Practical use of **ANTICOAGULANTS** to manage patients with

ATRIAL FIBRILLATION

Preventing Thrombosis, Minimizing Bleeding, and Exploring Reversal Agents

A CME-CERTIFIED CLINICAL TOPICS GRAND ROUNDS PROGRAM

Jointly provided by Potomac Center for Medical Education and Rockpointe
Supported by an educational grant from Daiichi Sankyo, Inc.

pcme Rockpointe

Learning Objectives

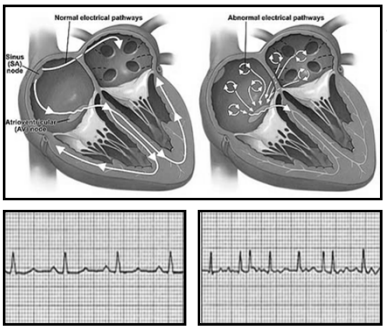
- Identify AFib patients who are at risk for developing ischemic stroke and comply with treatment guidelines for their management
- Evaluate options to overcome the limitations of vitamin K antagonists to reduce the risk of new and recurrent strokes
- Individualize antithrombotic treatments to find the right drug at the right dose for the right patient

Lecture Overview

- **Prevalence and Incidence of Atrial Fibrillation (AF)**
- Risk Stratification for Stroke and Bleeding
- Clinical Properties of Warfarin
- Clinical Properties of Non-vitamin K Oral Anticoagulants
- Current Guidelines on Management of AF
- Preventing and Managing Bleeding (Reversal Agents)
- Considerations for Choosing an Anticoagulant

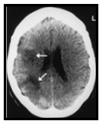
The ECG of Atrial Fibrillation

Normal sinus rhythm

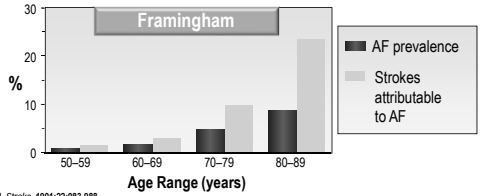


Atrial fibrillation

Stroke and Atrial Fibrillation Burden



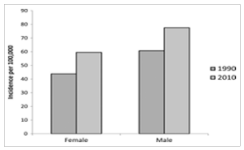
- ▶ More than 2.2 million individuals in the US have AF
- ▶ AF increases risk of stroke about 5-fold
- ▶ Strokes in patients with AF strokes lead to worse outcomes
- ▶ Costly health care ~$16 billion/year



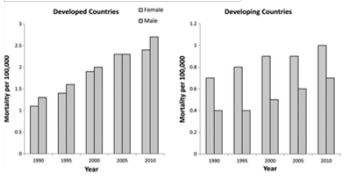
Wolf PA et al. *Stroke.* 1991;22:983-988.

Atrial Fibrillation: An Epidemic

Age-adjusted Global Incidence



AF-related Mortality



Chugh SS et al. *Circulation.* 2014;129:837-847.

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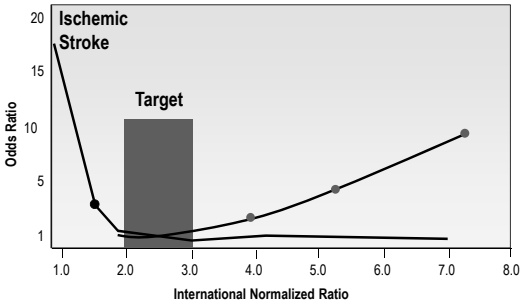
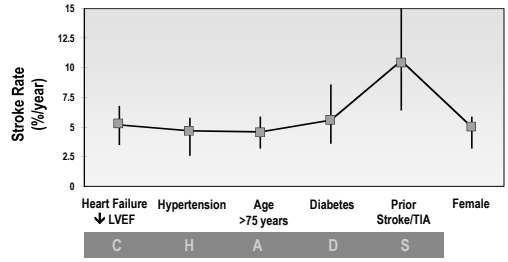
Efficacy and Safety of Warfarin



