A Decade of DOACs: What Have We Learned?

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Oklahoma Heart Institute

No financial disclosures

15th Annual
OKLAHOMA HEART RESEARCH AND EDUCATION FOUNDATION PRESENTS

What are DOACs?

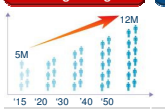
- DOACs – Direct oral anticoagulants
- Also called NOACs- Newer oral anticoagulants
  - Dabigatran (Pradaxa)
  - Rivaroxaban (Xarelto)
  - Apixaban (Eliquis)
  - Edoxaban (Savaysa)

Outline

- Atrial fibrillation and stroke risk
- Warfarin
- Direct oral anticoagulants (DOACs)
- Who do I anti coagulate ?
- Real world outcomes
- What is valvular atrial fibrillation ?
- Management of bleeding complications
- Peri Opearative management of DOACs

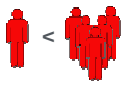
Scope of the Problem

AF = most common cardiac arrhythmia, and growing



~5 M
people with AF in U.S., expected to more than double by 2050[1]

AF increases risk of stroke



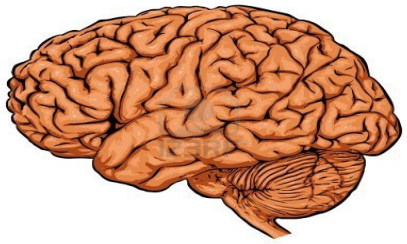
5x
greater risk of stroke with AF[2]

- Higher stroke risk for older patients and those with prior stroke or TIA
- 15-20% of all strokes are AF-related
- AF results in greater disability compared to non-AF-related stroke
- High mortality and stroke recurrence rate

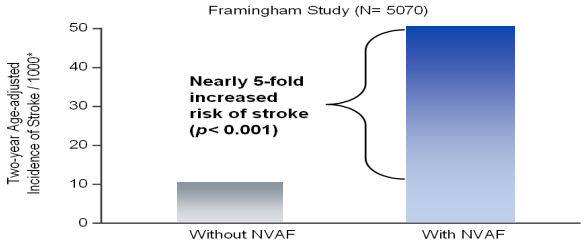
1. Go AS. et al, Heart Disease and Stroke Statistics—2013 Update: A Report From the American Heart Association. Circulation. 2013; 127: e6-e245.
2. Holmes DR, Atrial Fibrillation and Stroke Management: Present and Future, Seminars in Neurology 2010;30:528–536.

15th Annual

Prime Directive: Preserve the Brain



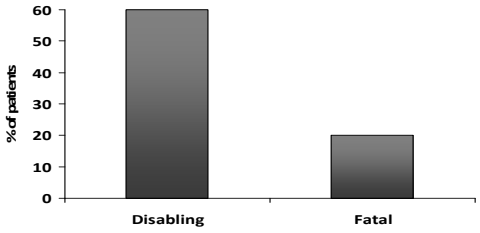
Atrial Fibrillation Causes Stroke



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

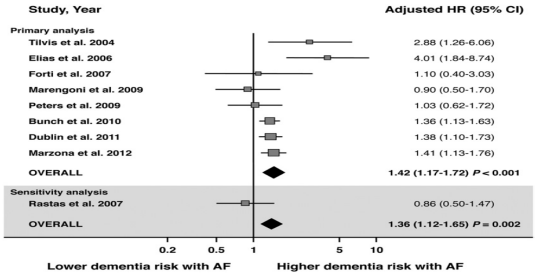
Stroke Severity in AF

Effect of first ischemic stroke in patients with AF (n=597)



Gladstone DJ et al. *Stroke.* 2009; 40:235-240

AF and Cognitive Decline



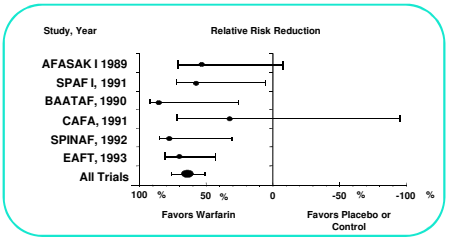
Heart Rhythm 2012;9:1761–1768

Warfarin for AF

6 Trials

2,900 patients

Warfarin reduces risk of stroke by 64%

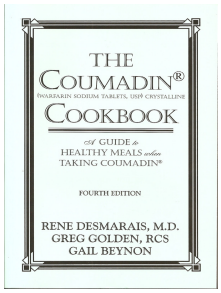


From: Hart RG, et al *Ann Intern Med.* 2007;146:857-867

Warfarin

- Synthesized 1948
- Rodenticide 1952
- Approved for human use 1954

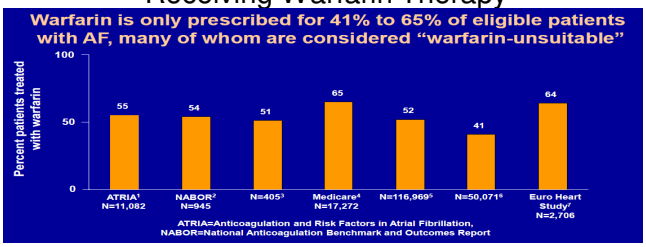
Barriers to Effective Warfarin Anticoagulation



Barriers to effective anticoagulation with Warfarin

- Patient factors
  - Food / Drug interactions
  - Dosing complexity
  - Medication / Monitoring Compliance
  - Bleeding Complications
    - Severe bleeding (e.g., intracranial hemorrhage)
- Medical staff factors
  - Burden of INR follow-up
  - Stopping / restarting for invasive procedure
  - Underestimated benefit/overestimated risk

