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ORAL ANTICOAGULANTS

History

- ~ 1920: ‘cattle’s disease’ in the USA
  = severe bleeding diathesis in cattle after eating sweet clover
- Clover ‘Melilotus alba or officinalis’ produces a toxin if moist and not fresh
- Toxin was called ‘dicumarol’
- The Lancet 1943: *“Heparin and a rival… “*

ORAL ANTICOAGULANTS

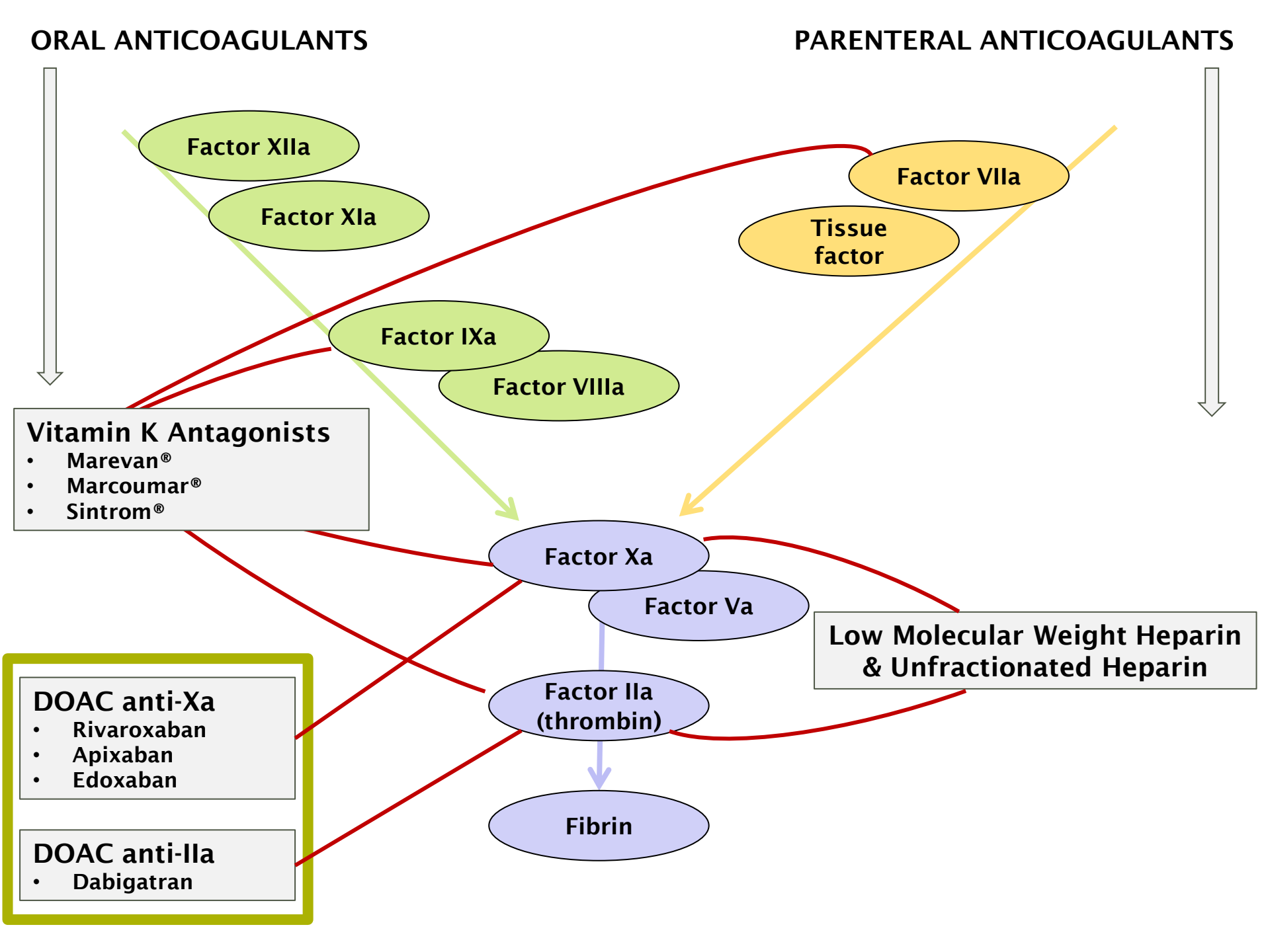
Vitamin K antagonists or *VKA*

- Many decennia of experience
- Safe and effective, if high time in therapeutic range
- Slow onset and offset of action
- Narrow therapeutic window
- Regular monitoring needed (INR)
- Numerous food and drug interactions
- Risk of under- or overtreatment

