PCNA
Anticoagulation: Old and New

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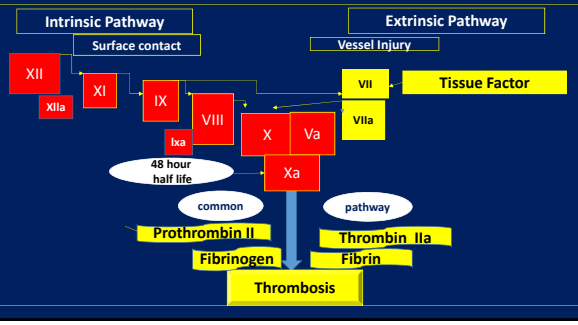
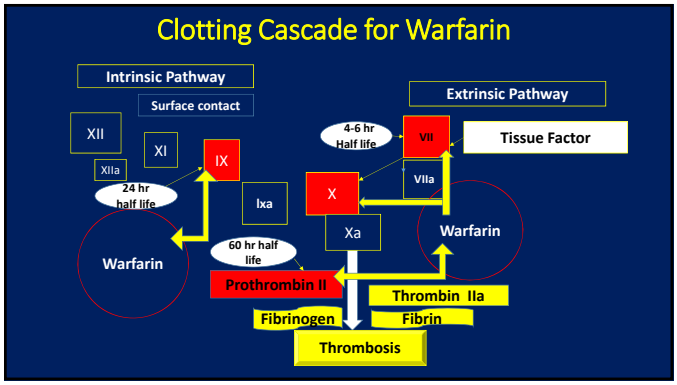
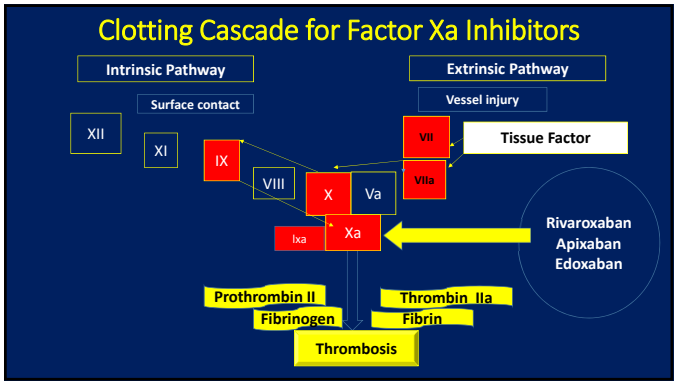
Objectives

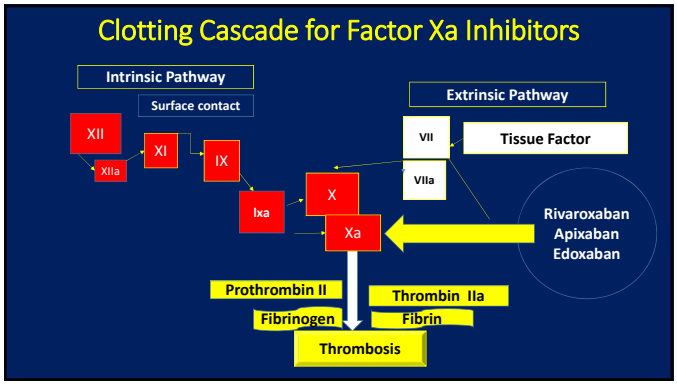
- Identify the steps in the coagulation cascade in which warfarin, dabigatran, rivaroxaban and apixaban work
- Identify 2 sources of evidence based guidelines for anti-thrombotic therapy in the reduction of cardiometabolic risk in the patient with non-valvular atrial fibrillation
- List the major finding from each of the landmark trials RE-LY; ROCKET-AF; ARISTOTLE.
- Define the impact of renal function and patient age on the choice of anticoagulation agent
- Distinguish which of the novel anticoagulants are indicated for treatment of VTE and DVT prophylaxis in the patient undergoing orthopedic surgery.
- Discuss drug metabolism in aging and special concern when treating with anticoagulation.

Clotting Cascade




Clotting Cascade for Warfarin
Intrinsic Pathway
Surface contact
XII
XI
XIIa
IX
24 hr half life
IXa
Warfarin
60 hr half life
Prothrombin II
Extrinsic Pathway
4-6 hr Half life
VII
Tissue Factor
VIIa
X
Xa
Warfarin
Thrombin IIa
Fibrinogen
Fibrin
Thrombosis


Clotting Cascade for Factor Xa Inhibitors
Intrinsic Pathway
Surface contact
XII
XI
IX
VIII
X
Va
IXa
Xa
Extrinsic Pathway
Vessel injury
VII
Tissue Factor
VIIa
Rivaroxaban
Apixaban
Edoxaban
Prothrombin II
Fibrinogen
Thrombin IIa
Fibrin
Thrombosis


Clotting Cascade for Factor Xa Inhibitors
Intrinsic Pathway
Surface contact
XII
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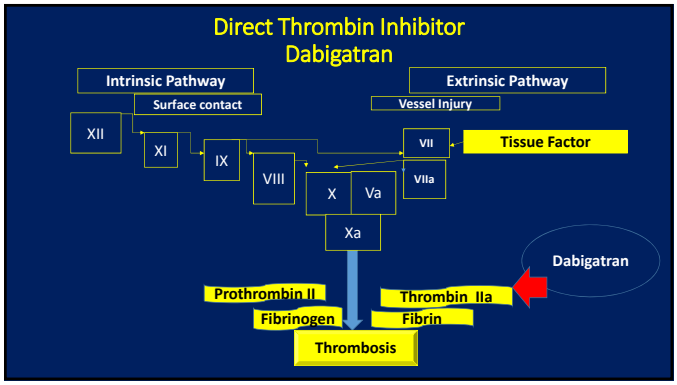
Apixaban
Edoxaban
Prothrombin II
Fibrinogen
Thrombin IIa
Fibrin
Thrombosis



Evidence Based Guidelines

Classification of Recommendations and Levels of Evidence

*Data available from clinical trials or registries about the usefulness/efficacy in different subpopulations, such as gender, age, history of diabetes, history of prior myocardial infarction, history of heart failure, and prior aspirin use. A recommendation with Level of Evidence B or C does not imply that the recommendation is weak. Many important clinical questions addressed in the guidelines do not lend themselves to clinical trials. Even though randomized trials are not available, there may be a very clear clinical consensus that a particular test or therapy is useful or effective.

