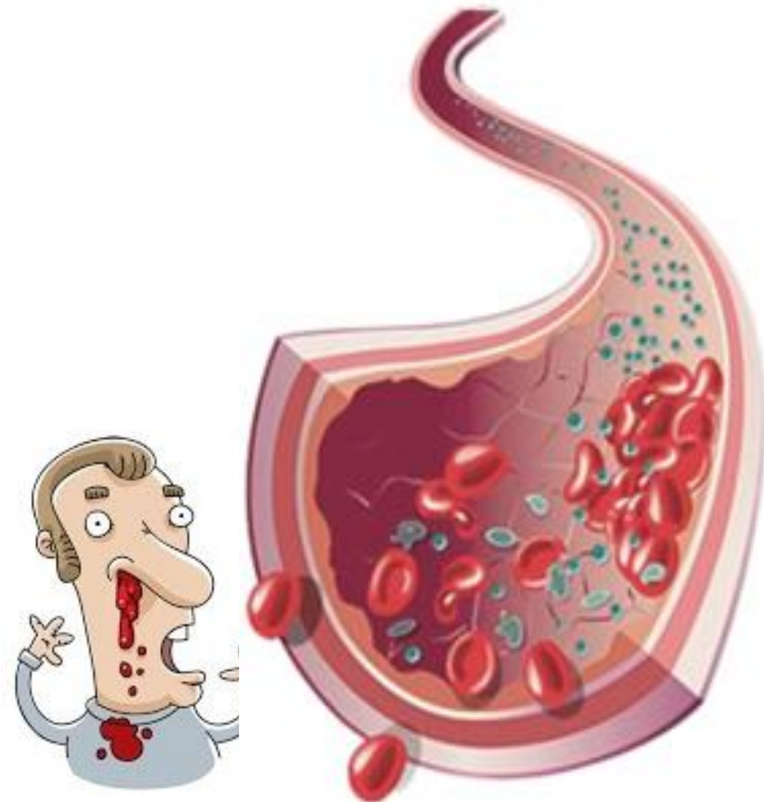


DOACs

Pharmacist-Managed Anticoagulation Clinic

臺北榮總 藥學部 黃詩惠藥師
2018.11.08

What Is the Role of DOACs in Anticoagulation Clinic?

Warfarin

Target INR

DOACs

10 Choices

- Dabigatran 75/110/150 mg
- Rivaroxaban 10/15/20 mg
- Apixaban 2.5/5 mg
- Edoxaban 30/60 mg

Service Points

- Choosing the most appropriate drug and dose
- Periprocedural management
- Adherence

- Choosing the most appropriate drug and dose
- Periprocedural management
- Adherence

1. Choosing the most appropriate drug and dose – (1)

● Clinical trials of DOACs for AF

DOAC vs VKA HR (95% CI)	RE-LY[a] (dabigatran 110 mg/150 mg)	ROCKET AF (rivaroxaban 20 mg)	ARISTOTLE (apixaban 5 mg)	ENGAGE AF-TIMI 48 (edoxaban 30 mg/60 mg)
Ischemic stroke	1.11 (0.89-1.40)[a] 0.76 (0.60-0.98)[a] *p*=0.03	0.94 (0.75-1.17)	0.92 (0.74-1.13)	1.41 (1.19-1.67) *p*<0.001 1.00 (0.83-1.19)
Systemic embolism	Not reported	0.23 (0.09-0.61) *p*=0.003	0.87 (0.44-1.75)	1.24 (0.72-2.15) 0.65 (0.34-1.24)
Hemorrhagic stroke	0.31 (0.17-0.56) *p*<.0001 0.26 (0.14-0.49) *p*<0.001	0.59 (0.37-0.93) *p*=0.024	0.51 (0.35-0.75) *p*<0.001	0.33 (0.22-0.50) *p*<0.001 0.54 (0.38-0.77) *p*<0.001
Major bleed	0.80 (0.69-0.93) *p*=0.003 0.93 (0.81-1.07) *p*=0.3	1.04 (0.90-1.20)	0.69 (0.60-0.80) *p*<0.001	0.47 (0.41-0.55) *p*<0.001 0.80 (0.71-0.91) *p*<0.001
Intracranial bleed	0.31 (0.20-0.47) *p*<0.001 0.40 (0.27-0.60) *p*<0.001	0.67 (0.47-0.93) *p*=0.02	0.42 (0.30-0.58) *p*<0.001	0.30 (0.21-0.43) *p*<0.001 0.47 (0.34-0.63) *p*<0.001
Gastrointestinal bleed	1.10 (0.86-1.41) 1.15 (1.19-1.89) *p*<0.001	3.2 vs 2.2[b] *p*<0.001	0.89 (0.70-1.15)	0.67 (0.53-0.83) *p*<0.001 1.23 (1.02-1.50) *p*=0.03
All-cause mortality	0.91 (0.80-1.03) 0.88 (0.77-1.00) *p=0.051*	0.85 (0.70-1.02)	0.89 (0.80-0.98) *p*=0.047	0.87 (0.79-0.96) *p*=0.006 0.92 (0.83-1.01)
Cardiovascular mortality	0.90 (0.77-1.06)[a] 0.85 (0.72-0.99)[a] *p*=0.04	0.89 (0.73-1.10)	0.89 (0.76-1.04)	0.85 (0.76-0.96) *p*=0.008 0.86 (0.77-0.97) *p*=0.013