Fang MC et al. *Ann Intern Med.* **2004;141:745.**
Hylek EM et al. *N Engl J Med.* **1996;335:540.**

Nonvalvular Atrial Fibrillation

Stroke Rates Without Anticoagulation According to Isolated Risk Factors



Hart RG et al. *Neurology.* **2007;69:546-554.**

Redefining Risk: CHA_2DS_2-VASc

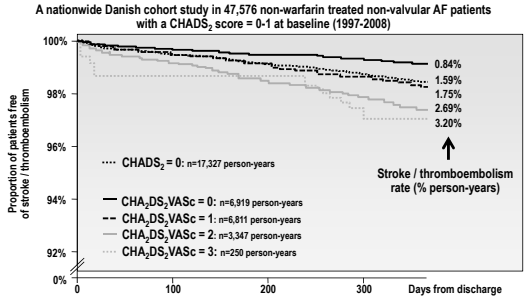
Risk Factor	Points	CHA_2DS_2-VASc Score	Stroke (% / yr)
CHF / LV Dysfunction	1	1	0 %
Hypertension	1	2	1.3 %
Age ≥75	2	3	2.2 %
Diabetes Mellitus	1	4	4.0 %
Stroke / TIA / Embolism	2	5	6.7 %
Vascular Disease	1	6	9.8 %
Age 64-74	1	7	9.6 %
Sex Category (female)	1	8	6.7 %
Maximum Score	9	9	15.2 %

ESC Guidelines. *Eur Heart J.* **2010;31:2369-2429.**

CHA_2DS_2-VASc Refines Stroke Risk

Stratification in $CHADS_2$=0 vs CHA_2DS_2VASc

A nationwide Danish cohort study in 47,576 non-warfarin treated non-valvular AF patients with a $CHADS_2$ score = 0-1 at baseline (1997-2008)



Olesen et al. *Thromb Haemost.* **2012;107:1172-1179.**

Initiation of OAC to Reduce Stroke Risk in Patients with AF

- The CHA_2DS_2-VASc scoring system helps clinicians determine stroke risk and to choose oral anticoagulation (OAC) therapy
- OAC therapy options: New direct oral anticoagulants (DOAC) or vitamin K antagonists (VKA); The most commonly used VKA is warfarin
- Drug interactions should also be considered when prescribing

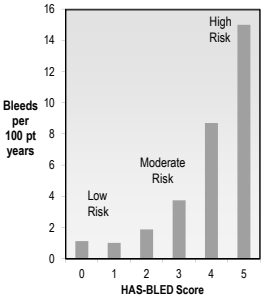
	Risk Factor	Points
C	Congestive heart failure (or left ventricular systolic dysfunction)	1
H	Hypertension (blood pressure consistently above 140/90 mmHg)	1
A_2	Age ≥75 years	2
D	Diabetes mellitus	1
S_2	Prior stroke or TIA or thromboembolism	2
V	Vascular disease (peripheral artery disease, MI, aortic plaque)	1
A	Age 65-74 years	1
Sc	Sex category (i.e. female sex)	1

Total Score		Anticoagulation Stroke Option
0	Low stroke risk	No antithrombotic therapy (or aspirin 75-325 daily)
1	Moderate	Either DOAC or warfarin at an internationalized ratio (INR) of 2.0-3.0
≥2	High	Either DOAC or warfarin at INR 2.0-3.0

Kovacs RJ et al. *J Am Coll Cardiol.* **2015;65:1340-1360.**

Bleeding Risk: HAS-BLED

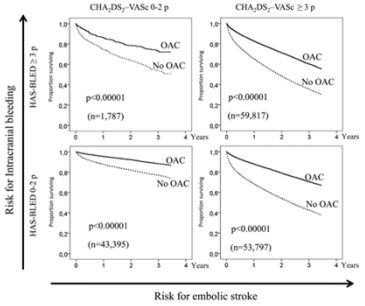
Letter	Clinical Characteristic	Points
H	Hypertension	1
A	Abnormal Liver or Renal Function	1 or 2
S	Stroke	1
B	Bleeding	1
L	Labile INR	1
E	Elderly (age >65)	1
D	Drugs or Alcohol	1 or 2
	Maximum Score	9



ESC Guidelines. *Eur Heart J*. 2010;31:2369-2429.

