Anticoagulation Management Update: The Old and New Frontier

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Dr. Tambunan is a frequent and popular FMX presenter. He practices internal medicine and has been teaching for 20 years. He specializes in anticoagulation, venous thromboembolism, and viral hepatitis.

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Learning Objectives

1. Utilize a systematic process of care, including initiation and assessment of therapy and dosing adjustments, to optimize effectiveness and minimize adverse effects of patients taking warfarin.
2. Consider new agents in patients, with atrial fibrillation and at least one other risk factor for stroke, that do not require frequent laboratory monitoring are as effective as warfarin for prevention of stroke or systemic embolism and have comparable risks of major bleeding.
3. Develop collaborative care plans with patient education to counsel patients on safe and effective self-administration of anticoagulants, emphasizing self-monitoring to prevent complications.
4. Establish or revise existing practice-level protocols for anticoagulation management, based on current evidence-based recommendations and guidelines, including having clearly defined staff roles and responsibilities.

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Audience Engagement System

Step 1 Step 2 Step 3

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Arterial vs Venous

- Arterial - thrombosis does *not* occur if endothelium is intact & functional. The usual cause is vascular damage through atherosclerotic plaque formation and eventual rupture
- Venous - "Virchow's" triad - endothelial injury, circulatory stasis and hypercoagulable state

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VIRCHOW's TRIAD

- Circulatory STASIS:

  immobility, CHF, advanced age, obesity and venous obstruction
- Endothelial Injury (TRAUMA):

  surgery (e.g., orthopedic), postpartum, infections & valve damage
- HYPERCOAGULABLE state:

  Factor V Leiden, oral contraceptives, cancer, deficiencies of protein C&S or ATIII , homocysteine, impaired fibrinolysis

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Hypercoagulable Studies

- Factor V Leiden
- Antiphospholipid Antibodies
- Homocysteine
- Prothrombin gene 20210 A allele
- Elevated Factor VIII (> 90th percentile)
- Antithrombin III deficiency
- Protein C deficiency
- Protein S deficiency

Federman DG, Kirsner RS. Arch Intern Med. 2001;161:1051-1056

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AES Question

B.V. is a 35 y/o Caucasian gentleman who comes to the ER with complaint of left leg pain and swelling for 3 days. Denies any insect bite, fall or trauma. Denies any shortness of breath or chest pain.

PE: Afebrile, B/P 110/70. Normal exam except assymmetric thigh size and mild tenderness on palpation. No chords palpable and negative Homan's sign.

Would you include hypercoagulable studies now?

A. No
B. Yes

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VTE Prophylaxis

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AES Question

- A 54-year-old Indonesian morbidly obese gentleman was admitted to the hospital for acute abdominal pain. Upon further work up by the ED physician pt was diagnosed of having suspected cholecystitis. PMH: DM type 2, HTN and hyperlipidemia. SH: occasional alcohol. Meds: metformin, glyburide, lisinopril, aspirin and pravastatin
- PE: T=100.6, P=104, R=16, B/P=138/86. General: awake, non-resp distress. Exam is normal except abdomen shows tenderness on deep palpation on the RUQ area, +/- Murphy sign, no rebound, bowel sound is hypoactive, no mass palpable.
- Labs: Normal CBC and CMP except WBC is at 14.4, AST/ALT = 88/74, Alk P = 258, Bili = 2.8
- He is scheduled for possible open cholecystectomy by the surgeon tomorrow AM. **Which of the following peri-operative orders would be the most acceptable?**
  - A. No peri-operative orders needed since he is a fairly healthy gentleman
  - B. Continue with metformin
  - C. Enoxaparin 40 mg subcut daily
  - D. UFH 15,000 units subcut twice daily

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Thrombophylaxis in Surgical Patients: ACCP Risk Classification

- Low Risk (<10%)
  - Minor surgery
  - Medical pt's who are mobile
- Moderate Risk (10-40%)
  - Most surgery
  - Medical pt's who are bedrest/sick
- High Risk (40-80%)
  - Hip/knee arthroplasty
  - History of VTE
  - **Hip or total joint procedures**
  - Spinal cord injury; major trauma

Kahn SR, Gould MK, Falck-Ytter Y. Chest 2012; 141:195S-325S.

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Thromboprophylaxis in Surgical Patients

- Low risk: No prophylaxis
- Moderate risk: LDUH (5,000 U bid) or LMWH
- High risk: LMWH or Warfarin or Fondaparinux or Novel anticoagulants + IPC

Kahn SR, Gould MK, Falck-Ytter Y. Chest 2012; 141:195S-325S.

