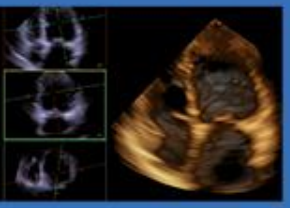

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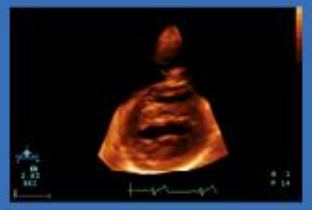


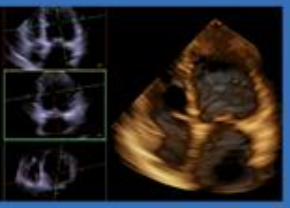
Atrial fibrillation in valvular heart disease: Is there a role for DOACs?

Cécile Oury, PhD

GIGA-Cardiovascular

University of Liège, Belgium

www.eurovalvecongress.com



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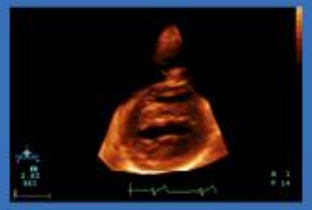

Faculty disclosure

Cécile Oury

I have **no financial relationships** to disclose

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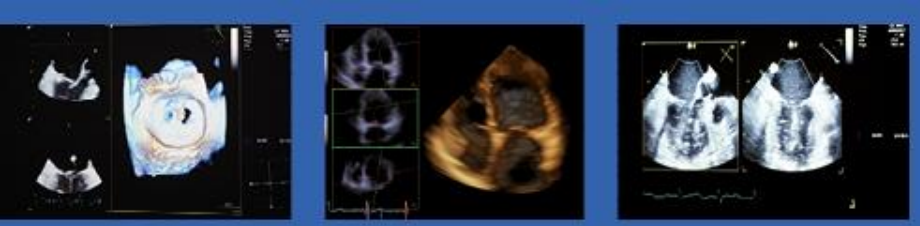


DOACs/NOACs: what is available?

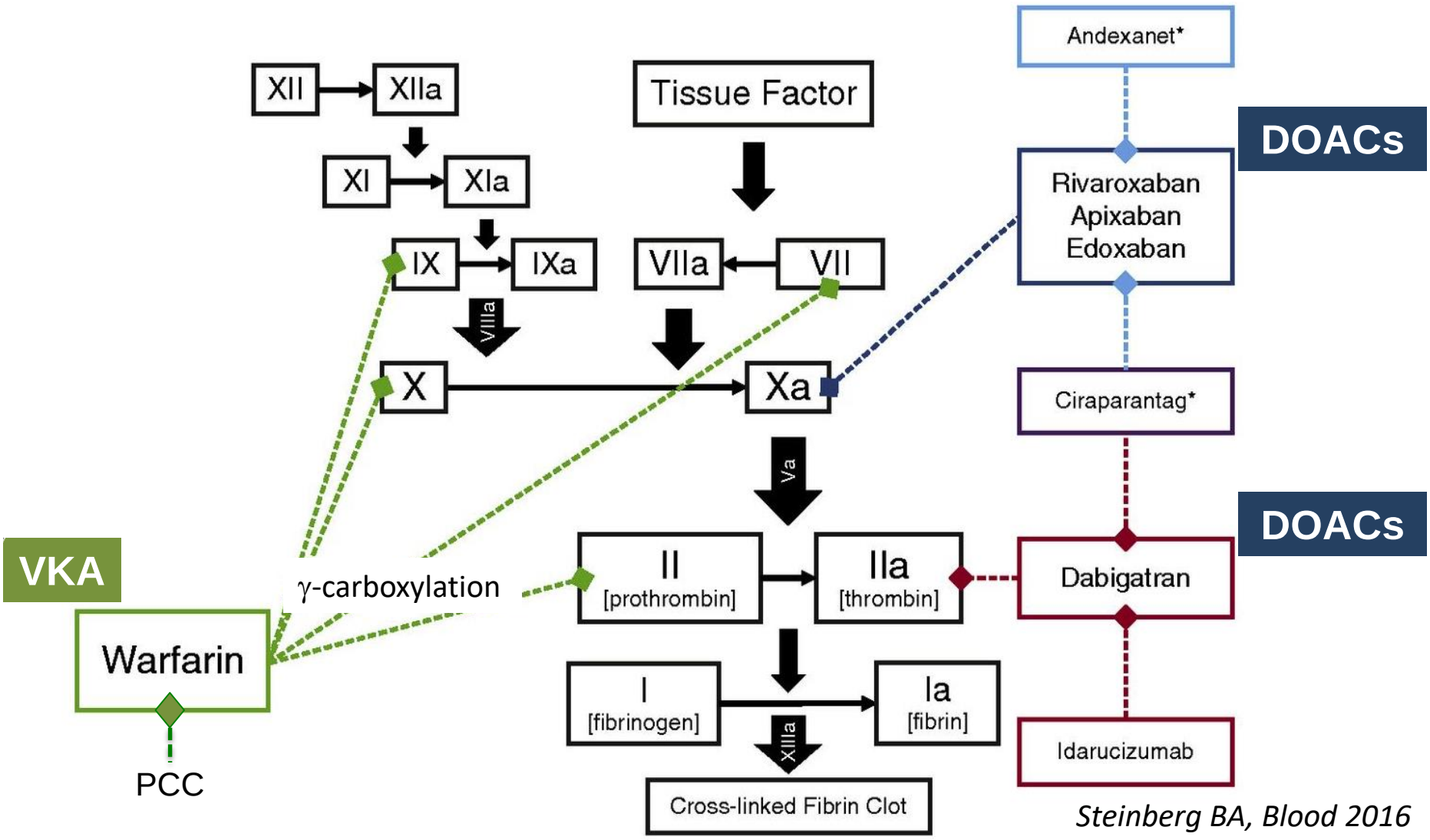
- Direct thrombin inhibitor:

  dabigatran etexilate (Pradaxa; Boehringer Ingelheim)

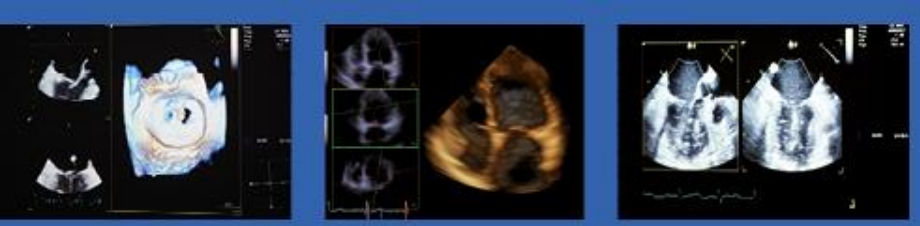
- Direct factor Xa inhibitors:
  - apixaban (Eliquis; Bristol-Myers Squibb/Pfizer)
  - edoxaban (Savaysa or Lixiana; Daiichi Sankyo)
  - rivaroxaban (Xarelto; Johnson and Johnson/Bayer HealthCare)
  - betrixaban (Bevyxxa; Portola Pharmaceuticals)

Levy JH et al Nat Rev Cardiol 2018

Oral anticoagulants: mode of action



Steinberg BA, Blood 2016



DOACs *vs* VKAs

	Warfarin	DOACs
Onset of action	Slow	Rapid (peak: 1-3h)
Dosing	Variable	Fixed
Food interactions	Yes	No
Drug interactions	Many	Few
Routine laboratory monitoring	Yes	No (but possible)
Duration of blood-thinning effect	Long (half-life=36-42h)	Short (half-life=10-14h)
Reversal agent available	Yes	Yes

