신경과진료에서 새로운 경구용 항응고제의 임상적적용

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Practical use of NOAC in neurology practice

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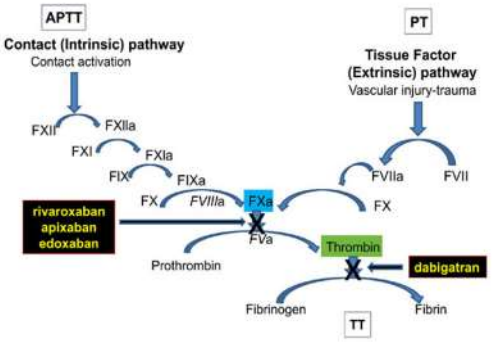
Problems with oral VKA

- Narrow therapeutic range
- Needs regular blood tests for monitoring
- Various drug and food interactions
- Significant risk of bleeding

All bleeding: 10-17% per year
Major bleeding: 2-5% per year
Fatal bleeding: 0.5-1% per year
ICH: 0.2-0.4% per year



Terminology

NOAC
New Oral Anticoagulants
Novel Oral Anticoagulants
Non–Vitamin K–Dependent Direct Oral Anticoagulants

DOAC
Direct-acting Oral Anticoagulants
Direct Oral Anticoagulants

	Dabigatran	Apixaban	Edoxaban *	Rivaroxaban
Action	Direct thrombin inhibitor	Activated factor Xa (FXa) inhibitor	Activated factor Xa (FXa) inhibitor	Activated factor Xa (FXa) inhibitor
Dose	150 mg BID 110 mg BID	5 mg BID 2.5 mg BID	60 mg QD 30 mg QD 15 mg QD	20 mg QD 15 mg QD
Phase III clinical trial	RE-LY [1]	ARISTOTLE [2] AVERROES [3]	ENGAGE-AF [4]	ROCKET-AF [5]

	Xarelto rivaroxaban tablets	Pradaxa dabigatran etexilate	Eliquis apixabantablets	Lixiana edoxaban tablets
administration	QD With food	bid	bid	QD
formulation	tablet	capsule	tablet	tablet
CYP metabolism	extensive	None	extensive	<4%
Renal elimination	35%	80%	25%	50%
Protein binding	92~95%	35%	87%	40~59%
Half life	9~13 hrs	14~17 hrs	8~15 hrs	9~10 hrs
Tmax	2.5~4 hrs	2~3 hrs	3~4 hrs	1~2 hrs
bioavailability	60~100 %	6~7 %	50~60 %	62%
transporter	P-gp/BCRP	P-gp	P-gp/BCRP	P-gp
GI tolerability	No problem	Dyspepsia 5~10%	No problem	No problem

Stroke or systemic embolism

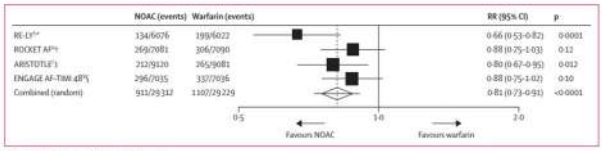
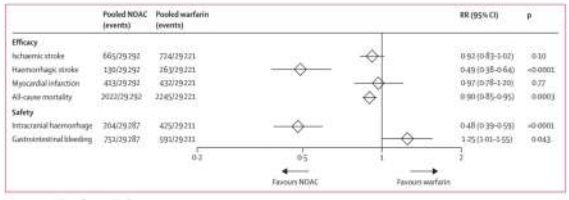


Figure 1: Stroke or systemic embolic events
Data are n/N, unless otherwise indicated. Heterogeneity: I^2=47%; p=0·13. NOAC=new oral anticoagulant. RR=risk ratio. *Dabigatran 150 mg twice daily. †Rivaroxaban 20 mg once daily. ‡Apixaban 5 mg twice daily. §Edoxaban 60 mg once daily.

