Anticoagulation in Atrial Fibrillation

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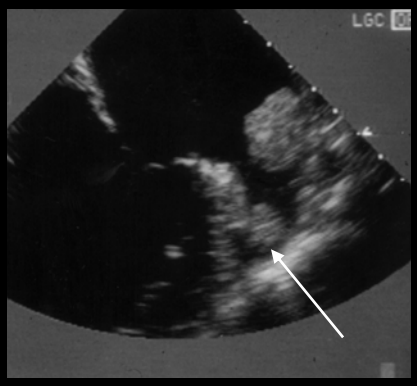
Disclosures

Eliquis Speakers Bureau

Clinical Scenario

- Ms. L is a 76F admitted to the stroke service with a dense right sided hemiparesis
- A workup for the CVA includes a TEE
- She later has paroxysmal Afib seen on telemetry for which she was asymptomatic
- No previous history of palpitations



Al Saady et al. *Heart 1999;82:547-554*

Cornerstones of AFib Management

Therapeutic Goals	Rate Control	Rhythm Control	Anticoagulation
	Control of symptoms	Control of symptoms	Prevention of thromboembolism
	Treatment or prevention of Tachycardia Induced Cardiomyopathy (CMP)	Reduction in Hospitalizations	Minimization of bleeding risk
	Reduction in Hospitalizations		

Practical Rate and Rhythm Management of Atrial Fibrillation

Stroke and cardioembolism prevention

Afib and Embolism/Stroke

- AF, whether paroxysmal, persistent, or permanent, and whether symptomatic or silent, significantly increases the risk of thromboembolic ischemic stroke
- 69000/795000 yearly strokes in the USA are attributable to AFib
- Nonvalvular AF increases the risk of stroke 5 times (MS related AF up to 20 fold)
- Afib related CVA is associated with a greater risk of recurrent stroke, more severe disability and mortality
- The appropriate use of antithrombotic therapy and the control of other risk factors including hypertension, and hypercholesterolemia substantially reduces stroke risk

January, CT et al.
2014 AHA/ACC/HRS Atrial Fibrillation Guideline

Stroke Risk Stratification

$CHADS_2$ -> CHA_2DS_2VASc

CHADS2 Risk	Score
CHF	1
Hypertension	1
Age > 75	1
Diabetes	1
Stroke or TIA	2

CHA2DS2-VASc Risk	Score
CHF or LVEF ≤ 40%	1
Hypertension	1
Age ≥75	2
Diabetes	1
Stroke/TIA/ Thromboembolism	2
Vascular Disease	1
Age 65 - 74	1
Female	1

From ESC AF Guidelines http://escardio.org/guidelines-surveys/esc-guidelines/GuidelinesDocuments/guidelines-afib-FT.pdf

Stroke Risk Stratification With the $CHADS_2$ and CHA_2DS_2-VASc Scores

	Adjusted Stroke Rate (% per y)
$CHADS_2$*	
0	1.9
1	2.8
2	4.0
3	5.9
4	8.5
5	12.5
6	18.2
CHA_2DS_2-VASc†	
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	15.20

Craig T. January et al. Circulation. 2014;130:e199-e267

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

- **CHA_2DS_2-VASc score of > 2 (class I)**
  - **Oral anticoagulants are recommended**
  - **Options include warfarin (INR 2.0 to 3.0), *dabigatran, rivaroxaban, or apixiban***
- **CHA_2DS_2-VASc score of 0 (class IIa)**
  - **It is reasonable to omit antithrombotic therapy**
- **CHA_2DS_2-VASc score of 1 (class IIb)**
  - **no antithrombotic therapy or treatment with an oral anticoagulant or aspirin may be considered**

Stroke Risk Reduction

- Despite guidelines and tools anticoagulation is under prescribed, which exposes patients with AF to the risk of debilitating strokes
- National Anticoagulation Benchmark Outcomes Report (NABOR)
  - Risk factors indicated that 86% of patients had a high risk for stroke only 55% were anticoagulated

Physician's Fear of Anticoagulant Therapy in Nonvalvular Atrial Fibrillation. Sen et al . Am J Med Sci 2014;348(6):513–521

Perceived Fears

- Anticoagulants rank high in drugs associated with adverse outcomes
- "first do no harm"
- Patient apprehension and lack of compliance
- Concomitant medications
  - Antiplatelets, NSAIDs
- No clear guideline or risk stratification scheme to assess bleeding risk

