Saudi Society of Clinical Pharmacy
الجمعية السعودية للصيدلة الإكلينيكية

الهيئة السعودية للتخصصات الصحية
Saudi Commission for Health Specialties

DIRECT ORAL ANTICOAGULANTS (DOACs) CLINICAL PATHWAY

Table of Content

ACS	Acute coronary syndrome	**PCC**	Factor IX complex, made up of clotting factors II, IX, and X
AF	Atrial fibrillation	**SE**	Systemic embolism
APS	Antiphospholipid syndrome	**TT**	Thrombin time
ESRD	End stage renal disease	**NG**	Nasogastric
FXa	Factor Xa	**GT**	Gastrostomy
OAC's	Oral anticoagulants	**PCC**	Factor IX complex, made up of clotting factors II, IX, and X
P-gp	P-glycoprotein	**SE**	Systemic embolism
VTE	Venous thromboembolism	**TT**	Thrombin time
CYP	Cytochrome P450		

Disclaimer: The following recommendations should be used as a clinical guidance and does not override the clinical judgment of healthcare professionals. The provided recommendations were made based on the best available evidence and are subject to change.

1. *Introduction:*

1.1. AHFS Therapeutic Classes:

- Rivaroxaban; Apixaban; Edoxaban: 20:12.04.14 Direct Factor Xa Inhibitors
- Dabigatran: 20:12.04.12 Direct Thrombin Inhibitors

1.2. Targeted Audience: Physicians in primary, secondary and tertiary care hospitals, clinical pharmacists, and nurses

1.3. Inclusion Criteria:

- Adult patients ≥18 years
- Without valvular atrial fibrillation (AF) (i.e. AF with moderate-to-severe mitral stenosis and/or mechanical heart valve)

1.4. Exclusion Criteria:

- Pediatric patients <18 years
- Patients with valvular AF
- Patients with antiphospholipid syndrome
- *Patients with active cancer*

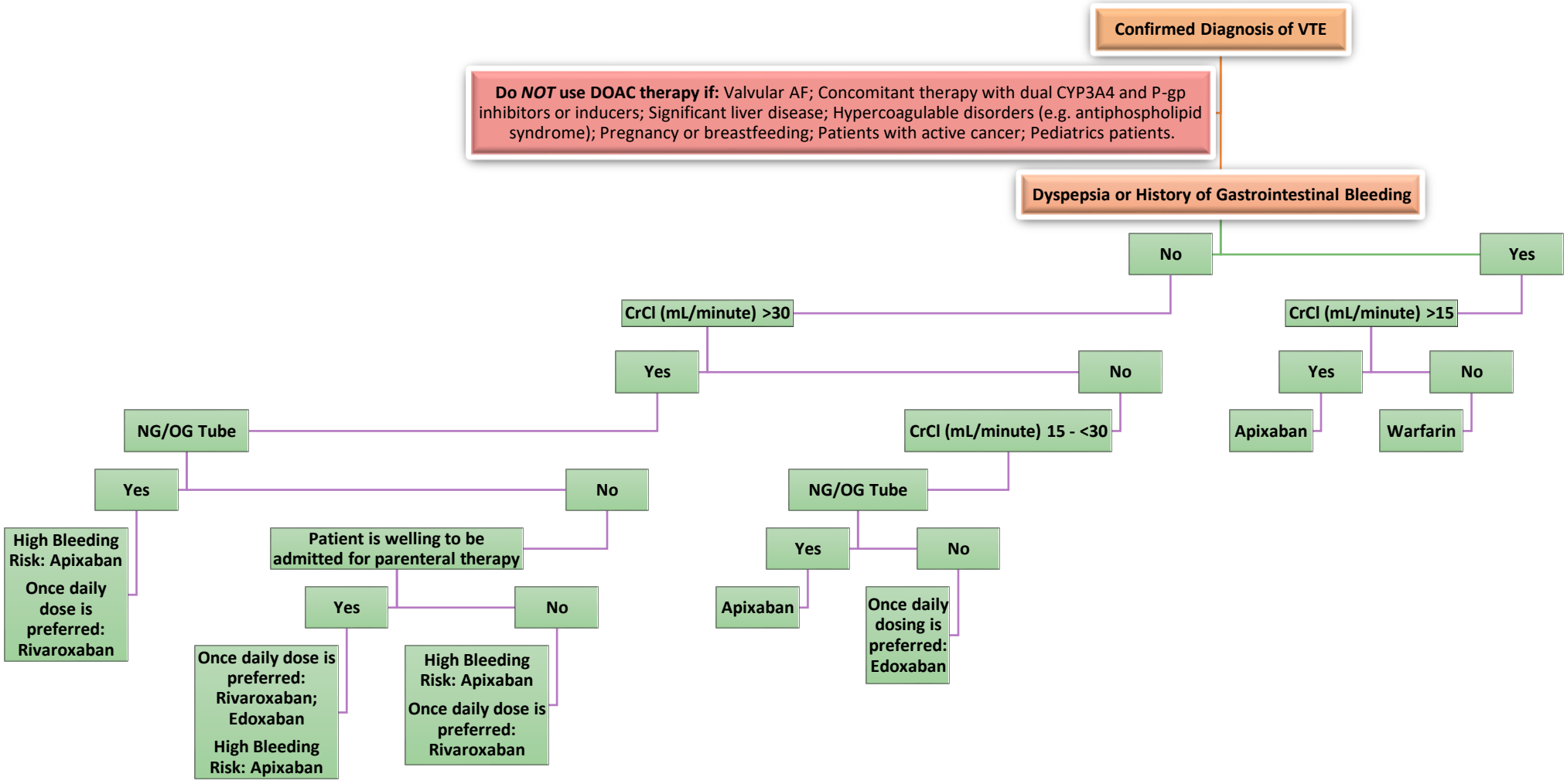
2. *Direct Oral Anticoagulants (DOACs) Approved Indications and Dosing in Normal Renal and Hepatic Functions*

