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NO CONFLICT OF INTEREST TO DECLARE

Oral Anticoagulation: Education of the EP patient

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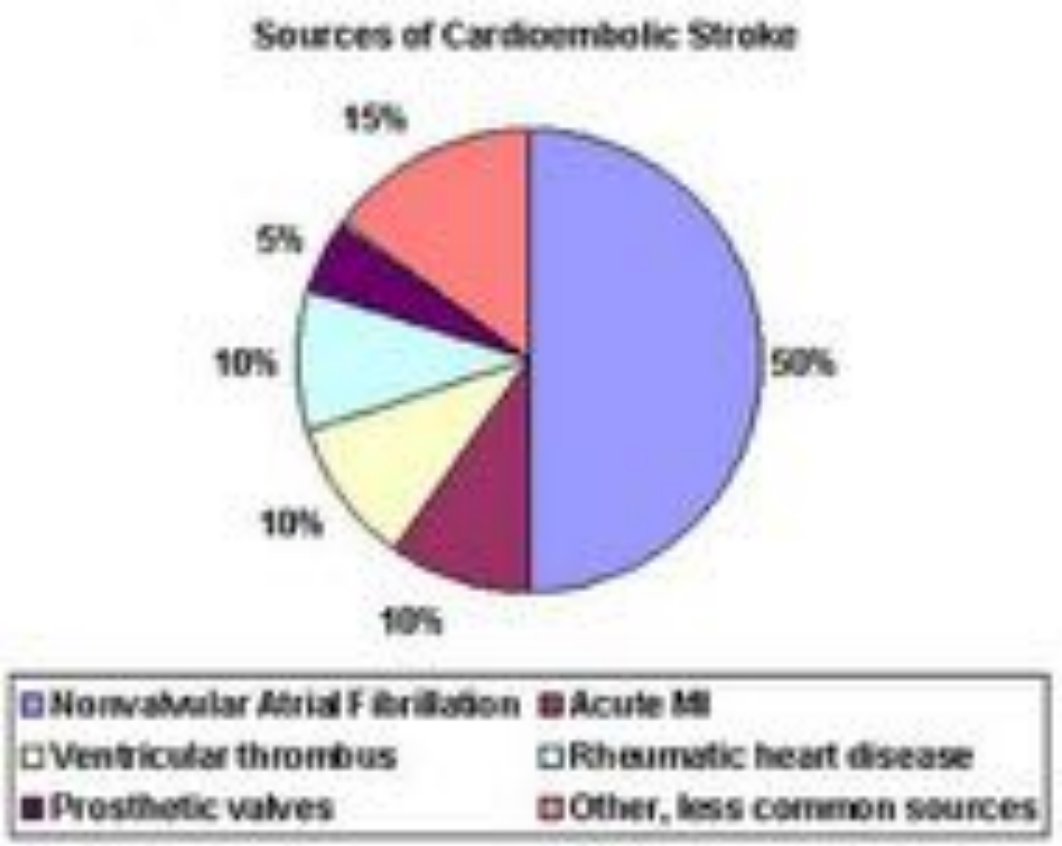
Cardioembolic Stroke and AF



Approximately 20% of ischemic strokes are considered Cardioembolic in nature. Of those, approximately 50% are as a result of AF.

Determine Thromboembolic Risk and Risk of Bleeding

	Score
CHA_2DS_2-VASc	
Congestive heart failure	1
Hypertension	1
Age ≥75 years	2
Diabetes mellitus	1
Stroke, TIA, or thromboembolism	2
Vascular disease[a]	1
Age 65–74 years	1
Sex category (i.e., female sex)	1
Maximum score	9
HAS-BLED[b]	
Hypertension (systolic blood pressure > 160 mm Hg)	1
Abnormal renal and liver function (1 point each)	1 or 2
Stroke	1
Bleeding tendency or predisposition	1
Labile international normalized ratios (if on warfarin)	1
Elderly (e.g., age >65 years)	1
Drugs or alcohol (1 point each)	1 or 2
Maximum score	9

[a] Previous myocardial infarction, peripheral artery disease, or aortic plaque.
[b] "Hypertension" is defined as systolic blood pressure 160 mmHg. "Abnormal kidney function" is defined as the presence of chronic dialysis or renal transplantation or serum creatinine ≥200 mmol/L. "Abnormal liver function" is defined as chronic hepatic disease (e.g., cirrhosis) or biochemical evidence of significant hepatic derangement (e.g., bilirubin.2× upper limit of normal, in association with aspartate aminotransferase/alanine aminotransferase/alkaline phosphatase.3× upper limit normal, etc.). "Bleeding" refers to previous bleeding history and/or predisposition to bleeding, e.g., bleeding diathesis, anemia, etc. "Labile INRs" refers to unstable/high INRs or poor time in therapeutic range (e.g., 60%). Drugs/alcohol use refers to concomitant use of drugs, such as antiplatelet agents, non-steroidal anti-inflammatory drugs, or alcohol abuse, etc. INR 1/4 international normalized ratio. Adapted from Pisters et al. (2010).
TIA, transient ischemic attack.

