Anticoagulation – Focus on Direct Oral Anticoagulants

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Objectives

- Overview of the direct oral anticoagulants (DOACs) as treatment for venous thromboembolism
- Summary of pivotal trials of DOACs
- Monitoring DOACs
- Peri-op management
- Thrombophilia workup on DOACs
- Reversal of DOACs
- Patient selection for DOACs

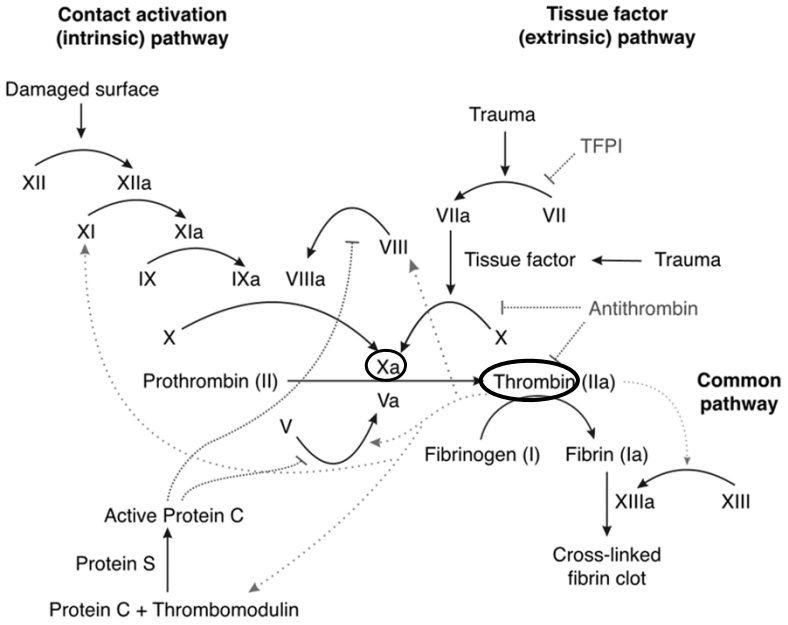
"New" and old anticoagulants

Features	Warfarin	DOACs
Onset	Slow	Rapid
Dosing	Variable	Fixed
Food/drug interactions	Many	Few
Monitoring	Yes	No
Half-life	Long	Short
Antidote	Yes	No - except for dabigatran

Direct oral anticoagulants (DOACs)

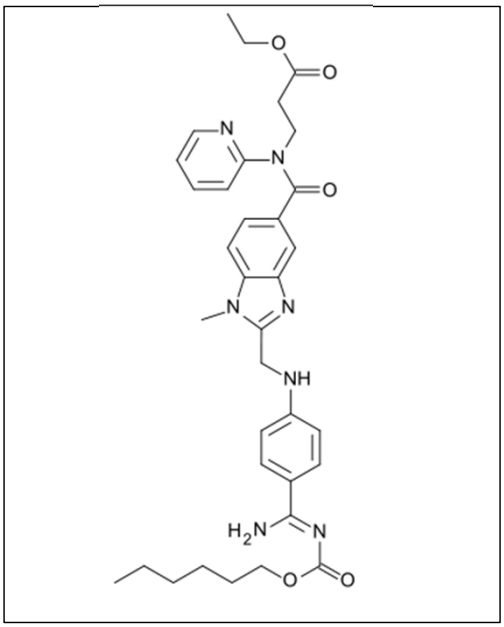
	Dabigatran	Rivaroxaban	Apixaban	Edoxaban
Mechanism of action	direct thrombin inhibitor	direct factor Xa inhibitor	direct factor Xa inhibitor	direct factor Xa inhibitor
Bioavailability	6-7 %	>80 %	~66 %	62%
Prodrug	Yes	No	No	No
T max	2 hrs	3 hrs	3-4 hrs	1.5 hrs
Half life	7-17 hrs	6-13 hrs	8-13 hrs	10-14 hrs
Dosing	bid	Once daily	bid	Once daily
Protein Binding	35 %	90 %	90 %	40-59%
Metabolism	80-85% renal (activated by liver)	67% renal 33% fecal	25% renal 75% fecal	33% renal
Drug interaction	p-glycoprotein inducer/inhibitor	CYP 3A4 p-glycoprotein	CYP 3A4 p-glycoprotein	p-glycoprotein