Indication	Rivaroxaban	Apixaban	Edoxaban [h]	Dabigatran
Nonvalvular atrial fibrillation [a]	20 mg daily	5 mg twice daily [g]	60 mg daily	150 mg twice daily
Treatment of venous thromboembolism (VTE) [b]	15 twice daily for 21 days; then 20 mg daily	10 mg twice daily; then 5 mg twice daily	≤60 kg: 30 mg daily [i] >60 Kg: 60 mg daily [i]	150 mg twice daily [i]
Indefinite anticoagulation [c]	10 mg daily			
Coronary artery disease (stable) or peripheral artery disease [d]	2.5 mg twice daily			
Venous thromboembolism prophylaxis in acutely ill medical patients	10 mg daily for 31 to 39 days [f]			
Venous thromboembolism prophylaxis in total hip or knee arthroplasty [e]	10 mg daily	2.5 twice daily		220 mg daily [j]

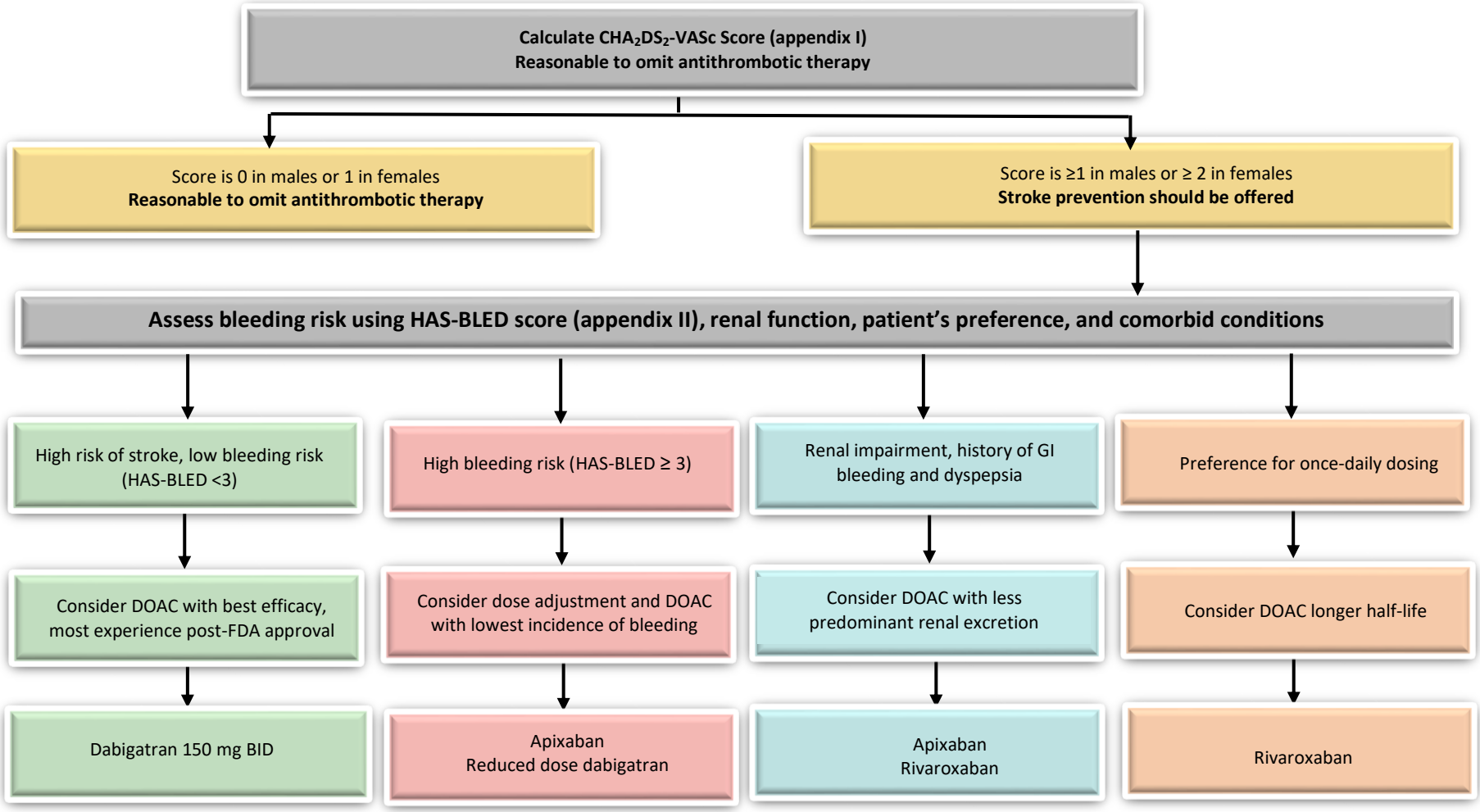
Approved
Unapproved

[a] To reduce the risk of stroke and systemic embolism in patients with atrial fibrillation without moderate-to-severe mitral stenosis and/or mechanical heart valve.
[b] Deep vein thrombosis and/or pulmonary embolism to reduce risk of VTE following initiation of therapy.
[c] Reduced intensity dosing against venous thromboembolism recurrence. For patients at elevated risk of recurrent VTE following 6 months or more of therapeutic anticoagulation. This is not recommended if indefinite full anticoagulant therapy is indicated.
[d] In selected patients with high risk of cardiovascular events and low risk of bleeding if therapeutic anticoagulation or dual antiplatelet therapy is not required for another indication.
[e] Initiated ≥6 to 10 hours after surgery or when hemostasis established. For 10 to 14 days a for total knee arthroplasty and for 35 days for total hip arthroplasty.
[f] Including hospitalization and post-discharge.