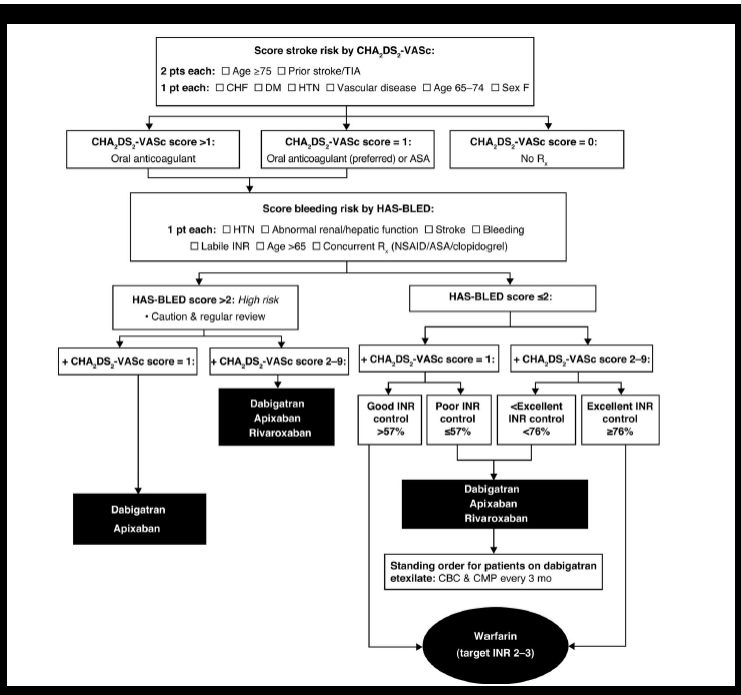
Physician's Fear of Anticoagulant Therapy in Nonvalvular Atrial Fibrillation. Sen et al . Am J Med Sci 2014;348(6):513–521

TABLE 2. Clinical criteria for HAS-BLED bleeding risk score

Clinical criteria[a]	Score
Hypertension	1
Abnormal renal or liver function (1 pt each)	1 or 2
Stroke	1
Bleeding	1
Labile INR	1
Elderly	1
Drug or alcohol use (1 pt each)	1 or 2
Maximum	9

HAS-BLED score	Bleeds/100 patient-yr[b]
0	1.13
1	1.02
2	1.88
3	3.74
4	8.70

Am J Med Sci 2014;348(6):513–521

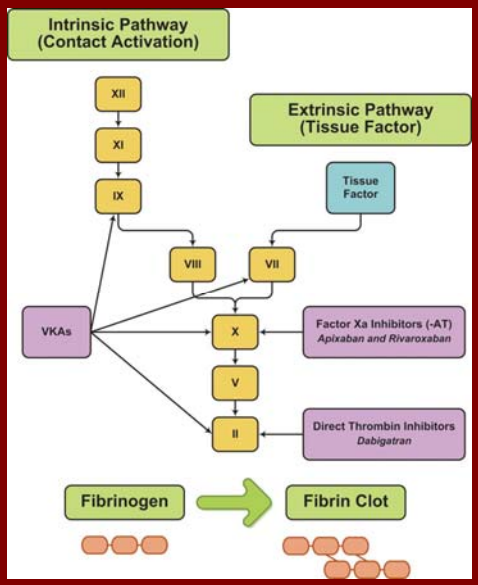


Am J Med Sci 2014;348(6):513–521

Anticoagulants

- Warfarin
- NOACs – For NonValvular Afib
  - Dabigatran
  - Rivaroxaban
  - Apixaban
  - Edoxaban

Coagulation cascade.



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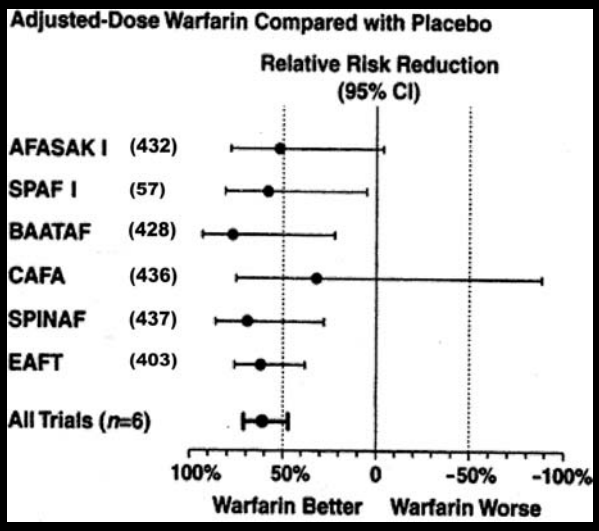
Warfarin

