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West Yorkshire Regional Foundation Year 2 Teaching

Anticoagulation Therapy in AF: Focus on DOACs

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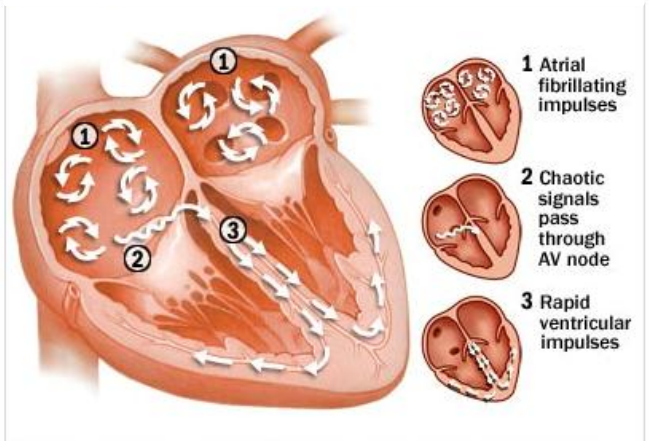
AF: Commonest arrhythmia



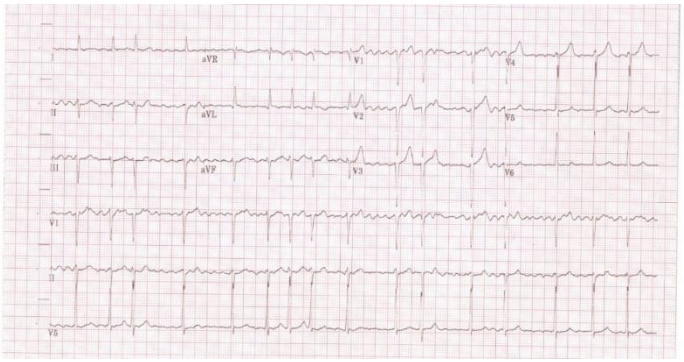
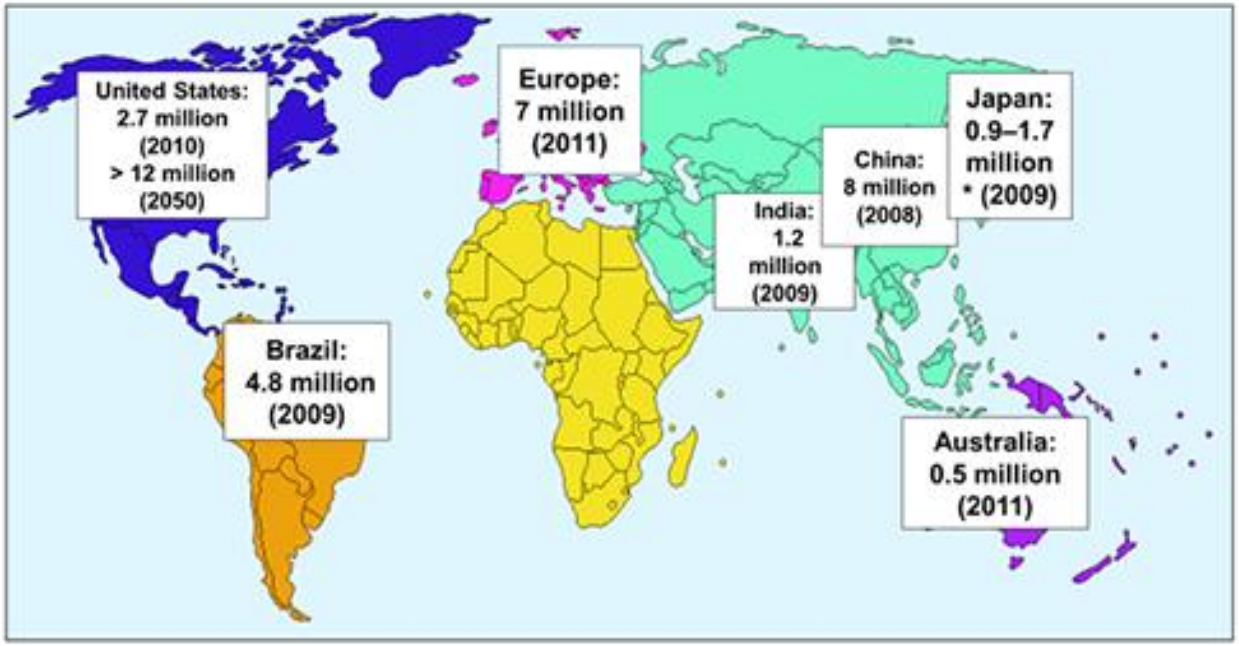


Table 3 Cardiovascular morbidity and mortality associated with atrial fibrillation

Event	Association with AF
Death	Increased mortality, especially cardiovascular mortality due to sudden death, heart failure or stroke.
Stroke	20–30% of all strokes are due to AF. A growing number of patients with stroke are diagnosed with 'silent', paroxysmal AF.
Hospitalizations	10–40% of AF patients are hospitalized every year.
Quality of life	Quality of life is impaired in AF patients independent of other cardiovascular conditions.
Left ventricular dysfunction and heart failure	Left ventricular dysfunction is found in 20–30% of all AF patients. AF causes or aggravates LV dysfunction in many AF patients, while others have completely preserved LV function despite long-standing AF.
Cognitive decline and vascular dementia	Cognitive decline and vascular dementia can develop even in anticoagulated AF patients. Brain white matter lesions are more common in AF patients than in patients without AF.

AF = atrial fibrillation; LV = left ventricular.

Prevalence of Atrial Fibrillation
A Global Disease



Fegin VL, et al. *Lancet*. 2014;383:245-254.[2]

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AF Rx : Challenges

- Do you routinely pulse check?
- What % of patients have asymptomatic AF/PAF?
- Are patients adequately risk stratified?
  - Stroke risk
  - Bleeding risk
- Are they adequately receiving SPAF Rx?
  - If no then what are the limitations?
- Are they directly referred to AC clinic?
- What is your experience with VKA (Warfarin)?
- Do you prescribe DOAC(s)?
  - If Yes then any issues?
  - If No then why?
- Are their symptoms (due to AF) controlled?
- Do they also have angina / HF / CKD?
- Which AF patients get to hospital via GPs?
- Do we refer any patients directly for ablation Rx?

