Pharmacotherapy Updates: New Oral Anticoagulants

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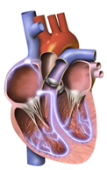
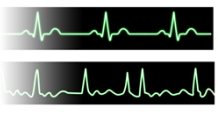
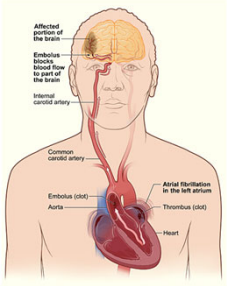
Objectives

- By the end of this presentation, the participant should be able to:
  - Compare and contrast the pharmacologic properties of new oral anticoagulants
  - Discuss practice guidelines related to atrial fibrillation
  - Describe the evidence supporting new oral anticoagulants
  - Discuss available reversal agents for new oral anticoagulants

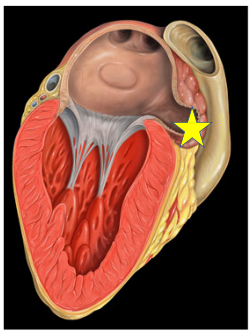
Atrial Fibrillation: Clinical considerations







Left Atrial Appendage = Danger Zone

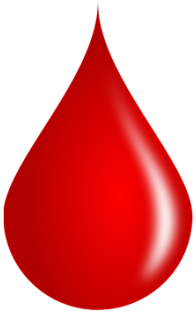


Definition of Non-Valvular Atrial Fibrillation

- **2019 AHA/ACC/HRS Focused Update to 2014 AF Guidelines**
  - Non-valvular atrial fibrillation defined as AF in the absence of:
    - **Moderate-to-severe mitral stenosis**
    - **Mechanical heart valve**
- Rationale for change:
  - Most AF DOAC trials enrolled ~20% pts with various forms of VHD including **mild MS**, MR, AS, AR, TR
  - Some trials enrolled pts with **valve repair**, valvuloplasty, or **bioprosthetic valves**

January CT, et al. *J Am Coll Cardiol* 2019.

Balancing Bleeding vs. Clotting



Comparing stroke risk calculators

$CHADS_2$
- **C**ongestive heart failure
- **H**ypertension
- **A**ge > 75
- **D**iabetes
- **S**troke or TIA (2 points)

CHA_2DS_2-VASc
- **C**ongestive heart failure
- **H**ypertension
- **A**ge > 75
- **D**iabetes
- **S**troke or TIA (2 points)
- **V**ascular disease (2 points)
- **A**ge 65-74
- **S**ex **C**ategory (female)

https://www.mdcalc.com/chads2-score-atrial-fibrillation-stroke-risk
https://www.mdcalc.com/cha2ds2-vasc-score-atrial-fibrillation-stroke-risk

Bleeding Risk

- **H**ypertension
- **A**bnormal renal/liver function (1 point each)
- **S**troke
- **B**leeding (prior) or predisposition to bleeding
- **L**abile INR
- **E**lderly (age > 65)
- **D**rugs (aspirin, NSAIDS, or clopidogrel) or alcohol use ≥ 8 drinks/week

https://www.mdcalc.com/has-bled-score-major-bleeding-risk

Antithrombotic Treatment based on CHADS-VASc Score

% Risk of Stroke without Antithrombotic Therapy	CHADS-VASc Score	Recommendation
Low Risk (0-1%/year)	0 (males) 1 (females)	**No antithrombotic preferred** OR aspirin only
Moderate Risk (1-2%/year)	1 (males) 2 (females)	**Anticoagulation preferred** OR Aspirin only OR No antithrombotic
High Risk (2-15%/year)	≥ 2 (males) ≥ 3 (females)	**Anticoagulation strongly recommended** (NOAC>warfarin)

If prior cardioembolic stroke = OAC
If valvular AF: warfarin preferred

Lip, et al. *CHEST* 2018.
January CT, et al. *J Am Coll Cardiol* 2019.

Name that plant:

This plant, first described in the mid-1500s for its' medicinal uses in the treatment of dropsy and as an emetic agent, was named after its' thimble-like appearance.

