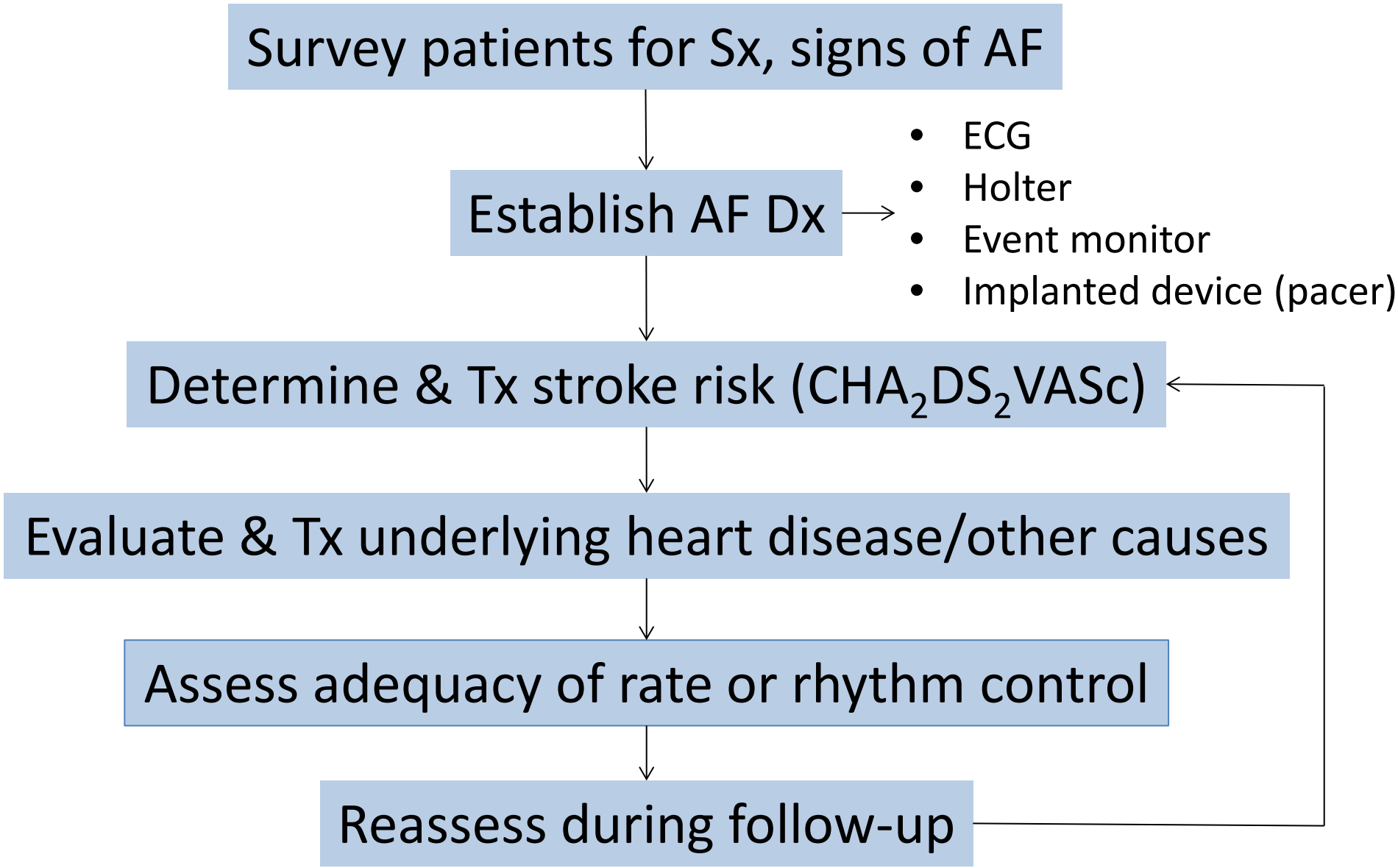
Provider Atrial Fibrillation Toolkit

Suggested General Approach to Managing Atrial Fibrillation



CHA_2DS_2VASc Score For AF Stroke Stratification

	Risk Factor		If Yes add:
C	**C**ongestive Heart Failure	History of heart failure; significant LV dysfunction	+1
H	**H**ypertension	History of hypertension, controlled or not	+1
A	**A**ge	≥ 75 years	+2
D	**D**iabetes	Diabetes	+1
S	**S**troke	Prior stroke, TIA, embolism	+2
V	**V**ascular disease	Coronary artery disease, peripheral vascular disease, aorta atherosclerosis	+1
A	**A**ge	65-74 years	+1
Sc	**S**ex category	Women	+1

