TRIPLE ANTI-THROMBOTIC THERAPY AND MANAGEMENT FOR CARDIOVASCULAR PATIENTS IN PRIMARY CARE

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OBJECTIVES

• To recognize the type of cardiovascular patient that may be on or requiring triple anti-thrombotic therapy
• To differentiate the pharmacologic profiles of oral anti-platelets, oral anticoagulants, and aspirin therapy
• To describe the indications and guidelines of one therapy versus another
• To review the pre operative management and post operative management of triple anti-thrombotic therapy
• To discuss a number of pertinent case studies of patients on triple anti-thrombotic therapy
TRIPLE ORAL ANTITHROMBOTIC THERAPY (TOAT)

- Defined as the administration of both therapeutic oral anticoagulation (OAC) and dual antiplatelet therapy (DAPT) to patients with indications for both treatments
- DAPT=aspirin and a platelet inhibitor
- There is general apprehension to administer TOAT due to concern for bleeding
- While the use of TOAT agents reduces the rate of ischemic events, risk of bleeding significantly increases compared to one or two antithrombotic agents

TOAT IS A COMPLICATED PROCESS

- Formulating recommendations for the duration of antithrombotic therapy in patients with indications is complicated
- Because there is a broad range for the benefit (prevention of ischemic events) to risk (bleeding) ratio
- No randomized controlled trials have evaluated the efficacy & safety of the combination of warfarin & DAPT compared with either therapy alone
- Since the evidence base upon which recommendations can be made is weak, recommendations represent consensus of experts in some cases and a range of approaches in others

CHRONIC ORAL ANTICOAGULATION

- Necessary in patients with mechanical heart valves and in patients with atrial fibrillation (AF) and a CHA₂DS₂VASc score ≥1
- About 30% of these patients have concomitant coronary artery disease
- When these patients have to undergo PCI additional antiplatelet therapy (DAPT) with aspirin and clopidogrel becomes indicated to prevent stent thrombosis
- In our rapidly aging population, the number of patients experiencing both AF and CAD is steadily increasing
TRIPLE THERAPY

- Produces a higher annual bleeding risk of up to 45%
- Associated with major bleeding events, blood transfusion and increased mortality risk
- Triple therapy, including vitamin K antagonists (VKAs), aspirin, and clopidogrel (for as short a time as possible)
- Recommended by the 2010 European guidelines
- Recently, new evidence has emerged suggesting that the increased bleeding risk outweighs the efficacy (preventing stent thrombosis, MI, stroke, thromboembolism) benefit of triple therapy in these patients
- Possibly a new strategy of VKA and a P2Y₁₂ inhibitor alone could be preferred

Figure. Decision algorithm for antithrombotic therapy in patients with AF and a coronary artery stent.

Figure. Double and triple antiplatelet therapy risks in AF and PCI

CASE STUDY 1

- 71 year old man
- Cardiovascular evaluation post recent hospitalization for shortness of breath, lower extremity edema, HFpEF, CKD stage III

PMH

- CAD s/p PCI 2007, 3V CABG 8/12 complicated by heart block requiring PPM
- Aortic stenosis, severe s/p AVR (bioprosthetic)
- Ejection fraction 60+% (echocardiogram, 3/12)
- Post OHS conduction system disease: PPM, 8/12
- Intolerant of statins w/ severe muscle aches
- Permanent Atrial Fibrillation on coumadin therapy
- Carotid artery disease s/p LICA stent, 2007. RICA. CEA 8/12
- Hypertension
- NIDDM
- Lt knee laparoscopic surgery

MEDICATIONS

- Lovenox 100 Unit/ML 8 units sq daily morning
- Metoprolol Succinate ER 75 mg 1 by mouth twice a day
- Insulin HCL 0.4 mg 1 cap by mouth daily at bedtime hold abp e100mm
- Polycaccharide Iron Complex 150 mg 1 capsule orally twice a day
- Humalog Kwikpen 100 Unit/ML 5 units sq TID before meal hold BS <100 or if not lasting
- Vitamin D3 High Potency 1000 Unit 1 capsule orally every day
- Furosemide 20 mg 3 tablets (60mg) by mouth twice a day
- Potassium Chloride ER 20 Meq 2 tabs in the a.m. 1 tab in the p.m.
- Plavix 75 mg 1 by mouth every day
- Cardizem 120 mg 1 by mouth every day
- Warfarin as directed
- Gabapentin 100 mg 2 tabs po twice daily
- Aspirin 81 mg 1 tab PO daily
QUESTION

