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Novel oral anticoagulants in adult CHD

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Korean Heart Rhythm Society
COI Disclosure

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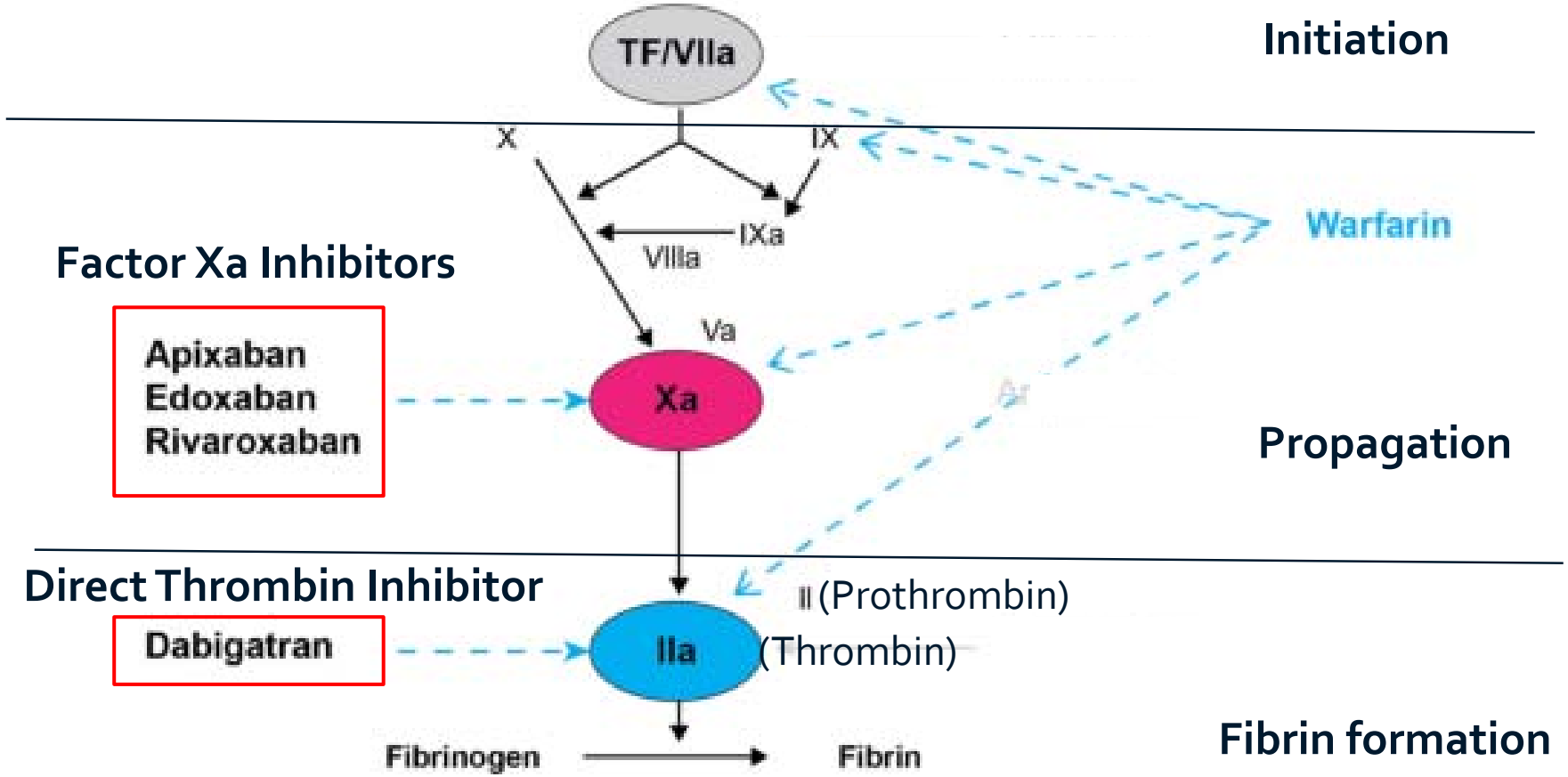
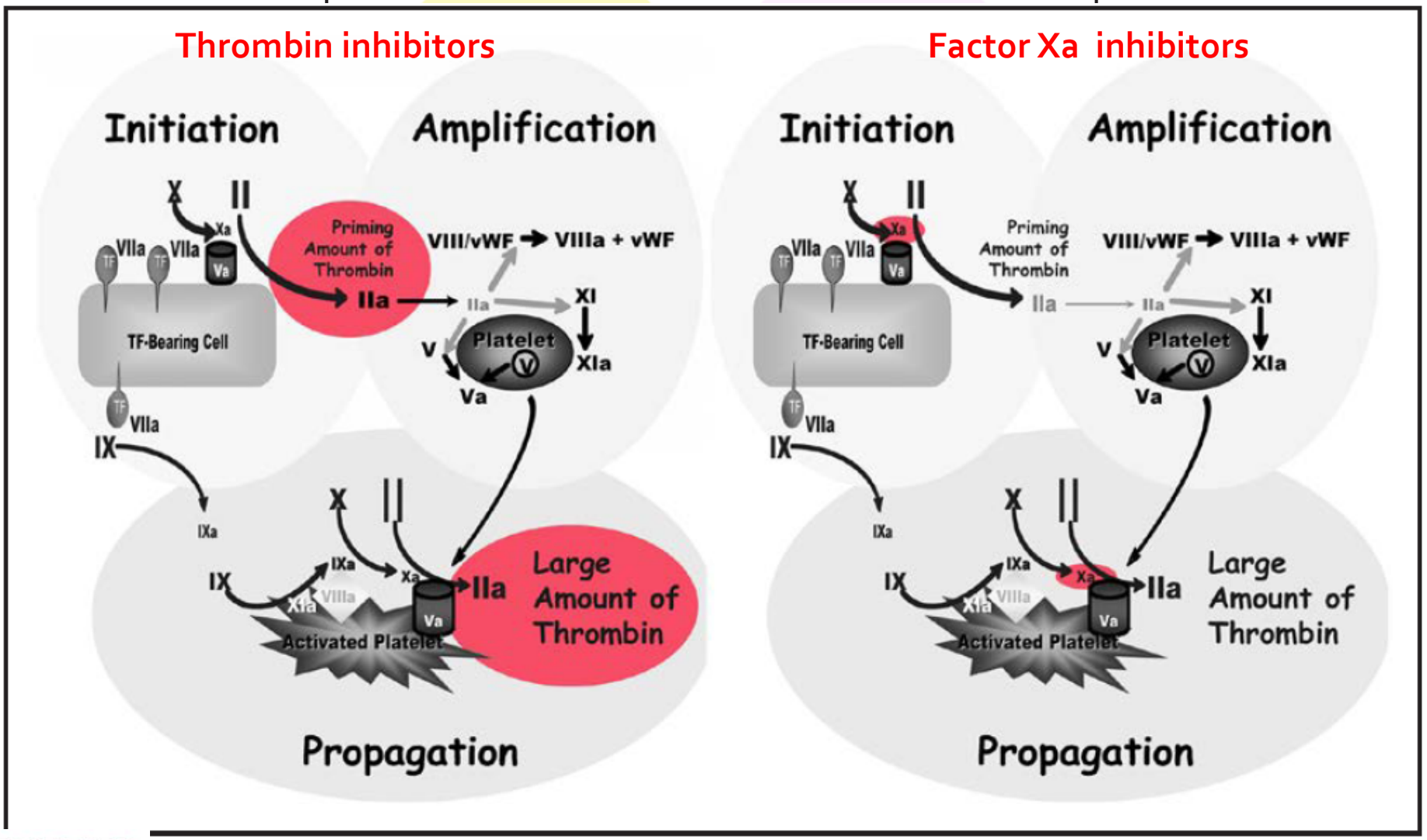
The authors have no financial conflicts of interest to disclose concerning the presentation

Non-Vitamin K Antagonist Oral Anticoagulants (NOACs)



J Thromb Haemost 2016

NOACs in a cell based model of coagulation.