Meta-analysis of randomised trials.Lancet 2014; 383: 955–62

Secondary efficacy and safety outcomes



Meta-analysis of randomised trials. Lancet 2014; 383: 955–62

Major bleeding

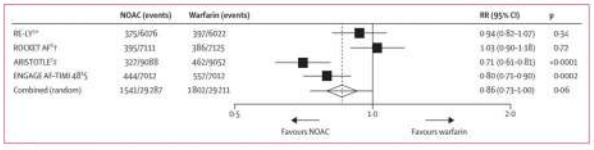
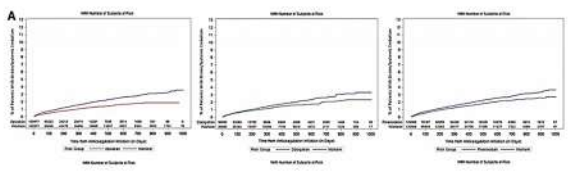


Figure 2: Major bleeding
Data are n/N, unless otherwise indicated. Heterogeneity: I^2=83%; p<0·001. NOAC=new oral anticoagulant. RR=risk ratio. *Dabigatran 150 mg twice daily. †Rivaroxaban 20 mg once daily. ‡Apixaban 5 mg twice daily. §Edoxaban 60 mg once daily.

Meta-analysis of randomised trials.Lancet 2014; 383: 955–62

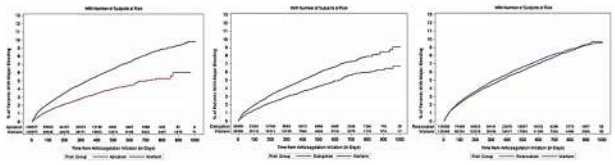
NOAC vs. Warfarin

Stroke/Systemic embolism



Observational Pooled Analysis with 434, 046 patients.
Stroke. 2018;49:2933

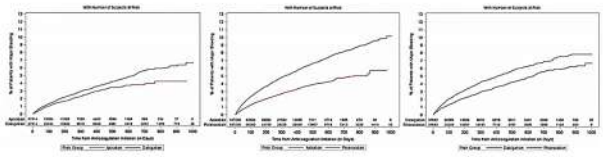
NOAC vs. Warfarin
Major Bleeding



Apixaban | Dabigatran | Rivaroxaban

Observational Pooled Analysis with 434, 046 patients.
Stroke. 2018;49:2933

NOAC vs. NOAC
Stroke/Systemic embolism



Apixaban vs. Dabigatran | Apixaban vs. Rivaroxaban | Dabigatran vs. Rivaroxaban

Observational Pooled Analysis with 434, 046 patients.
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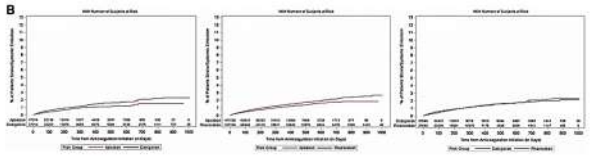
NOAC vs. NOAC
Stroke/Systemic embolism



Apixaban vs. Dabigatran | Apixaban vs. Rivaroxaban | Dabigatran vs. Rivaroxaban

Observational Pooled Analysis with 434, 046 patients.
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Indication for use

- Stroke prevention in non-valvular atrial fibrillation
- Treatment of DVT and PE
- Prevention of recurrent DVT and PE
- Prevention of thromboembolism after total hip replacement

European Heart Journal
doi:10.1093/eurheartj/ehw210

ESC GUIDELINES

2016 ESC Guidelines for the management of atrial fibrillation developed in collaboration with EACTS

The Task Force for the management of atrial fibrillation of the European Society of Cardiology (ESC)

Developed with the special contribution of the European Heart Rhythm Association (EHRA) of the ESC

Endorsed by the European Stroke Organisation (ESO)

Kirchhof P, et al. 2016 ESC Guidelines for the management of AF. EHJ doi:10.1093/eurheartj/ehw210