[g] Reduce to 2.5 mg twice daily if age ≥80 years ***and*** body weight ≤60 kg.
[h] Do not use if CrCl > 95 mL/minute (Cockcroft-Gault equation).
[i] After at least 5 days of initial therapy with a parenteral anticoagulant, transition to edoxaban or dabigatran in hemodynamically stable patients.
[j] 110 mg given 1 to 4 hours after completion of surgery and establishment of hemostasis or when dabigatran is not initiated on day of surgery, give an initial dose of 220 mg after hemostasis has been achieved; then continue maintenance dose of 220 mg once daily. For 10 to 14 days a for total knee arthroplasty and for 35 days for total hip arthroplasty.

3. *Use of DOACs in Venous Thromboembolism (VTE) Clinical Pathway*



4. *Use of DOACs in Non-Valvular Atrial Fibrillation Clinical Pathway*



For dosing, please refer to table 1, 5.1 or 5.2
Source: *J Thorac Dis* 2015;7:115-31

5. *DOACs Dosing in Special Population*

5.1 In Renal Impairment (As determined by Cockcroft-Gault equation)*

<table>
<tr><th>CrCl (mL/minute)</th><th colspan="2">Rivaroxaban</th><th>Apixaban [b]</th><th>Edoxaban</th><th colspan="2">Dabigatran</th></tr>
<tr><td>>95</td><td colspan="2" rowspan="2"></td><td rowspan="4"></td><td></td><td colspan="2" rowspan="2"></td></tr>
<tr><td>>50</td><td></td></tr>
<tr><td>30 to 50</td><td rowspan="2">AF: 15 mg daily</td><td>VTE [a]</td><td rowspan="2">30 mg daily</td></tr>
<tr><td>15 to <30</td><td>VTE [a]</td><td>AF: 75 mg twice daily</td><td>VTE</td></tr>
<tr><td><15</td><td colspan="2" rowspan="2"></td><td></td><td rowspan="2"></td><td colspan="2" rowspan="2"></td></tr>
<tr><td>ESRD</td><td>2.5 to 5 mg twice daily</td></tr>
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No dosage adjustment
Dosage adjustment is needed
Avoid use
Limited data available

