Atrial Fibrillation
Stroke Risk Reduction

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Presenter Disclosure Information

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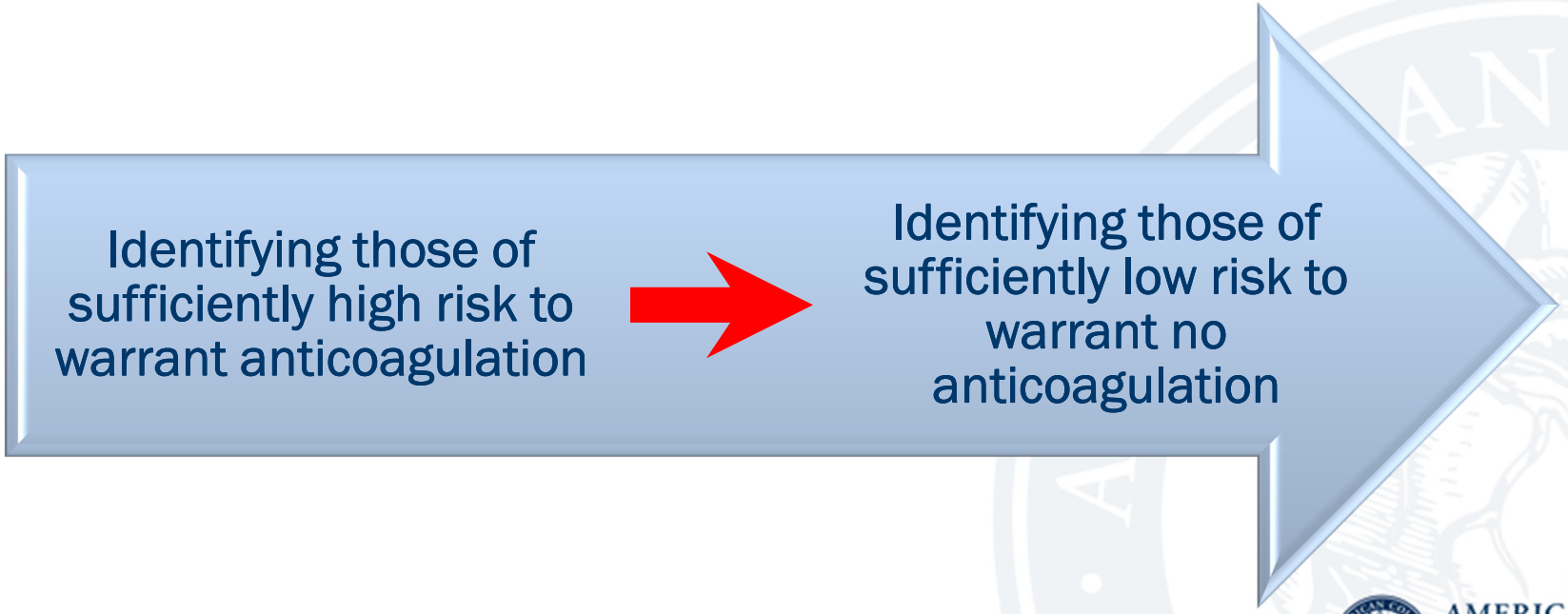
Objectives

- Effectively estimate stroke and bleeding risk in patients with atrial fibrillation (AF)
- Recognize key advantages and disadvantages of available oral anticoagulants
- When presented with a patient case recommend an appropriate oral anticoagulant to reduce thromboembolic risk associated with AF

Assessing Thromboembolic Risk



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Assessing Thromboembolic and Bleeding Risk

- Risk Stratification Schemes
  - $CHADS_2$
  - CHA_2DS_2-VASc
    - Broader score range
    - Larger number of risk factors
    - Incorporated into guideline recommendations
  - HAS-BLED
    - Higher scores identify those who require closer observation
    - Better than other scoring systems but only modest performance and poor predictive accuracy
    - Not necessarily applicable to non warfarin oral anticoagulants

CHA_2DS_2-VASc Risk Stratification

CHA_2DS_2-VASc acronym	Score
Congestive HF or LVEF < 40%	1
Hypertension	1
Age ≥ 75	2
Diabetes mellitus	1
Stroke/TIA/TE	2
Vascular disease (MI/PAD/aortic plaque)	1
Age 65-75 years	1
Sex category (i.e., female)	1
Maximum Score	9