Prevalence of Eligible AF Patients Receiving Warfarin Therapy

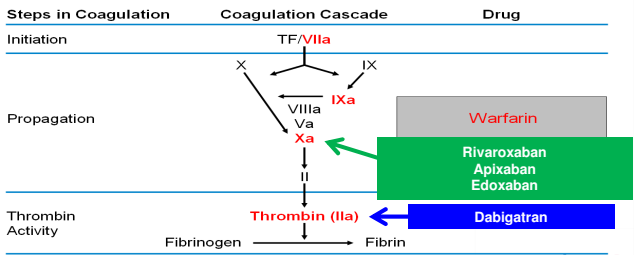


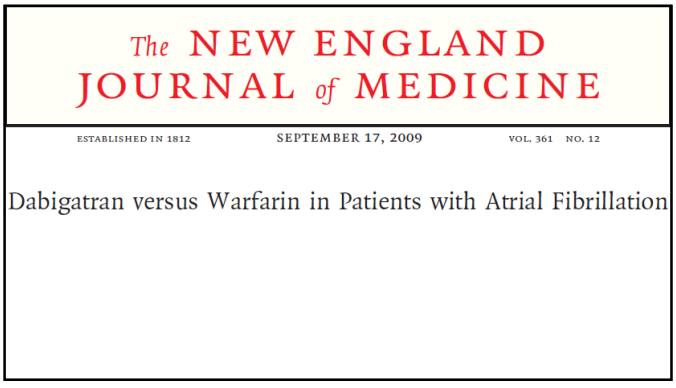
1.Go AS et al. *Ann Intern Med.* 1999;131:927-934.
2.Waldo AL et al. *J Am Coll Cardiol.* 2005;46:1729.
3.Hylek EM et al. *Stroke.* 2006;37:1075-1080.
4.Birman-Deych E et al. *Stroke.* 2006;37:1070-1074.
5.Walker AM, Bennett D. *Heart Rhythm* 2008;5:1365.
6.Williams CJ et al. American College of Cardiology 58th Annual Scientific Session; March 29-31, 2009;
7.Nieuwlaat R et al. *Eur Heart J.* 2006;27:3018-3026.

The DOACs

Medication	Trial	FDA Approval
Dabigatran (Pradaxa)	RE-LY (2009)	October 19, 2010
Rivaroxaban (Xarelto)	ROCKET-AF (2011)	November 4, 2011
Apixaban (Eliquis)	ARISTOTLE (2011) AVERROES (2011)	December 28, 2012
Edoxaban (Savaysa)	ENGAGE-AF-TIMI 48 (2013)	January 8, 2015

DOAC: Mechanisms

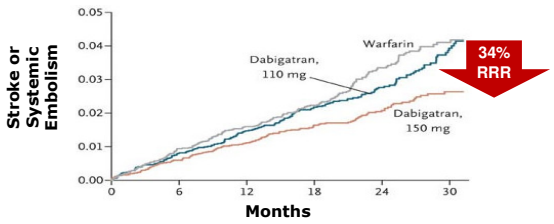




RE-LY Trial

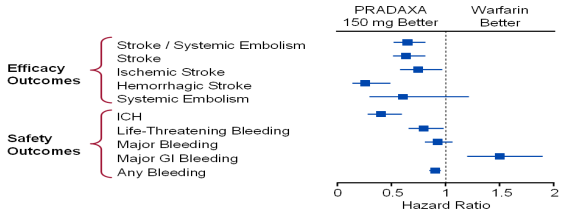
Dabigatran vs. Warfarin

18,113 pts with average age 71 and mean $CHADS_2$ = 2.1



Connolly S et al. N Engl J Med 2009;361:1139-51

Summary of Clinical Outcomes in Patients Treated with Dabigatran 150 mg bid or Warfarin



- The risk for myocardial infarction was numerically greater in patients who received PRADAXA 150 mg (1.5%) vs warfarin (1.1%)

Connolly S et al. N Engl J Med 2009;361:1139-51

The NEW ENGLAND JOURNAL of MEDICINE

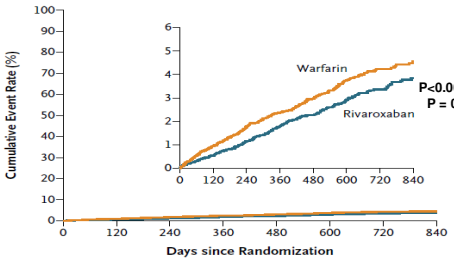
ESTABLISHED IN 1812 SEPTEMBER 8, 2011 VOL. 365 NO. 10

Rivaroxaban versus Warfarin in Nonvalvular Atrial Fibrillation

ROCKET-AF

Rivaroxaban vs. Warfarin

14,264 pts with median age 73 and mean $CHADS_2$ = 3.5



Patel MR et al. N Engl J Med 2011;365:883-91

The NEW ENGLAND JOURNAL of MEDICINE

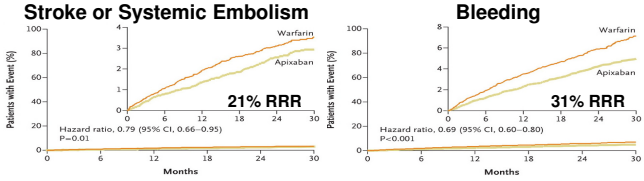
ESTABLISHED IN 1812 SEPTEMBER 15, 2011 VOL. 365 NO. 11

Apixaban versus Warfarin in Patients with Atrial Fibrillation

ARISTOTLE

Apixaban vs. Warfarin

18,201 patients with median age 70 and mean $CHADS_2$ = 2.1



11% reduction in total mortality (P = 0.047)

Granger CB et al. N Engl J Med 2011;365:981-92

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Apixaban in Patients with Atrial Fibrillation

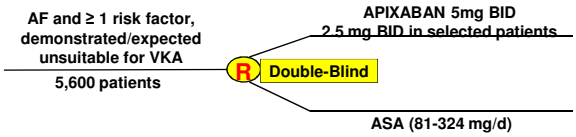
AVERROES Trail

Apixaban vs Aspirin for patients who cannot take warfarin.