* Creatinine Clearance= {((l 40–age) x weight)/(72xSCr)}x 0.85 (if female)
[a] Contraindicated for VTE treatment, reduced intensity for VTE recurrence, or prophylaxis for medically ill patients or after total hip or knee arthroplasty.
[b] Reduce apixaban dose to 2.5 twice daily in patients with atrial fibrillation if serum creatinine ≥1.5 mg/dL (133 micromol/L) ***and*** either ≥80 years ***or*** body weight ≤60 kg.

5.2 In Hepatic Impairment (Based on Child- Pugh Score for Classification of Hepatic Impairment; Appendix III)

Child- Pugh Score	Rivaroxaban	Apixaban	Edoxaban	Dabigatran
A				
B				
C				

No dosage adjustment

Use with caution

Contradicted

6. DOACs Major Drug Interactions

Agent	Drug Interaction	Effect of DOAC	Recommendations
Dabigatran	P-gp inhibitors	Increase in Concentration	Reduce dose or avoid depending on renal function
	P-gp inducers	Significant reduction in concentration	Avoid use
	Antacids	Moderate reduction in concentration	No dose adjustments required; consider spacing regiments by 2 h
Apixaban	Strong CYP3A4 inhibitor + P-gp inhibitor	Significant increase in concentration	Reduce dose or avoid use
	Moderate CYP3A4 inhibitor + P-gp inhibitor	Moderate increase in concentration	No dose adjustments required; use with caution Avoid use in patient with severe renal insufficiency
	Strong CYP3A4 inducer or P-gp inducer	Significant reduction concentration	Avoid use
Rivaroxaban	Strong CYP3A4 inhibitor + P-gp inhibitor	Significant increase in concentration	Avoid use
	Moderate CYP3A4 inhibitor + P-gp inhibitor	Moderate increase in concentration	No precaution necessary Avoid use in patient with severe renal insufficiency
	Strong CYP3A4 inducer or P-gp inducer	Significant reduction concentration	Avoid use
Edoxaban	P-gp inhibitors	Increase in concentration	AF: Do not reduce dose VTE treatment: Reduce dose
	P-gp inducers	Significant reduction in concentration	Avoid use with rifampin
Drug Interaction Examples			
Strong CYP3A4 inhibitors + combined P-gp inhibitor		Itraconazole, ketoconazole, ritonavir	
Moderate CYP3A4 inhibitors + combined P-gp inhibitor		Clarithromycin, diltiazem	
Strong CYP3A4 inducer + combined P-gp inducer		Carbamazepine, rifampin, St. John's wort	
Strong CYP3A4 inducers		Phenytoin	
P-gp inhibitors		Amiodarone, clarithromycin, cyclosporine, dronedarone, erythromycin ivacaftor, ketoconazole, nifedipine, quinidine, ranolazine, ticagrelor, tolvaptan, verapamil	
P-gp inducers		Rifampin	

Source: American Heart Association, Inc.