NOACs – The New Standard of Care

Recommendations	Class[a]	Level[b]
When oral anticoagulation is initiated in a patient with AF who is eligible for a NOAC (apixaban, dabigatran, edoxaban, or rivaroxaban), a NOAC is recommended in preference to a Vitamin K antagonist.	I	A
Antiplatelet monotherapy is not recommended for stroke prevention in AF patients, regardless of stroke risk.	III (harm)	A

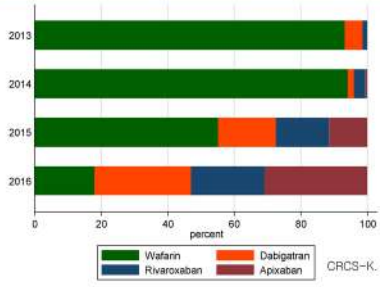
Kirchhof P, et al. 2016 ESC Guidelines for the management of AF. EHJ doi:10.1093/eurheartj/ehw210

Current US guidelines

- For patients with AF and an elevated CHA2 DS2 -VASc score of 2 or greater in men or 3 or greater in women, oral anticoagulants are recommended. (Class I, LOE A)
- ***NOACs (dabigatran, rivaroxaban, apixaban, and edoxaban) are recommended over warfarin*** in NOAC-eligible patients with AF (except with moderate-to-severe mitral stenosis or a mechanical heart valve) (Class I, LOE A)

Circulation. 2019;140:e125–e151

Also a new standard of care in Korea



CRCS-K. Unpublished data

심평원 급여 기준

- NVAF
  - TIA, ischemic stroke, or thromboembolism
  - >=75 years
  - 2 out of 6 risk factors (CHF, HTN, DM, Vascular disease, 65-74, Woman)
- Prevention of DVT or PE
  - Provoked: Upto 6 months
  - Idiopathic: indefinite (2019.2)
- Hip or Knee replacement

Table 1 Valvular indications and contraindications for NOAC therapy in AF patients

	Eligible	Contra-indicated
Mechanical prosthetic valve		✓
Moderate to severe mitral stenosis (usually of rheumatic origin)		✓
Mild to moderate other native valvular disease	✓	
Severe aortic stenosis	✓ Limited data. Most will undergo intervention	
Bioprosthetic valve[a]	✓ (except for the first 3 months post-operatively)	
Mitral valve repair[a]	✓ (except for the first 3–6 months post-operatively)	
PTAV and TAVI	✓ (but no prospective data; may require combination with single or double antiplatelets: consider bleeding risk)	
Hypertrophic cardiomyopathy	✓ (but no prospective data)	

PTAV, percutaneous transluminal aortic valvuloplasty; TAVI, transcatheter aortic valve implantation.
[a]American guidelines do not recommend NOAC in patients with biological heart valves or after valve repair.[9]

Initiation of anticoagulation

- Establish indication for anticoagulation
- Baseline blood works
  - Hemoglobin, renal and liver function, coagulation panel
- Choose anticoagulant and correct dose
- Decide on need for proton pump inhibitor

Checklist during follow-up

- Adherence
- Thromboembolism
- Bleeding
- Co-medications
- Blood sampling
  - Yearly: patients other than below
  - 6-monthly >= 75 years
  - X-monthly. If renal function CrCl <_60 mL/min: recheck interval = CrCl/10
- Assess for optimal NOAC and correct dosing

Renal Excretion Rates of NOACs

NOACs 신장 배설률[1-4] (대사되지 않은 모약물로서, %)

Rivaroxaban[1,a]	Apixaban[2]	Edoxaban[3]	Dabigatran[4,b]
33%	27%	50%	85%

Please note this information is based on the respective prescribing information of products and it is not intended as a head to head comparison. Therefore it should be carefully interpreted.