AVERROES

Trial Design

36 countries, 522 centers

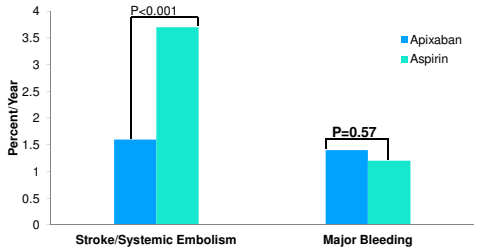


Primary Outcome: Stroke or systemic embolism

N Engl J Med 2011;364:806-17

AVERROES

Stroke/Systemic Embolism and Major Bleeding



N Engl J Med 2011;364:806-17

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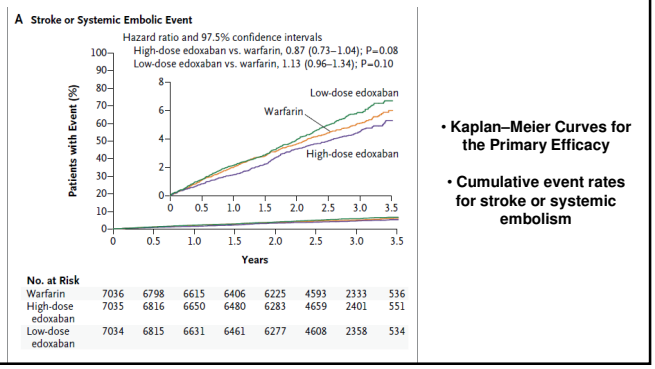
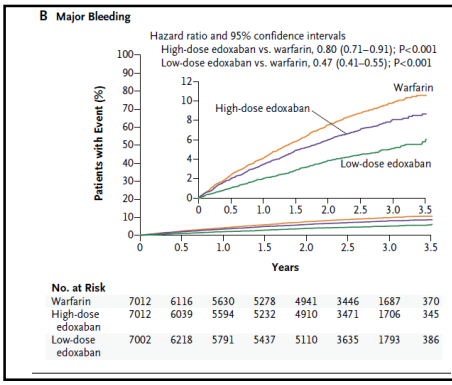
ORIGINAL ARTICLE

Edoxaban versus Warfarin in Patients with Atrial Fibrillation

ENGAGE AF-TIMI 48 Trial



- **Kaplan–Meier Curves for the Primary Efficacy**
- **Cumulative event rates for stroke or systemic embolism**



- **Kaplan–Meier Curves for the Primary Safety End Point.**
- **Major Bleeding**

	Dabigatran	Rivaroxaban	Apixaban	Edoxaban
Drug Class	Direct Thrombin Inhibitor	Factor Xa Inhibitor	Factor Xa Inhibitor	Factor Xa Inhibitor
Dose Frequency	Twice Daily	Once Daily	Twice Daily	Once Daily
Renal Excretion	80%	35%	27%	50%
Dosing Based On Renal Function	150 mg BID (CrCl >30) 75 mg BID (CrCl 15-30)	20 mg QD (CrCl>50) 15 mg QD (CrCl 30-49)	5 mg BID 2.5 mg BID with 2 of 3: age≥80,Cr≥1.5,wt≤60Kg	60 mg QD (CrCl >50-95) 30 mg QD (CrCl 15-50)
Clinical Trial	RE-LY	ROCKET-AF	ARISTOTLE	ENGAGE-AF-TIMI 48
Number of Patients (Randomized)	18,113	14,264	18,201	21,105
Study Population	Age 71.5 $CHADS_2$ = 2.1 TTR 64%	Age 73 $CHADS_2$ = 3.5 TTR 57.8%	Age 70 $CHADS_2$ = 2.1 TTR 62.2%	Age 72 $CHADS_2$ = 2.8 TTR 65%
Median Duration of Trial F/U (years)	2	1.6	1.7	2.8
Stroke Risk Reduction	Superior	Non-Inferior	Superior	Superior
Bleeding Risk	Similar	Superior	Superior	Superior
Mortality Benefit	12% (p=0.051)	8% (p=0.15)	11% (p=0.047)	Reduction in CV Mortality: 14% (p=0.01)

Who do I anticoagulate ?

Stroke Risk Stratification in AF

$CHADS_2$

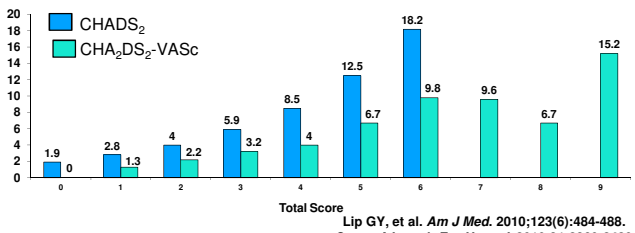
Risk Factor	Score
Congestive Heart Failure	1
Hypertension	1
Age ≥ 75	1
Diabetes Mellitus	1
Stroke/TIA/Thromboembolism	2
Maximum Score	6

CHA_2DS_2-VASc

Risk Factor	Score
Congestive Heart Failure	1
Hypertension	1
Age ≥ 75	2
Diabetes Mellitus	1
Stroke/TIA/Thromboembolism	2
Vascular Disease	1
Age 65-74	1
Female	1
Maximum Score	9

