Aggiornamento in terapia cardiovascolare Salo' 03/03/2018

Gestione delle complicanze emorragiche in corso di terapia con i DOAC

A Bianchi Ospedale S. Luca Milano

The best way to overcome the fear of bleeding is...

to know the facts.

The Questions

- Burden of the bleeding risk
- Prevention of the bleeding risk
- Reduction of the bleeding risk
- Management of the bleeding

First Question

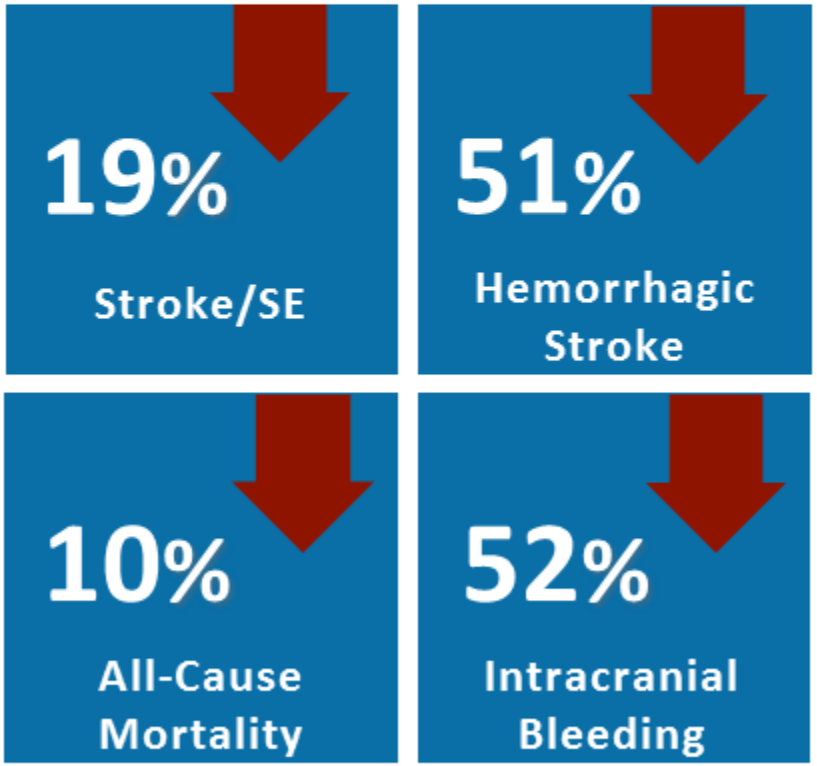
What is the burden of the bleeding risk with the anticoagulation theraphy ?

Major Bleeding on NOAC Treatment

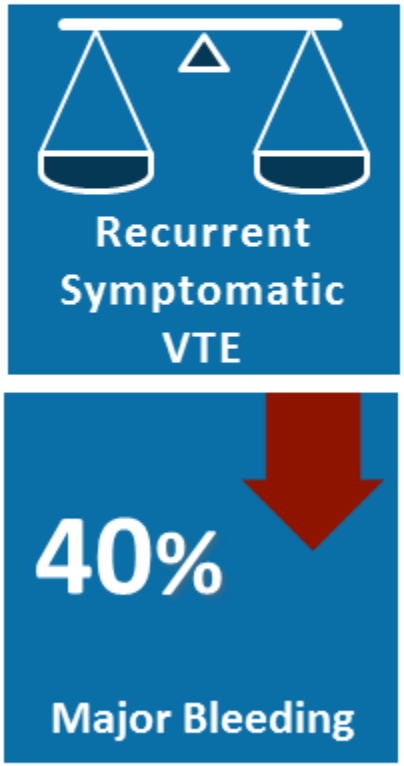
- Less common than with warfarin
- Less severe than with warfarin (ICH ↓ by 30-70%)
- Drugs have shorter half-life than warfarin

NOACs vs VKAs: Efficacy and Safety Profiles in Clinical Trials

Stroke prevention in AF[a]



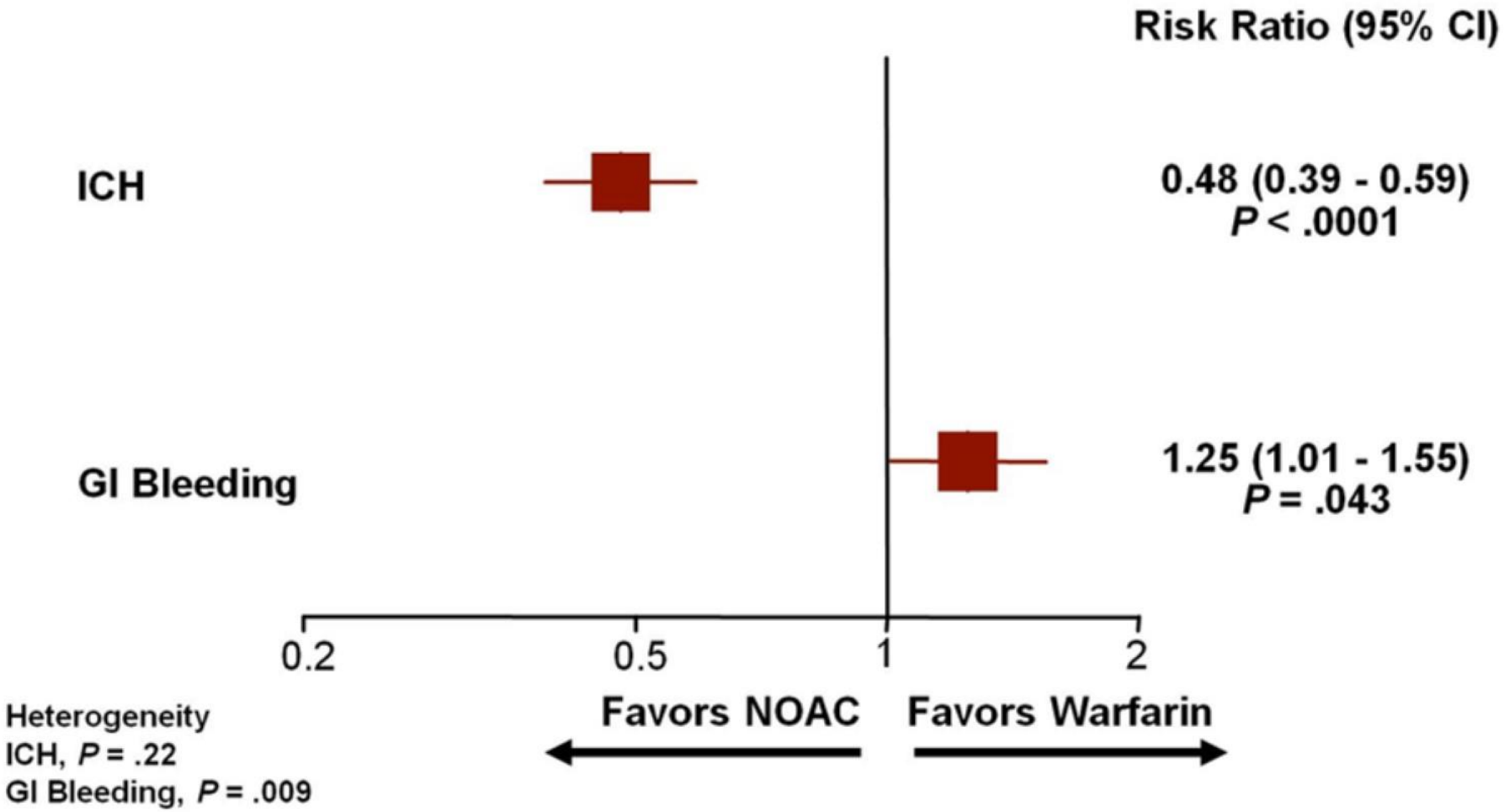
DVT/PE treatment[b]



a. Ruff C, et al. *Lancet*.2014;383:955-962.
b. Hirschl M, Kundi M.*Vasa*.2014;43:353-364.

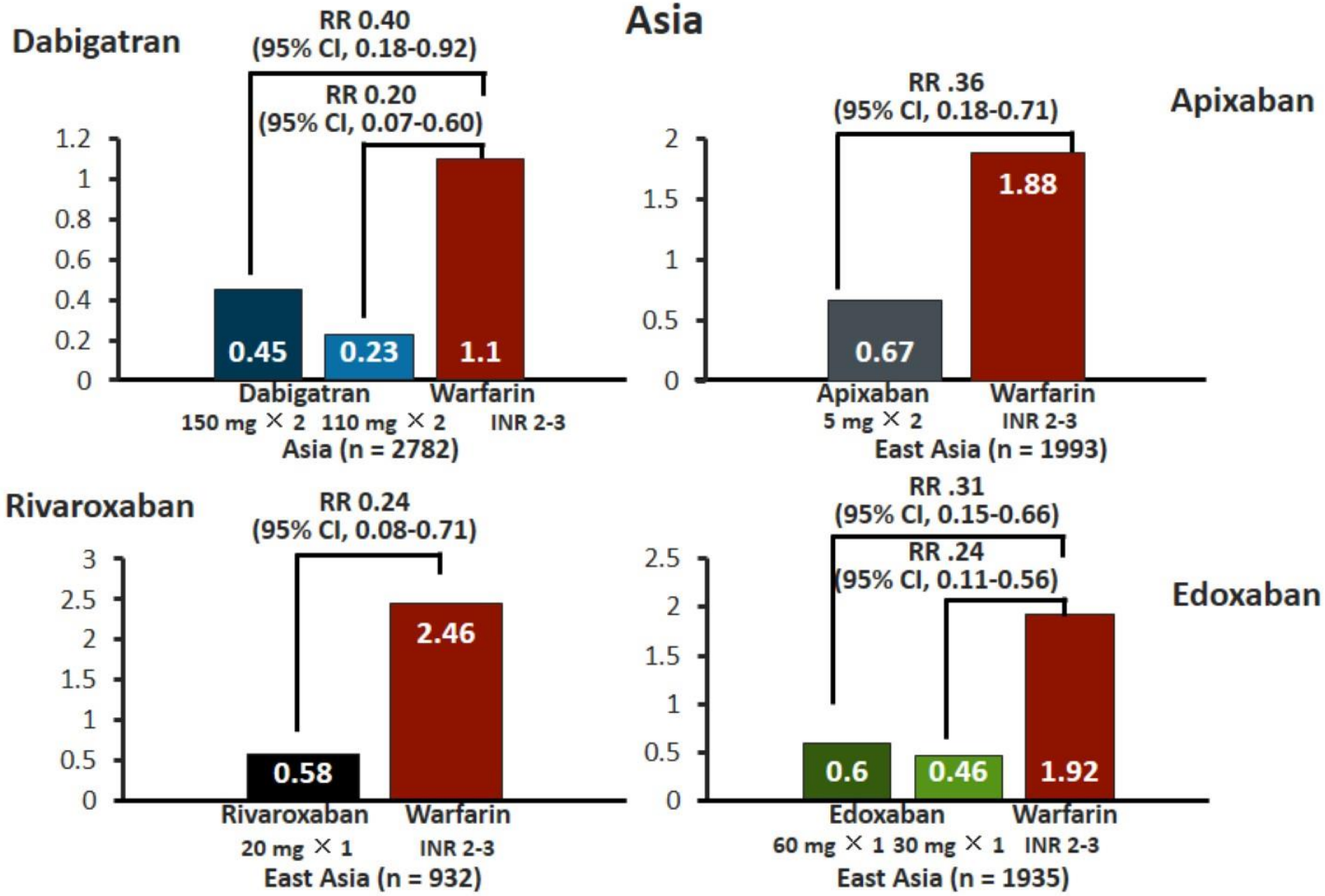
Bleeding Risk

NOACs vs Warfarin



Ruff CT, et al. *Lancet.* 2014;383:955-962.

Incidence of ICH: *Warfarin vs NOAC*

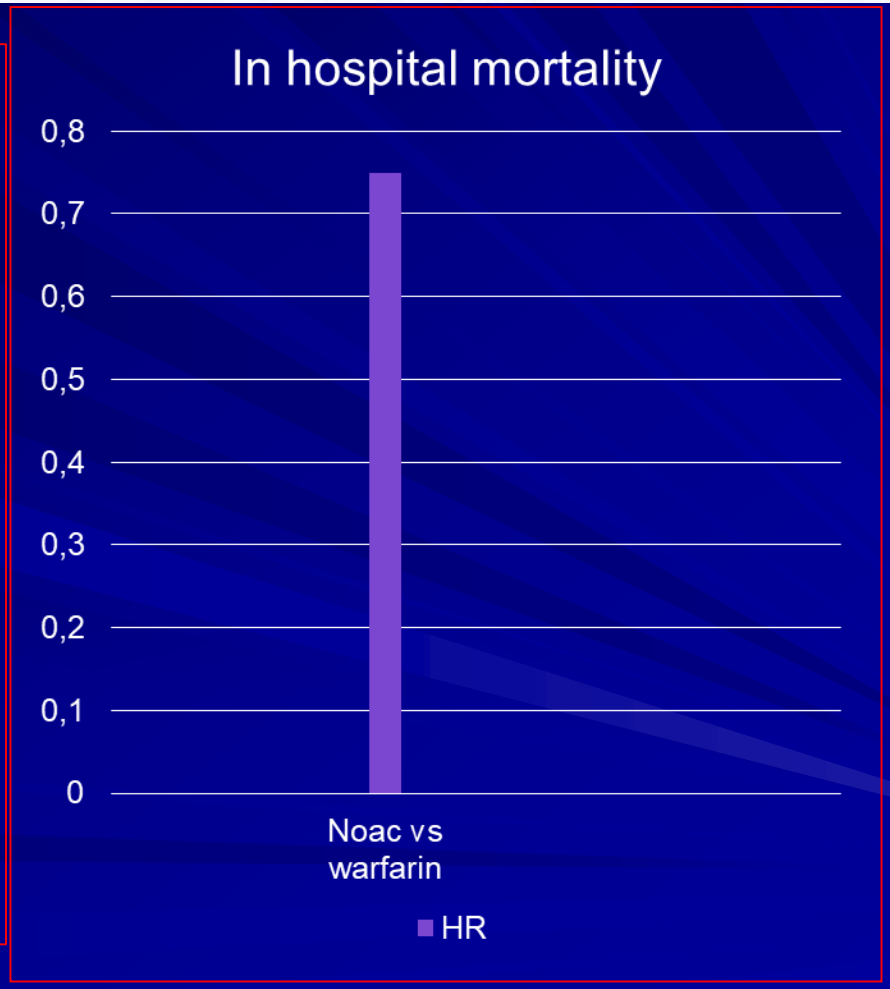


Yasaka M, Lip GYH. *Circ J.* 2014;78:2367-2372.