Somberg J, et al. *J Clin Pharmacol* 1985;25:484-489.

What is the foxglove plant?

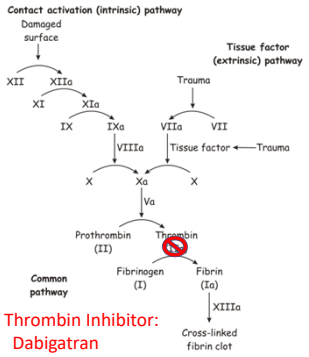
The *digitalis* plant is the source for the development of the drug digoxin, which is less preferred maintenance treatment of atrial fibrillation due to its' acute and chronic toxicities.

Key NOAC Takeaways from 2019 Focused update

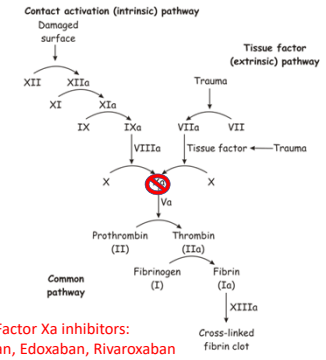
- Edoxaban added to list of NOACs utilized for stroke prevention
- NOACS > warfarin except in patients with moderate-severe mitral stenosis or prosthetic heart valve
- NOACs should be used regardless of AF classification (paroxysmal or persistent)
- Renal & hepatic function should be checked before initiating NOAC & annually thereafter

January CT, et al. *J Am Coll Cardiol* 2019.

New Oral Anticoagulant Review



Direct Thrombin Inhibitor:
Dabigatran



Factor Xa inhibitors:
Apixaban, Edoxaban, Rivaroxaban

Direct Thrombin Inhibitor: Dabigatran

- ↓ risk of stroke and ICH; ↑ GI bleeding risk vs. warfarin (RE-LY)
  - Mean CHADS = 2.1
- Dosing: 150 mg PO BID
  - Off-label: If increased risk of bleeding: 110 mg PO BID
  - CrCl 15-30 mL/min: 75 mg PO BID
- Side effects:
  - Common: bleeding/bruising, GI symptoms
- Contraindications:
  - Hypersensitivity to dabigatran
  - Mechanical prosthetic heart valve

Connoly SJ, et al. *N Eng J Med* 2009.
Lexi-Comp Online.

Factor Xa inhibitor: Apixaban

- ↓ risk of stroke and ↓ bleeding risk vs. warfarin (ARISTOTLE)
  - Mean CHADS = 2.1
- MOA: Factor Xa inhibitor
- Dosing: 5 mg PO BID
  - Unless 2 or more of the following: $\geq 80\ yo, \leq 60\ kg\ or\ SCr\ \geq 1.5\ mg/dL$
  - CrCl < 25 mL/min or severe hepatic disease: avoid use
- Side effects:
  - Common: bleeding/bruising
- Contraindications:
  - Hypersensitivity to apixaban
  - Active bleeding

Granger CB, et al. *N Eng J Med* 2011.
Lexi-Comp Online.

Factor Xa inhibitor: Edoxaban

- Non-inferior stroke reduction and ↓ bleeding risk vs. warfarin (ENGAGE AF-TIMI 48)
  - Mean CHADS = 2.8
- MOA: Factor Xa inhibitor
- Dosing: 60 mg PO daily
  - Do not use if CrCl > 95 mL/min
  - CrCl 15-50 mL/min: 30 mg PO daily
- Side effects:
  - Common: bleeding/bruising, abnormal LFTs
- Contraindications:
  - Hypersensitivity to edoxaban
  - Active bleeding

Guigliano RP, et al. *N Eng J Med* 2013.
Lexi-Comp Online.

Factor Xa inhibitor: Rivaroxaban

- Non-inferior in stroke reduction and bleeding vs. warfarin (ROCKET-AF)
  - Mean CHADS = 3.5
- MOA: Factor Xa inhibitor
- Dosing: 20 mg PO daily with the evening meal
  - Off-label: post-PCI, in combination with clopidogrel: 15 mg PO daily
  - CrCl 15-50mL/min: 15 mg PO daily with the evening meal
  - CrCl <15 mL/min or moderate-severe hepatic disease: avoid use
- Side effects:
  - Common: bleeding/bruising, increased LFTs
- Contraindications:
  - Hypersensitivity to rivaroxaban
  - Active bleeding

Patel MR, et al. *N Eng J Med* 2011.
Lexi-Comp Online.

