Overview

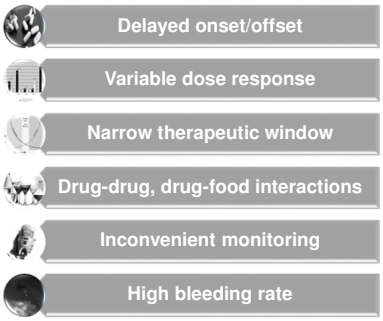
- For decades, warfarin has been the cornerstone for anticoagulation in patients with AF and for those with VTE.
- The widespread adoption of the NOACs has ushered in a new era of anticoagulation.
- Providers are now faced with the challenge of interpreting the data from a host of pivotal randomized controlled trials and selecting from a variety of anticoagulants, each with specific advantages and disadvantages.

The Rationale for Non-Vitamin K Oral Anticoagulants (NOACS)

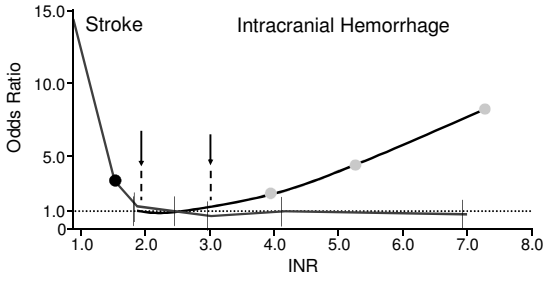
Warfarin for Long-Term Anticoagulation

- Excellent efficacy
- Low cost ($4/month; $10/ 3 mos)
- Long track Record (1954)
- Anticoagulation clinics maintain time in therapeutic range (TTR)>60%
- Pharmacogenomics may improve dosing
- Point-of-care self-testing
- INR Testing q12 weeks if stable

Disadvantages of Warfarin

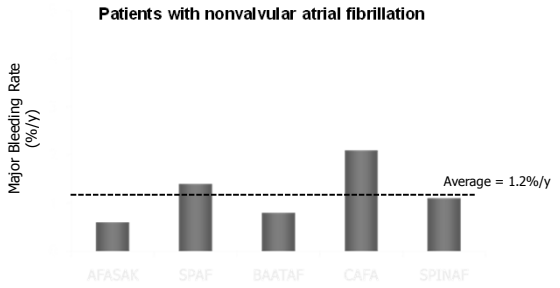


Narrow Therapeutic Window



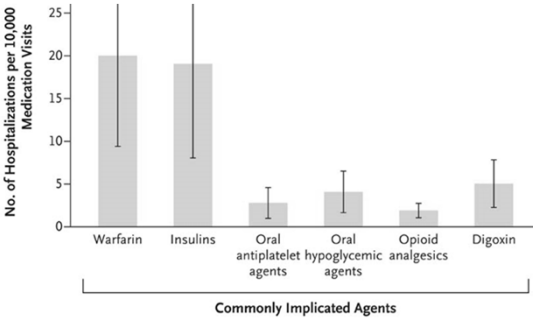
Fuster V, et al. J Am Coll Cardiol 2001;38:1231

Annual Rates of Major Bleeding in Stroke Prevention Trials



Fuster V, et al. Circulation 2011;123:e269

Emergency Hospitalizations for Adverse Drug Events in Older U.S. Adults (2007–2009)



Budnitz DS, et al. N Engl J Med 2011;365:2002

Challenges Monitoring Warfarin

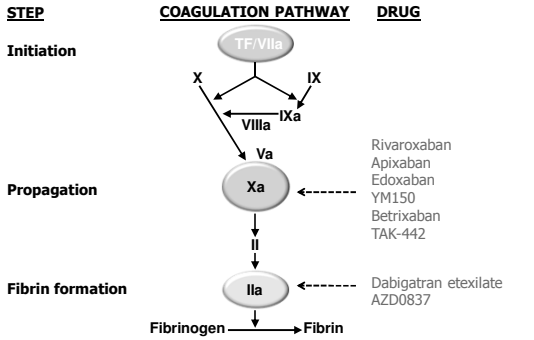
(n=168, mean age 86 years)	Frequency
Managed warfarin by themselves	53%
Had warfarin-associated adverse drug reactions	61%
Had INR >8 and requiring ED visit for reversal	7%
Anticoagulation Management Service could not reach patient	13%
Patient missed appointment with Anticoagulation Management Service	11%
Had therapeutic INR ≤60% of the time	16%