[a] RE-LY reported relative risk instead of hazard ratio (HR); ischemic or uncertain stroke instead ischemic stroke, and vascular mortality instead cardiovascular mortality

[b] Incidence/year (%), HR not reported

1) Ann Hematol. 2016;95:437-49. 2) Expert Rev Hematol. 2017;10:1005-22.

1. Choosing the most appropriate drug and dose – (2)

- **Thromboembolism/bleeding risk**

Thrombo-embolic risk	Bleeding risk	Recommendation	Avoid
High	Low	First choice Dabigatran 150 mg Alternative Apixaban, edoxaban 60 mg, rivaroxaban, dabigatran 110 mg	Edoxaban 30 mg
Low	High	First choice Edoxaban 30 mg, apixaban Alternative Edoxaban 60 mg, dabigatran 110 mg	Dabigatran 150 mg, rivaroxaban
Moderate	Moderate	First choice Apixaban, edoxaban 60 mg, dabigatran 110 mg Alternative Rivaroxaban, dabigatran 150 mg	Edoxaban 30 mg
High	High	First choice Apixaban Alternative Rivaroxaban, edoxaban 60 mg, dabigatran 150 mg	Edoxaban 30 mg

1) Ann Hematol. 2016;95:437-49. 2) Eur Heart J. 2018;39:1330-93.

1. Choosing the most appropriate drug and dose – (3)

- **Medical concern**
  - Mechanical prosthetic valve; moderate to severe mitral stenosis
  - CAD
  - Hyperthyroidism
  - Malignancy
- **ADR management**
  - GI bleeding: Xa inhibitors are preferred to dabigatrain for patients with the prior episodes of lower gastrointestinal bleeding
- **Compliance**
  - Once daily: rivaroxaban or edoxaban is preferred
- **DDI**
  - Dronedarone: Avoid dabigatran and rivaroxaban; consider dose adjustment for concomitant edoxaban
  - Verapamil: Consider dose adjustment for concomitant dabigatran
  - Clarithromycin/Erythromycin: Consider dose adjustment for concomitant edoxaban
  - Itraconazole/Ketoconazole/Voriconazole: Avoid dabkgatran, apixaban, and rivaroxaban; consoder dose adjustment for edoxaban
- **Others: Renal function, age, body weight, and etc.**

1) Ann Hematol. 2016;95:437-49. 2) Eur Heart J. 2018;39:1330-93.

2. Periprocedural management

- Renal function
- Surgical factors
- Age
- History of bleeding complication
- Thromboembolic risk
- Concomitant medication
  - Antiplatelet

Eur Heart J. 2018;39:1330-93.

3. Adherence

- Patient education
  - Why they need to take a DOAC
  - General ADR management
  - Maximum hold days of DOACs for surgery
- Follow up / phone follow up

Case Sharing

Clinical Situation 1

3/28 OPD
Initial use

Subjective

- 63 y/o male has past history of AF, CAD, s/p CABG on 2018/3/7, HTN, and DM
- He was transferred to our OPD due to initial use of a DOAC

Objective

- Crea 0.80 mg/dl; Ccr 104.4 ml/min
- T. Bil 0.43 mg/dl; ALT 26 U/L; AST 18 U/L
- $CHADS_2$-VASc 3 (HTN, DM, CAD)
- HAS-BLED 1 (significant DOACs interacting)
- SAMe-TT_2R_2 3 (non white, HTN+DM+CAD)

Current medication

- Rivaroxaban tab 10 mg 1# QDCC (CV)
- Amiodarone tab 200 mg 1# BID (CV)
- Clopidogrel tab 75 mg 1# QD (CVS)
- Aspirin tab 100 mg 1# QDCC (CVS)