Pharmacokinetic Summary

Table 4 Absorption and metabolism of the different NOACs

	Dabigatran	Apixaban	Edoxaban[a]	Rivaroxaban
Bio-availability	3–7%	50%	62%[17]	66% without food Almost 100% with food
Prodrug	Yes	No	No	No
Clearance non-renal/renal of absorbed dose (if normal renal function; see also Section 8)	20%/80%	73%/27%[18]	50%/50%[9]	65%/35%
Liver metabolism: CYP3A4 involved	No	Yes (elimination; minor CYP3A4 contribution)[19]	Minimal (< 4% of elimination)	Yes (elimination)
Absorption with food	No effect	No effect	6–22% more[20]	+39% more[21]
Intake with food recommended?	No	No	No official recommendation yet	Mandatory
Absorption with H2B/PPI	−12–30%[22–24]	No effect	No effect	No effect[21,25]
Asian ethnicity	+25%[24]	No effect	No effect[20]	No effect
GI tolerability	Dyspepsia 5–10%	No problem	No problem	No problem
Elimination half-life	12–17 h[13]	12 h	9–11 h[9]	5–9 h (young) 11–13 h (elderly)

[a]No EMA approval yet. Needs update after finalization of SmPC.
H2B, H2-blocker; PPI, proton-pump inhibitor; GI, gastro-intestinal.

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

Case #1

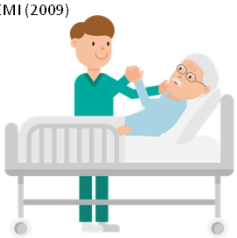
Any concerns with starting apixaban for this patient?

- BT is a 75 yo male
- New onset AF; PMH: HTN, HPL, essential tremor, STEMI (2009)
- Ht 5'9''; Wt 85 kg; SCr 1.2 mg/dL

Plan: start: start apixaban 5 mg PO BID

Home medication list:

- Primidone 50 mg PO daily
- Amlodipine 10 mg PO daily
- Pravastatin 10 mg PO daily
- Aspirin 81 mg PO daily
- Carvedilol 6.25 mg PO BID
- Lisinopril 10 mg PO daily



CYP3A4 inducer considerations

Oral anticoagulant option	CYP3A4 inducer example: primidone	Level of interaction
Apixaban	Primidone	X: avoid combination; ↓ serum apixaban concentration
Rivaroxaban	Primidone	X: avoid combination; ↓ serum apixaban concentration
Edoxaban	Primidone	No interactions identified.
Warfarin	Primidone	D: consider therapy modification; doses of warfarin may need to be increased 30-60%
Dabigatran	Primidone	C: monitor therapy

With strong CYP3A4 inducers on board, changes to anticoagulant recommendations should be considered

Source: Lexi-Comp Interaction Analysis.

Reversal Agents

Anticoagulant	Reversal agent
Dabigatran	Idarucizumab
Rivaroxaban, apixaban	Andexanet alfa
Warfarin	Vitamin K

January CT, et al. *Am Coll Cardiol* 2019;Jan 28. Epub ahead of print.

Cost comparison

Oral anticoagulant option	Estimated one month supply
Apixaban 5 mg BID	$448
Dabigatran 150 mg BID	$436
Edoxaban 60 mg daily	$368
Rivaroxaban 20 mg daily	$451
Warfarin 5 mg daily	$12

Source: Needy Meds Drug Pricing Calculator

Other clinical pearls

Case #2

- AL is a 45 yo male who is being discharged s/p PCI with a drug-eluting stent following STEMI. PMH includes: atrial fibrillation, HTN, hyperlipidemia

Medication list includes:
Aspirin 81 mg PO daily (new)
Clopidogrel 75 mg PO daily (new)
Metoprolol tartrate 25 mg PO BID (new)
Atorvastatin 40 mg PO BID
Apixaban 5 mg PO BID
Lisinopril 20 mg PO daily

Case #2, con't.