Net Clinical Benefit of Warfarin

All-cause Mortality, Ischemic Stroke, and ICH



Friberg L et al. *Circulation*. 2012;125:2298-2307.

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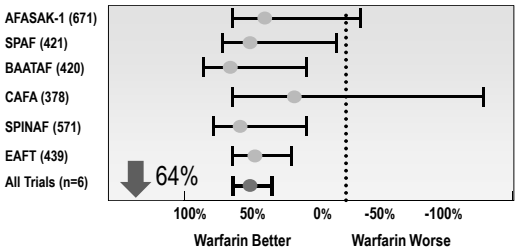
Stroke Prevention in AF

Warfarin vs Placebo (pooled analysis of 2900 participants)



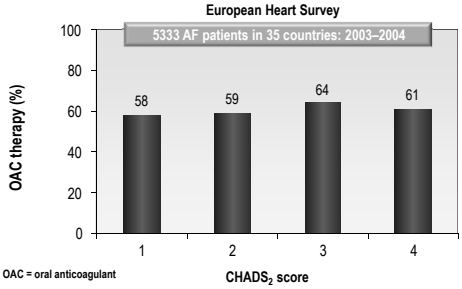
Hart RG et al. *Ann Intern Med*. 2007;146:857-867.

Limitations of Warfarin

- Delayed onset/offset
- Multiple food and drug interactions
- Genetic variability in metabolism (VKORC1 and CYP2C9)
- Requires frequent monitoring of INR due to limited therapeutic index; continual dose titration needed
- Increases risk of intracerebral hemorrhage and fatal bleeding

Modest Use of Vitamin K Antagonists

Even in High-risk Patients



OAC = oral anticoagulant

Nieuwlaat R et al. *Eur Heart J*. 2006;27:3018-3026.
Gage BF et al. *JAMA*. 2001;285:2864-2870.

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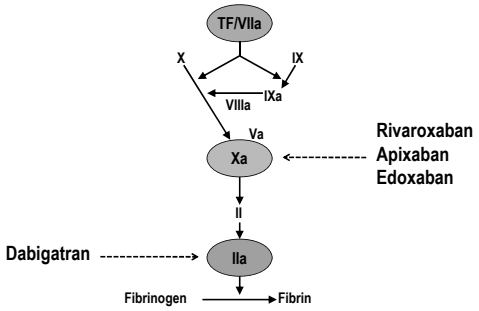
Properties of an Ideal Anticoagulant

Properties	Benefit
Oral, once-daily dosing	Ease of administration
Rapid onset of action	No need for overlapping parenteral anticoagulant
Minimal food or drug interactions	Simplified dosing
Predictable anticoagulant effect	No coagulation monitoring
Extra renal clearance	Safe in patients with renal disease
Rapid offset in action	Simplifies management in case of bleeding or intervention
Antidote	For emergencies

Non-Vitamin K Oral Anticoagulants



Adapted from: Weitz JI, Bates SM. *J Thromb Haemost.* 2005;3:1843-1853.