Kaatz et al. Am J Hematol. 2012;87:S141-145



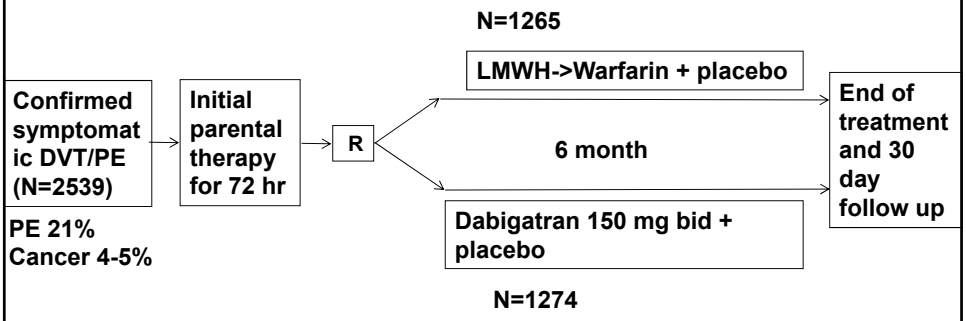
Author: Joe D CC BY-SA 3.0)

Dabigatran



RE-COVER I/II Study Schema

- Double-blinded, randomized controlled, non-inferiority study
- Primary efficacy: 6 month accumulative risk of recurrent VTE or related death
- Primary safety: Major bleeding



Schulman S, et al. N Eng J Med. 2009;361:2342-2352.

Primary Efficacy Outcome – RECOVER Study

- 6 month accumulative risk of recurrent VTE or related death
  - Warfarin vs Dabigatran: 2.1% vs 2.4%
  - HR 1.10, 95% CI 0.65-1.84, p<0.001 for non-inferiority criteria
- INR in range: 60%

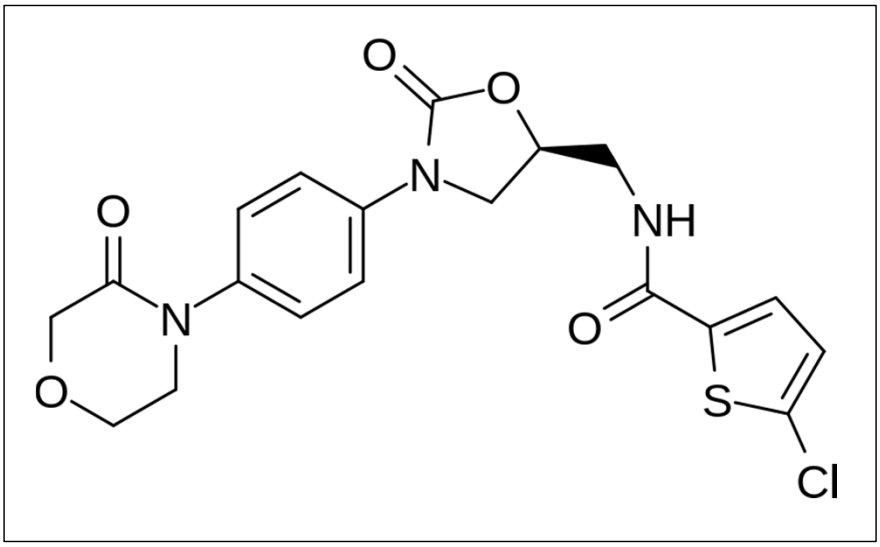
Schulman S, et al. N Eng J Med. 2009;361:2342-2352

Primary Safety Outcome – RECOVER Study

- **Major bleeding:**
  - **Warfarin vs Dabigatran: 1.9% vs 1.6%**
  - **HR 0.82, 95% CI 0.45-1.48, p=0.38**
- **All bleeding: 21.9% vs 16.1%**
  - **HR 0.71, 95% CI 0.59-0.85, p<0.001**
- **Patients with an adverse event leading to discontinuation of the study drug:**
  - **•6.8% vs 9.0%**
  - **HR 1.33; 95% CI 1.01 to 1.76; P=0.05**
  - **•Mainly dyspepsia: 0.6%vs 2.9%, P<0.001**