Total Score: _____

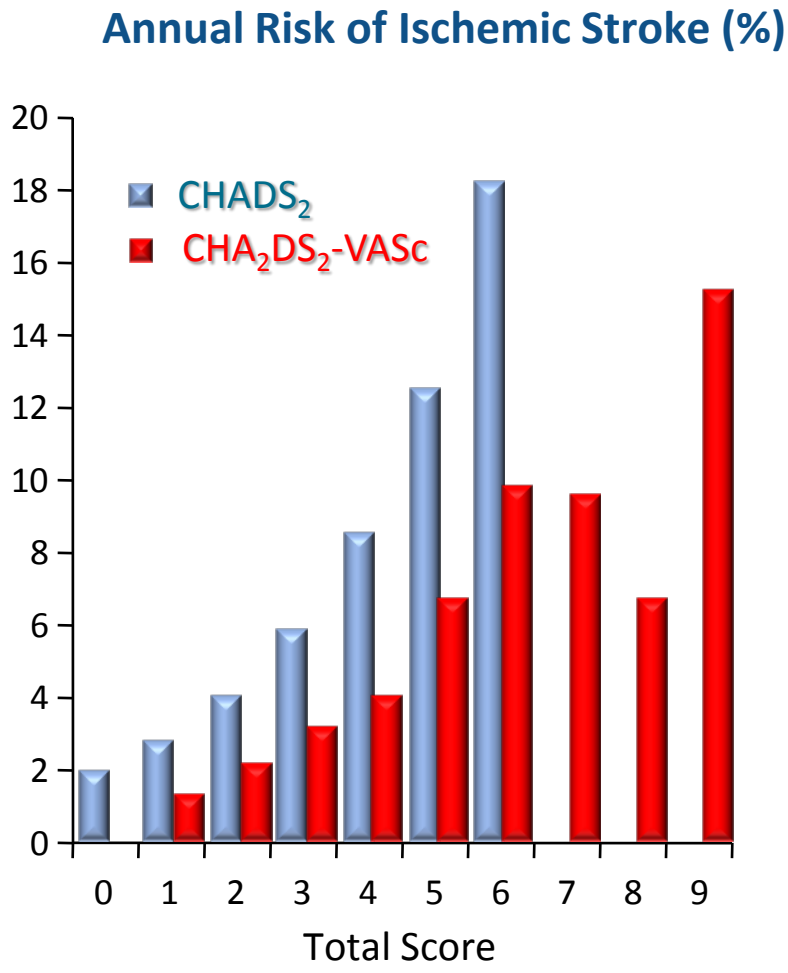
Stroke Risk Stratification in AF

$CHADS_2$

Risk Factor	Score
Cardiac failure	1
Hypertension	1
Age ≥75 years	1
Diabetes	1
Stroke	2

CHA_2DS_2-VASc

Risk Factor	Score
Cardiac failure	1
Hypertension	1
Age ≥75 years	2
Diabetes	1
Stroke	2
Vascular disease (MI, peripheral arterial disease, aortic atherosclerosis)	1
Age 65-74 years	1
Sex **c**ategory (female)	1



HTN = hypertension; MI = myocardial infarction.

Lip GY, et al. *Am J Med*. 2010;123(6):484-488. Camm AJ, et al. *Eur Heart J*. 2010:31;2369-2429.

What factors increase bleeding risk from anticoagulation?

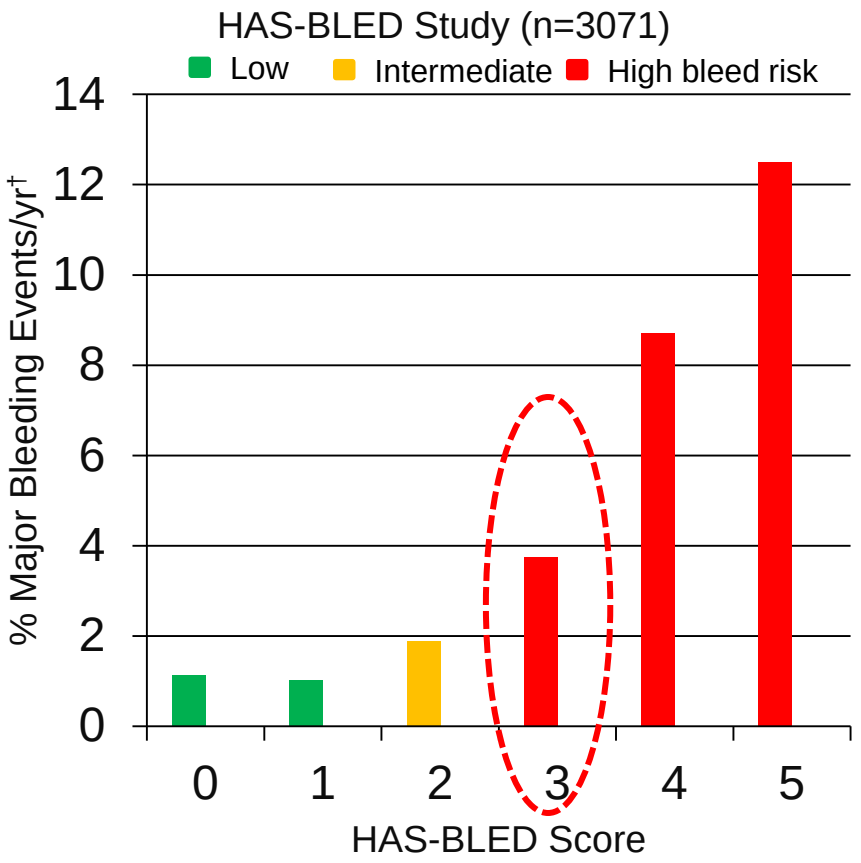
	Risk Factor		If Yes add:
H	**Hypertension**	Requiring ≥ 2 antihypertensive meds or poorly controlled	+1
A	**Abnormal renal/liver function**	Serum creatinine >2.3 mg/dl and/or liver function studies >3 x normal or known renal/liver disease (1 point each)	+1 or 2
S	**Stroke**	Stroke, TIA or arterial embolism history	+1
B	**Bleeding**	History of bleeding requiring hospitalization	+1
L	**Labile INH**	Highly variable INRs with time-in-therapeutic-range (TTR) <60%	+1
E	**Elderly**	Age >65 years	+1
D	**Drugs**	Antiplatelet medications or alcohol abuse (1 point each)	+1 or 2

Total Score: _____

HAS-BLED Bleeding Risk Score

Average risk of major bleed on warfarin ~2%/yr , but …

Letter	Clinical Characteristic*	Score
H	HTN (≥ 2 Rx; uncontrolled)	1
A	Abnormal renal (>2.3 mg/dL) and/or liver function (↑3x) (1 point each)	1 or 2
S	Stroke/TIA/embolism	1
B	Bleeding Hospitalization	1
L	Labile INRs (TTR<60%)	1
E	Elderly (age >65 years)	1
D	Drugs (antiplatelet) or alcohol abuse (1 point each)	1 or 2



†Fatal or clinically overt bleed with Hb decrease ≥ 2 g/dL, and/or ≥ 2u transfusion or bleed in critical anatomic site excluding brain

Camm AJ, et al. Eur Heart J. 2010;31(19):2369-2429. Pisters R. Chest. 2010;138:1093-1100. Lip GY J Am Coll Cardiol 2011;57:173-80, Olesen JB. J Thromb Haemost 2011;9:1460-7.

2014 AHA/ACC/HRS Guideline for the Management of Patients With Atrial Fibrillation

A Report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines and the Heart Rhythm Society

Class I

In patients with nonvalvular AF the CHA_2DS_2-VASc score is recommended for assessment of stroke risk (Level of Evidence B).