- Warfarin is a vitamin K antagonist in use since the 1950s as an oral anticoagulant for stroke prevention in patients with AF.
- Initially developed as rat poison
- Later developed at U of Wisconsin and given the name WARFarin
- Inhibits factors II, VII, IX and X

Warfarin

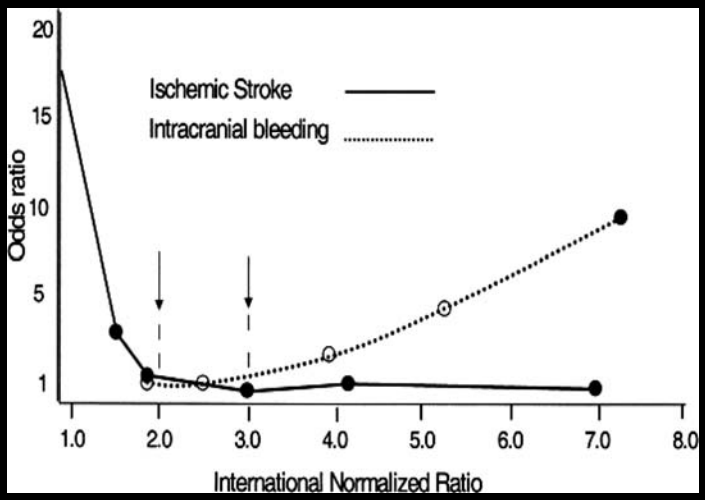
- 6 RCTs of 2,900 subjects in which adjusted-dose warfarin was compared with placebo or no treatment, the mean INR ranged from 2.0 to 2.9
- Adjusted-dose warfarin resulted in a 64% RR reduction for ischemic and hemorrhagic stroke compared with the placebo.
- The absolute risk reduction was 2.7% per year which yielded a NNT of 37 for 1 year to prevent 1 stroke and 12 for patients with prior stroke or TIA
- Standard of care for decades for cardioembolism risk reduction in higher risk Afib patients.

Effects on all stroke (ischemic and hemorrhagic) of therapies for patients with atrial fibrillation



Fuster, V. et al. J Am Coll Cardiol 2006;48:e149-e246

Adjusted odds ratios for ischemic stroke and intracranial bleeding in relation to intensity of anticoagulation



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Problems with Warfarin

- Dosing Varies
- Labor Intensive
- Food and Drug Interactions
- Unpredictability
- Bridging Issues

Novel Oral Anticoagulants

- Direct Thrombin Inhibitor
  - Dabigatran,
- Factor Xa Inhibitors
  - Rivaroxaban, Apixiban, Edoxaban
- Standardized dosing
- No INR monitoring
- Less labor intensive
- Minimal interactions
- Predictable pharmacokinetics
- Some concerns
  - Increased risk of thrombosis if drug is stopped?
  - No approved reversible agent
  - Not indicated for valvular atrial fibrillation

Dabigatran versus Warfarin in Patients with Atrial Fibrillation

Stuart J. Connolly, M.D., Michael D. Ezekowitz, M.B., Ch.B., D.Phil., Salim Yusuf, F.R.C.P.C., D.Phil., John Eikelboom, M.D., Jonas Oldgren, M.D., Ph.D., Amit Parekh, M.D., Janice Pogue, M.Sc., Paul A. Reilly, Ph.D., Ellison Themeles, B.A., Jeanne Varrone, M.D., Susan Wang, Ph.D., Marco Alings, M.D., Ph.D., Denis Xavier, M.D., Jun Zhu, M.D., Rafael Diaz, M.D., Basil S. Lewis, M.D., Harald Darius, M.D., Hans-Christoph Diener, M.D., Ph.D., Campbell D. Joyner, M.D., Lars Wallentin, M.D., Ph.D., and the RE-LY Steering Committee and Investigators*

- Unblinded for warfarin, Blinded for dabigatran dose
- Noninferiority trial
- Randomly assigned 18,113 patients who had NVAF and a risk of stroke to receive
  - Dabigatran 110 mg BID
  - Dabigatran 150 mg BID
  - Warfarin
- The median duration of the follow-up period was 2.0 years
- The primary outcome was stroke or systemic embolism.

N Engl J Med 2009;361:1139-51

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ANNUAL CVA OR EMBOLISM

Warfarin - 1.69%

Dabigatran 110mg - 1.53%

Dabigatran 150mg - 1.11%

The 110mg dose of dabigatran was noninferior to warfarin (P<0.001).

The 150-mg dose of dabigatran was superior to warfarin

ANNUAL BLEEDING RISK

Warfarin - 3.36%

Dabigatran 110mg - 2.71%

Dabigatran 150mg - 3.11%

Rates of life-threatening bleeding, intracranial bleeding, and major or minor bleeding were higher with warfarin (P<0.05 for all comparisons of dabigatran with warfarin).

