ANTICOAGULANTS

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Acknowledgments

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Objectives

1. History of oral anticoagulants
2. Anticoagulant types & Indications
3. Mechanism of Action
4. Switching between Anticoagulants
5. Perioperative Management of Anticoagulants
6. Monitoring and Reversal

Take Home Points

1. All of the new oral anticoagulants are at least as effective as warfarin and can be given without routine monitoring.
2. All DOACs reduce the risk of intracranial bleeding
3. New agents produce about a 10% reduction in mortality.
4. You don't need bridging with DOACs.
5. Most pts on warfarin don't need bridging.

History of oral Anticoagulation

Started with Warfarin

- ✓ Prior to 2009, warfarin was the only drug and has been in clinical use since 1955
- ✓ Reduces risk of stroke in AF by 66%
- ✓ Reduces risk of recurrent events, complications, and death from PE and DVT by at least 80%
- ✓ Markedly reduces risk of valve thrombosis and emboli in mechanical valve prostheses
- ✓ Perception of warfarin as “bad drug”

Pros of Warfarin

Three good things:

- ✓ It works
- ✓ It’s cheap, and
- ✓ It’s unaffected by renal function

Cons of Warfarin

It’s Difficult to Manage.

- ✓ Prolonged onset of effect
- ✓ Prolonged offset of effect
- ✓ Highly protein bound
- ✓ Highly affected by diet
- ✓ Highly affected by other medications
- ✓ Large individual variation in metabolism
- ✓ Need for frequent monitoring

The Ideal Anticoagulant

Desired Properties

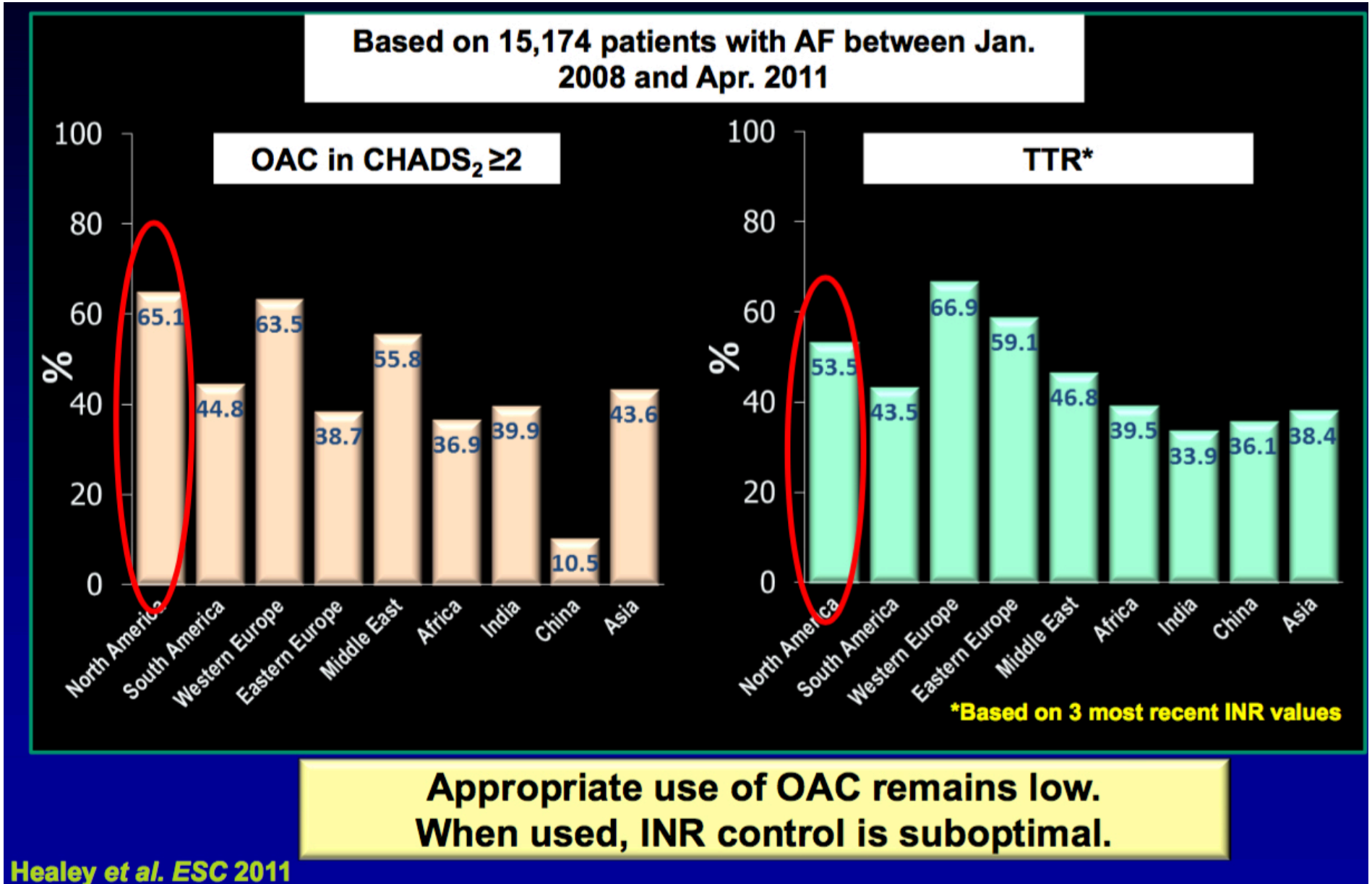
- ✓ Wide therapeutic margin
- ✓ Infrequent oral dosing
- ✓ Lack of food/drug interactions
- ✓ No need for laboratory monitoring
- ✓ Readily reversible effect
- ✓ Affordability