7. *Monitoring Parameters for DOACs*

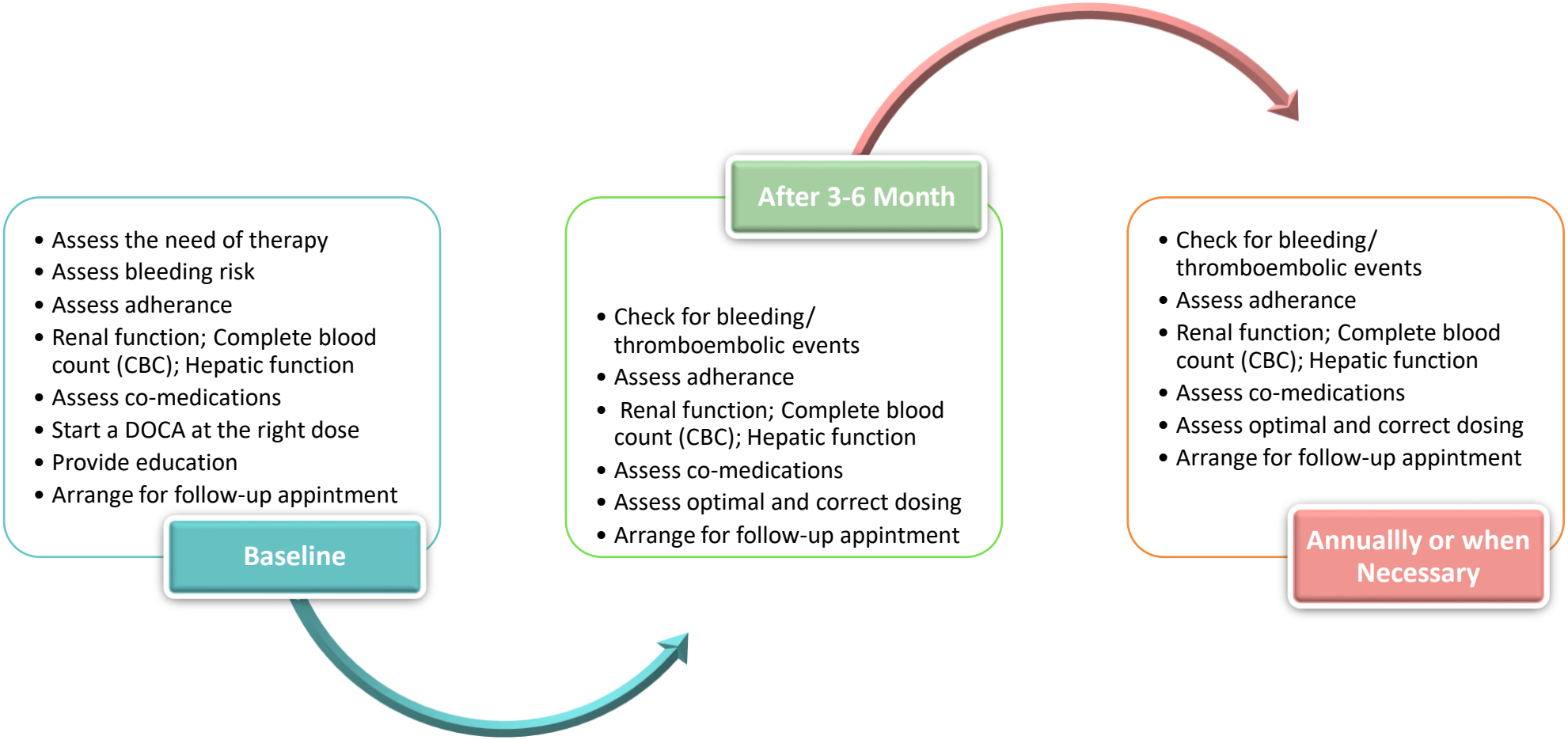
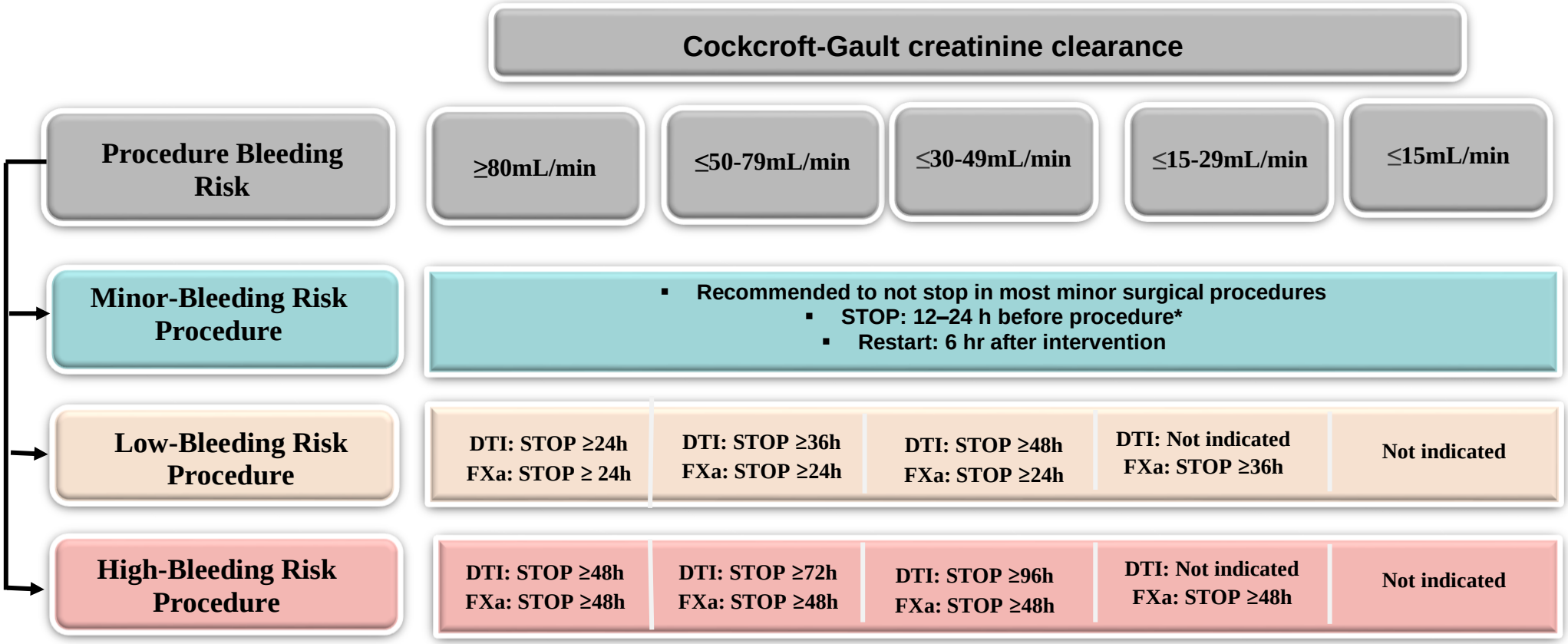