Ix for Anticoagulation in Adult CHD

Canadian J Cardiology 2017;33 1597-1603

Type of risk	
Thromboembolic	Bleeding
• Age 55 years or older	• Age 60 years or older
• Atrial arrhythmia	• History of significant bleeding
• CHA_2DS_2-VASc score ≥ 2	• Thrombocytopenia
• History of thromboembolism	• Acquired von Willebrand disease
• Eisenmenger physiology	• HAS-BLED score ≥ 2
• Pulmonary hypertension	• Pulmonary hypertension
• Fontan circulation	• Anticoagulation
• Valvular prosthesis, especially mechanical valves	• Vascular disease
• Pregnancy	
• Increased disease complexity	

CHA_2DS_2-VASc: stroke risk

	Condition	Points
C	Congestive heart failure (or Left ventricular systolic dysfunction)	1
H	Hypertension: blood pressure consistently above 140/90 mmHg (or treated hypertension on medication)	1
A_2	Age ≥75 years	2
D	Diabetes Mellitus	1
S_2	Prior Stroke or TIA or thromboembolism	2
V	Vascu	1
A	Age 6	1
Sc	Sex c	1

CHA2DS2-VASc and HAS-BLED scores have not been validated in pts with CHD.

HAS-BLED	Score
Hypertension i.e. uncontrolled BP	1
Abnormal renal/liver function	1 or 2
Stroke	1
Bleeding tendency or predisposition	1
Labile INR	1
Age (e.g. >65)	1
Drugs (e.g. concomitant aspirin or NSAIDSs) or alcohol	1

Bleeding risk

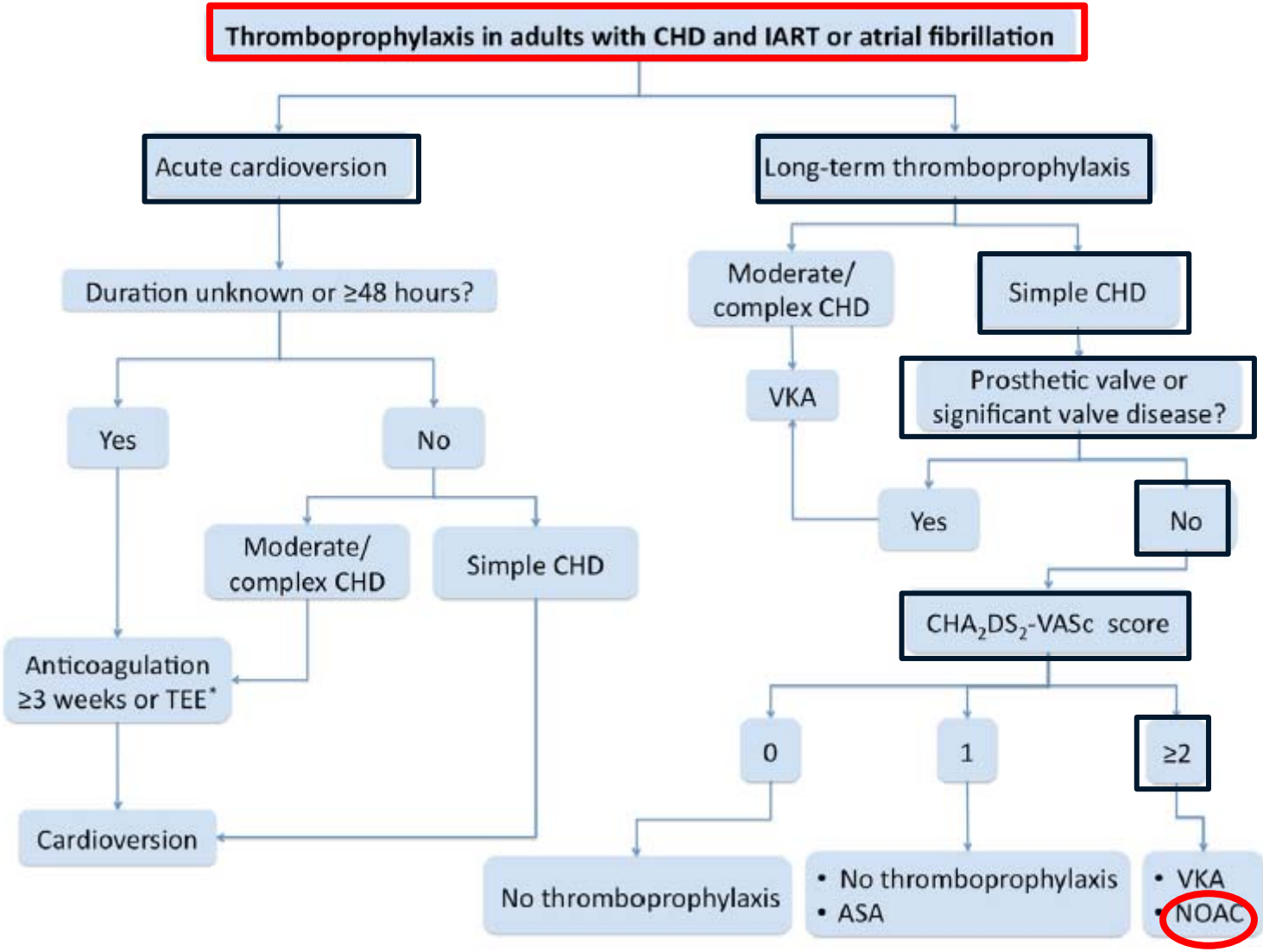
Classification of CHD complexity in adults CHD

ACHD low complexity lesions	ACHD of moderate complexity	ACHD complex lesions
isolated ventricular septal defect	Tetralogy of Fallot	Univentricular heart
persistent ductus arteriosus	Ebstein's anomaly	Eisenmenger's syndrome
isolated congenital valve disorders	aortic isthmus stenosis, discontinuous aortic arch	Transposition of the great arteries (TGA)
other congenital malformation of the great arteries	atrioventricular septal defect	other complex heart malformation, e.g. total anomalous pulmonary venous connection, common arterial trunk
	partial anomalous pulmonary venous connection	

European Heart J 2020; 41, 4168–4177

Atrial arrhythmias in ACHD

PACES/HRS Expert Consensus Statement on Arrhythmias in Adult CHD, 2014



Usefulness of Direct Oral Anticoagulants in Adult Congenital Heart Disease

Am J Cardiol 2016;117:450-455

Claudia Pujol, MD[a], Anne-Charlotte Niesert, MD[a], Andrea Engelhardt, MScBiol[a], Patric Schoen, MD[a], Ekatharina Kusmenkov, MD[a], David Pittrow, MD, PhD[b], Peter Ewert, MD, PhD[a], and Harald Kaemmerer, MD, VMD, PhD[a,*]

75 pts with adult CHD (mean age 50± 13 years, 22-74 yrs)

Congenital Heart Diseases	N (%)
Hypoplastic left heart	2 (3%)
Double inlet left ventricle	2 (3%)
Double outlet right ventricle (univentricular repair)	1 (1%)
Transposition of great arteries	10 (13%)
Congenital corrected transposition of great arteries	1 (1%)
Aortic coarctation	1 (1%)
Aortic stenosis	2 (3%)
Subaortic stenosis	1 (1%)
Aortic regurgitation	1 (1%)
Tetralogy of Fallot	5 (7%)
Double outlet right ventricle/Fallot-type	2 (3%)
Pulmonary atresia with ventricular septal defect	2 (3%)
Ventricular septal defect	2 (3%)
Patent ductus arteriosus	1 (1%)
Patent foramen ovale	9 (12%)
Atrial septal defect	22 (29%)
Ebstein's anomaly	6 (8%)
Aneurysm of Aorta	1 (1%)
Ectasia great arteries	2 (3%)
Others	2 (3%)