There was a significantly higher rate of major gastrointestinal bleeding with dabigatran at the 150-mg dose than with warfarin.

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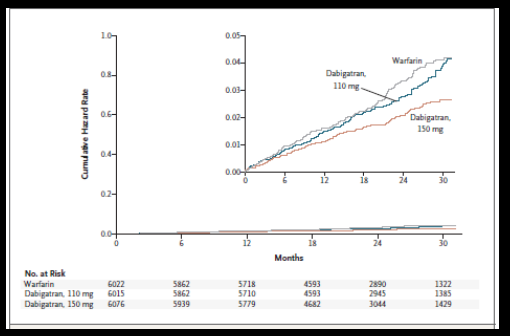
In patients with atrial fibrillation, dabigatran given at a dose of 110 mg was associated with rates of stroke and systemic embolism that were similar to those associated with warfarin, as well as lower rates of major hemorrhage.

Dabigatran administered at a dose of 150 mg, as compared with warfarin, was associated with lower rates of stroke and systemic embolism but similar rates of major hemorrhage.

Based on this data the FDA approved Dabigatran 150mg bid on October 19th, 2010

The 110mg dose was NOT approved



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Rivaroxaban versus Warfarin in Nonvalvular Atrial Fibrillation

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- Randomized, double-blind trial
- 14,264 patients with nonvalvular atrial fibrillation who were at increased risk for stroke to receive either
  - Rivaroxaban 20 mg (15mg for reduced GFR)
  - Warfarin
- The per-protocol, as-treated primary analysis was designed to determine whether rivaroxaban was noninferior to warfarin for the primary end point of stroke or systemic embolism.

N Engl J Med 2011;365:883-91.

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ANNUAL CVA OR EMBOLISM

Warfarin – 2.2%

Rivaroxaban – 1.7%

Rivaroxaban was noninferior to warfarin (P<0.001) for CVA/embolism

ANNUAL MAJOR BLEEDING

Warfarin - 3.4%

Rivaroxaban – 3.6%

Rates of critical site bleeding and intracranial bleeding were higher with warfarin

Transfusion rates and GI bleeding were higher for rivaroxaban

N Engl J Med 2011;365:883-91.

Rivaroxaban versus Warfarin in Nonvalvular Atrial Fibrillation

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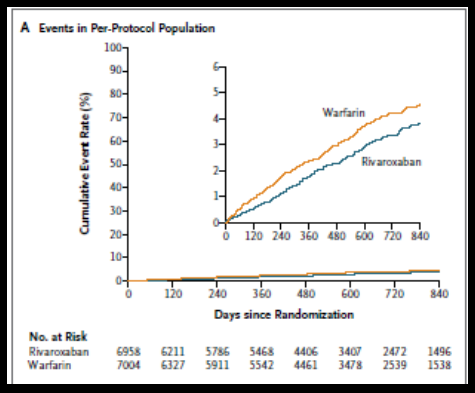
- *"In patients with atrial fibrillation, rivaroxaban was noninferior to warfarin for the prevention of stroke or systemic embolism. There was no significant between-group difference in the risk of major bleeding, although intracranial and fatal bleeding occurred less frequently in the rivaroxaban group"*
- *FDA approval Nov 4, 2011*



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Apixaban versus Warfarin in Patients with Atrial Fibrillation

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- Randomized, double-blind trial
- 18,201 patients with atrial fibrillation and at least one additional risk factor for stroke to receive either
  - Apixaban 5 mg bid (2.5mg in select patients)
  - Warfarin
- The primary outcome was ischemic or hemorrhagic stroke or systemic embolism.
- Test for noninferiority, with key secondary objectives of testing for superiority with respect to the primary outcome and to the rates of major bleeding and death from any cause.

N Engl J Med 2011;365:981-92.