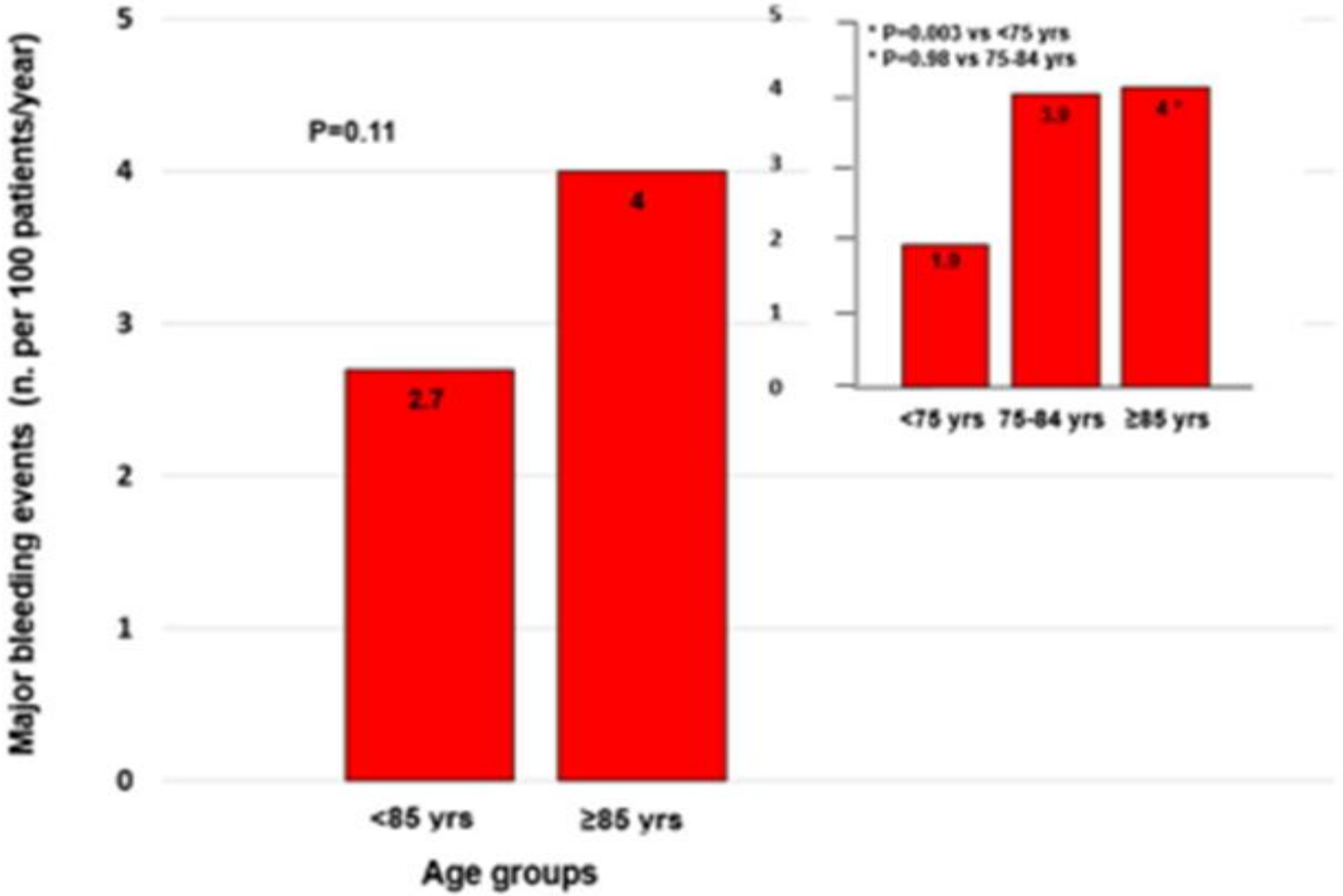
Inohara T, Xian Y, Liang L, et al.

Association of Intracerebral Hemorrhage Among Patients Taking Non–Vitamin K Antagonist vs Vitamin K Antagonist Oral Anticoagulants With In-Hospital Mortality. *JAMA* 2018;Jan 25:[Epub ahead of print].

- Retrospective study 2013→16
- 143311 pt.s ICH
- 85,9 % no anticoagulation
- 10,6% on warfarin
- 3,5% on NOAC

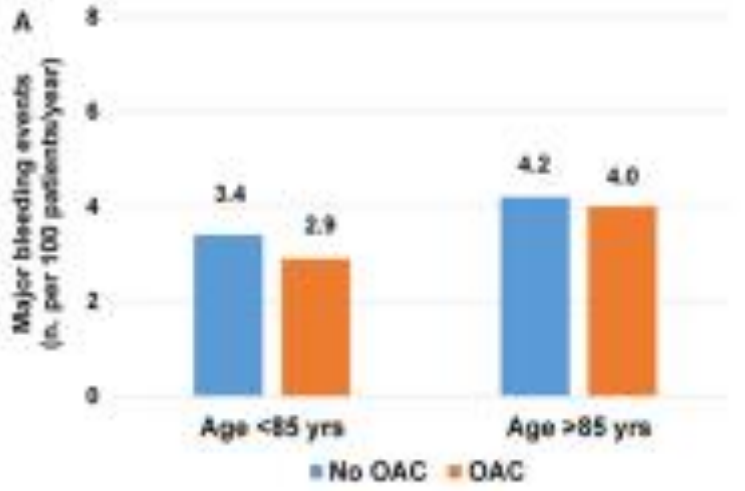


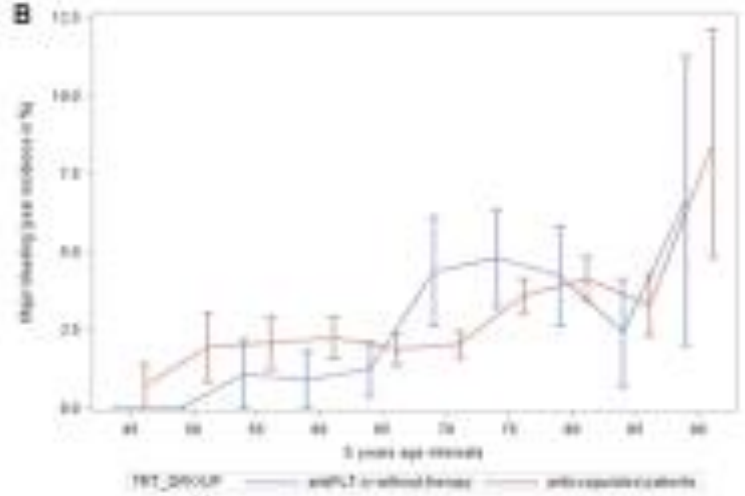
Incidence of major bleeding at 1 year in patients aged <85 and ≥85 years.



Giuseppe Patti et al. J Am Heart Assoc 2017;6:e005657

A, Incidence of major bleeding in patients aged <85 and ≥85 years receiving OAC or no OAC (antiplatelet therapy only or no antithrombotic drug).

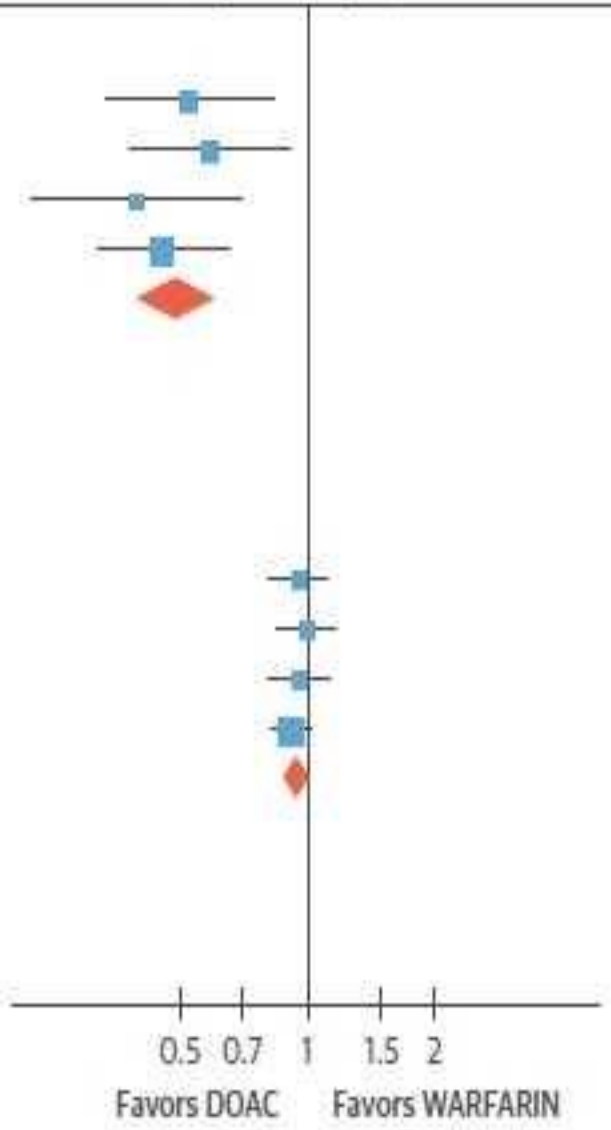




Giuseppe Patti et al. J Am Heart Assoc 2017;6:e005657

Study or Subgroup	DOAC Events	DOAC Total	WARFARIN Events	WARFARIN Total	Weight	Risk Ratio M-H, Random, 95% CI
BLEEDING VASCULAR DEATHS						
1. RE-LY	38	12091	36	6022	22.2%	0.53 [0.33, 0.83]
2. ROCKET AF	34	7081	58	7090	25.8%	0.59 [0.38, 0.90]
3. ARISTOTLE	17	9120	43	9081	14.6%	0.39 [0.22, 0.69]
4. ENGAGE AF-TIMI 48	59	14069	65	7036	37.3%	0.45 [0.32, 0.64]
Subtotal (95% CI)		**42361**		**29229**	**100.0%**	**0.49 [0.40, 0.61]**
Total events	148		202			
Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 1.56$, df = 3 (P = 0.67); $I^2 = 0\%$						
Test for overall effect: Z = 6.50 (P < 0.00001)						
NON-BLEEDING VASCULAR DEATHS						
1. RE-LY	504	12091	264	6022	20.0%	0.95 [0.82, 1.10]
2. ROCKET AF	341	7081	343	7090	19.9%	1.00 [0.86, 1.15]
3. ARISTOTLE	306	9120	318	9081	17.9%	0.96 [0.82, 1.12]
4. ENGAGE AF-TIMI 48	998	14069	546	7036	42.2%	0.91 [0.83, 1.01]
Subtotal (95% CI)		**42361**		**29229**	**100.0%**	**0.95 [0.89, 1.01]**
Total events	2149		1471			
Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 0.95$, df = 3 (P = 0.81); $I^2 = 0\%$						
Test for overall effect: Z = 1.70 (P = 0.09)						

Test for subgroup differences: $Chi^2 = 32.79$, df = 1 (P < 0.00001); $I^2 = 97.0\%$



Second Question

How we can prevent the bleeding ?

HAS-BLED Score

	Clinical Characteristic	Score
H	Hypertension	1
A	Abnormal renal or liver function (1 each)	1 or 2
S	Stroke	1
B	Bleeding	1
L	Labile INR	1
E	Elderly age	1
D	Drugs or alcohol (1 each)	1 or 2
	Maximum Score	9

Hypertension: systolic blood pressure > 160 mm Hg; Abnormal renal function: chronic dialysis, renal transplant, serum creatinine ≥ 200 µmol/L; Abnormal liver function: chronic hepatitis, bilirubin > 2x ULN in association with AST/ALT/ALP > 3 x ULN; Bleeding: previous history, predisposition; Labile INRs: unstable/high INRs, in therapeutic range < 60%; Age > 65 years; Drugs/alcohol: concomitant use of antiplatelet agents, nonsteroidal anti-inflammatory drugs, etc.