Pre-tricuspid shunt, 31 pts (41 %)
Complex CHD , 16 pts (21%)
CHA2-DS2-VASc score ≥ 2 in 23 (31%),
HAS-BLED score ≥ 2 in 9 (12%)

Previous TIA/strok, 15 pts (20 %)
previous corrective cardiac op, 17 pts (23%)
palliative surgery, 23 pts (31%)
cyanosis, 5 pts
Fontan circulation, 3 pts

Mean FU, 12 ± 11 months

Am J Cardiol 2016;117:450-455

75 pts with adult CHD (mean age 50± 13 years)

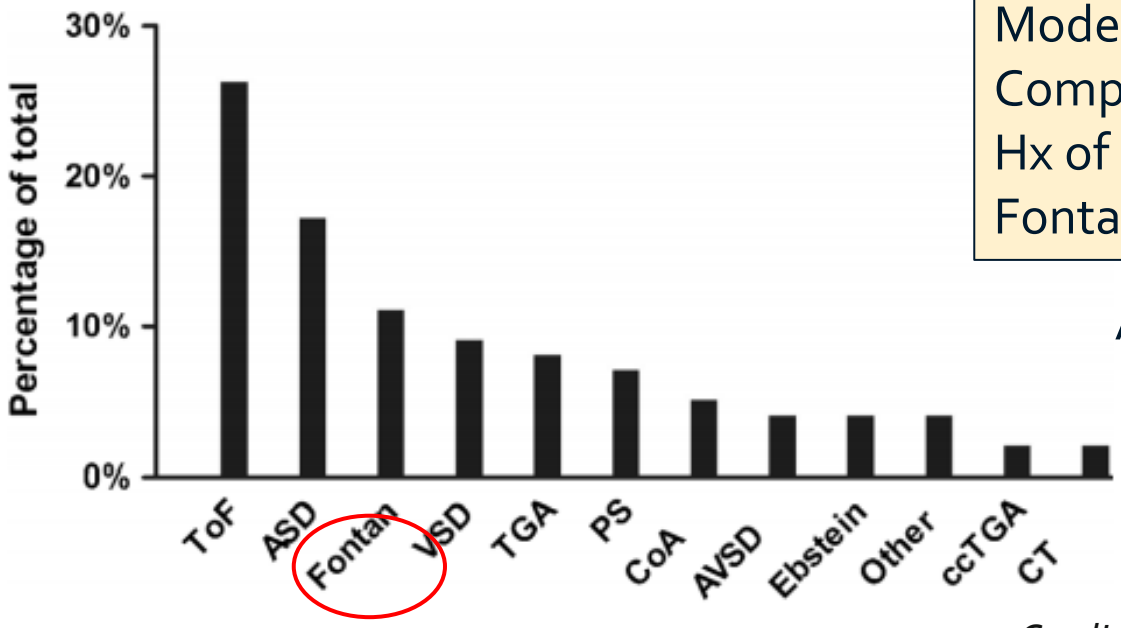
rivaroxaban (n= 55) or apixaban (n= 13) or dabigatran (n= 7)

Indications	N (%)	Diagnoses (N)	Dabigatran N (%)	Rivaroxaban N (%)	Apixaban N (%)
Atrial arrhythmias	57 (76%)	Hypoplastic left heart (2) Double inlet left ventricle (1) Transposition great arteries (10) Congenitally corrected TGA (1) Aortic coarctation (1) Aortic stenosis (2) Subaortic stenosis (1) Tetralogy of Fallot (2) DORV - Fallot type (3) Pulmonary atresia - VSD (2)	4 (7%)	44 (77%)	9 (16%)
		Aortic aneurysm (1) Ectasia of great arteries (1) Other (1)			
Stroke/TIA	15 (20%)	Hypoplastic left heart (1) Transposition great arteries (1) Tetralogy of Fallot (1) Patent foramen ovale (8) Atrial septal defect (3) Ebstein's anomaly (1)	3 (20%)	10 (67%)	2 (13%)
Deep vein thrombosis	4 (5%)	Patent foramen ovale (1) Atrial septal defect (1) Ebstein's anomaly (1) Ectasia of the great arteries (1)	1 (25%)	3 (75%)	-
Pulmonary embolism	1 (1%)	Ebstein's anomaly (1)	-	1(100%)	-
Atrial thrombus	3 (4%)	Atrial septal defect (1) Aortic regurgitation (1) Double outlet right ventricle (1)	-	1 (33%)	2 (67%)

There were neither thrombotic or major bleeding events nor major side effects.

NOTE registry (NOACs for Atrial Tachyarrhythmias in adult Congenital Heart Disease), April 2014~

Prospective cohort study
99 pts with adult CHD and atrial arrhythmias (median age 49 yrs)



Moderate CHD, 56 %
Complex CHD, 29%
Hx of heart failure, 33%
Fontan palliation, 11%

Apixaban (62%)

Cardiovasc Drugs Ther 2017; 31:413–417

99 pts with adult CHD

VKA → NOAC

	All (n = 99)	VKA (n = 54)	VKA-naive (n = 45)	p-value
Age at inclusion, y	48.8 (38–61)	47.3 (38–61)	52.0 (37–61)	0.784
Male, n(%)	52 (53)	24 (44)	28 (62)	0.078
Severity of congenital heart defect, n (%)				
Simple	15 (15)	8 (15)	7 (16)	0.918
Moderate	55 (56)	28 (52)	27 (60)	0.417
Complex	29 (29)	18 (33)	11 (24)	0.333
Fontan circulation	11 (11)	9 (17)	2 (4)	0.054
Pulmonary hypertension	7 (7)	3 (6)	4 (9)	0.519
Myocardial infarction	1 (1)	1 (1)	0	0.359
Major bleeding	9 (9)	8 (15)	1 (2)	0.030
Heart failure*	33 (33)	20 (37)	13 (29)	0.392
Hypertension	24 (24)	11 (20)	14 (30)	0.319
Diabetes mellitus	8 (8)	4 (7)	4 (9)	0.788

After 30 days of therapy,

54 pts with transitioning from VKA to NOACs,

-8 minor adverse events (5 minor bleeding; 3 side-effects)

45 VKA-naive pts

- No adverse events

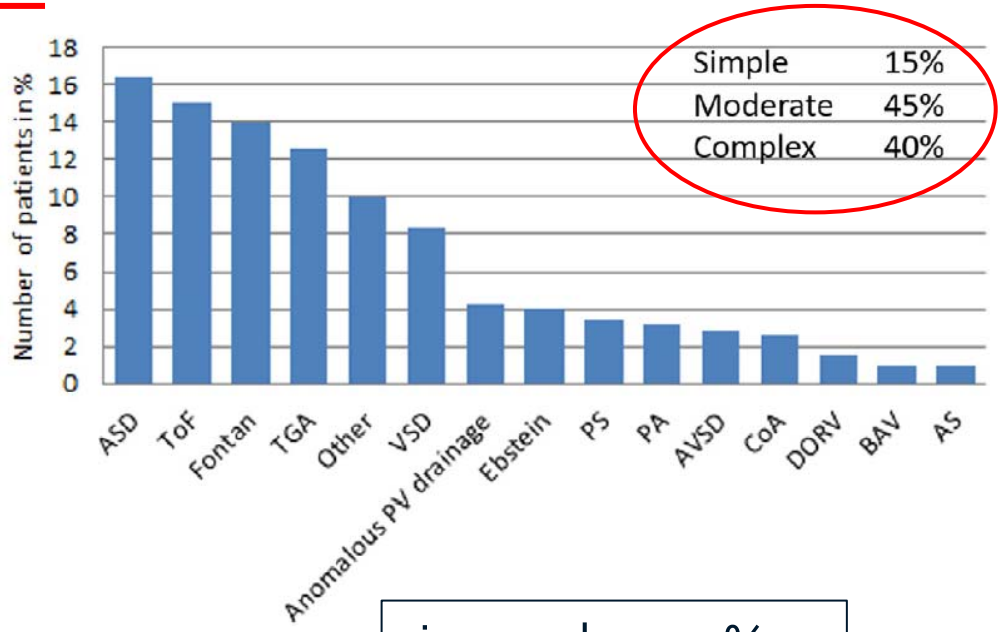
Non-vitamin K antagonist oral anticoagulants (NOACs) for thromboembolic prevention, are they safe in congenital heart disease? Results of a worldwide study☆