ORAL ANTICOAGULANTS

>10 years: ***non-vitamin K oral anticoagulants*** or ***NOACs***
= direct oral anticoagulants or ***DOACs***

- At least as safe and effective as VKA
- Shorter half-life
- More predictable, less labile anticoagulant effect
- Fixed dosing
- No food and fewer drug interactions
- No need for routine monitoring


ORAL ANTICOAGULANTS
PARENTERAL ANTICOAGULANTS
Factor XIIa
Factor XIa
Factor VIIa
Tissue factor
Factor IXa
Factor VIIIa
Vitamin K Antagonists
• Marevan®
• Marcoumar®
• Sintrom®
Factor Xa
Factor Va
Low Molecular Weight Heparin & Unfractionated Heparin
Factor IIa (thrombin)
Fibrin
DOAC anti-Xa
• Rivaroxaban
• Apixaban
• Edoxaban
DOAC anti-IIa
• Dabigatran

DOACs - Efficacy/Safety in AF trials

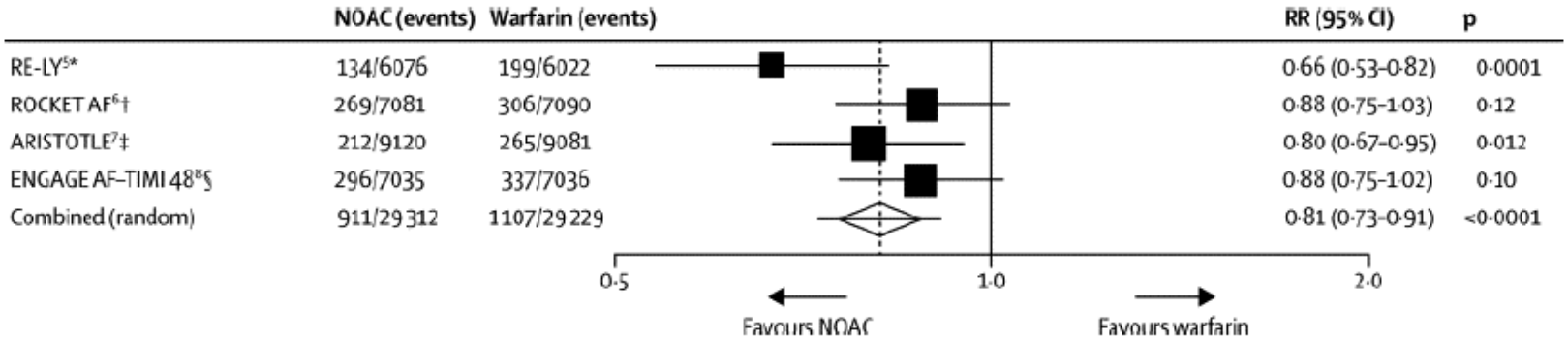


Figure 1. Stroke or systemic embolic events Data are n/N, unless otherwise indicated. Heterogeneity: I2=47%; p=0·13. NOAC=new oral anticoagulant. RR=risk ratio. *Dabigatran 150 mg twice daily. †Rivaroxaban 20 mg once daily. ‡Apixaban 5 mg twice daily. §Edoxaban...