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ANNUAL CVA OR EMBOLISM

Warfarin – 1.6%

Apixaban– 1.27%

Apixaban was superior to warfarin (P=0.01) for CVA/embolism

Mostly related to significant decrease in hemorrhagic CVA as pure ischemic CVA occurred at a similar rate

ANNUAL MAJOR BLEEDING

Warfarin - 3.09%

Apixaban– 2.13%

Apixaban was superior to warfarin in bleeding endpoints (mostly related to reduction in IC and fatal bleeding, GI bleeding occurrences were equivalent)

Overall mortality from any cause were 3.52% for Eliquis and 3.94% for warfarin (P = 0.047)

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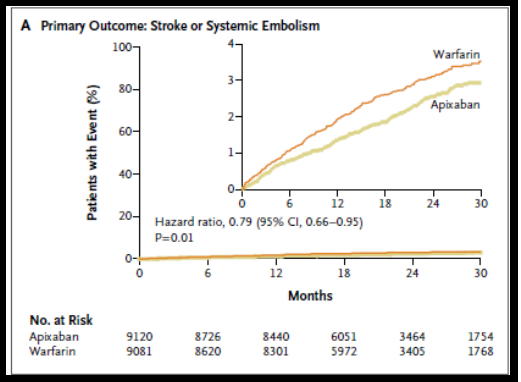
"In patients with atrial fibrillation, apixaban was superior to warfarin in preventing stroke or systemic embolism, caused less bleeding, and resulted in lower mortality."

FDA Approval Dec 28, 2012



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Edoxaban versus Warfarin in Patients with Atrial Fibrillation

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- Randomized, double-blind, double-dummy trial
- 21,105 patients with moderate to high-risk atrial fibrillation followed for 2.8 years
  - Edoxaban 30mg
  - Edoxaban 60mg
  - Warfarin
  - Edoxaban doses were cut in half if creatinine clearance of 30-50 ml per minute, a body weight of 60 kg or less, or the concomitant use of verapamil, dronedarone
- The primary efficacy end point was stroke or systemic embolism
- Each edoxaban regimen was tested for noninferiority to warfarin during the treatment period
- The principal safety end point was major bleeding.

Edoxaban versus Warfarin in Patients with Atrial Fibrillation

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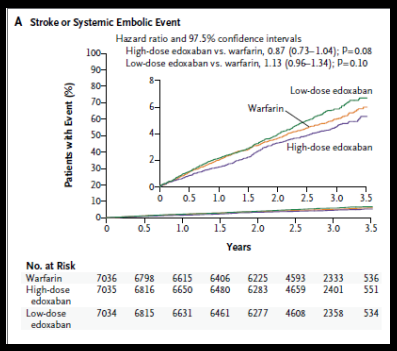
- For the total primary endpoint of CVA or embolism, both doses were noninferior to warfarin
- Edoxaban 30mg was inferior to warfarin for pure ischemic stroke (1.77% vs. 1.25% P<0.001)



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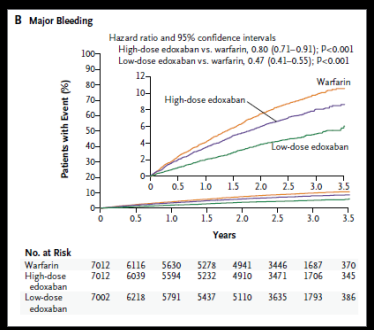
- The annualized rate of major bleeding events
  - 3.43% warfarin
  - 2.75% edoxaban 60mg
  - 1.61% edoxaban 30mg
- Consistently lower dose-related rates of all types of bleeding except for GI bleeding
- Significantly lower CV death
- FDA Approval Jan 8, 2015 of the 60mg dose



"Both once-daily regimens of edoxaban were noninferior to warfarin for the prevention of stroke or systemic embolism and were associated with significantly lower rates of bleeding and death from cardiovascular causes"

Novel Oral Anticoagulants

- Dabigatran (Pradaxa)
  - 150mg BID & 75mg BID (for CrCl 15-30 ml/min) for afib
- Rivaroxaban (Xarelto)
  - 20mg QD & 15mg QD (for CrCl 15-50 ml/min) for afib
- Apixaban (Eliquis)
  - 5mg BID & 2.5mg for special circumstances (Combined P-gp and strong CYP3A4 inhibitors, or any 2 of the following (age >80, wt<60kg, Cr >1.5)
  - Can be used on ESRD patients on HD (although not clinically studied)
- Edoxaban (Savaysa)
  - 60mg dose for CrCl 50-95 ml/min (should not be used if CrCl >95 ml/min)
  - 30mg dose for CrCl 15-50 ml/min

Table 1. Pharmacokinetics characteristics and indications of the new oral anticoagulants compared with warfarin.