Tan KM, et al. Eur Geriatr Med 2012;3:78

Warfarin vs. NOACs

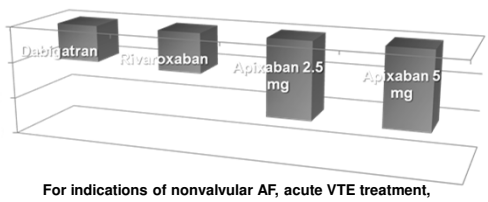
Feature	Warfarin	New Agents
Onset	Slow	Rapid
Dosing	Variable	Fixed
Food effect	Yes	No
Drug interactions	Many	Few
Routine lab monitoring	Yes	No
Half-life	Long	Short
Reversal agent	Yes	No

NOACs: Sites of Action



Hankey GJ and Eikelboom JW. Circulation 2011;123:1436

Medical Cost of NOACs vs. Warfarin: Fact from Fiction



For indications of nonvalvular AF, acute VTE treatment, and extended secondary prevention of recurrent VTE

Amin A, et al. J Med Econ 2015;18:399

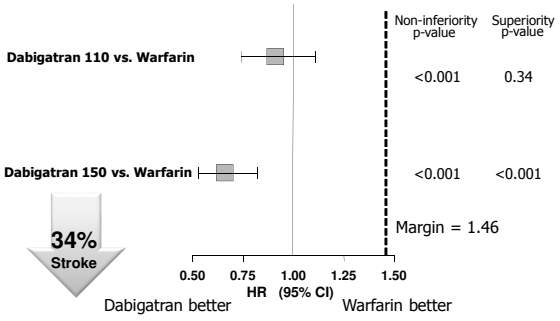
Optimal Anticoagulation for Stroke Prevention in Non-Valvular Atrial Fibrillation

Case No. 1

?

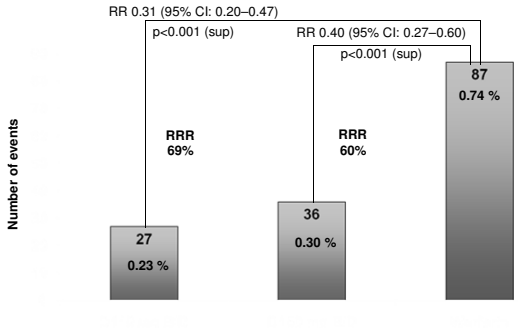
- A 75-year-old woman with hypertension presented to clinic with sudden onset palpitations.
- On ECG, she is found to have AF with a ventricular rate of 86 bpm.
- Her physical examination and routine laboratory evaluation are unremarkable.

RE-LY: Primary End Point



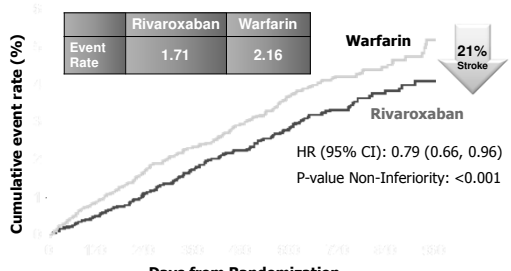
Connolly SJ, et al . N Engl J Med 2009; 361:1139

RE-LY: Intracranial Bleeding



Connolly SJ, et al . N Engl J Med 2009; 361:1139

ROCKET-AF: Primary End Point

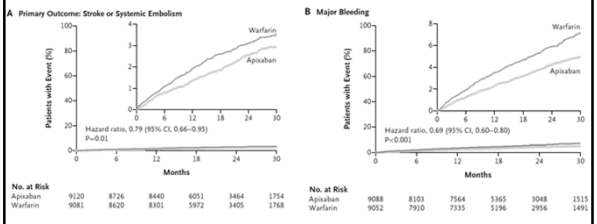


No. at risk:

Rivaroxaban	6958	6211	5786	5468	4406	3407	2472	1496	634
Warfarin	7004	6327	5911	5542	4461	3478	2539	1538	655

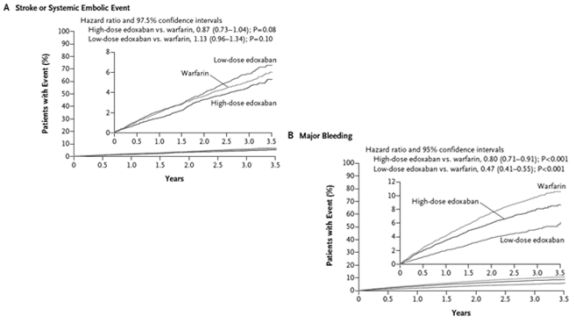
Patel MR, et al. N Engl J Med 2011;365:883