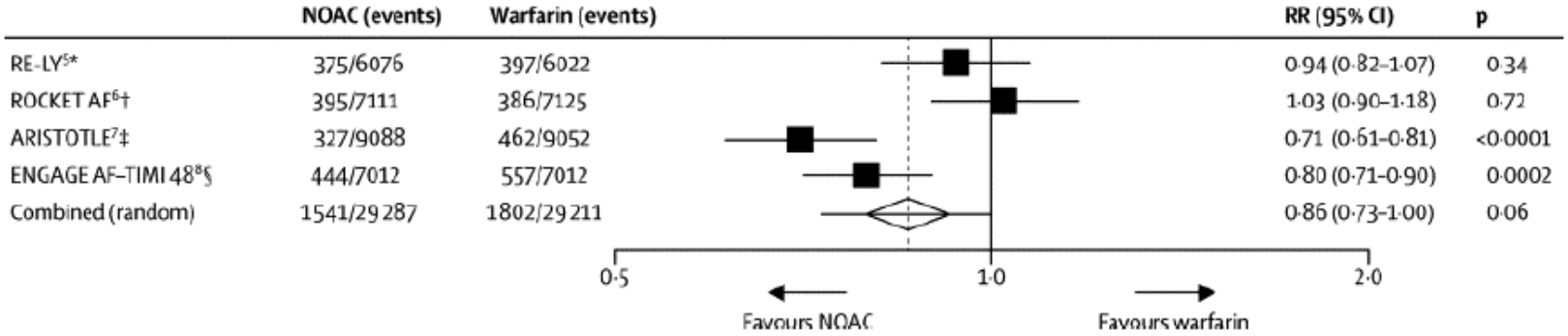
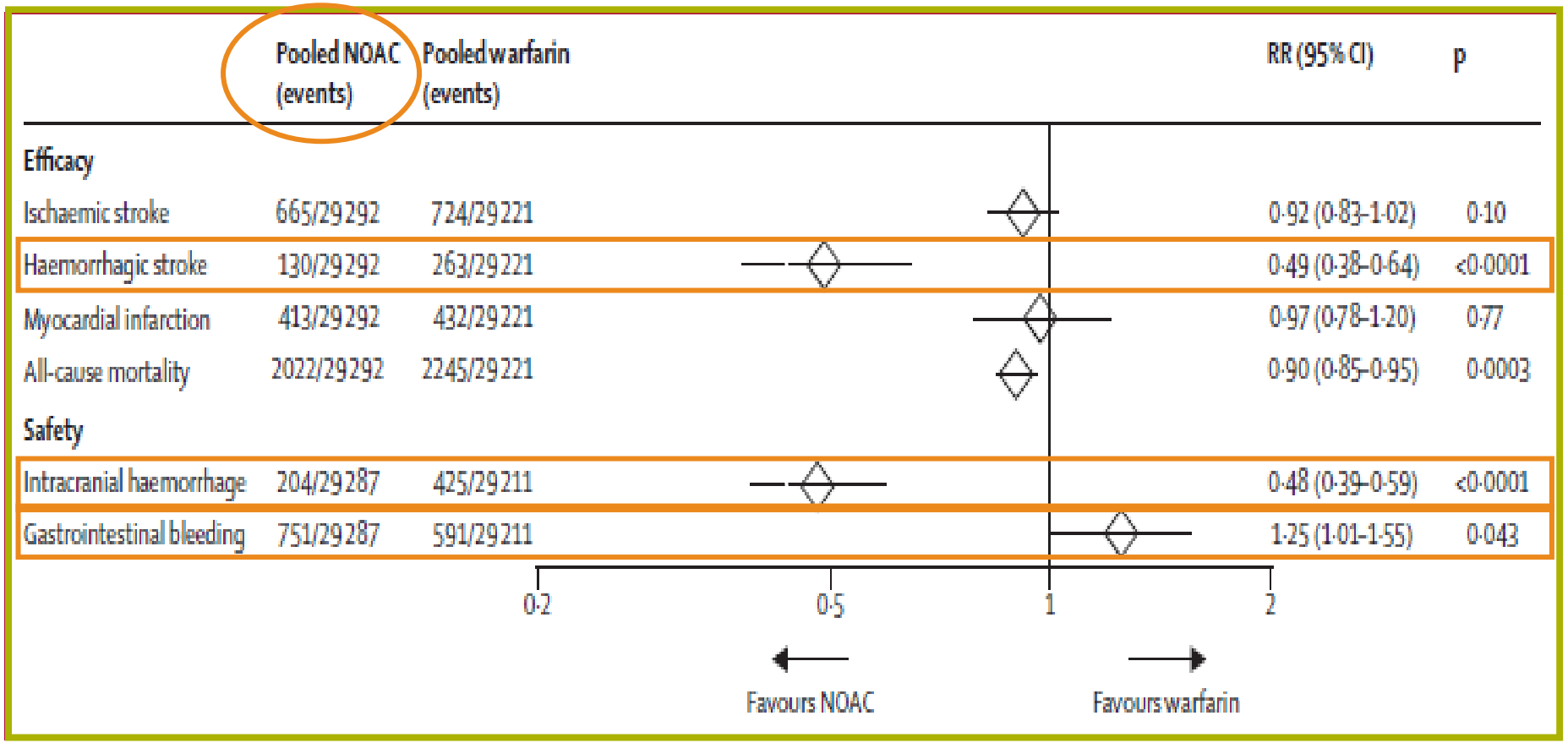


Figure 3 Major bleeding Data are n/N, unless otherwise indicated. Heterogeneity: I2=83%; p=0·001. NOAC=new oral anticoagulant. RR=risk ratio. *Dabigatran 150 mg twice daily. †Rivaroxaban 20 mg once daily. ‡Apixaban 5 mg twice daily. §Edoxaban 60 mg once daily.