H. Yang et al. Internation J Cardiol 2020;299: 123–130

Multicenter prospective study of NOACs in ACHD, 530 patients

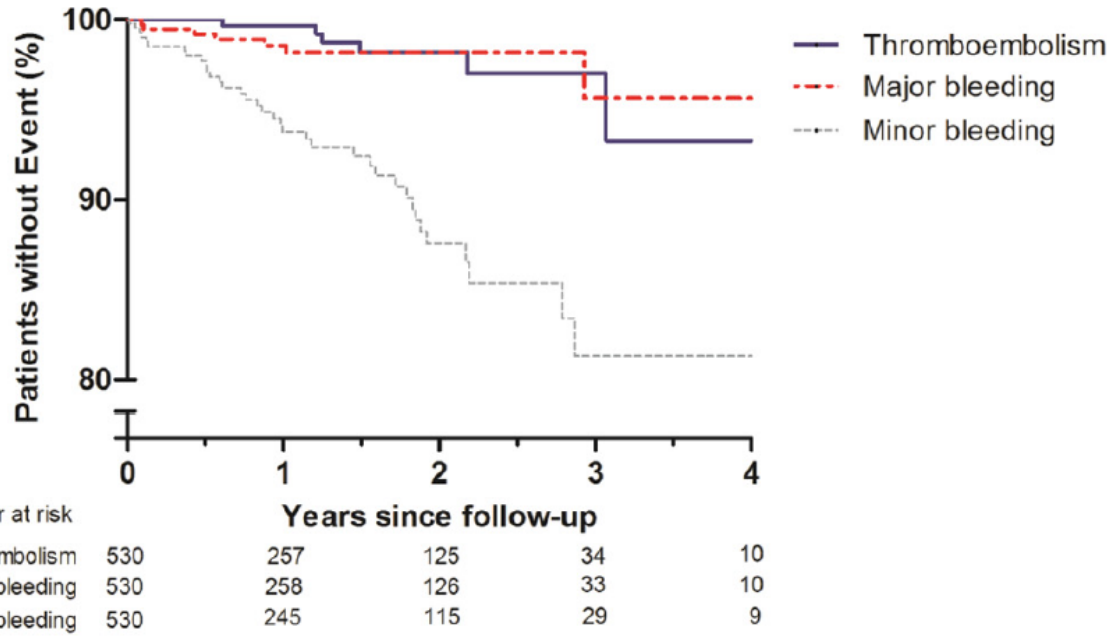
(April 2014 - August 2018)

	All (n = 530)	Previous VKA (n = 150)
Age at inclusion, y	47 SD15	47 SD16
Male, n (%)	289 (55)	74 (49)
Severity of congenital heart defect, n (%)		
Simple	79 (15)	22 (15)
Moderate	239 (45)	58 (39)
Complex	212 (40)	70 (47)
Defect repaired, n (%)	421 (79)	125 (87
Fontan circulation, n (%)	74 (14)	37 (25)
Bioprosthetic valves, n (%)	57 (11)	14 (9)
Significant valvular lesion, n (%)	243 (46)	65 (43)
Median CHA_2DS_2-VASc	1 [1–3]	2 [1–3]
Cardiovascular history, n (%)		
Stroke or TIA	54 (10)	17 (11)
Pulmonary embolism	22 (4)	10 (7)
Deep venous thrombosis	9 (2)	2 (1)
Intracardiac thrombus	11 (2)	4 (3)
Systemic embolism	9 (2)	3 (2)
Myocardial infarction	2 (0.5)	1 (1)
Other type of thrombus	4 (1)	2 (1)
Heart failure*	163 (31)	63 (42)
Hypertension	121 (23)	36 (24)
Diabetes mellitus	49 (9)	14 (9)
Median HASBLED	0 [0–1]	0 [0–1]
History of major bleeding, n (%)	17 (3)	11 (7)

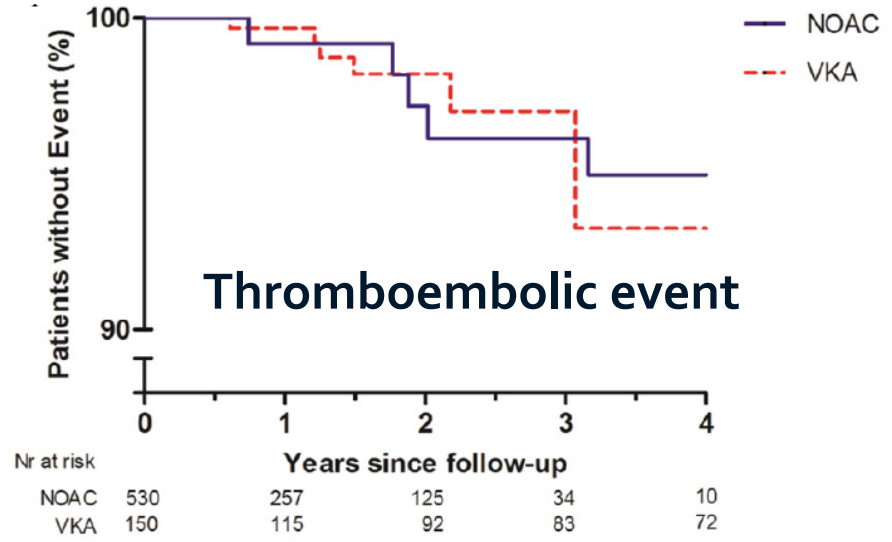


rivaroxaban 43%;
apixaban 39%;
dabigatran 12%;
edoxaban 7%

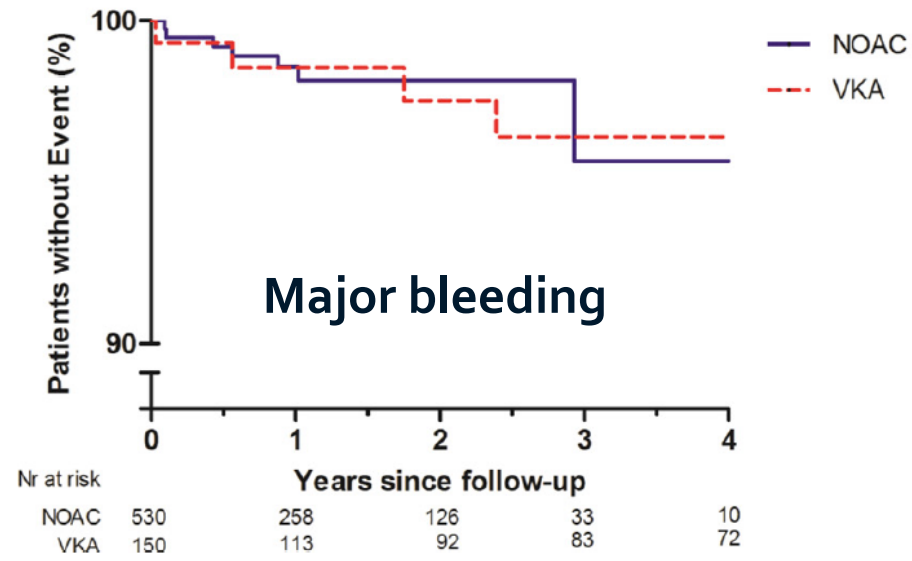
NOAC



Thromboembolic event



Major bleeding



H. Yang et al. International J Cardiol 2020;299: 123–130

Thromboembolism (N=6)

