DIRECT-ACTING ORAL ANTICOAGULANTS (DOACS)

Anti Xa

- **Rivaroxaban (Xarelto)**
- **Apixaban (Eliquis)**
- Edoxaban (Savaysa)

Antithrombin (anti IIa)

- **Dabigatran (Pradaxa)**

Non–vitamin K Oral Anticoagulants (NOACs)

Newer Oral Anticoagulants (NOACs, NOAGs)

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Dabigatran versus Warfarin in Patients with Atrial Fibrillation

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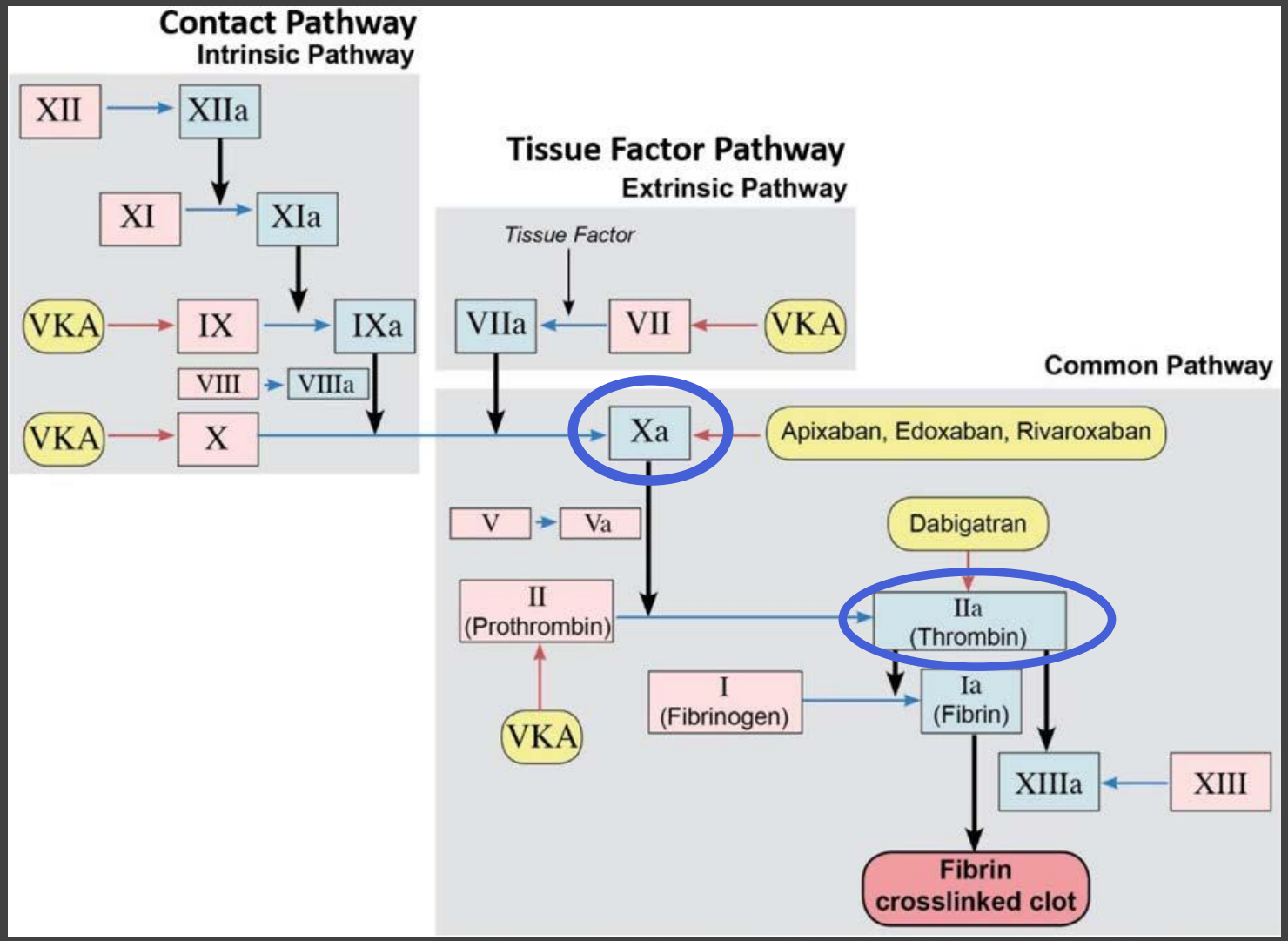