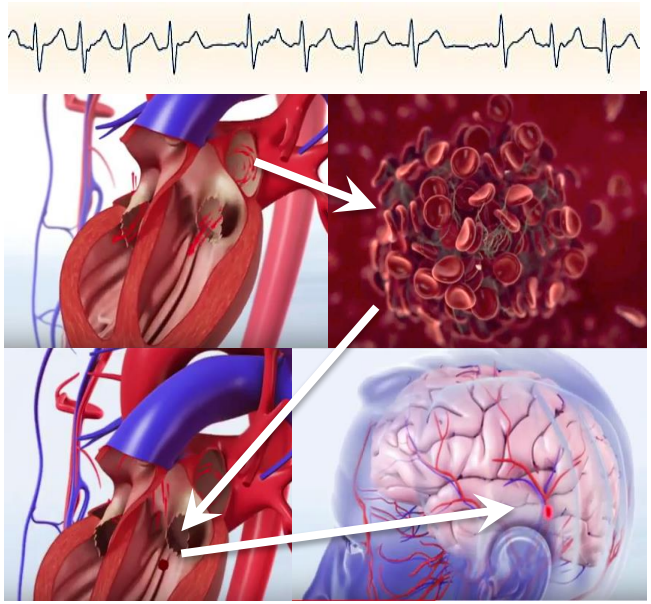
Levy JH et al Nat Rev Cardiol 2018

Atrial fibrillation

- Increases the risk of stroke by 5-fold

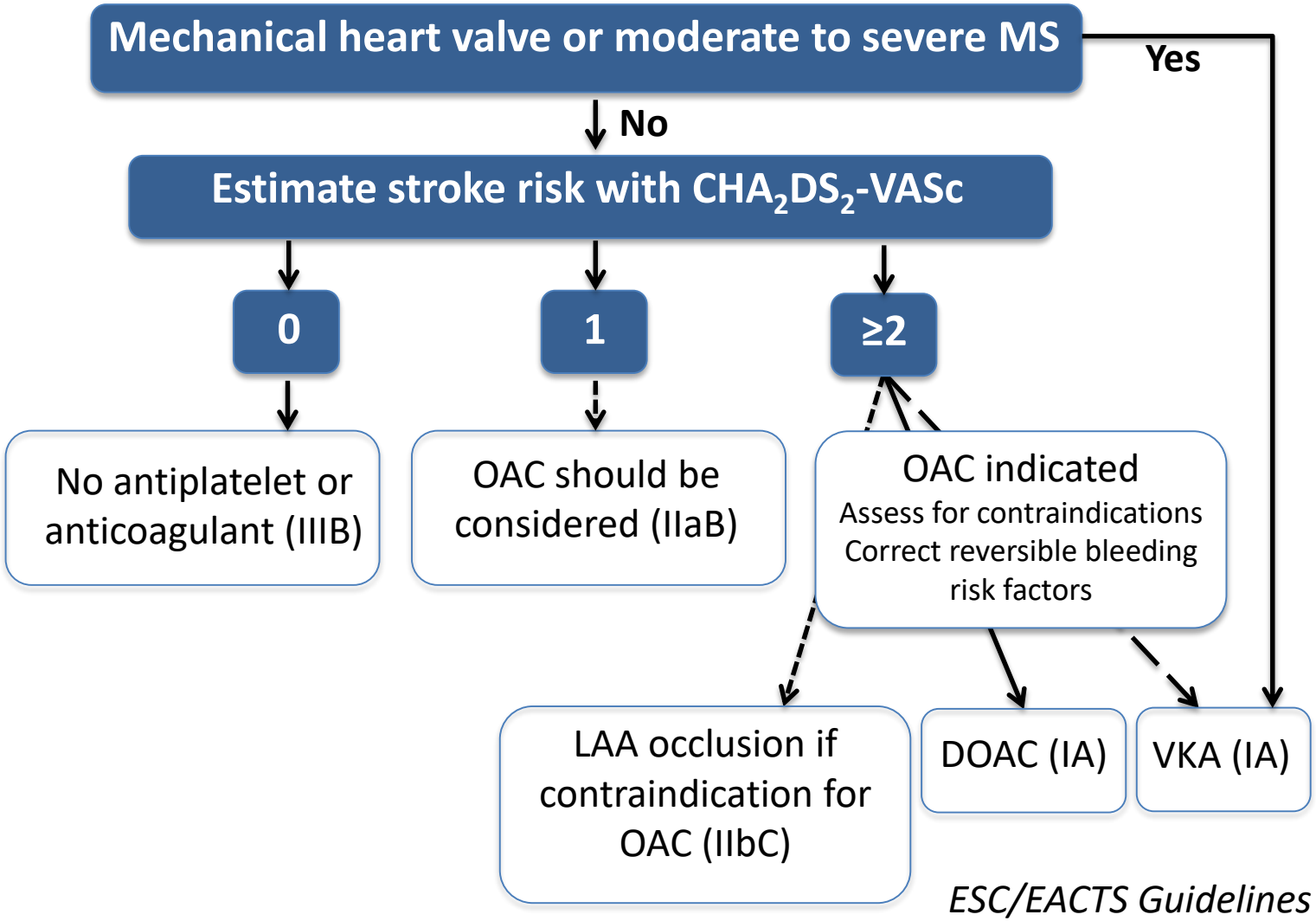
VIRCHOW's triad for thrombogenesis:

- Abnormal blood stasis in the atria
- Structural heart disease
- Abnormalities of blood coagulation

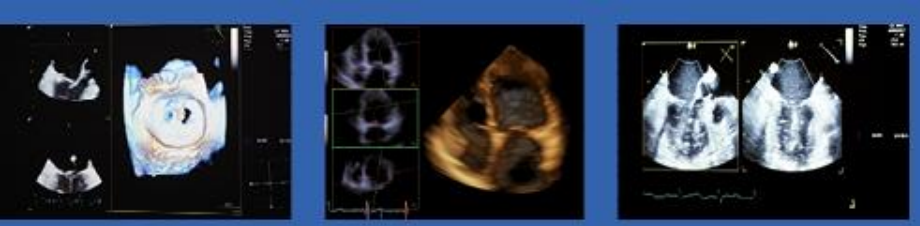


Watson T et al. Lancet 2009; *https://www.thrombosisadviser.com/hrc*

OACs for Stroke prevention in AF



ESC/EACTS Guidelines 2017



DOACs for Stroke prevention in AF

RCTs

- ARISTOTLE: apixaban 5mg compared with warfarin
- RE-LY: dabigatran 110mg and dabigatran 150mg compared with warfarin
- ENGAGE AF-TIMI-48: edoxaban 30mg and edoxaban 60mg compared with warfarin
- ROCKET-AF: rivaroxaban 20mg compared with warfarin

+ real life studies

DOACs: non inferior efficacy and improved safety in non-valvular AF (NVAF) as compared to VKAs

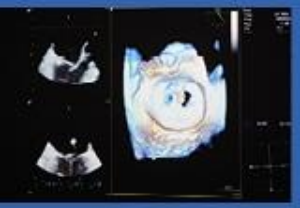
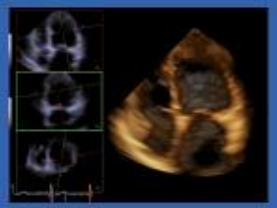
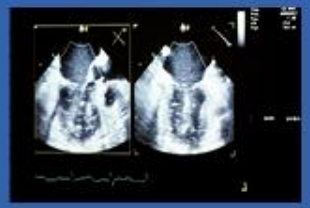
➢ The role of DOACs in valvular AF is less clear

Valvular AF *vs* NVAF

- Valvular AF excluded from RCTs (due to incremental thrombo-embolic risk)
- Different definitions → different exclusion criteria in trials

« Valvular AF refers to AF patients with either rheumatic valvular disease (predominantly mitral valve stenosis), or mechanical prosthetic heart valves »

ESC/EACTS Guidelines 2017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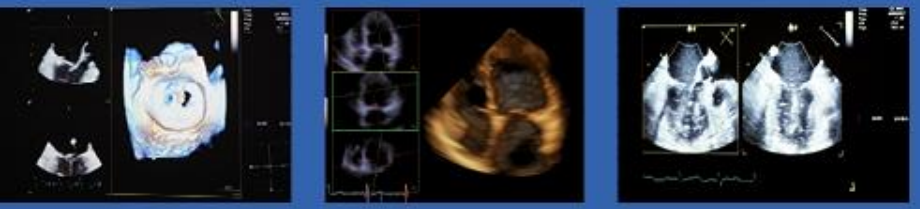
DOACs for stroke prevention in AF and VHD?