[a]Of the administered rivaroxaban dose, approximately two-thirds undergoes metabolic degradation, one-third is eliminated renally and one-third is eliminated by the faecal route. The remaining one-third of the administered dose of rivaroxaban is excreted directly from the kidneys as unchanged active substance in the urine, mainly by active renal secretion.
[b]Renal clearance of dabigatran is 85% of total clearance after intravenous administration.

1. Xarelto® (rivaroxaban). Summary of Product Characteristics, as approved by the European Commission. Available at: http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/000944/WC500050770.pdf, accessed on Mar 2018. 2. Eliquis® (apixaban). Product Monograph. Available at: https://pdf.hres.ca/dpd_pm/00044989.PDF, accessed on Mar 2018. 3. SAVAYSA® (edoxaban). Prescribing Information. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2015/206316lbl.pdf accessed on Jan 2018. 4. Pradaxa® (dabigatran). Prescribing Information. Available at http://docs.boehringer-ingelheim.com/Prescribing%20Information/Pradaxa/Pradaxa.pdf accessed on Jan 2018.

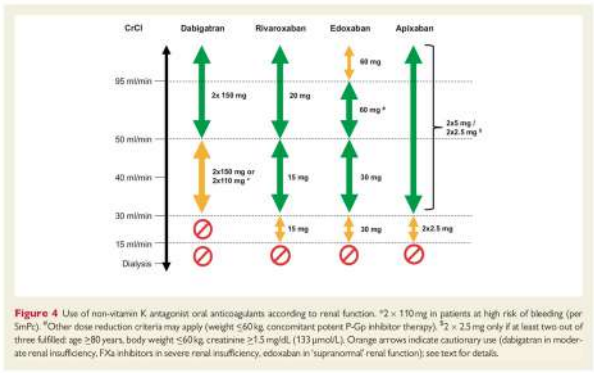
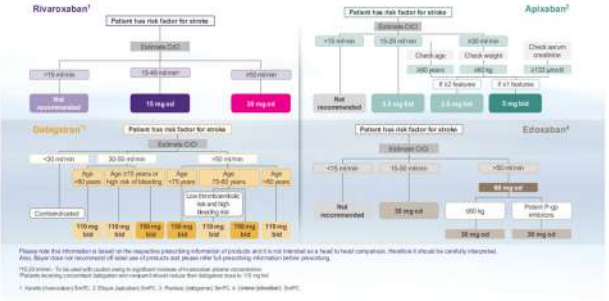


Figure 4 Use of non-vitamin K antagonist oral anticoagulants according to renal function. *2 × 110 mg in patients at high risk of bleeding (per SmPc). #Other dose reduction criteria may apply (weight ≤60 kg, concomitant potent P-Gp inhibitor therapy). ‡2 × 2.5 mg only if at least two out of three fulfilled: age ≥80 years, body weight ≤60 kg, creatinine ≥1.5 mg/dL (133 µmol/L). Orange arrows indicate cautionary use (dabigatran in moderate renal insufficiency, FXa inhibitors in severe renal insufficiency, edoxaban in 'supranormal' renal function); see text for details.

Creatinine Clearance calculation

- The Cockcroft–Gault method
- CrCl = (140 – age) × weight (in kg) × [0.85 if female]/72 × serum creatinine (in mg/dL)

NOAC Dosing Guide



Possible drug-drug interactions – Effect on NOAC plasma levels part 1

		Dabigatran	Apixaban	Edoxaban	Rivaroxaban
Atorvastatin	P-gp/ CYP3A4	↑18%		no effect	no effect
Digoxin	P-gp	no effect		no effect	no effect
Verapamil	P-gp/ wk CYP3A4	↑12–180%		↑ 53% (slow release)	
Diltiazem	P-gp/ wk CYP3A4	no effect	↑40%		
Quinidine	P-gp	↑50%		↑80%	↑50%
Amiodarone	P-gp	↑12–60%		no effect	
Dronedarone	P-gp/CYP3A4	↑70–100%			
Ketoconazole; itraconazole; voriconazole; posaconazole;	P-gp and BCRP/ CYP3A4	↑140–150%	↑100%		up to ↑180%