For patients with … prior stroke, transient ischemic attack (TIA) or CHA_2DS_2-VASc score of ≥ 2, oral anticoagulants are recommended.

Class IIa

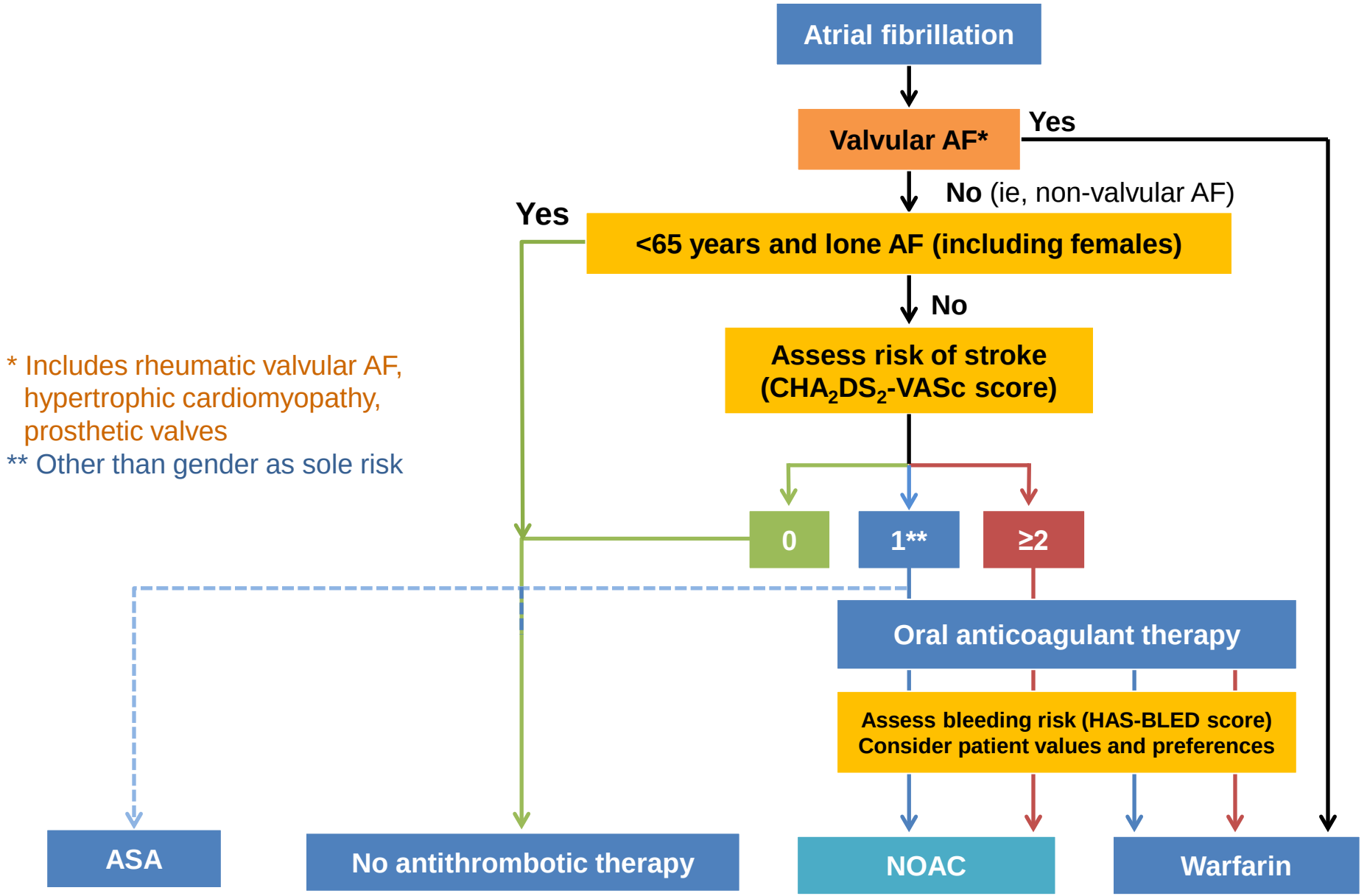
For patients with …a CHA_2DS_2-VASc score of 0 it is reasonable to omit antithrombotic therapy (Level of Evidence B)

Class IIb

For patients with …a CHA_2DS_2-VASc score of 1 no anthrombotic treatment or treatment with an oral anticoagulant or aspirin may be considered (Level of Evidence C).

Alpert JS et al. Circulation 2014;129. .

Anticoagulant Therapy Selection & Management



Camm AJ et al. *Eur Heart J*. 2012;33:2719-47.

Warfarin Dosing

- Most patients – start therapy at 5 mg daily and adjust according to INR
- Sensitive patients – start therapy at 1-2.5 mg daily and adjust according to INR

Novel Oral Anticoagulant Dosing

Drug	Recommended Dose	Adjustment	Comments
Apixaban	5 mg po bid	Decrease to 2.5 mg bid if 2 of following: age ≥ 80 yrs, weight ≤ 60 kg or serum creatinine ≥ 1.5 mg/dL	May be used in hemodialysis patients
Dabigatran	150 mg bid	Decrease to 75 mg bid if estimated CrCl* 15-30 mL/min	Contraindicated if CrCl <15 mL/min
Edoxaban	60 mg qd	Decrease to 30 mg qd if CrCl 15-50 mL/min;	Contraindicated if CrCl <15 mL/min or >95 mL/min
Rivaroxaban	20 mg qd with meal	Decrease to 15 mg qd if CrCl 15-50 mL/min	Contraindicated if CrCl <15 mL/min

Estimated creatinine clearance (CrCl) is calculated using the Cockcroft-Gault equation:
Men: (140-age) * wt in kg/(72 x serum creatinine in mg/dL) = glomerular filtration rate (GFR) in mL/min
Women: GFR (men) * 0.85