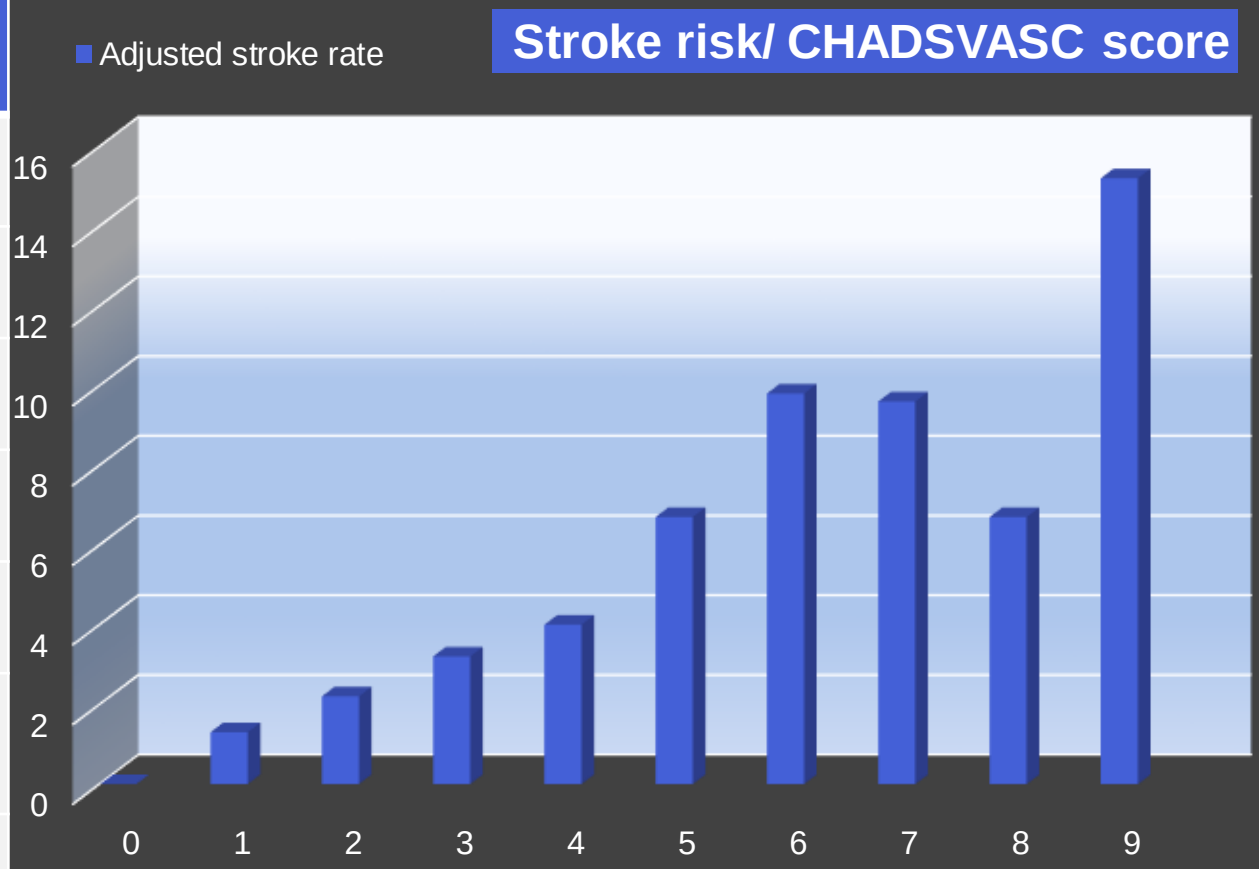
RAVAL ET AL, CIRCULATION. 2017;135:E604–E633