CHA_2DS_2-VASc Score	Adjusted stroke rate (% per 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%

HAS-BLED Risk Score

Condition	Points
Hypertension (SBP > 160)	1
Liver dysfunction*	1
Renal dysfunction**	1
Stroke	1
Bleeding***	1
Labile INRs (TTR < 60%)	1
Age > 65	1
NSAIDs/Antiplatelets	1
Alcohol (8 +/week)	1

HAS-BLED Score	Major Bleeds/year
0	1.13%
1	1.02%
2	1.88%
3	3.74%
4	8.7%
5	12.5%
6	–
7	–
8	–
9	–

*Dialysis, renal transplant, Scr > 2.3
**Chronic liver disease, bilirubin > 2x ULN with AST/ALT/ALP > 3x ULN
***Anemia or predisposition to bleeding

Selected 2014 AHA/ACC/HRS Recommendations

Class I

- In patients with nonvalvular AF, the CHA2DS2-VASc score is recommended for assessment of stroke risk (LOE B)
- Selection of antithrombotic therapy should be based on the risk of thromboembolism irrespective of whether the AF pattern is paroxysmal, persistent, or permanent (LOE B)
- In patients with AF, antithrombotic therapy should be individualized based on shared decision making after discussion of the absolute and relative risk of stroke and bleeding, and the patient's values and preferences. (LOE C)

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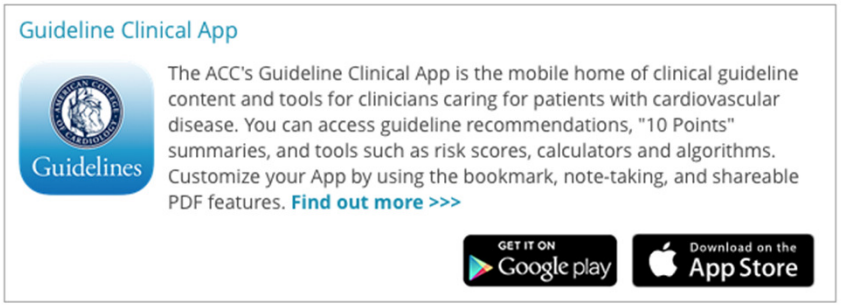
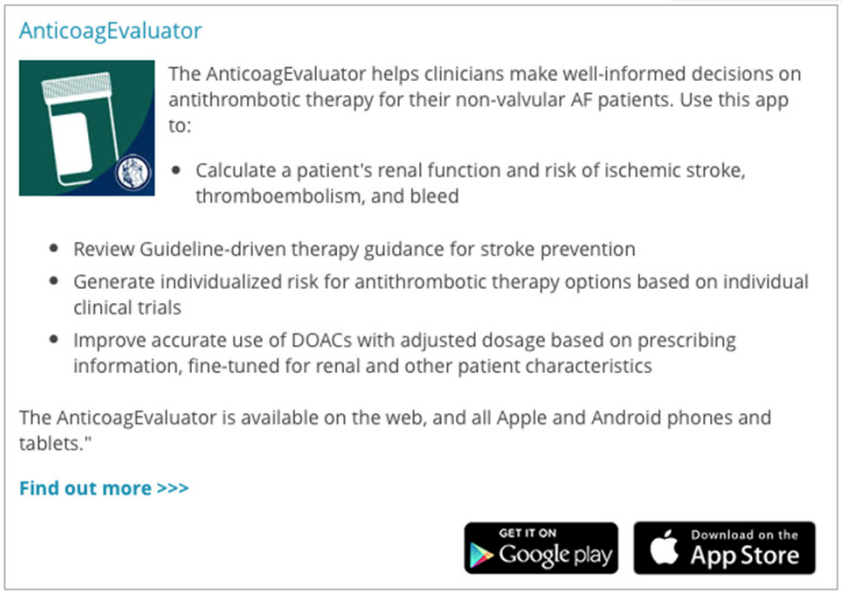
ACC Mobile Resources





http://www.acc.org/tools-and-practice-support/mobile-resources

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Selected 2014 AHA/ACC/HRS Recommendations