Pisters R, et al. *Chest*. 2010;138:1093-1100.[5]

HAS-BLED Bleeding Risk Score

- Hypertension
  - SBP < 160 mmHg
- Abnormal renal function
  - Chronic dialysis/renal transplantation/serum creatinine ≥ 200µmol/L
- Abnormal liver function
  - Chronic hepatic disease/biochemical evidence of significant hepatic derangement
- Bleeding tendency or predisposition
  - History of bleeding and/or predisposition to bleeding (eg, bleeding diathesis, anemia, etc.)
- Labile INRs
  - Unstable/high INRs or TTR < 60%
- Age
  - > 65 years
- Drugs/alcohol
  - + OACs, antiplatelet agents, NSAIDs, etc.

Pisters R, et al. *Chest*. 2010;138:1093-1100.

How to Measure If Novel Anticoagulants Are Having an Effect

- No definitive method for accurately measuring the effect of novel oral anticoagulants*, as there is for warfarin
- Dabigatran—if PTT is normal, the drug is having very little effect
- Rivaroxaban—if PT is normal, the drug is having very little effect
- Apixaban—less correlation between its effect and PTT/PT

**At the time of the initial recording, edoxaban was not available for use.*

PT = prothrombin time; PT = partial thromboplastin time

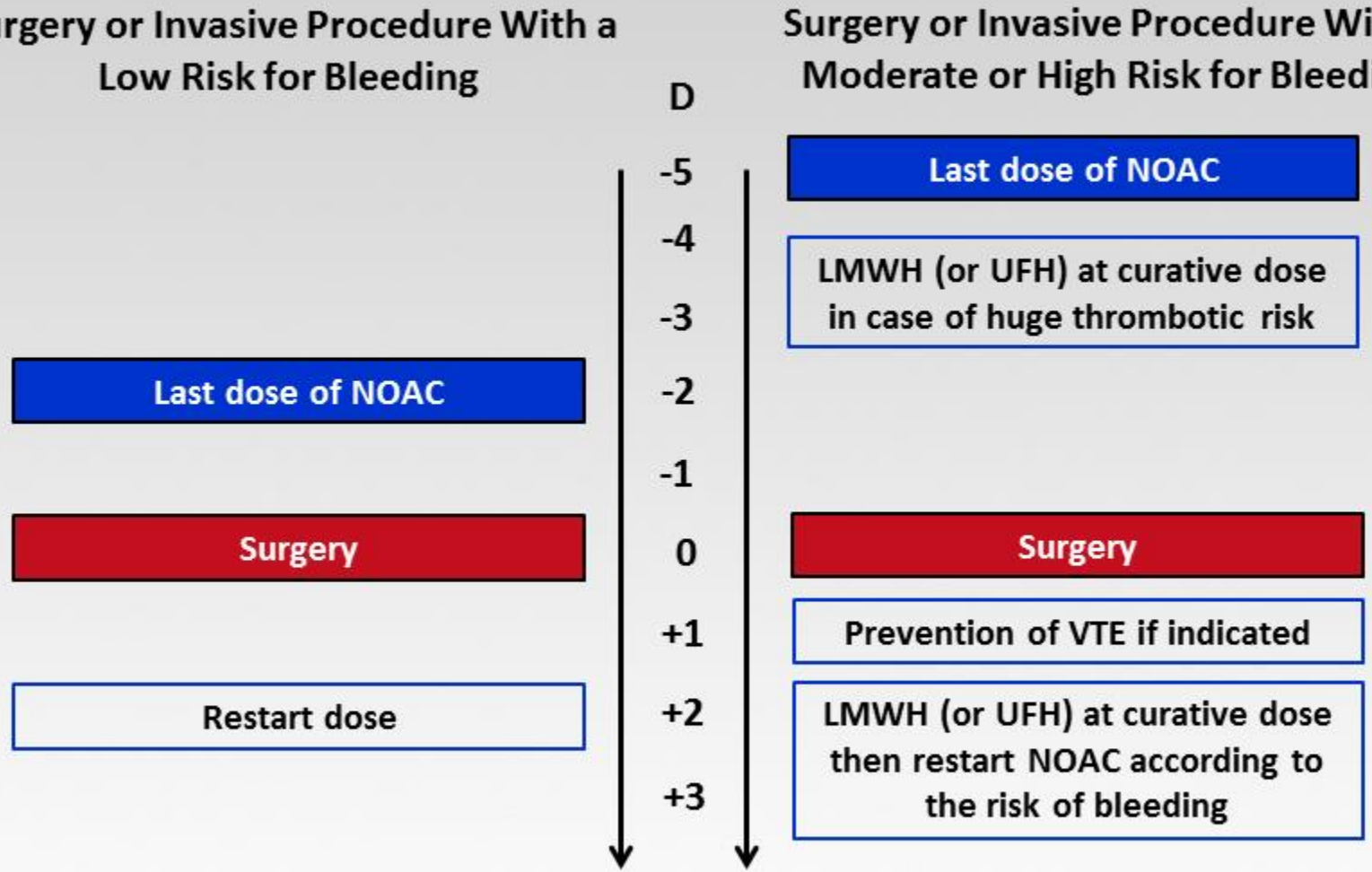
Barrett YC, et al. *Thromb Haemost.* 2012;104(6):1263-1271.
Schulman S, et al. *Blood.* 2012;119(13):3016-3023.
VanAmburgh JA. Medscape Pharmacists. January 28, 2013.

Classification of Interventional Procedures According to Bleeding Risk

Minimally Invasive Procedures	Minor Procedures	Major Procedures
• Superficial skin and oral mucosal surgery, including biopsies • Wound revisions • Non-extraction dental treatment	• Transluminal cardiac, arterial, and venous interventions • Pacemaker-related surgery • Pleura and ascites puncture • Cataract surgery • Arthroscopy, endoscopy, laparoscopy • Organ biopsies • Dental extraction • Hernia repair • Intramuscular and paravertebral injections	• Open pelvic, abdominal, and thoracic surgery • Brain surgery • Major orthopedic and trauma surgery • Vascular surgery

Beyer-Westendorf J, et al. *Eur Heart J.* 2014 Jan 6. [Epub ahead of print]

Management of Bleeding Complications in Patients Taking NOACs and Undergoing Surgery/Invasive Procedures: Recommendations from GIHP



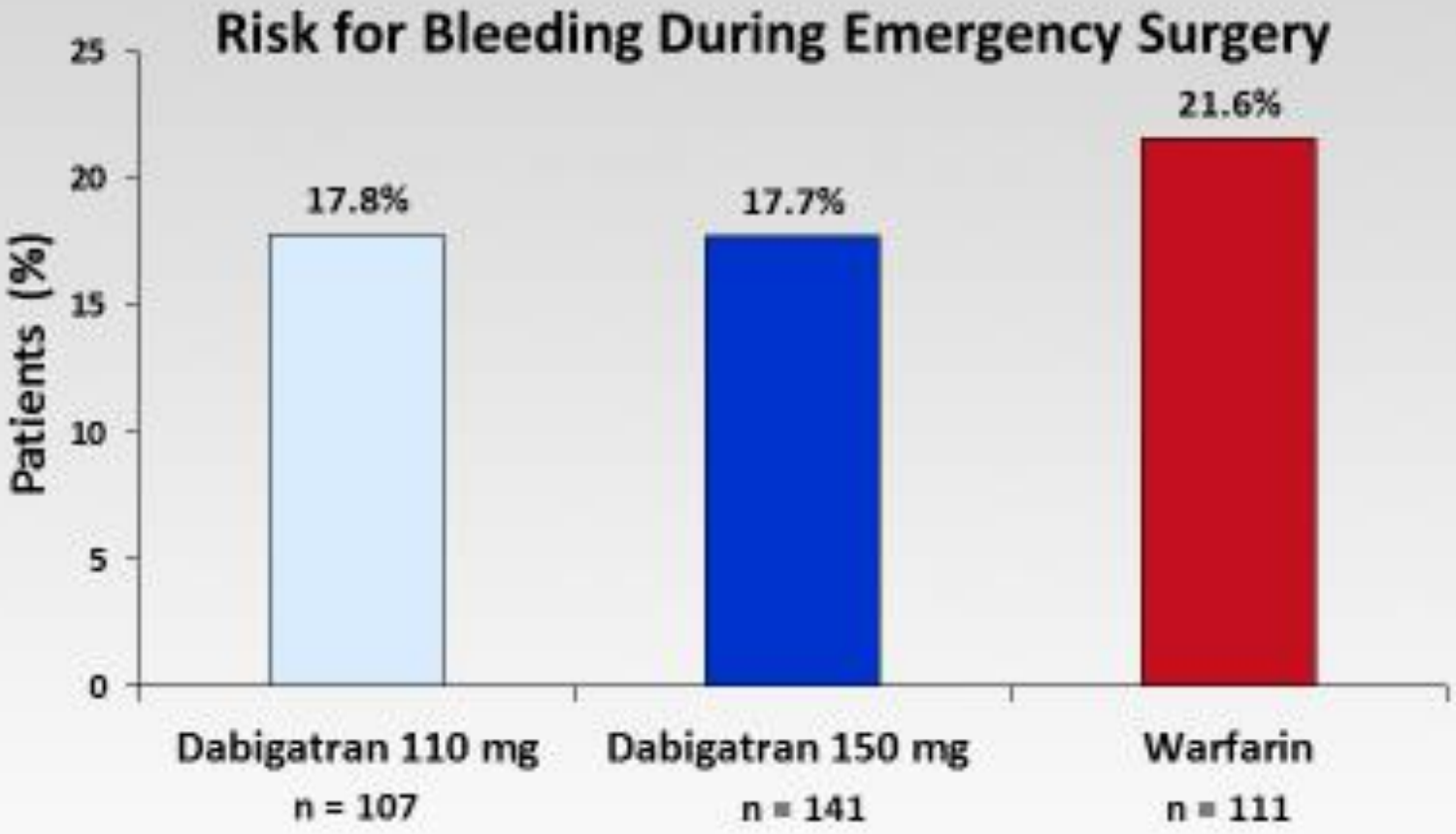
D = day; GIHP = Working Group on Perioperative Haemostasis; LMWH = low-molecular weight heparin; UFH = unfractionated heparin; VTE = venous thromboembolism

Arrhythmia & EP

Pernod G, et al. *Ann Fr Anesth Reanim*. 2013;32(10):691-700.

Medscape EDUCATION

Outcomes of Bleeding Events With Novel Oral Anticoagulants



Healey JS, et al. *Circulation*. 2012;126(3):343-348.

NOACs: Consider Last Intake of Drug & Renal Function Prior to Elective Surgical Intervention

Dabigatran

If no important bleeding risk and/or adequate local hemostasis possible: perform at trough level (ie, ≥12 or 24 h after last intake)

	Low Risk of Bleeding	High Risk of Bleeding
CrCl ≥80 mL/min	≥24 h	≥48 h
CrCl 50-80 mL/min	**≥36 h**	**≥72 h**
CrCl 30-50 mL/min*	**≥48 h**	**≥96 h**
CrCl 15-30 mL/min*	Not indicated	Not indicated

Apixaban-Edoxaban-Rivaroxaban

If no important bleeding risk and/or adequate local hemostasis possible: perform at trough level (ie, ≥12 or 24 h after last intake)

	Low Risk of Bleeding	High Risk of Bleeding
CrCl ≥80 mL/min	≥24 h	≥48 h
CrCl 50-80 mL/min	≥24 h	≥48 h
CrCl 30-50 mL/min*	≥24 h	≥48 h
CrCl 15-30 mL/min*	**≥36 h**	**≥48 h**

Bold values deviate from the common stopping rule of ≥ 24 h low risk, ≥48 h high risk.

Low risk = low frequency of bleeding and/or minor impact of a bleeding; high risk = high frequency of bleeding and/or important clinical impact.

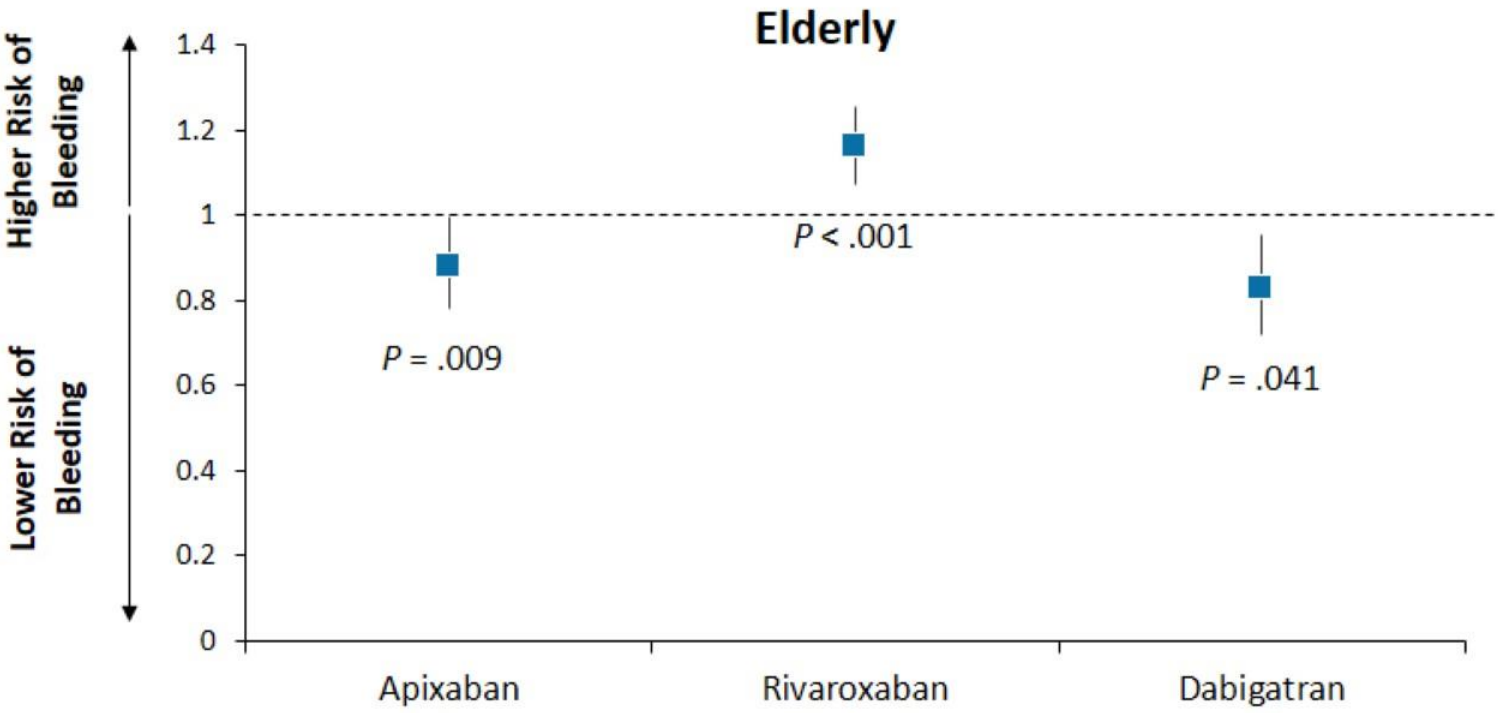
*Many of these patients may be on the lower dose of prescribed NOAC.