Apixaban: ARISTOTLE



Granger CB, et al. N Engl J Med 2011; 365:981

ENGAGE AF: Edoxaban



Giugliano RP, et al. N Engl J Med 2013; 369:2093

Advantage of NOACs for AF: Reduced Major Bleeding

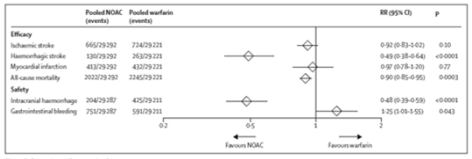


Figure 2: Secondary efficacy and safety outcomes

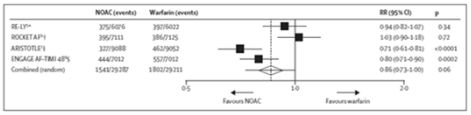


Figure 3: Major bleeding

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

Optimal Anticoagulation for Stroke Prevention in AF

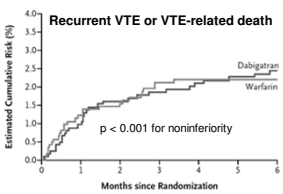
- NOACs for stroke prevention in nonvalvular AF show superiority or at least noninferiority to warfarin.
- NOACs offer greater convenience for patients and clinicians.
- Lower hemorrhagic stroke and major bleeding highlight the enhanced safety of the NOACs compared with warfarin.

Optimal Anticoagulation for Treatment of Acute Venous Thromboembolism

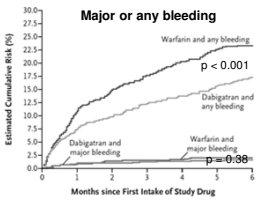
Case No. 2

- A 55-year-old man presented to the Emergency Department with sudden onset right calf edema and pain 2 weeks after a right ankle fracture repair.
- A venous ultrasound demonstrated a right femoral and popliteal deep vein thrombosis (DVT).
- His laboratory evaluation was unremarkable.

RE-COVER: Dabigatran for VTE

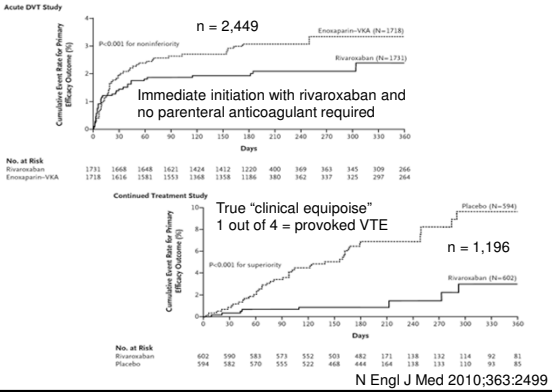


2,564 patients with objectively confirmed VTE were randomized to parenteral anticoagulation followed by fixed-dose dabigatran or dose-adjusted warfarin.



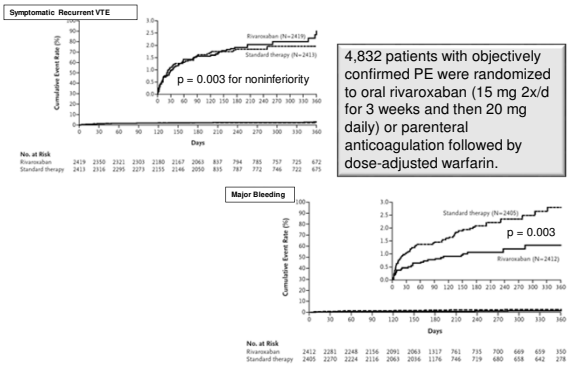
Schulman S, et al. N Engl J Med 2009;361:2342

EINSTEIN-DVT: Rivaroxaban for DVT



N Engl J Med 2010;363:2499

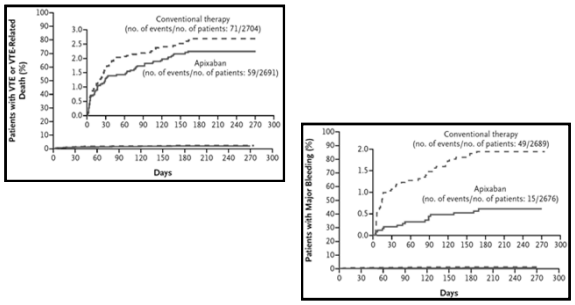
EINSTEIN-PE: Rivaroxaban for PE



4,832 patients with objectively confirmed PE were randomized to oral rivaroxaban (15 mg 2x/d for 3 weeks and then 20 mg daily) or parenteral anticoagulation followed by dose-adjusted warfarin.