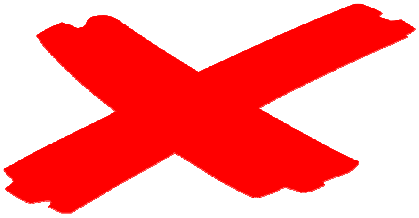
Lip GY, et al. *Am J Med.* 2010;123(6):484-488.
Camm AJ, et al. *Eur Heart J.* 2010:31;2369-2429

Annual Risk of Stroke (%)



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

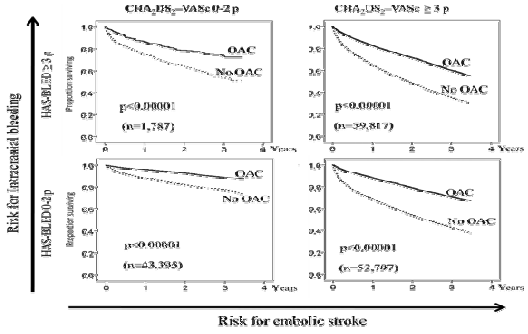
What is HAS-BLED score ?
Do we use it to defer anticoagulation?



HAS-BLED Score

	Clinical Characteristic	Score
H	Hypertension	1
A	Abnormal renal or liver function (1 each)	1 or 2
S	Stroke	1
B	Bleeding	1
L	Labile INR	1
E	Elderly age	1
D	Drugs or alcohol (1 each)	1 or 2
	Maximum Score	9

Hypertension: SBP > 160 mmHg; Abnormal renal function: Chronic dialysis, renal transplant, serum creatinine ≥ 200μmol/L; Abnormal liver function: Chronic hepatitis, bilirubin > 2x upper limit of normal (ULN) in association with AST/ALT/ALP > 3 x ULN; Bleeding: Previous history, predisposition; Labile INRs: unstable/high INRs, in therapeutic range < 60%; Age > 65 years; Drugs/alcohol: Concomitant use of antiplatelet agents, non-steroidal anti-inflammatory drugs, etc.
Pisters R, et al. *Chest*, 2010;138:1093-100



Leif Friberg et al.

CLINICIAN UPDATE

Use of the CHA_2DS_2-VASc and HAS-BLED Scores to Aid Decision Making for Thromboprophylaxis in Nonvalvular Atrial Fibrillation

Deirdre A. Lane, PhD; Gregory Y.H. Lip, MD

"HAS-BLED should not be used as an excuse not to prescribe anticoagulation, but rather to highlight those patients in whom caution with such treatment and regular review is warranted"

– Circulation 2012;126:860

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

January CT et al. *Circulation 2014; 130: e199-e267*

Antithrombotic therapy based on shared decision-making, discussion of risks of stroke and bleeding, and patient's preferences

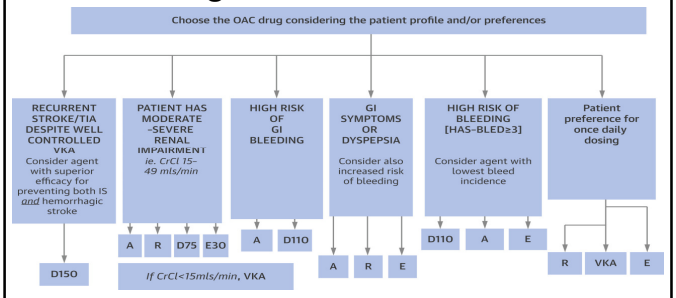
CHA_2DS_2-VASc score recommended to assess stroke risk

Warfarin recommended with mechanical heart valves. Target INR intensity should be based on the type and location of prosthesis

If end-stage CKD (CrCl<15 mL/min) or on hemodialysis, it is reasonable to prescribe warfarin for OAC [NOACs not recommended]

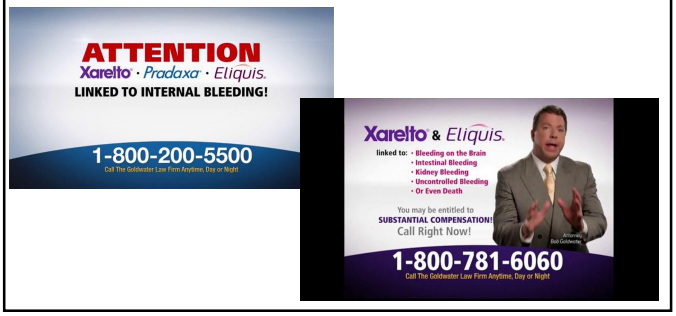
CHA_2DS_2-VASc ≥2	CHA_2DS_2-VASc=1	CHA_2DS_2-VASc=0
OAC, either VKA or NOAC (Class I)	No antithrombotic therapy, OAC, or aspirin (Class IIb)	No antithrombotic Rx (Class IIa)

Matching the NOAC to the Patient



J Am Coll Cardiol. 2015;66(21):2282-2284. doi:10.1016/j.jacc.2015.07.086

Real world outcomes of DOACs



Real world outcomes

- No randomized clinical trails comparing different DOACs
- Large registry data and meta analysis
- Results from these are mostly consistent with published randomized clinical trials.

Real world outcomes

- Good safety profile.
- Lower risk of Intra cranial hemorrhage
- Similar or slightly better in prevention of stroke or systemic thromboembolism in comparison to warfarin

Real world outcomes

- Benefits seem to be consistent in different population groups.
- Patients with CKD and CHF also seem to have similar benefits with DOACs when compared to Warfarin

Outline

- Atrial fibrillation and stroke risk
- Warfarin
- Direct oral anticoagulants (DOACs)
- Who do I anti coagulate ?
- Real world outcomes
- **What is valvular atrial fibrillation ?**
- Management of bleeding complications
- Peri Operative management of DOACs
- Comorbid conditions ie CKD and hepatic dysfunction

Which of these patients is not eligible for any DOAC ?