Comparison Overview of Non-vitamin K Oral Anticoagulants (NOCAs) with Warfarin

Features	Warfarin	NOACs
Onset	Slow	Rapid
Dosing	Variable	Fixed
Food effect	Yes	No
Drug interactions	Many	Few
Monitoring	Yes	No
Half-life	Long	Short
Antidote	Yes	No

Comparative PK/PD

Novel Oral Anticoagulants

	Dabigatran	Rivaroxaban	Apixaban	Edoxaban
Target	IIa (thrombin)	Xa	Xa	Xa
Hours to C_{max}	1-3	2-4	3-4	1-2
Half-life, hours	12-17	5-13	12	10-14
Renal Clearance, %	80	33*	27	50
Transporters	P-gp	P-gp	P-gp	P-gp
CYP Metabolism, %	None	32	~25	<4

CYP = cytochrome P450; P-gp = P-glycoprotein

*33% renally cleared; 33% excreted unchanged in urine

Pradaxa [package insert]. Ridgefield, CT: Boehringer Ingelheim Pharmaceuticals, Inc. 2013.
Xarelto [package insert]. Titusville, NJ: Janssen Pharmaceuticals, Inc. 2011.
Weinz et al. *Drug Dispos Metab.* 2009;37:1056-1064.
ELIQUIS Summary of Product Characteristics. Bristol-Myers Squibb/Pfizer EEIG, UK.
Matsushima et al. *Am Assoc Pharm Sci.* 2011; abstract.
Ogata et al. *J Clin Pharmacol.* 2010;50:743-753.
Mendell et al. *Am J Cardiovasc Drugs.* 2013;13:331-342.
Bathala et al. *Drug Metab Dispos.* 2012;40:2250-2255.

Stroke Prevention in Atrial Fibrillation Trials

Novel Oral Anticoagulants

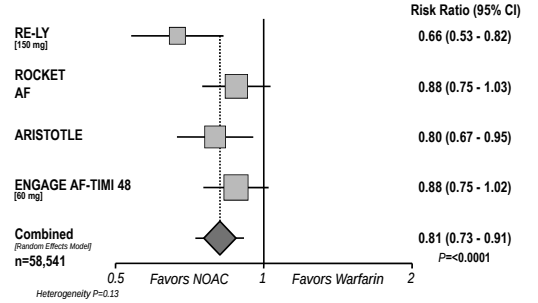
	RE-LY[a]	ROCKET-AF[b]	ARISTOTLE[c]	ENGAGE AF[d]
Drug	Dabigatran	Rivaroxaban	Apixaban	Edoxaban
# Randomized	18,113	14,266	18,201	21,105
Dose (mg)	150, 110	20	5	60, 30
Frequency	Twice Daily	Once Daily	Twice Daily	Once Daily
Dose Adjustment	No	20 → 15	5 → 2.5	60 → 30 30 → 15
At Baseline	0	21	5	25
After Randomization	No	No	No	8%
Target INR (Warfarin)	2.0-3.0	2.0-3.0	2.0-3.0	2.0-3.0
Design	PROBE*	2x blind	2x blind	2x blind

*PROBE = prospective, randomized, open-label, blinded, end-point evaluation

a. Connolly SJ et al. *N Engl J Med.* 2009;361:1139-1151.
b. Patel MR et al. *N Engl J Med.* 2011;365:883-891.
c. Granger CB et al. *N Engl J Med.* 2011;365:981-992.
d. Giugliano RP et al. *N Engl J Med.* 2013;369:2093-2104.

Meta-analysis of All NOACs vs Warwfarin

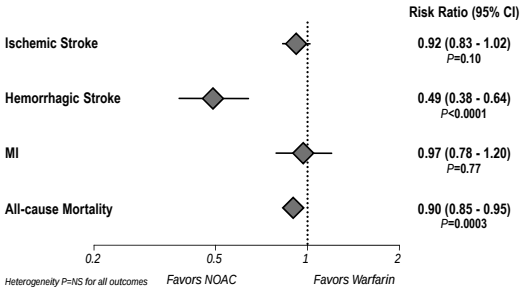
Stroke or Systemic Embolic Events



Ruff CT et al. *Lancet.* **2014;383:955-962.**

Meta-analysis of All NOACs vs Warfarin

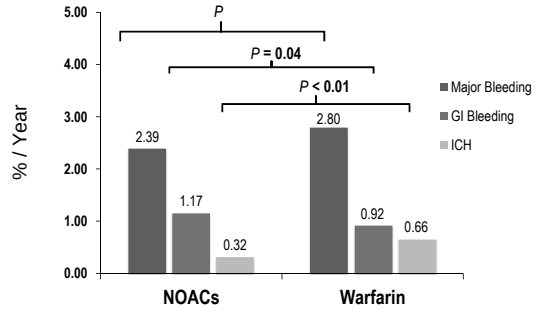
Secondary Efficacy Outcomes



Ruff CT et al. *Lancet.* **2014;383:955-962.**

How Frequent is Bleeding with NOACs?