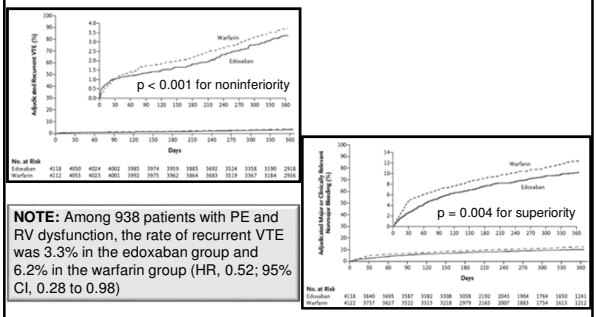
N Engl J Med 2012;366:1287

AMPLIFY: Oral Apixaban for Treatment of VTE



Agnelli G, et al. N Engl J Med. 2013; 369:799

Hokusai-VTE: Edoxaban vs. Warfarin



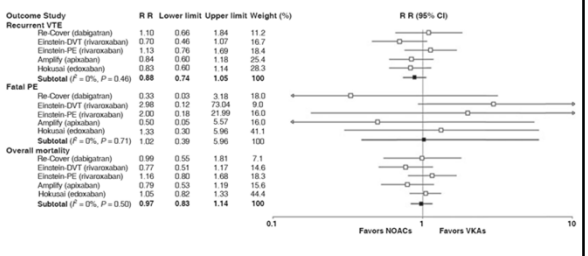
NOTE: Among 938 patients with PE and RV dysfunction, the rate of recurrent VTE was 3.3% in the edoxaban group and 6.2% in the warfarin group (HR, 0.52; 95% CI, 0.28 to 0.98)

The Hokusai-VTE Investigators. N Engl J Med 2013;369:1406

Anticoagulation Strategy in Evolution

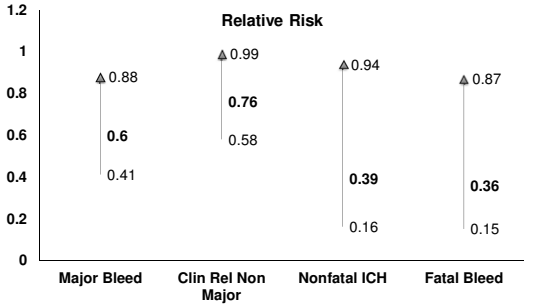
Overlapping	LMWH/Warfarin Bridge	UFH/Warfarin Bridge
Switching	LMWH to Dabigatran (**RE-COVER**)	LMWH to Edoxaban (**HOKUSAI-VTE**)
Oral Monotherapy	Rivaroxaban (15 mg 2x/d for 3 wks, then 20 mg/d) (**EINSTEIN**)	Apixaban (10 mg 2x/d for 1 wk, then 5 mg 2x/d) (**AMPLIFY**)

Efficacy of NOACs for VTE Treatment: Meta-Analysis



van der Hulle T, et al. J Thromb Haemost. 2014;12:320

Safety of NOACs for VTE Treatment: Meta-Analysis



van der Hulle T, et al. J Thromb Haemost. 2014;12:320

Optimal Anticoagulation for Treatment of Acute VTE

- NOACs offer similar efficacy but improved safety compared with warfarin.
- NOACs may facilitate home therapy of patients presenting with low-risk VTE to the outpatient and Emergency Department settings.

Optimal Anticoagulation for Acute VTE: 2016 CHEST Guideline Update

- **In patients with DVT of the leg or PE and no cancer, as long-term (first 3 months) anticoagulant therapy, we suggest dabigatran, rivaroxaban, apixaban or edoxaban over VKA therapy (all Grade 2B).**

Kearon C, et al. CHEST (2016), doi: 10.1016/j.chest.2015.11.026.