• Is this therapy indicated at this time?
  A. Yes
  B. No
• Do you need more information to make a decision?
  A. Yes
  B. No

QUESTION

• What would your first thoughts be as this patient’s provider?
  A. This patient is on appropriate anti-thrombotic therapy and no adjustments should be made
  B. After reviewing this patient’s PMH we should consider discontinuing the Plavix
  C. After reviewing this patient’s PMH we should consider discontinuing this patient’s aspirin
  D. After reviewing this patient’s PMH we should consider discontinuing this patient’s warfarin

ANY CONCERNS OR THOUGHTS ABOUT THIS PATIENT’S MEDICAL MANAGEMENT?
LETS START WITH A LITTLE PHARMACOLOGY

ANTIPLATELET THERAPY

ASPIRIN

- MOA: Irreversible inhibitor of COX-1 causing decrease in thromboxane A2 which is a powerful promoter of platelet aggregation; inhibition of platelet activation and aggregation
- Half-life: 3 hrs (salicylate)
- Time to peak effect: 1-3 hours
- Dosing: loading dose 160-325 mg
- Maintenance 80 or 81 mg daily
- Duration: Indefinite
ASPIRIN INDICATIONS

- 1st and secondary prevention of stroke and MI
- Cardiovascular disease primary prevention
- Coronary artery disease (established)
- Percutaneous intervention
- Peripheral artery disease
- Prosthetic heart valve
- Stroke/TIA
- Pericarditis (off label use)
- Coronary artery bypass grafting
- Atrial fibrillation
- Carotid artery stenosis
- Colorectal cancer risk reduction

DOSING OF ASPIRIN

- The appropriate dose of aspirin to prevent MI and stroke is uncertain
- Doses most frequently recommended are 80, 160, and 325 mg per day
- Because aspirin can cause major bleeding, the appropriate dose is the lowest dose that is effective in preventing both MI and stroke because these two conditions often co-exist
- The appropriate dose for primary prevention of stroke in men and women has not been established
- Appears to be equally effective for the prevention of vascular events at doses between 75 and 325 mg per day (UpToDate)
- The lowest dose to prevent recurrent MI or death in patients with stable CAD is 75 mg/day

THE ANTITHROMBOTIC TRIALISTS’ COLLABORATION

- Reviewed 287 studies involving 135,000 patients
- Compared antiplatelet therapy to controls
- The conclusion was that dose of 75 to 325 mg of aspirin are effective and that there is no additional benefit to doses higher than 325 mg per day
- 75 to 150 mg/day seems to be as effective as 325 mg and that the effects of doses less than 75 mg were less certain
- It is widely accepted that optimal dose is 325 mg/day or less
- There is no agreement whether the optimal dose is 80, 160, or 325 mg/day
- In order to minimize gastrointestinal toxicity and bleeding, the appropriate dose of aspirin is the lowest dose that is consistently effective in preventing MI and stroke
CLOPIDOGREL (PLAVIX)

- MOA: an inhibitor of platelet activation and aggregation through the irreversible binding of its active metabolite to the P2Y12 class of Adenosine diphosphate receptors (ADP), reducing platelet activation and aggregation
- Half-life: After a single, oral dose of 75 mg, clopidogrel has a half-life of 0.5 hours
- Time to peak effect: 6 hours (after load)
- Dosing: load 300-600 mg, maintenance dose 75 mg daily
- Duration: ACS: up to 1 year
  BMS: minimum 30 days
  DES: minimum 1 year

PRASUGREL (EFFIENT)

- MOA: Irreversible inhibitor of P2Y12 component of ADP receptor (preventing ADP binding and activation of platelets)
- Half-life: 7 hours (range 2-15 hrs)
- Time to peak effect: 4 hours (after load)
- Dosing: Loading dose 60 mg; maintenance 10 mg daily
- Duration: up to 1 year

TICAGRELOR (BRILINTA)