†In 2003, the ACC/AHA Task Force on Practice Guidelines developed a list of suggested phrases to use when writing recommendations. All guideline recommendations have been written in full sentences that express a complete thought, such that a recommendation, even if separated and presented apart from the rest of the document (including headings above sets of recommendations), would still convey the full intent of the recommendation. It is hoped that this will increase readers' comprehension of the guidelines and will allow queries at the individual recommendation level.

American College of Chest Physicians 2012

Classification **Recommendation**

1. **Afib, PAF** with intermediate or high risk suggest **dabigatran 150 mg bid** rather than VKA
2. Afib for >48 hr anticoagulation with adjusted VKA INR 2-3 **or dabigatran**
3. H/O ischemic stroke or TIA and Afib/PAF – suggest oral anticoagulation with **dabigatran 150 mg bid** over adjusted VKA dose INR2-3
4. Major **orthopedic surgery THA or TKA** recommend use of following for minimum of 10 to 14 days rather than no antithrombotic tx. **LMWH**, **Apixaban, dabigatran, rivaroxaban, VKA**

AHA/ASA/HRS 2014 Atrial fibrillation Guidelines

Classification **Recommendation**

CLASS I Recommendation – The procedure SHOULD be performed

- Antithrombotic therapy should be individualized based on shared decision making with patient
- Selection of antithrombotic should be based on the risk of thromboembolism irrespective of whether the AF is paroxysmal, persistent or permanent.
- Nonvalvular AF, the CHA_2DS_2-VASc score is recommended

Comparison of $CHADS_2$ and CHA_2DS_2-VASc

$CHADS_2$	Score
• Congestive HF	1
• HTN	1
• Age ≥75 y	1
• Diabetes mellitus	1
• Stroke/TIA/TE	2
• **Maximum score**	**6**

CHA_2DS_2-VASc	Score
• Congestive HF	1
• HTN	1
• Age ≥ 75 y	2
• Diabetes mellitus	1
• Stroke/TIA/TE	2
• Vascular ds (prior MI, PAD, or aortic plaque	1
• Age 65-74 y	1
• Sex category (ie: female)	1
• **Maximum score**	**9**

AHA/ASA/HRS 2014 Atrial fibrillation Guidelines

Classification	Recommendation
	• For patients with nonvalvularAF with prior stroke, TIA, or CHA_2DS_2-VASc score of 2 or greater, oral anticoagulants are recommended. Options include:
	• Warfarin (INR 2.0-3.0)
	• Dabigatran
	• Rivaroxaban
	• Apixaban

AHA/ASA/HRS 2014 Atrial fibrillation Guidelines

Classification	Recommendation
	• Patients with AF with mechanical heart valves, warfarin is recommended and the target INR (2.0-3.0 or 2.5 to 3.5) based on the type and location of the prosthesis.
	• **No Benefit - Harm** • The direct thrombin inhibitor, dabigatran ***should not*** be used in patients with AF and a mechanical heart valve.

AHA/ASA/HRS 2014 Atrial fibrillation Guidelines

Classification	Recommendation
	• **Harmful Not Recommended** • Direct thrombin, dabigatran, and factor Xa inhibitor, rivaroxaban, are not recommended with AF and end-stage CKD or on hemodialysis because of he lack of evidence from clinical trials regarding the balance of risks and benefits
	• For patients with nonvalvular AF with a CHA_2DS_2-VASc score of 2 or greater and who have end stage CKD CrCl<15 ml/in or are on hemodialysis, it is reasonable to prescribe warfarin (INR 2.0 to 3.0) for oral anticoagulation

Other Changes in the 2014 Atrial fibrillation Guidelines

- Bleeding scores- HAS-BLED, REITE, and HEMORR2HAGES helpful defining risk but evidence for specific recommendations not sufficient.
- Little benefit with aspirin

American Academy of Neurology 2014

- Blood Thinners Now Recommended for People With Irregular Heartbeat
- **Updated guideline from American Academy of Neurology** aims to reduce stroke risk
- Several new blood thinners have been developed since the last AAN guideline on the topic was released in 1998. These new drugs -- such as dabigatran (Pradaxa), rivaroxaban (Xarelto) and apixaban (Eliquis) -- are at least or more effective than the established drug warfarin and are less likely to cause bleeding in the brain, the new guideline states.

- SOURCE: American Academy of Neurology, news release, Feb. 24, 2014

RE-LY Trial

Summary of Dabigatran Trials

Study	Treatment	Total # of subjects	Primary Outcome	Major bleeding	Combined vascular events, bleeding, death	Findings
RE-LY Trial Afib with ≥1 RF • Previous stroke or TIA, • LVEF <40%, • Age ≥75, • age 65-74 with DM, • HTN or CAD • NEJM 2009.361;(12);1139-51	Dabigatran 110 mg BID Dabigatran 150 mg BID Warfarin INR 2-3	110 mg BID = N=6015 150 mg BID = N=6076 Warfarin N=6022	**Stroke or systemic embolization** _____ Dabigatran 110 (182 pt 1.53%/yr) Dabigatran 150 mg (134 pt. 1.11%/yr) Warfarin (199 pt. 1.69%/yr)	Dabigatran 110 mg (2.71% yr) Dabigatran 150 mg (3.11% yr) Warfarin (3.36% yr)	Dabigatran 110 mg (7.09% yr) Dabigatran 150 mg (6.91% yr) Warfarin (7.64% yr)	**Life threatening bleeding** 110 mg (145 pts; 1.22% yr) 150 mg (175 pts; 1.45% yr) Warfarin (212 pts; **1.80 % y** **GI Bleed** 110 mg; 133 pts; 1.12% yr 150 mg; 182 pts; **1.51% yr** Warfarin; 120 pts; 1.02% **Intracranial bleed** 110 mg 27 pts; 0.23% yr 150 mg 36 pts; .3% yr Warfarin 87 pts; .**74% yr**

