Tips and Tricks in Anticoagulants

By.Hend
Ibrahim,TQM,BCPS,BCCP

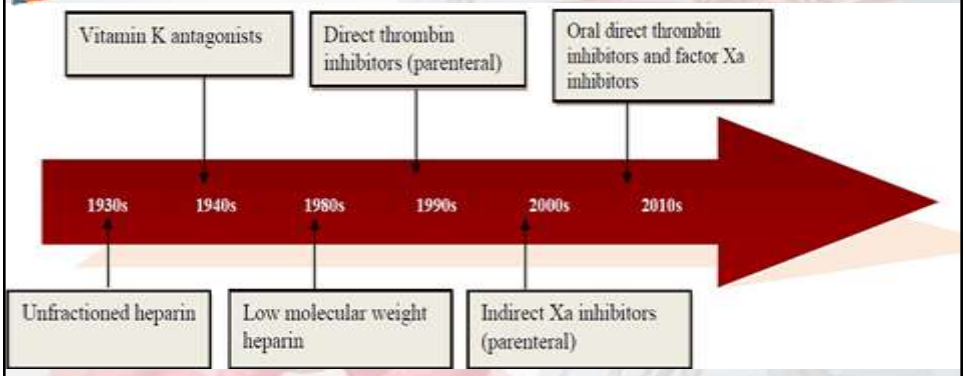
Content

- History and Overview on coagulent
- Types of anticoagulant

Parental: heparins and non-heparins
Oral: Warfren and NOACS

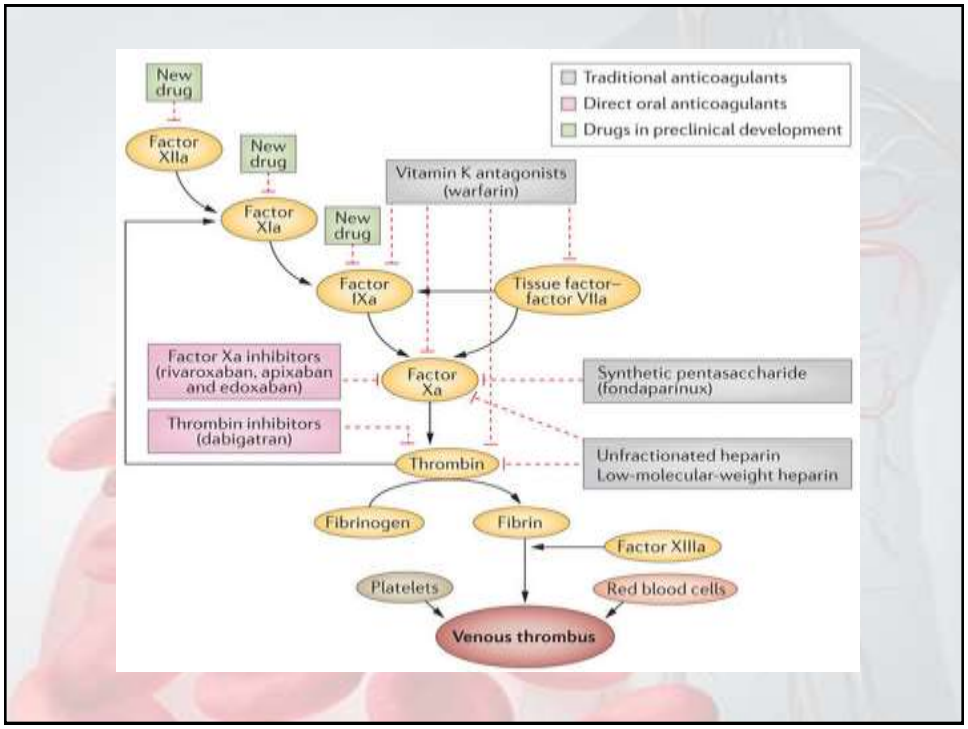
- Warfren major problems and interactions
- NOACs and comparison studies
- Reversal of NOACs
- Switching between anticoagulants
- When to stop NOACs before surgery?
- How to deal with missed doses?
- How to chose between NOACs?
- NOACs and INR

History of Anticoagulants



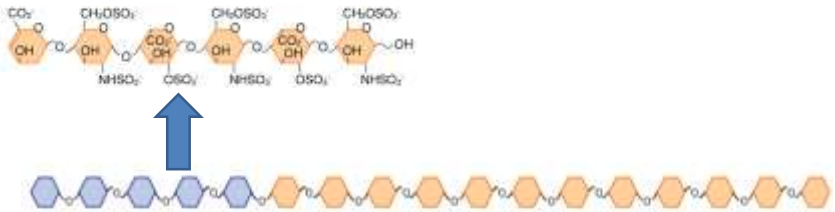
Coagulation Phase

- **Two major pathways**
  - **Intrinsic pathway**
  - **Extrinsic pathway**
- **Both converge at a common point**
- **13 soluble factors are involved in clotting**
- **Normally inactive and sequentially activated**