Schulman S, et al. N Eng J Med. 2009;361:2342-2352

Rivaroxaban



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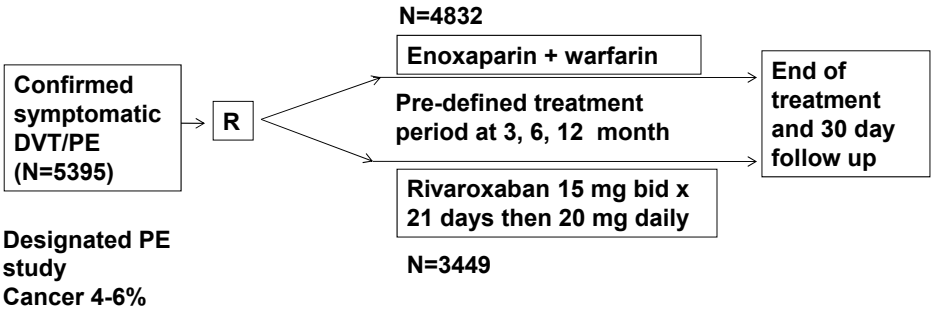
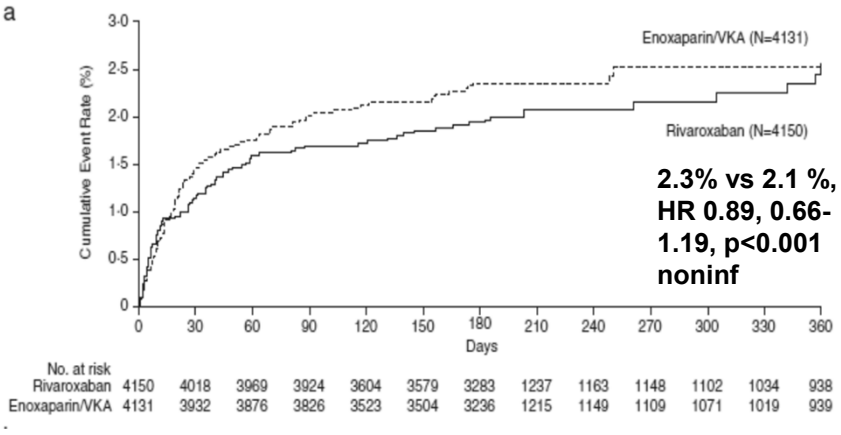
EINSTEIN DVT/PE Study Schema

- Open label, randomized controlled , non-inferiority study
- Primary efficacy: symptomatic and recurrent VTE
- Primary safety: Major and clinically relevant non-major bleeding



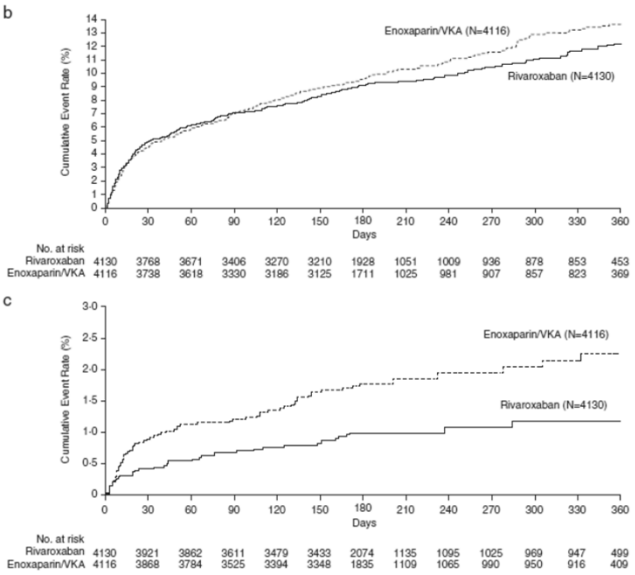
Primary Efficacy Outcome - Einstein study (combined DVT and PE studies)



2.3% vs 2.1 %, HR 0.89, 0.66-1.19, p<0.001 noninf

Prins MH et al. Thrombosis Journal 2013;11:21

Primary Safety Outcome - Einstein study (combined DVT and PE studies)