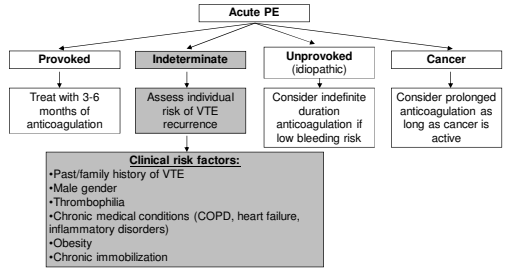
Optimal Anticoagulation for Long-Term Prevention of Venous Thromboembolism

Case No. 3

?

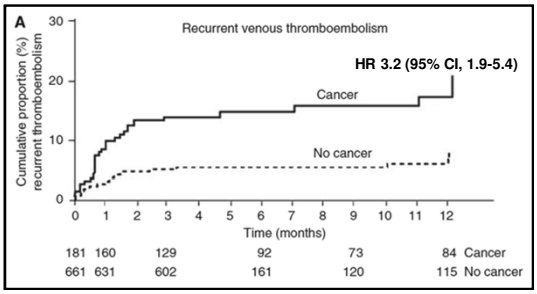
- A 73-year-old woman presented with sudden onset dyspnea and right-sided chest pain.
- She denied any recent trauma, surgery, or immobility.
- Her D-dimer was 2200 ng/mL.
- A chest computed tomogram demonstrated large bilateral PE.

Optimal Duration of Anticoagulation



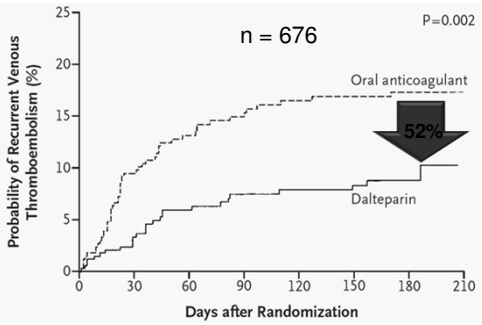
Goldhaber SZ and Piazza G. Circulation 2011;123:664

Cancer and Risk of VTE Recurrence



Prandoni P, et al. Blood 2002;100:3484

CLOT Trial: Dalteparin Monotherapy vs. Warfarin



Lee AYY, et al. N Engl J Med 2003;349:146

NOACs in VTE Patients with Cancer: Meta-analysis

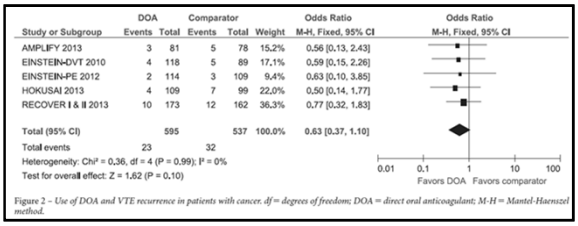
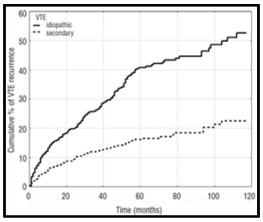


Figure 2 – *Use of DOA and VTE recurrence in patients with cancer. df = degrees of freedom; DOA = direct oral anticoagulant; M-H = Mantel-Haenszel method.*

Vedovati MC, et al. CHEST 2015;146:475

Prevention of Recurrent Unprovoked VTE

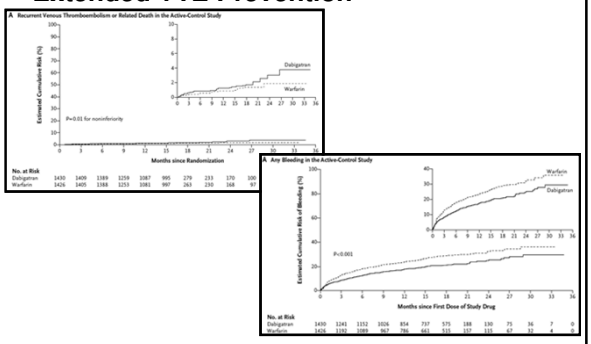


Study	Intervention	Recurrent VTE**
PREVENT	Warfarin, INR 1.5-2 vs. placebo	↓64%
ELATE	Warfarin, INR 2-3 vs. INR 1.5-2	↓63%
THRIVE III	Ximelagatran vs. placebo	↓84%
EINSTEIN-DVT	Rivaroxaban vs. placebo	↓82%
AMPLIFY-EXT	Apixaban vs. placebo	↓81%
RE-SONATE	Dabigatran vs. placebo	↓93%
RE-MEDY	Dabigatran vs. warfarin, INR 2-3	Non-inferior