- Class I
  - NVAF with CHA_2DS_2-VASc $\geq$ 2 oral anticoagulation with warfarin (LOE A), dabigatran, rivaroxaban, or apixaban (LOE B)
- Class IIa
  - NVAF with CHA_2DS_2-VASc of 0 it is reasonable to omit antithrombotic therapy (LOE B)
- Class IIb
  - NVAF with CHA_2DS_2-VASc of 1, no antithrombotic therapy or treatment with an oral anticoagulant or aspirin may be considered (LOE C)

Antithrombotic Options

- Aspirin (dose 81-325mg)
  - Only 1 trial (SPAF) showed benefit
  - In a meta-analysis (8 trials) aspirin reduced risk of stroke 19% (95% CI -1% to 35%) with absolute risk reduction of 0.8%/year (NNT 125)
    - Results were driven by the SPAF trial
    - For secondary prevention absolute risk reduction was 2.5%/year (NNT 40)

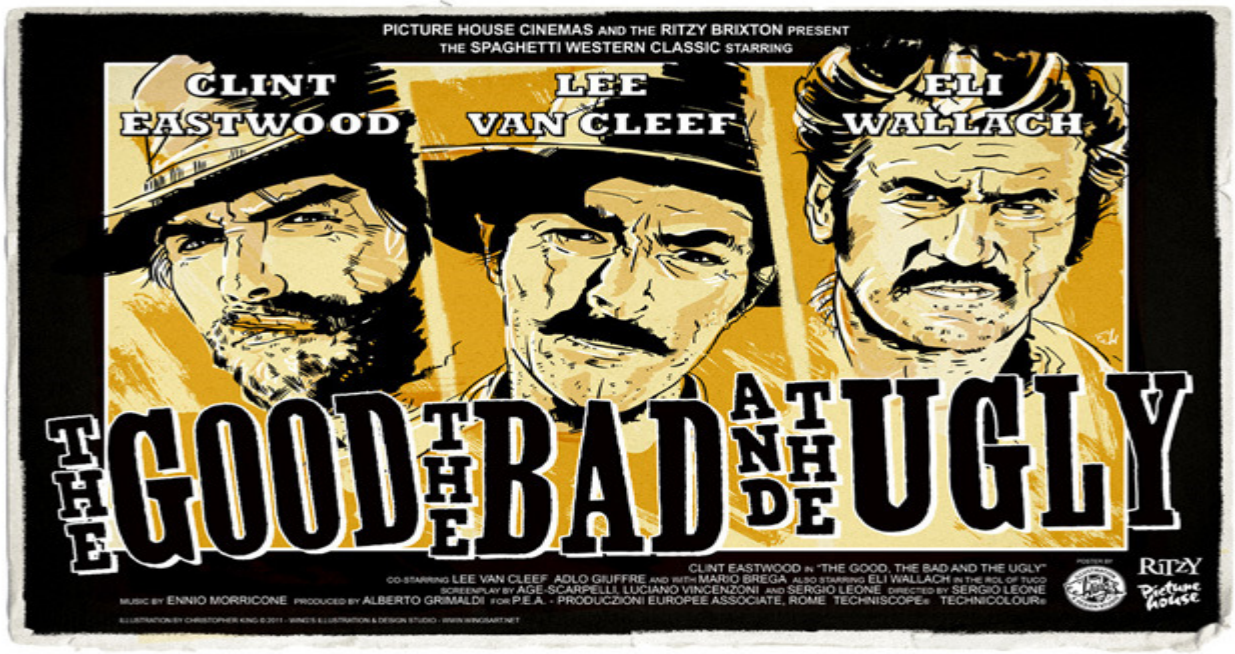
Antithrombotic Options

- Aspirin (75-100mg) + clopidogrel 75mg
  - ACTIVE-A: Combination reduced risk of stroke 28%, but increased risk of major bleeding 57% versus aspirin alone

Antithrombotic Options

- Aspirin (75-100mg) + clopidogrel 75mg
  - ACTIVE-W: Warfarin reduced risk of stroke 40% with a similar rate of major bleeding versus the above combination

Warfarin Therapy



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Warfarin Therapy - The Good

- More effective than aspirin in atrial fibrillation
  - 45% reduction in stroke rate
- More effective than combination of clopidogrel and aspirin in atrial fibrillation
  - ~30% reduction in stroke rate
- Contemporary meta-analysis of trial data shows a low residual risk of stroke 1.66%/year
- 30 million + outpatient prescriptions in 2004 (United States)

Lancet 2006; 367: 1903–12
Arch Intern Med. 2012;172(8):623-631
Arch Intern Med. 2007 Jul 9;167(13):1414-9