The 2014 AHA/ACC/HRS guidelines for the management of AF: OAC for patients with non-valvular AF or atrial flutter with prior stroke, TIA, or a CHA_2DS_2-VASc score ≥2.


Left Atrial Appendage

Current Oral anticoagulants utilized for prevention of Thromboembolism in AF

Vitamin K Antagonist:

- Warfarin (coumadin; jantoven)

Direct Thrombin Inhibitor:

- Dabigatran (Pradaxa)

Direct Factor Xa (ten-A) Inhibitors:

- Apixaban (Eliquis),
- Rivaroxaban (Xarelto) and
- Edoxaban (Savaysa)

- These are current options available in the US, your choices may differ slightly.

Warfarin: Patient education

- **MOA:** Interrupts normal clotting process of the blood by inhibiting how much Vitamin K is available for the liver to use.
- **Monitoring:** INR frequently until stable. Take Warfarin once every evening. If missed dose: call NP/MD.
- **Dietary restrictions:** Keep vitamin K intake consistent as possible. Do not avoid these foods, however keep consistent amount i.e.: one salad daily at dinner.
- **Smoking and Alcohol use:** Can cause variable INR. Avoid excess ETOH (no more than 1 drink/day) and encourage smoking cessation

Warfarin: Patient education

- **Sports:** Avoid contact sports, dangerous activities with risk of injury/blunt trauma should be d/t bleeding risk
- **Surgery:** Call prior to stopping for any reason. Bridging with LMWH may be necessary.
- **Contraindications:** Pregnancy (except with mechanical valve), bleeding disorders, active bleeding, recent neurologic, ocular or traumatic surgery, potential miscarriage, eclampsia/ pre-eclampsia, inadequate lab facilities/poor compliance, spinal puncture, regional or lumbar block anesthesia.
- **Adverse Reactions:**
  - Call your doctor right away if you have any signs of bleeding problems:
    - severe bruising
    - black, tarry, or bloody stools
    - bleeding gums, nose bleeds, bloody urine, coughing up blood, throwing up blood or "coffee grounds"
    - cuts that take a long time to stop bleeding
    - feel dizzy; feeling very tired or weak
    - pain or swelling
    - very bad headache
- Consider patient education materials available from manufacturer or other medical resources.
- **Cost:** approximately $53 US dollars/month (varies per insurance plan)

INR Elevation	*INR Depression
Amiodarone (2C9)	Rifampin (2C9)
Ciprofloxacin (1A2/3A4)	Secobarbital (2C9)
TMP/SMX (2C9)	Carbamazepine (2C9)
Metronidazole (2C9/3A4)	Phenytoin (2C9)
Fluconazole (2C9/3A4)	Phenobarbital (2C9)
Fluvastatin (2C9)	Primidone (2C9)
Fluvoxamine (2C9)	St John's wort (2C9)
Isoniazid (2C9)	Cigarette smoking (1A2)
Lovastatin (2C9)	Charbroiled food (1A2)
Phenylbutazone (2C9)	
Sertraline (2C9)	
Gemfibrozil (2C9)	
Ethanol (1A2)	
Clarithromycin (3A4)	
Erythromycin (3A4)	
Voriconazole (3A4)	

*mechanism for all agents listed, thought to be due to liver enzyme induction

Source: Adapted from Holbrook AM, et al., 2005[30]; Badyal DK , et al., 2004[31]; Stading JA, et al., 2007.[32]

Common herbal supplements that interact with Warfarin

Celery

Chamomile

Clove

Garlic

Gingko Biloba

Green Tea

Licorice

St. John’s Wort

Direct Thrombin Inhibitor: Dabigatran etexilate (Pradaxa)

- **MOA:** Inhibits free and fibrin bound thrombin, resulting in decreased coagulation.
- **Dose:**