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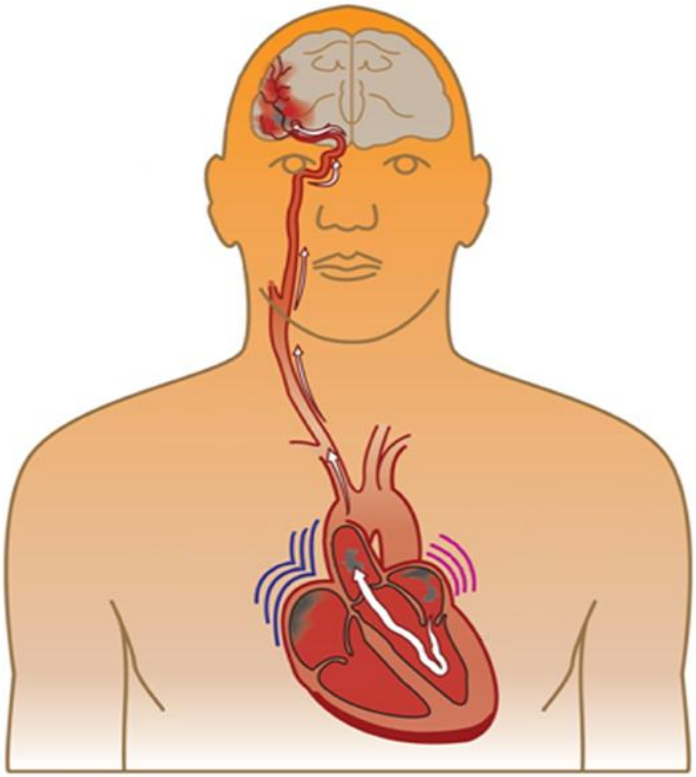
Atrial Fibrillation (AF) and Stroke

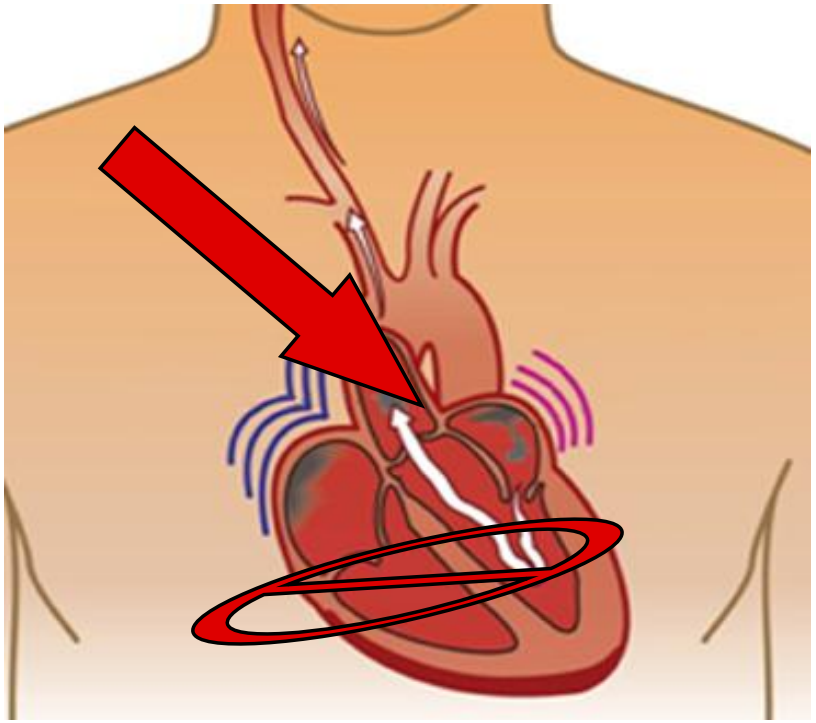
- AF prevalence roughly doubles with each advancing decade of life (9% at age 80-89 yrs)[1]
- Stroke prevalence increases nearly 5 fold when AF is present[2]
- In patients with AF, thrombus tend to form in the atria, esp. in left atrial appendage, due to abnormal blood flow and pooling
- These may travel to the brain, causing an ischaemic stroke, which are worst forms of ischaemic strokes
- Around 20% of ischaemic strokes: Cardioembolic; of these, AF is the most common cause[3]



1. NICE CG36 Atrial fibrillation 2006
2. Wolf PA *et al*. *Stroke* 1991;22:983–988;
3. Paciaroni M *et al*. *Stroke* 2007;38:423–430

AF-related stroke is preventable

- By preventing thrombus formation in the heart (thrombo-prophylaxis)
  - Antithrombotic therapy reduces the risk of stroke and thromboembolism but also increases the risk of bleeding
- Clinical decision-making requires an assessment of benefit–risk



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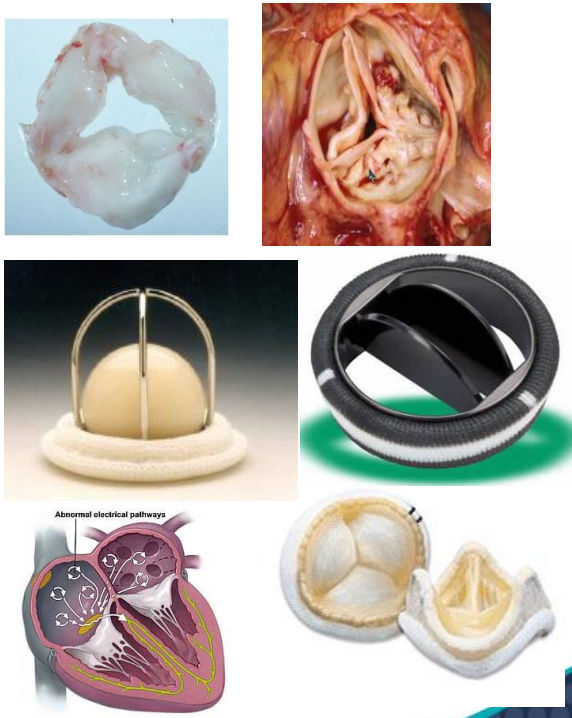
Stroke Prevention In Valvular Heart Disease

- Mechanical prosthetic valve
  - Greatest valvular stroke risk
  - Mitral position - further increase in risk
  - Bioprosthetic valve : usually within first 3 mo
  - Associated AF: Further increase in stroke
- Rheumatic MS/MR: more risk than MVP/degenerative VHD



OAC: Common Indications

- (Stroke prevention)SPAF Rx in valvular and NVAF
- After Cardiac Valve Replacement esp mechanical
- Prophylaxis and Treatment of Deep Vein Thrombosis
- Treatment of Symptomatic VTE
- After Acute Myocardial Infarction with cavity thrombus

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CHA_2DS_2-VASc complements $CHADS_2$ scoring system

$CHADS_2$	Score	CHA_2DS_2-VASc	Score
Congestive heart failure	1	Congestive heart failure/left ventricular dysfunction	1
Hypertension	1	Hypertension	1
Aged ≥75 years	**1**	**Aged ≥75 years**	**2**
Diabetes mellitus	1	Diabetes mellitus	1
Stroke/TIA/TE	2	Stroke/TIA/TE	2
Maximum score	**6**	**Vascular disease (prior MI, PAD, or aortic plaque)**	1
		Aged 65–74 years	1
		Sex category (i.e. female gender)	1
		Maximum score	**9**

CHA_2DS_2-VASc:

- In patients with a $CHADS_2$ score of 0–1, or
- When a more detailed stroke risk assessment is indicated

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HAS-BLED Bleeding Risk Score

Clinical Characteristic	Score
Hypertension	1
Abnormal renal/liver function (1 point each)	1 or 2
Stroke	1
Bleeding tendency or predisposition	1
Labile INRs (in patients taking wafarin)	1
Elderly (eg, age >65 years)	1 or 2
Drugs or alcohol (1 point each)	1 or 2
Maximum score	9

Hypertension = SBP >160 mmHg; abnormal kidney function = presence of chronic dialysis or renal transplantation or serum creatinine ≥200 µmol/L; abnormal liver function = chronic hepatic disease (eg, cirrhosis) or biochemical evidence of significant hepatic derangement (eg, bilirubin >2 x ULN, in association with AST/ALT/ALP >3 x ULN, etc); bleeding = previous bleeding history and/or predisposition to bleeding (eg, bleeding diathesis, anemia, etc.); labile INRs = unstable/high INRs or poor time in therapeutic range (eg <60%);drugs/alcohol use = concomitant use of drugs with oral anticoagulants, such as antiplatelet agents, NSAIDs, etc.