AF and VHD

- VHD is independently associated with incident AF
- AF worsens prognosis in patients with severe VHD, including those undergoing surgery or transcatheter interventions for aortic or mitral valve disease
- Rheumatic MS is still prevalent among patients with AF in Africa, Asia, and Middle East (19-25%)

  (The REMEDY study)

ESC/EACTS Guidelines 2017; Lip GYH et al Nat Rev Disease primer 2016; Zühlke L et al Circ 2016



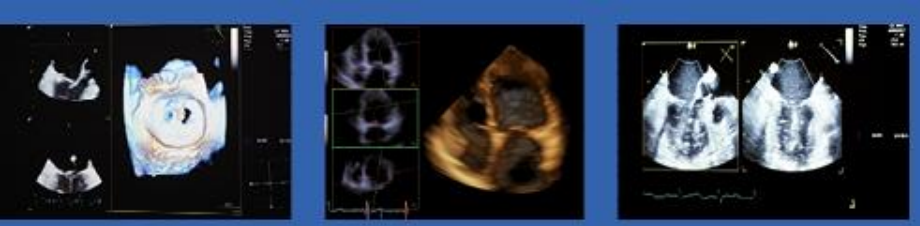
AF and VHD insights from ORBIT-AF

American Heart Association | American Stroke Association

- Among a community cohort of 9748 patients with AF, 2705 (27.7%) had significant VHD with prosthetic valve replacements, MS, and prior surgical repairs/balloon valvuloplasty
- Individuals with AF and moderate-to-severe biological VHD have more comorbidities and a higher mortality risk
- The combination of aortic stenosis and atrial fibrillation was associated with a significant increase in mortality
- Individuals with AF, bioprosthetic valves, prior surgical repair, and balloon valvuloplasty were not associated with higher odds of stroke, death, or bleeding relative to those without significant VHD in the setting of high rates of oral anticoagulation

➢ Treating comorbidities and anticoagulating individuals with AF and VHD will likely improve outcomes

Thomas K et al JAHA 2017



VHD subanalyses of DOACs in AF trials Results

- 13%-26% of patients enrolled in the 4 landmark trials had VHD
- 2 meta-analyses confirmed that DOAC use reduced the risk of stroke or systemic embolism to a similar degree in patients with AF and VHD compared with those with AF without VHD
- Patients with VHD were at higher risk of bleeding than those without VHD (HR, 1.24; 95% CI, 1.14-1.34; *P* = .25 for heterogeneity; I^2 = 26%), but bleeding rates did not significantly differ in patients with VHD treated with DOACs versus those treated with warfarin (HR, 0.93; 95% CI, 0.67-1.28; *P* = .0002 for heterogeneity; I^2 = 85%).

Renda G et al. J Am Coll Cardiol. 2017; Pan KL et al. J Am Heart Assoc. 2017

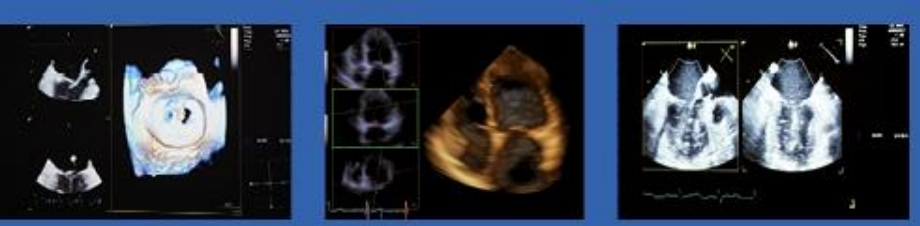
NOACs in valvular AF

Heart

Current recommendations for anticoagulant therapy in patients with valvular heart disease and atrial fibrillation: the ACC/AHA and ESC/EACTS Guidelines in Harmony …but not Lockstep!

