associated Bleeding Risk	Preoperative DOAC Interruption Schedule					Day of Surgical Procedure (No DOAC)	Postoperative DOAC Resumption Schedule			
		Day -5	Day -4	Day -3	Day -2	Day -1		Day +1	Day +2	Day +3	Day +4
Apixaban	High	→			[Shaded]		[Vertical Bar]	→			
	Low	→						→			
Dabigatran etexilate (CrCl ≥50 mL/min)	High	→			[Shaded]			→			
	Low	→						→			
Dabigatran etexilate (CrCl <50 mL/min) <sup>a</sup>	High	→	[Shaded]					→			
	Low	→				[Shaded]		→			
Rivaroxaban	High	→			[Shaded]			→			
	Low	→						→			

ONE DAY HOLD-(36- to 42-hour interval = ~3 DOAC half-lives)  
 TWO DAY HOLD (60- to 68-hour interval = ~ 5DOAC half-lives)

# PAUSE-Results



**Table 3. Primary Study Outcomes**

Outcome	DOAC Cohort		
	Apixaban (n = 1257)	Dabigatran Etexilate (n = 668)	Rivaroxaban (n = 1082)
<b>Primary</b>			
<b>Major bleeding<sup>a</sup></b>			
No. (%)	17 (1.35)	6 (0.90)	20 (1.85)
1-Sided 95% CI	0-2.00	0-1.73	0-2.65
P value	.051	.02	.36
<b>Arterial thromboembolism<sup>b,c</sup></b>			
No. (%)	2 (0.16)	4 (0.60)	4 (0.37)
1-Sided 95% CI	0-0.48	0-1.33	0-0.82
P value	<.001	.03	.001

# PAUSE-Results



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 C (n = 1082)
Low bleeding risk			
No. (%)	851 (67.7)	440 (65.9)	700 (65.5)
bleeding, % (95% CI)			

30 day major bleeding rate of 2.96, 0.88 and 2.95 with apixaban, dabigatran & rivaroxaban respectively

# PAUSE TRIAL



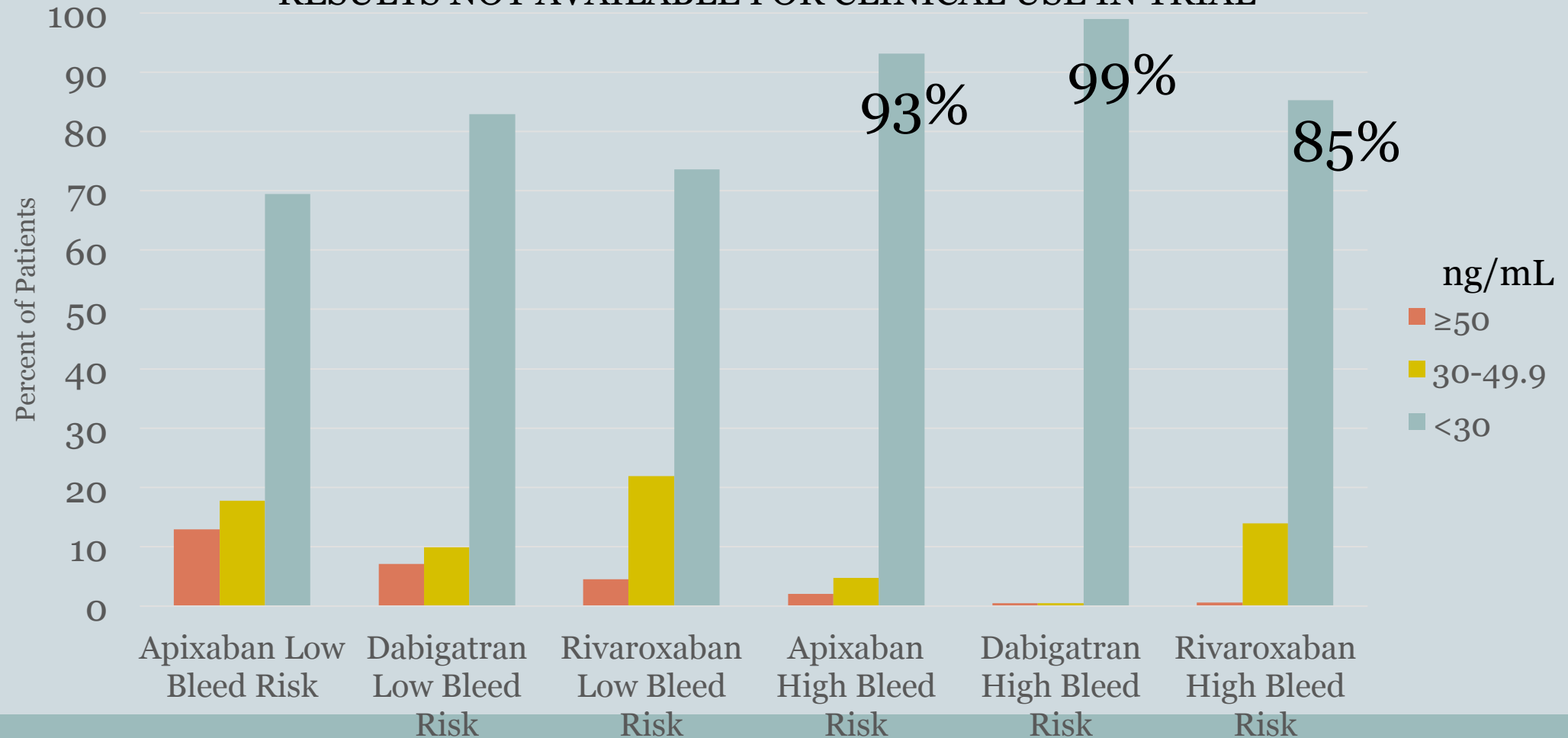
- CHADS<sub>2</sub> SCORE DID NOT PREDICT TE AND WAS NOT USED TO GUIDE MANAGEMENT
- NO BRIDGE THERAPY OFFERED
- PATIENTS COULD RECEIVE VTE PROPHYLAXIS POST OP (30%)