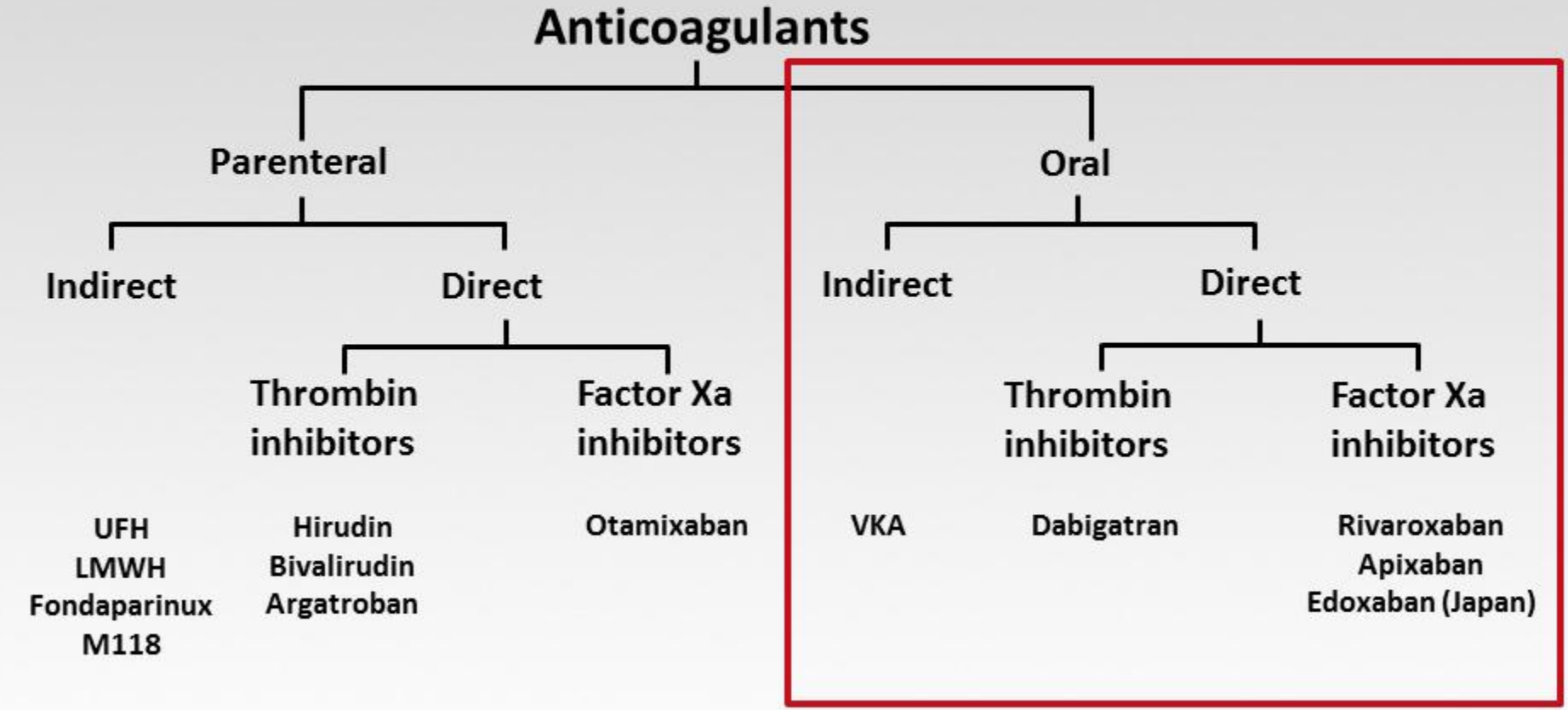
Pisters R, et al. *Chest*. 2010;138:1093-1100.[10]

Need for Anticoagulation in AF Patients

- Dependent on the risk for stroke vs the risk for bleeding
  - Patients with low stroke risk may not require anticoagulation therapy

Currently Available Anticoagulants

Classification Based on Route of Administration and Mode of Action



LMWH = low-molecular-weight heparin; UFH = unfractionated heparin; VKA = vitamin K antagonist

De Caterina R, et al. *Thromb Haemost*. 2013;109(4):569-579.

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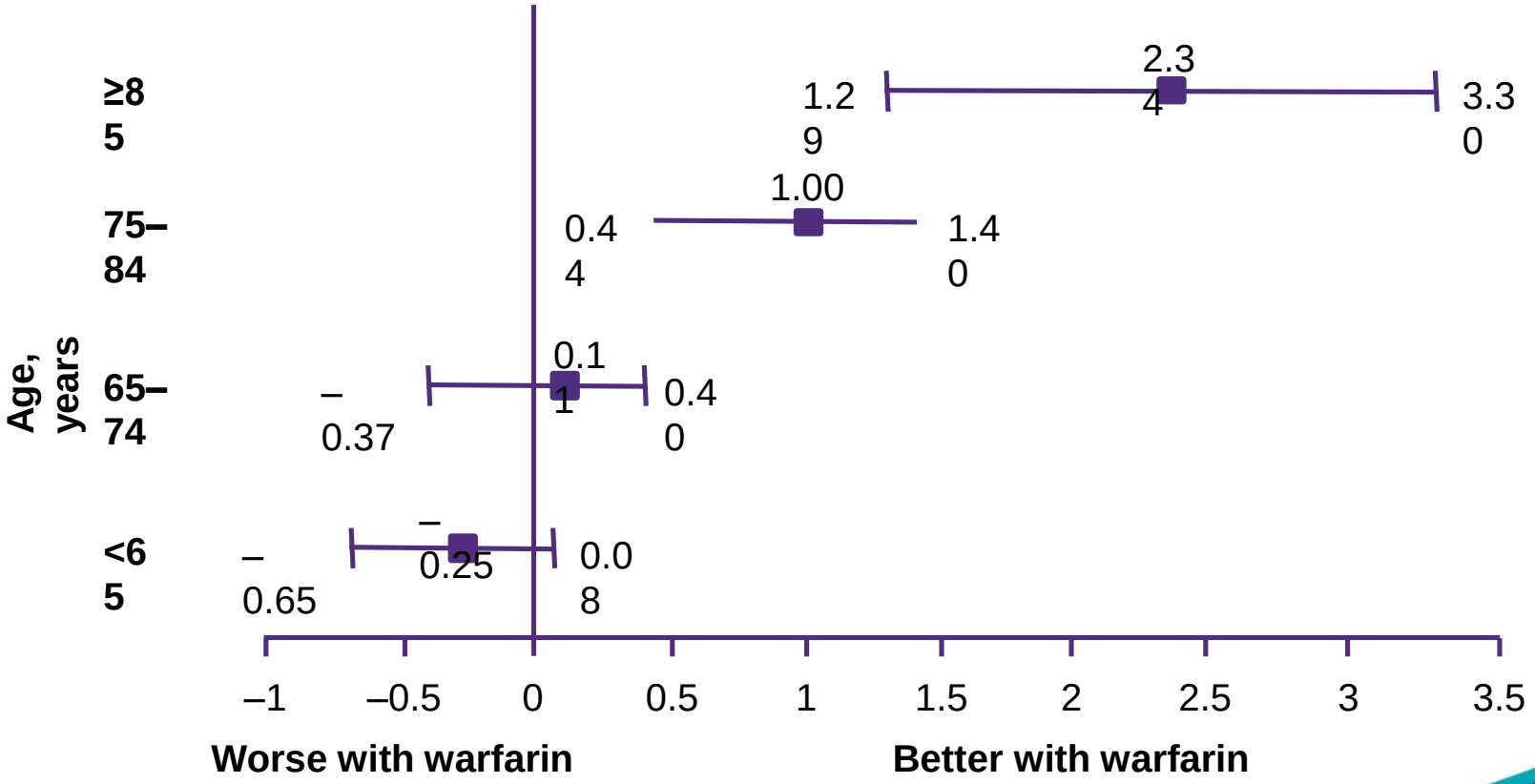
OAC: benefit–risk improves with increasing age