Red – contraindicated; orange – reduce dose; yellow – consider dose reduction if another yellow factor present; hatching – no data available; recommendation made from pharmacokinetic considerations

Possible drug-drug interactions – Effect on NOAC plasma levels part 2

	Interaction	Dabigatran	Apixaban	Edoxaban	Rivaroxaban
Fluconazole	CYP3A4	no data	no data	no data	↑42%
Cyclosporin; tacrolimus	P-gp	no data	no data	no data	↑50%
Clarithromycin; erythromycin	P-gp/ CYP3A4	↑15–20%	no data	no data	↑30–54%
HIV protease inhibitors	P-gp and BCRP/ CYP3A4	no data	strong increase	no data	up to ↑153%
Rifampicin; St John's wort; carbamezepine; phenytoin; phenobarbital	P-gp and BCRP/ CYP3A4/CYP2J2	↓66%	↓54%	↓35%	up to ↓50%
Antacids	GI absorption	↓12-30%	no data	no effect	no effect

Red – contraindicated; orange – reduce dose; yellow – consider dose reduction if another yellow factor present; hatching – no data available; recommendation made from pharmacokinetic considerations

Switching between anticoagulant regimens

VKA to NOAC	INR <2.0: immediate INR 2.0–2.5: immediate or next day INR >2.5: use INR and VKA half-life to estimate time to INR <2.5
Parenteral anticoagulant to NOAC: Intravenous unfractioned heparin (UFH) Low molecular weight heparin (LMWH)	Start once UFH discontinued (t½=2h). May be longer in patients with renal impairment Start when next dose would have been given
NOAC to VKA	Administer concomitantly until INR in appropriate range Measure INR just before next intake of NOAC Re-test 24h after last dose of NOAC Monitor INR in first month until stable values (2.0–3.0) achieved
NOAC to parenteral anticoagulant	Initiate when next dose of NOAC is due
NOAC to NOAC	Initiate when next dose is due except where higher plasma concentrations expected (e.g. renal impairment)
Aspirin or clodipogrel to NOAC	Switch immediately, unless combination therapy needed

www.escardio.org/EHRA

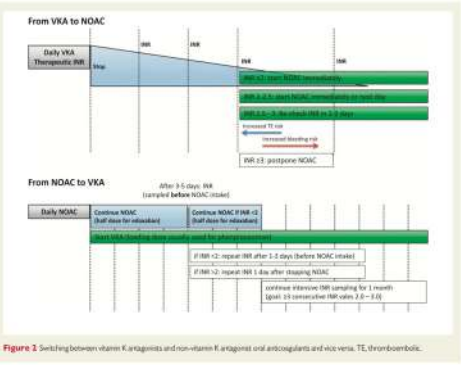
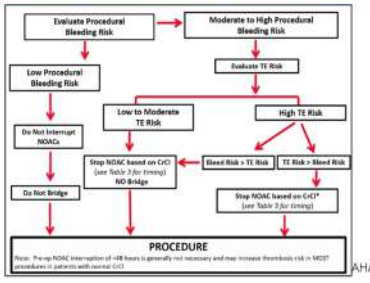


Figure 1 Switching between vitamin K antagonists and non-vitamin K antagonist oral anticoagulants and vice versa. TE, thromboembolic.

Periprocedural management



AHA statement. Circulation. 2017:135

Bleeding Risk Classification

- Minor
  - Dental
    - Implant positioning
  - Cataract or glaucoma
  - Endoscopy wo biopsy
  - Superficial surgery
- Low
  - Endoscopy w biopsy
  - Prostate or bladder biopsy
  - Cardiac catheterization
- High
  - Cardiovascular surgery
  - Intra-abdominal/Pelvic surgery
  - Major orthopedic surgery
  - Neurosurgery