Ruff C et al. *Lancet* 2014;383:955-62

CAVE: no head-to-head comparison between dabigatran, rivaroxaban, apixaban and edoxaban

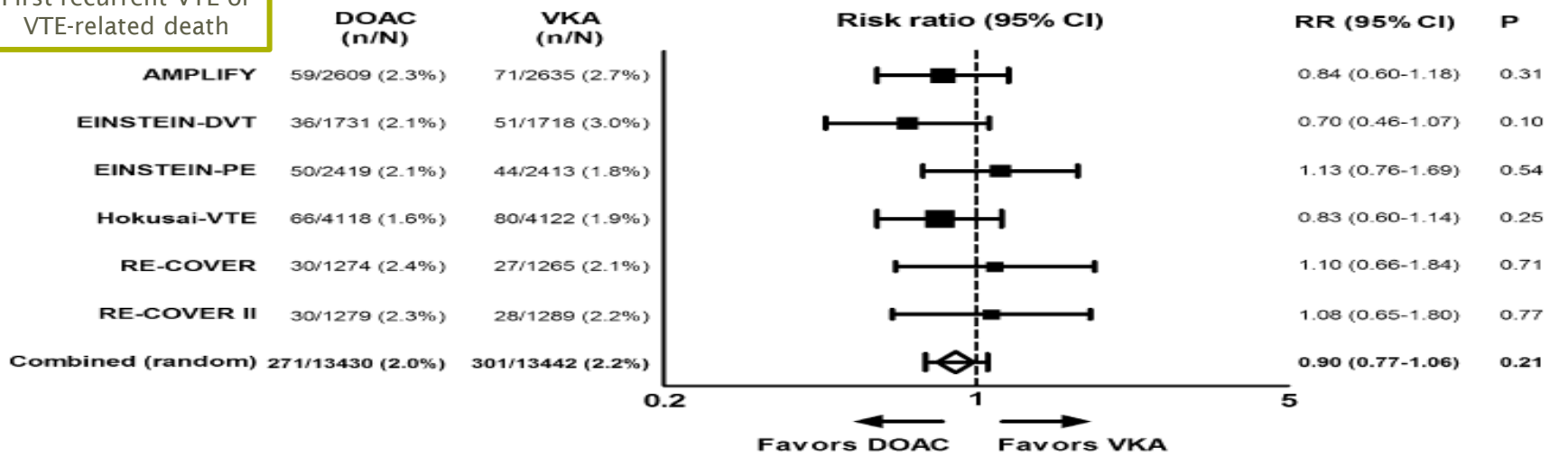
DOACs - Efficacy/Safety in AF Trials



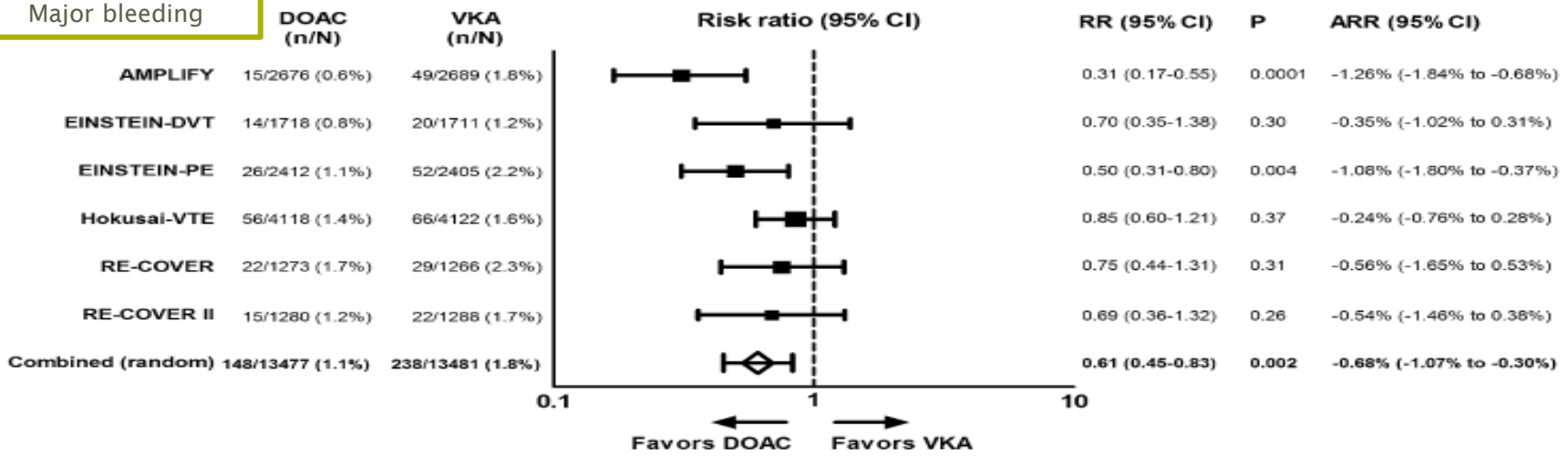
Ruff C et al. *Lancet* 2014;383:955-62

DOACs - Efficacy/Safety in VTE Trials

First recurrent VTE or VTE-related death



Major bleeding



van Es N et al. Blood 2014; 124:1968-1975

DOACs - Indications

- Primary prevention of deep vein thrombosis (DVT) and pulmonary embolism (PE) in major orthopedic surgery
- Prevention of stroke and systemic embolism in non-valvular atrial fibrillation (AF)
- Treatment of acute DVT and PE
- Secondary prevention of DVT and PE
- Low dose rivaroxaban in combination with aspirin: secondary prevention of atherothrombotic complications in coronary artery disease or symptomatic peripheral artery disease with high risk of ischemic events

DOACs – Pharmacologic properties

	Dabigatran (Pradaxa®)	Rivaroxaban (Xarelto®)	Apixaban (Eliquis®)	Edoxaban (Lixiana®)
Mechanism of Action	Direct FIIa inhibition	Direct FXa inhibitor	Direct FXa inhibitor	Direct FXa inhibitor
Bioavailability	3-7%	~66-100%	~50%	~50%
Time to Cmax	1-2 h	2.5-4 h	3 h	1-2 h
Half-life	12-17 h	5-9 h	8-15 h	8-10 h
Renal excretion	80%	36%	~27%	35-39%
Protein Binding	35%	35%	87%	40-59%
Potential drug interactions	P-gp inhibitor	CYP 3A4 substrate and P-gp inhibitor	CYP 3A4 substrate and P-gp inhibitor	P-gp inhibitor