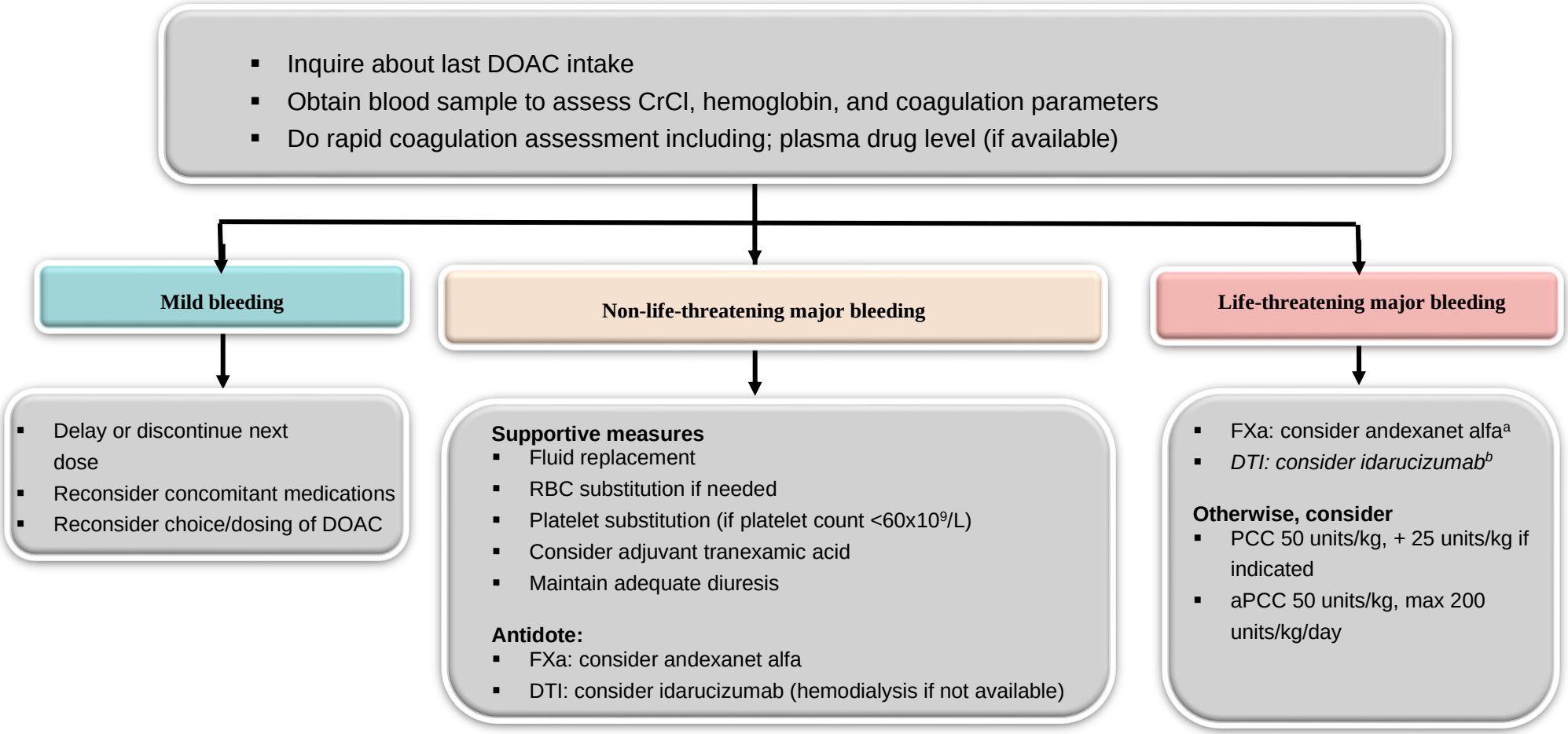
Figure 1. *Direct Oral Anticoagulants (DOACs) Monitoring Parameters*