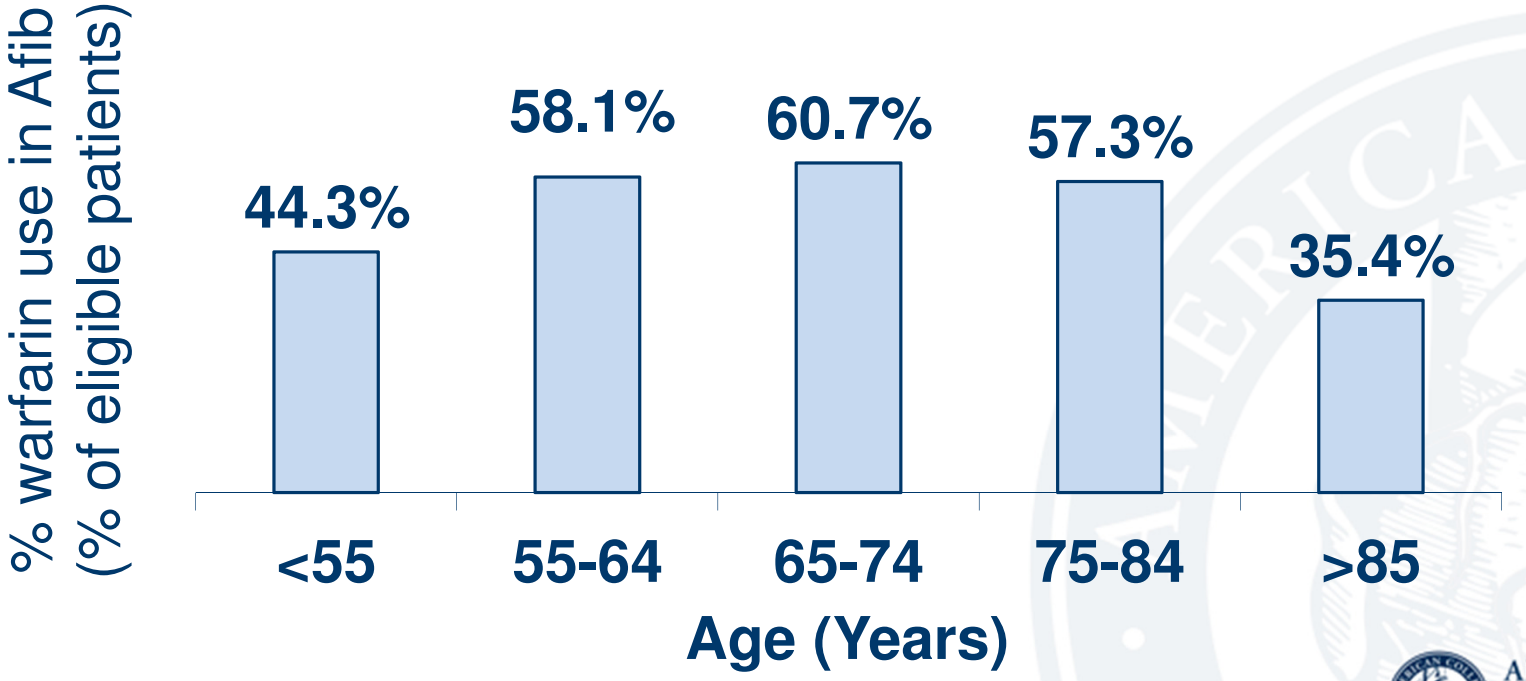
Warfarin Therapy - The Bad

- FDA's Adverse Event Reporting System
  - Warfarin among top 10 drugs with the largest number of serious adverse events (1990-2006)

- US death certificates
  - Anticoagulants ranked first in 2003 and 2004 in the number of total mentions of deaths for drugs causing "adverse effects in therapeutic use"

Arch Intern Med 2007;167: 1414-9

Warfarin Therapy - The Ugly



Stroke. 2006;37:1070-74
Ann Intern Med 1999;131:927-34

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Challenges With Warfarin Therapy

- Slow onset/offset of action
- Narrow therapeutic window
  - Genetic polymorphisms
    - CYP2C9
    - VKORC1
- Need for INR monitoring
- Multiple drug and food interactions
- Bleeding risk
- Need for close patient follow up/education
- Resource allocation

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Annu Rev Med 2011;62:61-57

Shouldn't We Just Throw Warfarin Under the Bus?