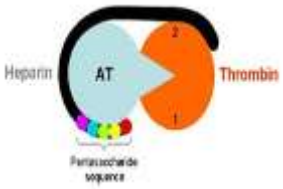


Parental Anticoagulant:
1. Heparins

is a polymer composed of heterogeneous polysaccharide units



- Any size of heparin chain can inhibit the action of **factor Xa** by binding to antithrombin (AT)
- In contrast, in order to inactivate thrombin (IIa), the heparin molecule must be long enough to bind both antithrombin and thrombin

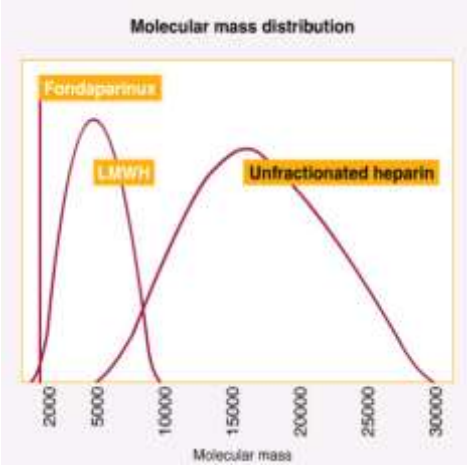


Unfractionated heparin

Standard Unfractionated heparin,derived from from pig intestine or bovine lung tissue, is a hetregounase mixture of polysacaride chains of varying length.

MW range from 3000 to 30,000 Da with mean MW 15,000Da

Only about 1/3 of these molecules contain the pentasacharide chain

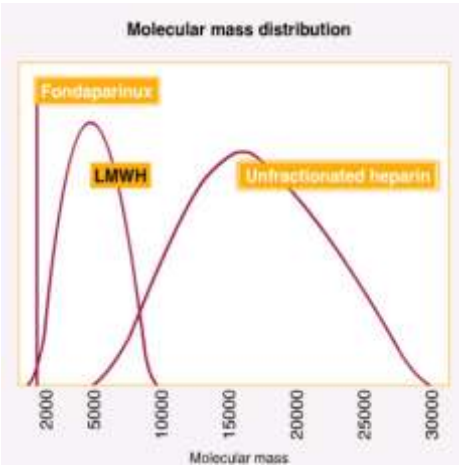


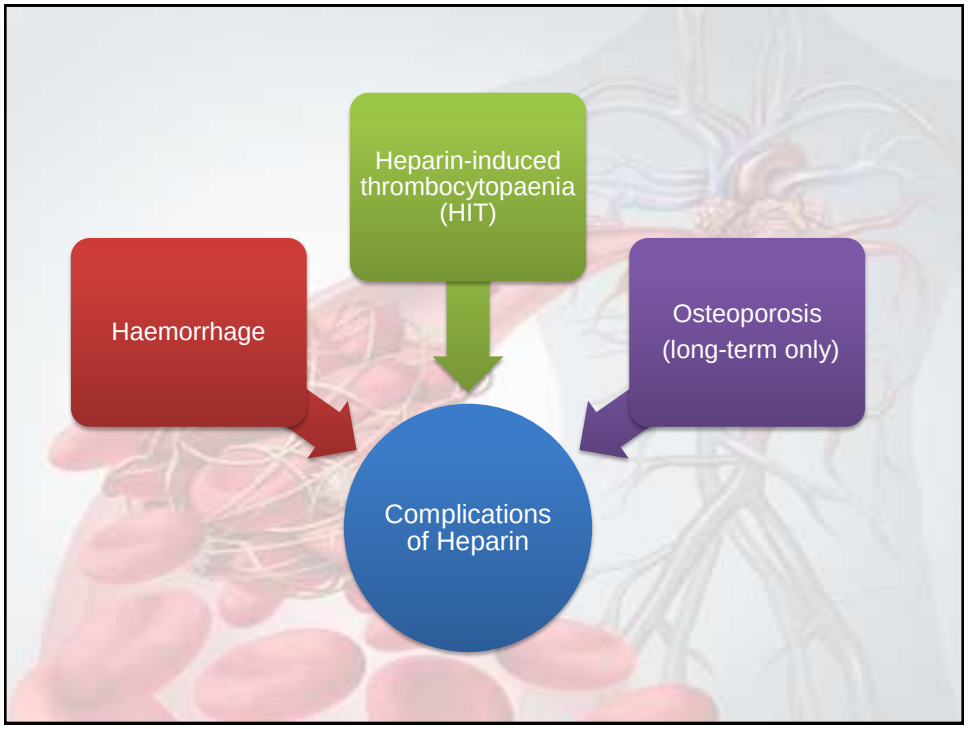
molecular weight heparin

LMWHs are derived from chemical or enzymatic degradation of UFH into fragments approximately one third of the size of heparin

MW ranging from 1000 to 10,000 Da

Shorter chain make it longer half life

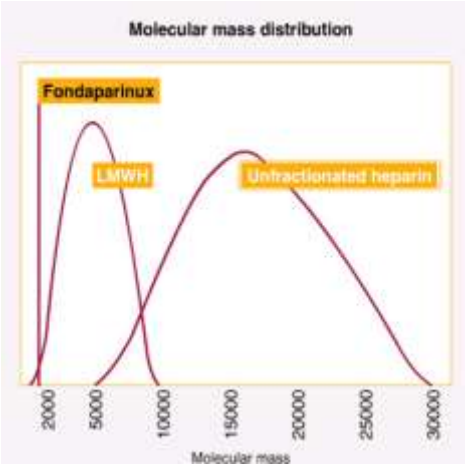




Fondaparinux

Chemically synthesized and consist of pentasaccharide structure .