1. End stage renal disease
2. Severe Mitral regurgitation
3. Mild Mitral stenosis
4. Mechanical Aortic valve replacement

"Valvular AF" Criteria

- 2014 AHA/ACC/HRS AF Guidelines
  - Mitral stenosis
  - Mechanical or bioprosthetic heart valve
  - Mitral repair
- 2016 ESC AF Guidelines
  - Moderate-severe mitral stenosis
  - Mechanical heart valves

- **RE-LY trial (Dabigatran)** Exclusion: prosthetic valve or hemodynamically significant valve disease, resulting in the exclusion of patients with AF and severe mitral or aortic insufficiency or severe AS
- **ROCKET-AF trial (Rivaroxaban) :** Excluded only hemodynamically significant mitral valve stenosis and prosthetic heart valves. Permitted inclusion of patients with other diseases in native valves, as well as patients treated with annuloplasty, commisurotomy or valvuloplasty.
- **ARISTOTLE (Apixaban) .** Excluded clinically significant (moderate or severe) mitral stenosis and mechanical aortic valves.
  Included patients with native valvular heart disease except mitral stenosis and bioprosthetic heart valves .
- **ENGAGE-AF study (Edoxaban)** Exclusion criteria : moderate or severe mitral stenosis or a mechanical heart valve" were excluded
  Included: bioprosthetic heart valves and/or valve repair.

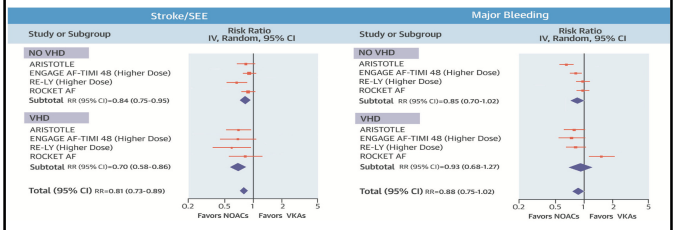
NOACs in AF with Valvular Heart Disease

TABLE 2 Frequency of Valvular Heart Disease Subtypes in Patients Randomized in RE-LY, ROCKET AF, ARISTOTLE, and ENGAGE AF-TIMI 48 Trials

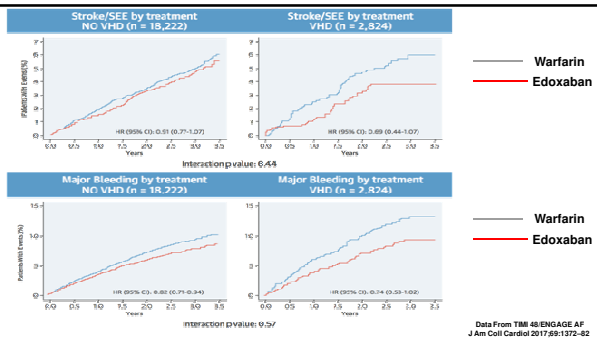
VHD Subtype	RE-LY (n = 3,950)	ROCKET-AF (n = 2,003)	ARISTOTLE (n = 4,808)	ENGAGE AF-TIMI 48 (n = 2,824)
Moderate/severe mitral regurgitation	3,101 (78.5)	1,756 (87.7)	3,526 (73.3)	2,250 (79.6)
Mild mitral stenosis*	193 (4.9)	NR	131 (2.7)	254 (9.0)
Moderate/severe aortic regurgitation	817 (20.7)	486 (24.3)	887 (18.4)	369 (13.0)
Moderate/severe aortic stenosis	471 (11.9)	215 (10.7)	384 (8.0)	165 (5.8)
Moderate/severe tricuspid regurgitation	1,179 (29.8)	NR	2,124 (44.0)	NR
Valve surgery (other than mechanical prosthetic heart valve)	NR	106 (5.3)†	251 (5.2)	516 (18.2)

Renda G et al J Am Coll Cardiol 2017;69:1363–71

NOACs in AF with Valvular Heart Disease



Renda G et al J Am Coll Cardiol 2017;69:1363–71



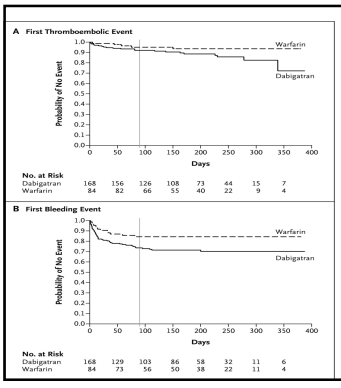
Data From TIMI 48/ENGAGE AF
J Am Coll Cardiol 2017;69:1372–82

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Dabigatran versus Warfarin in Patients with Mechanical Heart Valves

- Trial terminated prematurely because of an excess of thrombo-embolic and bleeding events among patients in the dabigatran group.
- Dabigatran was associated with higher rates of ischemic stroke (5%, vs. 0% with warfarin) and major bleeding (4% vs. 2%).



Kaplan–Meier Analysis of Event-free Survival.

- Trial terminated prematurely because of an excess of thrombo-embolic and bleeding events among patients in the dabigatran group.
- Dabigatran was associated with higher rates of ischemic stroke (5%, vs. 0% with warfarin) and major bleeding (4% vs. 2%).

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EXPERT CONSENSUS DECISION PATHWAY

2017 ACC Expert Consensus Decision Pathway on Management of Bleeding in Patients on Oral Anticoagulants

A Report of the American College of Cardiology Task Force on Expert Consensus Decision Pathways

Managing Bleeding complications with DOACs

- Measuring levels with specialized assays.