Why We Need a Replacement for Warfarin in AF

Limitations of Warfarin

- ✓ Slow onset of action
- ✓ Unpredictable and variable anticoagulant effect
- ✓ Numerous food and drug interactions
- ✓ High risk of intracranial bleeding
  - ✓ Undertreatment of AF patients
  - ✓ Suboptimal anticoagulant control in patients treated with warfarin

Worldwide Utilization of Oral Anticoagulation in AF: Results from a Global Registry



FDA approves DOACs

- ✓2010 : Dabigatran (PRADAXA) for stroke prevention in AF
- ✓2011 : Rivaroxaban (XARELTO) for stroke prevention in AF
- ✓2014 : Apixaban (ELIQUIS) for VTE (DVT &PE) treatment
- ✓2015 : Edoxaban (Savaysa) for stroke prevention

Direct Oral Anticoagulants (DOACs)

- ✓ Dabigatran (PRADAXA) – direct Factor IIa (thrombin) inhibitor
- ✓ Rivaroxaban (XARELTO) – direct Factor Xa inhibitor
- ✓ Apixaban (ELIQUIS) – direct Factor Xa inhibitor
- ✓ Edoxaban (Savaysa) – direct Factor Xa inhibitor

Types of Anticoagulants

Anticoagulants

Parenteral

- Heparin
- LMWH (Enoxaparin, Dalteparin, etc)
- Fondaparinux
- Parenteral DTIs (Bivalirudin, Argatroban, Desirudin)
- No parenteral direct factor Xa inhibitors

Oral

- Warfarin
- Dabigatran (Pradaxa)
- Rivaroxaban (Xarelto)
- Apixaban (Eliquis)
- Edoxaban (Savaysa)

Mnemonic For Anticoagulants

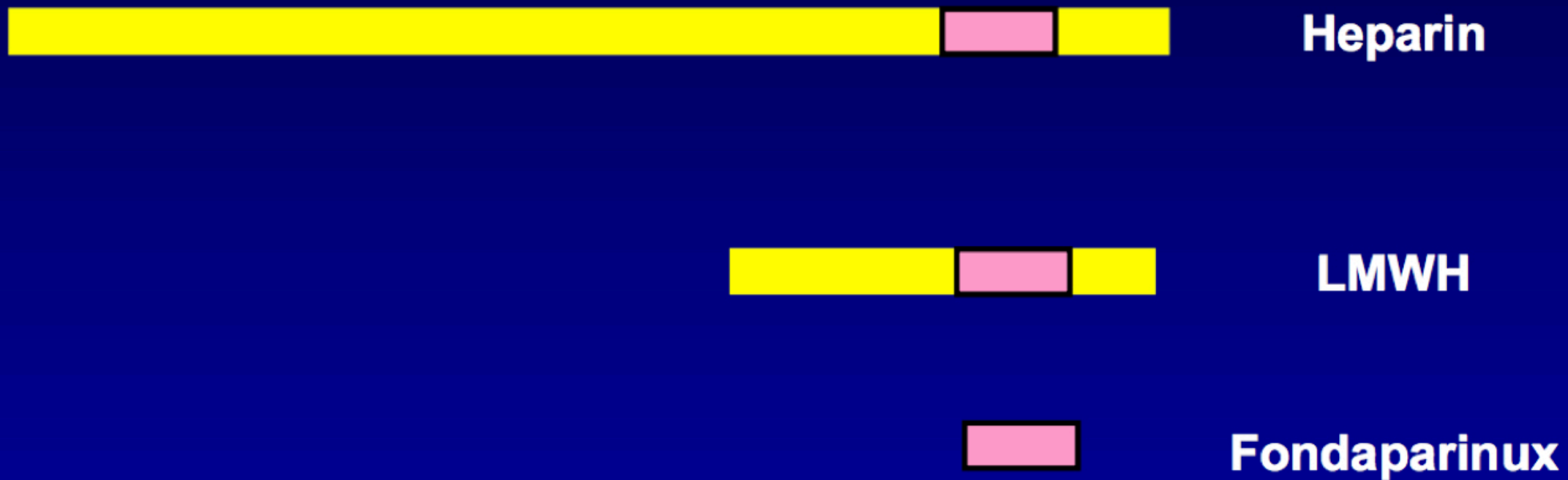
- ✓IIa : Dabigatran, Bivalirudin, ArgaTroban
- ✓Xa : ApiXaban, RivaroXaban, FondaparinuX
- ✓Both Factors (Pair): Heparins - UFH, LMWHs (Enoxparin, Dalteparin, etc)
- ✓Don’t forget Warfarin that is a vitamin K antagonist

Indications for Anticoagulants

Indications for Parenteral Anticoagulants

- ✓ *Prevention* of venous thromboembolism (VTE)
- ✓ *Initial treatment* of arterial or venous thrombosis
- ✓ Revascularization Procedures
- ✓ Unstable angina, myocardial infarction, coronary stenting
- ✓ Heparin-induced thrombocytopenia (i.e. non-heparin parenteral anticoagulants)

Evolution of Heparin



Advantages of LMWHs

- ✓ Once-daily subcutaneous administration
- ✓ No need for routine monitoring
- ✓ Low risk of HIT