Net clinical benefit: events prevented per 100 person-years[1]



Singer DE et al. *Ann Intern Med* 2009;151:297–305

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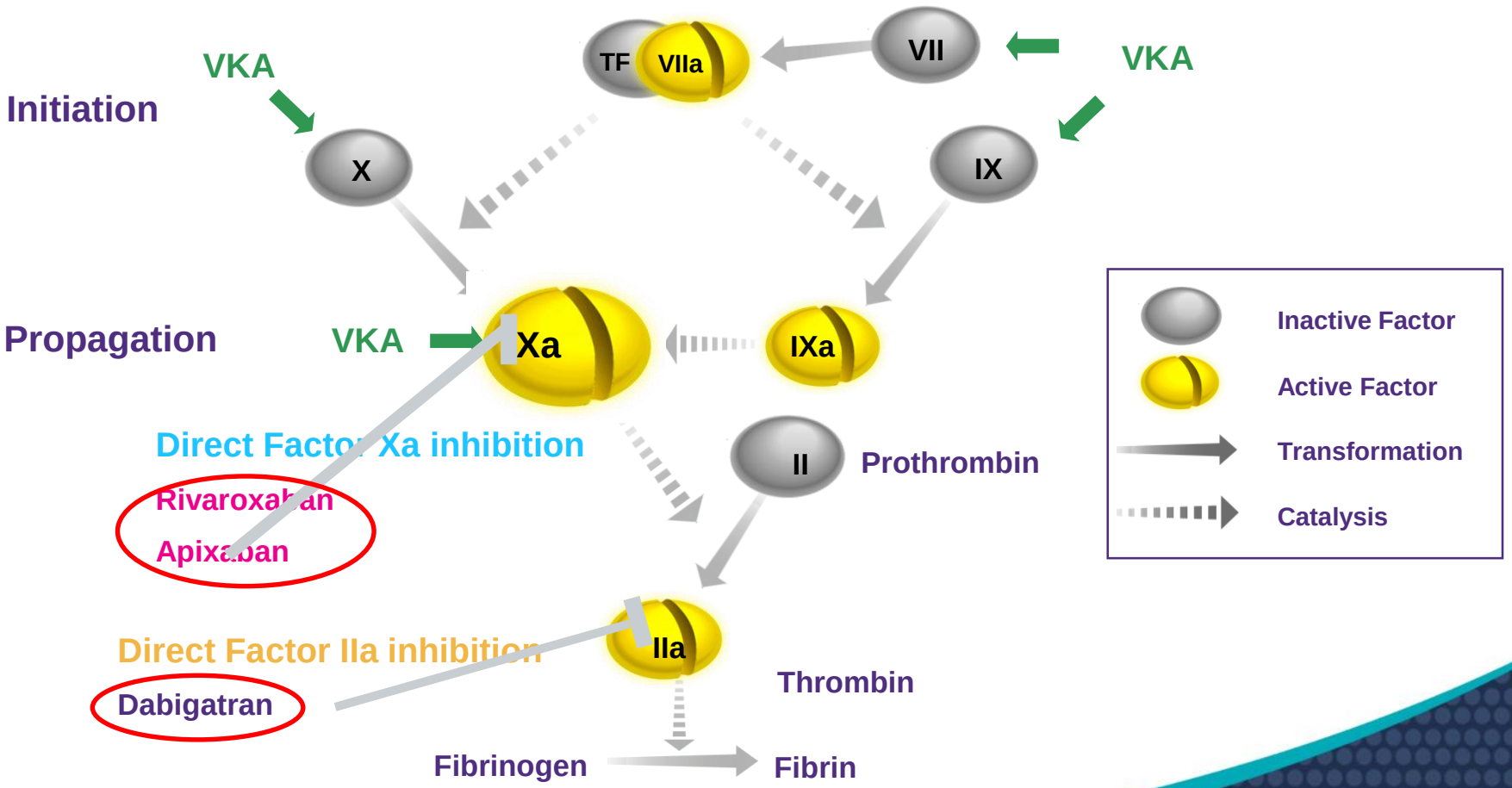
Coagulation pathway



Spronk HMC *et al. Expert Opin Investig Drugs* 2007;16:431–440 (adapted from)

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VKA Rx: Limitations

Narrow therapeutic window (INR range 2–3)[1] → **Risk of stroke**; **Risk of bleeding[1]**

Considerable variability in dose-response (genetic variations)[1]

Interactions with drugs and diet[1]

→ **Convenience not optimal:**
- **Frequent coagulation monitoring[1]**
- **Frequent dose adjustments[1]**

Long half-life

Slow onset and offset of action[1,2] → **Issue in perioperative anticoagulation (bridging)[2]**