Characteristics	Warfarin	Dabigatran	Apixaban	Rivaroxaban	Betrixaban	Edoxaban
Molecular weight (Da)	308	628	460	436	452	548
Bioavailability (%)	98	6-7	66	63-79	40-80[a]	50[a]
t_{max} (h)	72-120	2-3	1-3	2-4	NR	1-3
$t_{1/2}$ (h)	20-40	7-17	8-15	7-13	19	9-11
Protein binding (%)	99	35	87	95	NR	54
Food effect	Yes	Delayed absorption	No	Delayed absorption	No	No
Dosing regimen	once daily	twice daily	twice daily	once daily	once daily	once daily
Metabolism/ elimination	100% liver	80% renal 20% liver	25% renal 75% fecal	1/3 renal 2/3 liver	5% renal 95% liver	35% renal 65% liver
Substrate CYP	2C9, 3A4	No	3A4	3A4, 2J2	No	3A4
Substrate P-gp	No	Yes	Yes	Yes	No	yes
Food interaction	Yes	No	No	No	No	NR
Monitoring required	INR	No	No	No	No	No
Target	II, VII, IX, X, P-S, P-C	II	Xa	Xa	Xa	Xa
Antidote	Yes	No	No	No	No	No
Typical effective dose	INR guided	150 mg or 220 mg once daily (VTE prophylaxis)* 75 mg or 150 mg twice daily (AF) ‡	2.5 bid (VTE prophylaxis)*	10 mg once daily (VTE prophylaxis)* 15 mg twice daily (1–21) followed by 20 mg once daily (DVT treatment/ prevention of recurrent VTE) 20 mg once daily (AF)‡	In development	30 mg (VTE prophylaxis)
Approved indications	Approved for VTE prevention and treatment of the thromboembolic complications associated with AF and cardiac valve replacement, and secondary prevention after MI	Approved for VTE prevention after elective hip or knee replacement in adults and for prevention of stroke and systemic embolism in patients with nonvalvular AF	Approved for VTE prevention after elective hip or knee replacement in adults. Stroke prevention and systemic embolization in nonvalvular AF	Approved for VTE prevention after elective hip or knee replacement in adults, for prevention of stroke and systemic embolism in patients with nonvalvular AF, and for treatment of acute DVT and prevention of VTE recurrence	Has not been approved yet	Only approved in Japan for VTE prophylaxis joint replacement

Adapted from Poulsen et al. (2012), Lip et al. (2012) and Perez et al. (2013).
ACS, acute coronary syndrome; AF, atrial fibrillation; CYP, cytochrome P450; DVT, deep vein thrombosis; INR, international normalized ratio; MI, myocardial infarction; NR, not reported; P-C, protein C; P-gp, P glycoprotein; P-S, protein S; $t_{1/2}$, terminal elimination half life; t_{max}, time to reach maximal plasma concentration; VTE, venous thromboembolism.
*Approved dose for VTE prevention in adults patients undergoing elective hip or knee replacement surgery.
†Approved dose for treatment of acute DVT and pulmonary embolism (PE) recurrent DVT and PE.
‡Approved dose for prevention of stroke and systemic embolism in adult patients with nonvalvular AF.

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Novel Oral Anticoagulants

BLACK BOX WARNINGS!!!!

- Premature discontinuation of any oral anticoagulant increases the risk of thrombotic events. To reduce this risk, consider coverage with another anticoagulant if the drug is discontinued for a reason other than pathological bleeding or completion of a course of therapy
- Epidural or spinal hematomas may occur in patients treated with these agents who are receiving neuraxial anesthesia or undergoing spinal puncture. These hematomas may result in long-term or permanent paralysis. Monitor patients frequently for signs and symptoms of neurological impairment and if observed, treat urgently. Consider the benefits and risks before neuraxial intervention in patients who are or who need to be anticoagulated.

Specific Black Box - SAVAYSA

- **REDUCED EFFICACY IN NONVALVULAR ATRIAL FIBRILLATION PATIENTS WITH CRCL > 95 ML/MIN**
- **SAVAYSA should not be used in patients with CrCL > 95 mL/min**
- **In the ENGAGE AF-TIMI 48 study, nonvalvular atrial fibrillation patients with CrCL > 95 mL/min had an increased rate of ischemic stroke with SAVAYSA 60 mg once daily compared to patients treated with warfarin. In these patients another anticoagulant should be used**

Many, Many Questions…

- Are they safe?
- I take warfarin now, should I switch?
- What happens if I need surgery?
- What happens if I bleed?