Indirect FX inhibtor



Heparin Anticoagulants - Systemic

Agent	Available in Egypt
Fondaparinux[5]	

AriXtra® (fondaparinux sodium) for injection

2013 Clinical Practice Guideline on the Evaluation and Management of Adults with Suspected HIT
Linkins LA et al. American College of Chest Physicians. Chest. 2012;141(2 Suppl):e495S.

Non Heparin Anticoagulants - Systemic

Recombinant Hirudin – RB variant

Direct thrombin inhibitor

Thrombexx®

MINAPHARM PHARMACEUTICALS

(Hansenula derived recombinant Hirudin - RB variant)

COMPOSITION :
Each ampoule(1ml) contains :
Recombinant Hirudin 15 mg.

Available in Egypt

2.Non Heparin Anticoagulants

Recombinant Hirudin – RB variant

Thrombexx®

Lepirudin (Refludan, produced by Cellgene, U.K.) became the first direct thrombin inhibitor (DTI) available for treating heparin-induced thrombocytopenia (HIT) in 1997. While in early 2012 the Bayer Group stopped marketing lepirudin, smaller companies took over the marketing rights in some countries (e.g., Pharmore in Germany). At the time this chapter was finalized it remained unclear in which jurisdictions lepirudin will be available. There are two other recombinant hirudins (r-hirudins) available, desirudin (Revasc/Iprivask, Canyon Pharmaceuticals, Basel, Switzerland; available in Europe and North America) and RB variant-hirudin (Thrombexx, Rhein-Minapharm, Cairo, Egypt; available in many countries in Asia and Africa). The pharmacokinetics and biologic activities of the different r-hirudins are very similar. Thus the data obtained in preclinical and clinical studies with lepirudin in HIT may help guide the use of other r-hirudins, especially in countries where lepirudin is not/no longer available.

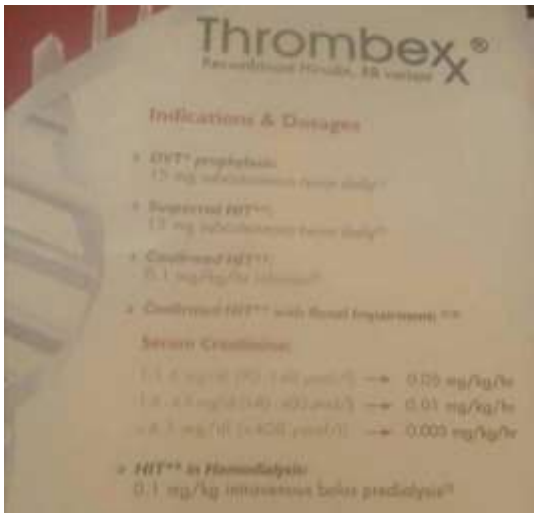
Published: October 2012
eBook ISBN: 9781841846637
ISBN: 9781841846606
Edition: 1.th
Pages: 554

Recombinant hirudin for the treatment of heparin-induced thrombocytopenia

Book: Chapter 14 Heparin-Induced Thrombocytopenia, Fifth Edition

Non Heparin Anticoagulants - Systemic

Recombinant Hirudin – RB variant



Oral Anticoagulant

1.Warfren

Bleeding

Thrombus

Pharmacology of oral anticoagulant drugs

	Warfarin	NOACs
Bioavailability	99%	6-80% (some active drug in large bowel)
Tmax	72-96 hours	2-4 hours
Half-life	40 hours	5-17 hours
Metabolism	Cytochrome P450	Biliary/Renal
Drug Interactions	Many	Not so many
Food Interactions	Yes	No
Genetic Variation	Major effects	Minor effects (?)
Monitoring	PT/INR	None
Reversal	Vit K/PCC/FFP	PCC? Dialysis?

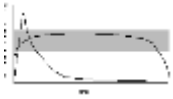
Vitamin K antagonists

Problems with Warfarin

- Food and drug interactions

- Genetic variation in metabolism

- narrow therapeutic window



- slow onset of action

dosage adjustments & freq. monitor with INR

overlap with parenteral drugs

Drug -Drug Interactions

Drug	Effect on INR	Mechanism	Onset	Offset	Management
Acetaminophen	↑INR Moderate	↓ warfarin metabolism	2-5 days	NR (t1/2 = 2-4 hr.)	Monitor INR when starting or stopping higher doses, minimize use of drug (e.g., <2 g/d for short courses [<1 week])
Amiodarone	↑INR Moderate - Major	Inhibition of warfarin Metabolism (CYP 1A2, 2C9)	3-7 days	~ 90days (t ½ = 26 – 107 days)	Monitor INR closely (i.e., weekly) when starting or stopping Amiodarone, warfarin dose Reduction depended on Amiodarone dose
NSAIDs	↑risk of bleeding	Gastric irritation ↓platelet function	1-3 days	5-7 days	Minimize use of drug and monitor for bleeding
Metronidazole Tavanic	↑INR major	↓warfarin metabolism (CPY 2C9)	3-5 days	2 days	Monitor INR closely when starting or stopping, decrease warfarin in long-term use