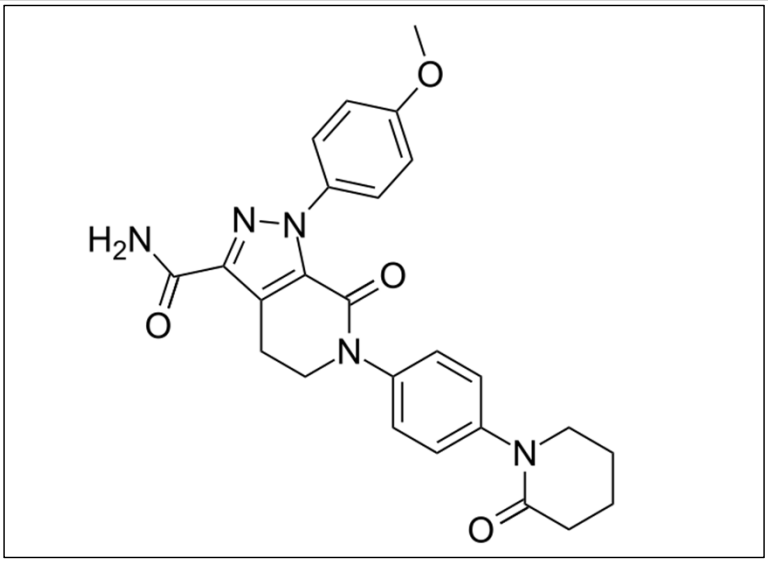


Primary safety: 10% vs 9.4%, HR 0.93, 0.81-1.06, p=0.27

MB: 1.7% vs 1.0%, HR 0.54, 0.37-0.79, p=0.002

Prins MH et al. Thrombosis Journal 2013;11:21

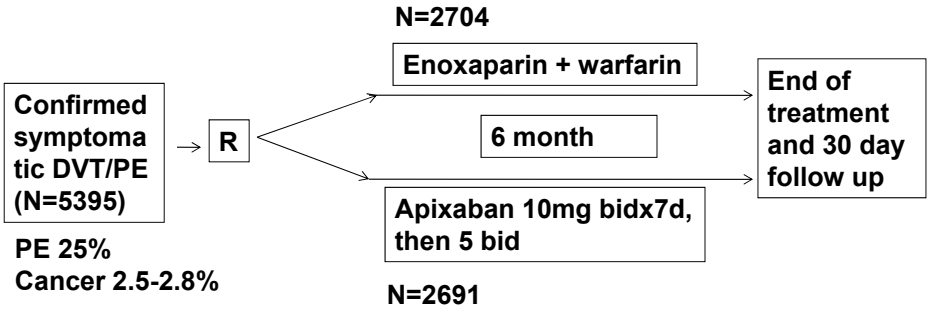
Apixaban



Author: Ed (Edgar181)

AMPLIFY Study

- Open label, randomized controlled, non-inferiority study
- Primary efficacy: Recurrent VTE or related death
- Primary safety: Major bleeding



Agnelli G et al. N Engl J Med 2013;369:799-808.

Primary Efficacy Outcome – AMPLIFY Study

- Recurrent VTE or related death:
  Warfarin vs Apixaban: 2.7% vs 2.3%
  HR 0.84, 95% CI 0.60-1.18, p<0.001 for non-inferiority
- INR in range: 61%

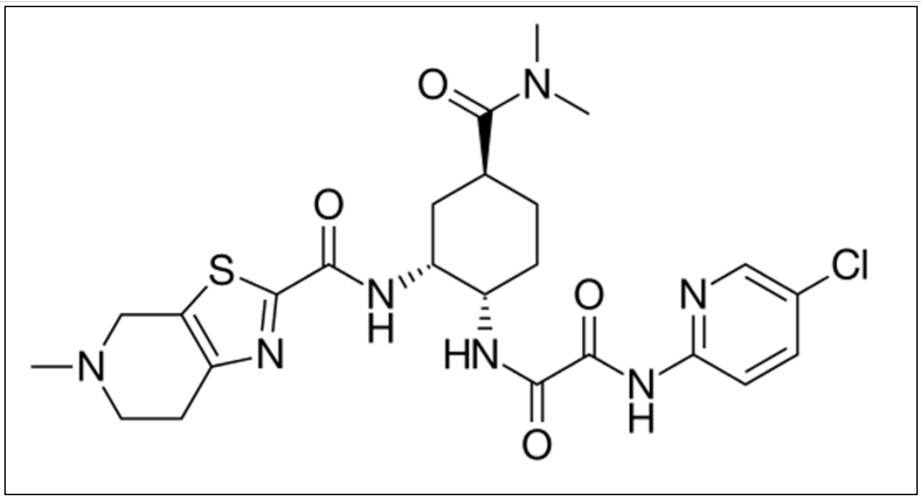
Agnelli G et al. N Engl J Med 2013;369:799-808.