- AL presents to your primary care clinic within one week following his hospitalization. He asks you "I'm not a big fan of taking multiple pills a day. How long do I need to take these new medications, forever?"

- Your reply…

Triple therapy controversy

- In at-risk AF patients who have undergone coronary artery stenting, double therapy with clopidogrel and low-dose rivaroxaban (15 mg daily) or dabigatran (150 twice daily) is reasonable to reduce the risk of bleeding as compared to triple therapy (COR IIa, B-R).

January CT, et al. *Am Coll Cardiol* 2019;Jan 28: Epub ahead of print.

AUGUSTUS trial

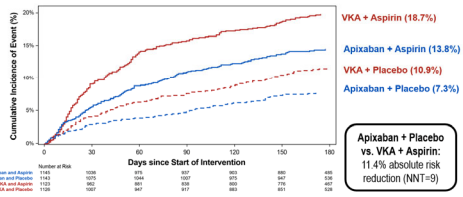
Objective: Determine the optimal antithrombotic treatment strategy for patients with AF + recent ACS/PCI

Study Design	2x2 factorial randomized clinical trial
Intervention	Open-label warfarin (INR 2-3) or apixaban + P2Y12 inhibitor + double-blind aspirin or placebo
Population & Baseline characteristics	4,614 patients from 494 sites in 33 countries median age 70.6, 1/3 patients female mean CHADS-VASC score 3; mean HAS-BLED score 2.9 ½ of patients had been on prior oral anticoagulant 92.6% patients on clopidogrel
Primary outcome at 6 months	incidence of ISTH/major CRMN bleeding event HR 0.69, 95% CI 0.58-0.81 for apixaban vs. warfarin; NNT 24 Bleeding events HR 1.89, 95% CI 1.59-2.24 for aspirin vs. placebo NNH 14
Secondary outcomes	Apixaban vs. warfarin Death/rehospitalization HR 0.83, 95% CI 0.74-0.96; NNT 26 No difference in death/rehospitalization for aspirin vs. placebo comparison. No significant differences between apixaban vs. warfarin or aspirin vs. placebo related to death/ischemic events Apixaban treatment resulted in lower stroke incidence HR 0.50, 95% CI 0.26-0.97

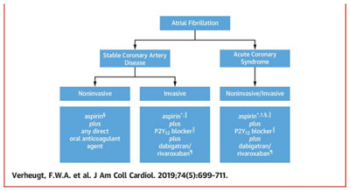
Vora AN, et al. *Am Coll Cardiol* 2019;

AUGUSTUS, con't.

Major / CRNM Bleeding



Antithrombotic strategy in CAD + A-Fib



Verheugt, F.W.A. et al. J Am Coll Cardiol. 2019;74(5):699-711.

If triple therapy is prescribed for patients with AF who are at increased risk of stroke and who have undergone PCI with stenting for ACS, ***a transition to double therapy at 4-6 weeks may be considered.*** *(IIb)*

Marked Safe From

Triple Antithrombotic Therapy

Today

Practice Pearls for Patients with ESRD

- For patients with CHA_2DS_2-VASc score ≥ 2 *in men or* ≥ 3 *in women*, & CrCl < 15 mL/min or patients on dialysis, it is reasonable to use warfarin or apixaban
  - Apixaban > warfarin with lower rate of embolism and death with warfarin with lower rate of embolism/mortality
- Dabigatran & rivaroxaban had more embolic events and bleeding than aspirin or warfarin in NVAF with CKD
  - Aspirin had lowest rate of embolic events/bleeding

January CT, et al. *Am Coll Cardiol* 2019; Jan 28. Epub ahead of print.
Siontis, et al. *Circulation* 2018;138(15):1519-29.
Chan, et al. *Circulation* 2015;131;972-79.