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Thromboprophylaxis in Knee/Hip Orthopedic Surgical Patients

- Low molecular weight heparin (LMWH)
- Warfarin, rx 2 days prior to surgery or immediately post surgery (INR 2.0-3.0)
- Fondaparinux 2.5 mg daily
- Novel anticoagulant – Dabigatran 220 mg daily, Rivaroxaban 10 mg daily, Apixaban 2.5 mg BID, Edoxaban 30 mg daily (hip, 28–35 days & knee, 10-12 days)
- Intermittent pneumatic compression is only an **adjuvant therapy**
- Low dose unfractionated heparin is ***inadequate***.

Kahn SR, Gould MK, Falck-Ytter Y. Chest 2012; 141:195S-325S.

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Venous Thromboembolism (VTE)

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UF-Heparin

- MW = 35-50,000 Kd
- Poor bioavailability due to binding to proteins
- Targets Xa, ATIII, & thrombin
- Needs regular lab monitoring - Q 6 hrs
- Rapid plasma clearance
- Needs platelet, H/H monitoring

LMWH

- MW = 5-10,000 Kd
- Good bioavail., little binding to proteins
- Targets Xa & ATIII only
- No lab monitoring needed, except in obese (>110 kg) or renal dz
- Slow plasma clearance
- Needs platelet, H/H monitoring

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Pentasaccharides

- Mode of mechanism: Inhibits factor Xa only
- Indicated for VTE prophylaxis and treatment
- VTE treatment (dose varies with weight)
  - < 50 kg --- 5.0 mg SC
  - > 50 to 100 kg --- 7.5 mg SC
  - > 100 kg --- 10.0 mg SC
- Monitor platelets frequently
- Caution in pts with renal insuff (CrCl < 30 mL /min)
- Caution in underweight pts (< 45 kg)

EPHESUS and PENTATHLON study, 2000

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RECOVER

- 2,564 patients (mean age 55 years) with acute symptomatic VTE and normal renal function randomized to dabigatran 150 mg orally twice daily plus warfarin-like placebo vs. warfarin plus dabigatran-like placebo for 6 months
  - all patients initially given parenteral anticoagulation therapy for median 9 days
  - primary outcome was time to first occurrence of composite of symptomatic VTE or VTE-related death
  - comparing dabigatran vs. warfarin
    - symptomatic VTE or VTE-related death at 6 months in 2.3% vs. 2.2% (noninferiority met)
    - any death in 1.6% vs. 1.7% (not significant)
    - major bleeding episodes in 1.6% vs. 1.9% (not significant)
    - any bleeding episodes in 16.1% vs. 21.9% (p < 0.05, NNT 18)
  - no significant differences in acute coronary syndromes or abnormal liver function tests
  - Reference - RE-COVER trial N Engl J Med 2009 Dec 10;361(24):2342

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EINSTEIN

- 3,449 patients with acute symptomatic DVT randomized to rivaroxaban (15 mg po BID for 3 wks then 20 mg daily) vs standard therapy (enoxaparin SubQ + warfarin)
- Results:
  - Early treatment discontinuation 11.3% v 14.2% (p=0.01)
  - Symptomatic recurrent VTE 2.1% v 3% (HR 0.68, CI 0.44-1.04
  - Major bleeding 0.8% v 1.2% (NS)

EINSTEIN Investigators, Bauersachs R, Berkowitz SD, et al. N Engl J Med 2010 Dec 23;363(26):2499.

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EINSTEIN - PE

- 4,883 patients with acute symptomatic PE +/- DVT randomized to rivaroxaban (15 mg po BID for 3 wks then 20 mg po daily thereafter) vs standard therapy (enoxaparin SubQ + warfarin)
- Results:
  - symptomatic VTE 2.1% v 1.8% (NS)
  - major bleeding 1.1% v 2.2% (p = 0.003)
  - major bleed or nonmajor bleed 10.3% v 11.4% (NS)
  - mortality 2.4% v 2.1% (NS)

EINSTEIN-PE Investigators, Buller HR, Prins MH, et al. N Engl J Med 2012 Apr 5;366(14):1287