1. Weitz et al. Eur J Haematol 2010;85 (Suppl 72);1–28.

2. Camm et al. Eur Heart J 2010;31:2369–429.

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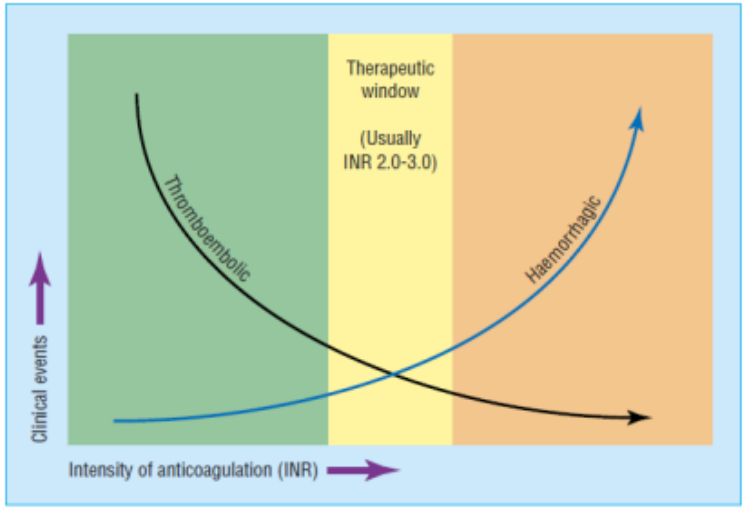
Time within the therapeutic range (TTR)

- The benefit of VKA for reducing the risk of stroke in patients with AF depends on the time in which patients remain in the optimum therapeutic range (INR 2.0–3.0)[1]
- There are large variations in TTR between individuals, sites, and countries[1]
- In well monitored clinical trials, patients remain in the therapeutic window only between about 50% and 80% of the time[2–5]
- Observational data from usual clinical practice often show lower means[6]



Blann et al. BMJ 2003;326:153–6.

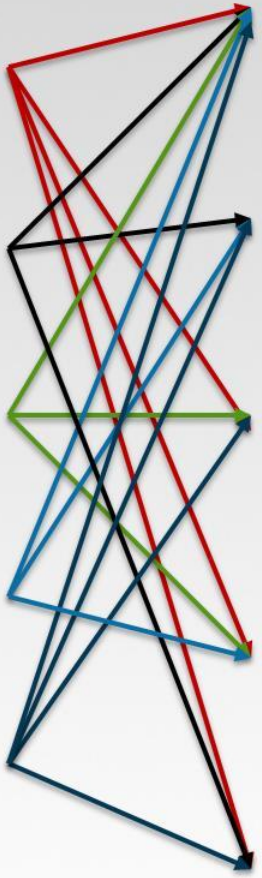
1. *Wallentin et al. Lancet 2010;376:975–83.*
2. *Executive Steering Committee for the SPORTIF III Investigators. Lancet 2003;362:1691–8.*
3. *Executive Steering Committee for the SPORTIF V Investigators. JAMA 2005;293:690–8.*
4. *The ACTIVE Writing Group on behalf of the ACTIVE Investigators. Lancet 2006;367:1903–12.*
5. *Connolly et al. Circulation 2008;118:2029–37.*
6. *Samsa et al. Arch Intern Med 2000;160:967–73.*
7. *Granger et al. N Engl J Med 2011;365:981–92.*

In ARISTOTLE, patients in the warfarin group had an INR in the therapeutic range (2.0–3.0) for a median of 66.0%[7]

The Reasons for Nonadherence Are Often Multifactorial

Types of nonadherence

- Not filling a prescription
- Forgetting to take a dose
- Taking an incorrect dose
- Taking medication at the wrong time
- Stopping therapy too soon



Patient-related factors

Medication-related factors

Prescriber-related factors

Pharmacy-related factors

Healthcare system-related factors

Aslam F, et al. *Hot Topics in Cardiology.* 2012;28:7-14.[2]

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DOACS : Benefits

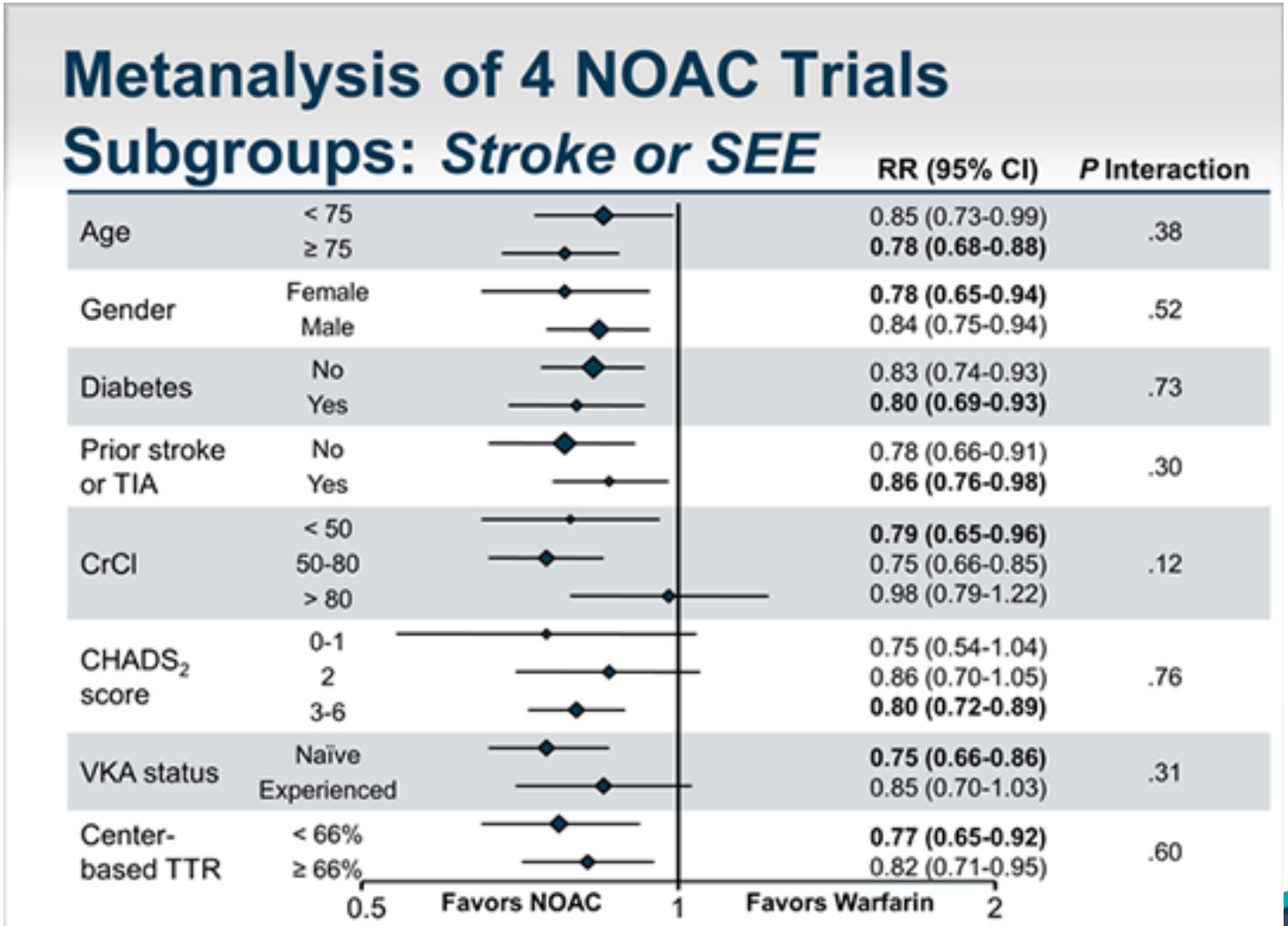
- Superior efficacy vs. antiplatelet drugs
- At least comparable efficacy vs. VKA
- Greater safety, notably in terms of bleeding risk
- Greater convenience for both physicians and patients
- Rapid onset of action
- More stable anticoagulation
- Lesser risk of ICH
- Much shorter offset period than VKA
- Minimal interaction with food/lifestyle
- Fewer drug-drug interactions
- PS: ONLY FOR NVAF (NOT MITRAL STENOSIS OR PHV)
- NO DIRECT ANTIDOTE apart from Dabigatran