- MOA: Reversibly modifies P2Y12 component of ADP receptor (preventing ADP binding and activation of platelets)
- Half-life: 9 hours (range 6.7-9.1 hrs)
- Time to peak effect: 2 hours (after load)
- Dosing: Loading dose 180 mg; maintenance 90 mg BID
- Duration: up to 1 year
- With dual platelet therapy aspirin dose must be 81 mg daily; higher doses decrease the efficacy of brilinta
<table>
<thead>
<tr>
<th>Drug</th>
<th>Aspirin</th>
<th>Plavix</th>
<th>Effient</th>
<th>Brilinta</th>
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<tbody>
<tr>
<td>Indications</td>
<td>-Primary &amp; secondary prevention of stroke &amp; MI &lt;br&gt; -ACS &lt;br&gt; -PCI with stent&lt;br&gt; -PVD</td>
<td>-ASA intolerance or failure &lt;br&gt; -Primary &amp; secondary prevention of stroke &amp; MI &lt;br&gt; (+/- ASA) &lt;br&gt; -ACS (+ASA) &lt;br&gt; -PCI (+ASA) &lt;br&gt; -PVD</td>
<td>-with ASA, for treatment of ACS in patients treated with PCI&lt;br&gt; -Contraindicated&lt;br&gt; -Age &gt;75 years &lt;br&gt; -OR &lt;60 kg &lt;br&gt; -OR History of stroke &lt;br&gt; -NON-FORMULARY</td>
<td>-with ASA, for treatment of ACS</td>
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<td>Class</td>
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<td>Second generation thienopyridine (prodrug)</td>
<td>Third generation thienopyridine (prodrug)</td>
<td>Cyto-pentyl-trizaolopyrimidine</td>
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<td>CYP Metabolism</td>
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<td>CYP2C19</td>
<td>CYP3A4, CYP2B6</td>
<td>CYP3AA/5</td>
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<td>When to hold dose prior to surgery</td>
<td>7 days (optional)</td>
<td>5-7 days</td>
<td>7 days</td>
<td>5 days</td>
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### Anticoagulant Therapy

### Atrial Fibrillation and Stroke

- Stroke is the most common complication of AF
- Incidence of stroke in AF patients is 5%
- ~1.5% of all strokes in the U.S. are caused by AF
- (~75,000 strokes a year)
- 90% of NVAF strokes are ischemic
- Elderly (≥75 years old) AF patients (no AC) have a 5.49% increased risk of ischemic stroke vs. <65 years old
- Annual stroke rate is 3.2% in paroxysmal and 3.3% in persistent AF
- Ischemic stroke associated with AF is often more severe than stroke from any other etiology
- Stroke risk persists even in asymptomatic AF
**RECOMMENDATIONS FOR USE OF ORAL ANTIICOAGULANTS FOR PATIENTS WITH NONVALVULAR AF**

- Prior CVA/TIA
- CHA₂DS₃-VASc Score ≥ 2.0

**WARFARIN (COUMADIN)**

- MOA: Vitamin K antagonist; Warfarin is thought to interfere with clotting factor synthesis
- Half life: 20-60 hrs, peak effect 72-96 hrs
- Until recently was one of the most efficacious treatment for stroke prevention
- Difficult to keep INR at a therapeutic range
- Delayed onset/offset
- Multiple food and drug interactions
- Genetic variability in metabolism (VKORC1 and CYP2C9)
- Requires frequent monitoring of INR due to limited therapeutic index

**WARFARIN**

- Patients must be within therapeutic range more than 70% of the time to be effectively anticoagulated
- Unfortunately, achieving and maintaining therapeutic warfarin levels are complicated by medication and food interactions, adherence issues, genetic variability, and the skill of the practitioner managing the patient
- Adverse reactions, thromboembolism, and major bleeding were directly related to inadequate anticoagulation or over coagulation
- Anticoagulation clinics (AC) provide better outcomes in terms of the percentage of therapeutic range for patients
- Providers using the AC model have the opportunity to review prescriptions, OTC medications, diet, alcohol consumption to better manage warfarin dosing

NOVEL ORAL ANTICOAGULANTS FOR STROKE PREVENTION IN AF

- Dabigatran
- Rivaroxaban
- Apixaban
- Edoxaban

- These agents inhibit a single step in anticoagulation, at major variance from VKAs, which block multiple steps because they reduce the synthesis of the vitamin K dependent coagulation factor
- Can be costly to the patient

DABIGATRAN (PRADAXA)