No indication for use of any of the drugs for CrCl < 15 mL/min

No need for bridging with LMWH/UFH when anticoagulant stopped

Heidbuchel H, et al. *Europace.* 2015. [Epub ahead of print]

Risk of Bleeding Among Elderly Patients on NOACs



- Both elderly AF patients, and all AF patients, who initiated apixaban or dabigatran had a lower risk of bleeding than patients who initiated warfarin
- Patients who initiated rivaroxaban had a higher risk of bleeding compared to those who initiated warfarin

Lin I, et al. ESC 2016. Advances in Science 2065.

Third Question

How we can decrease the bleeding risk ?

Factors that might increase bleeding risk

Pharmacodynamic factors	■ Age ≥75 years
Factors increasing dabigatran plasma levels	**Major** ■ Moderate renal impairment (CrCl 30–50 mL/min) ■ P-glycoprotein inhibitor co-treatment **Minor** ■ Low body weight (<50 kg)
Pharmacodynamic interactions	■ Aspirin ■ NSAIDs ■ Clopidogrel
Special haemorrhagic risks	■ Congenital or acquired coagulation disorders ■ Thrombocytopenia or functional platelet defects ■ Active ulcerative GI disease ■ Recent GI bleeding ■ Recent biopsy or major trauma ■ Recent ICH ■ Brain, spinal, or ophthalmic surgery ■ Bacterial endocarditis

Before Prescribing a NOAC, Consider:

Factors Affecting Bleeding Risk

- Advanced age
- Prior history of GI bleeding
- Concurrent use of antiplatelets
- Improper dosing of the NOAC
- Depending on the NOAC chosen, impaired renal or hepatic function may also increase the risk of bleeding

Checklist to Review

- Adequately assess any prior history of bleeding
- Ensure age-appropriate cancer screening has been completed
- Ensure that the dosage of the medication is appropriate, based on patient's age and renal status

Factors Linked to Raised Plasma Concentrations of NOACs

	Dabigatran	Rivaroxaban	Apixaban	Edoxaban*
Age ≥80 years	Reduce dose			No data
Age ≥75 years				No data
Weight ≤60 kg				Reduce dose
Renal impairment				
Other risk factor†				

Consider dose reduction if ≥2 yellow factors.

†Other risk factors include:

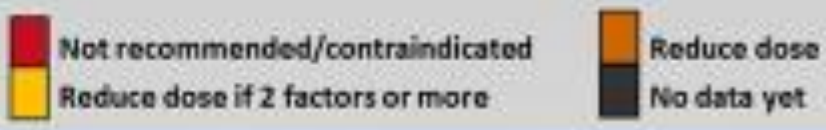
- Pharmacodynamic interactions
  - Antiplatelet drugs
  - NSAIDs
  - Systemic steroid therapy
  - Other anticoagulants
- Recent critical organ surgery (eg, brain, eye)
- Thrombocytopenia (eg, chemotherapy)
- HAS-BLED score ≥3

NSAIDs = nonsteroidal anti-inflammatory drugs

Medscape EDUCATION

Heidbuchel H, et al. *Eur Heart J.* 2013;34(27):2094-2106.

Effect on NOAC Plasma Levels From Drug-Drug Interactions, and Recommendations



	via	Dabigatran	Apixaban	Edoxaban*	Rivaroxaban
Atorvastatin	P-gp weak CYP3A4	+18%	No data	No effect	No effect
Digoxin	P-gp	No effect	No data	No effect	No effect
Verapamil	P-gp weak CYP3A4	+12%-180% reduce dose, take together	No data	+53% (SR) Reduce dose	Minor effect Use with caution if CrCl: 15-50 mL/min
Diltiazem	P-gp weak CYP3A4	No effect	+40%	No data	Minor effect Use with caution if CrCl: 15-50 mL/min
Quinidine	P-gp	+50%	No data	+80% Reduce dose	+50%
Amiodarone	P-gp	+12%-60%	No data	No effect	Minor effect Use with caution if CrCl: 15-50 mL/min
Dronedarone	P-gp weak CYP3A4	+70%-100%	No data	+88% Reduce dose	No data

*Not approved for clinical use

Heidbuchel H, et al. *Europace*. 2013;15(5):625-651.

NOAC Dose Reduction

RE-LY[a] Dabigatran

- For US regulators: CrCl 15-30 mL/min: 75 mg twice daily
- Age >80 years
- CrCl 30-50 mL/min + P-gp inhibitor, dronedarone, or ketoconazole

ROCKET -AF[b] Rivaroxaban

- 20 → 15 mg once daily for:
  - Creatinine clearance <30-49 mL/min

ARISTOTLE[c] Apixaban

- 5 → 2.5 mg twice daily for ANY TWO of:
  - Age ≥80 years
  - Body weight ≤60 kg
  - Serum creatinine ≥1.5 mg/dL
- US regulators
  - Strong dual inhibitors of CYP3A4 and P-gp

ENGAGE-AF[d] Edoxaban

- 60 → 30 mg once daily for
  - Creatinine clearance 30-50 mL/min
  - Body weight ≤60 kg
  - Use of quinidine, verapamil, or dronedarone

a. Connolly SJ, et al. *N Engl J Med.* 2009;361:1139-1151.
b. Patel MR, et al. *N Engl J Med.* 2011;365:883-891.
c. Granger CB, et al. *N Engl J Med.* 2011;365:981-992.
d. Giugliano RP, et al. *N Engl J Med.* 2013;369:2093-2104.

Suggestions to Decrease Risk of Bleeding with Novel Anticoagulants

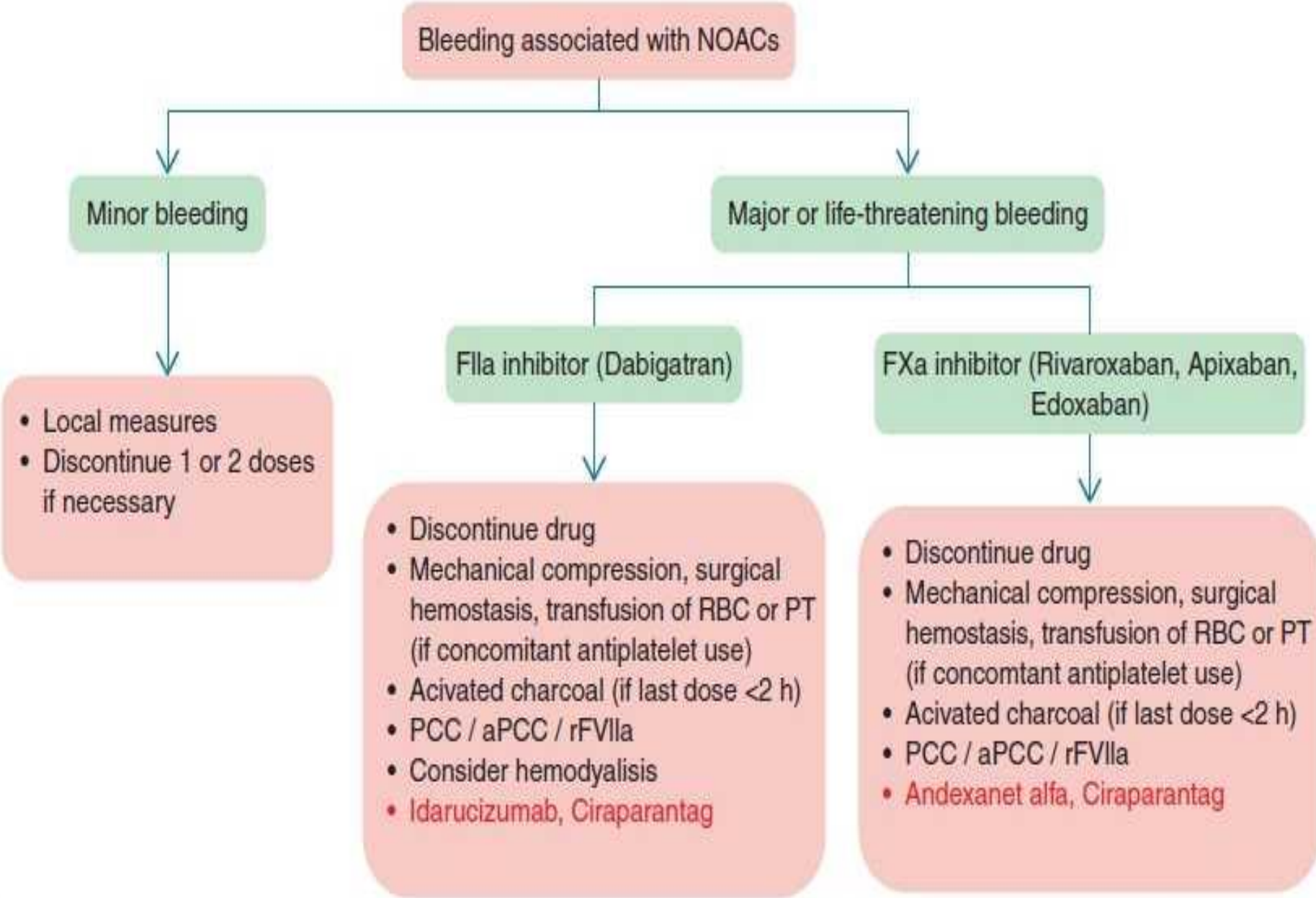
- Select patients based on knowledge of renal function
- Monitor renal function by checking creatinine clearance once or twice per year especially in the following scenarios:
  - Exacerbation of heart failure
  - Hypotensive episode
  - Any event contributing to deterioration in renal performance
- Physicians must accept responsibility for guiding the dose

Fourth Question

What is the correct bleeding management ?

Guidance for patients: bleeding

- Seek emergency care right away for:
  - Unusual bruising
  - Pink or brown urine
  - Red or black, tarry stools
  - Coughing up blood
  - Vomiting blood, or vomit that looks like coffee grounds
- Get prompt medical attention for:
  - Pain, swelling, or discomfort in a joint
  - Headaches, dizziness, or weakness
  - Recurring nosebleeds
  - Unusual bleeding from gums
  - Bleeding from a cut that takes a long time to stop
  - Vaginal bleeding that is heavier than normal



GI Bleeding and NOACs

- Historic risk for GI bleeding in warfarin clinical trials (0.3%-0.5% per year)[a]
- Certain AF patients are at increased risk of bleeding (eg, elderly, with comorbid medical conditions, taking concomitant medications)[b]
- GI bleeding can occur at any level along GI tract[c]