Suggested Warfarin Dose Adjustments Based on INR

INR Goal 2-3	Dosing adjustment
INR <1.5	• Consider one-time booster dose of 1 ½ -2 x daily maintenance dose • Continue prior maintenance dose if INR low because of missed dose(s) • If persistent, increase maintenance dose by 10-20%
INR 1.5-1.7	• Consider one-time booster dose of 1 ½ - 2 x daily maintenance dose • Continue prior maintenance dose if INR low because of missed dose(s) • If persistent, increase maintenance dose by 5-15%
INR 1.8-1.9	• Consider one-time booster dose of 1 ½ -2x daily maintenance dose • Continue prior maintenance dose if INR low because of missed dose(s) • If persistent, increase maintenance dose by 5-10%
INR 2-3	
INR 3.1-3.2	• Continue prior maintenance dose if caused by transient factor (EtOH) • If persistent, decrease maintenance dose by 5-10%
INR 3.3-3.4	• Continue prior maintenance dose if caused by transient problem (EtOH) • Consider one-time reduction to ½ dose or hold 1 dose • If persistent, decrease maintenance dose by 5-10%
INR 3.5-3.9	• Continue prior maintenance dose if caused by transient problem (EtOH) • Consider one-time hold of 1 dose • If persistent, decrease maintenance dose by 5-15%
INR ≥ 4 but no bleeding	• Continue prior maintenance dose if caused by transient problem (EtOH) • Consider minidose oral Vitamin K (phytonadione ¼ of 5 mg tablet or ~1 mg) • If persistent, decrease maintenance dose by 5-15%
INR ≥ 5 but no bleeding	• Hold warfarin & repeat INR q24 hours • Consider oral Vitamin K (phytonadione ¼ - ½ of 5 mg tablet or ~1-2.5 mg)

Characteristics of New Oral Anticoagulants

Drug	Dabigatran	Rivaroxaban	Apixaban	Edoxaban
Mechanism of action	Reversible direct thrombin inhibitor	Reversible direct factor Xa inhibitors		
Bioavailability	6.5%	>95% with food; 66% without	66%	62% with food; 45% without
Protein binding†	35%	>90%	87%	40-59%
Peak activity (hrs)	2-3	2.5-4	1-3	1-1.5
$T_{1/2}$ (hrs)	14-17	5-9	12	6-12
Regimen	75-150 mg BID[1]	15-20 mg QD[2]	2.5-5 mg BID[3]	30-60 mg QD[4]
Renal excretion	~80%	36%-45%	25%-30%	35%
Special concerns	Pro-drug, GI Sx	Dose with food	Approved in hemodialysis	Avoid if CrCl >95 ml/min
Potential for drug interactions	P-glycoprotein substrate (P-gp)	CYP3A4, CYP2J2 & P-gp substrate	CYP3A4 , CYP1A2, CYP2J1 & P-gp substrate	CYP3A4 & P-gp substrate

1: 75 mg if CrCl 15-30; 2: 15 mg if CrCl 15-50; 3: 2.5 mg if 2/3 of age ≥80 yrs wt ≤60 kg creat ≥1.5 mg/dL 4: 30 mg if CrCl 15-50 & avoid if >95ml/min
† Dialyzable if low %protein binding

Usman MH, et al. *Curr Treat Cardiovasc Med.* 2008;10(5):388-397. Piccini JP, et al. *Curr Opin Cardiol*. 2010;25(4):312-320; DeLoughery TG. Am J Hematol 2011;86:586-90.

Summary of Major Trials of Warfarin vs Novel Oral Anticoagulant Agents

	RE-LY (33) (N = 18,113) (3 arms)*	ROCKET-AF (34) (N = 14,264)	ARISTOTLE (35) (N = 18,201)	ENGAGE AF-TIMI 48 (36) (N = 21,105) (3 arms)†
Drug, dose	Dabigatran, 150 mg bid	Rivaroxaban, 20 mg daily	Apixaban, 5 mg bid	Edoxaban, 60/30 mg daily
Adjusted dose?	No	Yes, at randomization only: 15 mg daily if CrCl 30–49 ml/min	Yes, at randomization only: 2.5 mg bid if 2 of: age ≥80 yrs, weight <60 kg, SCr ≥1.5 mg/dl	Yes, at randomization and during study: both doses halved if any 1 of the following: CrCl 30–50 ml/min, weight ≤60 kg, use of verapamil, quinidine, or dronedarone
Design	Randomized open-label	Randomized double-blind, double-dummy	Randomized double-blind, double-dummy	Randomized double-blind, double-dummy
Mean age, yrs	71.5	73	70	72
Prior stroke/ transient ischemic attack/systemic embolism	20%	55%	19%	28%
Mean $CHADS_2$	2.2	3.5	2.1	2.8
Warfarin-naïve	50.4%	37.6%	43%	41%
Comparator warfarin INR 2–3	67% TTR (median)	58% TTR (median)	66% TTR (median)	68% (median)
Comparator Warfarin INR 2–3	64% TTR (mean)	55% TTR (mean)	62% TTR (mean)	65% (mean)
Outcome, RR (95% CI)				
Stroke/systemic embolism	0.66 (0.53–0.82)	0.88 (0.75–1.03)	0.79 (0.66–0.95)	0.88 (0.75–1.03)
Ischemic stroke	0.76 (0.60–0.98)	0.94 (0.75–1.17)	0.92 (0.74–1.13)	1.00 (0.83–1.19)
Hemorrhagic stroke	0.26 (0.14–0.49)	0.59 (0.37–0.93)	0.51 (0.35–0.75)	0.54 (0.38–0.77)
Major bleeding	0.93 (0.81–1.07)	1.04 (0.90–1.20)	0.69 (0.60–0.80)	0.80 (0.71–0.91)
Intracranial hemorrhage	0.40 (0.27–0.60)	0.67 (0.47–0.93)	0.42 (0.30–0.58)	0.47 (0.34–0.63)
Gastrointestinal bleeding	1.50 (1.19–1.89)	1.39 (1.19–1.61)	0.89 (0.70–1.15)	1.23 (1.02–1.50)
Cardiovascular mortality	0.85 (0.72–0.99)	0.89 (0.73–1.10)	0.89 (0.76–1.04)	0.86 (0.77–0.97)
All-cause mortality	0.88 (0.77–1.00)	0.85 (0.70–1.02)	0.89 (0.80–0.998)	0.92 (0.83–1.01)

Estimate creatinine clearance (CrCl) using Cockcroft-Gault formula: ([140 − age] × weight [in kg] × 0.85 if female)/(72 × creatinine [in mg/dl]). *Results are shown for dabigatran 150 mg bid. †Results are shown for edoxaban 60 mg daily.