Practice Pearls for Perioperative Management

TABLE 4 Recommended Durations for Withholding DOACs Based on Procedural Bleed Risk and Estimated CrCl When There Are No Increased Patient Bleed Risk Factors

	Dabigatran					Apixaban, Edoxaban, or Rivaroxaban		
CrCl, mL/min	≥80	50-79	30-49	15-29	<15	≥30	15-29	<15
Estimated drug half-life, h	13	15	18	27	30 (off dialysis)	6-15	Apixaban: 17 Edoxaban: 17 Rivaroxaban: 9	Apixaban: 17 (off dialysis) Edoxaban: 10-17 (off dialysis) Rivaroxaban: 13 (off dialysis)
Procedural bleed risk								
Low	≥24 h	≥36 h	≥48 h	≥72 h	No data. Consider measuring dTT and/or withholding ≥96 h	≥24 h	≥36 h	No data. Consider measuring agent-specific anti Xa level and/or withholding ≥48 h
Uncertain, intermediate, or high	≥48 h	≥72 h	≥96 h	≥120 h	No data. Consider measuring dTT	≥48 h	No data. Consider measuring agent-specific anti Xa level and/or withholding ≥72 h	

NOTE: The duration for withholding is based upon the estimated DOAC half-life withholding times of 2 to 3 half-lives for low procedural bleeding risk and 4 to 5 drug half-lives for uncertain, intermediate, or high procedural bleeding risk (47-53).

CrCl = creatinine clearance; DOAC = direct-acting oral anticoagulant; dTT = dilute thrombin time.

Tomaselli GF, et al. *J Am Coll Cardiol* 2017

SSRI interactions (this is here for Dr. Paxos)

ROCKET-AF Analysis

Table 5. Adjusted Comparisons of Efficacy and Safety End Points by SSRI Use and Randomized Warfarin vs Rivaroxaban (Matched Cohorts)

Outcomes	*P* Value for Interaction of SSRI and Treatment	Rivaroxaban Patients: SSRI vs No SSRI HR (95% CI)	Warfarin Patients: SSRI vs No SSRI HR (95% CI)	SSRI Patients: Rivaroxaban vs Warfarin HR (95% CI)	No SSRI Patients: Rivaroxaban vs Warfarin HR (95% CI)
Safety Outcomes					
Major/NMCR bleeding	0.69	1.11 (0.82, 1.51)	1.21 (0.91, 1.60)	0.99 (0.72, 1.35)	1.07 (0.83, 1.38)
Major bleeding	0.40	1.13 (0.62, 2.06)	1.58 (0.96, 2.60)	0.69 (0.38, 1.25)	0.96 (0.58, 1.61)
Efficacy outcomes					
Stroke/non-CNS embolism	0.44	1.61 (0.71, 3.64)	1.09 (0.60, 1.96)	0.74 (0.33, 1.68)	0.50 (0.24, 1.03)
Ischemic stroke	0.41	1.72 (0.64, 4.61)	1.04 (0.53, 2.02)	0.71 (0.29, 1.77)	0.43 (0.18, 1.01)

Models are the same as in Table 3, with the addition of a term for the interaction between SSRI use and randomized treatment. CI indicates confidence interval; CNS, central nervous system; HR, hazard ratio; NMCR, nonmajor clinically relevant; SSRI, selective serotonin reuptake inhibitor.

Quinn GR, et al. *Am J Heart Assoc* 2018;7(15):e00875

Summary

- For patients with AF (unless moderate-severe mitral stenosis or prosthetic heart valve) and high stroke risk via CHADS-VASc score, begin treatment with NOAC > warfarin
- Choice of NOAC depends on many patient-specific factors including bleeding risk, renal/hepatic function, drug interactions, and cost amongst other factors
- Reversal agents are available for most anticoagulation options
- Perioperative management depends on renal function & bleed risk associated with procedure

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Use of NOACs vs. VKA after TAVR

- GALILEO
- ATLANTIS (NCT02664649)
- ENVISAGE-TAVI (NCT02943785)
- Joccheim D, et al
  - Comparable composite primary outcome (all-cause mortality, MI, and any cerebrovascular event) and bleeding risk at 1-year between NOACs and VKA
- PARTNER II
  - Patients with AF, CHADS-VASC score >/= 2, antiplatelet +/- OAC associated with decreased risk of stroke at 2 years

References, Appendix

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