71,683 Patients: 4 Phase III AF NOAC Trials



Ruff CT et al. *Lancet.* **2014;383:955-962.**

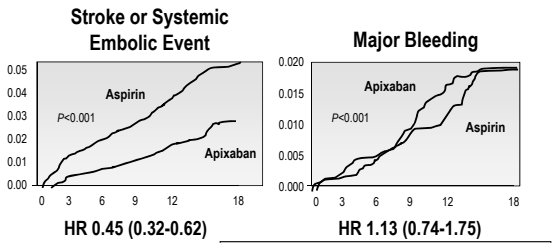
AHA, ACC, and HRS Guidelines for the Management of Patients with AF

- Use CHA_2DS_2-VASc instead of $CHADS_2$ for patients with non-valvular AF
- A CHA_2DS_2-VASc score of 1 in patients with non-valvular AF should be treated with either no anti-coagulation therapy, aspirin, or an oral anticoagulant
- A CHA_2DS_2-VASc score of ≥2 warrants use of an oral anticoagulant, if there are no contraindications
- A CHA_2DS_2-VASc score of ≥2 warrants use of an oral anticoagulant, either warfarin, dabigatran, rivaroxaban, apixaban, or edoxaban

Updated from January CT et al. *Circulation.* **2014;130:2071-2104.**

Is Aspirin as Effective and Safe as NOACs?

Data from Apixaban in the AVERROES Trial



Aspirin is less efficacious and has similar bleeding to apixaban.

Connolly SJ et al. *N Engl J Med.* **2011;364:806-817.**

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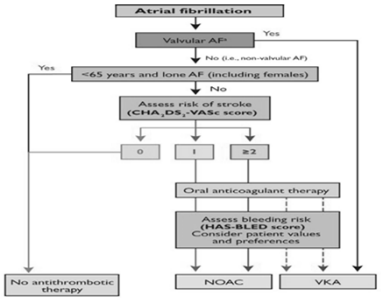
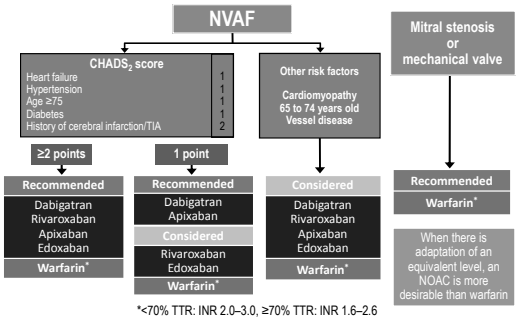
Choice of Anticoagulant in Patients with AF
ESC Guidelines



Camm AJ et al. *Eur Heart J.* 2012;33:2719-2747.

Japanese Circulation Society 2014 Guidelines
Antithrombotic Therapy in AF



*<70% TTR: INR 2.0–3.0, ≥70% TTR: INR 1.6–2.6

JCS Joint Working Group. *Circ J.* 2014;78:1997-2021.