Patient	Age (yr)	Sex	CHD	TE location	NOAC	Indication	CHA_2DS_2-VASc	HASBLED	Bioprosthetic valves	Significant valvular lesions
1	30	♂	Coronary AV fistula	Deep vein thrombosis	Dabigatran	Atrial arrhythmia	3	2	No	TR
2	42	♂	Fontan	Pulmonary embolism	Apixaban	Atrial arrhythmia	0	3	No	No
3	25	♂								
4	44	♂								
5	23	♂								
6	25	♀								

median FU 1.0 year,
thromboembolic event rate , 1.0% (n = 6) per year
major bleeding , 1.1% (n = 7)
minor bleeding, 6.3% (n = 37)

Major bleeding (N= 7)

Patient	Age (yr)	Sex	CHD	Bleeding location	NOAC	Indication	CHA_2DS_2-VASc	HASBLED	Bioprosthetic valves	Significant valvular lesions
1	56	♀	Fontan	GI-bleeding	Apixaban	Atrial arrhythmia	2	1	No	MR
2	71	♀	PAPVC	GI-bleeding	Rivaroxaban	Atrial arrhythmia	3	1	No	TR
3	23	♀	CoA	Menorrhagia	Rivaroxaban	Atrial arrhythmia	2	0	Aortic & pulmonary	No
4	42	♀	Eisenmenger	Menorrhagia	Rivaroxaban	Secondary prevention of pulmonary embolism	3	2	No	No
5	41	♀	Fontan	Menorrhagia	Apixaban	Atrial arrhythmia	4	0	No	MR
6	80	♂	ToF	Hematuria	Apixaban	Atrial arrhythmia	4	1	No	PS
7	67	♀	Fontan	Menorrhagia	Rivaroxaban	Atrial arrhythmia	2	2	No	No

H. Yang et al. Internation J Cardiol 2020;299: 123–130

NOAC in adults Fontan circulation

Yang H, *et al. Open Heart* 2019;6:e000985

NOTE registery, 74 pts with a Fontan op
(mean age 32±10 years (range 18–68), 54% male)
median FU, 1.2 yrs

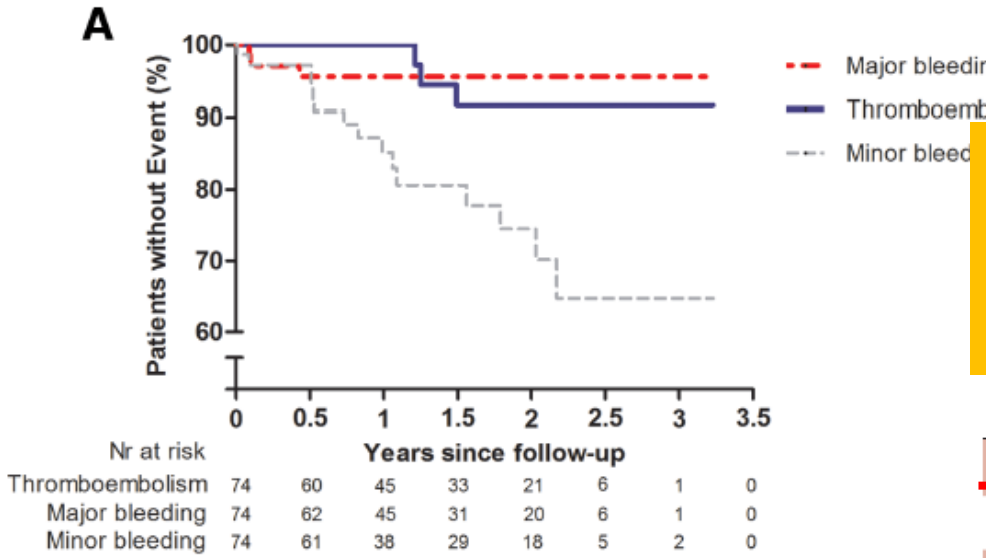
Congenital heart defect, n (%)	
Tricuspid atresia	27 (36)
Pulmonary atresia	10 (14)
Double outlet right ventricle	11 (15)
Double inlet left ventricle	14 (19)
Other anomalies	12 (16)
Type of Fontan, n (%)	
Atriopulmonary	26 (35)
Total cavopulmonary connexion	48 (65)
Previous antithrombotic medication, n (%)	
None	18 (24)
Vitamin K antagonist	37 (50)
Aspirin	19 (26)

Indication for NOAC, n (%)	
Atrial arrhythmias	52 (70)
Primary thrombotic prophylaxis	12 (16)
Secondary thrombotic prophylaxis	10 (14)
Median CHA_2DS_2-VASc	1 (0–2)
Median HASBLED	0 (0–1)
Cardiovascular history, n (%)	
Stroke or transient ischaemic attack (TIA)	8 (11)
Pulmonary embolism	4 (5)
Deep venous thrombosis	1 (1)
Intracardiac thrombosis	7 (9)
Inferior vena cava thrombosis	4 (5)
Superior vena cava thrombosis	1 (1)

anabaptist, n=27; dabigatran, n=7; edoxaban, n=4; rivaroxaban, n=36

Adult Fontan pts using NOACs

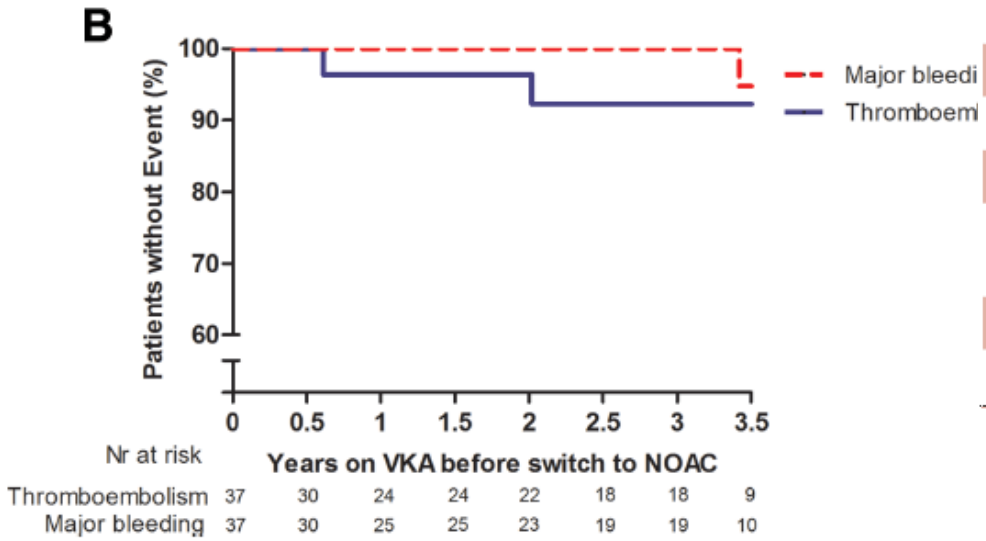
Yang H, et al. Open Heart 2019;6:e000985



median FU duration, 1.2 yrs
Thromboembolic events 3 (4.1%)
Major bleeding, 3 (4.1%)

Type of bleeding, n (%)	All patients (n=74)
Major bleeding	
Total	3
Menorrhagia	2
Gastrointestinal bleeding	1
Minor bleeding	
Total	15
Menorrhagia	6
Skin haematoma	3
Epistaxis	2
Bleeding leading to change in antithrombotic therapy	2
Prolonged bleeding after minor cut	1
Gingival bleeding	1