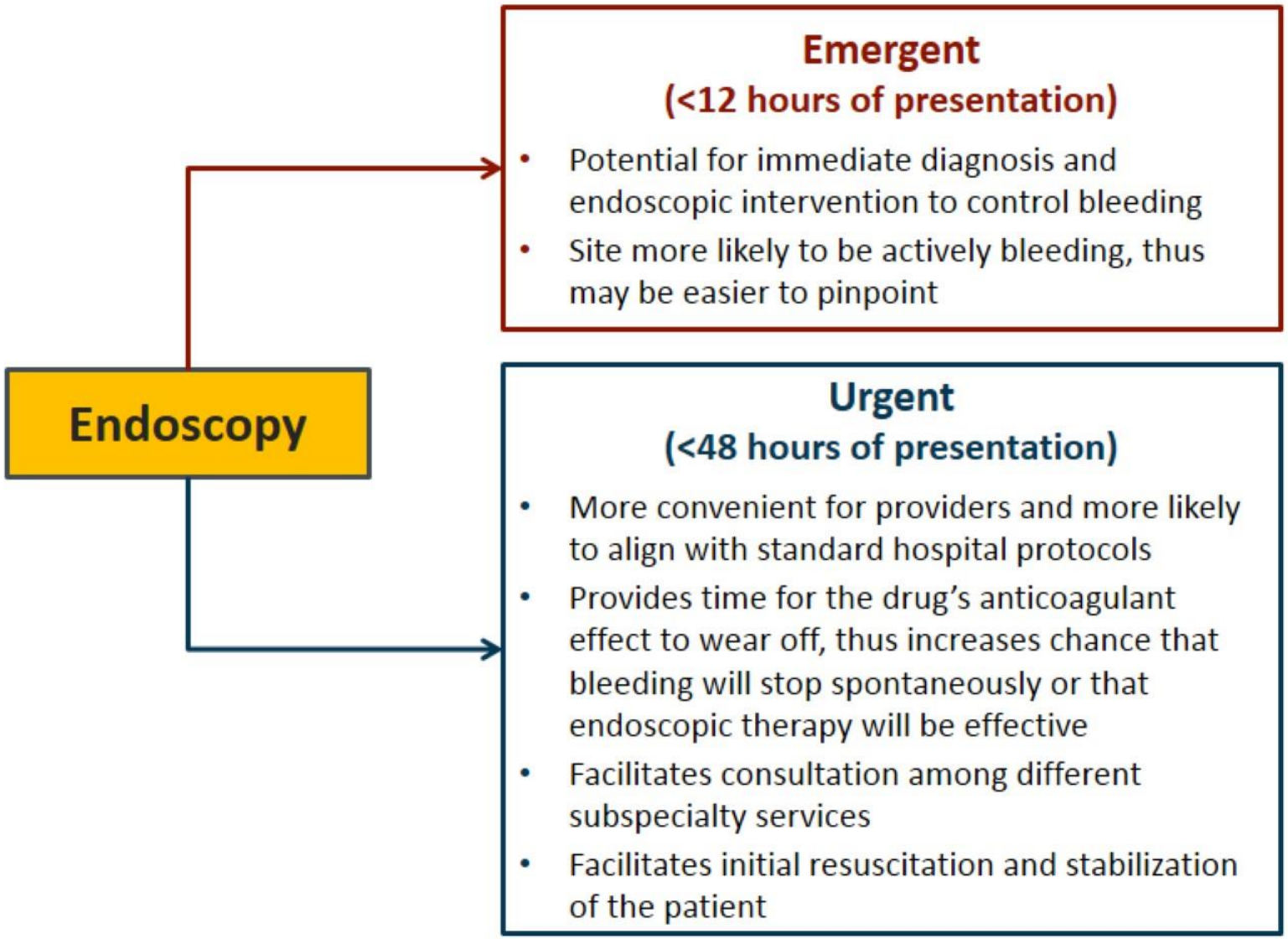
AF = atrial fibrillation

a. Coleman CI, et al. *Int J Clin Pract*. 2012;66(1):53-63.
b. Bauer KA. *Hematology Am Soc Hematol Educ Program*. 2013;2013:464-470.
c. Desai J, et al. *Thromb Haemost*. 2013;110(2):205-212.

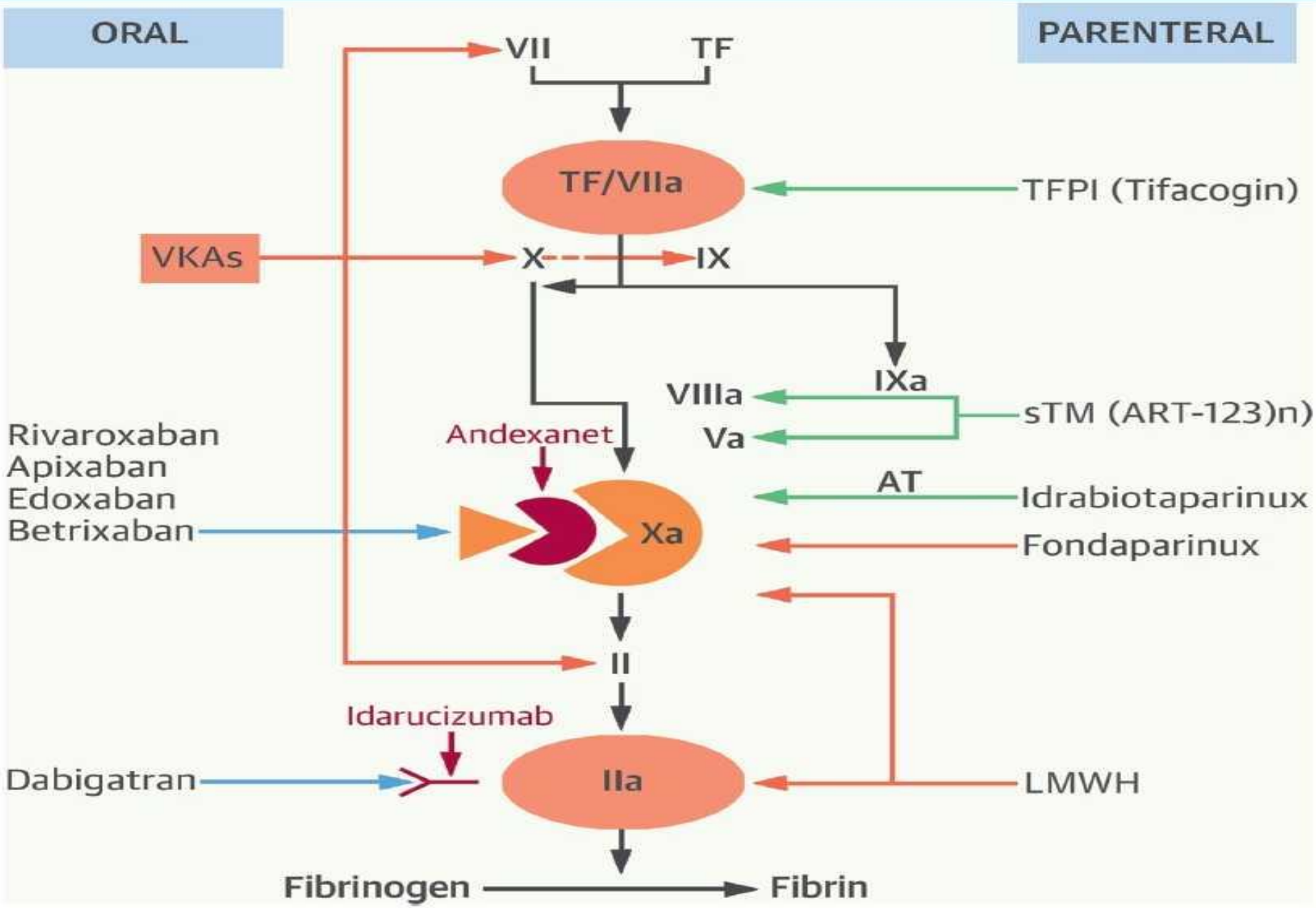
Triage of GI Bleeding in Patients Taking NOACs: Points to Consider

- Collaborative effort of all disciplines involved
- Is the patient stable?
  - Vital signs
  - Physical appearance
  - Hemoglobin and hematocrit
- When was the last dose of the NOAC ingested?
- What is the patient's renal function?

Endoscopy in GI Bleeding With NOACs



Desai J, et al. *Thromb Haemost*. 2013;110:205-212.



Becattini, C. et al. J Am Coll Cardiol. 2016;67(16):1941-55.

Short half life is probably best antidote of NOACs

	Xabans			DTI
	Rivaroxaban	**Apixaban**	**Edoxaban**	**Dabigatran**
Target	Factor Xa			Thrombin
Prodrug	No	No	No	Yes
Oral bioavailability	80–100%*	50%	62%	6.5%
Renal clearance of absorbed active drug	33%	27%	~55-60%	>80%
T_{max} (h)	2–4	1–3	1–2	2–6#
Half-life (h)	5–13	8–13	10–14	12–14
Fixed Dosing (SPAF indication)	OD	BID	OD	BID

**15–20 mg to be taken with food; #Postoperative period*

{ *1. Eriksson BI et al. Annu Rev Med. 2011;62:41-57; 2. Frost et al. J Thromb Haemost. 2007;5(Suppl 2):P-M-664;*
3. Kubitza D et al. Clin Pharmacol Ther. 2005;78(4):412-421; 4. Ogata K et al. J Clin Pharmacol. 2010;50(7):743-753;
5. Stangier J et al. J Clin Pharmacol 2005;45(5):555-563; 6. Dabigatran SmPC;
7. Apixaban SmPC; 8. Rivaroxaban SmPC; 9. Edoxaban SmPC; 10. Heidbuchel et al. Europace 2013;15(5):625-651 }

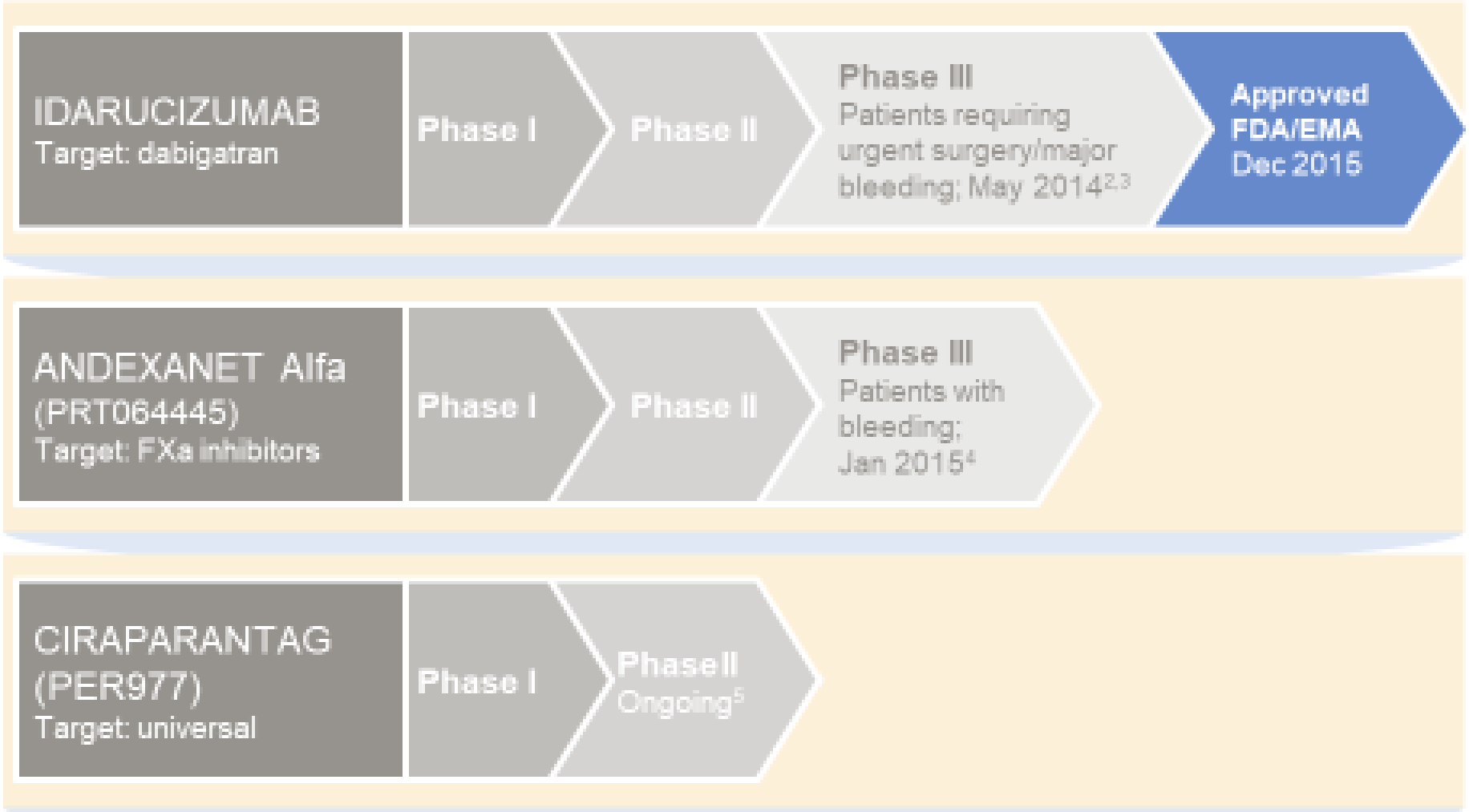
Questions to Ask Before Using a Reversal Agent With Bleeding from a NOAC

- When did the patient take the last dose?
- Is the bleeding critical or life threatening?
- Is the patient hemodynamically stable?
- Did the bleeding start more than 24 hours ago?
- What is the renal function?
- What are the results of the coagulation assays?

Candidates for Reversal Agents

- Patients presenting with bleeding
  - Life-threatening bleeding (eg, intracranial)
  - Critical organ or closed-space bleeding (eg, pericardial, retroperitoneal)
  - Ongoing bleeding despite measures to control bleeding
- Patients at high risk of bleeding
  - Requiring emergent/urgent procedure
  - Expected long delay in spontaneous restoration of normal hemostasis (eg, over-anticoagulation, renal failure)

Antidotes



1. Adapted from Greinacher et al. Thromb Haemost 2015; 2. Clinicaltrials.gov: NCT02104947; 3. Pollack C, et al. NEJM 2015; 4. ClinicalTrials.gov Identifier: NCT02329327; 5. ClinicalTrials.gov Identifier: NCT02207257

Idarucizumab

Reversal Agent for Dabigatran

- Humanized Fab fragment
- Specific, with high affinity for dabigatran
- Renal excretion
- Short half-life
- No intrinsic procoagulant or anticoagulant activity
- Immediate, complete, and sustained reversal of dabigatran

Pollack CV, et al. *N Engl J Med*. 2015;373:511-520.