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Warfarin – No Longer King of the Mountain, but Not Off of It Either

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When May Warfarin be Preferred

- Mechanical heart valves
- Significant renal dysfunction
- Old of the old (> 80)?
- When you need to know, you can know
  - Adherence issues
  - Specific drug interactions
- Patient preference
- Economic considerations

Models of Warfarin Management

Usual Care

No systematic program for education, follow-up, dosing

Anticoagulation Clinics

Dedicated personnel with systematic polices

Patient self-testing

Patient monitors INR at home with dosing managed by usual care model or anticoagulation clinic

Patient self-management

Patient monitors INR at home and adjusts dose

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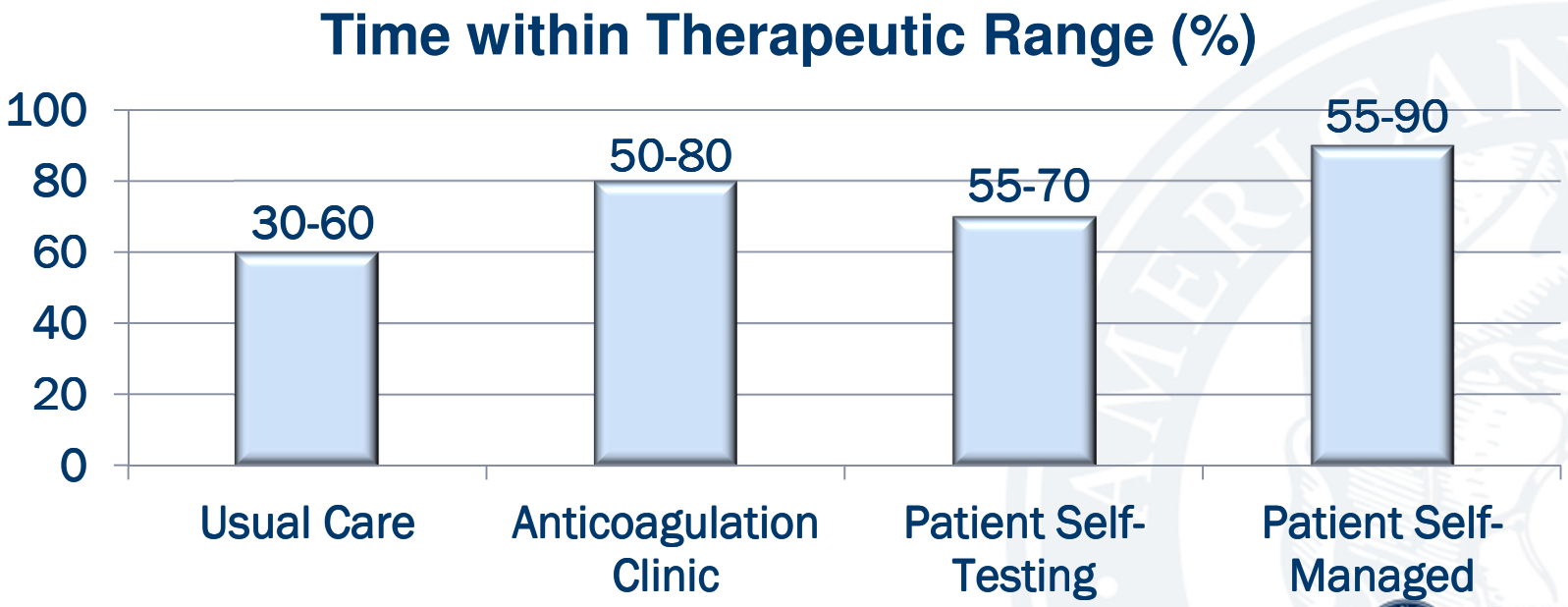
Models of Warfarin Management and Time within Therapeutic Range



Ansell J, et al. Chest, 2008; 133: 160S-198S.