Disadvantages of LMWHs

- ✓ Potential for accumulation in patients with renal impairment
- ✓ Lack of an antidote
- ✓ Risk of catheter thrombosis if used as the sole anticoagulant

Indications for Oral Anticoagulants

- ✓ *Prevention* of venous thromboembolism (VTE)
- ✓ *Treatment* of VTE
- ✓ Atrial fibrillation to prevent embolic stroke

Advantages of DOACs

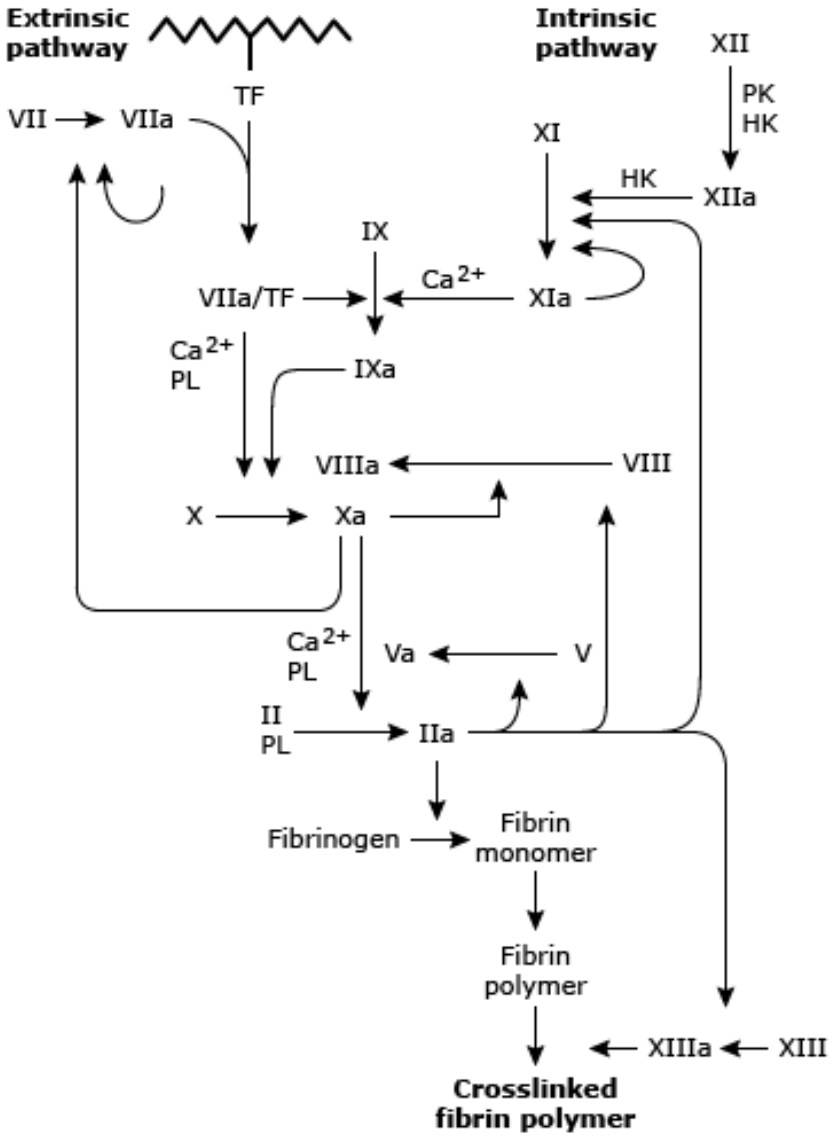
- ✓ Affects only one coagulation factor (either Xa or IIa)
- ✓ Independent of anti-thrombin III unlike heparins
- ✓ Active against free (soluble) and clot-bound thrombin unlike heparins which are only active against soluble facts leading to the possibility of thrombus extension while on heparin tx
- ✓ Do not induce immune-mediated thrombocytopenia
- ✓ Less Intracranial bleeding, even though overall risks of bleeding are similar to VKAs.
- ✓ No need for laboratory monitoring. Both Heparin and Warfarin have narrow therapeutic widows and more variable dose response relationship that depends on a variety of factors, as such need frequent monitoring.
- ✓ Not affected by diet or vit K intake as much as Warfarin.
- ✓ Less interactions with other drugs.

Advantages of New Oral Anticoagulants Over Warfarin

Feature	Warfarin	New DOAC
Onset	Slow	Rapid
Dosing	Variable	Fixed
Food effect	Yes	No
Interactions	Many	Few
Monitoring	Yes	No
Offset	Long	Shorter