Assessment

- **Evaluate DDI between rivaroxaban and dual antiplatelet**

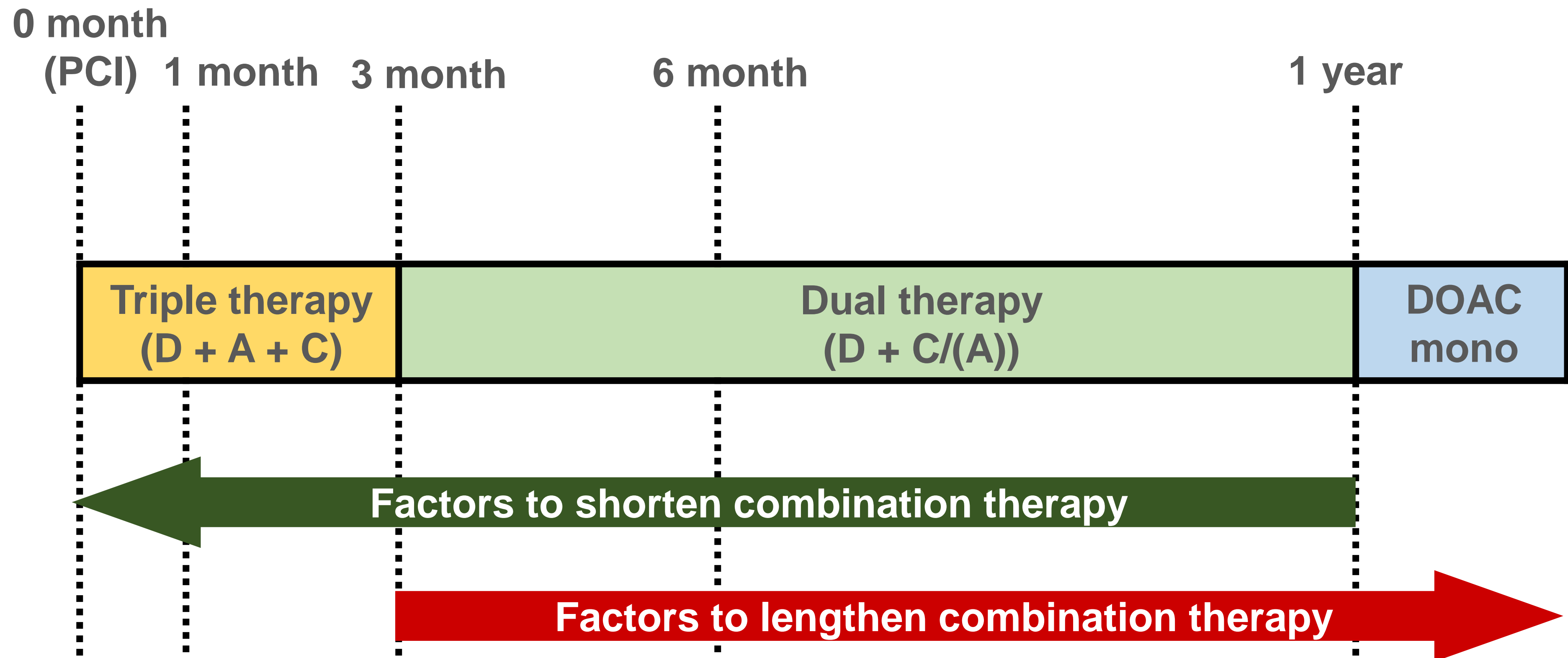
Dose Adjustment of DOACs for Combination Therapy

1. Rivaroxaban **PIONEER AF-PCI**
   - Rivaroxaban 10-15 mg QD + Clopidogrel
   - Rivaroxaban 2.5 mg BID + Clopidogrel + Aspirin
   - Warfarin + Clopidogrel + Aspirin
2. Dabigatran **RE-DUAL PCI**
   - Dabigatran 110/150 mg BID + Clopidogrel/Ticagrelor
   - Warfarin + Clopidogrel + Asipirin
3. Apixaban (Ongoing) **AUGUSTUS trial**
   - Apixaban 2.5-5 mg BID + P2Y12 inhibitor + Aspirin
   - Apixaban 2.5-5 mg BID + P2Y12 inhibitor
   - Warfarin + P2Y12 inhibitor + Aspirin
   - Warfarin + P2Y12 inhibitor
4. Edoxban (Ongoing) **ENTRUST AF-PCI**
   - Edoxaban 60 mg QD + P2Y12 inhibitor
   - Warfarin + Clopidogrel + Asipirin

1) N Engl J Med. 2016 Dec 22;375(25):2423-2434. 2) N Engl J Med 2017;377:1513–24. 3) Am Heart J. 2018 Jun;200:17-23. 4) Am Heart J. 2018 Feb;196:105-112.

Duration of Combination Therapy

- **Recent ACS Developing New-Onset AF**



Abbreviation:
ACS: acute coronary syndrome; mono: monotherapy; D: DOACs, C: clopidogrel; A: aspirin

Eur Heart J. 2018;39:1330-93.