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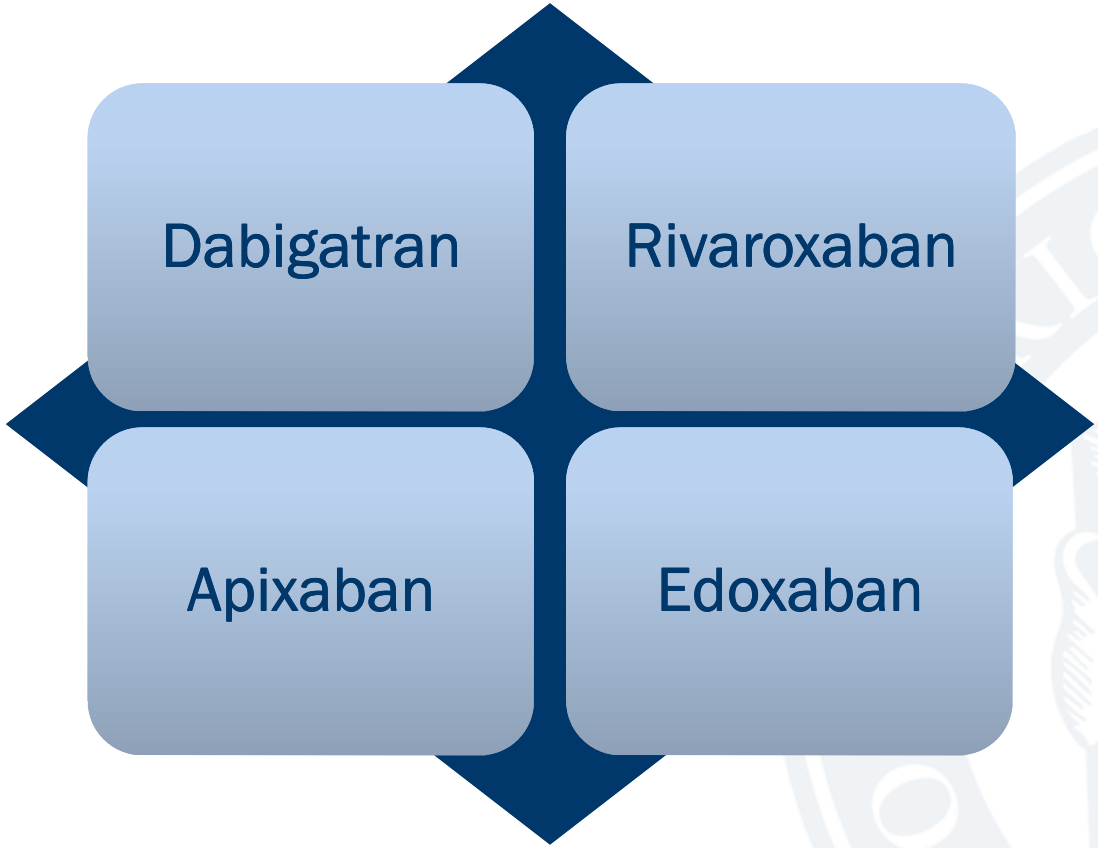
"Ideal" Oral Anticoagulant

- Wide therapeutic window
  - No monitoring
  - Standard dosing
- Acceptable benefit-risk profile
- Rapid onset and withdrawal
  - No "bridge" therapy needed
- Reversible/Antidote
- Minimal drug and food interactions
- No impact with organ dysfunction
  - Renal / Hepatic
- Reasonable cost

Target Specific Oral Anticoagulants (TSOACs)



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Comparison: Baseline Characteristics

	RE-LY		ROCKET-AF		ARISTOLE		ENGAGE-AF	
	D150	VKA	Riva	VKA	Apix	VKA	E 60	VKA
Age	71.5	71.6	73	73	70	70	72	72
$CHADS_2$	2.2	2.1	3.48	3.46	2.1	2.1	2.8	2.8
Prior MI	17%	16%	17%	18%	15%	14%	n/a	n/a
Prior CVA	20%	20%	55%	55%	19%	20%	28%	28%
Prior VKA	50%	49%	62%	63%	57%	57%	58.8%	58.8%
VKA TTR		64%		55%		62%		65%

TTR = Time (mean) in therapeutic range; n/a = not available
D150 = dabigatran 150mg twice daily; E 60 = edoxaban 60mg daily