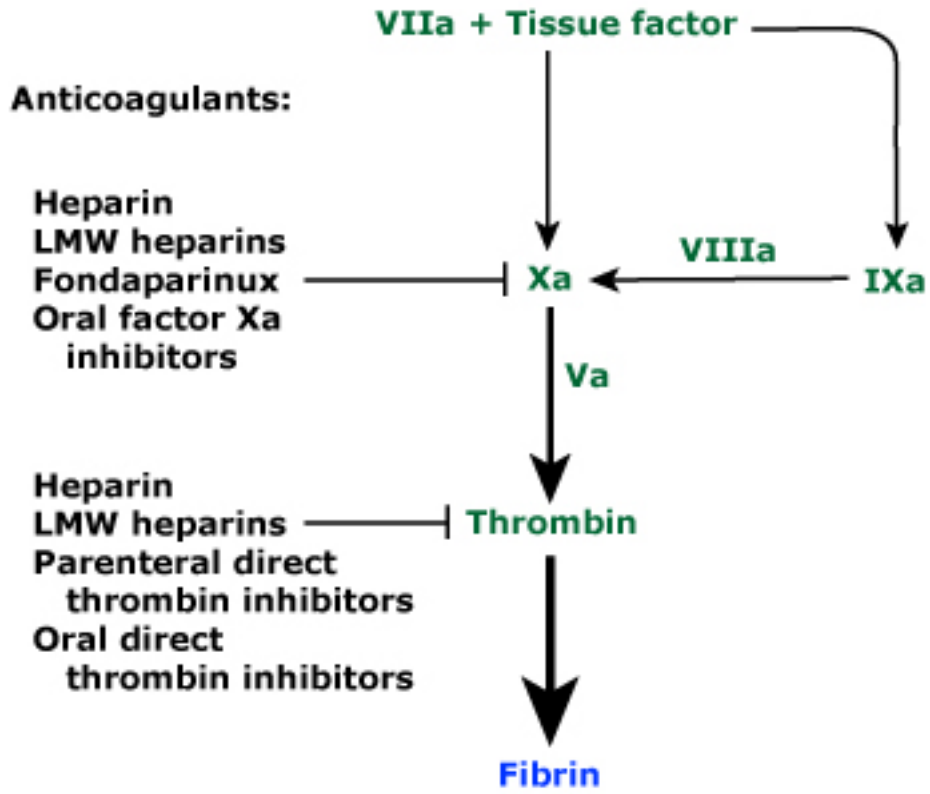
MOA of DOACs

Coagulation Cascade



Schematic representation of the coagulation.
HK: high-molecular-weight kininogen; PK: prekallikrein; PL: phospholipid.
From: Uptodate.com

Coagulation cascade: Anticoagulant effects



Mechanism of Action: Clinical Implications

- ✓ Compared to warfarin, DOACs do not inhibit *production* of clotting factors.
- ✓ They bind to the factors directly. E.g. DTIs bind directly to thrombin rather than enhancing the activity of antithrombin as is done by heparin.
- ✓ Thus, rapid onset and offset of effect
- ✓ DOACs do not involve Vitamin K metabolism.
- ✓ DOACS not affected by food/vitamin K intake
- ✓ Anticoagulant effect of DOACs not reversed by vitamin K

Comparative Pharmacology

Characteristic	Rivaroxaban	Apixaban	Dabigatran
Target	Factor Xa	Factor Xa	Thrombin
Prodrug	No	No	Yes
Bioavailability	80%	60%	6%
Dosing	o.d. (b.i.d)	b.i.d	b.i.d. (o.d.)
Half life	7-11h	12h	12-17h
Renal	33% (66%)	25%	80%
Monitoring	No	No	No
Interactions	3A4/P-gp	3A4/P-gp	P-gp

Pharmacokinetics, Dosage Forms, Administration

	Warfarin	Dabigatran	Rivaroxaban	Apixaban	Edoxaban
Pharmacokinetics					
Tmax (hours)	4	1.25–3	2–4	3–4	1–2
T ½ (hours)	40	12–17; Up to 27 in severe renal impairment	5–9; 11–13 in elderly patients	12	10–14
Metabolism	CYP2C9 primary, (CYP3A4, 1A2, 2C19 minor pathways)	Conjugation (no CYP involvement)	Oxidation (via CYP3A4 and CYP2J2) and hydrolysis	Oxidation (via CYP3A4) and conjugation	Minimal by oxidation, conjugation and hydrolysis
Elimination	Renal, primarily as metabolites	Renal (80% unchanged drug)	Renal (36% unchanged drug)	Renal (27% unchanged drug)	Renal (35% unchanged drug)
Dosage Forms, Administration					
Strengths (mg)	1, 2, 2.5, 3, 4, 5, 6, 7.5, 10	75, 150	10, 15, 20	2.5, 5	15, 30, 60
Dosage Form	Tablet	Capsule	Tablet	Tablet	Tablet
Splitting, Crushing, or Chewing	May split tablet in half May crush tablet and mix with water or applesauce immediately before use	No; will increase exposure to medication	May crush tablet and mix with water or applesauce immediately before use	May be crushed and suspended in 60 mL D5W and immediately delivered through nasogastric tube	No recommendations provided

Clinical Trials

Clinical Trials of DOACs: Atrial Fibrillation

- RE-LY ------dabigatran
- ROCKET AF -----rivaroxaban
- ARISTOTLE -----apixaban

Each of these trials randomly assigned 15,000 to 20,000 patients to warfarin versus another oral anticoagulant (dabigatran, rivaroxaban, or apixaban, respectively)

*RE-LY (**R**andomized **E**valuation of **L**ong-Term Anticoagulant Therap**y**), ROCKET AF (**R**ivaroxaban **O**nce daily, oral direct factor Xa inhibition **C**ompared with vitamin **K** antagonism for prevention of stroke and **E**mbolism **T**rial in **A**trial **F**ibrillation), and ARISTOTLE (**A**pixaban for **R**eduction in **S**troke and **O**ther **T**hromboembolic Events in Atrial Fibrillation)*