Warfarin –Herbs/Foods Interactions

Increase INR	Decrease INR	Increase bleeding
-Capsicum -Carnitine -Celery -Chamomile -Dong Quai -Garlic -Ginkgo -Licorice root -Papain -Papaya extract -Fish oil -Grapefruit -Mango	-Co-enzyme Q10 -Ginseng -Green tea -Psyllium -Rose Hip -Avocado -High vitamin K content food -Soy milk -Sushi contains seaweed	-Clove -Ginger -Policosanol -Termeric

2.NOAC

- **Dabigatran (Pradaxa®)** – Thrombin inhibitor
  - FDA approval 2010: stroke prevention in non-valvular Afib; approved 2014 for VTE treatment
- **Rivaroxaban (Xarelto®)** – Xa inhibitor
  - FDA approval 2010/11: postop VTE prophylaxis, str prevention in Afib, treatment of VTE
- **Apixaban (Eliquis®)** – Xa inhibitor
  - FDA approval 2012: stroke prevention in Afib; approved 2014 for VTE prophylaxis after major orthopec
  - FDA approval for VTE treatment 2014
- **Edoxaban (Savayasa®)** – Xa inhibitor
  - FDA approval 1/2015: stroke prevention in Afib; treatment of acute VTE

	Rivaroxaban	Dabigatran	Apixban
Doses : **Deep vein thrombosis (DVT), pulmonary embolism (PE) treatment:**	Initial: 15 mg twice daily with food for 21 days followed by 20 mg once daily with food.	150 mg twice daily (after 5 to 10 days of parenteral anticoagulation)	10 mg twice daily for 7 days followed by 5 mg twice daily.
Reduction in the risk (secondary prevention) of recurrent DVT/PE after at least 6 months of initial anticoagulant treatment:	10 mg once daily	**Postoperative thromboprophylaxis:** Oral: Hip replacement surgery: Initial: 110 mg given 1 to 4 hours after completion of surgery and establishment of hemostasis; if not initiated on the day of surgery, initiate therapy with 220 mg once daily after hemostasis has been achieved; maintenance: 220 mg once daily	2.5 mg twice daily
Nonvalvular atrial fibrillation:	20 mg once daily with the evening meal	150 mg twice daily.	5 mg twice daily unless patient has any 2 of the following: Age ≥80 years, body weight ≤60 kg, or serum creatinine ≥1.5 mg/dL, then reduce dose to 2.5 mg twice daily.
Renal : **DVT, PE, reduction of the risk of recurrent DVT/PE:**	**CrCl <30** mL/minute: Avoid use	**CrCl <50** mL/minute and is receiving concomitant P-gp inhibitors, then avoid coadministration **CrCl <30** mL/minute: Avoid use	serum creatinine >2.5 mg/dL or **CrCl <25** mL/minute: Avoid use
Nonvalvular atrial fibrillation:	**CrCl 15 to 50** mL/minute: 15 mg once daily with the evening meal **CrCl <15** mL/minute: avoid use	**CrCl 30 to 50** mL/minute: concomitant dronedarone or oral ketoconazole, :reduce dabigatran to 75 mg twice daily. **CrCl <30** mL/minute: Avoid use CrCl 15 to 30 mL/minute: 75 mg twice daily **unless** patient receiving concomitant P-gp inhibitor, then avoid concurrent use	Serum creatinine <1.5 mg/dL: No dosage adjustment necessary *unless* ≥80 years of age **and** body weight ≤60 kg, then reduce dose to 2.5 mg twice daily Serum creatinine ≥1.5 mg/dL **and** *either* ≥80 years of age **or** body weight ≤60 kg: 2.5 mg twice daily. serum creatinine >2.5 mg/dL or

Apixaban Interaction

- *For patients receiving dual **strong CYP3A4 and P-glycoprotein inhibitors** (eg, ketoconazole, itraconazole, ritonavir) and apixaban doses >2.5 mg twice daily, reduce apixaban dose by 50%.*
- *Note: Avoid concomitant use with dual strong CYP3A4 and P-glycoprotein inhibitors if patient is already taking apixaban 2.5 mg twice daily or patient meets 2 of the following criteria: Age ≥80 years, body weight ≤60 kg, or serum creatinine ≥1.5 mg/dL.*

Dabigatran Interaction

- ***Dosing adjustment with concomitant medications:***
- DVT and pulmonary embolism (treatment and prevention)or (hip rPostoperative thromboprophylaxis eplacement):
- *Any P-glycoprotein inducer (eg, rifampin):* Avoid concurrent use.
- *Any P-glycoprotein inhibitor (eg, amiodarone, clarithromycin, dronedarone, quinidine, verapamil, and others) with CrCl <50 mL/minute:* Avoid concurrent use.