NEJM 2009;361:1139-51, NEJM 2011;365:883-91, NEJM 2011;365:981-92, NEJM 2013;369:2093-104

Relative Risk Reduction with TSOACs vs. Warfarin

	RE-LY		ROCKET-AF	ARISTOTLE	ENGAGE-AF
	Dabigatran 150mg	Dabigatran 110mg	Rivaroxaban	Apixaban	Edoxaban 60mg
Efficacy Stroke and Systemic Embolism	0.66 (p<0.001)	0.91 (p=0.34)	0.88 (p=0.12)	0.79 (p=0.01)	0.87 (p=0.08)
NNT	173	--	--	239	--
Safety Major Bleeding	0.93 (p=0.31)	0.8 (p=0.003)	1.04 (p=0.58)	0.69 (p<0.001)	0.8 (p<0.001)
NNT	--	154	--	105	147
Safety Intracranial bleeding	0.4 (p<0.001)	0.31 (p<0.001)	0.67 (p=0.02)	0.42 (p<0.001)	0.47 (p<0.001)
NNT	227	196	500	212	217

p-values for superiority

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NEJM 2009;361:1139-51, NEJM 2011;365:883-91, NEJM 2011;365:981-92, NEJM 2013;369:2093-104

TSOACs vs. Warfarin in NVAF: The Bottom Line?

	D150	Riva	Apix	E60
Study	**RE-LY**	**ROCKET-AF**	**ARISTOTLE**	**ENGAGE-AF**
Efficacy (stroke and systemic embolism)	Superior	Non-inferior	Superior	Non-inferior
Ischemic stroke	Superior	Similar	Similar	Similar
Safety (major bleeding)	Similar	Similar	Superior	Superior
Intracranial hemorrhage	Superior	Superior	Superior	Superior
Fatal Bleeding	Superior	Superior	Superior	Superior
GI Bleeding	Inferior	Inferior	Superior	Inferior
Mortality	Favorable trend	Favorable trend	Superior	Favorable trend

NEJM 2009;361:1139-51, NEJM 2011;365:883-91, NEJM 2011;365:981-92, NEJM 2013;369:2093-104

D150 = dabigatran 150mg twice daily; E 60 = edoxaban 60mg daily

Selected Pharmacokinetic Parameters of TSOACs

Parameter	Dabigatran Etexilate	Rivaroxaban	Apixaban	Edoxaban
Bioavailability	3.7%	80-100% (10 mg dose)* 6-90% (20 mg dose)*	50%	62%
Activation	Esterase-catalyzed hydrolysis	Not needed	Not needed	Not needed
Tmax (hours)	1-2	2-4	3-4	1-2
T½ (hours)	12-17**	5-9**	12**	10-14**
Protein binding	35%	>90%	87%	55%
Metabolism (major)	Conjugation (no CYP450)	CYP 3A4, CYP2J2	CYP 3A4	Hydrolysis (<4% CYP450)
P-gp Substrate	Yes	Yes	Yes	Yes
Renal elimination of unchanged drug	80%	36%	25%	35%
Significant removal by dialysis	Yes (60% within 2-3 hours)	Not expected	Not expected	Not expected
Effect of Food	No significant effect	Doses >10 mg to be taken with dinner to enhance absorption	No significant effect	No significant effect

Tmax = time to maximum concentration; T1/2 = half-life
* Bioavailability with 10mg is with or without food; bioavailability with 20mg dose is 66% in fasting state and 90% with food
** T1/2 displayed is for healthy individuals; half-life prolonged in patients with severe renal dysfunction

Long J., Parra D. Reducing cardioembolic risk in the patient with atrial fibrillation. Monthly Prescribing Reference 2015. http://www.empr.com/atrial-fibrillation/section/4477/

Navigating Drug Interactions with TSOACs

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Navigating Drug Interactions with TSOACs

- While less drug interactions that with warfarin all TSOACs do have significant drug-drug interactions that may vary between agents and whose significance may change based on renal function
- Many drug interactions with TSOACs have probably not been adequately characterized yet (e.g. tacrolimus, cyclosporine)
- Drug interactions that may not be critical by themselves may become critical in the presence of additional interacting drugs
- The deemed significance of potential interactions may vary amongst drug references, package inserts, and even over time
- Due diligence is key