Adult Fontan pts using VKA during 3.5 yrs previous to NOACs use



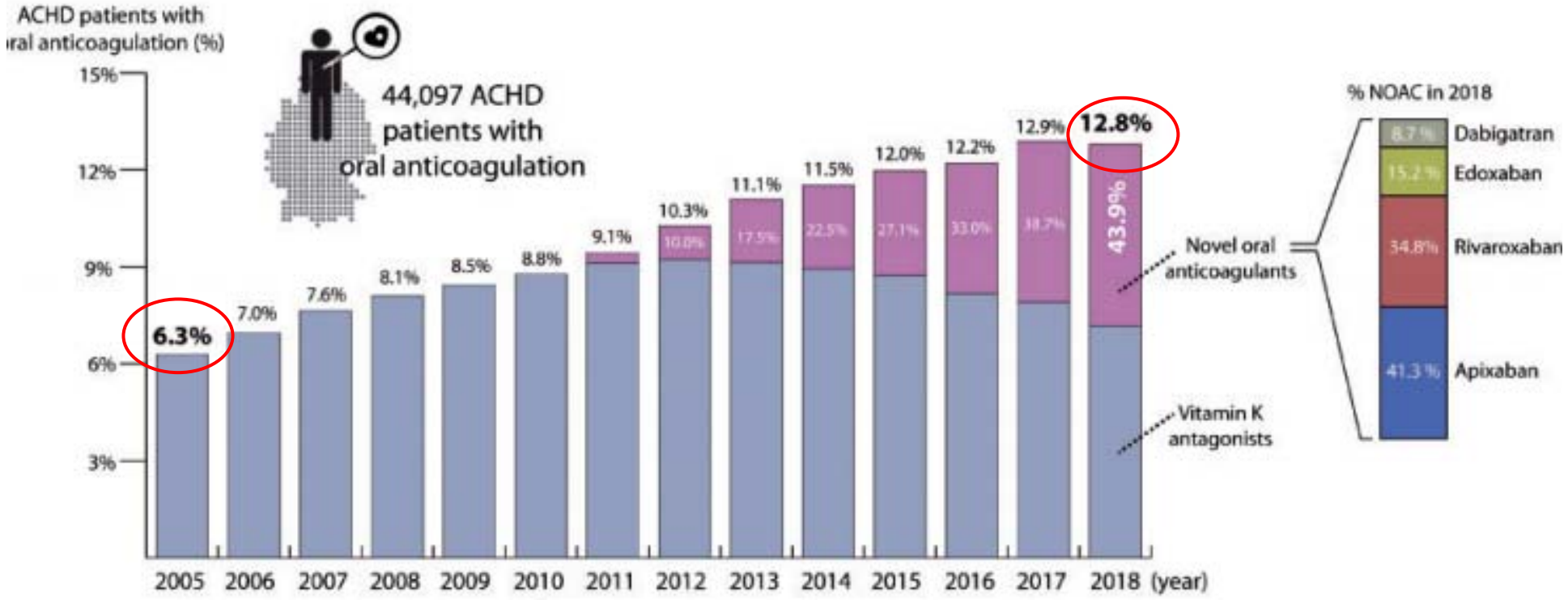
Current use and safety of novel oral anticoagulants in adults with congenital heart disease: results of a nationwide analysis including more than 44 000 patients (2005 – 2018)

Eva Freisinger[1], Joachim Gerß[2], Lena Makowski[1], Ursula Marschall[3], Holger Reinecke [1], Helmut Baumgartner [4], Jeanette Koeppe [2†], and Gerhard-Paul Diller [4,5†*]

European Heart J 2020; 41: 4168–4177

	ACHD cohort (2005–18)	Simple defect group[a]	Moderate complexity group[a]	Complex cardiac defects[a]
Total cohort	*N* = 44 097 (100%)	*N* = 31 129 (70.6%)	*N* = 9456 (21.4%)	*N* = 3512 (8.0%)
median age—years (IQR)	44 (25–66)	45 (24–68)	43 (26–63)	37 (25–62)
Male gender—*n* (%)	16 970 (44.6)	13 776 (44.3)	4274 (45.2)	1620 (46.1)
Oral anticoagulation[b]—*n* (%)	9783 (22.2)	6517 (20.9)	2211 (23.4)	1057 (30.1)
Oral anticoagulation % p.p.y.	9.9 %	8.9 %	10.6 %	14.0 %
	OAC status in 2018: *N* = 5465 ACHD patients			
VKAs	3165 (7.2)	2163 (7.0)	677 (7.2)	325 (9.3)
NOAC	2478 (5.6)	1684 (5.4)	584 (6.2)	210 (6.0)
• Apixaban	1088 (43.9)	716 (42.5)	270 (46.2)	102 (48.6)
• Dabigatran	204 (8.2)	132 (7.8)	54 (9.3)	18 (8.6)
• Edoxaban	402 (16.2)	293 (17.4)	79 (13.5)	30 (14.3)
• Rivaroxaban	895 (36.1)	627 (37.2)	203 (34.8)	65 (31.0)
Additional TAI	463 (8.5)	337 (9.1)	98 (8.0)	27 (5.2)
Additional heparin	869 (15.9)	600 (16.1)	187 (15.3)	82 (15.7)
Any OAC/TAI	5916 (13.4)	4037 (13.0)	1313 (13.9)	566 (16.1)

(2005 – 2018)