TABLE 2 Suggestions for Laboratory Measurement of DOACs When Specialized Assays are Available

	Clinical Objective		
	Exclude Clinically Relevant* Drug Levels		Measure On-Therapy or Above On-Therapy Drug Levels
Drug	Suggested Test	Interpretation	Suggested test
Dabigatran	Dilute TT ECT ECA	Normal result probably excludes clinically relevant* levels	Dilute TT ECT ECA
Apixaban, edoxaban, or rivaroxaban	Anti-Xa	Absent chromogenic anti-Xa assay activity probably excludes clinically relevant* levels	Anti-Xa†

Dabigatran : dilute TT(Thrombin time), ECA-Ecarin Chromogenic assay and ECT- Ecarin clotting time.

Unfortunately, these assays are not widely available, particularly on an emergent basis .

In their absence, the thrombin time (TT) and aPTT may be used for qualitative assessment

J Am Coll Cardiol. 2017 Dec 19;70(24):3042-3067.

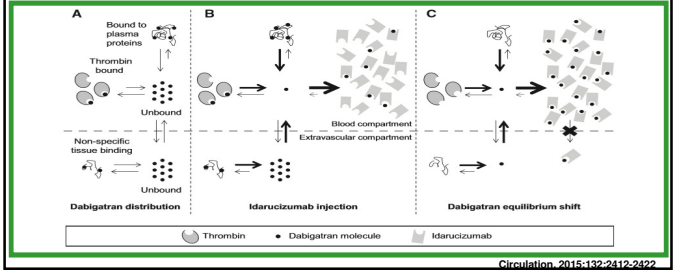
- **Factor Xa inhibitors (apixaban, edoxaban, and rivaroxaban)**
  - **Preferred test is a chromogenic anti-Xa assay.**
- If an anti-Xa assay is not available, the **PT may be useful only for qualitative assessment** of edoxaban and rivaroxaban. A **prolonged PT suggests on-therapy or above on-therapy levels** for these agents. However, depending on the sensitivity of the PT reagent, a normal PT may not exclude on-therapy levels .
- **PT and aPTT are insensitive to apixaban.** A prolonged PT suggests the presence of clinically important apixaban levels, but a normal PT and aPTT do not exclude on-therapy or even above on-therapy levels of the drug

Managing Bleeding complications and reversal agents.

New Drugs and Technologies

Idarucizumab
The Antidote for Reversal of Dabigatran

John W. Eikelboom, MBBS, FRCPC; Daniel J. Quinlan, MBBS; Joanne van Ryn, PhD; Jeffrey I. Weitz, MD, FRCPC



Circulation. 2015;132:2412-2422

- **Currently no specific antidotes clinically available for reversal of direct factor Xa (FXa) inhibitors**
- Coagulation factor supplementation with 4F-PCC or aPCC is generally used. It is a nonspecific reversal strategy for the direct FXa inhibitors.
  - 4F-PCC -- 4-factor prothrombin complex concentrate
  - aPCC- activated prothrombin complex concentrate.

- **Andexanet alfa (andexanet) is a specific reversal agent for FXa inhibitors currently under clinical development.**
  - Recombinant protein with a similar structure to endogenous FXa that binds FXa inhibitors but is not enzymatically active.
- Andexanet is being currently evaluated in Phase 3b/4 clinical trials. ANNEXA-4 Trial (Andexanet Alfa in Patients Receiving a FXa Inhibitor Who Have Acute Major Bleeding) .
- Ciraparantag (PER977). Another drug in early stages of development.

TABLE 5 Available Reversal Agents and Suggested Use

Reversal Agent	Vitamin K Antagonists (Warfarin)	Factor IIa Inhibitor (Dabigatran)	Factor Xa Inhibitor (Apixaban, Edoxaban and Rivaroxaban)
4F-PCC (56)	First line	Second line	First line
aPCC	Not indicated	Second line	Second line
Idarucizumab	Not indicated	First line	Not indicated
Plasma	If 4-PCC is unavailable	Not indicated	Not indicated

4F-PCC = 4-factor prothrombin complex concentrate; aPCC = activated prothrombin complex concentrate.

J Am Coll Cardiol. 2017 Dec 19;70(24):3042-3067.

Outline

- Atrial fibrillation and stroke risk
- Warfarin
- Direct oral anticoagulants (DOACs)
- Who do I anti coagulate ?
- Real world outcomes
- What is valvular atrial fibrillation ?
- Management of bleeding complications
- **Peri operative management of DOACs**

EXPERT CONSENSUS DECISION PATHWAY

2017 ACC Expert Consensus Decision Pathway for Periprocedural Management of Anticoagulation in Patients With Nonvalvular Atrial Fibrillation

A Report of the American College of Cardiology Clinical Expert Consensus Document Task Force

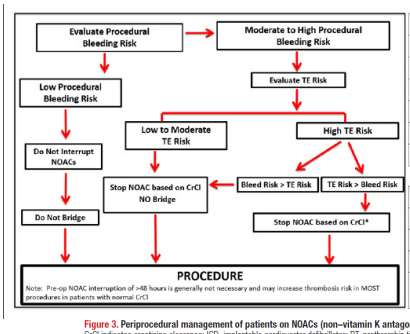
AHA SCIENTIFIC STATEMENT

Management of Patients on Non–Vitamin K Antagonist Oral Anticoagulants in the Acute Care and Periprocedural Setting

A Scientific Statement From the American Heart Association

Periprocedural management of DOACs

- Assess Thromboembolic risk of patient
  - Atrial Fibrillation – CHADS and CHADS-Vasc scores
  - DVT. Recent DVT?
- Assess Peri-procedural bleeding risk .
  - High bleeding risk procedure vs low bleeding risk procedure.
- Restarting DOACs post procedure