RE-LY

- ✓ Dabigatran 150 mg bid was superior to warfarin in preventing embolic stroke
- ✓ Dabigatran 150 mg bid was equivalent to warfarin in bleeding complications
- ✓ 110 mg bid dose was equivalent to warfarin in preventing embolic stroke and was associated with less bleeding
- ✓ Both doses of dabigatran were associated with LESS intracranial hemorrhage
- ✓ More GI bleeding with dabigatran

ROCKET-AF

- ✓ Sicker group of patients
- ✓ Rivaroxaban 20 mg daily was noninferior to warfarin in preventing embolic stroke
- ✓ Rivaroxaban was associated with the same amount of overall bleeding as warfarin
- ✓ Rivaroxaban was associated with LESS intracranial and fatal hemorrhage
- ✓ Was associated with more GI bleeding

ARISTOTLE

- ✓ Apixaban 5 mg bid was superior to warfarin in preventing embolic stroke
- ✓ Apixaban was associated with less major hemorrhage than warfarin
- ✓ Less intracranial hemorrhage
- ✓ NO greater incidence of GI bleeding
- ✓ Overall mortality lower compared to warfarin

Highlights of Clinical Trials in AF

- ✓ All DOACs either as good or better than warfarin in preventing embolic stroke in AF
- ✓ All DOACs associated with either the same or less bleeding than warfarin in AF
- ✓ All DOACS associated with LESS intracranial hemorrhage compared to warfarin
- ✓ DOACS associated with slightly less (10%) mortality compared to warfarin

Phase 3 Trials of DOACs vs. Standard of Care for Acute VTE Treatment

Trial	RECOVER 1 and 2 pooled analysis (n=5107)	EINSTEIN pooled analysis (n=8282)	AMPLIFY (n=5395)	HOKUSAI-VTE (n=8240)
DOAC	Dabigatran	Rivaroxaban	Apixaban	Edoxaban
Dosing	Parenteral anticoagulation ≥ 5 days, then 150 mg PO BID	15 mg PO BID x 21 days, then 20 mg PO daily	10 mg PO BID x 7 days, then 5 mg PO BID	Parenteral anticoagulation ≥5 days, then 60 mg PO daily
Comparator	Parenteral anticoagulation (UFH, LMWH, or fondaparinux) bridge to VKA			
Duration of therapy (months)	6	3, 6, or 12	6	3, 6, or 12
Recurrent VTE	2.4% Dabigatran vs. 2.2% VKA	2.1% Rivaroxaban vs. 2.3% VKA	2.3% Apixaban vs. 2.7% VKA	3.2% Edoxaban vs. 3.5% VKA
Major bleeding, % *ICH, n* *GI, n*	*1.4% Dabigatran vs.2% VKA* *ICH: n=2 Dabigatran vs. 5 VKA* *GI: n=48 Dabigatran vs. 33 VKA*	*1.0% Rivaroxaban vs. 1.7% VKA*[a] *ICH: n=5 Rivaroxaban vs. 13 VKA* *GI: n=1 Rivaroxaban vs. 3 VKA (only fatal events reported)*	*0.6% Apixaban vs. 1.8% VKA*[a] *ICH: n=3 Apixaban vs. 6 VKA* *GI: n=7 Apixaban vs. 18 VKA*	*1.4% Edoxaban vs. 1.6% VKA* *ICH: n=6 Edoxaban vs. 18 VKA* *GI: n=1 Edoxaban vs. 2 VKA (only fatal events reported*

[a]Statistically significant reduction with DOAC.

Italics = actual number of cases of ICH and GI bleeding reported.

BID = twice daily; DOAC = direct oral anticoagulant; ICH = intracranial hemorrhage; LMWH = low-molecular-weight heparin; PO = by mouth; UH = unfractionated heparin; VKA = vitamin K antagonist; VTE = venous thromboembolism

Conclusions

DOACs were noninferior to standard therapy (LMWH with transition to warfarin) in the treatment of acute DVT and PE and was associated with similar rates of major bleeding

Choosing Between Agents

With Less Hemorrhagic Stroke, Why Not Switch Everyone to New Oral Anticoagulants?

Drug	NNT*
Dabigatran (150mg)	182
Rivaroxaban	333
Apixaban	238

*NNT: Number needed to treat to prevent one hemorrhagic stroke compared with warfarin

How Do We Choose Amongst the Agent

Characteristic	Drug choice	Rationale
CrCl30-50ml/min	Rivaroxaban or apixaban	Less affected by renal impairment than dabigatran
Ischemic stroke on warfarin	Dabigatran	Lower risk of ischemic stroke with dabigatran (150 mg)
Dyspepsia or upper CI complaints	Rivaroxaban or apixaban	Dyspepsia with dabigatran in up to 10% of patients
Recent GI bleed	Apixaban	More GI bleeding with dabigatran (150 mg) or rivaroxaban
Significant CAD	Rivaroxaban or apixaban	Small MI signal with dabigatran
Poor compliance with-twice daily dosing	Rivaroxaban	Only agent given once-daily

When a Heparin or VKA is Preferable

- ✓ **Prosthetic heart valves** – DOACs are **contraindicated** 2/2 greater risk of valve thrombosis, which may be fatal.
- ✓ **Pregnancy** – DOACs are **contraindicated** during pregnancy 2/2 lack of clinical experience in this setting; Use LMW heparin.
- ✓ **Renal impairment (Poor CrCl)** –Heparin or warfarin may be preferable to DOACs in pts with renal impairment. DOACS are renally excreted to variable degrees. Thus, heparin generally is used in hospitalized pts with renal insufficiency. For outpts, warfarin or dose-adjusted LMWH is preferred over a DOAC in those with reduced renal function (eg, CrCl ≤ 30 mL/min) who require long-term anticoagulation. Exception is Eliquis which is FDA approved for use in pts with renal failure including those on dialysis.
- ✓ **Stable on the warfarin.** Pts who are doing well on warfarin w/ no issues have no advantage in switching.