European Heart J 2020; 41: 4168–4177

Outcome of VKAs vs. NOACs

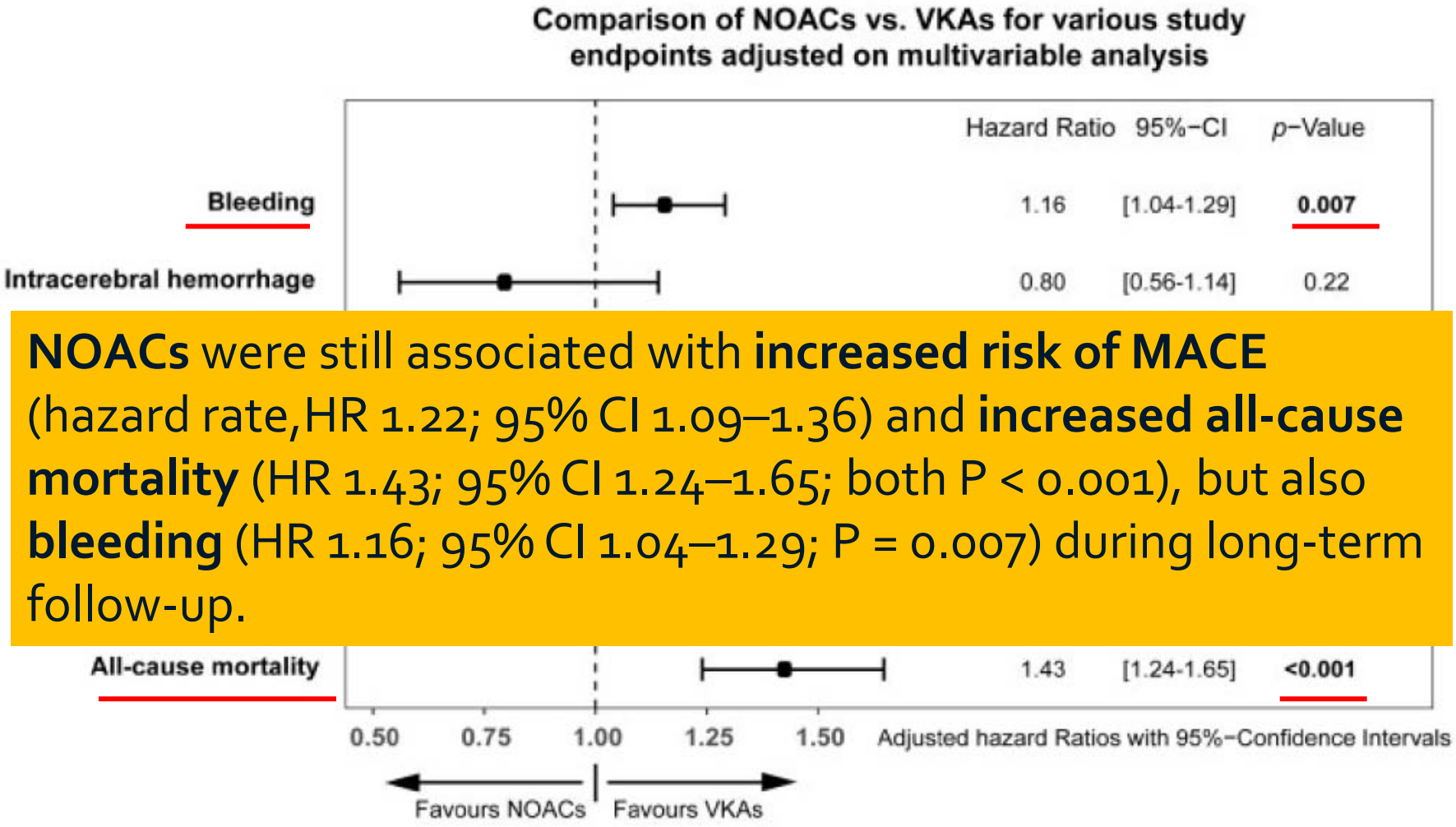
	Entire cohort		Vitamin K antagonists		Novel oral anticoagulants		P-value	
	1-year rate	2-year rate	1-year rate	2-year rate	1-year rate	2-year rate	1 year	2 years
All-cause mortality								
Event rate (95% CI)	3.0% (2.7–3.5)	5.4% (4.8–6.0)	2.8% (2.3–3.2)	5.0% (4.3–5.6)	4.0% (3.1–5.1)	6.8% (5.5–8.2)	**0.013**	**0.006**
Risk difference NOAC—VKA (95%-CI)	-	-	REF	REF	1.24 (0.16–2.32)	1.81 (0.33–3.29)		
Bleeding event								
Event rate (95% CI)	9.5% (8.8–10.2)	15.5% (14.6–16.5)	8.8% (8.0–9.6)	15.2% (14.1–16.3)	11.5% (10.0–13.1)	16.3% (14.5–18.3)	**0.001**	0.105
Risk diffe								
Major-blee								
Event rat								0.217
Risk diffe								
Intracranial								
Event rat								0.879
Risk diffe								
Thromboembolic event								
Event rate (95% CI)	4.6% (4.1–5.1)	7.8% (7.1–8.5)	4.4% (3.8–5.0)	7.3% (6.5–8.1)	5.3% (4.3–6.4)	9.3% (7.8–10.8)	0.148	0.015
Risk difference NOAC—VKA (95% CI)	—	—	REF	REF	0.88 (-0.36–2.12)	1.97 (0.28–3.66)		
Major-thromboembolic event								
Event rate (95% CI)	3.0% (2.6–3.4)	5.1% (4.6–5.7)	2.8% (2.3–3.3)	4.7% (4.1–5.4)	3.7% (2.9–4.7)	6.4% (5.1–7.6)	0.057	**0.016**
Risk difference NOAC—VKA (95% CI)	—	—	REF	REF	0.93 (-0.11–1.97)	1.56 (0.15–2.97)		
Major adverse cardiovascular events								
Event rate (95% CI)	6.5% (5.9–7.1)	11.6% (10.7–12.4)	6.0% (5.4–6.7)	10.8% (9.9–11.8)	7.8% (6.5–9.2)	13.8% (12.1–15.7)	**0.015**	**0.002**
Risk difference NOAC—VKA (95% CI)	—	—	REF	REF	1.74 (0.25–3.23)	2.98 (0.93–5.03)		

NOACs had higher thromboembolic (3.8% vs. 2.8%), MACE (7.8% vs. 6.0%), bleeding rates (11.7% vs. 9.0%), and all-cause mortality (4.0% vs. 2.8%; all P < 0.05) after 1 year of therapy compared with VKAs.

European Heart J 2020; 41: 4168–4177

NOACs vs. VKAs

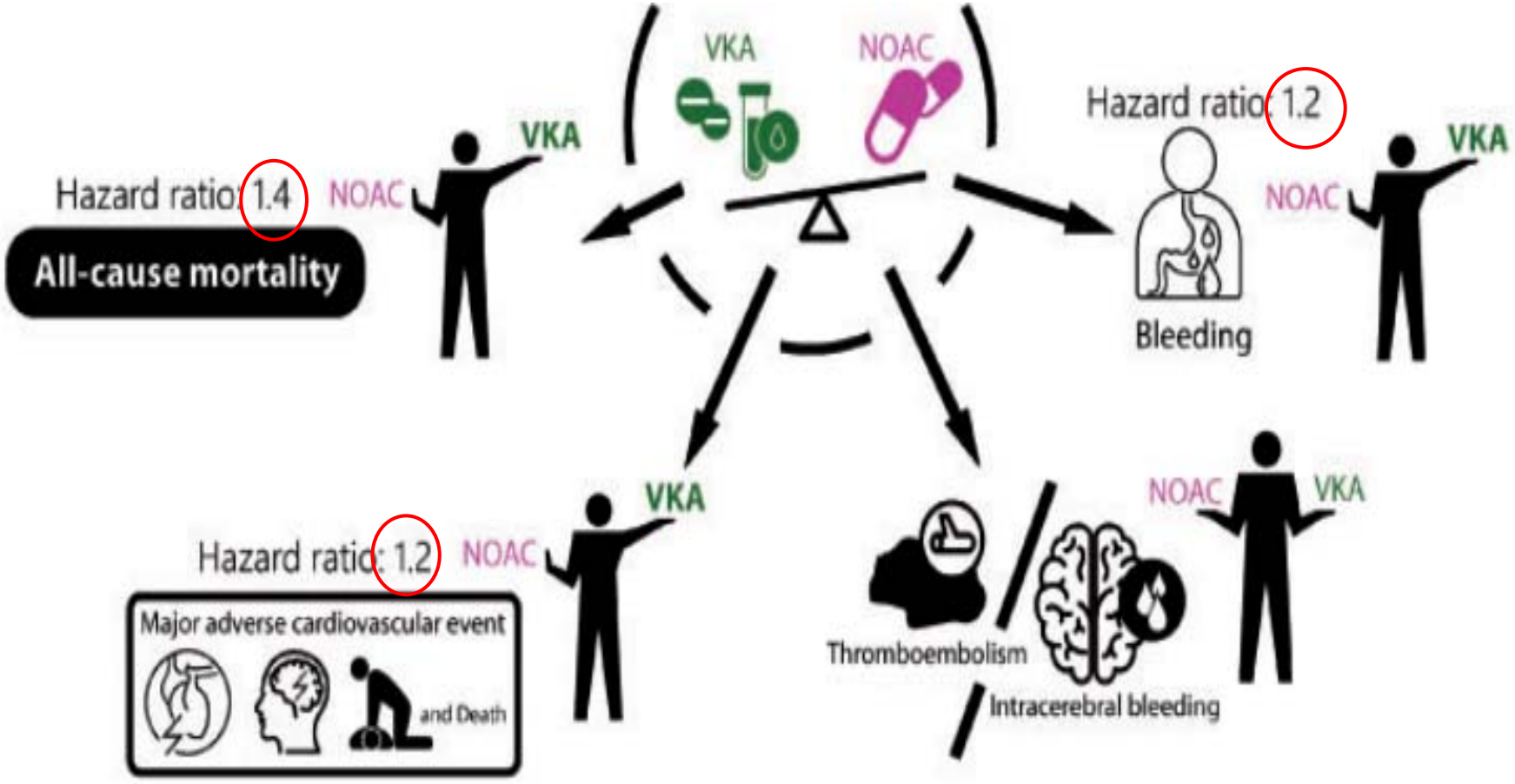
N= 6504, median FU : NOAC, 39 months vs. VKA, 90 months



NOACs were still associated with **increased risk of MACE** (hazard rate,HR 1.22; 95% CI 1.09–1.36) and **increased all-cause mortality** (HR 1.43; 95% CI 1.24–1.65; both P < 0.001), but also **bleeding** (HR 1.16; 95% CI 1.04–1.29; P = 0.007) during long-term follow-up.