- Nonvalvular atrial fibrillation (to prevent stroke and systemic embolism):
- *Dronedarone or ketoconazole (oral) with CrCl 30 to 50 mL/minute:* Reduce dabigatran dose to 75 mg twice daily.
- *Any P-glycoprotein inducer (eg, rifampin):* Avoid concurrent use.
- *Any P-glycoprotein inhibitor (eg, amiodarone, clarithromycin, dronedarone, quinidine, verapamil, and others) with CrCl <30 mL/minute:* Avoid concurrent use.

Randomized controlled trial commparing NOACs to warfarin

- **Atrial Fibrillation**
- *RE-LY* Dabigatron (Paradaxa)
- *ROCKET AF* Rivaroxaban (Xarelto)
- *ARISTOTLE* Apixaban (Eliquis)
- *ENGAGE-AF* Edoxaban
- **Treatment of DVT and PE**
- *EINSTEIN DVT* Rivaroxaban
- *EINSTEIN PE* Rivaroxaban

Exclusion criteria in the trials

- Prosthetic heart valves
- Significant heart valve disease (ed. Mitral stenosis)
- Sever renal impairment
- Active liver disease
- pregnancy

LESSONS FROM AF TRIALS WITH NOACS

- Main result: New agents at least as effective as warfarin, can be given without routine monitoring
- Other/unexpected findings:
  - Reduction in intracranial bleeding
  - Higher MI rates (Dabigatran)
  - Higher rates of GI bleeding (dapigatran or rivaroxaban)
  - Extracranial bleeding risk higher in older patients

Bleeding rates with dabigatran vs warfarin in atrial fibrillation: a "real-world" study

JAMA Intern Med. 2015 Jan;175(1):18-24. doi: 10.1001/jamainternmed.2014.5388.

Risk of bleeding with dabigatran in atrial fibrillation.

Hernandez I[1], Baik SH[1], Piñera A[2], Zhang Y[1].

Author information

Abstract

IMPORTANCE: It remains unclear whether dabigatran etexilate mesylate is associated with higher risk of bleeding than warfarin sodium in real-world clinical practice.

OBJECTIVE To compare the risk of bleeding associated with dabigatran and warfarin using Medicare data.

DESIGN, SETTING, AND PARTICIPANTS: In this retrospective cohort study, we used pharmacy and medical claims in 2010 to 2011 from a 5% random sample of Medicare beneficiaries. We identified participants as those newly diagnosed as having atrial fibrillation from October 1, 2010, through October 31, 2011, and who initiated dabigatran or warfarin treatment within 60 days of initial diagnosis. We followed up patients until discontinued use or switch of anticoagulants, death, or December 31, 2011.

EXPOSURES: Dabigatran users (n = 1302) and warfarin users (n = 8102).

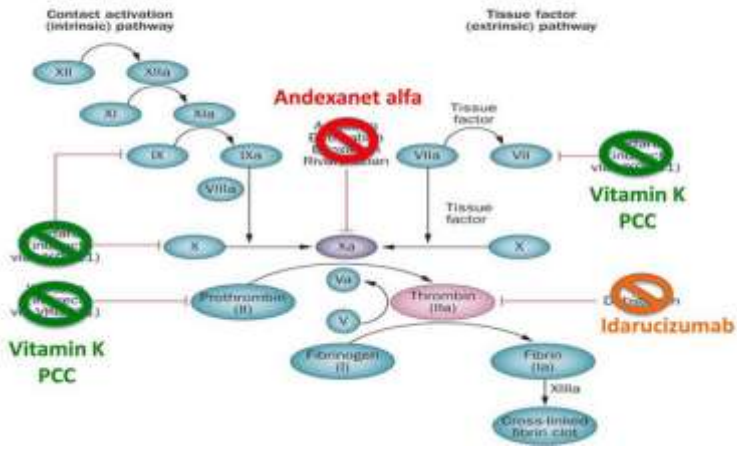
MAIN OUTCOMES AND MEASURES: We identified any bleeding events and categorized them as major and minor bleeding by anatomical site. Major bleeding events included intracranial hemorrhage, hemoperitoneum, and inpatient or emergency department stays for hematuria, gastrointestinal, or other hemorrhage. We used a propensity score weighting mechanism to balance patient characteristics between 2 groups and Cox proportional hazards regression models to evaluate the risk of bleeding. We further examined the risk of bleeding for 4 subgroups of high-risk patients: those 75 years or older, African Americans, those with chronic kidney disease, and those with more than 7 concomitant comorbidities.