John Preston Erwin III and Bernard Iung

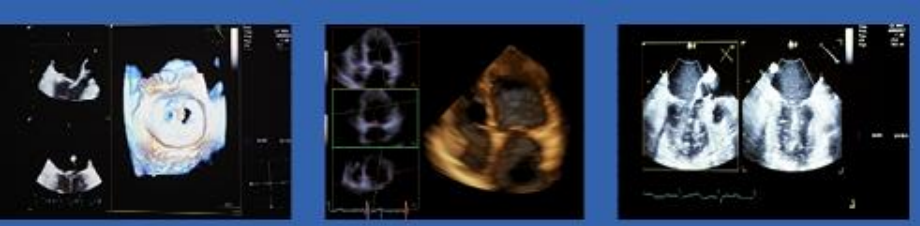
Heart published online January 11, 2018



NOACs in valvular AF

2017 ESC/EACTS guidelines			2017 update AHA/ACC		
Native valve disease					
	I	C	Anticoag indicated if AF + CHA_2DS_2-VASc ≥ 2 in AVD, TVD or MR	I	C-LD
DOACs should be considered as alternative to VKAs in AS, AR, and MR with AF	IIa	B	DOACs reasonable alternative to VKA in AVD, TVD or MR with AF and CHA_2DS_2-VASc ≥ 2	IIa	C-LD
Keep VKA for moderate to severe MS and persistent AF	-		VKA indicated for rheumatic MS with AF	I	B NR
DOACs not recommended in moderate and severe MS with AF	III	C			

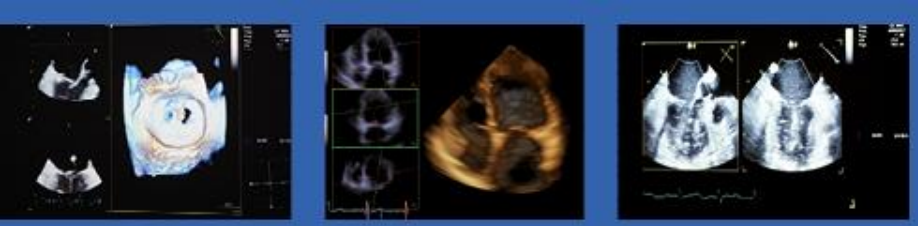
Erwin and Lung Heart 2018



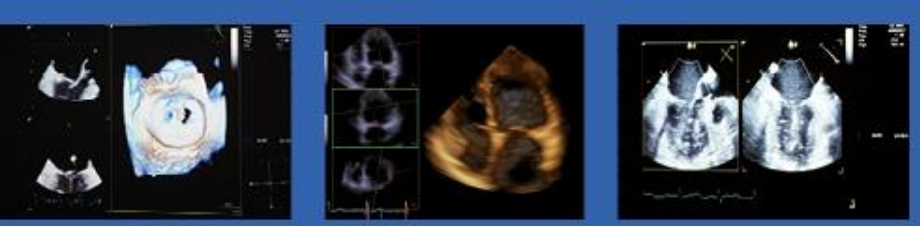
NOACs in valvular AF

2017 ESC/EACTS guidelines			2017 update AHA/ACC		
Bioprostheses					
DOACs should be considered as alternative to VKAs after 3 month post-TAVR or SAVR in patients with AF	IIa	C			
Mechanical prostheses					
DOACs are contraindicated	III	B	Direct thrombin inhibitors or anti-Xa agents should not be used	III	B

Erwin and Lung Heart 2018



The optimal and duration of the antithrombotic regimen after bioprosthetic valve replacement with or without AF is not defined yet



DOACs after valve replacement in AF

Bioprosthesis (SAVR/TAVR)

- After the 3-6 month post-operative period: OACs are indicated for AF as Class I, irrespective of the risk of stroke (ESC/EACTS) (AHA/ACC)
- DOACs are considered as an alternative to VKA (ESC/EACTS) (IIa, C)

Bioprosthesis (MVR)

- OACs should be extended indefinitely after the 3-6 month in case of AF
- DOACs may be a suitable alternative to VKA ???