# PAUSE-Results



## Pre-Procedure Anticoagulant Level

RESULTS NOT AVAILABLE FOR CLINICAL USE IN TRIAL



# Conclusion



- Standard perioperative strategy
- No heparin bridging
- No laboratory testing
- Questions remaining:
  - WHAT ABOUT PATIENTS WITH LOW CRCL < 30 ML/MIN OR ON DIALYSIS
  - WHAT ABOUT PATIENTS ON LOW DOSE RIVAROXABAN 2.5 MG BID
  - WHAT ABOUT VERY VERY HIGH BLEED RISK PROCEDURES-CRANIOTOMY, NEURAXIAL ANESTHESIA
  - PRE OP RIVAROXABAN LEVELS HIGHER

# Example of Guideline

Suggested management of DOACs & VKAs before an invasive procedure

UCSF Medical Center | SF Health Network | San Francisco General Hospital

GUIDELINES FOR THE PERI-PROCEDURAL MANAGEMENT OF ADULTS TAKING TARGET SPECIFIC ANTICOAGULANTS (TSOACs): DABIGATRAN, RIVAROXABAN, APIXABAN, EDOXABAN

Drug	Renal Function	Low Procedural Bleed Risk (~2-3 half-lives between last dose & procedure)	High Procedural Bleed Risk (~4-5 half-lives between last dose & procedure)	Very High Procedural Bleed Risk (e.g., neuraxial, cardiothoracic, intracranial, spine)	Resumption of TSOAC	
					Low bleed risk procedures	High / Very High bleed risk procedures
Dabigatran (Pradaxa®) 75mg, 150mg BID	CrCl > 50 mL/min t½=14-17h	Interval between last dose and procedure: 48 hrs Last dose: 3 days prior	Interval between last dose and procedure: 96 hrs Last dose: 5 days prior	Interval between last dose and procedure: 120 hrs Last dose: 6 days prior	May resume 24 hrs postop	Very high thromboembolism risk: Resume no sooner than 48-72 hrs postop  Low/Int thromboembolism risk: resume no sooner than POD #5-7  Always discuss timing of resumption with proceduralist  For neuraxial anesthesia: first dose no sooner than 6 hrs after catheter removal. See Neuraxial guidelines for details.