- MOA- direct thrombin inhibitor (anti-IIa)
- Half-life-12-17 hrs with nml CrCl >80mL/min; if CrCl <30 ~27 hrs
- Peak effect- 2-3 hrs
- No routine laboratory testing is needed
- Dosing 75-150mg BID
- Renal dosing CrCl 15-30; 75mg BID, CrCl <15 not defined
- To convert from warfarin, start when INR <2, to convert from parenteral anticoagulant start 0-2 hr before next scheduled parenteral dose
- Dronedarone can increase the blood levels and effects of dabigatran, combining these medications may increase the risk of anemia and bleeding complications

RIVAROXABAN (XARELTO)

- MOA- Direct factor Xa inhibitor
- Half-life-9-12 hrs; 9-13 hrs in elderly and those with CKD
- Time to peak effect-2.5-4 hrs
- Dosing-20mg once daily with food (activity lower if fasting)
  - 15mg once daily if CrCL=30-49mL/min
  - 10mg once daily for DVT prevention
APIXABAN (ELIQUIS)

- MOA: a selective and reversible inhibitor of factor Xa, a key coagulation factor located at the junction of the extrinsic and intrinsic pathways of the coagulation cascade. By blocking factor Xa, apixaban decreases the generation of thrombin.
- Half-life: 12 hrs
- Time to peak effect: 3 hrs
- Dosing: 5mg twice daily
  - 2.5mg twice daily for high risk (ARI)
- Decrease dose to 2.5 mg PO BID in patients with any 2 of the following characteristics:
  - Age ≥ 80 years
  - Weight ≤ 60 kg
  - Serum creatinine ≥ 1.5 mg/dL

EDOXABAN (LIXIANA)

- MOA: Factor Xa Inhibitor
- Peak plasma concentrations in 1.5 hours
- Half life 10-14 hours
- Relatively high bioavailability of 62%
- Dosing: 60mg daily
- Adjust for CrCl 15-50mL/min-30mg daily
- Not yet FDA approved

CURRENTLY APPROVED NOACS: SPAF

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<tr>
<th>AGENT</th>
<th>Recommended Dosing</th>
<th>Comments</th>
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</thead>
<tbody>
<tr>
<td>Dabigatran</td>
<td>150mg BID (CrCl &gt;30mL/min) or 75mg BID (CrCl 15-30mL/min)</td>
<td>*Contraindicated if CrCl &lt;15mL/min or dialysis</td>
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<tr>
<td>Rivaroxaban</td>
<td>20mg qd (CrCl &gt;50mL/min) or 15mg qd (CrCl 15-50mL/min) with evening meal</td>
<td>*Avoid use if CrCl &lt;15mL/min or dialysis</td>
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| *Avoid use if CrCl <15mL/min or dialysis
| *If a dose is missed, administer dose ASAP (but do not administer 2 doses on same day) |
| Apixaban       | 5mg bid with or without food                                                    | If co-administered with strong dual inhibitors of CYP3A4 and P-gp, 2.5mg is recommended
| *Avoid use with rifampin
| *Avoid use with strong dual inhibitors of CYP3A4 and P-gp
| Edoxaban       | 60mg qd (CrCl >50 and ≤ 95mL/min) or 30mg qd (CrCl 15-50mL/min)                  | *Do not use if CrCl <15mL/min
| *Avoid use with strong dual inhibitors of CYP3A4 and P-gp
| *No dose reduction with P-gp inhibition
RESTRICTED USE OF DABIGATRAN, RIVAROXABAN, AND APIXABAN

- Renal impairment
- Pregnancy Category C: No adequate and well-controlled studies
- Labor and delivery
- Nursing mothers
- Pediatric use
- Prosthetic heart valves

RE-ALIGN trial stopped due to more thromboembolic and bleeding events with dabigatran in bi-leaflet mechanical prosthetic heart valves

SWITCHING PATIENTS FROM WARFARIN TO NOACS

- Dabigatran: stop warfarin and start dabigatran when INR <2.0
- Rivaroxaban: stop warfarin and start rivaroxaban when INR <3.0
- Apixaban: stop warfarin and start apixaban when INR <2.0

To switch from one NOAC to another consider just substituting new drug at next dose

NOACS: REVERSING ANTICOAGULATION EFFECTS

- There is no established way to reverse the anticoagulant effect of NOACS
- Dabigatran is dialyzable
- Apixaban and rivaroxaban are not dialyzable because of high plasma protein binding
- Protamine sulfate and vitamin K, hemostatics or antifibrinolytic agents would not be expected to affect the anticoagulant activity of NOACs
- Use of procoagulant reversal agents such as prothrombin complex concentrate, activated prothrombin complex concentrate, or recombinant factor VIIa may be considered but has not been evaluated carefully in clinical studies
- Activated oral charcoal reduces absorption apixaban, thereby lowering plasma concentrations. This approach may be useful with dabigatran and rivaroxaban
EMERGING ANTIDOTES FOR NOACS