~2h

~12h

DOACs - Pharmacologic properties

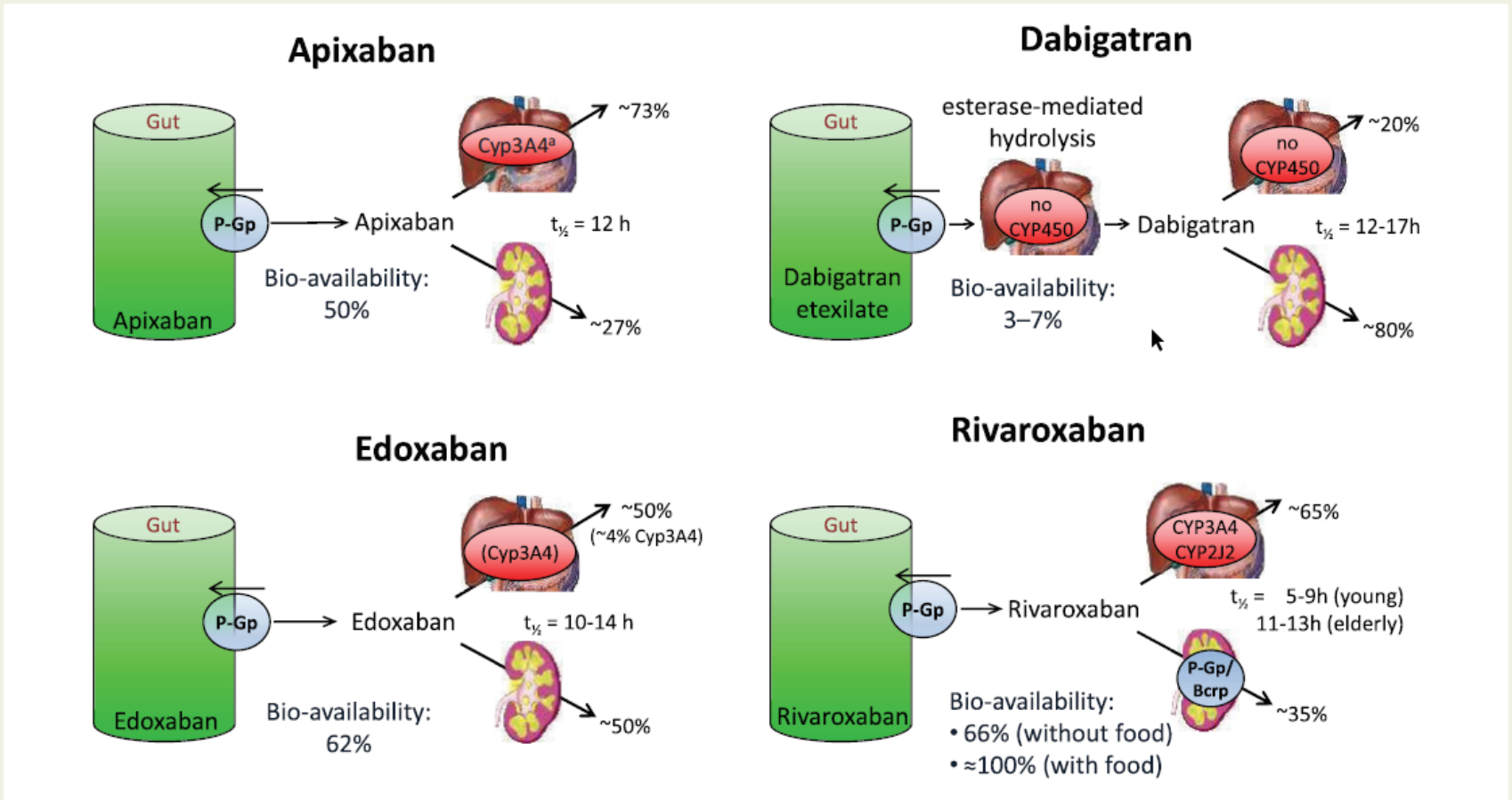


Figure 5 Absorption and metabolism of the different NOACs. There are interaction possibilities at the level of absorption or first transformation, and at the level of metabolization and excretion. [a]Also via CYP1A2, CYP2J2, CYP2C8, CYP2C9, and CYP2C19. NOAC, non-vitamin K antagonist oral anticoagulant.