Bleeding rates with dabigatran vs warfarin in atrial fibrillation: a "real-world" study

Outcome	Incidence Rates, % (95% CI)[a] Warfarin (n = 8102)	Dabigatran (n = 1302)	*P* Value
By severity			
Any	26.5 (24.3-28.6)	32.7 (29.9-35.4)	<.001
Major	5.9 (5.1-6.6)	9.0 (7.8-10.2)	<.001
Minor	23.6 (21.4-25.8)	28.6 (25.8-31.3)	<.001
By anatomical site			
Intracranial bleeding	1.8 (1.4-2.2)	0.6 (0.3-0.8)	<.001
Gastrointestinal bleeding	10.0 (9.0-11.0)	17.4 (15.7-19.2)	<.001
Hematuria	8.8 (6.9-10.7)	12.0 (9.3-14.7)	<.001
Vaginal bleeding	0.3 (0.2-0.4)	0.7 (0.4-0.9)	.003
Hemarthrosis	0.2 (0.1-0.3)	0.5 (0.3-0.7)	.007
Hemoptysis	1.4 (0.9-1.8)	2.0 (1.3-2.7)	.03
Epistaxis	3.1 (2.5-3.6)	2.0 (1.5 -2.5)	.002
NOS hemorrhage	5.9 (4.9-6.9)	4.4 (3.5-5.4)	.003

JAMA Intern Med 2015;175:18

Reversal of NOAC:
Clotting Cascade



Reversal of NOAC:
IDARUCIZUMAB FOR DABIGATRAN REVERSAL

- Idarucizumab (Praxbind®) is a monoclonal antibody fragment that binds to dabigatran with high affinity (350x that of thrombin)
- 5 mg of idarucizumab (2 x 2.5 mg vials) completely reverses the anticoagulant effect of dabigatran when the drug is taken at usual recommended doses
- This effect occurs within minutes of drug administration and restores normal hemostasis *(NEJM 2015; 373:511)*
- Idarucizumab approved by FDA in October 2015

ANDEXANET ALFA FOR FACTOR Xa INHIBITOR REVERSAL

- Modified recombinant factor Xa lacking procoagulant activity
- Binds factor Xa inhibitors with high affinity and thus acts as a “decoy protein”
- Short half-life: given as bolus plus a 1-2 hour infusion
- In healthy volunteers taking either apixaban or rivaroxaban, the drug reduced anti-factor Xa activity by > 90% and restored normal hemostatic function in >95% of subjects *(NEJM 2015;373:2413)*

❖ *Not yet FDA-approved*

FACTOR Xa INHIBITOR REVERSAL

- Activated charcoal reduces drug absorption if administered within a few hours of drug ingestion
- 4-factor prothrombin complex concentrate (PCC) reverses laboratory indices of drug effect (limited clinical data)
- Dialysis in case of Dabigatran

Switching between anticoagulants:

VKA to NOAC	INR <2.0: immediate INR 2.0–2.5: immediate or next day INR >2.5: use INR and VKA half-life to estimate time to INR <2.5
Parenteral anticoagulant to NOAC: Intravenous unfractioned heparin (UFH) Low molecular weight heparin (LMWH)	 Start once UFH discontinued (t½=2h). May be longer in patients with renal impairment Start when next dose would have been given
NOAC to VKA	Administer concomitantly until INR in appropriate range Measure INR just before next intake of NOAC Re-test 24h after last dose of NOAC Monitor INR in first month until stable values (2.0–3.0) achieved
NOAC to parenteral anticoagulant	Initiate when next dose of NOAC is due
NOAC to NOAC	Initiate when next dose is due except where higher plasma concentrations expected (e.g. renal impairment)
Aspirin or clodiprogel to NOAC	Switch immediately, unless combination therapy needed