****Regardless of thrombophilia status**

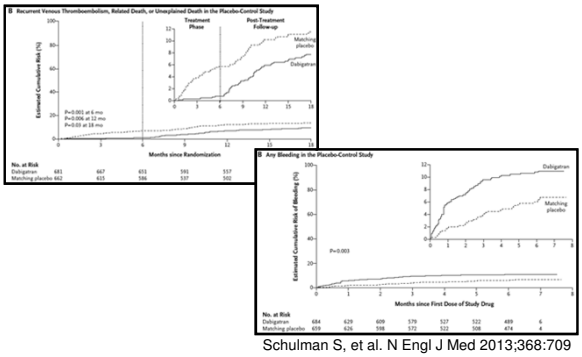
Prandoni P, et al. Haematologica 2007;92:199
Goldhaber SZ and Piazza G. Circulation 2011;123:664

RE-MEDY: Dabigatran vs. Warfarin for Extended VTE Prevention



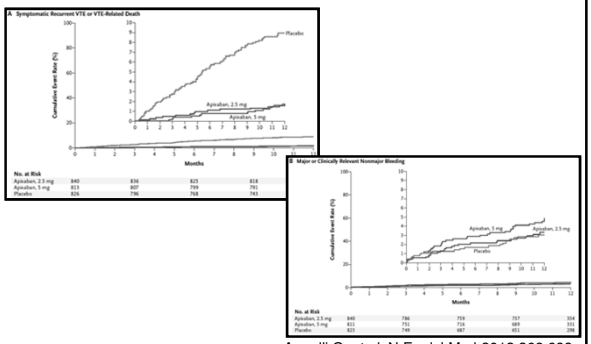
Schulman S, et al. N Engl J Med 2013;368:709

RE-SONATE: Dabigatran vs. Placebo for Extended VTE Prevention



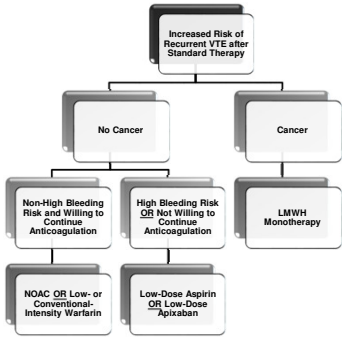
Schulman S, et al. N Engl J Med 2013;368:709

AMPLIFY-EXT: Apixaban vs. Placebo for Extended VTE Prevention



Agnelli G, et al. N Engl J Med 2013;368:699

Selecting the Optimal Agent for Extended Therapy

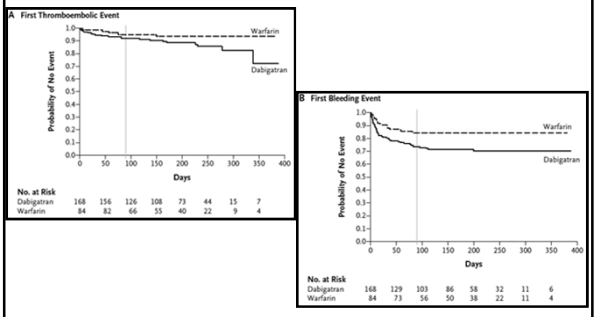


Optimal Anticoagulation for Long-Term Prevention of VTE

- Selecting the optimal agent for extended prevention of VTE requires consideration of bleeding risk and patient preference.
- NOACs have improved patient access to extended duration anticoagulation by providing more consistent anticoagulation, improved safety, and greater convenience.

Optimal Anticoagulation for Mechanical Heart Valves

Dabigatran vs. Warfarin in Patients with Mechanical Heart Valves: RE-ALIGN



Eikelboom JW, et al. N Engl J Med 2013; 369:1206

Managing Bleeding and Emergency Surgery in the New Era of Anticoagulation

Case No. 4

?

- A 66-year-old man with AF presented to the Emergency Department with 12 hours of hematochezia.
- He was taking dabigatran 150 mg PO twice daily for stroke prevention.
- His last dose was the morning of presentation.
- Physical examination was remarkable for a heart rate of 120 bpm and blood pressure of 86/44 mm Hg.
- His hematocrit was 28.