  CrCl >30 mL/min: 150 mg PO BID

  CrCl 15-30 mL/min: 75 mg PO BID

  CrCl <15 mL/min or dialysis: No data available; not recommended
- **Monitoring:** Initial labs: CBC, renal function and PTT
- **Dietary restrictions:** None
- **Alcohol:** Avoid use
- **Sports:** Avoid contact sports/blunt trauma/injury
- **Cost:** Approximately $314 US dollars/month (varies)
- **Interactions:** Numerous drug-drug interactions
- Not used at our EP clinic due to GI bleeding, inferiority when compared to effectiveness of Warfarin anticoagulation.
- Not recommended for use in the elderly or in those with renal impairment
- A post-hoc analysis demonstrated significant age interaction , those >75 years had rates of major bleeding similar to Warfarin when on reduced doses; with a trend towards more bleeding with 150 mg BID dosing.

Direct Thrombin Inhibitor: Dabigatran etexilate (Pradaxa)

Increase serum concentration of Dabigatran:

- Amiodarone (Class III antiarrhythmic)
- Dronedarone (antiarrhythmic)
- Verapamil (Class IV antiarrhythmic/ Calcium Channel Blocker)
- Herbs (eg, Alfalfa, Anise, Bilberry)
- Vitamin E
- NSAID's , Clopidogrel, Naproxen, Aspirin
- Omega 3-Fatty Acids

Decrease serum concentration of Dabigatran:

- Proton Pump Inhibitors
- Progestin
- Atorvastatin
- Antacids

Similarities and differences of the Direct Factor Xa Inhibitors

Apixaban (Eliquis)	Rivaroxaban (Xarelto)	Edoxaban (Savaysa)
MOA: Inactivate circulating and clot bound Factor Xa	Same	Same
Check Creatinine before start. No further monitoring.	Same	Same
Unaffected by food	Requires protein for absorption; Bioavailability in fasting state is 66%	Unaffected by food
Dose: 5 mg twice daily Or 2.5 mg twice daily, If 2+: ≥80 years, weight ≤ 60kg; Creat ≥ 1.5 mg/dl; or use of CYP3A4 and P-gp inhibitors	Dose: CrCl > 50 mL/min= 20 mg with the evening meal Or CrCl 15-50 mL/min: 15 mg with evening meal	Dose: CrCl ≥ 50 mL/min= 60 mg once daily Or CrCl 30-50 mL, weight ≤ 60 kg, or use of P-gp inhibitors; Do not use if CrCl >95 mL/min d/t ↑ischemic stroke risk
Interacts with drugs that are both CYP3A4 and P-gp inhibitors= ↑bleeding	Interacts with drugs that are both CYP3A4 and P-gp inhibitors= ↑bleeding	Aspirin, NSAIDS, SSRI's ↑ bleeding
Pregnancy category B	Pregnancy category C	Pregnancy category C
Cost: $315 USD/month *varies	Cost: $314 USD/month *varies	Cost:: $277 USD/month *varies

Safety Data

- Apixaban: ARISTOTLE trial with 18,000 patients found Apixaban to be superior to Warfarin in preventing stroke or systemic embolism 1.3 versus 1.6 percent, caused less major bleeding (2.1 versus 3.1 percent), and resulted in lower overall mortality (3.5 versus 3.9 percent)
- Apixaban was also shown to be superior to Aspirin with 1.62% vs 3.63% stroke/embolism rate with similar bleeding risks.
- Rivaroxaban: ROCKET AF trial with 14,000 patients found Rivaroxaban to be non-inferior (1.7 versus 2.2 percent per year, respectively) with regard to the primary composite end point of stroke or non-central nervous systemic embolism
- Reversal agents:
  - Direct Xa Inhibitors and Direct thrombin inhibitors: No direct antidote available in US; current recommendation is to use antifibrinolytic agent (eg, tranexamic acid, aminocaproic acid) for life-threatening/major bleeding
  - Warfarin: Vitamin K
- Your country may have accessibility to reversal agents not listed here

Advantages and disadvantages of oral anticoagulants (warfarin versus versus direct oral anticoagulants*)