$CHADS_2$ = Congestive heart failure, Hypertension, Age ≥75 years, Diabetes mellitus, Stroke or transient ischemic attack; CI = confidence interval; CrCl = creatinine clearance; DOAC = direct-acting oral anticoagulant; INR = international normalized ratio; RR = risk ratio; SCr = serum creatinine; TTR = time in therapeutic range.

Kovacs RJ. J Am Coll Cardiol 2015;65:1340-60.

Summary of Major Trials of Anti-Thrombotic Drugs for Nonvalvular AF (1/5)

SOE = significance of effect

Outcome	Number of Studies (Subjects)	SOE and Magnitude of Effect[a] (95% CI)
ASA vs. Warfarin		
Ischemic stroke	4 (170,642)	**SOE = Moderate** 4 retrospective studies showing consistent reduction in stroke with warfarin
Bleeding	3 (99,876)	**SOE = Moderate** Warfarin associated with increased rates of bleeding
All-cause mortality	1 (601)	**SOE = Insufficient**
Warfarin + ASA vs. Warfarin Alone		
Ischemic stroke	1 (69,264)	**SOE = Moderate** Increased with warfarin + ASA (HR 1.27; 95% CI 1.14 to 1.40)
Bleeding	1 (69,264)	**SOE = Moderate** Increased with warfarin + ASA (HR 1.83; 95% CI 1.72 to 1.96)
Clopidogrel + ASA vs. ASA Alone		
Any stroke	2 (8,147)	**SOE = Moderate** Lower rates with combined therapy (HR 0.72; 95% CI 0.62 to 0.83)
Ischemic stroke	2 (8,147)	**SOE = Low** Lower rates with combined therapy (HR 0.68; 95% CI 0.57 to 0.80)
Hemorrhagic stroke	2 (8,147)	**SOE = Moderate** Similar between therapies in both studies
Systemic embolism	1 (7,554)	**SOE = Moderate** Similar between therapies (HR 0.96; 95% CI 0.66 to 1.40)
Major bleeding	1 (7,554)	**SOE = High** Clopidogrel + ASA associated with higher rates (HR 1.57; 95% CI 1.29 to 1.92)
Minor bleeding	1 (7,554)	**SOE = High** Clopidogrel + ASA associated with higher rates (HR 2.42; 95% CI 2.03 to 2.89)
Intracranial bleeding	2 (8,147)	**SOE = Low** Higher rates with clopidogrel + ASA (HR 1.87; 95% CI 1.19 to 2.94)
Extracranial bleeding	2 (8,147)	**SOE = High** Higher rates with clopidogrel + ASA (HR 1.51; 95% CI 1.21 to 1.88)
All-cause mortality	2 (8,147)	**SOE = Moderate** No difference (HR 0.98 [95% CI 0.89 to 1.08] in one study; HR 1.12 [95% CI 0.65 to 1.90] in other study)
Death from vascular causes	2 (8,147)	**SOE = Low** No difference based on large RCT (HR 1.00; 95% CI 0.89 to 1.12), although a smaller study showed a trend toward a benefit of ASA alone (HR 1.68; 95% CI 0.83 to 3.42)
Myocardial infarction	2 (8,147)	**SOE = Low** No difference based on large RCT (HR 0.78; 95% CI 0.59 to 1.03), although a smaller study showed a trend toward a benefit of ASA alone (HR 1.43; 95% CI 0.51 to 4.01)
Hospitalization	1 (593)	**SOE = Insufficient**
Clopidogrel vs. Warfarin		
Ischemic stroke	1 (54,636)	**SOE = Moderate** Increased risk with clopidogrel (HR 1.86; 95% CI 1.52 to 2.27)
Bleeding	1 (54,636)	**SOE = Moderate** Similar between therapies (HR 1.06; 95% CI 0.87 to 1.29)

Lopes RD et al. Stroke prevention in atrial fibrillation: Comparative effectiveness review No 123. AHRQ Publication No 13-EHC113-EF. Rockville MD: Agency for Healthcare Research and Quality: August 2013. www.effectivehealthcare.ahrq.gov/reports/final.cfm

Summary of Major Trials of Anti-Thrombotic Drugs for Nonvalvular AF (2/5)

SOE = significance of effect

Outcome	Number of Studies (Subjects)	SOE and Magnitude of Effect[a] (95% C)
Clopidogrel + ASA vs. Warfarin		
Stroke or systemic embolism	2 (60,484)	**SOE = High** Increased risk with clopidogrel + ASA in both studies (HR 1.56 [95% CI 1.17 to 2.10] in one study; HR 1.72 [95% CI 1.24 to 2.37] in other study)
Hemorrhagic stroke	1 (6,706)	**SOE = Moderate** Increased risk with warfarin (HR 0.34; 95% CI 0.12 to 0.93)
Major bleeding	2 (60,484)	**SOE = Low** Similar rates between therapies (HR 1.10; 95% CI 0.83 to 1.45)
Minor bleeding	1 (6,706)	**SOE = High** Increased risk with clopidogrel + ASA (HR 1.23; 95% CI 1.09 to 1.39)
Intracranial bleeding	1 (6,706)	**SOE = Insufficient**
All-cause mortality	1 (6,706)	**SOE = High** No difference (HR 1.01; 95% CI 0.81 to 1.26)
Death from vascular causes	1 (6,706)	**SOE = Moderate** No difference (HR 1.14; 95% CI 0.88 to 1.48)
Myocardial infarction	1 (6,706)	**SOE = Moderate** No difference (myocardial infarction occurred at rates of <1% per year with both therapies)
Warfarin + Clopidogrel vs. Warfarin Alone		
Ischemic stroke	1 (52,349)	**SOE = Low** Trend toward benefit of warfarin + clopidogrel (HR 0.70; 95% CI 0.35 to 1.40)
Bleeding	1 (52,349)	**SOE = Moderate** Higher for patients on warfarin + clopidogrel (HR 3.08; 95% CI 2.32 to 3.91)
Warfarin Alone vs. Warfarin + ASA + Clopidogrel		
Ischemic stroke	1 (52,180)	**SOE = Low** Trend toward being higher for patients on triple therapy (HR 1.45; 95% CI 0.84 to 2.52)
Bleeding	1 (52,180)	**SOE = Moderate** Higher for patients on triple therapy (HR 3.70; 95% CI 2.89 to 4.76)
Factor IIa Inhibitor (Dabigatran 150 mg) vs. Warfarin		
Stroke or systemic embolism	1 (12,098)	**SOE = High** Dabigatran reduced risk (RR 0.66; 95% CI 0.53 to 0.82)
Ischemic or uncertain stroke	1 (12,098)	**SOE = Moderate** Dabigatran reduced risk (RR 0.76; 95% CI 0.60 to 0.98)
Hemorrhagic stroke	1 (12,098)	**SOE = High** Dabigatran reduced risk (RR 0.26; 95% CI 0.14 to 0.49)
Major bleeding	1 (12,098)	**SOE = High** No difference (RR 0.93; 95% CI 0.81 to 1.07)
Minor bleeding	1 (12,098)	**SOE = Moderate** Dabigatran reduced risk (RR 0.91; 95% CI 0.85 to 0.97)
Intracranial bleeding	1 (12,098)	**SOE = High** Dabigatran reduced risk (RR 0.40; 95% CI 0.27 to 0.60)
All-cause mortality	1 (12,098)	**SOE = Moderate** No difference (RR 0.88; 95% CI 0.77 to 1.00)
Death from vascular causes	1 (12,098)	**SOE = Moderate** Dabigatran reduced risk (RR 0.85; 95% CI 0.72 to 0.99)