→ Impact of renal and hepatic function

DOACs – Dosing and renal function

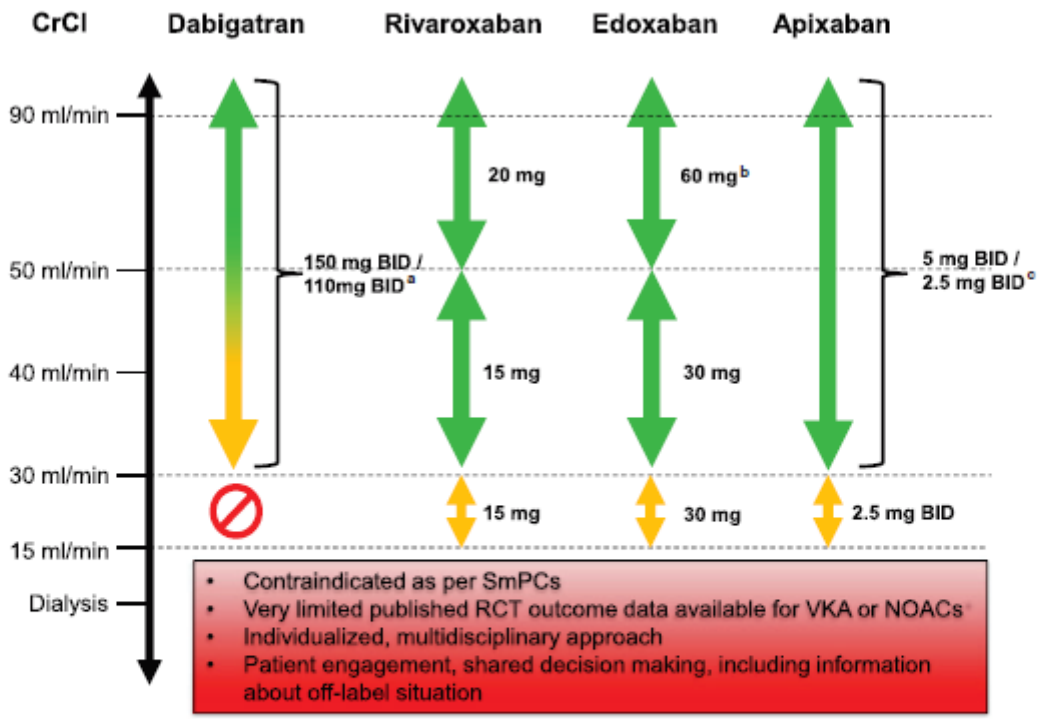
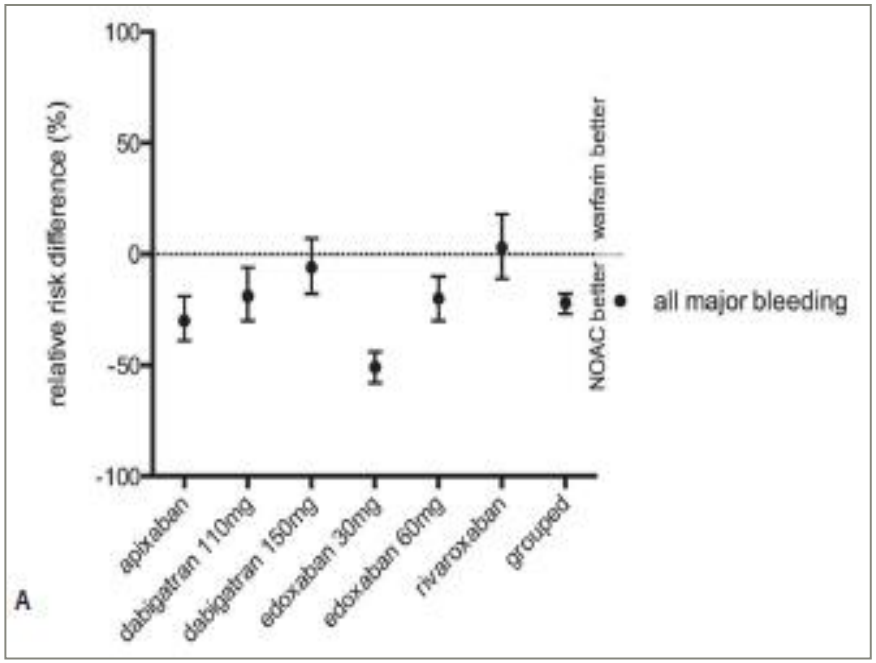


Figure 7 Use of NOACs according to renal function. [a]110 mg BID in patients at high risk of bleeding (per SmPc). [b]Other dose reduction criteria may apply (weight ≤ 60 kg, concomitant potent P-Gp inhibitor therapy). According to EMA, SmPc edoxaban should be used in 'high CrCl only after a careful evaluation of the individual thromboembolic and bleeding risk'.[473] See text for details. [c]2 × 2.5 mg only if at least two out of three fulfilled: age ≥80 years, body weight ≤60 kg, creatinine ≥1.5 mg/dL (133 µmol/L). Orange arrows indicate cautionary use; see text for details. BID, twice daily; CrCl, creatinine clearance; EMA, European Medicines Agency; NOAC, non-vitamin K antagonist oral anticoagulant; RCT, randomized clinical trial; VKA, vitamin K antagonist.