When a Heparin or VKA is Preferable

- ✓ **Frequent missed doses** – Don't use DOAC's in pts at risk for noncompliance. 1) You can't monitor. 2) Missing one or two doses can leave the patient inadequately anticoagulated; in contrast, missing a couple of doses of warfarin is unlikely to substantially increase the time outside the therapeutic range.
- ✓ **GI disease** – GI bleeding, Severe liver disease. Avoid DOACs with no antidote in pts with increased risk of GI bleed. Pts with severe dyspepsia may not tolerate dabigatran.
- ✓ **Dosing convenience** – Dabigatran and apixaban require BID dosing vs. Warfarin that is qd.
- ✓ **Cost** – VKA are typically much cheaper than DOACs.

Starting or Switching Between Diff. Oral Agents

Approved Dosing of Warfarin and DOACs for AF and VTE

Drug	Atrial Fibrillation[b]	VTE Treatment
Warfarin	Individualize dosing to goal INR 2–3	Individualize dosing to goal INR 2–3
Dabigatran	CrCl >30 mL/min: 150 mg BID CrCl 15-30 mL/min: 75 mg BID CrCl <15 mL/minute or on dialysis: Dosing recommendation cannot be provided	CrCl >30 mL/minute: LMWH or UFH x 5-10 days, then dabigatran 150 mg BID CrCl ≤30 mL/minute or on dialysis: Dosing recommendation cannot be provided Extended treatment to prevent VTE recurrence with CrCl >30 mL/min: 150 mg BID
Rivaroxaban	CrCl >50 mL/min: 20 mg daily CrCl 15-50 mL/min: 15 mg daily CrCl <15 mL/min: Avoid	15 mg BID x 21 days, then 20 mg daily for CrCl ≥ 30 mL/min CrCl <30 mL/min: Avoid Extended treatment to prevent VTE recurrence: 20 mg daily
Apixaban	Most patients: 5 mg BID If with two or more factors: SCr ≥1.5 mg/dL or age ≥80 years or weight ≤60 kg: 2.5 mg BID	10 mg BID x 7 days, then 5 mg BID No dose adjustment recommended for renal function Extended treatment to prevent VTE recurrence: 2.5 mg BID
Edoxaban	CrCl > 95 mL/min: Do not use CrCl 51–95 mL/min: 60 mg daily CrCl 15–50 mL/min: 30 mg daily CrCl <15 mL/min: use is not recommended	CrCl >50 mL/min: LMWH or UFH x 5–10 days, then edoxaban 60 mg daily CrCl 15–50 mL/min: 30 mg daily CrCl <15 mL/min: use is not recommended Patients ≤60 kg: 30 mg daily

bDOACs are indicated only for non-valvular AF.

Switching from VKA (Warfarin) to a DOAC

- ✓ Peak onset of action of new agents occurs within 2 to 3 hours
- ✓ D/c the VKA, monitor PT/INR and initiate the DOAC when INR is ≤ 2.0
- ✓ Remember the resolution of the warfarin effect may take several days.

Switching from DOAC to VKA (Warfarin)

- ✓ Remember that the full effect of the VKA doesn't not occur for the first few days despite prolongation of the PT/INR.
- ✓ **Dabigatran to Warfarin**
  - ✓ Overlap the two agents. The number of days of overlap depends on the pts renal function.
  - ✓ CrCl ≥ 50 – Start VKA three days b4 you d/c dabigatran
  - ✓ CrCl 30 to 50 – Start VKA two days b4 you d/c dabigatran
  - ✓ CrCl 15 to 30 – Start VKA one day before you d/c dabigatran
- ✓ **Rivaroxaban or Apixaban to Warfarin** - Prescribing info suggests stopping rivaroxaban or apixaban and providing a parenteral agent during warfarin initiation because the INR cannot be monitored adequately during administration of a direct factor Xa inhibitor.

Perioperative Management

Perioperative Mgt of Pts Receiving Anticoagulants

General Approach

1. Estimate *Thromboembolic (TE) Risk*
2. Estimate *Bleeding Risk* during the procedure
3. Determine the *timing of anticoagulant interruption*
4. Determine whether to use *bridging anticoagulation*

Estimate Thromboembolic (TE) Risk

1. Higher TE risk increases importance of minimizing interval without anticoagulation.
2. Major factors that increase TE risk are *AF, prosthetic heart valves, and recent venous or arterial TE* (e.g. within the preceding 3 months).
3. AF pts: Estimate TE risk based on age and comorbidities. E.g. CHA2DS2-VASc
4. VTE (PE or DVT) pts: Estimate TE risk based on interval since diagnosis.
5. If TE risk is transiently increased (e.g. recent stroke, recent PE), it's best to delay surgery until it returns to baseline, if possible.
6. For pts w/ more than one comorbidity that predisposes to TE, the condition with the highest TE risk takes precedence.

Estimate Procedural Bleeding Risk (BR)

1. BR is determined mainly by *type & urgency of surgery*.
2. Also some pt. comorbidities e.g. old age, decr. renal function may incr. BR.
3. Meds that affect hemostasis may incr BR.
4. Categorize the procedure into minimal risk, low risk, or high BR.