Primary Safety Outcome – AMPLIPY Study

- **Major bleeding:**
  Warfarin vs Apixaban: 1.8% vs 0.6%
  HR 0.31, 95% CI 0.17-0.55, p<0.001

Agnelli G et al. N Engl J Med 2013;369:799-808.

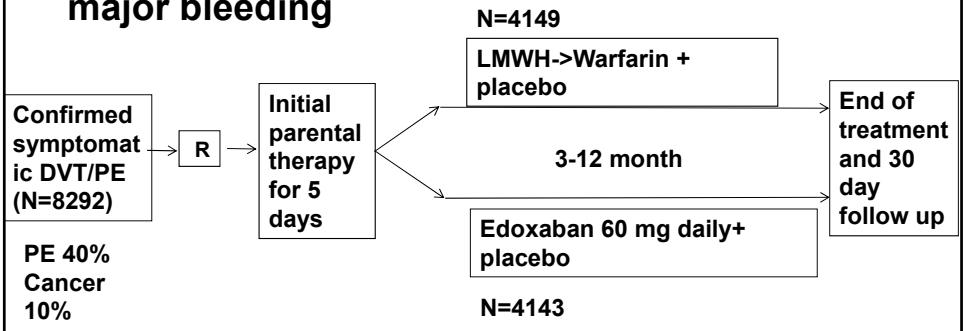
Edoxaban



Author: Vaccinationist

Hokusai Study Schema

- Double-blinded, randomized controlled, non-inferiority study
- Primary efficacy: symptomatic recurrent VTE
- Primary safety: Major and clinically relevant non-major bleeding



Primary Efficacy Outcome – Hokusai Study

- Symptomatic recurrent VTE:
  Warfarin vs Edoxaban: 3.5% vs 3.2%
  HR 0.89, 95% CI 0.70-1.13, p<0.001 for non-inferior
- INR in range: 63.5%

The Hokusai-VTE Investigators. N Engl J Med 2013;369:1406-1415

Primary Safety Outcome – Hokusai Study

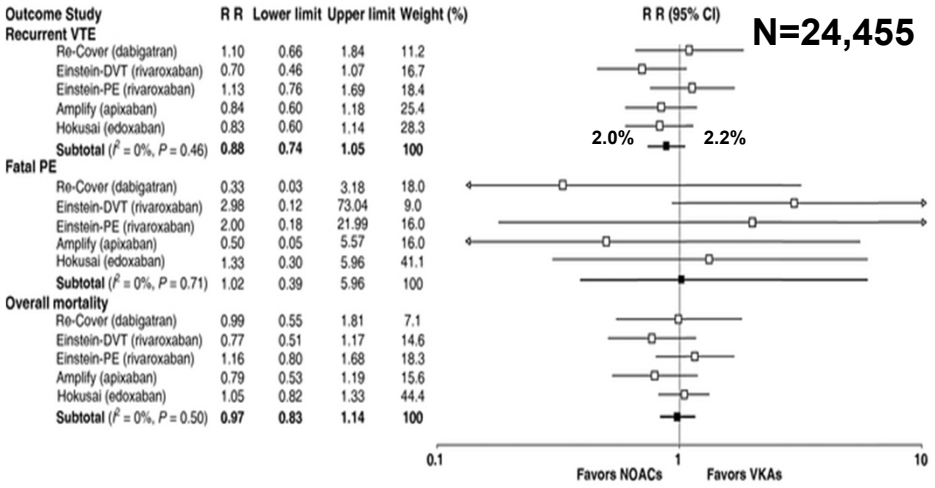
- **Major and clinically relevant non-major bleeding**
  Warfarin vs Edoxaban: 10.3% vs 8.5%
  HR 0.81, 95% CI 0.71-0.94, p=0.004
- **Major Bleeding: 1.4% vs 1.6%, p=0.35**