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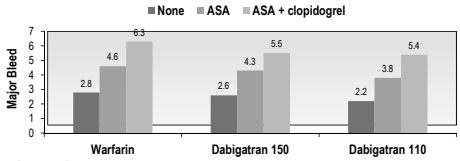
Are We Using Too Much Aspirin in Patients with AF? *Bleeding According to Antiplatelet Treatment*



- Series of no, single, and dual antiplatelet therapy
- HRs adjusted for age, gender, warfarin experience, SBP, CAD, HF, hypertension, diabetes, TIA, CrCl, and statin use

Concomitant antiplatelet drugs appeared to increase the risk for major bleeding in RE-LY without affecting the advantages of dabigatran over warfarin

ASA = aspirin; CAD = coronary artery disease; HF = heart failure; SBP = systolic blood pressure

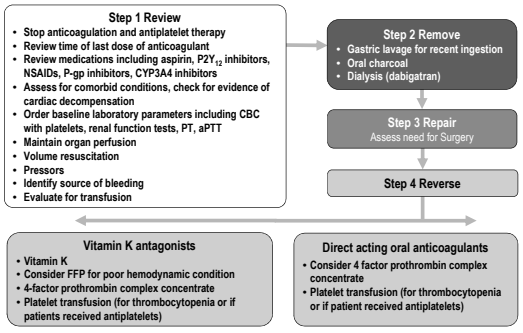
Hans DL et al. *Circulation.* 2013;127:634-640.

Renal Function and NOACs

- All 4 Phase III NOAC trials excluded patients with an eGFR <25-30 mL/min
- Renal impairment is an independent risk factor for stroke, bleeding, and death
- All NOACs require dose adjustment for renal failure:
  - Dabigatran 150 mg bid for CrCl >30 mL/min
  - 75 mg bid if CrCl 15-30 mL/min
  - Rivaroxaban 20 mg once daily for CrCL >50 mL/min
  - 15 mg once daily if CrCL 15-50 mL/min
  - Edoxaban 60 mg once daily if CrCL >50 to <95 mL/min
  - 30 mg once daily if CrCL<15-50 mL/min; should not be used if CrCl >95 mL/min
  - Apixaban 5 mg bid
  - 2.5 mg twice daily with 2 of 3: age ≥80 y, weight ≤ 60 kg, serum creatinine ≥1.5 mg/dL

CrCL = creatinine clearance
Package inserts for dabigatran, rivaroxaban, edoxaban, and apixaban

Managing Bleeding with NOACs



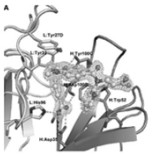
Kovacs RJ et al. *J Am Coll Cardiol.* 2015;65:1340-1360.

Non-specific Reversal Agents

Only after D/C drug and supportive care (fluids / transfusions)

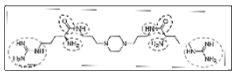
Agent	Clotting Factors Replaced	Dose
4 Factor-PCC	Factors II, VII, IX, X	25-50 units/kg
3 Factor-PCC	Factors II, IX, X	25-50 units/kg
aPCC	Factors II, VIIa, IX, X	80 units/kg
rFVIIa	FVIIa	90 ug/kg

New and Emerging Antidotes



Idarucizumab (BI 655075)
Target: Dabigatran
FDA approved: October 2015
Structure: humanized antibody fragment (FAb) to dabigatran

Andexanet alfa (PRT064445)
Target: FXa inhibitors
Structure: FXa lacking catalytic and binding activity



Aripazine (PER977; Ciraparantag)
Target: Universal – all NOACs, heparin, LMWH
Structure: synthetic small molecule (D-arginine)

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Patients Not Well Suited for an NOAC

- **Mechanical heart valves**
- **Moderate-severe mitral stenosis and AF**
- **Pregnancy and nursing mother**
- **Stage V CKD**
  (apixaban OK in patients on stable hemodialysis per the US FDA)
- **Moderate-severe hepatic failure**
- **Children**
- **Extremes of physiology (e.g. weight, age)**
- **Malabsorption**

Optimal Candidates for NOACs

- Almost all patients with non-valvular AF should be considered as candidates for NOACs
- Patients with normal renal function
- European and Japanese guidelines recommend NOACs over VKA
- Ineligible patients include
  - Those who are pregnant
  - Those with mechanical heart valve or in early post-operative cardiac surgery