Rivaroxaban Trials

Summary of Rivaroxaban Trials

Study	Treatment	Total # subjects	Major & non major bleeding	↓ Hgb ≥2 gm	Intracranial	Primary end point	Findings
Rocket AF	Rivaroxaban 20 mg/d or Warfarin INR 2-3	14,264	**Total major & non major bleeding:** Rivaroxaban 14.9% Warfarin 14.5% **Major GI bleeding:** Rivaroxaban 224 events/3.2% Warfarin: 154 events/3.2% _____ NEJM 2011.365;(10);883-91	Rivaroxaban: 4.3% Warfarin 3.6%	Rivaroxaban 0.5% Warfarin 0.7%	**Primary:** Stroke or systemic embolization. **Secondary:** composite of stroke, systemic embolism, or death from CV causes or MI and individual composite endpoints	**Primary:** Rivaroxaban was noninferior to warfarin **Secondary:** No significance between the groups in risk of major bleeding, although intracranial and fatal bleeding occurred less frequently in the rivaroxaban group.

Summary Rivaroxaban Trials

Study	Treatment	Total Subjects	Major bleeding	Recurrence DVT	Primary Outcome	Findings
Einstein PE Studies NEJM 2012;366:1287-97	Rivaroxaban 15 mg bid x 3 weeks, followed by 20 mg qd with standard therapy with enoxaparin followed by adjusted dose warfarin 3,6, 12 months	Total 4832 pts Rivaroxaban N=2419 Enoxaparin and VKA (standary therapy) N=2413 Acute symptomatic PE with or without DVT	Any major bleeding: Rivaroxaban : 26 events (1.1%) Standard tx: 52 events(2.2%	Rivaroxaban 2.1% Standard tx: 1.8%	**Primary:** Recurrent venous thromboembolism _____ **Principal Safety outcome:** Major bleeding or clinically relevant non-major bleeding in the initial treatment study and major bleeding on the continued treatment study. Primary Same as above Principal same	**Primary:** Rivaroxaban noninferior to standard therapy for initial and long-term tx PE 50 events in Rivaroxaban group vs. 44 events in the standard therapy group 1.8%. **Principal Safety** 10.3% o rivaroxaban group and 11.4% in standard tx. **Major bleeding** 26 Pts (1.1%) Rivaroxaban 52 pts (2.2%) standard tx.

Summary of Rivaroxaban Trials

Study	Treatment	Total Subjects	First major or clinically relevant nonmajor bleed	Recurrence of DVT	Primary efficacy outcome	Findings
Einstein DVT **NEJM 2010.363:2499-2510**	**DVT:** Rivaroxaban alone 15 mg bid x 3 weeks then 20 mg qd Enoxaparin plus VKA antagonist either Warfarin or acenocoumarol	DVT: total 3449 Rivaroxaban N=1731 Enoxaparin/VKA N=1718	Rivaroxaban: 139 patients (8.1%) Enoxaparin/VKA 138 patients (8.1%)	Rivaroxaban: 36 events (2.1%) Enoxaparin/VKA 51 events (3.0%)	**Primary:** Recurrent venous thromboembolism _____ **Principal Safety outcome:** Major bleeding or clinically relevant nonmajor bleeding in the initial treatment study and major bleeding on the continued treatment study. **Primary** Same as above **Principal** same	**DVT:** Rivaroxaban had non-inferiorior efficacy with respect to the **Primary outcome** 36 events (2.1%) vs. 51 events (3%) with enoxaparin-VKA **Safety outcome** Occurred same in both groups 8.1%

Summary of Rivaroxaban Trials

Study	Treatment	Total Subjects	Rate of Recurrence	Primary efficacy outcome for both studies	Findings
EINSTEIN Continued Treatment Study **NEJM 2010;363:2499-510**	Continued tx study Rivaroxaban 20 mg qd vs. placebo	602 patients Rivaroxaban 594 placebo	Rivaroxaban ↓ 82% from 7.1 to 1.3 clinical events	**Primary:** Symptomatic recurrent venous thromboembolism defined as composite of DVT or non-fatal or fatal pulmonary embolism	Acceptable benefit to risk profile

Summary of Rivaroxaban Trials

Study	Treatment	Total Subjects	Primary Outcome Primary Safety	Findings
RECORD I NEJM 2008;358:2765-75	Rivaroxaban 10 mg qd vs. Enoxaparin 40 mg qd sc	Total 3153 patients in superiority analysis Total 4433 in safety analysis	**Primary outcome**: composite of DVT (either symptomatic or detected by venography, nonfatal PE or death from any cause at 36 days. **Secondary outcome**: major DVT (proximal DVT, nonfatal PE or death from venous thromboembolism Primary Safety Outcome: major bleeding	**Primary outcome** occurred in 18 of 1595 pts.(1.1%) in Rivaroxaban grp. And 58 of 1558 pts (3.7%) in enoxaparin grp. **Secondary**: 4 of 1686 pts (0.2%) in rivaroxaban and 33 of 1678 pts (2.0%) enoxaparin grp

Summary of Rivaroxaban Trials

Study	Treatment	Total Subjects	Primary Outcome	Findings
RECORD II Lancet 2008.372,Issue 9632:31-39	Rivaroxaban 10 mg qd (31-39 days) plus placebo injection 10 – 14 days) OR Enoxaparin 40 mg sc qd 10-14 days plus placebo tab 31-39 days	Total 2509 prior to elective total hip Rivaroxaban N=1252 Enoxaparin N=1257	**Primary outcome:** composite of DVT, non-fatal PE and all cause mortality up to day 30-42.	**Primary outcome:** modified intention to treat population 864 in Rivaroxaban grp. And 869 in Enoxaparin grp. Primary outcome occurred in 17 (2.0%) pts in the rivaroxaban grp. Compared with 81 (9.3% in the enoxaparin grp Extended tx. with rivaroxaban was significantly more effective than short term enoxaparin for the prevention of DVT. Incidence of bleeding same in both groups (81) (6.6%) in 1228 pts in Rivaroxaban; (68) (5.5%) of 1229 pts in Enoxaparin