The Hokusai-VTE Investigators. N Engl J Med 2013;369:1406-1415

Summary of use of DOAC for VTE

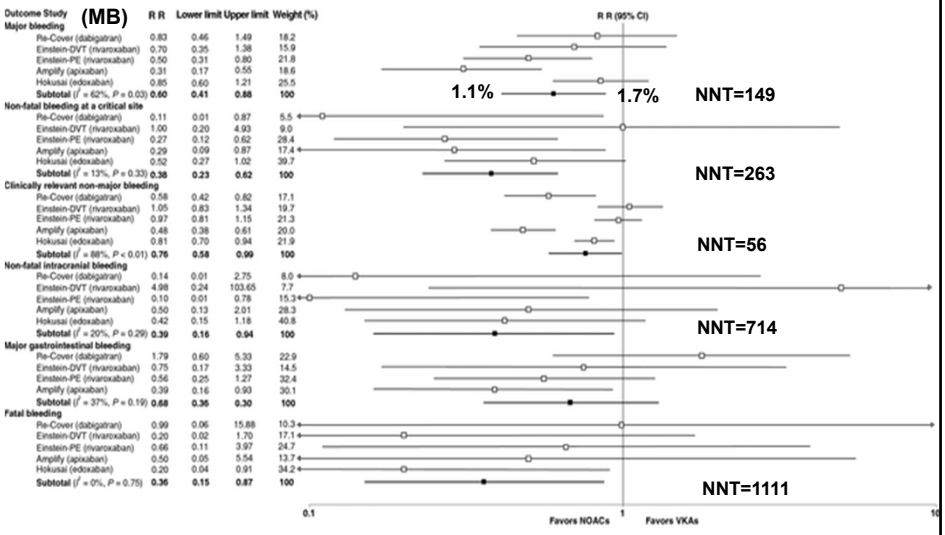
Drug	Recurrent Thrombosis	Major Bleeding	Major and CRNMB
Dabigatran	Equal	Equal	Reduced
Rivaroxaban	Equal	Reduced	Equal
Apixaban	Equal	Reduced	Reduced
Edoxaban	Equal	Equal	Reduced

Effectiveness of novel oral anticoagulants as compared with vitamin K antagonists in the treatment of acute symptomatic venous thromboembolism: a systematic review and meta-analysis



Journal of Thrombosis and Haemostasis
Volume 12, Issue 3, pages 320-328, 5 MAR 2014 DOI: 10.1111/jth.12485

Safety of novel oral anticoagulants as compared with vitamin K antagonists in the treatment of acute symptomatic venous thromboembolism: a systematic review and meta-analysis



Journal of Thrombosis and Haemostasis
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2016 ACCP guideline

- **For VTE and no cancer, as long-term anticoagulant therapy, we suggest dabigatran, rivaroxaban, apixaban, or edoxaban over vitamin K antagonist (VKA) therapy (Grade 2B).**
- **For VTE and cancer, we suggest LMWH over VKA (Grade 2B), dabigatran, rivaroxaban, apixaban, or edoxaban.**
- **For VTE treated with anticoagulants, we recommend against an inferior vena cava filter (Grade 1B).**

FDA activity

	Dabigatran Pradaxa®	**Rivaroxaban Xarelto®**	**Apixaban Eliquis®**	**Edoxaban Savaysa®**
VTE treatment	FDA approved 4/7/2014	FDA approved 11/2/2012	FDA approved 8/22/2014	FDA approved 1/8/2015
VTE secondary prevention	FDA approved 11/23/2015	FDA approved 11/2/2012	FDA approved 8/22/2014	No FDA activity
Atrial fibrillation	FDA approved 10/19/2010	FDA approved 11/4/2011	FDA approved 12/28/2012	FDA approved 1/8/2015
VTE prevention (ortho surgery)	FDA approved 11/24/2015	FDA approved 7/1/2011	FDA approved 3/14/2014	No FDA activity