Special Situations with Anticoags

- Transitioning
- Perioperative Management
- Bridging
- Bleeding

TABLE 6. Suggested Approaches to Switching to and From the NOAs for Purposes of Therapeutic Anticoagulation[a,b]

NOA of choice	Approach and timing of conversion
From VKAs to NOAs	
Dabigatran	Discontinue VKA and start dabigatran when the INR is <2
Rivaroxaban or apixaban	Discontinue VKA and initiate rivaroxaban or apixaban when the INR falls to <3 or <2, respectively
From NOAs to VKAs	
Dabigatran	Transition to VKAs depends on CrCl: • CrCl ≥50 mL/min/1.73 m^2, start VKA 3 d before stopping dabigatran • CrCl ≥30 to <50 mL/min/1.73 m^2, start VKA 2 d before stopping dabigatran • CrCl 15-30 mL/min/1.73 m^2, start VKA 1 d before stopping dabigatran (VKA effect on INR truly reflected only after dabigatran stopped for ≥2 d)
Rivaroxaban	Transition to VKAs depends on CrCl: • CrCl ≥50 mL/min/1.73 m^2, start VKA 4 d before stopping rivaroxaban • CrCl ≥30 to <50 mL/min/1.73 m^2, start VKA 3 d before stopping rivaroxaban • CrCl 15-30 mL/min/1.73 m^2, start VKA 2 d before stopping rivaroxaban (VKA effect on INR truly reflected only after rivaroxaban stopped for ≥1 d)
Apixaban	• Due to insufficient data; based on the package insert, apixaban should be discontinued and warfarin coinitiated along with a bridging parenteral anticoagulant until a therapeutic INR is achieved
From NOAs to parenteral anticoagulants	
Dabigatran	Parenteral anticoagulation should be initiated a minimum of 12 h (CrCl >30 mL/min/1.73 m^2) or 24 h (CrCl <30 mL/min/1.73 m^2) after the last dose of dabigatran
Rivaroxaban or apixaban	Discontinue rivaroxaban or apixaban and initiate parenteral anticoagulation at the time the next dose of rivaroxaban or apixaban is due
From parenteral anticoagulants to NOAs	
Dabigatran	• Initiate dabigatran ≤2 h before the next regularly scheduled dose of the discontinued subcutaneous anticoagulant • Continuous UFH: initiate dabigatran at the time of discontinuation of the continuous infusion
Rivaroxaban or apixaban	• Initiate rivaroxaban or apixaban ≤2 h before the next regularly scheduled dose of the discontinued subcutaneous anticoagulant • Continuous UFH: initiate rivaroxaban or apixaban at the time of discontinuation of the continuous infusion

[a]CrCl = creatinine clearance; INR = international normalized ratio; NOA = new oral anticoagulant; UFH = unfractionated heparin; VKA = vitamin K antagonist.
[b]SI conversion factor: To convert CrCl values to mL/s/m^2, multiply by 0.0167.

Mayo Clin Proc. 2013;88(5):495-511

Perioperative Management of Antithrombotic Therapy

Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines

- ***Warfarin***
  - ***In patients who require temporary interruption of a VKA before surgery, we recommend stopping VKAs approximately 5 days before surgery instead of stopping VKAs a shorter time before surgery*** *(Grade 1C)*
  - ***In patients who require temporary interruption of a VKA before surgery, we recommend resuming VKAs approximately 12 to 24 h after surgery (evening of or next morning) and when there is adequate hemostasis instead of later resumption of VKAs*** *(Grade 2C)*

Perioperative Management - NOACs

Renal function (CLcr ml/min)	Dabigatran		Rivaroxaban		Apixaban	
	Standard risk of bleeding	High risk of bleeding	Standard risk of bleeding	High risk of bleeding	Standard risk of bleeding	High risk of bleeding
>50	24 h	2–4 days	24 h	3 days	24–36 h	3 days
30–50	48 h	4 days	48 h	3 days	48 h	4 days
<30	2–5 days	>5 days	3 days	4 days		

Adapted from van Ryn *et al.* [2010], Spyropoulos and Douketis [2012] and Baumann Kreuziger *et al.* [2012].
CLcr, creatinine clearance.

Drug	Low bleeding risk surgery	High bleeding risk surgery
Dabigatran	Resume on day after surgery (24 h postoperative), 150 mg twice daily	Resume 2–3 days after surgery (48–72 h postoperative), 150 mg twice daily*
Rivaroxaban	Resume on day after surgery (24 h postoperative), 20 mg once daily	Resume 2–3 days after surgery (48–72 h postoperative), 20 mg once daily§
Apixaban	Resume on day after surgery (24 h postoperative), 5 mg twice daily	Resume 2–3 days after surgery (48–72 h postoperative), 5 mg twice daily§

Adapted from Spyropoulos and Douketis [2012].
Standard dosages shown, consider dose reduction in cases of renal function impairment (creatinine clearance < 50 ml/min).
*For patients at high risk for thromboembolism, consider administering a reduced dose of dabigatran (e.g. 110–150 mg once daily) on the evening after surgery and on the following day (first postoperative day) after surgery.
§Consider a reduced dose (i.e. rivaroxaban 10 mg once a day or apixaban 2.5 mg twice a day) in patients at high risk of thromboembolism.