AHA statement. Circulation. 2017:135

Peri-procedural Thromboembolic Risk

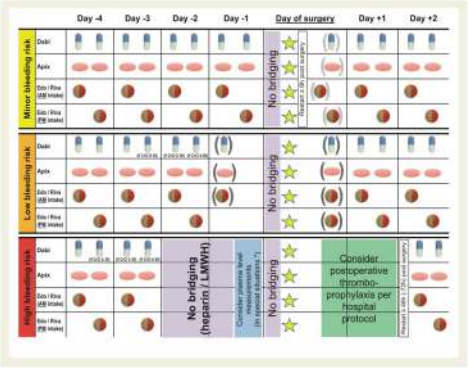
- Low
  - CHA_2DS_2VASc <=1
  - No Stroke/TIA, VTE within 3 months
  - Heterozygous Factor V Leiden
  - Heterozygous PT gene mutation
- High
  - CHA_2DS_2VASc > 2
  - Stroke/TIA, VTE within 3 months
  - Protein C or S deficiency
  - Antithrombin deficiency
  - Antiphopholipid syndrome

AHA statement. Circulation. 2017:135

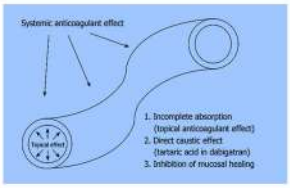
Table 11 Timing of last non-vitamin K antagonist oral anticoagulant intake before start of an elective intervention

	Dabigatran		Apixaban – Edoxaban – Rivaroxaban	
	No important bleeding risk and/or adequate local haemostasis possible: perform at trough level (i.e. 12 h or 24 h after last intake)			
	Low risk	High risk	Low risk	High risk
CrCl ≥80 mL/min	≥24 h	≥48 h	≥24 h	≥48 h
CrCl 50–79 mL/min	≥36 h	≥72 h	≥24 h	≥48 h
CrCl 30–49 mL/min	≥48 h	≥96 h	≥24 h	≥48 h
CrCl 15–29 mL/min	Not indicated	Not indicated	≥36 h	≥48 h
CrCl <15 mL/min	No official indication for use			
No bridging with LMWH/UFH				
Resume full dose of NOAC ≥24 h post-low bleeding risk interventions and 48 (–72) h post-high-bleeding risk interventions (see also Figure 8)				
Patients undergoing a planned intervention should receive a written note indicating the anticipated date and time of their intervention, and the date and time of the last intake of their NOAC (and any other medication)				

Low risk: with a low frequency of bleeding and/or minor impact of a bleeding; high risk: with a high frequency of bleeding and/or important clinical impact. See also Table 12.
CrCl, creatinine clearance; LMWH, low molecular weight heparin; UFH, unfractionated heparin.



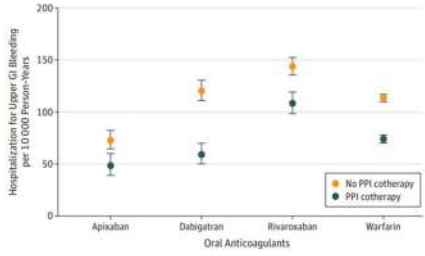
NOAC and GI Bleeding



- Risk factors
  - Dabigatran, rivaroxaban
  - Concomitant ulcerogenic drugs
    - ASA, NSAID, steroid
  - Older age
  - Renal impairment
  - H.pyroli infection

World J Gastroenterol 2017 March 21

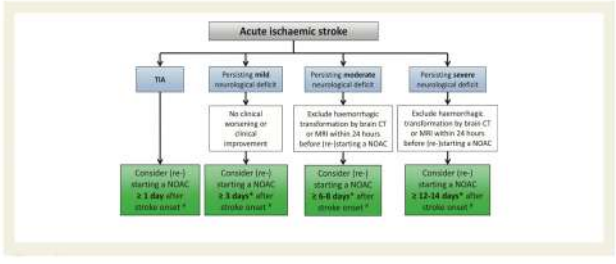
Figure 1. Adjusted Incidence of Hospitalization for Upper Gastrointestinal (GI) Tract Bleeding by Individual Oral Anticoagulants[a]