Understanding the Pharmacology of the NOACs

	Dabigatran	Rivaroxaban	Apixaban	Edoxaban
Mechanism of Action	Direct Thrombin Inhibitor	Factor Xa Inhibitor	Factor Xa Inhibitor	Factor Xa Inhibitor
Clearance	80% renal	66% renal	25% renal	50% renal
Peak action	1-3h	1-3h	1-3h	1-2h
Half-life	12-14h (18 to ≥ 24h if GFR < 50)	7-11h	12h	9-11h
Substrate or CYP Enzymes	No	Major (CYP3A4, CYP2J2)	Minor (CYP3A4)	Minor (CYP3A4)
Dosing	Twice Daily	Once Daily	Twice Daily	Once Daily

Nonspecific Reversal Techniques for NOACs

Drug	Vit. K	FFP	4-factor PCC	aPCC (FEIBA)	rFVIIa	Dialysis
Dabigatran	-	-	+/-	+	-	+
Rivaroxaban	-	-	+	+	-	-
Apixiban	-	-	+	+	+/-	-
Edoxaban	-	-	+	+	+/-	-

Siegal DM and Crowther MA. Eur Heart J 2013;34:489

Siegal DM and Cuker A. J Thromb Thrombolysis 2013;35:391

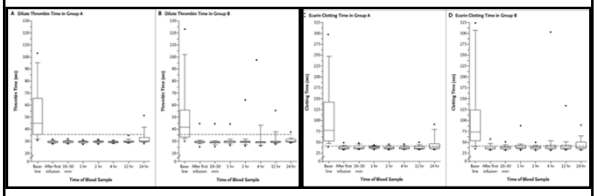
Specific Reversal Agents

- Direct inhibitors of coagulation such as NOACs offer an opportunity to develop specific antidotes.

Company	Agent	Target	Phase
Boehringer-Ingelheim	**Idarucizumab:** Fully humanized monoclonal Fab	Dabigatran only	FDA-Approved
Portola Pharmaceuticals, Inc.	**Andexanet alfa:** Recombinant, modified human Factor Xa	Factor Xa Inhibitors (Riva; Apix; Edox; Betrix) LMWH, fondaparinux	III
Perosphere, Inc.	**Aripazine:** Di-arginine piperazine	All NOACs (Dabi; Riva; Apix; Edox) UFH, LMWH, fondaparinux	II

Akwaa F and Spyropoulos AC. Curr Treat Options Cardiovasc Med 2013;15:288

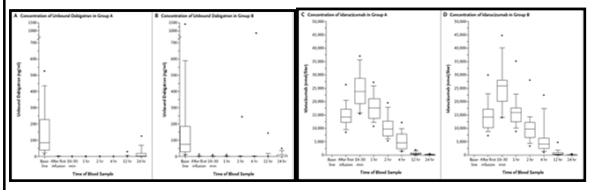
Idarucizamab for Dabigtran Reversal: RE-VERSE AD



Thrombin time and ecarin clotting time reverse within minutes of administration of idarucizamab in patients with active bleeding (Group A) and those undergoing surgery (Group B)

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

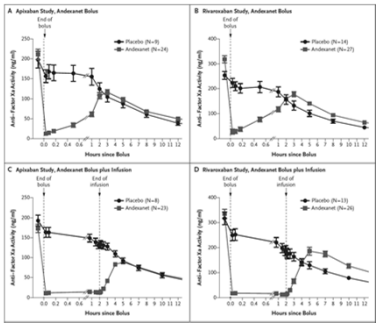
Idarucizamab for Dabigtran Reversal: RE-VERSE AD



Concentration of unbound dabigatran become undetectable within minutes of administration of idarucizamab in patients with active bleeding (Group A) and those undergoing surgery (Group B). Idarucizamab concentrations remain high for about 4 hours.

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

Andexanet Alfa for the Reversal of Factor Xa Inhibitor Activity



Siegal DM, et al. N Engl J Med 2015 Nov 11. [Epub ahead of print]

Take-Home Points

- The NOACs offer enhanced safety and similar or superior efficacy compared with warfarin for stroke prevention in nonvalvular AF, acute treatment of VTE, and long-term prevention of VTE.
- Optimal selection of anticoagulation in this new era requires consideration of advantages, disadvantages, cost implications, and patient preferences.
- The availability of specific reversal agents will further improve the safety profile of the NOACs and may increase patient and provider comfort with their use.