Navigating Drug Interactions with TSOACs

	via	Dabigatran	Apixaban	Edoxaban	Rivaroxaban
Antiarrhythmic drugs:					
Amiodarone	moderate P-gp competition	+12-60%[58]	No PK data[$]	+40%[63, 64, 244]	Minor effect[$] (use with caution if CrCl <50 ml/min)
Digoxin	P-gp competition	No effect[245]	No data yet	No effect	No effect[246, 247]
Diltiazem	P-gp competition and weak CYP3A4 inhibition	No effect[58]	+40%[60]	No data yet	Minor effect[#] (use with caution if CrCl 15-50 ml/min)
Dronedarone	P-gp competition and CYP3A4 inhibition	+70-100% (US: 2 x 75 mg if CrCl 30-50 ml/min)	No PK or PD data: caution	+85% (Reduce NOAC dose by 50%)	Moderate effect[#] but no PK or PD data: caution and try to avoid
Quinidine	P-gp competition	+53%[248 & SMPC]	No data yet	+77%[240, 249, 250] (No dose reduction required by label)	Extent of increase unknown
Verapamil	P-gp competition (and weak CYP3A4 inhibition)	+12-180%[58] (reduce NOAC dose and take simultaneously)	No PK data	+53% (SR)[64, 249] (No dose reduction required by label)	Minor effect[$$] (use with caution if CrCl 15-50 ml/min)

Updated European Heart Rhythm Association Practical Guide on the use of non-vitamin K antagonist anticoagulants in patients with non-valvular atrial fibrillation. Europace (2015) 17, 1467–1507 doi:10.1093/europace/euv309

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Direct Acting Oral Anticoagulants: Renal Dosing-Summary

- When evaluating renal function and TSOAC dosing actual body weight should be used along with Cockcroft Gault equation
- FDA approved dosing may provide recommendations for degrees of renal dysfunction that were excluded from the pivotal clinical trials
- Renal dosing may differ between indications (i.e. NVAF vs. VTE)
- Renal dosing may be influenced by drug-drug interactions

Direct Acting Oral Anticoagulants: Renal Dosing

	Dabigatran	Rivaroxaban	Apixaban	Edoxaban
Nonvalvular Atrial Fibrillation	•CrCl 15-30ml/min: Reduce dose to 75mg bid •P-gp inhibitors in patients with CrCl 30-50 mL/min: Consider reducing dose or avoid □ P-gp inhibitors in patients with CrCl < 30 mL/min: Avoid •CrCl < 30 ml/min: Excluded from pivotal trials	•CrCl 15-50 ml/min: Reduce dose to 15 mg once daily •Combined P-gp and moderate CYP3A4 inhibitors with CrCl 15-80ml/min: Use only if potential benefit justifies potential risk •CrCl < 30 ml/min: Excluded from pivotal trials	•Reduce to 2.5mg BID if 2 or more of the following criteria are met: - SCr ≥ 1.5 mg/dL - ≥ 80 yrs - Wt ≤ 60 kg •SCr > 2.5 mg/dL or CrCl < 25 ml/min: Excluded from pivotal trials	•CrCl 15-50ml/min: Reduce to 30mg once daily **•CrCl > 95ml/min AVOID** •CrCl < 30ml/min: Excluded from pivotal trials
VTE Treatment or Prophylaxis	•CrCl < 30 ml/min: Avoid •CrCl < 50 ml/min and on concomitant P-gp inhibitors: Avoid •Not approved for VTE prophylaxis in TKA	•CrCl < 30 ml/min: Excluded from pivotal trials	•SCr > 2.5 mg/dL or CrCl < 25 ml/min (VTE treatment): Excluded from pivotal trials •CrCl < 30ml/min (VTE prophylaxis): Excluded from pivotal trials	•CrCl 15-50ml/min: Reduce dose to 30mg once daily or if weight < 60kg or P-gp inhibitor •CrCl < 30ml/min: Excluded from pivotal trials Not approved for VTE prophylaxis or extended treatment

Data from respective package inserts as of 8/2016

TSOACs: Other Key Considerations

- Reversal agent: dabigatran only
- Reduction in ischemic stroke component of primary composite endpoint: dabigatran only
- Dietary interaction: rivaroxaban > 10mg to be taken with evening meal, dabigatran with a full glass of water
- Storage: dabigatran in original bottle
- Once daily dosing: apixaban, edoxaban
- Feeding tube: dabigatran no, rivaroxaban depends on placement

Bottom Line

"Careful and considerate prescribing is crucial—you're not giving chocolates to patients, you are giving powerful anticoagulants.

They will work well if you give them correctly and use them appropriately."

-Gregory Lip, MD

theheart.org.; Jun 20, 2012. Accessed at http://www.theheart.org/article/1417787.do

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