Idarucizumab Prescribing Information in the US*

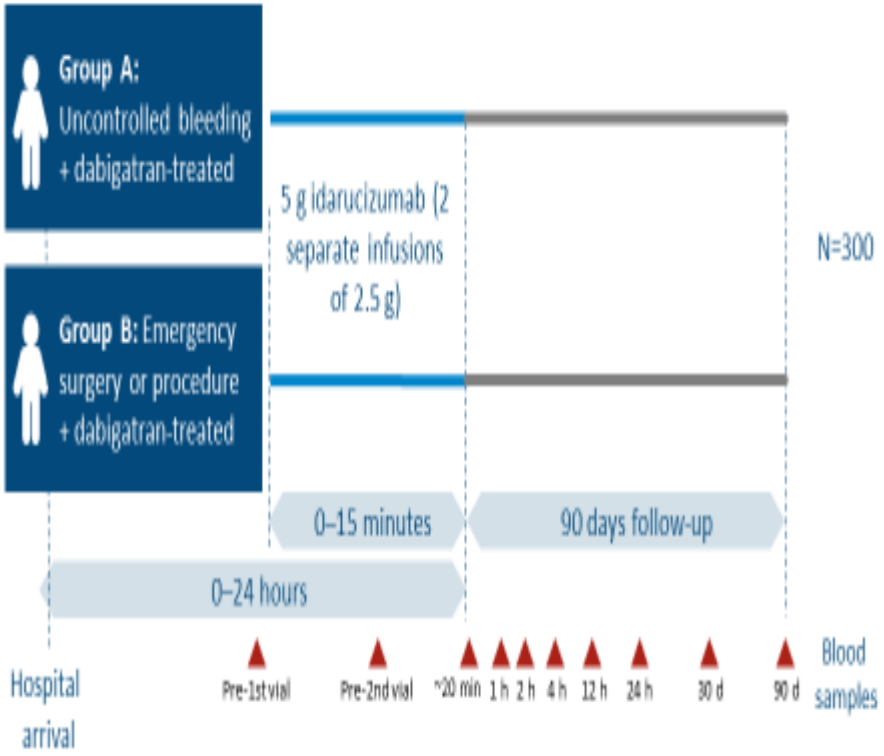
- For emergency surgery/urgent procedures
- In life-threatening or uncontrolled bleeding

*Please refer to prescribing information for specifics of dosing in the US. The EMA has recommended approval of idarucizumab. EU-wide marketing authorization is pending.

Praxbind ® 2015

http://docs.boehringer-ingelheim.com/Prescribing%20Information/PIs/Praxbind/Praxbind.pdf?DMW_FORMAT=pdf

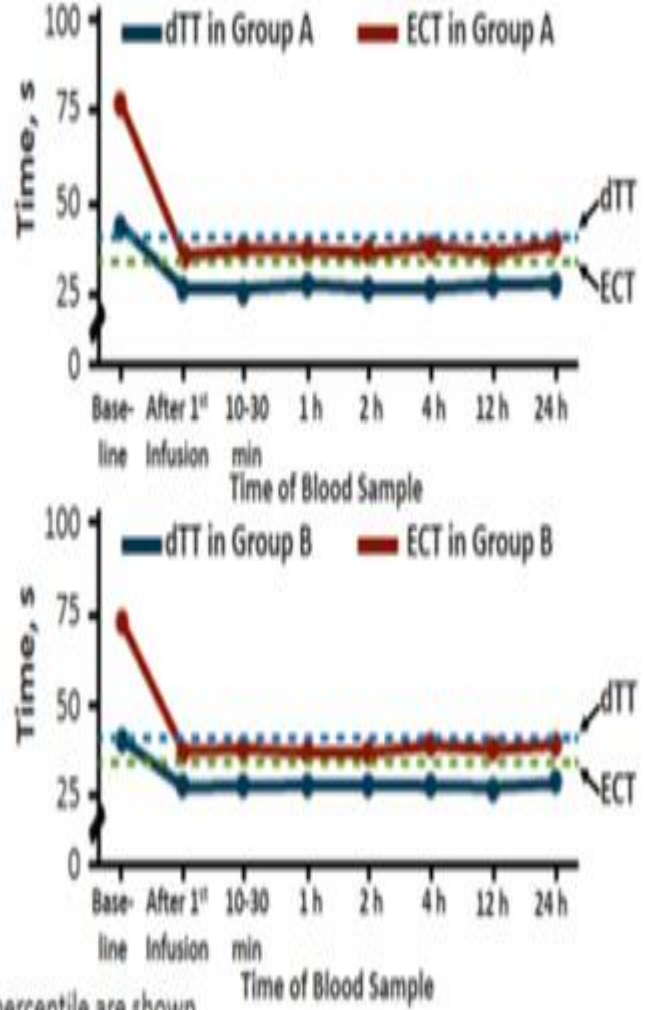
RE-VERSE AD: Multicenter, Ongoing, Open-label, Single-arm, Phase 3 Study



Pollack CV, et al. *N Engl J Med* 2015; June 22 [Epub ahead of print].

RE-VERSE AD

Idarucizumab Interim Analysis



Data for the 50th percentile are shown.

Dashed lines indicate the upper limit of the normal range for the tests.

Pollack CV. *N Engl J Med*. 2015;373:511-520.

RE-VERSE AD: Conclusions

In a cohort of elderly patients with multiple comorbidities taking dabigatran who presented with life-threatening emergencies:

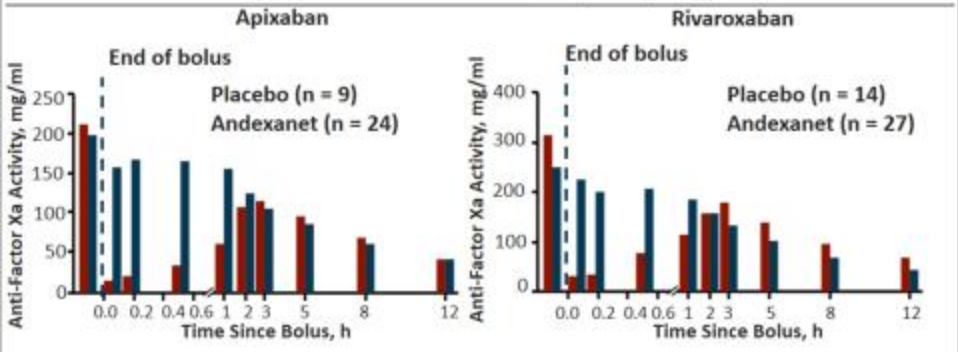
- One 5 g dose of idarucizumab resulted in immediate and complete reversal of dabigatran anticoagulation in 88-98% of patients
- Mean time to cessation of bleeding in Group A was < 12 hours*
- Operator judged intraoperative haemostasis as "normal" in 92% of evaluable Group B patients
- No safety concerns identified to date in the analysis

*Assessment of bleeding cessation may be difficult in internal bleeding into confined space such as intramuscular or intracranial bleeding.

Pollack CV, et al. *NEJM.* 2015.June 22. [Epub ahead of print].

Other Reversal Agents in Development

Company	Agent	Target
Portola Pharmaceuticals, Inc.	Andexanet alfa: recombinant, modified human FXa	Factor Xa Inhibitors (rivaroxaban; apixaban; edoxaban)
Perosphere Inc.	Aripazine (PER977): di-arginine piperazine	All NOACs (dabigatran; rivaroxaban; apixaban; edoxaban) UFH, LMWH, fondaparinux



Greinacher A, et al. *Thromb Haemost*. 2015;113;931-942;
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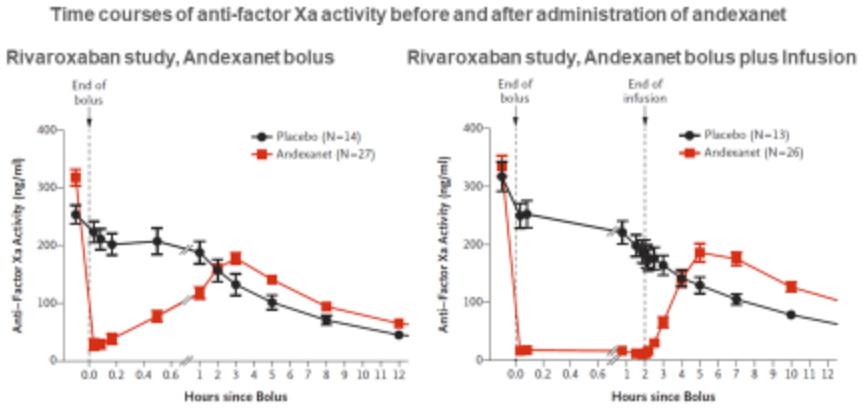
Andexanet alfa for the reversal of factor Xa inhibitor activity



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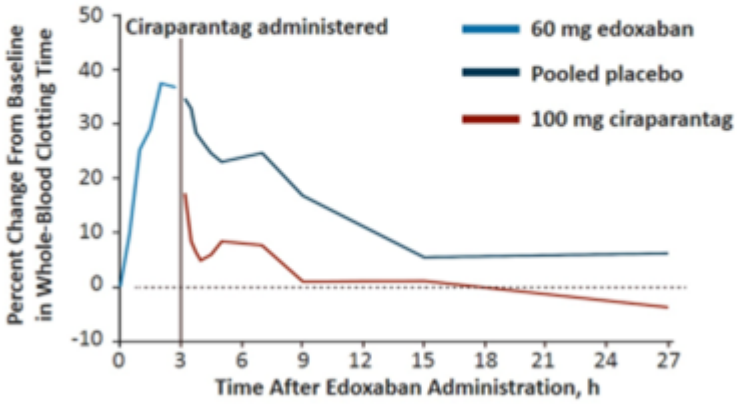
Siegal DM et al. NEJM 2015;373:2413-24

Ciraparantag/Aripazine
Reversal of Edoxaban Activity



Ansell JE, et al. *N Engl J Med*. 2014;371:2141-2142.

Prothrombotic Complications of Reversal Agents

- Uncommon with PCCs
  - About 2%
- NOACs
  - To date, no clinical evidence of hypercoagulability with idarucizumab or andexanet alfa
    - Biochemical lab tests may show a little hyperactivation of coagulation system

Conclusions

- NOACs increasingly used in practice, especially in older comorbid patients with atrial fibrillation
- Risk and severity of major bleeding is lower for NOACs than with warfarin
- When bleeding on NOACs *does* occur, most cases can be readily managed with general measures
- When reversal is indicated, specific reversal agents would streamline and optimize care

Philosophical considerations.....

- Bleeding events are associated with the physician.
- Ischemic events are associated with fate.
- Prevention is not adequately recognized.
- None of us has ever received a thank you letter for a stroke that did not happen!

NOAC Bleeding
Pooled Analysis

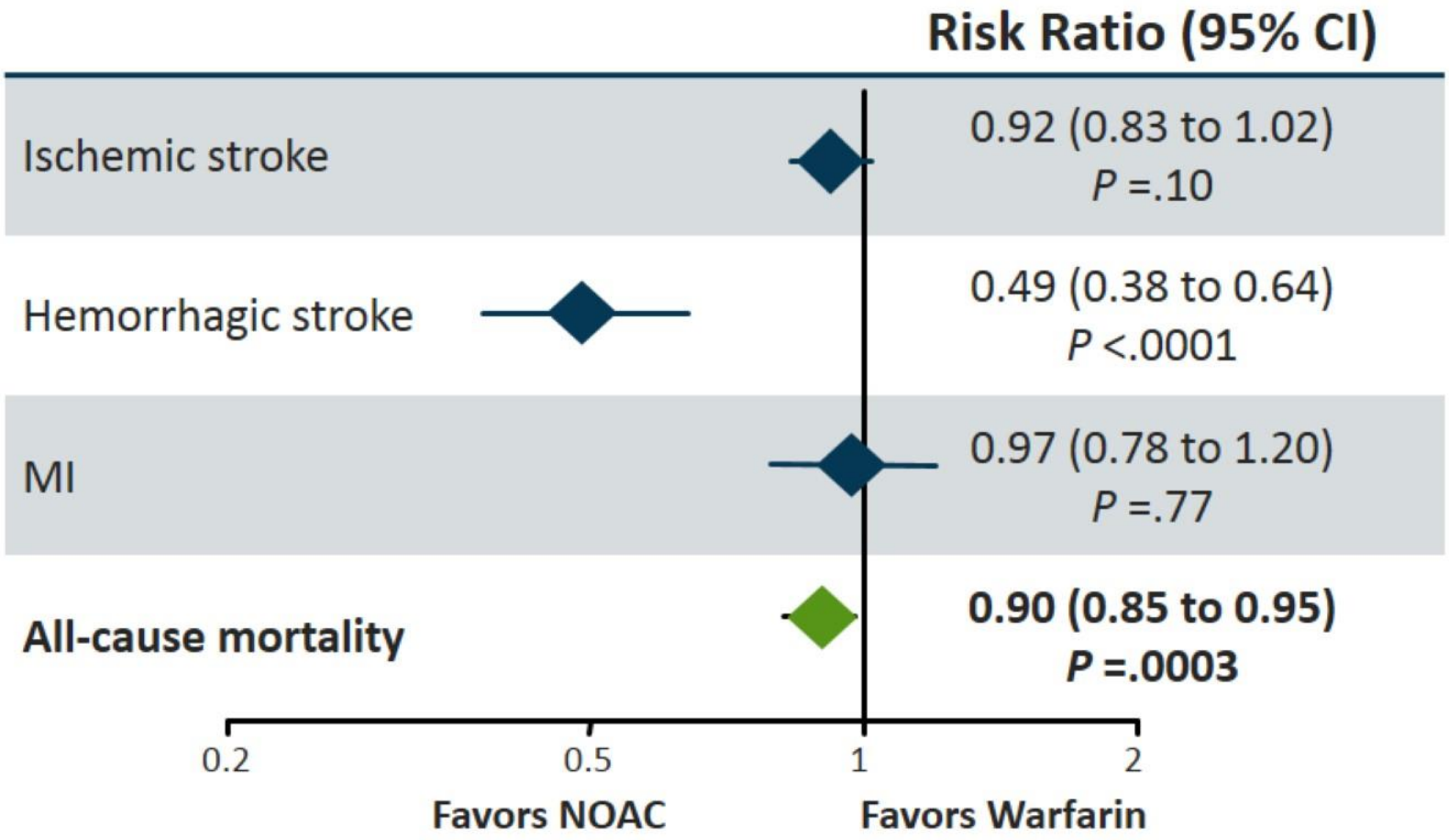
	RR* (95% CI)	*P* Value
Hemorrhagic stroke	0.49 (0.38-0.64)	< .0001
All-cause mortality	0.90 (0.85-0.95)	.0003
Intracranial hemorrhage	0.48 (0.39-0.59)	< .0001

*vs warfarin.