8. *Perioperative Management of DOACs Clinical Pathway*



- Minor-bleeding-risk interventions: dental, cataract, glaucoma, endoscopy without biopsy or resection, superficial surgery;
- Low-bleeding-risk interventions: endoscopy with biopsy, prostate biopsy, bladder biopsy, pacemaker or implantable cardioverter-defibrillator implantation, noncoronary angiography, electrophysiological study/catheter ablation
- High-bleeding-risk intervention: major surgery, spinal puncture or placement of spinal/epidural catheter, other situations in which complete hemostasis is required
- *Skip 1 dose of dabigatran or apixaban; no dose of edoxaban or rivaroxaban is skipped.

9. *Management of Bleeding in Patients taking DOACs*

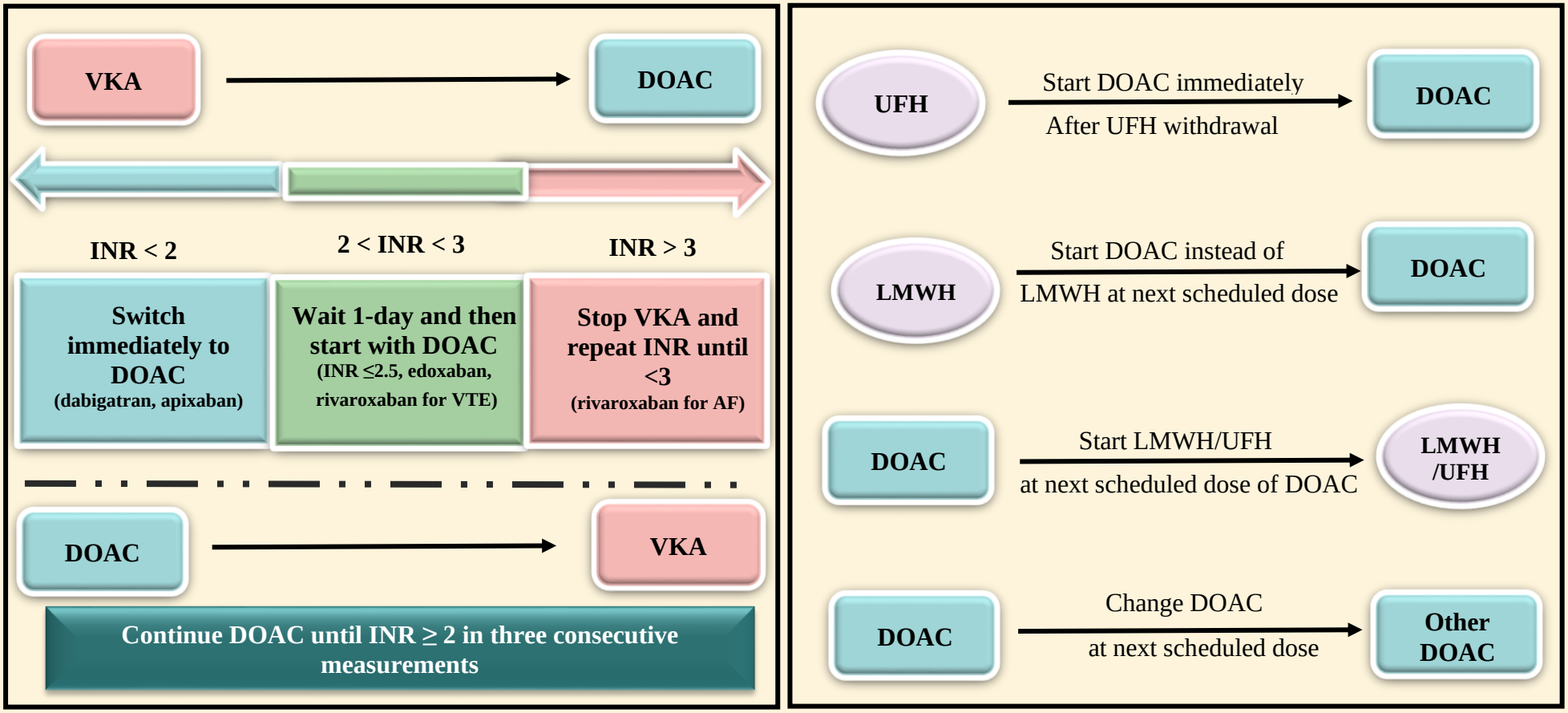


[a] Dosing depends on when and what was the last dose of DOAC; **high dose:** initial IV bolus 800mg; target infusion rate of 30mg/min, follow-on IV infusion at 8mg/min for up to 120 min, **low dose:** initial IV bolus 400mg; target infusion rate of 30mg/min, follow-on IV infusion at 4mg/min for up to 120 min. **Use high dose with** rivaroxaban >10mg or dose unknown, or apixaban >5mg or dose unknown, both if dose was received <8hrs or unknown. **Use low dose with** rivaroxaban ≤10mg (any timing from last dose), apixaban ≤5mg (any timing from last dose), rivaroxaban>10mg or dose unknown (≥8hrs from last dose), or apixaban >5mg or dose unknown (≥8hrs from last dose).

[b] 5 gm IV x 1, limited evidence supports additional 5gm.

Source: 2018 EHRA Practical Guide on NOACs in AF

10. Transitioning Between Anticoagulants



Source: *Front Cardiovasc Med*. 2019;6:17.