DOAC IN AFIB

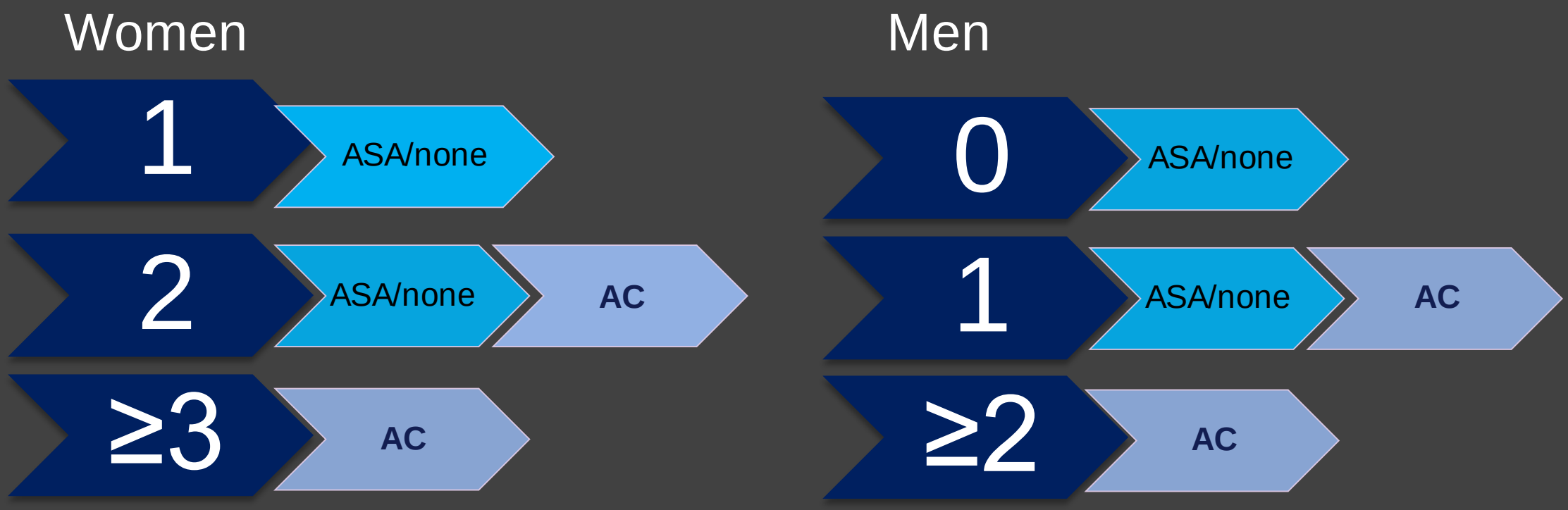
- **Paroxysmal ⇔ Permanent Afib's risk of stroke** **(SPAF) Hart, JACC 2000**
- Thrombus source in non-valvular Afib is the left atrial appendage (LAA) due to stasis
- Atrial flutter anticoagulation managed same as afib

CHA2DS2-VASc score

Risk factor	Score
CHF/ LVEF≤40%	1
HTN	1
Age ≥75	2
Diabetes Mellitus	1
Stroke/TIA/Thromboembolism	2
Vascular disease: prior MI, PVD, aortic plaque	1
Age 65-74	1
Female gender	1



CHA2DS2-VASC ANTICOAGULATION MANAGEMENT



HELPFUL APPS

- Calculate by QxMD app (Android or Iphone): CHADSAVASC, HASBLED…
- AntioagEvaluator App by ACC

ATRIAL FIBRILLATION: DOACS VS. WARFARIN ?

- Consistent evidence of *at least* non-inferiority of DOACs for the combined endpoint of stroke/ systemic embolism
- Superior safety profile, meta-analysis:
  - Major Bleeding 0.85
  - **ICH 0.48**
  - GIB 1.26 (except apixaban and lower doses of edoxaban and dabigatran)
- =>DOACs recommended as first line therapy over warfarin

WHEN DOAC SHOULD BE USED

- Due to consistent efficacy and superior safety profile: first line Rx over warfarin
- Difficult to maintain INR
- Logistics preventing INR check (lives remotely and/or no access to home INR)
- Drug-drug interactions (amiodarone, antibiotics, …)
- Patient wants dietary freedom!

HOUSEKEEPING ISSUES: DOAC

- Renal function and hepatic function should be evaluated before initiation of a DOAC and be reevaluated at least annually (more frequently if CKD or on nephrotoxic medications (ACE/ARB, diuretics…)

- CBC ~twice a year is advisable (occult bleeding, thrombocytopenia)

- Emphasize compliance

WHEN DOAC SHOULD NOT BE USED

- Warfarin is the **ONLY** choice with **moderate-to-severe mitral stenosis** or with **mechanical** heart valve
- Not used in Antiphospholipid Antibody Syndrome
- **ESRD or on dialysis:** dabigatran rivaroxaban, or edoxaban are not recommended because of the lack of evidence from clinical trials that benefit exceeds risk => ***apixaban* or warfarin**
- Avoid DOACs in cirrhosis with Child-Pugh *B* or **C**