DOACS in AF: When to Consider

- **<u>When adjusted-dose warfarin is not suitable</u>:**
  - Lifestyle issues: INR monitoring not practical (work, distance, homebound)
  - Side effects from warfarin (hair loss / skin rashes)
  - Wide fluctuations in INR (genetic polymorphisms affecting metabolism)
  - Consistently poor TTR not due to compliance issues
  - Poly therapy requiring frequent dose changes
  - When concomitant drugs used for short courses, i.e. antibiotics (eg patients with recurrent infections)
- **<u>Patient indicated preference</u>**

DOACS: Evidence

Metanalysis of 4 NOAC Trials
Subgroups: *Stroke or SEE*



Reprinted from Ruff CT, et al. *Lancet*. 2014;383:955-962,[16] with permission from Elsevier.

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DOACS: Choices

TABLE 1

Table 1. Pharmacological characteristics of the main NOACs

DRUG	DABIGATRAN ETEXILATE	RIVAROXABAN	APIXABAN	EDOXABAN
Mechanism of action	direct thrombin inhibitor	direct factor Xa inhibitor	direct factor Xa inhibitor	direct factor Xa inhibitor
Oral bioavailability	6.5%	80-100%	50%	62%
Time to max inhibition	0.5-2 h	1-4 h	1-4 h	1-2 h
Half-life	12-14 h	5-13 h	8-15 h	10-14 h
Renal excretion (fraction of absorbed dose)	85%	66% (36% unchanged and 30% inactive metabolites)	27%	50% (of the absorbed drug)
Potential metabolic drug interaction	Inhibitors of P-gp: verapamil --> reduce dose; dronedarone --> avoid Potent inducers P-gp*: avoid	Potent inhibitors of CYP3A4# and P-gp†: avoid Potent inducers of CYP3A4‡ and P-gp*: use with caution	Potent inhibitors of CYP3A4# and P-gp†: avoid Potent inducers of CYP3A4‡ and P-gp*: use with caution	Potent inhibitors of P-gp†: reduce dose Potent inducers of P-gp*: avoid
Dose in VTE prevention and treatment°	220 mg OD or 150 mg OD (prev.) 150 BID (treat.)	10 mg OD (prev.) 15 mg BID, then 20 mg OD (treat.)	2.5 mg BID (prev.) 5 mg BID (treat.)	60 mg OD (treat.)
Dose in AF°	110 mg BID or 150 mg BID	20 mg OD or 15 mg OD for CrCl 30-49	5 mg BID or 2.5 BID for risk categories	60 mg OD (30 mg for risk categories) or 30 mg OD (15 mg for risk categories)
Dose in ACS°		2.5 BID		

* Rifampicin, St. John's wort (Hypericum perforatum), carbamazepine, phenytoin
# Antifungals (e.g., ketoconazole, intraconazole, voriconazole, posaconazole), chloramphenicol, clarithromycin and protease inhibitors (e.g., ritonavir, atanazavir)
† Verapamil, amiodarone, quinidine and clarithromycin
‡ Phenytoin, carbamazepine, phenobarbital and St. John's wort
° Phase III clinical trials - Results for ENGAGE-AF still pending, therefore in this case the dosages do not refer to approved use
CYP = cytochrome P450 isoenzyme; F = factor; P-gp = P-glycoprotein; OD = once daily, BID = twice daily

DOACS

Agent	Warfarin	Dabigatran	Rivaroxaban	Apixaban	Edoxaban
Target	IIa, VIIa, IX, Xa	IIa	Xa	Xa	Xa
Peak effect	4-5 days	1.5-3 h	2-4 h	1-3 h	1-2 h
Half-life (h)	40	12-17	5-9	9-14	9-11
Renal element (%)	None	80	33	25	35-50
Dialyzability	No	Yes	No	No	No
Interactions	Many	P-gp	3A4, P-gp	3A4, P-gp	3A4, P-gp
Monitoring	Yes	No	No	No	No
Antidote	Vitamin K	Idarucizumab	No	No	No
Laboratory monitoring	INR	aPTT, diluted TT	PT, anti-Xa	PT, anti-Xa	PT, anti-Xa

P-gp=Glycoprotein; 3A4=Cytochrome P4503A4; aPTT=Activated partial thromboplastin time; TT=Thrombin time; PT=Prothrombin time;