Renal Function and NOACs

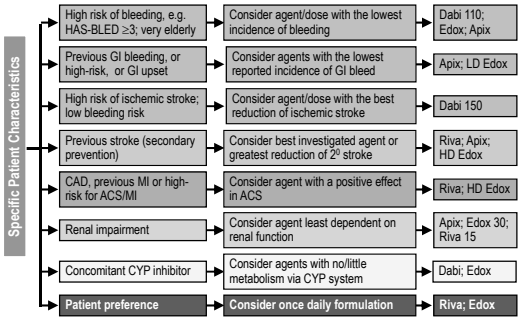
- All 4 Phase III NOAC trials excluded patients with an eGFR <25-30 mL/min
- Dabigatran is 80% renally eliminated, greater than rivaroxaban (33% renally metabolized and 33% excreted unchanged by kidneys), edoxaban (50%), and apixaban (27%)[a]
- Renal impairment is an independent risk factor for stroke, bleeding, and death
- 150 mg twice daily of dabigatran: use cautiously in the elderly (>80 yr) and with renal impairment (<40 mL/min)[b]
- All NOACs require dose adjustment for renal failure:
  - Dabigatran 75 twice daily if CrCl 15-30 mL/min (US FDA)
  - Rivaroxaban 15 mg once daily if CrCL <15-49 mL/min
  - Edoxaban 30 mg once daily if CrCl <15-50 mL/min[c]; should not be used if CrCl >95 mL/min
  - Apixaban 2.5 mg twice daily with 2 of 3: age ≥80 y, weight ≤60 kg, SCr ≥1.5 mg/dL

a. Heidbuchel H et al. *Europace*. 2013;15:625-651.
b. Dabigatran SMPC. www.ema.europa.eu/docs/en_GB/document_library/EPAR_Product_Information/human/000829/WC500041059.pdf.
c. Edoxaban Package Insert. www.accessdata.fda.gov/drugsatfda_docs/label/2015/206316lbl.pdf.

Important Factors when Considering an NOAC

- All patients with atrial fibrillation should be considered for an NOAC, except if mechanical valve, rheumatic MS, pregnant, children
- NOACs decrease intracerebral hemorrhage (50%) and major bleeding (14%) compared to warfarin
- NOACs decrease stroke/systemic embolism (18%) and death (10%) compared to warfarin
- NOACs are not all the same, so selection of which NOAC depends on patient characteristics

"Pointers" Regarding Which NOAC to Choose*



* All of these "pointers" are debatable

Savelieva I et al. *Clin Cardiol.* **2014;37:32-47.**
Gonzelz-Quesada CJ, Giugliano RP. *J Thromb Thrombolysis.* **2015;39:129-138.**

Conclusions

Properties of Ideal Anticoagulant

Do NOACs Fit the Bill?

- ✓ Proven efficacy
- ✓ Low bleeding risk
- ✓ Fixed dosing
- ✓ Good oral bioavailability
- ✓ No routine monitoring needed
- ✓ Reversibility: ?PCC, FEIBA, rVIIa
- ✓ Rapid onset of action
- ✓ Few drug or food interactions

Additional Issues Regarding Direct OACs

1. How do we compare the different drugs and studies in the absence of head-to-head studies?
2. Would more flexible dosing improve safety:efficacy (e.g. in patients who bleed or are at extremes of age, weight)?
3. Are NOACs "better" if patients are well controlled on warfarin?
4. How should we incorporate measures of drug concentration or anticoagulation levels in clinical practice, if at all?
5. Is the fast offset a problem if patients are not compliant?
6. Are there specific adverse drug reactions?
7. Which drug and what dose when dual antiplatelets are needed (e.g. ACS or post-stenting)
8. How do we best evaluate cost-effectiveness?

CME Credit

- **Post-activity Survey**
  - Now that the program has completed, *please take a moment* to answer the Post-activity Survey questions on your form
  - Your answers are important and will help us identify remaining educational gaps and shape future CME activities
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