Lopes RD et al. Stroke prevention in atrial fibrillation: Comparative effectiveness review No 123. AHRQ Publication No 13-EHC113-EF. Rockville MD: Agency for Healthcare Research and Quality: August 2013. www.effectivehealthcare.ahrq.gov/reports/final.cfm

Summary of Major Trials of Anti-Thrombotic Drugs for Nonvalvular AF (3/5)

SOE = significance of effect

Outcome	Number of Studies (Subjects)	SOE and Magnitude of Effect[a] (95% C)
Myocardial infarction	1 (12,098)	**SOE = Moderate** Dabigatran increased risk (RR 1.38; 95% CI 1.00 to 1.91)
Hospitalization	1 (12,098)	**SOE = High** No difference (RR 0.97; 95% CI 0.92 to 1.03)
Adverse events	1 (12,098)	**SOE = Moderate** Dyspepsia more common with dabigatran (11.3% of patients with dabigatran 150 mg vs. 5.8% with warfarin; p <0.001). No differences in liver function or other adverse events between therapies.
Factor IIa Inhibitor (Dabigatran 110 mg) vs. Warfarin		
Stroke or systemic embolism	1 (12,037)	**SOE = High** No difference (RR 0.91; 95% CI 0.74 to 1.11)
Ischemic or uncertain stroke	1 (12,037)	**SOE = Moderate** No difference (RR 1.11; 95% CI 0.89 to 1.40)
Hemorrhagic stroke	1 (12,037)	**SOE = High** Dabigatran reduced risk (RR 0.31; 95% CI 0.17 to 0.56)
Major bleeding	1 (12,037)	**SOE = High** Dabigatran reduced risk (RR 0.80; 95% CI 0.69 to 0.93)
Minor bleeding	1 (12,037)	**SOE = High** Dabigatran reduced risk (RR 0.79; 95% CI 0.74 to 0.84)
Intracranial bleeding	1 (12,037)	**SOE = High** Dabigatran reduced risk (RR 0.31; 95% CI 0.20 to 0.47)
All-cause mortality	1 (12,037)	**SOE = Moderate** No difference (RR 0.91; 95% CI 0.80 to 1.03)
Death from vascular causes	1 (12,037)	**SOE = Moderate** No difference (RR 0.90; 95% CI 0.77 to 1.06)
Myocardial infarction	1 (12,037)	**SOE = Low** Dabigatran increased risk, although the difference did not reach statistical significance (RR 1.35; 95% CI 0.98 to 1.87)
Hospitalization	1 (12,037)	**SOE = High** Dabigatran reduced risk (RR 0.92; 95% CI 0.87 to 0.97)
Adverse events	1 (12,037)	**SOE = Moderate** Dyspepsia more common with dabigatran (11.8% of patients with dabigatran 110 mg vs. 5.8% with warfarin; p <0.001). No differences in liver function or other adverse events between therapies.
Xa Inhibitor (Apixaban) vs. Warfarin		
Stroke or systemic embolism	2 (18,423)	**SOE = High** Apixaban reduced risk (HR 0.79; 95% CI 0.66 to 0.95)
Ischemic stroke	1 (18,201)	**SOE = High** No difference (HR 0.92; 95% CI 0.74 to 1.13)
Hemorrhagic stroke	1 (18,201)	**SOE = High** Apixaban reduced risk (HR 0.51; 95% CI 0.35 to 0.75)
Systemic embolism	2 (18,423)	**SOE = Moderate** No difference (HR 0.87; 95% CI 0.44 to 1.75)
Major bleeding	2 (18,423)	**SOE = High** Apixaban reduced risk (HR 0.69; 95% CI 0.60 to 0.80)
Intracranial bleeding	1 (18,201)	**SOE = High** Apixaban reduced risk (HR 0.42; 95% CI 0.30 to 0.58)
All-cause mortality	2 (18,423)	**SOE = Moderate** Apixaban reduced risk (HR 0.89; 95% CI 0.80 to 0.998)

Lopes RD et al. Stroke prevention in atrial fibrillation: Comparative effectiveness review No 123. AHRQ Publication No 13-EHC113-EF. Rockville MD: Agency for Healthcare Research and Quality: August 2013. www.effectivehealthcare.ahrq.gov/reports/final.cfm

Summary of Major Trials of Anti-Thrombotic Drugs for Nonvalvular AF (4/5)