	Warfarin	Direct oral anticoagulants*
Dosing	Once daily dosing may be more convenient	May require more frequent dosing
Dietary restrictions	Need to ensure relatively constant level of vitamin K intake	None; rivaroxaban should be taken with food when used for atrial fibrillation thromboprophylaxis
Monitoring therapy	PT/INR monitoring is required, which entails periodic visits to a facility for most patients (point of care devices may be an option for some)	Not required; however, non-compliance will not be as readily apparent
Drug interactions	Many	Rivaroxaban interacts with CYP-3A4 and P-glycoprotein inhibitors; dabigatran may be affected by P-glycoprotein inducers or inhibitors
Time in therapeutic range	Approximately 65 percent based on clinical trials	Expected to be superior to warfarin, although therapeutic ranges have not been established
Reversal agent (s)	Several available (eg, vitamin K, FFP, PCC, rFVIIa)	None (although several are in development). Activated charcoal; antifibrinolytic agents; PCC may be used for life-threatening bleeding. Hemodialysis could be used in severe cases for dabigatran (but not rivaroxaban or apixaban).
Monitoring reversal	PT/INR can be used	TT can be used for dabigatran; anti-factor Xa can be used for apixaban
Effect of comorbid conditions		Renal function affects pharmacokinetics; dosing unclear in those with obesity

The factors listed may be considered in making decisions regarding choice of oral anticoagulant, but these must be considered together with clinical information regarding efficacy and toxicity in specific medical conditions. Refer to the UpToDate topic reviews on specific medical conditions for clinical data and expert opinion regarding the choice of oral anticoagulants. Refer to UpToDate topics on warfarin and direct thrombin and factor Xa inhibitors for further details on administration of these agents and management of bleeding associated with their use. Refer to UpToDate tables on drug interactions for all agents described herein.

PT: prothrombin time; INR: international normalized ratio; FFP: fresh frozen plasma; PCC: prothrombin complex concentrates; rVIIa: recombinant activated factor VII; TT: thrombin time.
* Direct oral anticoagulants include direct thrombin inhibitors (eg, dabigatran) and direct factor Xa inhibitors (eg, rivaroxaban, apixaban, edoxaban).

Pre and Post Ablation Anticoagulation Protocol at CPMC

Pre-Procedure:

- Uninterrupted OAC pre-ablation: Preference at CPMC Apixaban, Rivaroxaban, Warfarin. (Use of intracardiac echo during CA).
- Venture-AF trial: Uninterrupted rivaroxaban in patients undergoing CA (for NVAF) experienced a low number of events and similar to that for uninterrupted VKA.
- Missed doses or INR <2.0: TEE prior to ablation.
- INR's: check weekly x 1 month pre-ablation.
- Review protocol at consult, pre-op visit , discharge and post-op. Highlight need for OAC use for at least 6 months, longer if LAA isolated or if SR not maintained.
- Review LAA physiology and regarding possibility for long-term OAC need due to increased risk of TE even if SR is maintained.

Intraoperative Anticoagulation Protocol at CPMC

- Intraoperative use of IV heparin to achieve ACT >300; reversed prior to end of procedure with protamine.
- Femoral venous access, pressure held post-sheath removal for at least 20 minutes to achieve hemostasis.
- Post-operative bed rest x 6 hours to decrease hematoma risk.

- Immediate post-operative education:
  - For the first 48 hours: with cough, sneeze, bowel movement, place pressure over groin access sites.
  - No driving x 2 days.
  - No travel x 2-3 days post-ablation, lifting and activity restriction, wheelchair ride through airport.
  - 5 days post-ablation: no heavy lifting, pushing, pulling >10 lbs, no strenuous activity or exercise.
  - May return to work 2-3 days post-procedure if job does not require lifting or sooner if appropriate.

Post Ablation Anticoagulation Protocol at CPMC

Post-Procedure:

- Patients needing to stop OAC for any reason post-ablation: discuss with MD
- Left Atrial Appendage isolation teaching is reinforced regarding anticoagulation
- Heart card event monitoring performed once daily x first week post-ablation, then 3 x weekly x 3 months.
- If Sinus rhythm at 3 months: Call with NP , wean any rate control/AAD drugs, continue HC recordings until 5 months post ablation.
- **No LAA isolation**: 7 day monitor 6 months post-procedure, Echo (TTE) and MD follow up visit
- **LAA delayed/isolated:** 7 day monitor at 6 months post-ablation, TEE and MD follow up visit
- OAC will not be discontinued if underlying coagulopathy, mechanical valve, history of DVT/PE, or if CHA_2DS_2-VASc score indicates need for ongoing anticoagulation.

Final Thoughts

- Provide EP patients with data regarding cost, dosing, interactions and impact on lifestyle that each OAC may have.
- Instruct patients to call with any changes to medications.
- Educate importance and rationale of adherence to dosing schedule and of not missing/skipping doses.
- Call EP team if needing to stop OAC for any reason prior to doing so.
- Report any side effects or adverse reactions immediately EP team.
- Confirm patient understanding of teaching at multiple points of interaction.