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AMPLIFY

- 5,395 adults (mean age 57 years) with acute symptomatic proximal deep vein thrombosis or pulmonary embolism were randomized conventional therapy vs apixaban 10 mg BID first 5 days then 5 mg BID for 6 months. Followed up for 7 months
- primary outcome was composite of recurrent symptomatic venous thromboembolism (VTE) and VTE-related death
- comparing apixaban vs. conventional therapy
  - primary outcome in 2.3% vs. 2.7% (95% CI for difference -1.3% to +0.4%, noninferiority met)
  - major bleeding in 0.6% vs. 1.8% (p < 0.001, NNT 84)
  - clinically relevant non-major bleeding in 3.8% vs. 8% (p < 0.05, NNT 24)
  - all-cause death in 1.5% vs. 1.9% (not significant)
  - any serious adverse event in 15.6% vs. 15.2% (no p value reported)

Reference - AMPLIFY trial N Engl J Med 2013 Aug 29;369(9):799

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Hokusai-VTE

- 4921 pts with DVT & 3319 pt with PE were randomized to conventional therapy vs LMWH/UFH + edoxaban 60 mg daily. Followed up for 12 months.
- Primary outcome was composite of VTE and VTE related death
- Comparing edoxaban vs conventional therapy
  - Primary outcome in 3.2% v 3.5 (95% CI 0.70-1.13, noninferiority met)
  - Major bleeding 8.5 v 10.3 (CI 0.71-0.94, superiority)
  - Any bleeding 21.7 v 25.6 (CI 0.75-0.90, superiority)

The Hokusai-VTE Investigatos, Buller HR, Decousus H, et al. N Engl J Med 2013;369:1406-15

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	Dabigatran	Apixaban	Rivaroxaban	Edoxaban
Indications	Nonvalvular a. fib. DVT & PE treatment DVT prophylaxis	Nonvalvular a. fib. DVT & PE treatment DVT prophylaxis	Nonvalvular a. fib. DVT & PE treatment DVT prophylaxis	Nonvalvular a. fib. DVT & PE treatment DVT prophylaxis
Mechanism of action	Thrombin inhibitor	Factor Xa inhibitor	Factor Xa inhibitor	Factor Xa inhibitor
Clearance	Renal	Renal & Hepatic	Renal & Hepatic	Renal & Hepatic
Usual dosage for VTE treatment/a fib	150 mg BID	5 mg BID	20 mg QD	60 mg QD
Usual dosage for VTE prophylaxis	110 mg 1-4 hrs after surgery then 220 mg daily	2.5 mg BID	10 mg QD	30 mg QD
Antidote	Idarucizumab	?PCC	?PCC	? PCC
Pregnancy	C	B	C	C
Drug interactions (key: **bold – increase**, nl – decrease)	**Azoles, amiadarone,** rifampin, anticonvulsants	**Azoles, diltiazem, macrolide, protease inh** rifampin, anticonvulsants	**Azoles, quinidine, HIV protease inh, macrolide** rifampin, anticonvulsants	**Verapamil, macrolide, Quinidine, azoles** rifampin, anticonvulsants
Dose adjustments	CrCl 15-30 mL/min – 75 mg BID CrCl < 15 -- **avoid**	If + on 2 out of 3: 1. Age > 80 yrs old 2. Body weight <60 kg 3. Creat > 1.5 mg/dL Reduce dose to 2.5 mg BID	CrCl 15-50 – 15 mg daily CrCl < 15 - **avoid** * Food is mandatory	Do not use if CrCl is > 95 CrCl 15- 50 – 30 mg daily CrCl < 15 - **avoid**

VTE treatment – Chest Guideline 2016

No cancer

1. NOACs over VKA
2. VKA over LMWH

With cancer

- LMWH over VKA or NOACs

Kearon C, Alk E, et al. Chest 2016;149:315-352

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CLOT Study

- 676 pts with cancer who had a VTE were randomized to receive dalteparin 200 IU/kg SC on first month then 150 IU/kg SC on the next five months vs conventional therapy of concurrent dalteparin & VKA for five to seven days then VKA for six months. 50% are female
- Primary outcome was recurrent symptomatic VTE
- Comparing of dalteparin vs conventional tx
  - Primary outcome in 27/336 vs 53/336, p = 0.002
  - Major bleeding 6% v 4, p = 0.27
  - Death 39 % v 41, p = 0.53

The CLOT Investigators, Lee AY, Levine MN, et al. N Engl J Med 2003;349:146-53

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Guidelines for Initiating Warfarin