Summary of Rivaroxaban Trials

Study	Treatment	Total Subjects	Primary Outcome	Findings
RECORD III	Rivaroxaban 10 mg qd beginning 6-8 hrs after surgery OR Enoxaparin 40 mg qd beginning 12 hrs after surgery	Total 2531 total knee arthroplasty	**Primary:** composite of DVT,non fatal PE or death from any cause within 13 to 17 days after surgery. **Secondary:** major DVT (proximal DVT, non fatal PE or death related to thromboembolism) and symptomatic DVT. **Primary Safety Outcome:** Major bleeding	**Primary:** occurred in 79 of 824 pts (9.6%) in Rivaroxaban grp.and in 166 of 878 pts who received enoxaparin. **Secondary:** major DVT occurred in 9 of 908 pts (1.0%) of Rivaroxaban grp. And 24 of 925(2.6%) given enoxaparin. **Primary Safety:** Major bleeding occurred in 0.6% of pts In rivaroxaban grp and 0.5% pts in enoxaparin Rivaroxaban was superior toenoxaparin for thromboprophylaxis after total knee arthroplasty with similar rates of bleeding.

Summary of Apixaban Trials

Summary of Apixaban Trials

Trial	Apixaban Dose	Comparative dose	Bleeding	Primary Outcome	Findings
AVERROES 2011 N=5599 Non-valvular AFib NEJM 2011.364:806-817	5 mg bid	Aspirin 81-324 mg	**Apixaban** 1.4% per yr **Aspirin** 1.2% per year	Primary:VTE per year **Aspirin** 3.7% **Apixaban** 1.6% P <.001 for superiority Primary safety: Major bleeding/yr	Major bleeding per year Aspirin 1.2 % /yr Apixaban 1.4% /yr P =.57

Summary of Apixaban Trials

Trial	Apixaban dose	Comparative dose	Bleeding	Secondary outcomes	Primary outcomes	Findings
ARISTOTLE 2011 N=18,201 A Fib at least 1 RF for stroke NEJM 2011;365:981-92	5 mg BID	Warfarin INR 2-3	**Major bleeding:** Apixaban 327 pts (2.13%/yr) Warfarin 462 pts (3.09%/yr) **Intracranial** Apx: 52 pts 0.33% Warf: 122 pts .80% **GI:** Apixaban 105 pts, 0.76% Warfarin 119 pts, 0.86%	**Death any cause:** Apixaban 3.52% vs. Warfarin 3.94%/year Warfarin **Death CV causes:** 1.80%/yr Apixaban 2.02%/yr Warfarin **Rate of death non-CV** Apixaban 1.14%/yr Warfarin 1.22%/yr **Rate of MI:** Apixaban 90 events 0.53% Warfarin 102 events 0.61% - not significant	**Primary efficacy:** Ischemic or hemorrhagic stroke or embolism **Stroke:** Apixaban **Total 212 pts** (1.27%) N=9120 Warfarin **Total 265 pts** (1.60%) N=9081	Apixaban was superior to warfarin in preventing stroke or systemic embolism caused less bleeding and resulted in lower mortality.

Summary Apixaban Trials

Trial	Apixaban dose	Comparative dose	Bleeding	Primary outcome	Findings
ADVANCE-1 Trial N=3,195 Total Knee replacement NEJM 2009. 361:594-604	2.5 mg bid Started 12 to 24 hr. prior to surgery and continued for 10 to 14 days N=1599	Enoxaparin 30 mg q 12 hrs. Started 12 to 24 hr. prior to surgery and continued for 10 to 14 days N=1596	Composite incidence of major bleeding and clinically relevant non-major bleeding was **Apixaban 2.9%** **Enoxaparin 4.3%**	Composite of asymptomatic and symptomatic DVT, non fatal PE and death from any cause during treatment **Apixaban** 9.0% **Enoxaparin** 8.8%	Compared with enoxaparin for efficacy of thromboprophylaxis after knee replacement, apixaban did not meet the pre-specified statistical criteria for non-inferiority but its use was associated with lower rates of clinically relevant bleeding and it had a similar adverse event profile.

Summary of Apixaban Trials

Trial	Apixaban dose	Comparative dose	Bleeding	Primary outcome	Findings
ADVANCE-2 Trial Elective unilateral or bilateral total knee replacement Lancet 2010. 375;9717.	2.5 mg bid N=1528 **Apixaban** started 12 to 24 hr after wound closure continued for 10-14 days	Enoxaparin 40 mg qd N=1529 **Enoxaparin** started 12 hr before surgery continued for 10-14 days	Major or clinically relevant non-major bleeding occurred in **Apixaban** 53 (4%) of 1501 patients **Enoxaparin** 72 (5%) of 1508 pts	Composite of asymptomatic and symptomatic DVT, on-fatal PE and all cause death during treatment **Apixaban** 147 pts (15% of 976 pts) **Enoxaparin** 243 (24% of 997 pts).	Apixaban 2.5 mg bidstartingonthe morning after TKR offers a convenientand more effective orally administered alternative to 40 mg daily of enoxaparin without increased bleeding

Summary Apixaban Trials

Trial	Apixaban dose	Comparative dose	Bleeding	Primary outcome	Findings
ADVANCE-3 Trial N=5407 patients Total hip replacement NEJM 2010. 363;26.	2.5 mg bid **Apixaban** started 12 to 24 hr after closure of surgical wound- continued for 35 days post-op	**Enoxaparin** 40 mg sq q 24 hr Enoxaparin started 12 hr prior to surgery- continued for 35 days after surgery	Composite outcome of major and clinically relevant non major bleeding occurred **in 129** of 2673 pts assigned to **Apixaban (4.8%)** and **14** of 2659 **Enoxaparin (5%)**	Composite of asymptomatic or symptomatic DVT, non-fatal PE, or death from any cause during the treatment period. Pts. Followed 60 additional days after last med dose **Apixaban** 27 pts (1.4%) **Enoxaparin** 74 pts (3.9%)	Apixaban was assoc. with lower rates of venous thromboembolism without increased bleeding