Plan

- **Agree with rivaroxaban 10 mg qdcc for triple therapy**
- **Please consider to hold aspirin if bleeding signs is noted**

Clinical Situation 2

- **Subjective**
  - The patient had nasal bleeding on the first day of triple therapy
  - Hold aspirin after discussion with pharmacy counseling
  - No further bleeding signs after holding aspirin
- **Objective**
  - $CHADS_2$-VASc 3 (HTN, DM, CAD)
  - HAS-BLED 1 (significant DOACs interacting)
  - SAMe-TT_2R_2 3 (non white, HTN+DM+CAD)
- **Current medication**
  - Rivaroxaban tab 10 mg 1# QDCC (CV)
  - Amiodarone tab 200 mg 1# BID (CV)
  - Clopidogrel tab 75 mg 1# QD (CVS)
  - Aspirin tab 100 mg 1# QDCC (CVS) ← DC on 4/2

Assessment

- ADR management

Plan

- Encourage patient to keep current medication

Clinical Situation 3

- **Subjective**
  - 63 y/o male has past history of AF, CAD, s/p CABG on 2018/3/7, HTN, and DM
  - The patient intended to perform colonoscopy on 2018/11/20
- **Objective**
  - Crea 0.80 mg/dl; Ccr 104.4 ml/min
  - $CHADS_2$-VASc 3 (HTN, DM, CAD)
  - HAS-BLED 1 (significant DOACs interacting)
  - SAMe-TT_2R_2 3 (non white, HTN+DM+CAD)
- **Current medication**
  - Rivaroxaban tab 10 mg 1# QDCC (CV)
  - Amiodarone tab 200 mg 1# BID (CV)
  - Clopidogrel tab 75 mg 1# QD (CVS) ← DC on 10/8
  - Aspirin tab 100 mg 1# QDCC (CVS) ← DC on 4/2

Assessment

- **Evaluate perioperative management for colonoscopy**

Time to Interrupt DOACs from Last Dose

Table 3. Last intake of drug before elective surgical intervention				
	Dabigatran		Rivaroxaban, apixaban, edoxaban	
	∗No important bleeding risk: perform at trough level			
Ccr (ml/min)	**Low risk**	**High risk**	**Low risk**	**High risk**
≥ 80	≥ 24 h	≥ 48 h	≥ 24 h	≥ 48 h
50-80	≥ 36 h	≥ 72 h	≥ 24 h	≥ 48 h
30-50	≥ 48 h	≥ 96 h	≥ 24 h	≥ 48 h
15-30			≥ 36 h	≥ 48 h
< 15				

Eur Heart J. 2018;39:1330-93.

Bleeding Risk of Elective Surgical Interventions

Minor Bleeding Risk	Low Bleeding Risk	High Bleeding Risk
• Dental intervention – Extraction of 1-3 teeth – Paradontal surgery – Abscess incision – Implant positioning • Ocular intervention – Cataract – Glaucoma • Endoscopy without biopsy or resection • Superficial surgery – Abscess incision – Dermatologic excisions	• Endoscopy with biopsy • Prostate or bladder biopsy • Electrophysiological study or catheter ablation (except complex procedures) • Non-coronary angiography • Pacemaker or ICD implantation	• Complex endoscopy – Polypectomy – ERCP with sphincterotomy • Spinal or epidural anaesthesia; lumbar diagnostic puncture • Thoracic surgery • Abdominal surgery • Major orthopaedic surgery • Liver or renal biospy • Transurethral prostate resection • Extracorporeal shockwave lithotripsy (ESWL)

Eur Heart J. 2018;39:1330-93.

Stopping and Re-Initiation of DOACs

		Day -4	Day -3	Day -2	Day -1	Day of surgery	Day +1	Day +2
Minor bleeding risk	Dabi					No bridging; Restart ≥ 6h post surgery		
	Apix							
	Edo / Riva (AM intake)							
	Edo / Riva (PM intake)							
Low bleeding risk	Dabi		(if CrCl ≥ 30)	(if CrCl ≥ 50) (if CrCl ≥ 80)		No bridging		
	Apix							
	Edo / Riva (AM intake)							
	Edo / Riva (PM intake)							
High bleeding risk	Dabi	(if CrCl ≥ 30)	(if CrCl ≥ 50) (if CrCl ≥ 80)	No bridging (heparin / LMWH)	Consider plasma level measurements (in special situations *)	No bridging	Consider postoperative thrombo-prophylaxis per hospital protocol	Restart ≥ 48h (-72h) post surgery
	Apix							
	Edo / Riva (AM intake)							
	Edo / Riva (PM intake)							

Eur Heart J. 2018;39:1330-93.

Plan

- Suggest to hold rivaroxaban for 2 days and resume it after colonoscopy on 2018/11/20 (confirmed with Dr. Chang)
- Follow up actual hold days at the next appointment on 2018/12/05
- Remind physician that dual antiplatelet therapy has been discontinued by CVS

- **What is the appropriate regimen in AF undergoing PCI for Asian?**
- **After dual antiplatelet therapy was discontinued, should we titrate the dose of DOACs?**