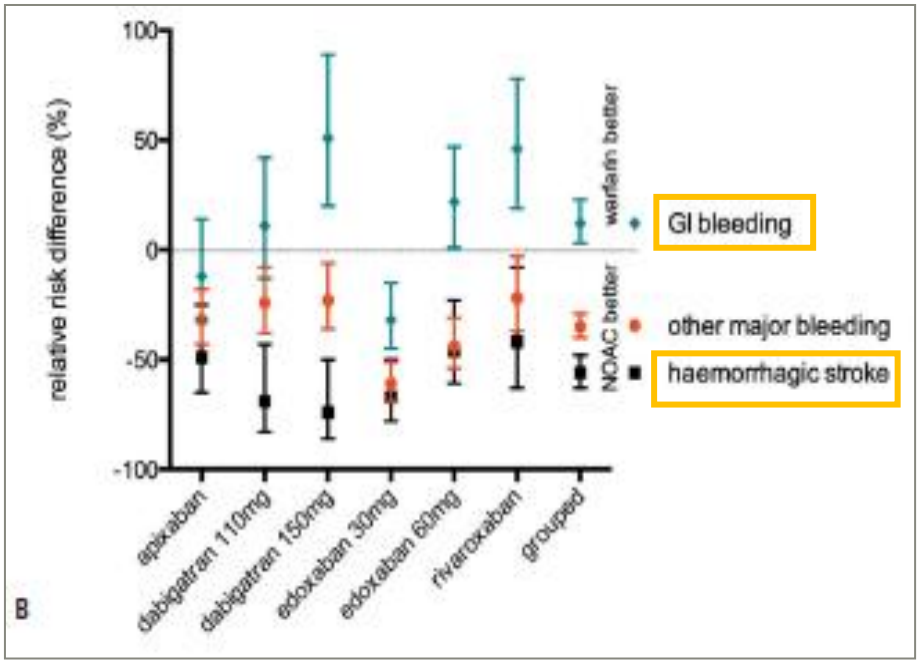
EHRA Guidelines - Europace 2021

DOACs – Bleeding pattern

RCT in AF: 84540 patients / 4781 bleeding events



Overall major bleeding
Relative risk (± 95% CI)



Organ-specific bleeding
(Gastrointestinal, haemorrhagic stroke, other)
Relative risk (± 95% CI)

Vanassche T et al. *Thromb Haemost* 2014;112:918-923

DOACs – Bleeding pattern

✓ **Table 1: Gastrointestinal effects of warfarin and direct acting oral anticoagulants.**

	Bioavailability	Active drug in the gut?	Intraluminal levels of active drugs
Warfarin	95–100%	No	<5% (inactive)
Dabigatran	7%	Yes (prodrug, activated by gut esterases)	~ 80% (28)
Rivaroxaban	66%	Yes	~ 30% (30)
Apixaban	50%	Yes	~35% (29)
Edoxaban	62%	Yes	~50% (27)

- ✓ Local activation of drug by gut esterases (dabigatran)
- ✓ High dose vs reduced dose (local drug concentration)
- ✓ Once vs twice daily intake (local drug concentration)
- ✓ Older vs slightly younger study population (asymptomatic mucosal lesions)

Vanassche T et al. *Thromb Haemost* 2014;112:918-923

DOACs – Antidote

- Direct FIIa inhibitor - *reimbursed in Belgium*

  Idarucizumab (Praxbind®)

  - Humanized antibody fragment directed against dabigatran
  - Completely reverses anticoagulant effect of dabigatran within minutes
  - IV bolus

- Direct FXa inhibitor - *awaiting approval*

  Andexanet alfa (PRT064445)

  - Recombinant modified FXa molecule
  - IV bolus + infusion

- Antidote for direct FIIa and Xa inhibitor, LMWH, fondaparinux - *studies ongoing*

  Aripazine (PER977, ciraparantag)

  - Synthetic small molecule with broad activity

DOACs – Laboratory issues

- No need for routine *monitoring*

- *Measuring*, only in special indications
  - Unexpected thrombotic or bleeding event, emergence procedure
  - Sub- or supra-therapeutic drug levels
  - Calibrated assays for quantification of drug levels: anti-Xa levels (anti-Xa DOACs) or dilute thrombin time (anti-IIa DOAC)
  - CAVE: no established therapeutic ranges, nor correlation with clinical outcome

DOACs – Laboratory issues

- Routine clotting assays (PT/INR, APTT)
  - Do not reflect accurately DOAC drug levels or anticoagulant effect
  - Degree of prolongation is highly dependent on DOAC, time since last intake and reagent used for the assay

- Effect on coagulation parameters
  - DOACs affect conventional tests of haemostasis

    → careful interpretation of results from thrombophilia screening or coagulation factors

DOACs – Tailored treatment

- Correct DOAC
  - No head-to-head comparison
- Correct use and dosing
  - Indication / bleeding risk
- Drug interactions
  - P-gp inducers/inhibitors
  - CYP450 (CYP3A4) enzyme inducers/inhibitors
  - Check list (f.i. EHRA Guidelines 2021)
  - Antiplatelet agents
- Renal insufficiency, hepatic impairment, age, body weight:
  - check by start and follow up regularly renal and hepatic function
  - adapt eventually dosing

DOACs … in evolution

Progress since first study data

- ✓ Real world data reassuring
- ✓ Development of drug specific calibrated assays
- ✓ Development of specific antidotes
- ✓ Doctors' familiarity in drug management
- ✓ …

Limitations

- ✓ Lack of data in some specific disease groups
- ✓ Anti-Xa reversal agents not yet available
- ✓ Doctors' familiarity in drug management
- ✓ …

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