Edoxaban Trial

Study	Total subjects	Dose	Primary Outcome	Primary Events	Secondary Events	Findings
ENGAGE AF-TIMI 48 NEJM 2013.369;2093 -2104 Cardiosource Nov.19, 2013	21,105 patients AFib with moderate to high risk stroke Followed for mean 2.8 yrs	Compare high 60 mg/d and low dose 30 mg/d edoxaban with warfarin INR 2-3 • For patients with CrCl <50 ml/min • body wt ≤60 kg, or • taking meds that inhibit P-gp system- • dose adjustment was made. 60 mg -30 mg; 30 mg-15 mg.	**Primary:** Stroke or systemic embolization **Secondary:** composite stroke, embolization or CV death	**Stroke:** 1.18%/yr 60 mg Edoxaban 1.61%/yr 30 mg Edoxaban 1.50%/yr Warafarin **Major bleed:** 2.75% 60 mg 1.61% 30 mg 3.43% warfarin	**Composite stroke, embolization** 3.85% 60 mg 4.23% 30 mg 4.43% Warfarin **CV death** 2.74% edoxaban 3.17% warfarin	• Both Edoxaban regimens were noninferior to warfarin for the prevention of stroke or systemic embolic event. • High dose of edoxaban more effective • Edoxaban safe no unexpected side effects

Warfarin Trials

Warfarin Trials Non-Rheumatic Atrial Fibrillation

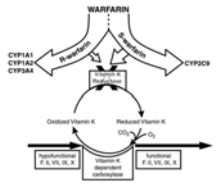
	Sample size	Sample size	INR	Thromboembolism	P value	% Major Bleeding	
Study	Warfarin treated Pts	Control Pts	INR	% risk reduction	P value	Warfarin treated Patients	Control Patients
AFASKA	335	336	2.8-4.2	60	0.027	0.6	0.0
SPAF	210	211	2.0-4.5	67	0.01	1.9	1.9
BAATAF	212	208	1.5-2.7	86	<0.05	0.9	0.5
CAFA	187	191	2.0-3.0	45	0.25	2.7	0.5
SPINAF Warfarin Prescribing information	260	265	1.4-2.8	79	0.001	2.3	1.5

Pharmacokinetics

Pharmacokinetics

	Dabigatran	Rivaroxaban	Apixaban	Warfarin
Metabolism	Oral direct thrombin inhibitors Prodrug rapid biotransformation to active drug Inhibit free and fibrin-bound FXa activity Fixed dosing – no coagulation monitoring required Few food/less drug interactions Renal excretion: 80%	Oral direct FXa inhibitors Directly acting compound – no biotransformation Inhibit free and fibrin-bound FXa activity & prothrombinase Fixed dosing – no coagulation monitoring required Few food/less drug interactions Renal excretion: 66%	Oral direct FXa inhibitor Directly acting compound – no biotransformation Inhibit free and fibrin bound FXa activity & prothrombinase Fixed dosing – no coagulation monitoring required Few food/less drug interactions Renal excretion: 27%	Inhibits synthesis of vitamin K dependent clotting factors II, VII, IX and X and the anticoagulant proteins C and S

Warfarin Metabolism



Ebby,C. Clinical Laboratory New.2009;Vol35, No.6
Original
Thrombosis Journal 2008;6:7

Key Genes May Affect Warfarin Dose

- Genetic polymorphisms in the CYP450 2C9 gene
  - Two most common alleles (CYP2C9*2 and CYP 2C9*3) decrease the clearance of S warfarin by approximately 20% and 33% per allele
  - Leading to increased plasma levels and poor metabolism
- Vitamin K Epoxide Reductase, Complex I

Vitamin K Epoxide Reductase, Complex I (VKORC I)

- Mutations in VKORC I cause warfarin resistance and multiple coagulation factor deficiency type 2
- VKORC I synthesizes vitamin K epoxide reductase (VKOR) which resides in the endoplasmic reticulum of the hepatocyte and other cells
- VKOR is inhibited by warfarin, especially S-warfarin
- VKOR activity is required for post translational modification of Glu residues on clotting factors II, VII, IX, X and proteins C, S, and Z
- VKORC 1 may be part of a complex

Pharmacokinetics

	Dabigatran Etexilate	Rivaroxaban	Apixaban	Warfarin
Metabolism	Conjugation No CYP450	CYP 3A4 CYP 3A5 CYP 2J2	CYP 3A4 mainly CYP 1A2 minor CYP 2C8 minor CYP 2C9 minor CYP 2C19 CYP 2J2 minor	CYP 2C9 (principal) CYP 2C19 CYP 2C8 CYP 1A2 CYP 3A4
P-gp	Yes	Yes	No	No
Renal impairment	↓ dose	↓ dose	↓ dose	No dose adjustment
Hepatic impairment	No dose adjustment in moderate impairment	AVOID use in moderate hepatic impairment or hepatic associated coagulopathy -AUC ↑ up to 127%	No dose adjustment in mild impairment Recommendations not given for moderate impairment	May ↑response use caution in these pts.

Pharmacokinetics

	Dabigatran Etexilate	Rivaroxaban	Apixaban	Warfarin
Bio-availability	3-7%	80% to 100% (10 mg) no food 66% (20 mg) fasting ↑ AUC 39% to Cmax 76% with food	50% doses up to 10 mg	Peak concentration 4 hours after dose
Intake of food	No	Mandatory	No	No
Half life	12-17 hours	5-9 hours In healthy subjects 11-13 hours in elderly	8-15 hours	Range 20-60 hour mean 40 hours R warfarin – 37 to 89 hr S warfarin – 21 to 43 hr
Protein binding	35%	92-95%	87%	99%

Prescribing Information each drug

Indications

Drug	Indications
Dabigatran	1. Non-valvular atrial fibrillation ↓ risk of stroke or embolization
Rivaroxaban	1. Non-valvular atrial fibrillation ↓ risk of stroke or embolization 2. Treatment of DVT; PE; and reduction in risk of recurrent DVT and of PE 3. Prophylaxis of DVT in patients undergoing hip or knee replacement surgery
Apixaban	1. Non-valvular atrial fibrillation to ↓ risk of stroke or embolization 2. Prevention of DVT for patients undergoing total hip or knee replacement surgery 3/14/14
Warfarin	1. Prophylaxis and treatment of venous thrombosis and its extension pulmonary embolism. 2. Atrial fibrillation 3. Cardiac valve replacement 4. After myocardial infarction to prevent recurrent MI, prevention of thromboembolic events such as stroke or embolism