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Appendix I

CHA_2DS_2-VASc Score A clinical prediction tool to estimate the risk of stroke in patients with non-valvular atrial fibrillation.	
CHA_2DS_2-VASc Acronym	**Points**
Congestive Heart Failure	1 point
Hypertension	1 point
Age ≥ 75 years	2 point
Diabetes Mellitus	1 point
Stroke/TIA/TE	2 point
Vascular Disease (prior MI, PAD, Aortic plaque)	1 point
Sex Category (i.e. Female sex)	1 point
CHA_2DS_2-VASc Score	**Stroke Rate/Year**
0	0
1	1.3%
2	2.2%
3	3.2%
4	4.0%
5	6.7%
6	9.8%
7	9.6%
8	6.7%
9	15.2%

Appendix II

HAS-BLED Score Bleeding risk score to quantify the 1-year risk for major bleeding in patients with atrial fibrillation.	
HAS-BLED Acronym	**Points**
Hypertension (SBP>160 mmHg)	1 point
Abnormal liver or renal function (1 point each)	1 or 2 point
Stroke History	1 point
Bleeding History	1 point
Labile INRs	1 point
Elderly (>65 years old)	1 point
Drugs that promote bleeding or alcohol (1 point each)	1 or 2 point
HAS-BLED Score	**Bleeds per 100 Patients years**
0	1.13%
1	1.02%
2	1.88%
3	3.75%
4	8.70%
5	12.5%
6 7 8 9	Scores > 5 were too rare to determine risk in validation studies

Appendix III

Child- Pugh Score for Classification of Hepatic Impairment			
Score	**1**	**2**	**3**
Bilirubin	<2 mg/dL (<34.2 micromol/L)	2 to 3 mg/dL (34.2 to 51.3 micromol/L)	>3 mg/dL (>51.3 micromol/L)
Albumin	>3.5 g/dL (35 g/L)	2.8 to 3.5 g/dL (28 to 35 g/L)	<2.8 g/dL (<28 g/L)
Ascites	Absent	Mild	Moderate
Encephalopathy	None	Grade 1 to 2	Grade 3 to 4
INR	<1.7	1.7 to 2.3	>2.3
Grade A, <7 points; Grade B, 7 to 9 points; Grade C, 10 to 15 points.			