European Heart J 2020; 41: 4168–4177

Comparison of adverse outcome and all-cause mortality between NOACs and VKA



European Heart J 2020; 41: 4168–4177

Advantages and disadvantages of NOACs relevant to adults CHD

Canadian J Cardiol 2019; 35:1686e1697

Advantages	Disadvantages
• No dose adjustment required on the basis of frequent monitoring of coagulation parameters • Predictable anticoagulant effect • Fewer food and drug interactions than VKAs • Rapid onset of action • Consistently lower risk of intracranial haemorrhage compared with VKAs	• Precautions and contraindications on the basis of renal function • Higher cost than VKAs • Limited experience and availability of reversal agents • Risk of bleeding • Blood levels more difficult to monitor • Paucity of efficacy and safety data specific to adults with CHD • Contraindicated during pregnancy and breastfeeding

Practical tips for using NOACs relevant to adults with CHD

Canadian J Cardiol 2019; 35:1686e1697

Baseline information to decide on NOAC eligibility

- Knowledge of congenital cardiac anatomy and pathophysiology
- Knowledge of kidney function, age, and weight

*apixaban and edoxaban – best safety in pts with reduced renal fx

*Underweight pts (<60 kg) taking a NOAC – 4 fold higher risk of major bleeding

- Knowledge of comedications (AAD and antiepileptic drugs); d/t drug interactions
- Knowledge of Hx of bleeding, especially GI bleeding (HAS-BLED score)
- Establish that NOAC use is acceptable in light of the underlying CHD; if in doubt, favour VKA

Initiation of treatment

- Baseline blood tests: Hb, RFT, LFT, full coagulation panel

(*Fontan with liver Ds

- Rivaroxaban should not be used in pts with liver dysfunction)

- Choose NOAC and correct dose

Rivaroxaban should be adjusted to Cr clearance.

Edoxaban should be adjusted to body weight and Cr clearance.

Apixaban should be adjusted to serum Cr, age, and BW

- If switching from a VKA:

If INR < 2: start NOAC

If INR 2-2.5: start NOAC the next day

If INR > 2.5: repeat INR in 1-3 days

Follow-up

- Initial FU at 1 month then every 3-6 months

- Assess modifiable risk factors: HT, aspirin use, NSAID use, alcohol intake

- Determine need for blood tests (Hb, renal and liver function, full coagulation panel):

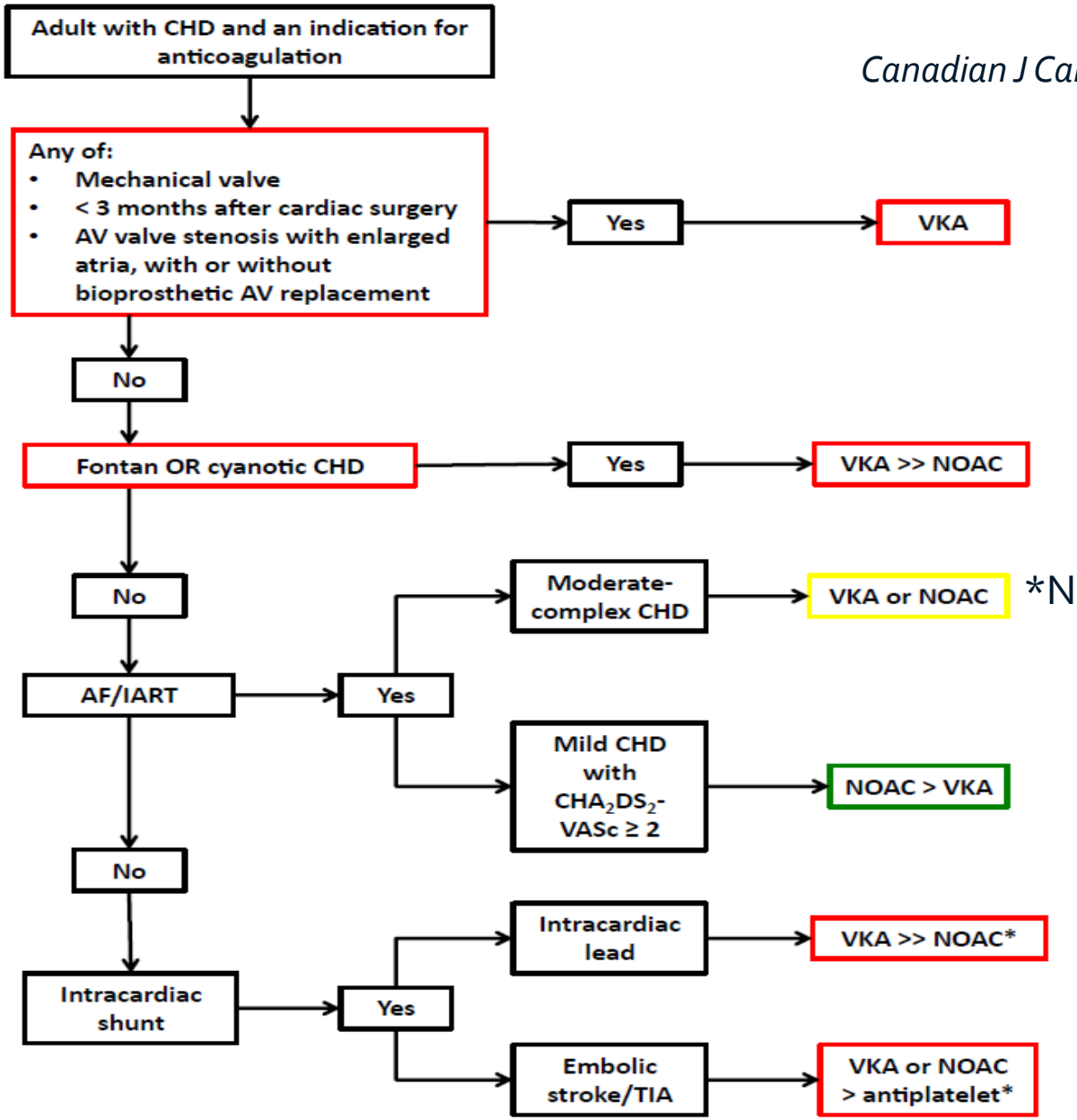
  Yearly for all

  Every 6 months if age older than 75 years or frail pts

  Tailored if decreased renal function

- Bridging generally not recommended if temporary interruption is needed

Suggested choices of antithrombotic medications in adults CHD



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*NOAC used with caution.

Patients who should not be treated with a NOAC

- Mechanical heart valve
- Moderate to severe mitral & tricuspid stenosis
- < 3 months after cardiac op
- Severe renal or hepatic impairment
- Pregnant or breast-feeding women
- Children under 18 years
- Poor adherence

Summary

- NOACs may be safe and effective for thromboembolic prevention in adults with heterogeneous forms of CHD.

- But the efficacy and safey data for NOACs in pts with high risk population (cyanotic CHD and Fontan physiology) are still limited. Larger series with longer follow-up are required.

Thank you for your attention !