Dosages

	Dabigatran Pradaxa®	Rivaroxaban Xarelto®	Apixaban Eliquis®	Edoxaban Savaysa®
VTE treatment	150 mg bid (CrCl >30 mL/min) after 5-10 days of parenteral	15 mg bid x 21 days then 20 mg daily (CrCl >30)	10 mg bid x 7 days then 5 mg bid (CrCl >25 and/or Cr <2.5)	•60 mg daily •30 mg daily (if CrCl 15-50, body weight is ≤60 kg, or strong p-GP inhibitors) after 5-10 days of parenteral
VTE secondary prevention	150 mg bid	20 mg daily	2.5 mg bid	N/A
Atrial fibrillation	•150 mg bid (CrCl >30) •75 mg bid (CrCl 15-30)	•20 mg daily (CrCl >50) •15 mg daily (CrCl 15-50)	•5 mg bid •2.5 mg bid (if ≥ 2 factors: age ≥80, weight ≤60 kg, Cr ≥1.5 mg/dL)	•60 mg daily •30 mg daily (if CrCl 15–50, body weight is ≤60 kg, or strong p-GP inhibitors)
Orthopedic VTE prevention	110 mg on first day, then 220 mg daily	10 mg daily	2.5 mg bid	N/A

Dose adjustment in renal dysfunction – more details

- **For apixaban use in A fib patients:**
  - **ESRD requiring HD: 5 mg bid, unless if age ≥80 or weight ≤ 60 kg, then 2.5 mg bid**
  - **This dosing is approved purely based on a single dose PK/PD study in 8 patients so the use needs to be cautious**
  - **Major guidelines recommend against use and recommend warfarin to be the anticoagulant of choice**
- **For edoxaban use in A fib patients, avoid use if CrCL > 95 mL/min**

Dose adjustment in hepatic dysfunction

	Child-Pugh Class A	Child-Pugh Class B	Child-Pugh Class C
Dabigatran	no dosage adjustment	no dosage adjustment	No information on package insert
Rivaroxaban	no dosage adjustment	no dosage adjustment	Avoid use
Apxiaban	no dosage adjustment	no dosage adjustment	Avoid use
Edoxaban	no dosage adjustment	Avoid use	Avoid use

Drug interaction

- **Strong P-gp inhibitors that require dose adjustment**
  - **Macrolide antibiotics: erythromycin, azithromycin, clarithromycin**
  - **Azole antifungals: itraconazole, ketoconazole**
  - **Protease inhibitors: ritonavir, nelfinavir, indinavir, saquinavir**
  - **Hormone agents: tamoxifen, enzalutamide, abiraterone**
  - **Tyrosine kinase inhibitors: imatinib, nilotinib, lapatinib, sunitinib, criozitinib, vandetanib**
  - **verapamil, quinidine**
  - **Immunosuppressants: cyclosporin, tacrolimus**
- **Reduce dose by 50% in dabigatran, apixaban, and edoxaban in patients using these medications concurrently, or avoid use (rivaroxaban)**

Use in patients with morbid obesity

- No dose adjustment specified in all DOACs
- International Society of Thrombosis and Haemostasis (ISTH) 2016 guideline:
  - Avoid use all DOACs in patients with a BMI > 40 kg/m2 or weight > 120 kg
  - If used, peak and trough levels using anti-Fx assays or mass spectrometry is recommended
  - Controversial and not evidence-based
- Meta-analysis of phase III pivotal trials showed that overweight patients had similar bleeding and thrombotic outcomes compared to normal weight patients (but few extremely high weight patients were enrolled)

K Martin et al. JTH. 2016;14:1-6.

Use in patients with cancer

- Meta-analyses of phase III studies showed DOACs to have similar efficacy and safety outcomes when compared to warfarin
- Indirect comparison to LMWH across studies also showed similar results
- However, no good qualify data on direct comparison are available
- Major guidelines (NCCN, ACCP, ASCO) continue to recommend LMWH over DOACs in cancer patients
- Awaiting the results of Hokusai cancer VTE study

Carrier M,et al. Thromb Res. 2014;134:1214-1219.
Vedovati MC et al. Chest 2015;147:475-483.