Erwin and Lung Heart 2018

Conclusions: Is there a role for DOACs?

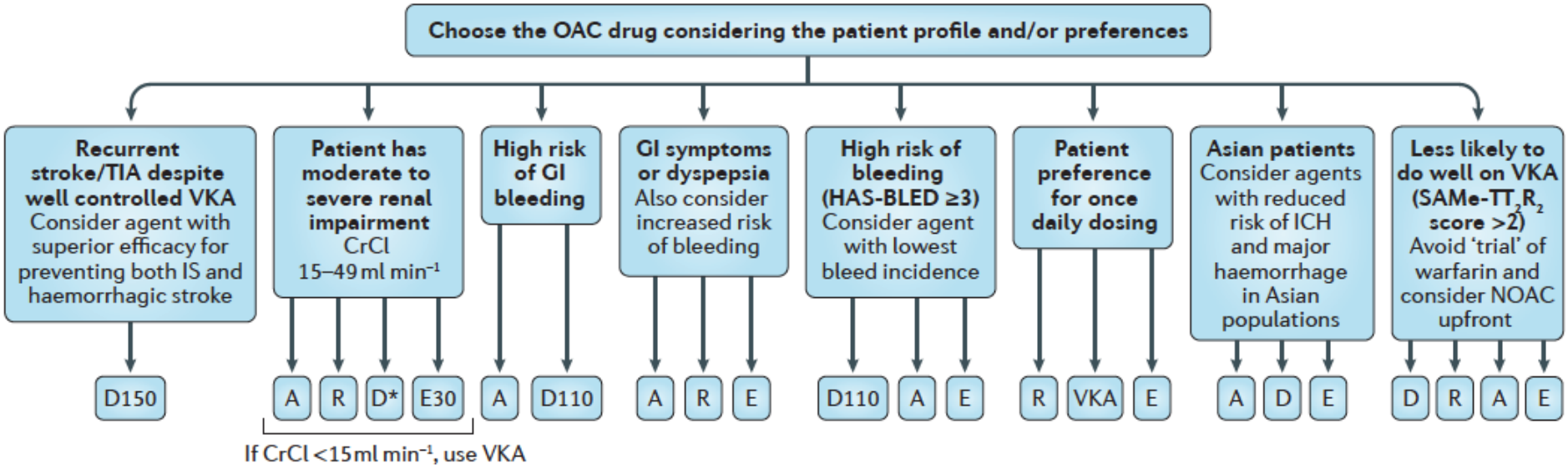
- DOACs should be considered as an alternative to VKAs in AS, AR and MR with AF
- Patients with moderate to severe MS and persistent AF should not receive DOACs

  BUT evidence is lacking: studies of safety and efficacy of DOACs in MS are awaited
- For bioprosthesis only, after a 3-month post-AVR period, DOACs are considered as an alternative to VKA in case of AF

  BUT further studies are needed to confirm superior efficacy and safety *vs* VKA in AVR

  Reliable data are lacking to assess suitability in MVR
- DOACs are contraindicated in patients with MHV
- Clinical effectiveness of NOACs on AF should be evaluated for specific VHD type

Which DOAC for which patient?



Major bleeding in VHD: Is there a role for reversal agents?

Need for VHD-specific ABC (age, biomarker, clinical history)stroke/bleeding/death risk scores?

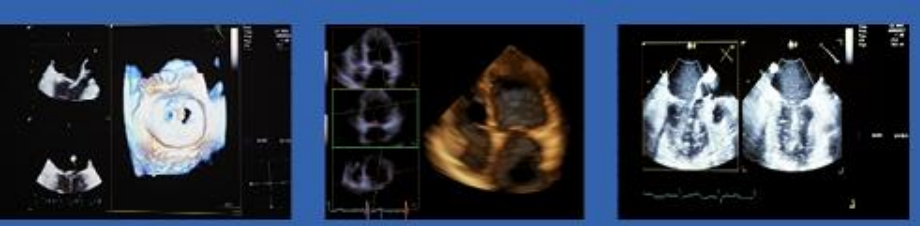
What about warfarin effect on vascular/valvular calcification?