Prescribing Information for each drug
www.medpaetoday.com/Cardiology/VenousThrombosis/44776

Pharmacokinetics of Anticoagulants

	Dabigatran	Rivaroxaban	Apixaban	Warfarin
Contraindicated	Active bleeding mechanical heart valve History of hypersensitivity to dabigatran	Active bleeding Severe hypersensitivity reaction.	Active major bleeding Hypersensitivity (anaphylactic) to apixaban	• Pregnancy except in women with mechanical heart valves • Hemorrhagic tendencies or blood dyscrasias • Recent or contemplated surgery CNS or eye or traumatic surgery • Bleeding tendencies associated with certain conditions • Threatened abortion, pre- or eclampsia • Unsupervised patients with potential high levels of non-compliance • Spinal puncture and other diagnostic or therapeutic procedures with potential for uncontrolled bleeding • Hypersensitivity to warfarin • Major regional or lumbar block anesthesia • Malignant hypertension
Prescribing Information				

ARS Question #1

- Which of the following is not metabolized in the CYP pathway?

1. Rivaroxaban
2. Warfarin
3. Dabigatran
4. Apixaban

Dosing

Drug	Dose
Dabigatran	150 mg bid (CrCl>30 ml/min) 75 mg bid (CrCl 15-30 ml/min) No recommendation CrCl<15ml/min Storage: Store in original bottles or blister packs. Opened bottle must be used within 60 days.
Rivaroxaban	**Afib** – CrCl >50 ml/min 20 mg qd with evening meal CrCl 15-50 ml/min 15 mg qd with evening meal **DVT** – 15 mg bid with food for 21 days then 20 mg qd with food for remaining treatment **To decrease risk of recurrent DVT** – 20 mg qd with food **Hip replacement surgery** – 10 mg qd for 35 days **Knee replacement surgery** – 10 mg qd for 12 days 15 mg and 20 mg tabs may be crushed and mixed with applesauce and served immediately followed by food 15 mg and 20 mg tabs may be crushed and mixed with 50 ml of water via NG tube or gastric tube –avoid if tube is distal to the stomach 15 mg and 20 mg tabs must be taken with food 10 mg tab may be taken with or without food Prescribing information 1/2014

Dosing

Drug	Dose
Apixaban	Most patients 5 mg bid For patients with any TWO of the following-Reduce dose 2.5 mg bid • Age ≥ 80 year • Body weight ≤ 60 kg • Sr. Cr. ≥ 1.5 mg/dL End Stage Renal Disease maintained on hemodialysis recommend 5 mg bid End Stage Renal Disease maintained with hemodialysis with ONE of the following characteristics-Reduce dose to 2.5 mg bid • Age ≥ 80 years • Body weight ≤ 60 kg • Prevention of DVT post THR or TKR 2.5 mg bid
Warfarin	Individualized based on patients INR response Atrial Fib or DVT – INR 2.5 (range 2.0-3.0) Mechanical and bioprosthetic heart valves • Aortic valve in NSR without LAE INR 2.5 (range 2.0-3.0) (tilting disc valve) • Mitral valve INR 3.0 (range 2.5-3.5) (tilting disk valve and bileaflet mechanical valves) • For caged ball or caged disk valves INR 3.0 (range 2.5-3.5) • Bioprosthetic valve in mitral position INR 2.5 (rage 2.0-3.0) x 3 months

Drug Interactions

Drug Interactions	Dabigatran	Rivaroxaban	Apixaban	Warfarin
P-gp inhibitor ↑ anticoagulant concentration	Diltiazem Verapamil Grapefruit large amt. Amiodarone quinidine clarithromycin No dose adjustment on these _____ Dronedarone ↓ dabigatran 75 mg bid CrCl 30-50 ml/min _____ **AVOID P-gp inhibitors CrCl 15-30 ml/m**	Diltiazem Felodipine Nicardipine Verapamil Amiodarone Dronedaone Naproxen	Diltiazem Felodipine Nicardipine Verapmil Amiodarone Dronedarone Ranolazine Naproxen	None
Prescribing information for each drug				

Drug Interactions

Drug Interaction	Dabigatran	Rivaroxaban	Apixaban	Warfarin
P-gp and/or CYP3A4 inhibitors ↑ Anticoagulant concentration	Dronedarone, ketoconazole, Quinidine, Verapamil if given at same time – separate by 2 hours	**AVOID (P-gp and CYP 3A4 combo**: Ketoconazol Itraconazole, lopinavir/ritonavir, Ritonavir, indinavir, conivaptan clarithromycin erythromycin Fluconazole ↑ in Rivaroxaban by 30% - 160%	↓ apixaban 2.5 mg bid with ketoconazole, itraconazole, ritonavir, clarithromycin _____ If already taking apixaban 2.5 mg bid, AVOID	**CYP 3A4**: Alprazolam, amiodarone, amlodipine, amprenavir, aprepitant, atorvastatin, atazzanavir, bicalulgamide, cilostazol, cimetidine, ciprofloxacin, clarithromycin, conivaptan, cyclosporine, darunavir/ritonavir, diltizem, erythromycin, fluconazole, fluoxetine, fluvoxamine, fosaminprenavir, imatinib, indinavir, isoniazid, itraconazole, ketoconazole, lopinavir/ritonavir, nefazodone, nelfinavir, nilotinib, oral contraceptives, posaconazole, ranitidine, ranolazine, ritonavir, saquinavir, telithromycin, tipranavir, voriconazole, zileuton. Not all inclusive.
Prescribing information for each drug				