	CrCl 30-50 mL/min t½=16-18h	Interval between last dose and procedure: 60 hrs Last dose: 3 days prior	Interval between last dose and procedure: ≥ 96 hrs Last dose: ≥5 days prior	Interval between last dose and procedure: >120 hrs Last dose: ≥ 6 days prior		
Confirm that pre-op PTT or thrombin time is normal						
Confirm that pre-op PTT or thrombin time is normal						
Rivaroxaban (Xarelto®) 15mg daily-BID, 20mg daily	CrCl > 30 mL/min t½=8-9h	Interval between last dose and procedure: 24 hrs Last dose: 2 days prior	Interval between last dose and procedure: 48 hrs Last dose: 3 days prior	Interval between last dose and procedure: 72 hrs Last dose: 4 days prior		
	CrCl 15-30 mL/min t½=9-10h	Interval between last dose and procedure: 48 hrs Last dose: 3 days prior	Interval between last dose and procedure: 72 hrs Last dose: 4 days prior	Interval between last dose and procedure: 120 hrs Last dose: 6 days prior		
Apixaban (Eliquis®) 2.5mg, 5mg, 10mg BID	CrCl > 50 mL/min t½=7-8h	Interval between last dose and procedure: 24 hrs Last dose: 2 days prior	Interval between last dose and procedure: 48 hrs Last dose: 3 days prior	Interval between last dose and procedure: 72 hrs Last dose: 4 days prior		
	CrCl 30-50 mL/min t½=17-18h	Interval between last dose and procedure: 48 hrs Last dose: 3 days prior	Interval between last dose and procedure: 96 hrs Last dose: 5 days prior	Interval between last dose and procedure: 120 hrs Last dose: 6 days prior		
Edoxaban (Savaysa®) 30mg, 60mg daily	CrCl > 50 mL/min t½=9-14h	Interval between last dose and procedure: 36 hrs Last dose: 2 days prior	Interval between last dose and procedure: 48 hrs Last dose: 3 days prior	Interval between last dose and procedure: 72 hrs Last dose: 4 days prior		

ACF Centers of Excellence:

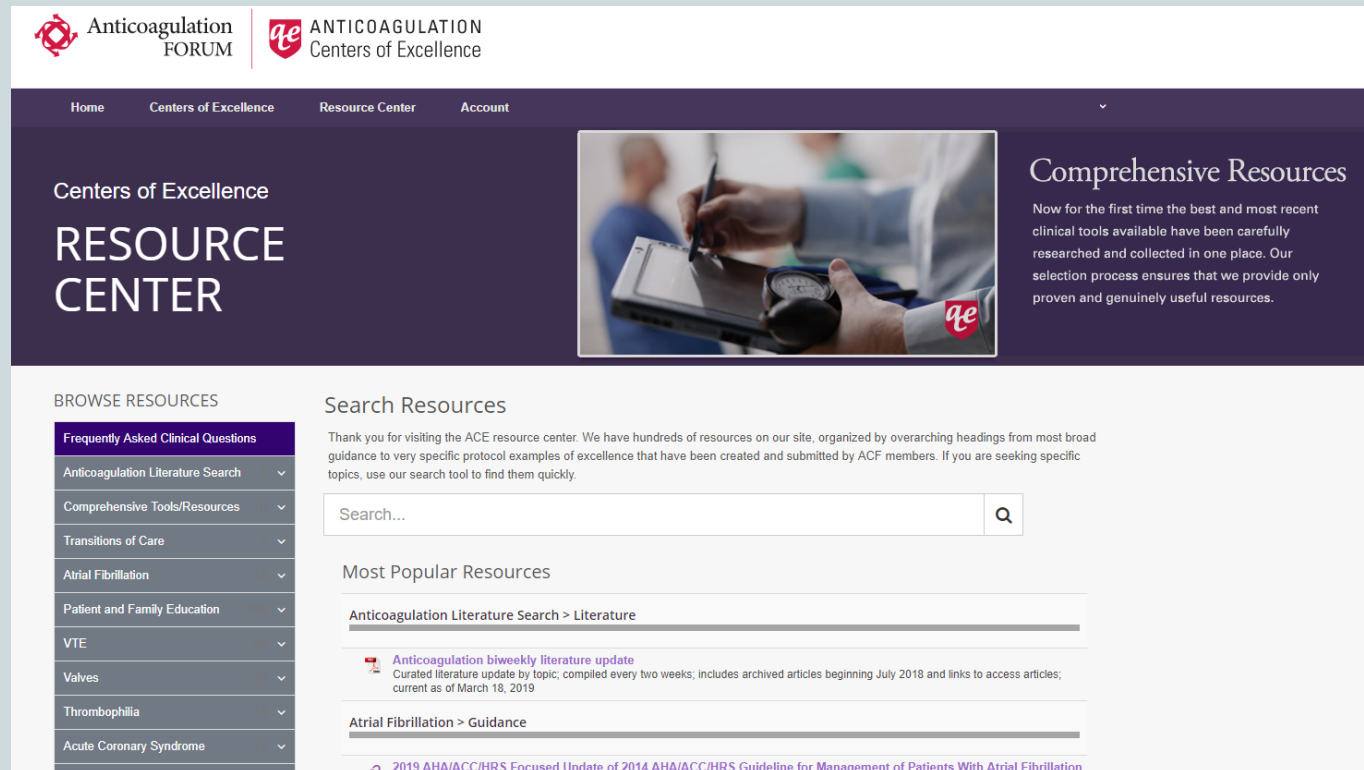
<https://acforum-excellence.org/Resource-Center/>