WHEN DOAC BETTER NOT BE USED

- Cost issues $$$$
- Compliance is key: if a patient forgets a dose or 2 then subRx, warfarin more forgiving
- Pregnancy
- Gastritis: dabigatran
- Drug interaction albeit <<< warfarin:
  - Avoid with **rifampin** (decreases levels)
  - Avoid P-gp and strong CYP3A4 inhibitors (increase levels) **ketoconazole**, **HIV protease inhibitors** (ritonavir…), dronaderone for dabigatran

PHARMACOKINETICS

- Onset of action **1-4** hours for DOACs (shortest are dabigatran and edoxaban)

- Plasma ½ life:
  - Dabigatran ~14 hours
  - Rivaroxaban ~7
  - Apixaban ~12
  - Edoxaban~12

TRANSITIONING FROM WARFARIN TO DOAC

- Dabigatran: d/c warfarin and start when INR<2
- *Rivaroxaban: d/c warfarin and start when INR<**3***
- *Apixaban: d/c warfarin and start when INR<2*
- Edoxaban: d/c warfarin and start when INR<2.5

TRANSITIONING TO WARFARIN

- **Apixaban and rivaroxaban prolong PT/INR so switch to parenteral AC for bridging** (can stop and start couple of days later if no need for bridging)

- Dabigatran:
  - For CrCl ≥50 mL/min, start warfarin 3 days before discontinuing PRADAXA.
  - For CrCl 30-50 mL/min, start warfarin 2 days before discontinuing PRADAXA.
  - For CrCl 15-30 mL/min, start warfarin 1 day before discontinuing PRADAXA.

- Edoxaban decrease dose to half and check INR before dosing edoxaban

TRANSITIONS, OTHER

- Discontinue current anticoagulant and start the new DOAC at the time of the next scheduled dose
- LMWH : D/C LMWH and start DOAC at the time of the next scheduled administration of LMWH
- Heparin: D/C the infusion and start DOAC 4 hours later

DOSING

Apixaban

- **AFIB:**
  - 5 mg BID
  - In patients with ≥ 2 of : age ≥80 years, Wt ≤60 kg, or Cr≥1.5 mg/dL then dose is 2.5 mg BID

- **(Rx of DVT/PE**: 10 mg BID for 7 days followed by 5 mg BID)

Rivaroxaban (take with food)

- AFIB:
  - CrCl >50 mL/min: 20 mg qd pm
  - CrCl ≤50 mL/min: 15 mg qd pm

- **(Rx of DVT/PE: 15 mg BID for the first 21 days followed by 20 mg orally qd)**

HOLDING PRIOR TO INVASIVE PROCEDURES

- Rivaroxaban:
  - Hold ≥24 hours prior to invasive procedures
- Apixaban:
  - Procedures with moderate-high risk of clinically significant bleeding hold ≥48 hours
  - Procedures with low risk of clinically significant bleeding hold≥24 hours
- Dabigatran before invasive or surgical procedures:
  - CrCl ≥50 mL/min 1-2 days
  - CrCl <50 mL/min 3-5 days
  - Consider longer times for patients undergoing major surgery, spinal puncture, or placement of a spinal or epidural catheter or port, in whom complete hemostasis may be required

DOAC WHAT'S NEW?

- **Can be used in patients with valvular disease** excluding moderate-severe MS or mechanical valve (AS, AI, MR, TR, *mild MS*…) when CHA2 DS2 -VASc >= 2
- But with bioprosthetic valves: limited data… (50-100 patients in trials of 10K)
- TAVR: Gallileo trial of rivaroxaban halted early by DSMD due to increased thromboembolic/death and bleeding complications
- AF catheter ablation: uninterrupted DOAC use *Calkins 2017*
- **Andexanet Alfa (Andexxa) for reversal of Xa inhibitors** (apixaban and rivaroxaban) approved May 2018 (NEJM study 2019)
- Idarucizumab (Praxbind) for reversal of dabigatran in 2015

IMPLICATIONS AND CONTROVERSIES OF DOACS IN CLINICAL PRACTICE

- **Age >75:** DOACs were found to be safer and more effective than warfarin for the treatment of AF in older patients (apixaban had the best data) *Malik, March 2019*

- CKD: most patients in trials are CKD 3 and had similar efficay and safety as warfarin-meta-analysis of all 4 drugs *Kimachi 2017.*

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THANK YOU

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