Peri-Procedural Bleeding Risk

Low	Moderate	High
Minor Dental	SVT ablation	Cardiovascular/Thoracic Surgery
Minor Dermatologic	ICD Implant	Intra-abdominal/Pelvic surgery
Opthalmologic	Endoscopy with Biopsy	Major Orthopedic Surgery
Endoscopy without Biopsy	Prostate Biopsy	Neurosurgery
	Cardiac catheterization via radial artery	Cardiac catheterization via femoral artery

Peri-Procedural Thromboembolic Risk

Low	Moderate to High
$CHA_2DS_2VASc \leq 1$	$CHA_2DS_2VASc > 2$
No Stroke/TIA, VTE within 3 months	Stroke/TIA, VTE within 3 months
Heterozygous Factor V Leiden Heterozygous PT gene mutation	Protein C or S Deficiency Antithrombin Deficiency Antiphospholipid Syndrome

Figure 3. Periprocedural management of patients on NOACs (non–vitamin K antagonist oral anticoagulants).
CrCl indicates creatinine clearance; ICD, implantable cardioverter-defibrillator; PT, prothrombin time; SVT, supraventricular tachycardia; TE, thromboembolic event; TIA, transient ischemic attack; and VTE, venous thromboembolism.
*Bridging may be considered in patients with a history of systemic embolus in the last 6 weeks.[11]a

UpToDate

Perioperative thrombotic risk

Risk stratum	Indication for anticoagulant therapy		
	Mechanical heart valve	Atrial fibrillation	VTE
Very high thrombotic risk*	Any mitral valve prosthesis Any caged-ball or tilting disc aortic valve prosthesis Recent (within six months) stroke or transient ischemic attack	CHA_2DS_2-VASc score of ≥6 (or $CHADS_2$ score of 5-6) Recent (within three months) stroke or transient ischemic attack Rheumatic valvular heart disease	Recent (within three months) VTE Severe thrombophilia (eg, deficiency of protein C, protein S, or antithrombin; antiphospholipid antibodies; multiple abnormalities)
High thrombotic risk	Bileaflet aortic valve prosthesis and one or more of the of following risk factors: atrial fibrillation, prior stroke or transient ischemic attack, hypertension, diabetes, congestive heart failure, age >75 years	CHA_2DS_2-VASc score of 4-5 or $CHADS_2$ score of 3-4	VTE within the past 3 to 12 months Nonsevere thrombophilia (eg, heterozygous factor V Leiden or prothrombin gene mutation) Recurrent VTE Active cancer (treated within six months or palliative)
Moderate thrombotic risk	Bileaflet aortic valve prosthesis without atrial fibrillation and no other risk factors for stroke	CHA_2DS_2-VASc score of 2-3 or $CHADS_2$ score of 0-2 (assuming no prior stroke or transient ischemic attack)	VTE >12 months previous and no other risk factors

Refer to UpToDate topics on perioperative anticoagulation management for details.

VTE: venous thromboembolism; $CHADS_2$: congestive heart failure, hypertension, age ≥75 years, diabetes mellitus, and stroke or transient ischemic attack; CHA_2DS_2-VASc: congestive heart failure, hypertension, age ≥75 years (2 points), diabetes mellitus, prior stroke or transient ischemic attack or thromboembolism (2 points), vascular disease (peripheral artery disease, myocardial infarction, or

Procedural bleeding risk

High bleeding risk procedure (two-day risk of major bleed 2 to 4 percent)
Any major operation of duration >45 minutes
Abdominal aortic aneurysm repair
Coronary artery bypass
Endoscopically guided fine-needle aspiration
Foot/hand/shoulder surgery
Heart valve replacement
Hip replacement
Kidney biopsy
Knee replacement
Laminectomy
Neurosurgical/urologic/head and neck/abdominal/breast cancer surgery
Polypectomy, variceal treatment, biliary sphincterectomy, pneumatic dilatation
Transurethral prostate resection
Vascular and general surgery
Low bleeding risk procedure (two-day risk of major bleed 0 to 2 percent)
Abdominal hernia repair
Abdominal hysterectomy
Arthroscopic surgery lasting <45 minutes
Axillary node dissection
Bronchoscopy with or without biopsy
Carpal tunnel repair
Cataract and noncataract eye surgery
Central venous catheter removal
Cholecystectomy
Cutaneous and bladder/prostate/thyroid/breast/lymph node biopsies
Dilatation and curettage
Gastrointestinal endoscopy ± biopsy, enteroscopy, biliary/pancreatic stent without sphincterotomy, endosonography without fine-needle aspiration
Hemorrhoidal surgery
Hydrocele repair
Noncoronary angiography
Pacemaker and cardiac defibrillator insertion and electrophysiologic testing

Perioperative management of oral direct thrombin inhibitors and factor Xa inhibitors

Anticoagulant	Renal function and dose	Interval between last dose and procedure NOTE: No anticoagulant is administered the day of the procedure		Resumption after procedure	
		High bleeding risk	Low bleeding risk	High bleeding risk	Low bleeding risk
Dabigatran	CrCl >30 mL/minute Dose 150 mg twice daily	Give last dose three days before procedure (ie, skip four doses on the two days before the procedure)	Give last dose two days before procedure (ie, skip two doses on the day before the procedure)	Resume 48 to 72 hours after surgery (ie, postoperative day 2 to 3)	Resume 24 hours after surgery (ie, postoperative day 1)
	CrCl 30 to 50 mL/minute Dose 150 mg twice daily	Give last dose five days before procedure (ie, skip eight doses on the two days before the procedure)	Give last dose three days before procedure (ie, skip four doses on the two days before the procedure)		
Rivaroxaban	CrCl >50 mL/minute Dose 20 mg once daily CrCl 30 to 50 mL/minute Dose 15 mg once daily	Give last dose three days before procedure (ie, skip two doses on the two days before the procedure)	Give last dose two days before procedure (ie, skip one dose on the day before the procedure)		
Apixaban	CrCl >30 mL/minute Dose 5 mg twice daily CrCl ≤30 mL/minute Dose 2.5 mg twice daily	Give last dose three days before procedure (ie, skip two doses on the two days before the procedure)	Give last dose two days before procedure (ie, skip two doses on the day before the procedure)		
Edoxaban	CrCl 50 to 95 mL/minute Dose 60 mg once daily CrCl ≤30 mL/minute* Dose 30 mg once daily	Give the last dose three days before the procedure (ie, skip two doses on the two days before the procedure)	Give the last dose two days before the procedure (ie, skip one dose on the day before the procedure)		