- Idarucizumab
  - Humanized Fab: specifically binds dabigatran (binding affinity~350 x higher than binding of dabigatran to thrombin)
  - REVERSE AID trial in progress
- Andexanet alfa
  - Recombinant, modified factor Xa molecule that sequesters factor Xa
  - Antidote for all factor Xa inhibitors
  - Initiated phase 3 trial with apixaban, rivaroxaban, ongoing phase 2 trial with edoxaban
- Aripazine (PER977)
  - Small molecule that reverses effect of dabigatran, rivaroxaban

HOT OFF THE PRESS

- Idarucizumab (PRAXBIND) FDA approved as of October 15, 2015
- Humanized monoclonal antibody fragment indicated in patients treated with PRADAXA when reversal of the anticoagulant effects of dabigatran is needed
- Injection: 2.5g/50 mL solution in a single-use vial
  - For emergency surgery
  - In life-threatening or uncontrolled bleeding

SUMMARY: NOVEL ANTICOAGULANTS IN AF

- Based on efficacy, safety, ease of use, new oral direct thrombin inhibitors and factor Xa inhibitor drugs will replace warfarin for many/most patients with non-valvular AF
- Novel anticoagulants have a lower rate of ICH compared to warfarin
- Dose adjustments need to be made based on renal function
- Role in DC Cardioversion: Limited data-no data for any of compounds that is concerning
- Safety/efficacy of novel anticoagulants for AF ablation procedures still under study
- Need for antidote
HOW DO WE DECIDE WHEN ANTICOAGULATION IS INDICATED?

CHADS2 SCORE FOR ATRIAL FIBRILLATION STROKE RISK

- Congestive Heart Failure: Yes +1
- Hypertension History: Yes +1
- Age >75: Yes +1
- Diabetes Mellitus History: Yes +1
- Stroke Symptoms previously or TIA?: Yes +2

RECOMMENDATIONS FOR ANTICOAGULATION

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<tr>
<th>Score</th>
<th>Risk</th>
<th>Anticoagulation Therapy</th>
<th>Considerations</th>
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<tr>
<td>0</td>
<td>Low</td>
<td>Aspirin</td>
<td>Aspirin daily</td>
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<tr>
<td>1</td>
<td>Moderate</td>
<td>Aspirin or Warfarin</td>
<td>Aspirin daily or raise INR to 2.0-3.0, depending on factors such as patient preference</td>
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<td>2 or greater</td>
<td>Moderate or High</td>
<td>Warfarin</td>
<td>Warfarin, except contraindicated (e.g. clinically significant GI bleeding, inability to obtain regular INR screening)</td>
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CHADS\textsuperscript{2}-VASc Risk Factors

<table>
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<tr>
<td>Hypertension</td>
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<td>Age ≥ 75</td>
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<td>Age 65-74</td>
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<tr>
<td>Diabetes mellitus</td>
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<tr>
<td>Stroke/TIA/thrombo-embolism</td>
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<td>Vascular disease</td>
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<td>Sex Female</td>
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Your score: 0

CHADS\textsuperscript{2}-VASc Clinical Risk Estimation

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<tr>
<td>8</td>
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<tr>
<td>9</td>
<td>14</td>
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</table>

HAS-BLED Clinical Characteristics

- HTN
- Abnormal renal fx
- Abnormal liver fx
- CVA
- Bleeding
- Labile INR’s
- Elderly >65
- Drugs
- Alcohol use

11/9/2015
HASBLED CLINICAL RISK ESTIMATION

<table>
<thead>
<tr>
<th>HAS BLED SCORE</th>
<th>NUMBER OF PATIENTS</th>
<th>NUMBER OF BLEEDING</th>
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<td>Total</td>
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ASA + CLOPIDOGREL

- Not indicated for anticoagulation for stroke prevention
- Oral anticoagulation therapy is superior to clopidogrel plus aspirin for prevention of vascular events in patients with AF at high risk for stroke

SHOULD PATIENTS ON LONG-TERM WARFARIN TAKE ASPIRIN FOR HEART DISEASE?