- **Start low**
  - initiate at 2-5 mg daily esp. , in elderly, high bleeding risk, heart failure, liver disease, impaired nutrition
  - determine INR frequently after administration of intial dose
  - educate patient. DuPont Pharma or Barr Labs has info booklets available.
    - 1-800-COUMADIN or 1-800-WARFARIN.
- **Stabilize**
  - titrate to appropriate INR of 2.0-3.0
  - once stabilized, determine INR 2-3 times weekly for 1-2 weeks, then less often depending on stability of INR
- **Monitor and adjust**
  - determine INR regularly (every 1-4 weeks) and adjust if necessary

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Optional Warfarin Initiation

Day	INR	Warfarin Dose
1	< 1.5	10
2	< 1.8	10
	1.8 - 2.0	5
	2.1 - 3.0	2.5
	> 3.0	0
3	< 1.6	15
	1.6 - 2.0	10
	2.1 - 3.0	5
	3.1 - 3.5	2.5
	> 3.5	0
4	< 1.6	15
	1.6 - 2.0	10
	2.1 - 2.5	7.5
	2.6 - 3.0	5
	3.1 - 3.5	2.5
	>3.5	0

Kovacs MJ, et al,. Ann Int Med 2003; 138:714-719.

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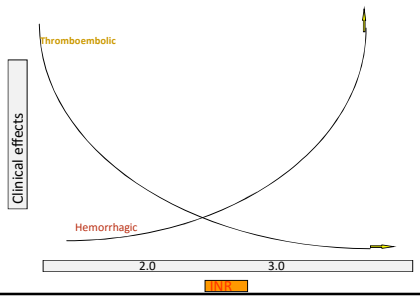

Therapeutic Ranges

INDICATION	INR	DURATION
Prophylaxis of DVT	2-3	7 days to 35 days
Treatment of DVT	2-3	Varies, see table
Prevention of cardioemb. stroke	2-3	Indefinite
S/P acute MI	2-3	Indefinite
A. fibrillation	2-3	Indefinite
Cardiomyopathy (<25%)	2-3	Indefinite
Valvular heart disease	2-3	Indefinite
Mechanical heart valve (mitral)	2.5-3.5	Indefinite
Hypercoagulable states	2-3	Indefinite
Tissue heart valve (mitral)	2-3	3 mths
Acute MI	2-3	< 3 mths

Chest 2012; 141:e895-e801S.

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Warfarin Drug Interactions

POTENTIATE

- **Antibiotics/Antifungal**
  - sulfamethoxazole, ciprofloxacin, tetracycline, metronidazole, all -azoles, isoniazid, macrolides
- **Cardiovas. agents**
  - amiodarone, disopyramide, propafenone
- **Others**
  - cimetidine, ASA, NSAID's, allopurinol, omeprazole, herbals; vitamin E, garlic, gingko biloba, garlic, ginseng

REDUCE

- **Antibiotics/Antifungal**
  - rifampin, nafcillin, dicloxacillin
- **Anticonvulsants**
  - phenytoin, barbiturates
- **Others**
  - sucralfate, cholestyramine, colestipol, chlorodiazepoxide, trazodone

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AES Question

A 47 y/o African-American gentleman was admitted to the hospital for severe left hand pain and swelling for ten days. States that he noticed it while gardening last week. He was started on oral dicloxacillin by his primary MD last week. He has history of atrial fibrillation and hypertension. His meds includes accupril, warfarin and simvastatin. He states that his INR has been well controlled for the last year. His physical exam shows his left hand is warm, tender to touch, erythematous, edematous, with a central lesion. Labs shows WBC = 15.9, Hgb = 11.3, Plt = 156 K, normal BMP. INR = 1.57

What is the reason of patient's sub therapeutic INR?

A. Non-compliance
B. Drug interaction with lisinopril
C. Drug interaction with dicloxacillin
D. Pt has a CYP2C9 mutation

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Warfarin Reversal Treatment: Non-bleeding

INR	Vit K dose	Route
<5	none	Hold dose
5-10	none	Hold dose
>10	2.5 mg	PO

* Check INR in 6-12 hrs and repeat if necessary.

! In severe/life threatening bleeding use Vit K 5-10 mg ***slow*** IV infusion and PCC or FFP

Holbrook A, Schulman S, et al. Chest 2012;141:e152S-e184S

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2012 ACCP Recommendations Duration of Therapy of VTE

- 3 months — - reversible risk factors* & 1st event
  - distal DVT
- 3 mths or **more** — - unprovoked VTE & 1st event depending on the risk-benefit ratio
- 3-6 months — -cancer, until resolved
- Indefinite — -second episode of unprovoked

*Transient immobilization, trauma, surgical operation, or pharmacologic estrogen use.