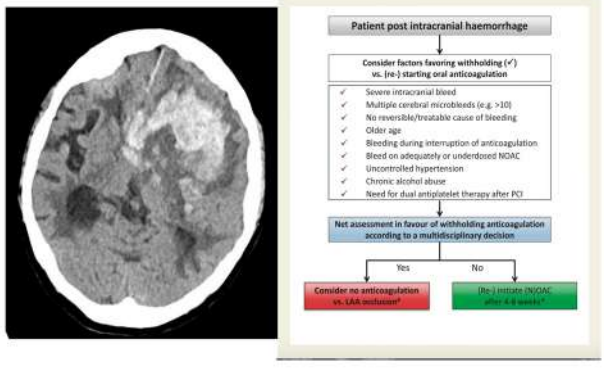


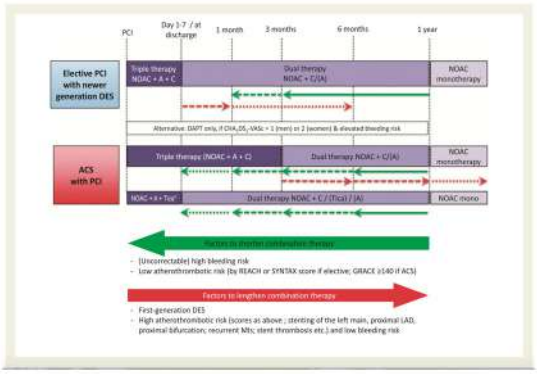
JAMA. 2018;320(21):2221-2230

Clinical Challenges

- Patients with atrial fibrillation
  - Acute stroke setting
  - Concomitant atherosclerotic cardiovascular disease
  - Carotid or intracranial stenting
  - Following Intracerebral hemorrhage
  - Frail patients (CKD, hepatic dysfunction, low body weight..)
  - Cost
- Cancer-associated thromboembolism
- Antiphospholipid syndrome

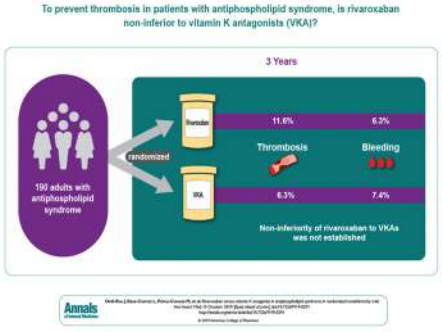


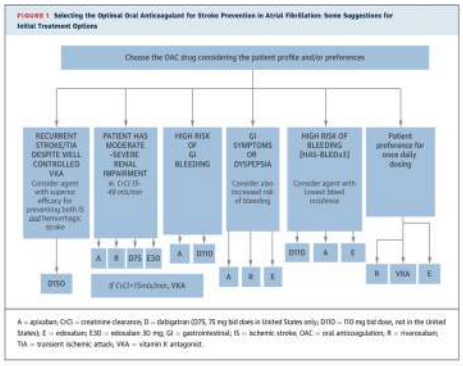




Atrial fibrillation and Malignancy

- Choose anticoagulant
  - Current standard of care: VKA/(LMWH).
  - NOACs: Available data scarce, but encouraging
  - Consider patient preference (VKA vs. NOAC)
- Protect the patient
  - Gastric protection (PPI/H2 blockers)
  - Beware of drug–drug interactions
  - Dose reduction/treatment interruption (if platelets <50k, renal dysfunction, bleeding, . . .)





Summary

- NOAC became a new standard care in preventing stroke in patients with AF.
- Type and dose of NOAC can be selected according to patient's characteristics and renal function.
- Risk of both thromboembolism and bleeding should be assessed in patients undergoing surgical procedures.
- Risk of GIB is increased with use of certain NOACs, and it might be ameliorated with concomitant administration of H2B or PPI.