www.escardio.org/EHRA

Gloucestershire Hospitals NHS
NHS Foundation Trust

Guidance on converting between anticoagulants

From \ To	Warfarin For initial warfarin dosing refer to Warfarin Initiation Protocol	LMWH	Rivaroxaban (formulary 1st choice NOAC)	Apixaban	Dabigatran
Warfarin For the management of warfarin during invasive procedures refer to the warfarin 'bridging' protocol.	For further advice on converting between anticoagulants contact Medicines Information ([illegible]) *In patients with renal impairment, higher than therapeutic plasma concentrations are expected and a longer interval may be required; contact Medicines Information for further advice.	**Treatment of DVT/PE**; stop warfarin and initiate treatment dose LMWH when INR <2.0. **Prevention of stroke and systemic embolism**; review thrombotic risk on a case-by-case basis and consider initiating prophylactic or treatment dose LMWH once INR <2.0.	**DVT, PE and prevention of recurrence**; stop warfarin and initiate rivaroxaban once INR is ≤2.5. **Prevention of stroke and systemic embolism**; stop warfarin and initiate rivaroxaban once INR ≤3.0.	Discontinue warfarin and commence apixaban as soon as INR is <2.0.	Discontinue warfarin and commence dabigatran as soon as INR is <2.0.
LMWH	Commence warfarin in combination with LMWH, and monitor INR. Discontinue LMWH once INR in therapeutic range for 2 consecutive days.		Discontinue LMWH and commence rivaroxaban 0-2 hours before the time that the next scheduled dose of LMWH would be due.	Discontinue LMWH and commence apixaban at the time that the next scheduled dose of LMWH would be due.	Discontinue LMWH and commence dabigatran 0-2 hours before the time that the next scheduled dose of LMWH would be due.
Rivaroxaban For advice during invasive procedures, refer to Newer anticoagulants and elective procedures guideline.	Commence warfarin in combination with rivaroxaban. Rivaroxaban should be discontinued when INR is in therapeutic range. Measure INR prior to each dose of rivaroxaban being administered.	Discontinue rivaroxaban and commence LMWH at the time that the next scheduled dose of rivaroxaban would be due.		Discontinue rivaroxaban and commence apixaban at the time that the next scheduled dose of rivaroxaban would be due*.	Discontinue rivaroxaban and commence dabigatran at the time that the next scheduled dose of rivaroxaban would be due*.
Apixaban For advice during invasive procedures, refer to Newer anticoagulants and elective procedures guideline.	Commence warfarin in combination with apixaban. Apixaban should be continued for 2 days, after which point INR should be measured prior to each dose of apixaban. Apixaban should be discontinued when INR is ≥ 2.0.	Discontinue apixaban and commence LMWH at the time that the next scheduled dose of apixaban would be due.	Discontinue apixaban and commence rivaroxaban at the time that the next scheduled dose of apixaban would be due*.		Discontinue apixaban and commence dabigatran at the time that the next scheduled dose of apixaban would be due*.
Dabigatran For advice during invasive procedures, refer to Newer anticoagulants and elective procedures guideline.	**Conversion protocol depends on renal function.** For CrCl ≥ **50ml/minute**, commence warfarin 3 days prior to discontinuing dabigatran. For **CrCl 30-50ml/minute**, commence warfarin 2 days prior to discontinuing dabigatran. NB: dabigatran can increase INR. INR measurements should be interpreted cautiously until dabigatran has been stopped for 2 days.	Discontinue dabigatran and commence LMWH 12-hours after the last dose of dabigatran was administered.	Discontinue dabigatran and commence rivaroxaban at the time that the next scheduled dose of dabigatran would be due*.	Discontinue dabigatran and commence apixaban at the time that the next scheduled dose of dabigatran would be due*.	

When to stop drug before surgery?

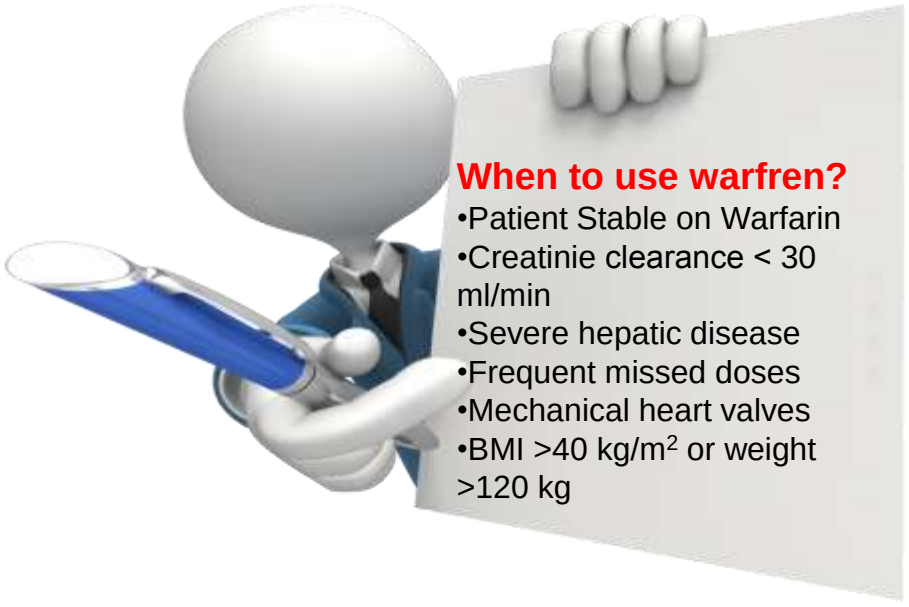
Cretinine clearance (ml/min)	Dabigatran		Apixaban		Rivaroxaban	
	Low Risk	High Risk	Low Risk	High Risk	Low Risk	High Risk
CrCl>80	≥ 24	≥48	≥ 24	≥48	≥ 24	≥48
CrCl 50-80	≥ 36	≥ 72	≥ 24	≥48	≥ 24	≥48
CrCl 30-50	≥48	≥ 96	≥ 24	≥48	≥ 24	≥48
CrCl 15-30	Not Indicated		≥ 36	≥48	≥ 36	≥48
CrCl <15	No Official indication for use					

www.escardio.org/EHRA

How to deal with Dosing error?

Missed dose:	BID: take missed dose up to 6 h after scheduled intake. If not possible skip dose and take next scheduled dose. QD: take missed dose up to 12 h after scheduled intake. If not possible skip dose and take next scheduled dose.
Double dose:	BID: skip next planned dose and restart BID after 24 h. QD: continue normal regimen.
Uncertainty about intake:	BID: continue normal regimen. QD: take another dose then continue normal regimen.
Overdose:	Hospitalization advised.