SOE = significance of effect

Outcome	Number of Studies (Subjects)	SOE and Magnitude of Effect[a] (95% C)
Death from cardiovascular causes	1 (18,201)	**SOE = High** No difference (HR 0.89; 95% CI 0.76 to 1.04)
Myocardial infarction	1 (18,201)	**SOE = Moderate** No difference (HR 0.88; 95% CI 0.66 to 1.17)
Adverse events	2 (18,423)	**SOE = Moderate** Adverse events occurred in almost equal proportions of patients in the apixaban and the warfarin therapy arms
Xa Inhibitor (Rivaroxaban) vs. Warfarin		
Stroke or systemic embolism	2 (15,544)	**SOE = Moderate** No difference (HR 0.88; 95% CI 0.74 to 1.03)
Ischemic stroke	1 (14,264)	**SOE = Moderate** No difference in on-treatment analyses (HR 0.94; 95% CI 0.75 to 1.17)
Hemorrhagic stroke	2 (15,544)	**SOE = Low** In on-treatment analyses, 1 large RCT demonstrated benefit of rivaroxaban (HR 0.59; 95% CI 0.37 to 0.93); a smaller study showed a trend toward no difference (HR 0.73; 95% CI 0.16 to 3.25)
Systemic embolism	1 (14,264)	**SOE = Moderate** Rivaroxaban reduced risk in on-treatment analyses (HR 0.23; 95% CI 0.09 to 0.61)
Major bleeding	2 (15,544)	**SOE = Moderate** No difference in 2 studies in on-treatment analyses (HR 1.04 [95% CI 0.90 to 1.20] in one study; HR 0.85 [95% CI 0.50 to 1.43] in other study)
Intracranial bleeding	2 (15,544)	**SOE = Moderate** Rivaroxaban reduced risk in on-treatment analyses (HR 0.67; 95% CI 0.47 to 0.93)
All-cause mortality	1 (14,264)	**SOE = High** No difference (HR 0.92; 95% CI 0.82 to 1.03)
Death from cardiovascular causes	1 (14,264)	**SOE = Moderate** No difference in on-treatment analyses (HR 0.89; 95% CI 0.73 to 1.10)
Myocardial infarction	1 (14,264)	**SOE = Moderate** No difference in on-treatment analyses (HR 0.81; 95% CI 0.63 to 1.06)
Xa Inhibitor (Apixaban) vs. ASA		
Stroke or systemic embolism	1 (5,599)	**SOE = High** Apixaban reduced risk (HR 0.45; 95% CI 0.32 to 0.62)
Ischemic stroke	1 (5,599)	**SOE = High** Apixaban reduced risk (HR 0.37; 95% CI 0.25 to 0.55)
Hemorrhagic stroke	1 (5,599)	**SOE = Moderate** Trend toward a reduction in risk with apixaban (HR 0.67; 95% CI 0.24 to 1.88)
Major bleeding	1 (5,599)	**SOE = High** No difference (HR 1.13; 95% CI 0.74 to 1.75)
Minor bleeding	1 (5,599)	**SOE = Moderate** Apixaban increased risk (HR 1.20; 95% CI 1.00 to 1.53)
Intracranial bleeding	1 (5,599)	**SOE = Low** Trend toward a reduction in risk with apixaban (HR 0.85; 95% CI 0.38 to 1.90)
All-cause mortality	1 (5,599)	**SOE = Low** Trend toward a reduction in risk with apixaban (HR 0.79; 95% CI 0.62 to 1.02)
Death from vascular causes	1 (5,599)	**SOE = Moderate** No difference (HR 0.87; 95% CI 0.66 to 1.17)

Lopes RD et al. Stroke prevention in atrial fibrillation: Comparative effectiveness review No 123. AHRQ Publication No 13-EHC113-EF. Rockville MD: Agency for Healthcare Research and Quality: August 2013. www.effectivehealthcare.ahrq.gov/reports/final.cfm

Summary of Major Trials of Anti-Thrombotic Drugs for Nonvalvular AF (5/5)

Outcome	Number of Studies (Subjects)	SOE and Magnitude of Effect[a] (95% C)
Myocardial infarction	1 (5,599)	**SOE = Moderate** No difference (HR 0.86; 95% CI 0.50 to 1.48)
Hospitalization	1 (5,599)	**SOE = High** Apixaban reduced risk (HR 0.79; 95% CI 0.69 to 0.91)
Adverse events	1 (5,599)	**SOE = Moderate** No differences in liver function or other adverse events between therapies

SOE = significance of effect

Lopes RD et al. Stroke prevention in atrial fibrillation: Comparative effectiveness review No 123. AHRQ Publication No 13-EHC113-EF. Rockville MD: Agency for Healthcare Research and Quality: August 2013. www.effectivehealthcare.ahrq.gov/reports/final.cfm

Potentially Important Drug-Drug Interactions with NOACs

Drug Interaction		Effect on NOAC metabolism			
Drug	Metabolism	Dabigatran	Rivaroxaban	Apixaban	Edoxaban
Digoxin	P-GP competition	No effect	No effect	No effect	No effect
Verapamil	P-GP competition + weak CYP3A4 inhibition	+12-180%	Minor effect	Unknown	+53%
Diltiazem	P-GP competition + weak CYP3A4 inhibition	No effect	Minor effect	+40%	Unknown
Quinidine	P-GP competition	+50%	+50%	Unknown	+80%
Amiodarone	P-GP competition	+12-60%	Minor effect	Unknown	No effect
Dronedarone	P-GP and CYP3A4 inhibition	+70-100%	Unknown	Unknown	+85%
Ketoconazole & other "azoles"	P-GP, BCRP competition, CYP3A4 competition	+140-150%	+160%	+100%	Unknown
Fluconazole	Moderate CYP3A4 competition	Unknown	+42%	Unknown	Unknown
HIV protease inhibitors	P-GP, BCRP competition & inducer, CYP3A4 inhibition	Unknown	+153%	Strong increase	Unknown
Rifampin, St Johns wort; carbamazapine, phenytoin, phenobarbital	P-BP, BCRP & CYP3A4/CYP2J2 inducers	-66%	-50%	-54%	-35%

Adapted after Heidbuchel H, et al. *Europace* 2013;15:625-651.