Classification of elective surgical procedures according to bleeding risk

Procedures not necessarily requiring interruption of DOAC anticoagulation (minimal bleeding risk):

Dental procedures (extraction of 1-3 teeth, periodontal surgery, abscess incision, implant moving)
Ophthalmology (Cataract extraction)
Endoscopy without biopsy
Superficial surgery (dermatologic excisions)
Central venous catheter removal

Procedures with low bleeding risk:

GI endoscopy ± biopsy, Bronchoscopy ± biopsy , enteroscopy, biliary/pancreatic stent without sphincterotomy, endosonography without fine-needle aspiration
Prostate or bladder biopsy
EP study or RF catheter ablation for SVT (including left-sided ablation with transseptal puncture)
Angiography (cardiac cath)
Pacemaker and cardiac defibrillator insertion (ICD implant) and electrophysiologic testing
Carpal tunnel repair
Cutaneous and bladder/prostate/thyroid/breast/lymph node biopsies
Noncoronary angiography
Cholecystectomy
Axillary node dissection
Hemorrhoidal surgery
Dilatation and curettage
Hydrocele repair

Procedures with high bleeding risk:

Any major operation (procedure duration >45 minutes)
Heart Surgery e.g. CABG, Heart valve replacement
Complex left-sided ablation
Abdominal aortic aneurysm repair
Spinal or epidural anesthesia or injections; lumbar puncture
Vascular and General Surgery
Thoracic surgery
Abdominal surgery
Major orthopedic surgery e.g. Bilateral knee replacement, Hip replacement
Liver or kidney biopsy
Endoscopically guided fine-needle aspiration
TURP (Transurethral prostate resection)
Most neurosurgical procedures (Laminectomy, etc)
Neurosurgical/urologic/head and neck/abdominal/breast *cancer surgery*
Polypectomy, variceal treatment, biliary sphincterectomy, pneumatic dilatation

Determine the timing of anticoagulant interruption

1. When should you give the last dose of the oral anticoagulant before procedure?
    1. Depends on the specific agent used.
    2. For Warfarin, it is 5 days before the procedure.
    3. For DOACs?

When to give last dose of DOACs before the Procedure

Anticoagulant	Renal function and dose	Interval between last dose and procedure NOTE: No anticoagulant is given the day of the procedure		Resumption after procedure	
		High bleeding risk	Low bleeding risk	High bleeding risk	Low bleeding risk
Dabigatran	CrCl >50 Dose 150 mg BID	Give last dose **3 days** before procedure (ie, skip four doses on the two days before the procedure)	Give last dose **2 days** before procedure (ie, skip two doses on the day before the procedure)	Resume 48 to 72 hours after surgery (ie, postoperative day 2 to 3)	Resume 24 hours after surgery (ie, postoperative day 1)
	CrCl 30 to 50 Dose 150 mg BID	Give last dose *5 days* before procedure (ie, skip eight doses on the four days before the procedure)	Give last dose *3 days* before procedure (ie, skip four doses on the two days before the procedure)		
Rivaroxaban	CrCl >50 Dose 20 mg qd	Give last dose **3 days** before procedure (ie, skip two doses on the two days before the procedure)	Give last dose **2 days** before procedure (ie, skip one dose on the day before the procedure)		
	CrCl 30 to 50 Dose 15 mg qd				
Apixaban	CrCl >50 Dose 5 mg BID	Give last dose **3 days** before procedure (ie, skip four doses on the two days before the procedure)	Give last dose **2 days** before procedure (ie, skip two doses on the day before the procedure)		
	CrCl 30 to 50 Dose 2.5 mg BID				
Edoxaban	CrCl 50 to 95 Dose 60 mg qd	Give the last dose **3 days** before the procedure (ie, skip two doses on the two days before the procedure)	Give the last dose **2 days** before the procedure (ie, skip one dose on the day before the procedure)		
	CrCl 15 to 50 Dose 30 mg qd				

Determine whether to use bridging anticoagulation

1. No bridging necessary with DOACs (b/c they have shorter t1/2.)
2. Most pts don't need bridging b/c it increases bleeding risk without reducing the rate of TE.
3. Only a few pts with very high TE risks who are taking warfarin need bridging.
4. When bridging, use LMWH for most pts. Exception is pts with renal insufficiency and / hemodialysis, for those, use UFH. Don't used DOACs for bridging.
5. Timing depends on the heparin product used and the procedural bleeding risk.

Monitoring and Reversal

Monitoring

- ✓ Warfarin: PT/ INR
- ✓ Heparin: aPTT; also get CBC (plts), CMP
- ✓ LMWH: Laboratory monitoring is not necessary.
- ✓ DOACs : Don’t need monitoring. None of the conventional coagulation assays (aPTT, prothrombin time, INR, ACT) can be reliably used to monitor DOACS. Some of these assays will be affected or prolonged by the DOACS but not in any predictable manner.