resource\_files/-2017-04-07-122011.pptx



# Where Do I Find Them?

Sample resources can be found at the Anticoagulation Centers of Excellence: <https://acforum-excellence.org/>



The screenshot shows the homepage of the Anticoagulation Forum Centers of Excellence Resource Center. The header includes the Anticoagulation Forum logo and the text "ANTICOAGULATION Centers of Excellence". The navigation menu contains "Home", "Centers of Excellence", "Resource Center", and "Account". The main content area features a large heading "Centers of Excellence RESOURCE CENTER" and a "Comprehensive Resources" section with a photograph of a person writing on a tablet. Below this, there is a "BROWSE RESOURCES" sidebar with a list of categories: "Frequently Asked Clinical Questions", "Anticoagulation Literature Search", "Comprehensive Tools/Resources", "Transitions of Care", "Atrial Fibrillation", "Patient and Family Education", "VTE", "Valves", "Thrombophilia", and "Acute Coronary Syndrome". The main content area also includes a "Search Resources" section with a search bar and a "Most Popular Resources" section listing "Anticoagulation Literature Search > Literature" and "Atrial Fibrillation > Guidance".

Anticoagulation FORUM | ANTICOAGULATION Centers of Excellence

Home | Centers of Excellence | Resource Center | Account

Centers of Excellence  
**RESOURCE CENTER**

**Comprehensive Resources**  
Now for the first time the best and most recent clinical tools available have been carefully researched and collected in one place. Our selection process ensures that we provide only proven and genuinely useful resources.

**BROWSE RESOURCES**

- Frequently Asked Clinical Questions
- Anticoagulation Literature Search
- Comprehensive Tools/Resources
- Transitions of Care
- Atrial Fibrillation
- Patient and Family Education
- VTE
- Valves
- Thrombophilia
- Acute Coronary Syndrome

**Search Resources**  
Thank you for visiting the ACE resource center. We have hundreds of resources on our site, organized by overarching headings from most broad guidance to very specific protocol examples of excellence that have been created and submitted by ACF members. If you are seeking specific topics, use our search tool to find them quickly.

Search...

**Most Popular Resources**

Anticoagulation Literature Search > Literature

**Anticoagulation biweekly literature update**  
Curated literature update by topic; compiled every two weeks; includes archived articles beginning July 2018 and links to access articles; current as of March 18, 2019

Atrial Fibrillation > Guidance

[2019 AHA/ACC/HRS Focused Update of 2014 AHA/ACC/HRS Guideline for Management of Patients With Atrial Fibrillation](#)

# Where Do I Find Them?

University of Washington Medicine Pharmacy Services:

<https://depts.washington.edu/anticoag/home/>

**UW Medicine**  
PHARMACY SERVICES

## Anticoagulation Services

[UW Medicine Anticoagulation Clinics](#) [Referrals](#) [Anticoagulant Conversions \("Switching"\)](#) [Patient education](#) [Permissions request](#)

### DRUGS

- Andexanet alfa (Andexxa)
- Apixaban (Eliquis) ▶
- Belrixaban (Bevyxxa) ▶
- Bivalirudin (Angiomax) ▶
- Dabigatran (Pradaxa) ▶
- Edoxaban (Savaysa) ▶
- Fondaparinux (Arixtra) ▶
- Heparin ▶
- Idarucizumab (Praxbind)
- Low molecular weight heparins (LMWH) ▶
- Rivaroxaban (Xarelto) ▶
- Warfarin (Coumadin) ▶

### CONDITIONS

- Monitoring Antithrombotic Therapy ▶
- Anticoagulation and neuraxial anesthesia ▶
- Bleeding Risk Assessment ▶
- Central venous catheter management
- Chronic antithrombotic therapy ▶
- Guidelines for reversal of anticoagulation ▶

### About UW Medicine Anticoagulation Services

This website contains UW Medicine recommendations, guidelines and protocols for the treatment and prevention of venous and arterial thrombosis, and the clinical use of antithrombotic agents in ambulatory and inpatient settings.