Kearon C, et al. Chest 2012;141:419S-494S

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Risk - Benefit

- >75 y/o
- Previous GI bleed
- Previous noncardioembolic stroke
- Chronic renal or hepatic disease
- Concomitant antiplatelet therapy
- Other serious illness
- Poor anticoagulant control
- Positive d-dimer
- Proximal DVT
- Antiphospholipid antibody
- Previous episode of VTE
- Hereditary thrombophilia
- Male
- Residual thrombosis in proximal veins
- Non-Asian ethnicity

Kearon C, et al. Chest 2012;141:419S-494S

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D-dimer for Anticoagulation Duration?

- 608 patients, prospective, three armed study with first episode of symptomatic, idiopathic proximal DVT &/or PE who has been treated at least for 3 months with warfarin.
- One arm – normal D-dimer, the other – abnormal D-dimer
  - placebo vs warfarin
- Objective: Composite recurrent VTE and major bleeding during 1.4 years of follow-up
- Results:
  - Normal: 24/385 (6.2%)
  - Abnormal and placebo: 18/120 (15.0%)
  - Abnormal and treated: 3/103 (2.9%)
  - p value = 0.02 (2/3 comparison)
  - Major bleeding: 1 on the treated group, 0 on the others.
- Conclusion: Consider longer therapy with warfarin if D-dimer is abnormal.

The PROLONG Investigators. N Engl J Med 2006;355:1780-9.

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Case Study

- RS, a 65 y/o WF comes in with acute shortness of breath for the last 2-3 days. Denies any cough, fever, or vomiting. Has h/o of type 2 DM, & hypercholesterolemia for 10 years, otherwise negative PMH. FH was noncontributory. Vitals, BP 125/85, P=100, R=24. Physical was normal except an asymmetric leg swelling R>L.

  Meds: Metformin, lisinopril, Estrogen, & atorvastatin

1. What test (s) would you order?
2. What do you think is the cause of the disorder?

- Pt was admitted and was placed on UFH. VQ scan shows intermediate probability and positive doppler U/S of the right lower extremity. After 5 days hospitalization, pt was noted to have epistaxis and platelet count of 50K, stable Hgb.

3. What treatment options do you have now?

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Heparin Induced Thrombocytopenia (HIT)

- Definition: + heparin antibody with fall of platelets (> 50%) or skin lesions at injection site or systemic reactions post heparin infusion
- Bovine UFH > porcine UFH > LMWH
- Recommend to monitor platelets every-other-day between days 4 – 14 (especially in postoperative patients)
- **DO NOT** use warfarin solely in HIT-associated DVT – may cause venous limb gangrene

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Direct Thrombin Inhibitor

- Identical to the natural hirudin found in leeches
- Cleared thru the kidney, adjust as needed
- Two agents: Argatroban and Lepirudin
- Lepirudin: Two prospective studies involving 380 pts, showing >90% platelet recovery and >75% effective anticoagulation. In addition, the difference in cumultative risk of death, limb amputation, or new thromboembolic complications are statistically significant in favor of lepirudine, p <0.004
  - Dosage: 0.4 mg/kg (max 110 kg) bolus, then 0.15 mg/kg (max 110 kg)
- Other agent is argatroban 2 mcg/kg/min IV to maintain aPTT 1.5-3 times baseline

Greinacher A, Lubenow N. Circulation. 2001;103:1479-1484.

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Atrial Fibrillation

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AES Question

A 65-year-old patient with sick sinus syndrome is coming for a follow up office visit. He is without complaints. He has a PMH of an old stroke, cardiac pacemaker placement and hypertension. His last echocardiogram shows an EF = 35%, LA size = 42 mm, and no valvular dysfunction. His medications are metoprolol, lisinopril, aspirin, and lasix.

What intervention, if any, should be considered for this patient at this time?