Lip GYH et al Nat Rev Disease primer 2016; Hijazi Z et al Eur Heart J 2018

Thank you!

DOACs: standard doses

- apixaban 5mg twice daily
- dabigatran 150-110mg twice daily
- edoxaban 60-30mg once daily
- rivaroxaban 20mg once daily



Reversal agents

- Direct thrombin inhibitor:

  Dabigatran etexilate

  Reversal agent: Idarucizumab (approved for emergency surgery, urgent procedures, life-threatening or uncontrolled bleeding)

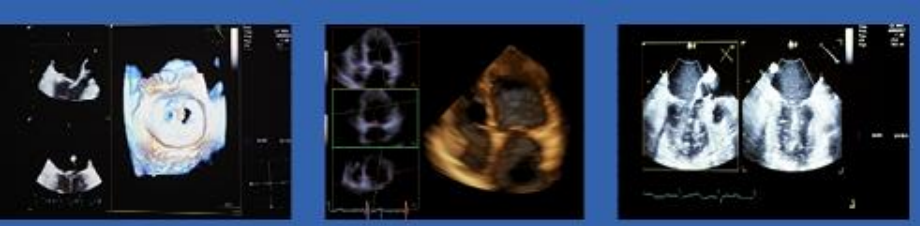
- Direct factor Xa inhibitors:
  - Apixaban
  - Betrixaban
  - Edoxaban
  - Rivaroxaban

  Reversal agent: andexanet alfa (under consideration by regulatory agencies)

Reversal agent: Ciraparantag (phase III)

OR prothrombin complex concentrates (life-threatening bleeding)

Levy JH et al Nature Reviews Cardiology **15**:273–281 (2018)



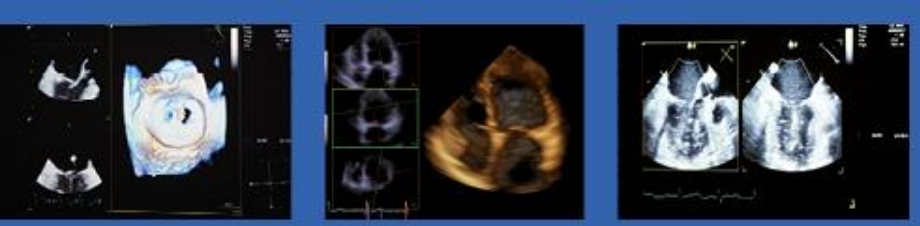
DOACs: indications

- Apixaban, dabigatran, edoxaban, and rivaroxaban:
  - ✓ stroke prevention in nonvalvular atrial fibrillation or flutter
  - ✓ treatment of venous thromboembolism
  - ✓ prevention of venous thromboembolism after hip or knee replacement surgery (edoxaban only in Japan)
- Betrixaban:
  - ✓ prevention of venous thromboembolism in medically ill patients (only in the USA)

Kidney clearance

apixaban: 25%, betrixaban: 6–13%, dabigatran: 80%, edoxaban: 50%, rivaroxaban: 33%

Levy JH et al Nat Rev Cardiol 2018



DOACs: contra-indications

- ✓ Known hypersensitivity
- ✓ Renal impairment:
  - Dabigatran: CrCl <30mL/min
  - Apixaban: CrCl <25mL/min
  - Rivaroxaban: CrCl <30mL/min (may be used CrCl 15-30mL/min for prevention of VTE after elective THR or TKR)
- ✓ Clinically significant active bleeding
- ✓ Significant inherited or acquired bleeding disorder
- ✓ Hepatic disease with coagulopathy
- ✓ Organ lesions at risk of bleeding including intracranial haemorrhage in previous 6 months
- ✓ Indwelling spinal or epidural catheter and during the first 6 hours after removal
- ✓ Pregnancy or breastfeeding mother
- ✓ Mechanical heart valve (RE-ALIGN study dabigatran *vs* VKA)

Clinical excellence Commission, 2017
Eikelboom JW et al. N Engl J Med. 2013