All Approved for Cardioversion

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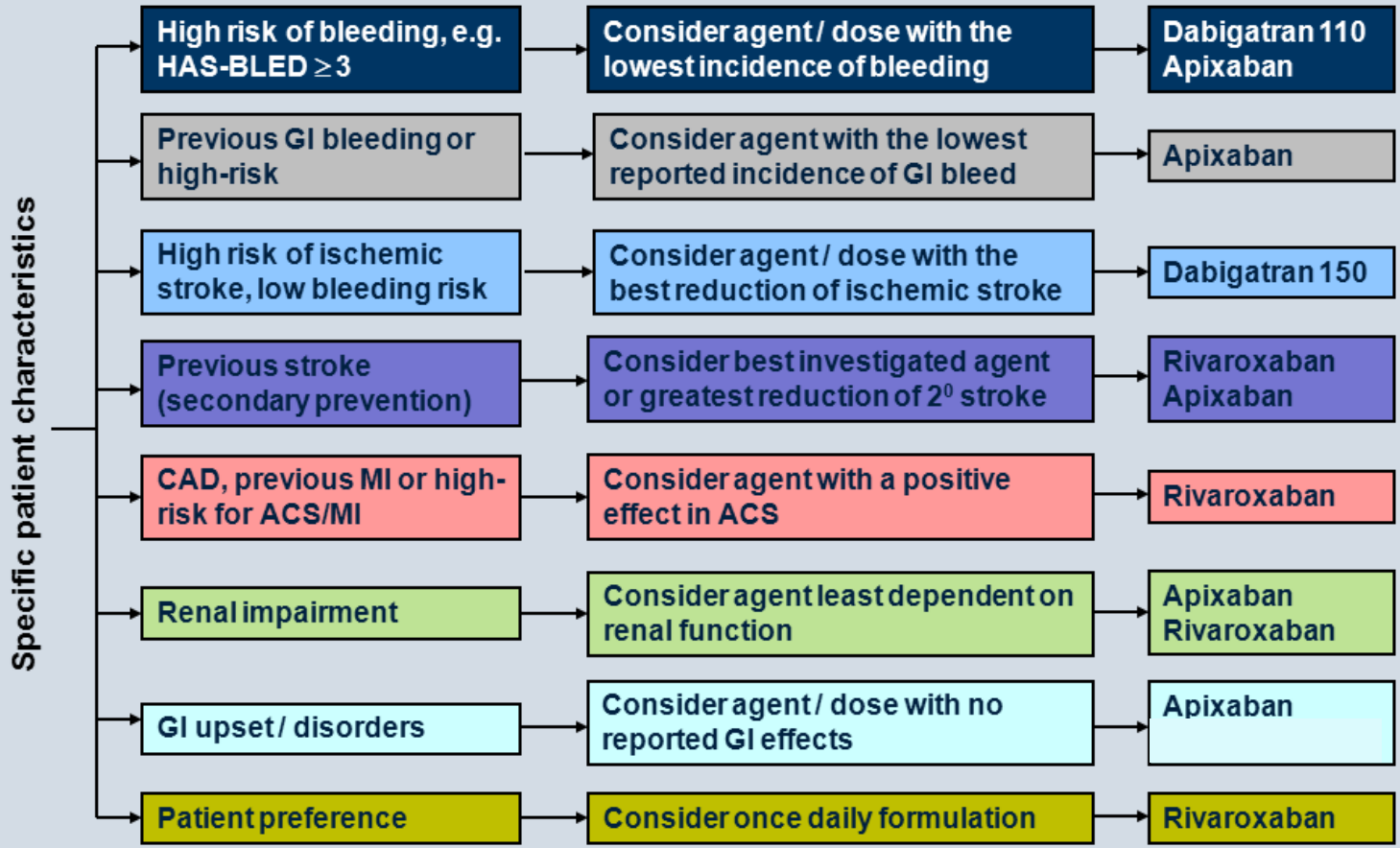
DOACs: Is there a choice?

Pointers



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DOACs & High bleeding risk

- CKD
  - Moderate eGFR 30-49 ml/min
  - Severe CKD eGFR 15-29 ml/min
  - Dialysis/EGFR < 15 ml/min
- Hepatic impairment
- Drugs affecting metabolism of DOACS
- Other factors
  - Poorly controlled HT
  - Active GI disease
  - Vascular retinopathy
  - Recent ICH / Aneurysms
  - Recent brain/spinal/eye surgery
  - H/o lung bleeding or bronchiectasis
  - Congenital/acquired bleeding disorders

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NOACs: How to Switch

- <u>To a NOAC from:</u>
  - Warfarin – when INR <2.0 or <3.0 for rivaroxaban
  - LMWH – just before the next dose is due
- <u>From NOAC to:</u>
  - Warfarin – prescribe concomitantly until INR is in the appropriate range
  - UFH or LMWH – just before the next dose is due
  - Another DOAC– just before the next dose is due.
- In all cases except warfarin, if the renal function is abnormal, special care is needed, as heparins and DOACs can accumulate to varying degrees.

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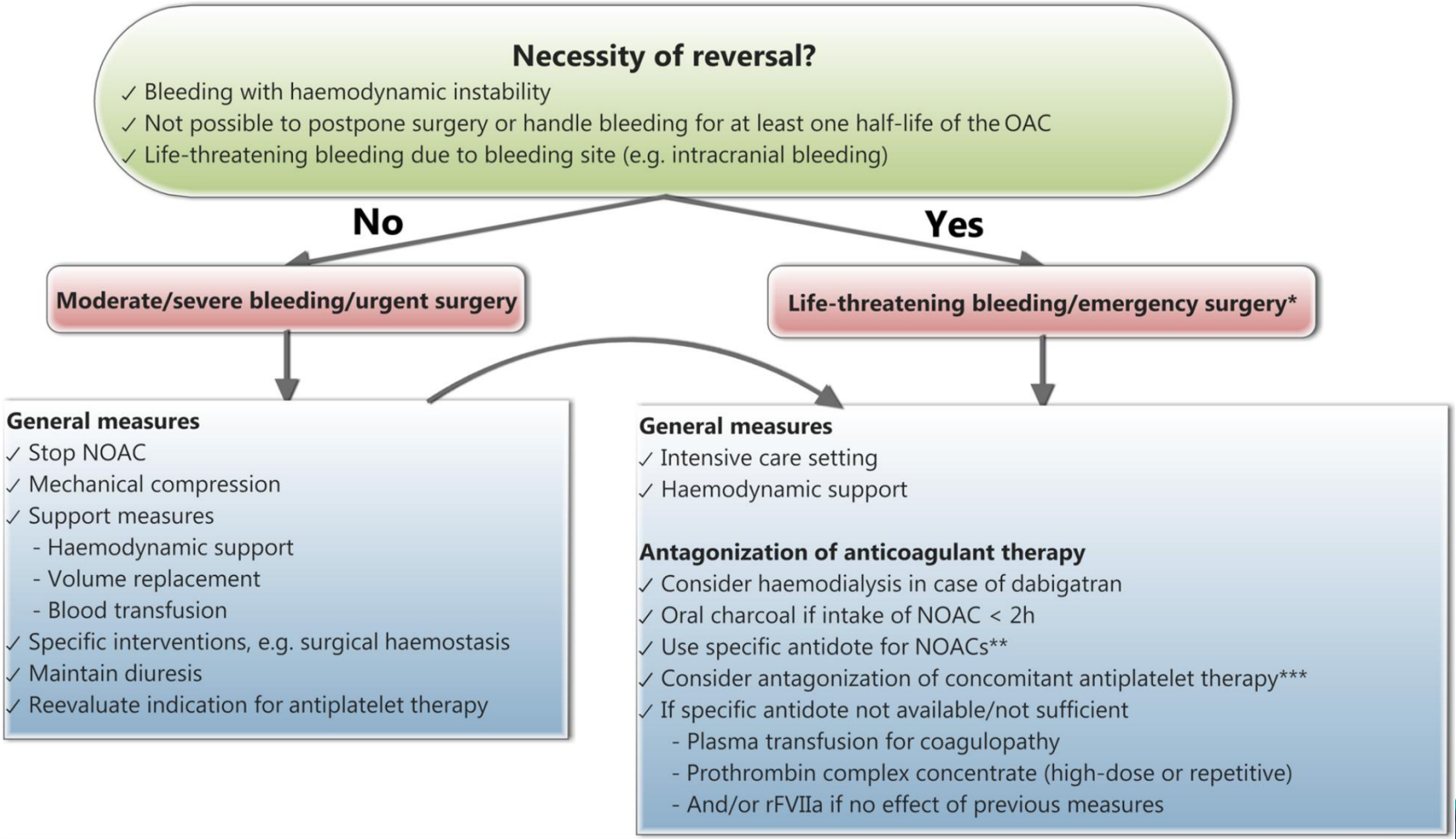
DOACs : Reversal