UW Medicine Anticoagulation Services is operated by the UW Medicine Department of Pharmacy, and collaborates with multidisciplinary specialties and providers across UW Medicine to develop and disseminate guidelines and to coordinate the use of antithrombotic agents across the UW Medicine enterprise.

UW Medicine Anticoagulation Services also provides management of anticoagulant therapy in pharmacist-managed anticoagulation clinics at the University of Washington Medical Center (UWMC), Seattle Cancer Care Alliance (SCCA) and Harborview Medical Center (HMC). Pharmacist providers in these clinics are involved in clinical practice, training and education, and research activities consistent with the mission of UW Medicine and the Department of Pharmacy.

*"The goals of pharmacist-managed anticoagulation services include treatment and prevention of thromboembolic disease and minimization of complications of antithrombotic therapy."*

Use the links to the left to navigate through the major sections of this site. The links at the top are the most frequently visited areas. BY USING THE SITE, YOU AGREE TO THE TERMS OF USE; IF YOU DO NOT AGREE, DO NOT USE THE SITE.

[Read more](#)


### UPDATE - UW Medicine restriction for Apixaban use in CrCl < 30ml/min REMOVED

Due to recently published literature using apixaban in patients receiving three times a week hemodialysis and changes in practice, the restriction for use of apixaban in patients with CrCl < 30 ml/min has been removed. Eliquis prescribing information has also been updated to reflect this information. Continue to exercise caution when using apixaban in patients with renal dysfunction.

[Read more](#)

### UPDATE - Guidelines for Reversing Coagulopathies in Patients with Symptomatic Spontaneous IPH

Updates to the Guidelines for Reversing Coagulopathies in Patients with Symptomatic Spontaneous IPH has been made. This changes Kcentra dosing



Anticoagulation  
Center of  
Excellence  
2017 – 2019

### MOST POPULAR

- Suggestions for converting to/from rivaroxaban
- Warfarin maintenance dosing nomogram
- UW Medicine alternative monitoring for antithrombotic agents
- Suggestions for converting to/from apixaban
- LMWH dosing guidelines
- Neuraxial guidelines
- Antithrombotic reversal guidelines
- Warfarin teaching booklets
- Refer a patient
- Washington State Anticoagulation Clinics

## Case



A 75 year old man with HTN, PAD, DM and AFIB on rivaroxaban is admitted with recurrent osteomyelitis of the foot. Given his poor perfusion he will need a TMA. How long should you hold his rivaroxaban before going to the OR?

- 1) 5-7 days, seemed to work for warfarin
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- 5) I have absolutely no idea but I do know I need more coffee

# Thromboembolism & Anticoagulation Workshop



- Approach to subsegmental PE, calf vein DVT and superficial vein thrombosis
- Determine duration of anticoagulation for VTE
- Review options for secondary prevention of VTE
- Manage anticoagulation in recurrent VTE
- Choose appropriate DOAC for VTE
- Role of thrombophilia work up

# Questions?



**Tracy Minichiello, MD**



# Reversal Agents for DOACs

Agent	Type	FDA approval	Other
<b>Idarucizumab (PRAXBIND)</b>	Specific for dabigatran	Bleeding, peri-procedural	
<b>Andexanet (ANDEXXA)</b>	Specific for FXa inhibitors	Bleeding w/ apixaban and rivaroxaban only	Off-label for other FXa inhibitors, procedures
<b>4F-PCC (KCentra)</b>	Nonspecific	Warfarin reversal	Off-label for DOACs
<b>aPCC (FEIBA)</b>	Nonspecific	Hemophilia A, B	Off-label for DOACs

# Periprocedural Bridging in Patients With Venous Thromboembolism: A Systematic Review



## Study Results

Number of procedures	Major bleeding pooled analysis	Thrombosis pooled analysis
With bridging (3448)	1.8%	0.7%
Without bridging (3459)	0.4%	0.5%