Ruff CT, et al. *Lancet.* 2014;383:955-962.

NOAC Meta-analysis

Secondary Efficacy Outcomes



Heterogeneity: *P* = NS for all outcomes.

Ruff CT, et al. *Lancet* 2014;383:955-962.

Intracranial haemorrages and NOACs

Study	$CHADS_2$	Intracranial haemorrages
RE-LY	2.1	0.3
ROCKET-AF	3.5	0.5
XANTUS (ph IV Rivaroxaban)	2.1	0.4
ENGAGE AF	2.8	0.3
ARISTOTLE	2.1	0.3
AVERROES	2.0	0.4

{.*Patel MR et al. N Engl J Med. 2011;365(10):883-891; Granger CB et al. N Engl J Med. 2011;365(11):981-992; Giugliano RP et al. N Engl J Med. 2013;369(22):2093-2104; Connolly SJ et al. N Engl J Med. 2009;361(12):1139-1151; Camm AJ et al, Eur Heart J 2015; doi: 10.1093/eurheartj/ehv466; Connoly et al NEJM 10.1056/nejmoa1007432 2 nejm.org*}

Minimizing the Burden of Bleeding With NOACs and Related Complications

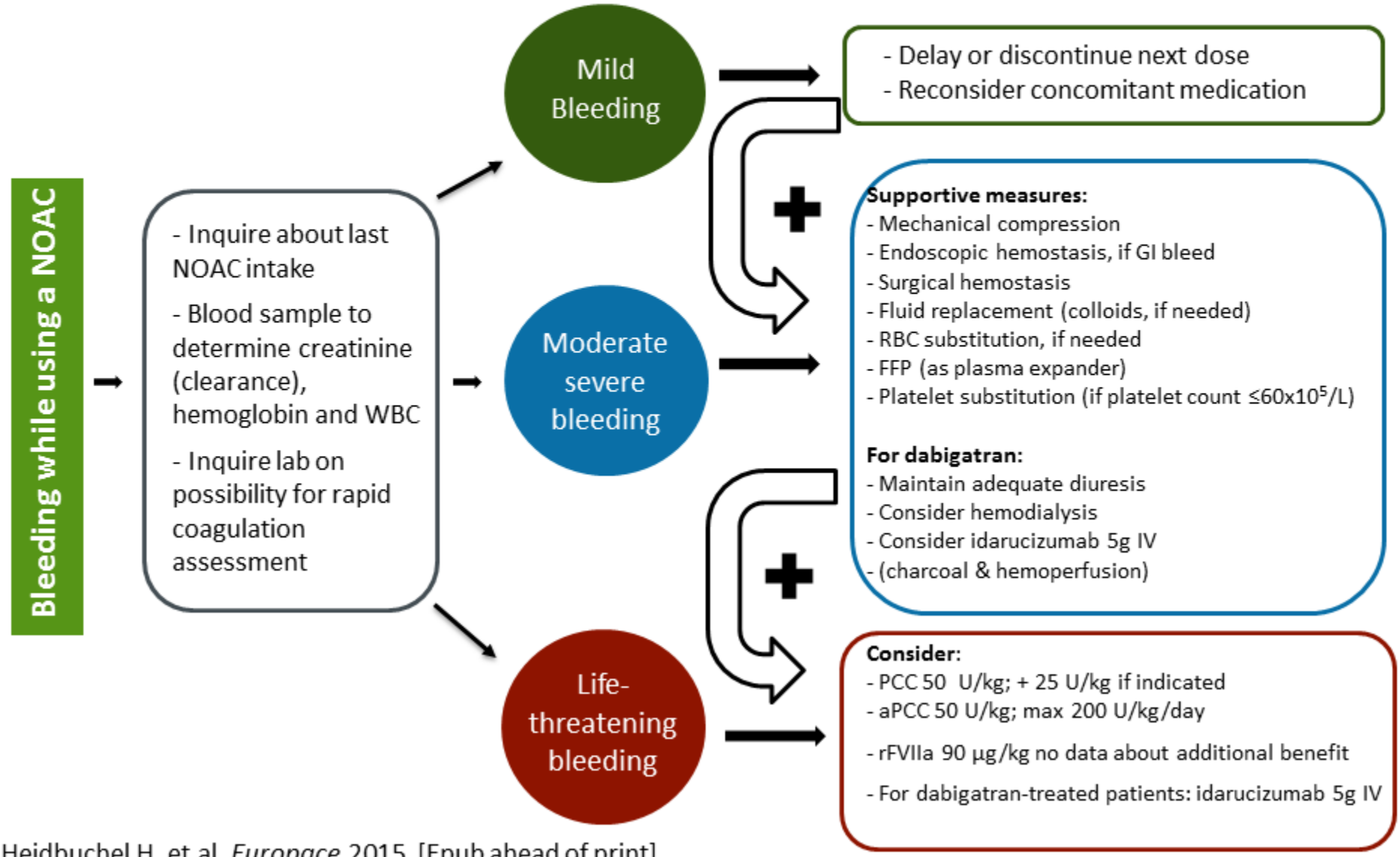
Prevention of bleeding

- Patient selection
- Drug and dose selection
- Consider modifiable bleeding risk factors

Management of bleeding

- Hold drug
- Secure hemostasis
- Resume anticoagulation when possible

NOACS: Management of Bleeding



Heidbuchel H, et al. *Europace.* 2015. [Epub ahead of print]

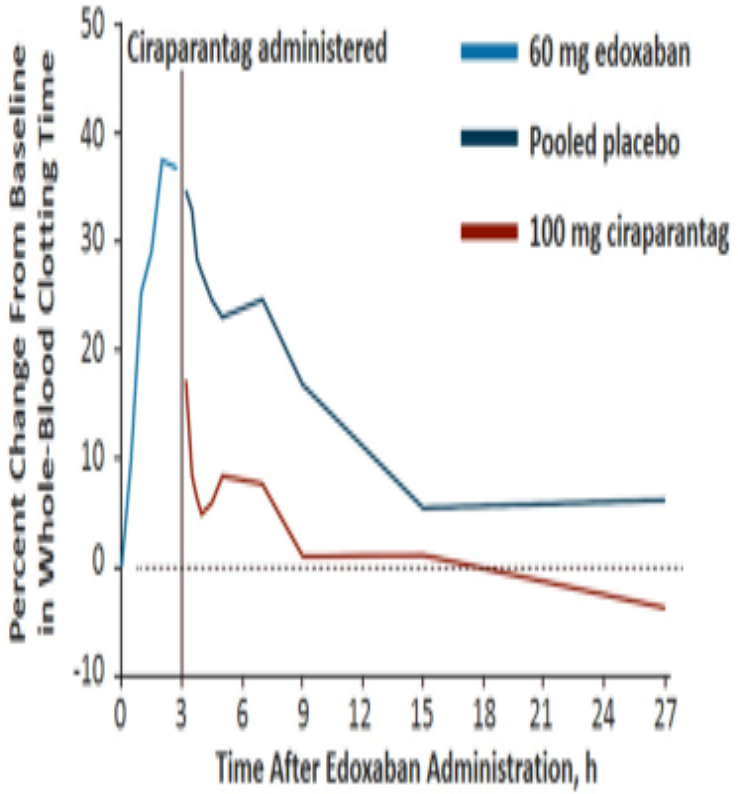
Ciraparantag

- Small synthetic molecule that binds to unfractionated heparin, LMWH, fondaparinux, dabigatran, and direct Xa inhibitor through hydrogen binding and charge-charge interaction
- Animal study: Seemed to reduce bleeding
- In volunteers: Reversed the effect of edoxaban
- Hypothesized to provide complete reversal of heparin, fondaparinux, dabigatran, rivaroxaban, apixaban, and edoxaban

Gomez-Outes, et al. *Recent Patients on Cardiovascular Drug Discovery*.2014;9:2-10.

Ciraparantag/Aripazine

Reversal of Edoxaban Activity



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Factors that might increase bleeding risk

Pharmacodynamic factors	Age ≥75 years
Factors increasing dabigatran plasma levels	**Major** Moderate renal impairment (CrCl 30–50 mL/min) P-glycoprotein inhibitor co-treatment **Minor** Low body weight (<50 kg)
Pharmacodynamic interactions	Aspirin NSAIDs Clopidogrel
Special haemorrhagic risks	Congenital or acquired coagulation disorders Thrombocytopenia or functional platelet defects Active ulcerative GI disease Recent GI bleeding Recent biopsy or major trauma Recent ICH Brain, spinal, or ophthalmic surgery Bacterial endocarditis

Guidance for patients: bleeding

- Seek emergency care right away for:
  - Unusual bruising
  - Pink or brown urine
  - Red or black, tarry stools
  - Coughing up blood
  - Vomiting blood, or vomit that looks like coffee grounds
- Get prompt medical attention for:
  - Pain, swelling, or discomfort in a joint
  - Headaches, dizziness, or weakness
  - Recurring nosebleeds
  - Unusual bleeding from gums
  - Bleeding from a cut that takes a long time to stop
  - Vaginal bleeding that is heavier than normal

Other Reversal Agents in Development

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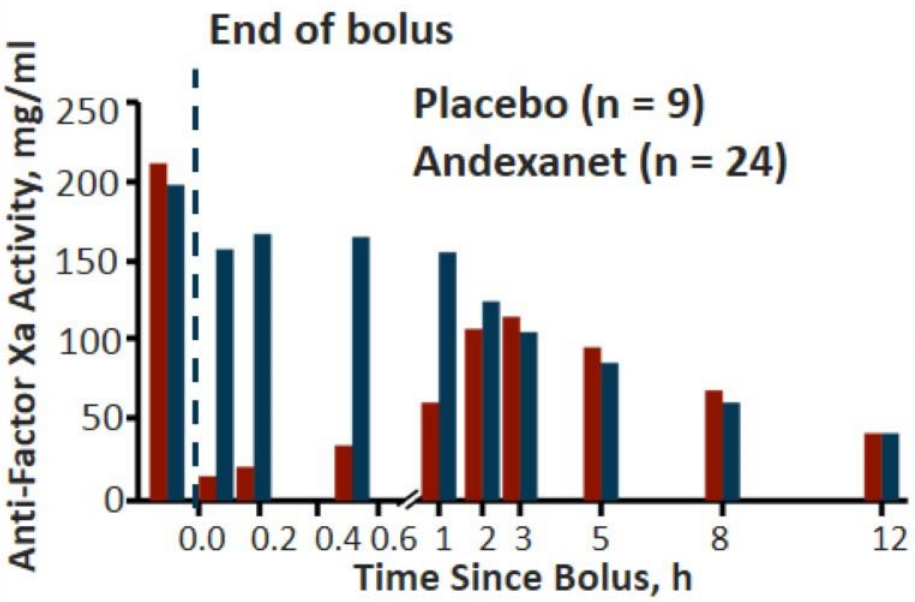
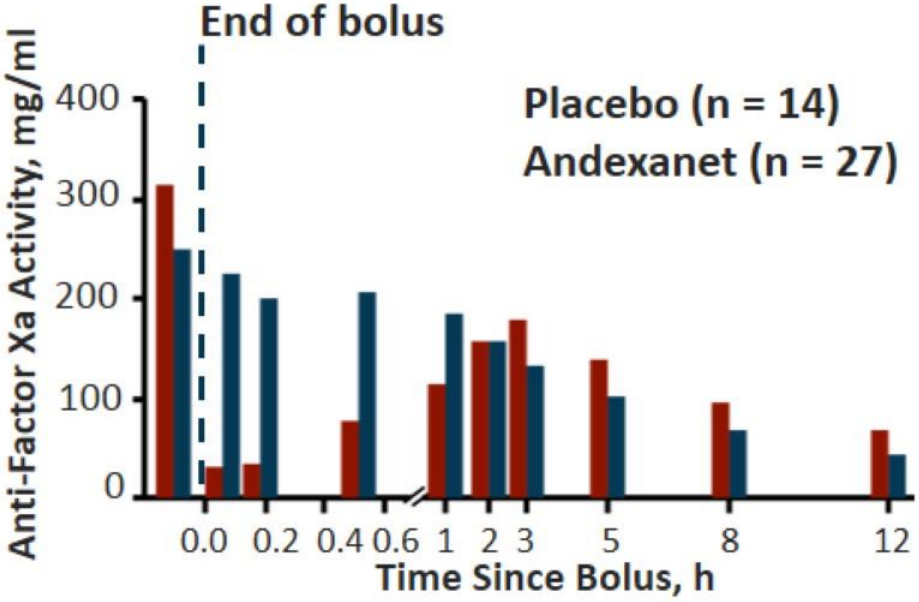
Apixaban