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DOACs : Reversal agents

Table 2 New reversal agents for non-vitamin K antagonist oral anticoagulants

	Idarucizumab	Andexanet	Ciraparantag (PER977)
Target	Dabigatran	Oral direct factor Xa-inhibitors, low-molecular-weight heparins and fondaparinux	Oral direct factor Xa and IIa inhibitors, low-molecular-weight heparins, un-fractionated heparin and fondaparinux
Structure	Humanized Fab fragment	Human rFXa variant	Synthetic small molecule
Immediate onset of reversal (<10 min)	Yes	Yes	Yes
Duration of effect	(12 to) 24 h	2 h	24 h
Re-administration possible	Yes, after 24 h	Unknown	Currently tested (NCT02207257)
Tested in healthy volunteers	Yes (NCT020287809)	Yes	Yes (NCT01826266, NCT02207257)
Elderly	Yes	Yes (NCT022207725)	No
Renally impaired	Yes	No	No
Tested in patients	Successful reversal of the specific effect of dabigatran (NCT02104947)	Ongoing (NCT02329327)	No
Pro-coagulation signals	No	Decrease of tissue factor pathway inhibitor activity	No

The clinical development program for Ciraparantag is currently at the Phase II stage, it is not possible to comment on the dose that will be studied in the Phase III trial and which is therefore more likely to be approved for clinical use.

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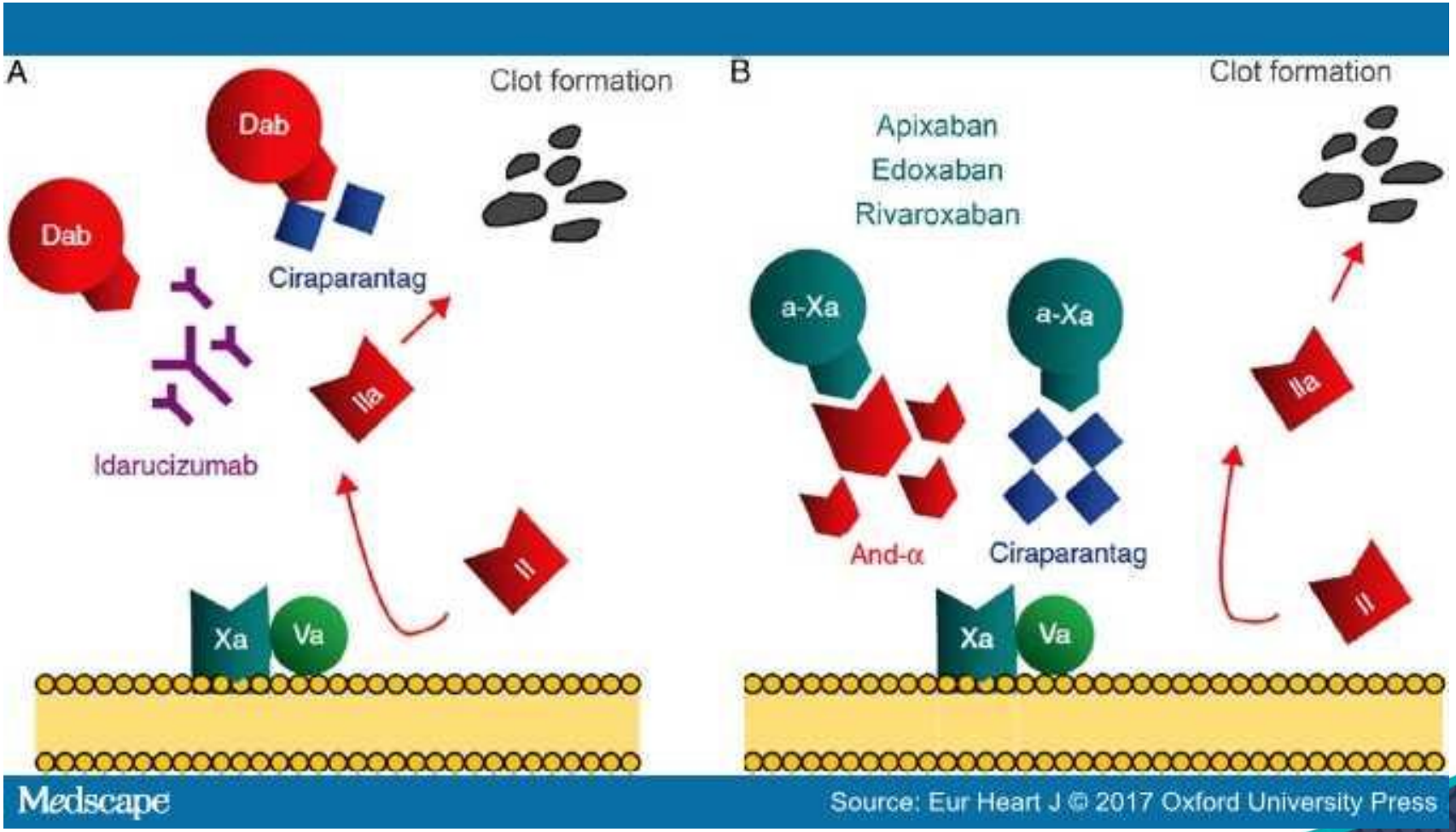
DOACs: Reversal



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AF: Recent Perspectives

- Emphasis on:
  - Routine Pulse check
  - Other modes of AF detection
  - CHA2DS2VASC & HASBELD scoring
  - TTR (Time in Therapeutic range) ≥ 60%
  - SPAF Education
  - VKA/NOACs
  - Explore reasons for poor INR with warfarin
  - Aspirin no more an option
  - Review patients not on anticoagulation regularly

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Global Challenges for OACs

- NOACs: Cost, Compliance, Indications, Reversibility
- Narrow therapeutic window of VKAs
- Variability of dose response (due to genetic factor)
- VKAs: Interaction with drug / diet
- Difficulty in lab standardization
- Poor patient understanding
- Poor initiation and monitoring
- OTC drugs: NSAIDS interactions, ATT: INH/Rifampicin: Affect INR
- Interaction with frequent antibiotics
- Self regulation for common problems (URI)
- Lack of awareness of target range esp PHV
- Low BMI: Lower doses needed
- Difficult challenges for procedures/ surgeries
- Need for dedicated Anticoagulation clinics
- Cost of travel as many patients dependent on higher/tertiary centres esp post valve op.

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SPAF: Ideal Anticoagulant

	Once daily	No Food Interactions	Predictable response	No routine coagulation monitoring	Fixed dosing	Wide therapeutic window	Easily Adaptable for compliance aids
IDEAL	Y	Y	Y	Y	Y	Y	Y
VKA	Y	N	N	N	N	N	N
DOAC	Y/N	Y Taken with/without food	Y	Y	Y	Y	Y

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There are known knowns. These are things we know that we know. There are known unknowns. That is to say, there are things that we know we don't know. But there are also unknown unknowns. There are things we don't know we don't know.

(Donald Rumsfeld)

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