Drug Interactions

Drug Interactions	Dabigatran	Rivaroxban	Apixaban	Warfarin
P-gp and/or CYP 3A4 inducers ↓ concentrations of anticoagulant	St. John's Wort Rifampin (avoid)	Nefazodone Prazosin, Razodone **AVOID P-gp and CYP 3A4 combo** **St. John's Wort, carbamazapine phenytoin, rifampin ↓ rivaroxaban by 50% (1/2014 FDA warning)**	Dexamethasone **Dual inducers: AVOID** **Rifampin, carbamazepine,phenytoin, St. John's wort**	**CYP 3A4**. Armodafinil, amprenavir, aprepitant, bosentan, carbamazepine, efavirenz, etravirine, modafinil, nafcillin, phenytoin, pioglitazone, prednisone, rifampin, rufinamide. Not all inclusive
Prescribing Information for each drug				

Drug Interactions

Drug Interaction	Dabigatran	Rivaroxaban	Apixaban	Warfarin
CYP 1A2 inhibitors ↑concentrations of anticoagulant				Acyclovir, allopurinol, caffeine, cimetidine, ciprofloxacin, disulfiram, enoxacin, famotidine, fluvoxamine, methoxsalen, mexiletine, norfloxacin oral contraceptives, phenylpropanolamine, propafenone, propranolol, terbinafine thiabendazole, ticlopidine, verapamil, zileuton. Not all inclusive
CYP 1A2 inducers ↓ concentrations of anticoagulant Prescribing Information				Montelukast, moricizine, omeprazole, phenobarbital phenytoin, cigarette smoking Not all inclusive

Drug Interactions

Drug Interactions	Dabigatran	Rivaroxaban	Apixaban	Warfarin
CYP2C9 Inhibitors ↑ concentration of anticoagulant				Amiodarone, capecitabine, cotrimoxazole, etravirine, fluvastatin, fluvoxamine, metronidazole, miconazole, oxandrolone, sulfinpyrazone, tigecycline, voriconazole, zafirlukast Not all inclusive
CYP2C9 Inducers ↓ concentration of anticoagulant				Aprepitant, boentan, carbamazepine, phenobarbital, rifampin Not all inclusive
Prescribing Information				

Drug Interactions
Anticoagulants, NSAIDs, Aspirin

Drug Interaction	Dabigatran	Rivaroxaban	Apixaban	Warfarin
Anticoagulants: Enoxaparin, heparin, argatroban, bivalrudin, desirudin, lepirudin	↑ risk of bleeding	Single dose – additive effect	↑ risk of bleeding	↑ risk of bleeding
Warfarin	↑ risk of bleeding	Single dose- additive effect	↑ risk of bleeding	
Antiplatelet: Aspirin, cilostazol,clopidogrel,dipyridamole, prasugrel, ticlopidine	↑ risk of bleeding	Concomitant use – RF for major bleeding	↑ risk of bleeding	↑ risk of bleeding
NSAIDs: celecoxib, diclofenac,ibuprofen, indomethacin, ketorolac, naproxen, oxaprozin, piroxicam, sulindac	↑ risk of bleeding	Concomitant use ↑ risk of bleeding	↑ risk of bleeding	↑ risk of bleeding
Seratonin Uptake Inhibitors: citalopram, fluoxetine; paroxetine; sertraline				↑ risk of bleeding

Switching from one anticoagulant to another

Switching from Warfarin to	
Dabigatran	Discontinue warfarin and start dabigatran when the INR is below 2.0
Rivaroxaban	Discontinue warfarin and start rivaroxaban when the INR is below **3.0**
Apixaban	Discontinue warfarin and start apixaban when the INR is below 2.0
Switching from __ to another anticoagulant other than warfarin	
Dabigatran	Wait 12 hours (CrCl ≥ 30 ml/min) or 24 hours (CrCl<30 ml/min) after the last dose of dabigatran before initiating treatment with a parenteral anticoagulant
Rivaroxaban	Discontinue rivaroxaban and give the first dose of the other anticoagulant (oral or parenteral) at the time of the next rivaroxaban dose would have been taken
Apixaban	Discontinue apixaban and begin the other at the next scheduled dose

Switching from one anticoagulant to warfarin

Convert from ____ to warfarin	
dabigatran	Adjust starting time of warfarin based on creatinine clearance CrCl ≥50 ml/min start warfarin 3 days before stopping dabigatran CrCl 30-50 ml/min start warfarin 2 days before stopping dabigatran CrCl 15-30 ml/min start warfarin 1 day before stopping dabigatran CrCl <15 ml/min no recommendations can be made
rivaroxaban	Discontinue rivaroxaban and begin both a parenteral anticoagulant and warfarin at the same time the next dose of rivaroxaban was due. Stop parenteral anticoagulation when INR therapeutic continue warfarin
apixaban	Discontinue apixaban and begin both a parenteral anticoagulant and warfarin at the same time the next dose of apixaban was due. Stop parenteral anticoagulation when INR therapeutic continue warfarin
Switch from anticoagulants other than warfarin	
Dabigatran	Start dabigatran 0 to 2 hours before the time that the next dose of the parenteral drug was to have been given or at the time of discontinuation of a continuously administered parenteral drug
Rivaroxaban	Start rivaroxaban 0 to 2 hours prior to the next scheduled evening dose (LMWH, non warfarin oral anticoagulant)
Apixaban	Discontinue one being taken and begin the other at the next scheduled dose

Reversal Agents

	Dabigatran	**Rivaroxaban**	**Apixaban**	**Warfarin**
Reversal agent	Activated charcoal (within 1-2 hours) Removed by hemodialysis (within 2-3 hrs); FFP, Prothrombin complex concentrates (aPCCs; e.g. FEIBA) or activated Factor VIIa or concentrates of coagulation factors II, IX or X Platelets concentrates Antedexanet an imitation factor xa under development (Not Available)	No specific antidote Activated charcoal Plasma products Not dialyzable Antedexanet (Not available)	No specific antidote Activated charcoal Prothrombin complex concentrate; activated prothrombin complex concentrate, or recombinant factor VIIa may be considered Antedexanet phase II trial Not available	Vitamin K
Prescribing Information for each drug				