Reversal of DOACs

- ✓ Only Dabigatran has a reversing agent: Idarucizumab (Praxbind)
- ✓ The rest have reversing agents in the works.
- ✓ Vitamin K does nothing
- ✓ Fresh Frozen Plasma does nothing
- ✓ Prothrombin Complex Concentrates (PCC) seem to work well but are very expensive
- ✓ Despite lack of reversal agents, bleeding complications are no more frequent and less severe than with warfarin

Reversing anticoagulation in warfarin-associated bleeding

Management option	Time to anticoagulation reversal	Comments and cautions
D/C Warfarin	5 to 14 days	Five days is typical for patients with an INR in the therapeutic range
Vitamin K*	6 to 24 hours to correct the INR, longer to fully reverse anticoagulation	Recovery of factors X and II (prothrombin) takes longer than 24 hours Risk of anaphylaxis with intravenous injection Impaired response to warfarin lasting up to one week may occur after large doses (ie, >5 mg)
Fresh frozen plasma	Depends on the time it takes to complete the infusion; typically 12 to 32 hours for complete reversal	Effect is transient and concomitant vitamin K must be administered Potential for volume overload (2 to 4 L to normalize INR) Potential for TRALI Potential for viral transmission
Prothrombin complex concentrate	15 minutes after 10-minute to 1-hour infusion	Effect is transient, and concomitant vitamin K must be administered; limited availability Cost Variable factor VII content depending on the product: a 4-factor PCC is preferred Potentially prothrombotic
Recombinant factor VIIa	15 minutes after bolus infusion	Effect is transient, and concomitant vitamin K must be administered Cost Potentially prothrombotic

Mgt of a Supratherapeutic INR

INR	Bleeding present	Recommended action*
>Therapeutic to 5.0	No	Lower warfarin dose, **or**
		Omit one dose and restart warfarin at a lower dose when INR is in therapeutic range, **or**
		No dose reduction needed if INR is minimally supratherapeutic
>5.0 to 9.0	No	Omit the next one to two doses of warfarin, monitor INR more frequently, and resume treatment at a lower dose when INR is in therapeutic range, **or**
		Omit a dose and administer 1 to 2.5 mg oral vitamin K1[¶]
>9.0	No	Hold warfarin and administer 2.5 to 5 mg oral vitamin K1. Monitor INR more frequently and administer more vitamin K1 as needed. Resume warfarin at a lower dose when INR is in therapeutic range.
Any	Serious or life-threatening	Hold warfarin and administer 10 mg vitamin K by slow IV infusion; supplement with four-factor prothrombin complex concentrate (4-factor PCC) or fresh frozen plasma, depending on clinical urgency. Monitor and repeat as needed.

Emergent reversal of anticoagulation from warfarin for life-threatening hemorrhage in adults

4-factor prothrombin complex concentrate (4F PCC) is available (preferred approach):
1. Give 4F PCC 1500 to 2000 units[¶] IV over 10 minutes. Check INR 15 minutes after completion of the infusion. If INR is not ≤1.5, give additional 4F PCC (check drug reference or consult pharmacy for details).
2. Give vitamin K 10 mg IV over 10 to 20 minutes.
B. 3-factor prothrombin complex concentrate (3F PCC) is available but 4F PCC is not available:
1. Give 3F PCC 1500 to 2000 units[¶] IV over 10 minutes. Check INR 15 minutes after completion of the infusion. If INR is not ≤1.5, give additional 3F PCC (refer to topic or drug reference for details).
2. Give Factor VIIa 20 mcg/kg IV **OR** give FFP 2 units IV by rapid infusion. Factor VIIa may be preferred if volume overload is a concern.
3. Give vitamin K 10 mg IV over 10 to 20 minutes.
C. Neither 3F PCC nor 4F PCC is available:
1. Give FFP 2 units IV by rapid infusion. Check INR 15 minutes after completion of infusion. If INR ≥1.5, administer 2 additional units of FFP IV rapid infusion. Repeat process until INR ≤1.5. May wish to administer loop diuretic between FFP infusions if volume overload is a concern.
2. Give vitamin K 10 mg IV over 10 to 20 minutes.

PCC products and what each contains

Unactivated prothrombin complex concentrates (PCC)	
4 factor: • Kcentra	Contain coagulation factors II, VII, IX, and X in inactive forms
3 factor: • Bebulin VH • Profilnine SD	Contain factors II, IX, and X (little to no factor VII)
Activated prothrombin complex concentrates (aPCC)	
4 factor: • FEIBA NF	Contains coagulation factors II, VII, IX; factor VII is mostly activated*

Reversal of Heparins

- ✓ Protamine Sulfate

Drug Interactions

1. DOACs are affected by Cytochrome P450 3A4 (CYP3A4) inhibitors and inducers and by inducers of P-glycoprotein (P-gp) drug efflux pump
2. Cyt P450 3A4 *inhibitors* include:
    1. Antifungals ending in –*azole*,
    2. Antivirals or antiretrovirals ending in –*vir*,
    3. Macrolides
    4. Non-dihydropyridine CCB – Verapamil and Diltiazem
    5. Grapefruit juice.
3. Cyt P450 3A4 inducers include:
    1. St John's wort
    2. Carbamazepine, Phenytoin
    3. Etc
4. Refer to a list of drug interactions when using meds.

In Conclusion

1. Follow-up is essential
2. Assess adherence and compliance
3. Evaluate for bleeding and adverse events
4. Periodic checks of renal function, hemoglobin, and new medications that could lead to adverse interaction

Take Home Points

1. All of the new oral anticoagulants are at least as effective as warfarin and can be given without routine monitoring.
2. All DOACs reduce the risk of intracranial bleeding
3. New agents produce about a 10% reduction in mortality.
4. You don't need bridging with DOACs.
5. Most pts on warfarin don't need bridging.

Sources

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Questions?

ANTICOAGULANTS

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