Switching Between Oral Anticoagulants

Converting Warfarin to NOAC

- Wait for INR < 2-2.5 (< 3 for rivaroxaban) → start NOAC

Converting NOAC to warfarin

- Consider overlapping therapies to avoid low anticoagulation troughs
- May take 5-10 days before INR in therapeutic range
- Measure INR just before next dose of NOAC & 24º after last NOAC dose
- If in doubt → parenteral anticoagulant coverage until INR ≥2

Creatinine Clearance	Suggested Warfarin Start Time
Normal (>80 ml/min)	~4 days before stopping NOAC
Mild (50-80 ml/min)	~3 days before stopping NOAC
Moderate (30-50 ml/min)	~2 days before stopping NOAC
Severe (15-30 ml/min)	~1 day before stopping NOAC

Converting NOAC to NOAC

- Initiate alternate NOAC when next dose due

Switching Between Parenteral Anticoagulants

Converting from parenteral anticoagulant to NOAC

Administration of Parenteral Anticoagulant	Recommended Starting Time for NOAC
Intermittent dosing (e.g. LMWH)	0-2 hours before time of next dose
Continuous infusion	At time of discontinuation

Converting from NOAC to parenteral anticoagulant

- Start parenteral anticoagulant at next scheduled dose of NOAC

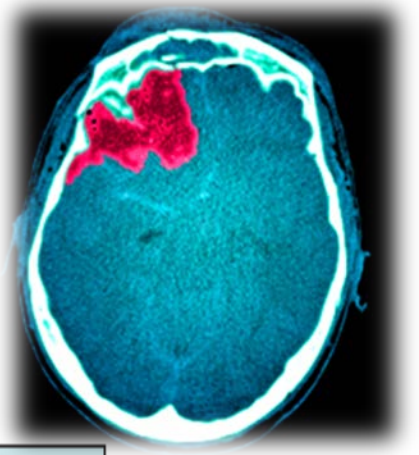
Temporary Discontinuation of NOACs Prior to Procedures

	Dabigatran		Apixaban		Edoxaban		Rivaroxaban	
	No important bleeding risk and/or adequate local haemostasis possible: perform procedure at trough level (i.e. ≥12h or 24h after last NOAC dose)							
	← Hold NOAC Dose Period for Presumed Procedural Bleeding Risk →							
	Low risk	High risk	Low risk	High risk	Low risk	High risk	Low risk	High risk
CrCl ≥80 ml/min	≥24h	≥48h	≥24h	≥48h	≥24h	≥48h	≥24h	≥48h
CrCl 50-80 ml/min	≥36h	≥72h	≥24h	≥48h	≥24h	≥48h	≥24h	≥48h
CrCl 30-50 ml/min	≥48h	≥96h	≥24h	≥48h	≥24h	≥48h	≥24h	≥48h
CrCl 15-30 ml/min	not known	not known	≥36h	≥48h	≥36h	≥48h	≥36h	≥48h

Restart when homeostasis has been achieved.

Adapted after Heidbuchel H, et al. *Eurospace* 2013;15:625-651.

Bleeding on anticoagulant Rx



Mild bleeding

- Delay or discontinue next dose
- Reconsoder concomitant medication

Moderate severe bleeding

Supportive measures:

- Mechanical compression
- Surgical hemostasis
- Fluid replacement (colloids if needed)
- RBC substitution if needed
- Fresh frozen plasma (as plasma expander)
- Platelet substitution (if platelet count $\leq 60 \times 10^9$/L)

For dabigatran:

- Maintain adequate diuresis
- Consider hemodialysis
- ((charcoal haemoperfusion?: await more data))

Life-threatening bleeding

Consider:

- PCC (e.g. CoFact®) 25 U/kg; repeat 1×/2× if indicated
- aPCC (Feiba®) 50IE/kg; max 200 IE/kg/day
- (rFVIIa (NovoSeven®) 90 µg/kg no data about additional benefit)

Adapted from Heidbuchel H et al. *Europace.* 2013;15:625-51.

Anticoagulant Drug Initiation and Follow-Up Strategy

Initiate anticoagulant treatment

- Set indication for anticoagulation
- Document CHA_2DS_2VASc, HAS-BLED scores
- Choose anticoagulant
- Baseline CBC, renal and liver function
- Provide education
- Review co-medications
- Organize follow-up
- Identify responsible coordinator for follow-up

1 month follow-up

Follow-up

Re-educate & Check:

- Compliance
- Thromboembolic events
- Bleeding events
- Other side effects
- Repeat CBC, renal function
- Co-medications
- CHA_2DS_2VASc, HAS-BLED scores

q follow-up
1 mo?
3 mo
6 mo

Adapted from Heidbuchel H et al. *Europace.* 2013;15:625-51.

Checklist During Follow-Up of Patients on Anticoagulation Therapy

Assessment	Interval	Comments
Compliance	Each visit	✓ Instruct patient to bring medication ✓ Re-educate on importance of strict intake schedule ✓ Inform about compliance aids (boxes, smartphone)
Thromboembolism	Each visit	✓ Review symptoms/signs of events
Bleeding	Each visit	✓ Assess nuisance bleeding ✓ Assess significant bleeding ✓ Reassess anticoagulation indication, dose
Side effects	Each visit	✓ Assess quality of life ✓ Need for temporary discontinuation for procedures
Co-medications	Each visit	✓ Instruct patient to bring all medications
Blood sampling	Yearly 6 monthly 3 monthly On indication	✓ CBC, renal and liver function ✓ Renal function if CrCl 30-60 mL/min or 15-30 mL/min ✓ If intercurring condition that may impact renal or hepatic function

Adapted from Heidbuchel H et al. *Europace.* 2013;15:625-51.

Suggested Provider Checklist During Follow-Up of Patients on Anticoagulation (NOAC) Therapy

Date	Serum Creatinine	Creatinine clearance	Hb/HCT	INR (if applicable)	Events	CHA_2DS_2-VASc score	HAS-BLED score
7/1/15	1.5	55	45	NA	nosebleed	4	2

Additional Information

- Websites
  - NATIONAL STROKE ASSOCIATION: www.stroke.org
  - AMERICAN HEART ASSOCIATION: www.heart.org
  - HEART RHYTHM SOCIETY: www.hrsonline.org
  - AMERICAN COLLEGE OF CARDIOLOGY: www.acc.org
  - Stop Afib: www.stopafib.org
- Smartphone Apps
  - inrpro.com/anticoagulation_apps.asp