Monitoring of DOACs

- Dabigatran
  - PT is insensitive
  - aPTT can be elevated but highly variable
  - Thrombin time is too sensitive
  - Dilute thrombin time and ecarin clotting time can be used but are not widely available
- Xa inhibitors
  - aPTT is insensitive
  - PT can be elevated with rivaroxaban but highly variable
  - Anti-Xa levels can be used but have to be calibrated against each particular anticoagulant, which is not widely available
- Actual drug levels by mass spectrometry (not widely available)

Peri-op management with NOACs

- Factors to consider-
  - Half-life of DOACs
  - Renal function (plus liver function for dabigatran)
  - Risk of bleeding according to the type of surgery
- In general, in patients with normal kidney function, stop 24 hours prior to a surgery with standard bleeding risk and 48 hours prior to a surgery with high risk of bleeding
- In patients with compromised kidney function (or liver dysfunction for dabigatran), decisions have to be individualized but generally at least double the time proposed above
- No bridging is required

Thrombophilia workup on DOACs

- Reliable
  - Genetic testing (FVL, prothrombin gene mutation)
  - Anti-cardiolipin and anti-beta-2-glycoprotein I antibody
  - Protein S (free and total), protein C, anti-thrombin antigen
- Not reliable
  - Protein S and protein C activity
  - Anti-thrombin activity
  - APC resistance assay
  - Lupus anticoagulant (Rivaroxaban can use high risk of false positivity)

Indirect Reversal Agents

- FFP, 3 factor PCC (prothrombin complex concentrate), 4 PCC factor, aPCC, aFVII have all been considered
- Evidence remains very poor, either based on animal model, human volunteers, or case reports on bleeding patients
- No high qualify data so cannot be recommended for routine use

Kaatz et al. Am J Hematol. 2012;87:S141-145.

Direct Reversal Agents

	IDARUCIZUMAB (Praxbind®)	ANDEXANET (PRT064445)	ARIPAZINE (PER977)
Mechanism of action	A humanized mouse monoclonal antibody (Fab fragment) directed against dabigatran	A recombinant, modified factor Xa molecule that sops up the anti-Xa anticoagulant	A synthetic small molecule (D-arginine compound) with broad activity against various anticoagulants
Drugs targeted against	Dabigatran	Rivaroxaban, apixaban, edoxaban, LMWH	Dabigatran, rivaroxaban, apixaban, edoxaban, heparin, LMWH
Status of clinical trials	Phase III study ongoing	Phase II/III studies ongoing	Not yet been used in humans
FDA activity	FDA approved 10/16/2015	FDA discussion in August 2016 but has not been approved	No activities

Idarucizumab

- **A humanized monoclonal antibody fragment specific for dabigatran, with 350 fold higher affinity than that of dabigatran for thrombin**
- **Reverse-AD study**
  - **The use of Idarucizumab to reverse dabigatran in patients with 1) bleeding, 2) urgent procedure in 8 hrs**
  - **Dose: 5 grams of IV infusion**
  - **Idarucizumab completely revered the anticoagulant effects of dabigatran within minutes (based on drug concentration, dilute thrombin time, and ecarin clotting time)**

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

Andexanet

- Andexanet is a recombinant engineered version of human actor Xa produced in CHO cells
- Acts as FXa decoy and binds up all FXa inhibitors with good affinity, but will not function as FXa to initiate coagulation cadcade
- The ANNEXA-4 study (The Ability of Andexanet Alfa to Reverse the Anticoagulant Activity-4) study is to evaluate the efficacy and safety of andexanet for serious bleeding in patients on rivaroxban, apixaban, edoxaban, or enoxaparin
- Dose: a bolus followed by 2 hr infusion
- Use of Andexanet following in all FXa inhibitors have been shown to cause a significant decrease in anti-Xa activity by ~90%, a significant decrease in anticoagulant drug concentration, and normalization of thrombin generation.

Connolly SJ et al. NEJM 2016;375:1131-1141.
http://www.slideshare.net/derosaMSKCC/k-martin

Things to consider prior to DOACs initiation

- The importance of compliance
- Pros
  - No need for regular lab monitoring
  - Less interaction with diet and medications
  - Reduced risk of bleeding
- Cons
  - Lack of antidotes in anti-Xa inhibitors
  - Lack of extensive experiences
  - Lack of monitoring
  - Potential higher co-pay
  - Poor evidence in special population: cancer, morbid obesity, rare thromboses, antiphospholipid syndrome, hearin-induced thrombocytopenia, etc.

Conclusions

- **DOACs is becoming the main stream of anticoagulation**
- **DOACs have been shown to have significantly reduced risk of bleeding and similar efficacy compared to warfarin**
- **Direct reversal agents are coming**
- **Thorough discussion or pros and cons should be done with patients prior to initiation of DOACs**
- **Hematology consultants can provide assistance in achieving the best care for these patients**