A. Cardiac catherization
B. Add non-dihydropiridine CCB
C. Anticoagulation
D. No intervention needed

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Management Decision

1. Stable or not
2. 48 hours
   - < 48 hours
     - Immediate cardioversion
   - > 48 hours
     - TEE guided cardioversion vs delayed cardioversion
3. Rate vs rhythm
   - Rate
     - Drugs v cardioversion
   - Rhythm
     - Drugs vs ablation (catheter v surgical)
4. Anticoagulation
   - CHADS2Vasc score
     - 0 or 1
     - 2 or more
       - Warfarin
       - Novel Anticoagulant
   - HAS-BLED score

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CHADS2

- **C**ongestive heart failure (any history) ------ 1
- **H**ypertension (prior history) ---------- 1
- **A**ge > 75 years ---------- 1
- **D**iabetes mellitus ---------- 1
- **S**troke or TIA ------ ---------- 2

Go AS, Hylek EM, Chang Y, et al.. JAMA 2003; 290:2685
Gage BF, Waterman AD, Shannon W. JAMA 2001; 285:2864

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Stroke Risk Based on CHADS2

0 --- 1.9 per 100 patient-years
1 --- 2.8
2 --- 4.0
3 --- 5.9
4 --- 8.5
5 --- 12.5
6 --- 18.2

Go AS, Hylek EM, Chang Y, et al. JAMA 2003; 290:2685
Gage BF, Waterman AD, Shannon W. JAMA 2001; 285:2864

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AES Question

You are being asked to decide whether to initiate anticoagulation for a patient with atrial fibrillation. Of the following factors which is the ***least*** important?

A. Gender
B. Age
C. Use of antiarrythmic medications
D. Peripheral vascular disease
E. Hypertension

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CHA2 DS2 - VASc

- Congestive heart failure or LV dysfunction 1
- Hypertension ---------- 1
- Age
  - 65 to 74 years ---------- 1
  - 75 and older ---------- 2
- Diabetes mellitus ---------- 1
- Stroke or TIA or thromboembolism ---------- 2
- Female sex (gender) ---------- 1
- MI, peripheral vascular dz or aortic plaque 1

Lip GY, Nieuwlaat R, Pisters R, et al. Chest 2010; 137(2):263-72

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Rate of Stroke/Thromboembolism

0 --- 0 %
1 --- 0.6%
2 --- 1.6%
3 --- 3.9%
4 --- 1.9%
5 --- 3.2%
6 --- 3.6%
7 --- 8.0%
8 --- 11.1%
9 --- 100%

Lip GY, Halperin JL. Am J Med 2010;123(6):484-8

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HAS-BLED score

- Hypertension
- Abnormal renal function
- Abnormal liver function
- Stroke
- Bleeding
- Labile INR
- Elderly (> 65 years)
- Drugs or alcohol (two points for both)

Lip GY, Frison L, Halperin JL, Lane DA. J Am Coll Cardiol 2011;57(2):173-80

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HAS-BLED score

0 --- 0.9%
1 --- 3.4%
2 --- 4.1%
3 --- 5.8%
4 --- 8.9%
5 --- 9.1%

- < 3 --- 9.1%
- > 3 --- 16.6%

Lip GY, Frison L, Halperin JL, Lane DA. J Am Coll Cardiol 2011;57(2):173-80
Apostolakis S, Lane DA, Guo Y, et al. J Am Coll Cardiol 2012;60(9):861-7

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Novel anticoagulants

- novel anticoagulant (dabigatran, rivaroxaban or apixaban, edoxaban) preferred over warfarin (ACC/AHA Class I, Level B)
- dabigatran 150 mg twice daily suggested rather than adjusted-dose VKA therapy (target INR range 2-3)
- rivaroxaban 20 mg daily may be as effective as warfarin for preventing stroke or systemic embolism
- apixaban 5 mg twice daily associated with reduced risk of stroke and major bleeding and might reduce risk of mortality compared to warfarin

Fuster V, Ryden LE, Cannom DS, et al. Circulation 2006;114(7):e257-354.
Wann LS, Curtis A, January CT, et al. J Am Coll Cardiol 2011;57(2):223-42.