Warnings

Dabigatran	Rivaroxaban	Apixaban	Warfarin
Boxed warning: discontinuing dabigatran places patients at an increased risk of thrombotic events. If anticoagulation with dabigatran must be discontinued for a reason other than pathological bleeding, consider coverage with another anticoagulant	**Boxed warning**: premature discontinuation of rivaroxaban increases the risk of thrombotic events. To reduce this risk, consider coverage with another anticoagulant if rivaroxaban is discontinued for a reason other than pathological bleeding or completion of a course of therapy. Spinal/Epidural Hematoma Epidural or spinal hematomas have occurred in patients treated with rivaroxaban 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.	**Boxed warning:** discontinuing apixaban places patients at an increased risk of thrombotic events. An increased rate of stroke was observed following discontinuation of apixaban in clinical trials in patients with nonvalvular atrial fib. If anticoagulation with apixaban must be discontinued for a reason other than patahological bleeding, coverage with another anticoagulant should be strongly considered	**Boxed warning**: Warfarin can cause major or fatal bleeding. Perform regular monitoring of INR in all treated patients. Drugs, dietary changes and other factors affect INR levels achieved with warfarin therapy. Instruct patients about prevention measures to minimize risk of leeding and toreport signs and symptoms of bleeding.
Package inserts for each drug			

Physiologic Changes with Age

Pharmacokinetic	Effects of Aging	Consequence
Absorption	↓ salivary flow ↓ gastric acid secretion Atrophic vili Delayed gastric emptying Slowed GI motility ↓ splanchnic blood flow	↓ absorption
Distribution	↓ lean body mass ↑ Adipose tissue ↓ total body water/vol of distribution ↓ albumin	↑ half life of lipophilic drugs ↑ half life of hydrophilic drugs (water sol ↑ free (active) drug
Metabolism	↓ hepatic mass ↓ hepatic blood flow	↓ Phase I reactions (oxidation, reduction, hydrolysis) ↓ first pass metabolism
Excretion	↓ renal blood flow Loss of cortical mass ↓ tubular secretion	↓ elimination of drugs

Katzung BG. Basic & Clinical Pharmacology 9th Ed 2004

Considerations in Choosing an Anticoagulant

Problem	Consideration	Anticoagulant
High risk of bleeding	Choose lowest incidence of bleeding	Dabigatran 10 mg bid or Apixaban
Previous GI bleeding or high risk of	Choose lowest reported incidence of GI bleed	Apixaban
High risk of ischemic stroke low bleeding risk	Choose agent and dose withbest reduction of ischemic stroke	Dabigatran 150 mg bid
Previous stroke (secondary prevention)	Choose best investigated agent or greatest reduction of secondary stroke	Rivaroxaban Apixaban
CAD, previous MI or hgh-risk of ACS/MI	Choose agent with a positive effect in ACS	Rivaroxban
Renal impairment	Choose agent least dependent on renal function	Apixaban Rivaroxaban
GI upset, disorders	Choose agent with no reported GI effects	Apixaban Rivaroxaban
Patient preference	Consider once daily formulation	rivaroxaban

Camm J. Am J Med 2013
http://eduation.ajmed.com/00000

ARS Question #2

- The pharmacokinetics of aging shows a decrease in all of the following except.

1. Gastric acid secretion
2. Lean body mass
3. Albumin
4. Adipose tissue

Case Study

- 78 y/o woman with hypertension, renal insufficiency with a serum creatinine of 1.8 mg/dL is found to be in atrial fibrillation during an office exam. Her weight is 158 pounds. She has a CHA_2DS_2VASc score of 3. (age ≥75 y; HTN, female)
- Current medications: diltiazem 120 qd, atorvastatin 10 mg qd, aspirin 81 mg qd,
- What would you consider?

ARS Question #3

- Which of the anticoagulant(s) could be considered for this patient?

1. Dabigatran 150 mg bid
2. Rivaroxaban 15 mg qd
3. Apixaban 5 mg bid
4. Warfarin
5. 2,3,4
6. 1,2,3

ARS Question #3

- Which of the anticoagulant(s) could be considered for this patient?

1. Dabigatran 150 mg bid (no would have to be reduced o 75 mg bid)
2. Rivaroxaban 15 mg qd (yes this is a reduced dose for CrCl 15-50)
3. Apixaban 5 mg bid (yes the dose can stay same because she only has one of the criteria Cr≥ 1.5 mg/dL)
4. Warfarin (yes, no dose adjustment necessary)
5. 2,3,4
6. 1,2,3

MDRD Calculation of GFR

Sr Cr	Age	Gender/Ethnicity	GFR	NKF Stage of renal disease
1.8	78	African American Male	44	Stage 3 Moderate
1.8	78	White/other Male	37	Stage 3 Moderate
1.8	78	African American Female	33	Stage 3 Moderate
1.8	78	White/other Female	27	Stage 4 Severe

Mdrd.com

Factors Affecting serum creatinine concentration

	Effect of Sr. Creatinine	Mechanism/comment
Older Age	Decrease	Reduction in creatinine generation due to age related decline in muscle mass
Female sex	Decrease	Reduced creatinine generation due to reduced muscle mass
African American	Increase	Higher creatinine generation rate due to higher average muscle mass in African Americans compared to Caucasians; not known how muscle mass in other races compares to that of African Americans or Caucasians
Restriction of Dietary Protein	Decrease	Decrease in creatinine generation
Ingestion of cooked meats	Increase	Transient increase in creatinine generation; however, this may be blunted by transient increase in GFR
Muscular	Increase	Increased creatinine generation due to increased muscle mass +/- reduced protein intake
Malnutrition/muscle Wasting/amputation	Decrease	Reduced creatinine generation due to reduced muscle mass +/- reduced protein intake
Obesity	No change	Excess mass is fat, not muscle mass, and does not contribute to increased creatinine generation

www.kidney.org/professionals/KIs/pdf/12-10-4004_KBB_FAQs

Summary

- New anticoagulants show great promise and ease of taking
- Warfarin has long, safe history when monitored and adjusted
- Consider the co-morbid conditions of the patient when choosing
- Consider the financial cost to the patient
- Consider potential drug interactions
- Consider the metabolic changes that occur with age and make appropriate adjustments
- Calculate the GFR on each patient