Rivaroxaban



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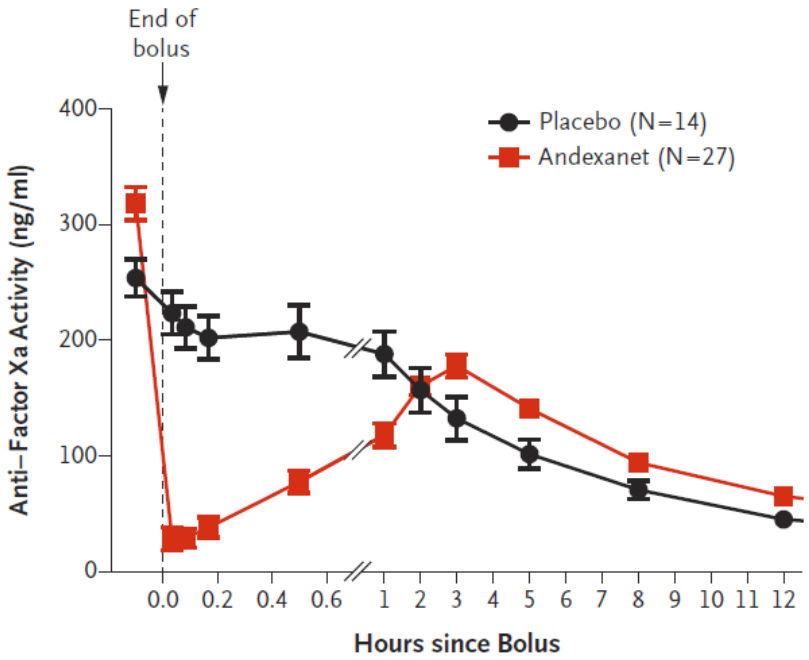
Siegal DM, et al. *N Engl J Med*. 2015. [Epub ahead of print].

Approval Number:
L.IT.MA.10.2017.3011

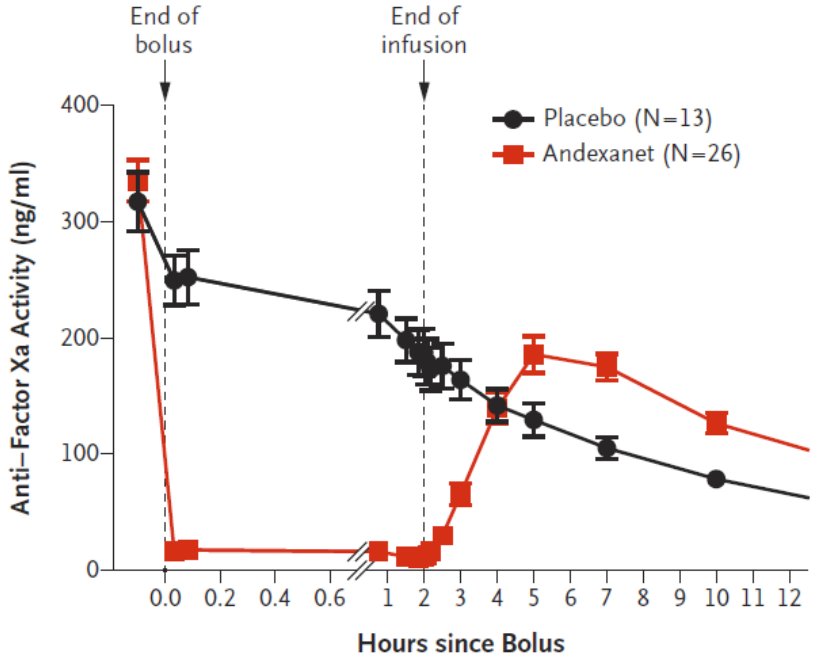
Andexanet alfa for the reversal of factor Xa inhibitor activity

Time courses of anti-factor Xa activity before and after administration of andexanet

Rivaroxaban study, Andexanet bolus



Rivaroxaban study, Andexanet bolus plus Infusion



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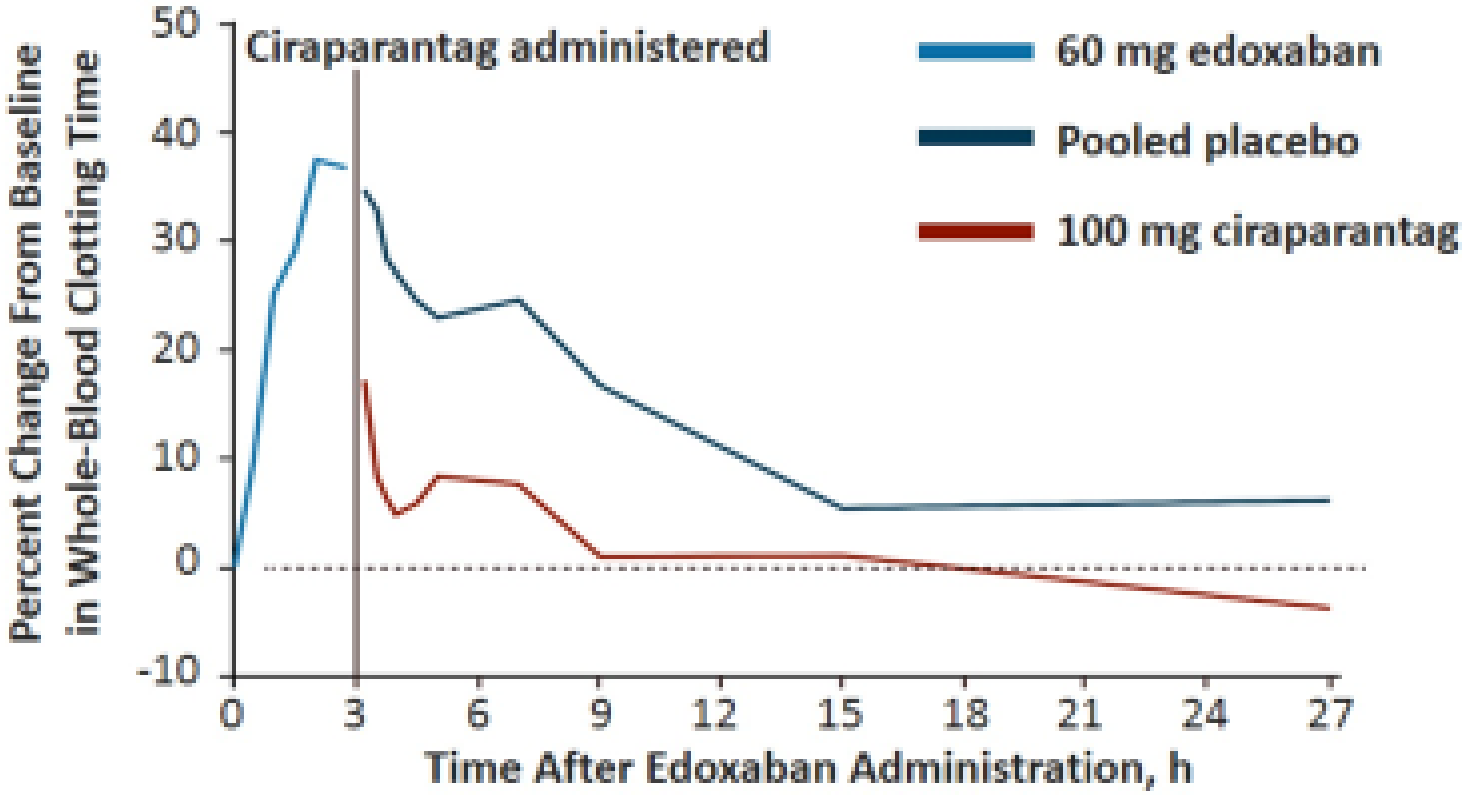


Ansell JE, et al. *N Engl J Med*. 2014;371:2141-2142.

Prior to Reversal

Factors to Consider

- NOAC: agent taken, dose, time of last ingestion
- Renal function
- Coagulation assessment
  - Dabigatran: aPTT, TT, dTT, ECT
  - Factor Xa inhibitors: hemostatic testing varies from patient to patient and depending on type of test

Need for rapid, readily available anti-factor Xa assays calibrated for each agent to measure drug levels

Candidates for Reversal Agents

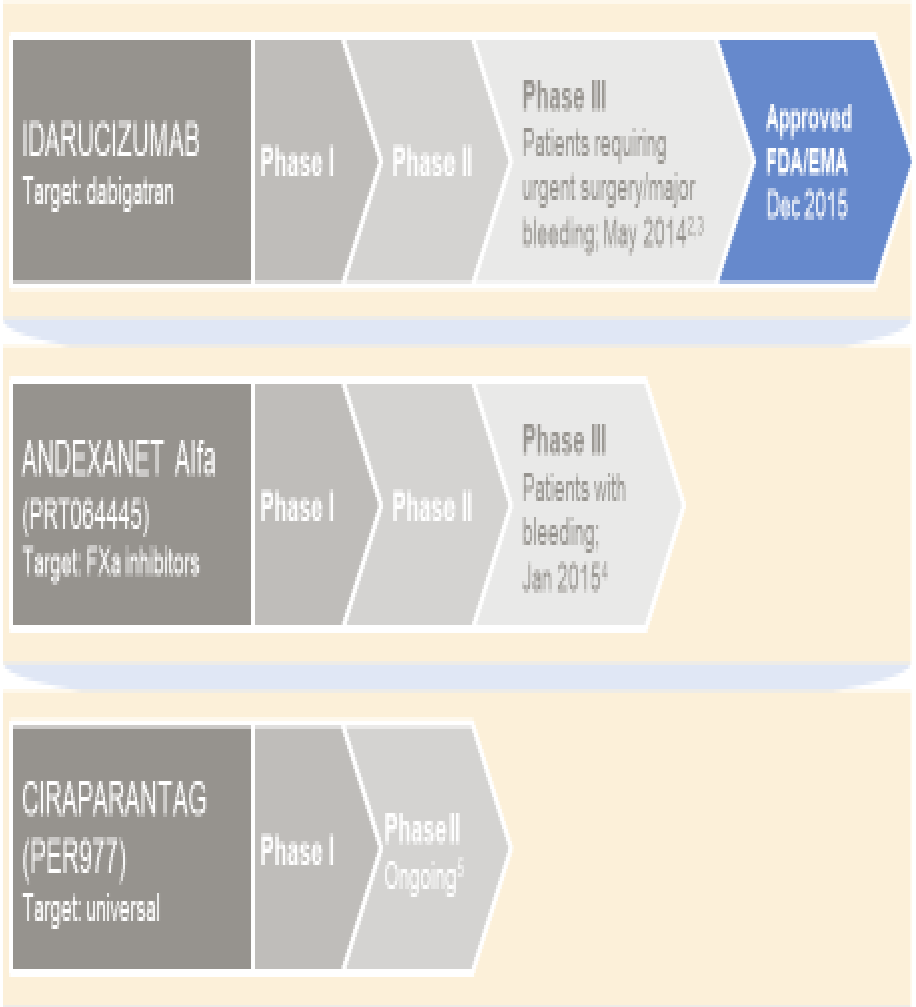
- Patients presenting with bleeding
  - Life-threatening bleeding (eg, intracranial)
  - Critical organ or closed-space bleeding (eg, pericardial, retroperitoneal)
  - Ongoing bleeding despite measures to control bleeding
- Patients at high risk of bleeding
  - Requiring emergent/urgent procedure
  - Expected long delay in spontaneous restoration of normal hemostasis (eg, over-anticoagulation, renal failure)

Heidbuchel H, et al. *Europace*. 2015;17:1467-1507.

General Approach to NOAC-related Major Bleeding

- Identify
- Assess
  - Drug
  - Time of last dose
  - Renal function
- Resuscitate and support
- Can sometimes assess extent of anticoagulation *qualitatively*

Antidotes



1. Adapted from Greinacher et al. Thromb Haemost 2015; 2. ClinicalTrials.gov: NCT02104947; 3. Pollack C, et al. NEJM 2015; 4. ClinicalTrials.gov Identifier: NCT02329327; 5. ClinicalTrials.gov Identifier: NCT02207257

NOAC Antidotes in Clinical Trials

Andexanet[a] (PRT064445)	• Antidote for factor Xa inhibitors • Recombinant protein, targets and sequesters direct and indirect factor Xa inhibitors with high specificity
Aripazine[b] (PER977)	• Antidote for factor Xa inhibitors, DTIs, LMWH, and fondaparinux • Synthetic small molecule; reversal effect through direct binding to anticoagulant
Idarucizumab[c] (BI 655075)	• Antidote for DTIs • Fully humanized antibody fragment

DTI = direct thrombin inhibitor; LMWH = low-molecular-weight heparin

a. ClinicalTrials.gov website[11]; b. Dolgin E. *Nat Med*. 2013;19:251[12]; c. ClinicalTrials.gov website.[13]