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RE-LY Study

- 18,113 pts with a. fib & additional stroke risk factors were randomized to dabigatran 110 mg po BID vs 150 mg po BID vs warfarin adjusted to INR 2-3. Mean f/u 24 mths
- Results;
  - 110 mg did not show significant difference against warfarin although reduced risk of major bleeding (5.6% v 6.9%, p = 0.003)
  - 150 mg BID vs warfarin
    - stroke or systemic embolism in 2.21% vs. 3.35% (p < 0.001, NNT 88)
    - all-cause mortality 7.2% vs. 8.1% (p = 0.051)
    - major bleeding in 6.57% vs. 6.99% (not significant)
    - life-threatening major bleeding in 2.9% vs. 3.5% (p = 0.04, NNT 200)
- Conclusion: Dabigatran 150 mg is superior to warfarin in reducing stroke

Connolly SJ, Ezekowitz MD, Yusuf S, et al. N Engl J Med 2009;361(12):1139-51

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ROCKET AF Study

- A non-inferiority trial
- 14,264 pts with nonvalvular a. fib. & increase risk of stroke randomized to rivaroxaban 20 mg daily vs warfarin INR adjusted to 2-3.
- Follow up is 22 months
- Results:
  - stroke or systemic embolism in 2.1% per year vs. 2.4% per year in intention-to-treat population (p < 0.001 for noninferiority, not significant for superiority)
  - major and nonmajor bleeding in 14.9% per year vs. 14.5% per year (not significant for superiority)
  - intracranial hemorrhage in 0.5% vs. 0.7% (p = 0.02 for superiority)
- Conclusion: Rivaroxaban is non-inferior to warfarin and has superior ICH numbers

Patel MR, Mahaffey KW, Garg J, et al. N Engl J Med 2011;365(10):883-91

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ARISTOTLE Study

- 18,201 patients with a. fib and 1 or more additional risk factor randomized to apixaban 5 mg twice daily vs warfarin INR adjusted 2-3. Follow up is 1.8 years.
- Results:
  - any stroke or systemic embolism in 1.27% per year vs. 1.6% per year (p = 0.01, NNT 303 per year)
  - hemorrhagic stroke in 0.24% per year vs. 0.47% per year (p < 0.001, NNT 435 per year)
  - ischemic or uncertain type of stroke in 0.97% per year vs. 1.05% per year (not significant)
  - major bleeding in 2.13% per year vs. 3.09% per year (p < 0.001, NNT 105 per year)
  - all-cause mortality 3.52% vs. 3.94% (p = 0.047, NNT 238)
- Conclusion: Apixaban shows is statistically significant in reducing stroke compare to warfarin in nonvalvular a. fib with decreased ICH or major bleeding.

Granger CB, Alexander JH, McMurray JJ, et al. N Engl J Med 2011;365(11):981-92

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ENGAGE AF-TIMI 48 Study

- 21,105 patients with moderate-to-high risk atrial fibrillation (mean f/u, 2.8 years) randomized to compare two once-daily regimens of edoxaban with warfarin. Primary endpoint was stroke or systemic embolism.
- Results:
  - any stroke or systemic embolism 1.18% vs 1.61 vs 1.50 (p = <0.001 and 0.05, respectively)
  - major bleeding 2.75 % vs 1.61 vs 3.43 (p = <0.001 on both)
  - cardiovascular causes 2.74% vs 2.71 vs 3.17 (p = 0.01 and 0.008, respectively)
- Conclusion: Both once-daily edoxaban was noninferior to warfarin on the prevention of stroke with lower rates of bleeding and cardiovascular causes

Giugliano RP, Ruff CT, Braunwald E, et al. N Engl J Med 2013;369:2093-2104.

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	Dabigatran	Apixaban	Rivaroxaban	Edoxaban
Indications	Nonvalvular a. fib. DVT & PE treatment DVT prophylaxis	Nonvalvular a. fib. DVT & PE treatment DVT prophylaxis	Nonvalvular a. fib. DVT & PE treatment DVT prophylaxis	Nonvalvular a. fib. DVT & PE treatment DVT prophylaxis
Mechanism of action	Thrombin inhibitor	Factor Xa inhibitor	Factor Xa inhibitor	Factor Xa inhibitor
Clearance	Renal	Renal & Hepatic	Renal & Hepatic	Renal & Hepatic
Usual dosage for VTE treatment/a fib	150 mg BID	5 mg BID	20 mg QD	60 mg QD
Usual dosage for VTE prophylaxis	110 mg 1-4 hrs after surgery then 220 mg daily	2.5 mg BID	10 mg QD	30 mg QD
Antidote	Idarucizumab	?PCC	?PCC	? PCC
Pregnancy	C	B	C	C
Drug interactions (key: **bold – increase,** nl – decrease)	**Azoles, amiadarone,** rifampin, anticonvulsants	**Azoles, diltiazem, macrolide, protease inh** rifampin, anticonvulsants	**Azoles, quinidine, HIV protease inh, macrolide** rifampin, anticonvulsants	**Verapamil, macrolide, Quinidine, azoles** rifampin, anticonvulsants
Dose adjustments	CrCl 15-30 mL/min – 75 mg BID CrCl < 15 -- **avoid**	If + on 2 out of 3: 1. Age > 80 yrs old 2. Body weight <60 kg 3. Creat > 1.5 mg/dL Reduce dose to 2.5 mg BID	CrCl 15-50 – 15 mg daily CrCl < 15 - **avoid** * Food is mandatory	Do not use if CrCl is > 95 CrCl 15- 50 – 30 mg daily CrCl < 15 - **avoid**