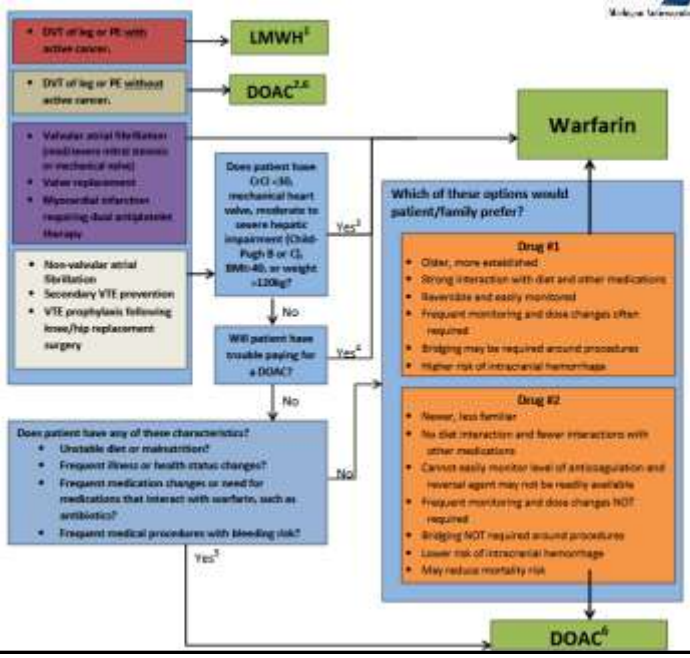
www.escardio.org/EHRA



How Do we choose Among the agents?

Characteristic	Drug Choice	Rational
CrCl 30-50 ml/min	Rivaroxaban or Apixaban	Less affected by renal impairment than Dabigatran
Ischemic stroke on warfarin	Dabigatran	Lowe risk of ischemic stroke with dabigatran (150mg)
Dyspepsia or upper GI complaints	Rivaroxaban or Apixaban	Dyspepsia with Dabigatran is up to 10 % of patients
Recent GI bleeding	Apixaban	More GI bledding with dapigatran or rivaroxaban
Significant CAD	Rivaroxaban or Apixaban	Small MI signal with Dabigatran
Poor compliance with twice –daily dosing	Rivaroxaban	Given once daily

First Choice of long-term anticoagulant



NOACs and Elevated INR

- Although use may be associated with an increase in INR, this increase does not relate to the effectiveness of therapy or provide a linear correlation

NOACs and elevated INR

International Normalized Ratio Is Significantly Elevated With Rivaroxaban and Apixaban Drug Therapies: A Retrospective Study.

Oliel F[1], Bar Chaim S[2], Kronenfeld M[3], Ziv-Baran T[4], Berkowitz M[5].

Author information

Abstract

PURPOSE: Direct factor Xa inhibitors such as rivaroxaban or apixaban may prolong prothrombin time (PT) and elevate international normalized ratio (INR). However, these tests are not reliable for assessing the anticoagulation effects of these agents. PT assay sensitivity is relatively weak at therapeutic drug concentrations and is subjected to significant variations depending on the reagent used. Conversion of PT to INR may even increase the variability. We conducted a retrospective cross-sectional study aiming to assess the prevalence and extent of INR elevation in hospitalized patients receiving rivaroxaban or apixaban as part of their home medications and to find out whether other existing factors could elevate INR apart from the drug entity itself.

METHODS: The data collected from 218 hospitalized patients' charts included PT and INR taken on admission, patients' characteristics, laboratory results, other medications regularly used, and coexisting clinical conditions.

FINDINGS: No statistically significant association between INR elevation and the parameters examined was found in our study. INR was significantly elevated in both drug groups ($P < 0.001$), with 84.2% of rivaroxaban patients and 78.3% of apixaban patients presenting with INR levels above the higher limit of the normal range. Furthermore, INR was significantly higher in the rivaroxaban group than in the apixaban group ($P < 0.001$).

IMPLICATIONS: Both of the reviewed drugs significantly elevated INR. Moreover, rivaroxaban elevates INR significantly more than apixaban, and there are apparently no other factors affecting INR but the drugs themselves. Larger prospective studies are needed to confirm and clarify the clinical significance of these results.

KEYWORDS: DOACs; INR elevation; anticoagulants; apixaban; direct anti-factor Xa inhibitors; rivaroxaban

PMID: 28476405 DOI: 10.1016/j.pharma.2017.04.007

Case study

- S.A female patient 84 years old,Cancer pa… lung,alzhimer ,AF
- Admitte… 20/1… …e… and L.L ed…
- Diagno…
- 20/1… …wice
- 22/… …arelto held
- 23/1… …TPA given
- Xa… …n 25/1
- 27/1 IN… was 4.8 and xarelto stoped
- 27/1 Left sided weakness MRI done and it showes left deep fronto-parital foci (recent small infarcts)

Should we give heparin on INR=5?

Is That happened by chance?

Date	21/1	22/1	23/1	24/1	25/1	26/1	27/1	28/1
INR	1.68	4.93	3.8	3.7	1.94		4.8	1.85


thank
you