Bleeding risk is determined primarily by the type of surgery; patient comorbidities may also play a role. In patients undergoing neuraxial anesthesia or a very high bleeding risk procedure, a longer period of interruption may be warranted. In many low bleeding risk procedures, the anticoagulant does not need to be interrupted. Bridging anticoagulation may be appropriate preoperatively in patients with a very high thromboembolic risk who require more

Normal Renal function:
Low bleeding risk : 1 day
High bleeding risk: 2 days

Outline

- Atrial fibrillation and stroke risk
- Warfarin
- Direct oral anticoagulants (DOACs)
- Who do I anti coagulate ?
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- **Special conditions. Hemodialysis, Hepatic dysfunction, CAD with recent PCI**

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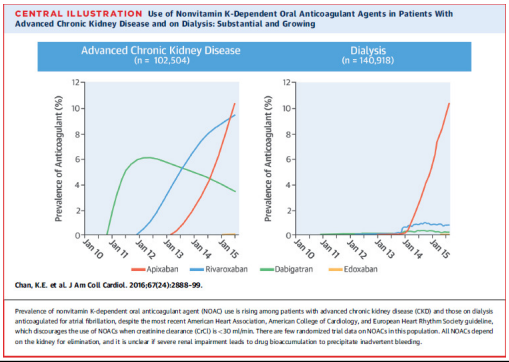
REVIEW TOPIC OF THE WEEK

Nonvitamin K Anticoagulant Agents in Patients With Advanced Chronic Kidney Disease or on Dialysis With AF

Kevin E. Chan, MD, MSc,[a,b] Robert P. Giugliano, MD, SM,[c] Manesh R. Patel, MD,[d] Stuart Abramson, MD,[e] Meg Jardine, MBBS, PhD,[f] Sophia Zhao, MD, PhD,[a] Vlado Perkovic, MBBS, PhD,[f] Franklin W. Maddux, MD,[b] Jonathan P. Piccini, MD, MHSc[d]

CENTRAL ILLUSTRATION Use of Nonvitamin K-Dependent Oral Anticoagulant Agents in Patients With Advanced Chronic Kidney Disease and on Dialysis: Substantial and Growing



Chan, K.E. et al. J Am Coll Cardiol. 2016;67(24):2888-99.

Prevalence of nonvitamin K-dependent oral anticoagulant agent (NOAC) use is rising among patients with advanced chronic kidney disease (CKD) and those on dialysis anticoagulated for atrial fibrillation, despite the most recent American Heart Association, American College of Cardiology, and European Heart Rhythm Society guideline, which discourages the use of NOACs when creatinine clearance (CrCl) is <30 mL/min. There are few randomized trial data on NOACs in this population. All NOACs depend on the kidney for elimination, and it is unclear if severe renal impairment leads to drug bioaccumulation to precipitate inadvertent bleeding.

- Limited data currently on use of DOACs in ESRD and dialysis patients
- All trials excluded patients with ERRD/Hemidialysis patients
- Dosing is currently based on pharmacokinetics/pharmacodynamics (PK/PD) studies with small number of patients.
- Await further real world data and future randomized studies

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 OCTOBER 19, 2017 VOL. 377 NO. 16

Dual Antithrombotic Therapy with Dabigatran after PCI in Atrial Fibrillation

Dabigatran + $P2Y_{12}$ inhibitor compared with Warfarin + $P2Y_{12}$ inhibitor + aspirin after PCI (in patients with atrial fibrillation)

- Risk of bleeding was lower with dabigatran therapy
- Prevention of thromboembolic events was similar with the two strategies

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 DECEMBER 22, 2016 VOL. 375 NO. 25

Prevention of Bleeding in Patients with Atrial Fibrillation Undergoing PCI

C. Michael Gibson, M.D., Roxana Mehran, M.D., Christoph Bode, M.D., Jonathan Halperin, M.D., Freek W. Verheugt, M.D., Peter Wildgoose, Ph.D., Mary Birmingham, Pharm.D., Juliana Ianus, Ph.D., Paul Burton, M.D., Ph.D., Martin van Eickels, M.D., Serge Korjian, M.D., Yazan Daaboul, M.D., Gregory Y.H. Lip, M.D., Marc Cohen, M.D., Steen Husted, M.D., Eric D. Peterson, M.D., M.P.H., and Keith A. Fox, M.B., Ch.B.

Who is not a good candidate for DOACs?

- Mechanical heart valves
  - RE-ALIGN Trial stopped early.
- Stable INR on warfarin
- Severe liver disease
- Use with caution in ESRD and Hemodialysis patients

Waldo AL Cardiology Today 2012;15:4-5

Conclusions

- AF increases the risk of stroke ~5X.
- Warfarin prevents thromboembolic events, but has multiple limitations.
- Compared to warfarin, the new anticoagulants are:
  - Easier to use.Faster onset/offset. No routine monitoring.
  - Noninferior/Superior at preventing stroke/systemic embolism.
  - Equivalent/Superior with regards to bleeding risk.
  - Less intra cranial hemorrhage

Thank You