Switching Anticoagulants

Agents	Recommendations
VKA to NOAC	INR <2.0: immediate INR 2.0-2.5: immediate or next day INR >2.5: follow INR till <2.5
NOAC to VKA	Administer concomitantly until INR is appr Re-test 24 hr after last dose of NOAC
Parenteral to NOAC: UFH LMWH	Start once UFH is discontinued. Caution: Renal Start when next dose would be given
NOAC to parenteral	Initiate when next dose of NOAC is due

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Which Anticoagulant is Preferred?

• Cancer	LMWH
• Poor compliance	VKA
• Pregnancy	LMWH
• Reversal agent needed	VKA, UFH, Dabigatran
• Liver disease & coagulopath	LMWH
• Renal disease & CrCl < 30 mL/min	VKA

Kearon C, Alk E, et al. Chest 2016;149:315-352

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MATCH Trial

- Randomised, double-blind, place-controlled trial (In the US and Europe)
  - Clopidogrel + ASA vs Clopidogrel
- 7599 patients with recent ischemic stroke or TIA & one vascular risk factor, mean age of 66 y/o (37% are women). Follow-up for 18 months.
  - Primary end point is composite of ischemic stroke, MI, vascular death, or rehospitalization for acute ischemia.
- Results:
  - 15.7% vs 16.7 (primary endpoint) P value = 0.244
  - 2.6% vs 1.3 (life-threatening bleeding) P value = <0.001
  - No difference in mortality
- Conclusion:
  - ADDING ASA TO CLOPIDOGREL ON HIGH RISK PATIENTS WITH RECENT ISCHEMIC STROKE, OR TIA INCREASE THE RISK OF LIFE THREATENING BLEEDING

Diener H, Bogousslavsky J, et al. Lancet 2004;364:331-37

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Anticoagulation Nutshell

- ASA ► stroke, AMI, UA, lone a-fib
- Factor Xa inhibitors ► a-fib, VTE prophylaxis and treatment
- G IIbIIIa inhbitors ► UA, AMI
- LMWH ► DVT/PE prophylaxis & treatment, UA
- Novel anticoagulants – a-fib, VTE prophylaxis and treatment (not all)
- $P2Y_{12}$ inhibitors – MI, UA
- Pentasacharrides ► DVT prophylaxis & treatment
- Phosphodiesterase inhibitors ► PVD
- Thienopyridines ► stroke, UA
- Thrombin inhibitors ► HIT, a-fib, VTE prophylaxis
- Thrombolytics ►AMI, acute stroke
- Unfractionated heparin ► DVT prophylaxis & treatment, UA, AMI, acute a-fib, PE
- Warfarin ► DVT prophylaxis & treatment, a-fib, PE, PVD, AMI

KEY:
AMI - acute myocardial infarction
DVT - deep vein thrombosis
HIT - heparin induced thrombocytopenia
PE – pulmonary embolus
UA - unstable angina
PVD - peripheral vascular disease

Practice Recommendations

- Calculate the annual thromboembolic risk with the regular implementation of CHADSVAsc scores on atrial fibrillation patients.
- Understanding of the current available oral anticoagulation - warfarin and the new novel anticoagulants and its side effects
- Do not load warfarin on the initial stage of the treatment of atrial fibrillation or VTE is still the mainstay

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QUESTIONS?

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Billing & Coding

When services performed in conjunction with:

Office Visit + EKG 992xx - 25 + 93000
Nutritional Therapy 97802-97804

Additional tests to confirm or monitor:

Home Management

G0248 Medicare: Initial demonstration home use INR
G02450 Medicare: Phys review of results, per 4 test result (once per week)
99363 Anti-coagulation home management, initial 90 days
99364 Anti-coagulation home management, subsequent 90 days
36416+85610 Finger stick + PT/INR

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Associated Session

- Anticoagulation Management Update: PBL

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Interested in More CME on this topic?
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