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Table 1—[Introduction] Suggested Risk Stratification for Perioperative Thromboembolism

Risk Stratum	Indication for VKA Therapy		
	Mechanical Heart Valve	Atrial Fibrillation	VTE
High[a]	• Any mitral valve prosthesis • Any caged-ball or tilting disc aortic valve prosthesis • Recent (within 6 mo) stroke or transient ischemic attack	• $CHADS_2$ score of 5 or 6 • Recent (within 3 mo) stroke or transient ischemic attack • Rheumatic valvular heart disease	• Recent (within 3 mo) VTE • Severe thrombophilia (eg, deficiency of protein C, protein S, or antithrombin; antiphospholipid antibodies; multiple abnormalities)
Moderate	• 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 y	• $CHADS_2$ score of 3 or 4	• VTE within the past 3-12 mo • Nonsevere thrombophilia (eg, heterozygous factor V Leiden or prothrombin gene mutation) • Recurrent VTE • Active cancer (treated within 6 mo or palliative)
Low	• Bileaflet aortic valve prosthesis without atrial fibrillation and no other risk factors for stroke	• $CHADS_2$ score of 0 to 2 (assuming no prior stroke or transient ischemic attack)	• VTE > 12 mo previous and no other risk factors

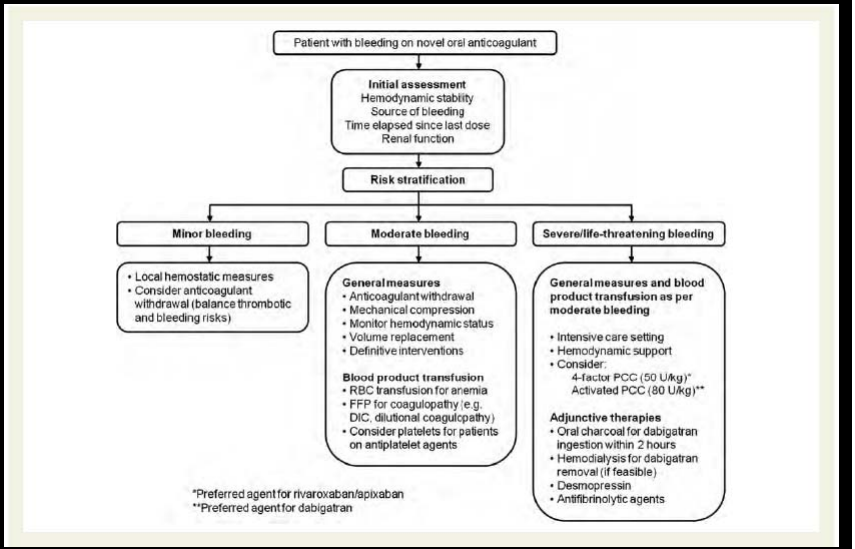
$CHADS_2$ = congestive heart failure, hypertension, age ≥ 75 years, diabetes mellitus, and stroke or transient ischemic attack; VKA = vitamin K antagonist.
[a]High-risk patients may also include those with a prior stroke or transient ischemic attack occurring > 3 mo before the planned surgery and a $CHADS_2$ score < 5, those with prior thromboembolism during temporary interruption of VKAs, or those undergoing certain types of surgery associated with an increased risk for stroke or other thromboembolism (eg, cardiac valve replacement, carotid endarterectomy, major vascular surgery).

- High risk patients should be bridged
- Low risk patients should not be bridged
- Moderate risk can be considered

Mitigating bleeding risk

- Change in renal function/liver function
- Concomitant medications
  - Antiplatelets
  - NSAIDs
  - SSRI, SNRI
- Patient Education

Reversal strategies?



Siegel et al. European Heart Journal (2013) 34, 489–500

Reversal Agents

- **Andexanet alfa: FXa Inhibitor Antidote**
- Acts as a Factor Xa decoy that targets and sequesters with high specificity both direct and indirect Factor Xa inhibitors in the blood.
- Phase 2 proof-of-concept studies
  - Immediately reversed the anticoagulation activity of apixaban, rivaroxaban and edoxaban
  - Well tolerated in clinical studies, with no thrombotic events or antibodies to Factor Xa or Factor X observed.
- Phase 3 studies – ANNEXA studies ongoing
- FDA designated orphan drug designation

Conclusions

- Cardioembolism and CVA is a significant cause of morbidity and mortality in patients with Afib
- Risk stratification with CHADS-VaSC2 score is important in approaching the patient with Afib
- Several options are now available for anticoagulation