- The literature on this topic is limited
- The decision to prescribe aspirin to patients already taking warfarin should be individualized
- The CV benefit of starting or continuing aspirin in patients already on warfarin outweighs the increased risk of bleeding in patients presenting with an ACS or those with mechanical heart valves or coronary stents
- For patients with stable CAD or at risk for CAD, the benefit of adding aspirin is not substantial, and continuing warfarin alone may be the preferred strategy

SHOULD PATIENTS ON LONG-TERM WARFARIN TAKE ASPIRIN FOR HEART DISEASE?

- Aspirin has been shown to reduce the rate of death due to all cause mortality ~18%
- Aspirin decreases the rate of vascular events by about 25-30%
- Warfarin is at least as effective as aspirin in reducing the rate of future CV events (if INR>2.5), with a higher bleeding risk

SHOULD PATIENTS ON LONG-TERM WARFARIN TAKE ASPIRIN FOR HEART DISEASE? ESTIMATED BLEEDING RISK.

- Patients taking warfarin: the risk of major bleeding is reported to be ~ 2-2.8% per person-year
- The risk of major bleeding with aspirin alone is ~0.13% per person-year
- Aspirin combined with warfarin: the risk increases significantly ~1.5 times higher with combination therapy than with warfarin alone

SHOULD PATIENTS ON LONG-TERM WARFARIN TAKE ASPIRIN FOR HEART DISEASE?

- ACS
- After PCI
- Mechanical heart valves

Conditions in which warfarin alone may be sufficient

- At risk for CAD
- Stable CAD without mechanical heart valves or stents
TAKE HOME POINTS

• The risk of bleeding is greater with combination therapy than with warfarin alone
• The CV benefits vary depending on the clinical situation
• Patients who have had an ACS or who have a stent or mechanical valve, combination therapy usually recommended (benefit outweighs the risk)
• Patients with stable CAD or those without CAD who are at risk of coronary events (risk outweighs the benefits)


PERIPRODECURAL MANAGEMENT OF ANTICOAGULATION

CASE STUDY 2

• 78 year old man is scheduled for elective colonoscopy with polypectomy next week
• He is receiving chronic warfarin for stroke prevention in PAF
• He has no prior history of stroke, DM, or HF
• He is treated with metoprolol both for HTN and rate control
• His INR is well controlled on a stable warfarin dose, and he has no history of major bleeding
QUESTION

• Should warfarin be held for the elective colonoscopy with polypectomy?
  1. Yes
  2. No

QUESTION

• If your answer is yes to holding warfarin, for how many days would you hold it?
  1. 3 days
  2. 4 days
  3. 5 days
  4. 7 days

QUESTION

• Do you think this patient needs to be bridged with LMWH?
  1. Yes
  2. No
RECOMMENDATIONS FOR CASE STUDY 2

- Warfarin is stopped 5 days before the colonoscopy with polypectomy.
- Given the relatively low thromboembolic risk, this patient would not be bridged with LMWH either before or after the procedure.
- Warfarin would be reinitiated on the same day as the procedure once hemostasis is adequately achieved.
- In addition, it is our practice to confer with the proceduralist to make sure that the procedure was uncomplicated and that warfarin re-initiation is safe.

BRIDGING MANAGEMENT FOR ANTICOAGULATION

- More than 2.5 million Americans are chronically anticoagulated for indications including venous thromboembolism (VTE), mechanical heart valve(s), or atrial fibrillation.
- Every year 10% of these patients require temporary interruption for invasive procedures.
- Defining the most appropriate management strategy for these patients requires an assessment of the peri-procedural risk of thromboembolism and major hemorrhage.
- Bridging therapy is a term to describe the application of a parenteral, short-acting anticoagulant during the interruption of warfarin.

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PROCEDURES THAT MAY BE SAFELY PERFORMED WITHOUT WARFARIN INTERRUPTION

- Dental extraction
- Bone marrow biopsy
- Endoscopy (mucosal biopsy)
- Cataract surgery
- Pacemaker placement
- Venography
- Dermatologic surgery
- Joint aspiration

PERIPROCEDURAL MANAGEMENT OF NOACS

- **Apixaban**:
  - Stop >48 hrs before elective surgery or invasive procedures with moderate or high risk of significant bleeding
  - Stop >24 hrs before elective surgery or procedures with low bleeding risk

- **Dabigatran**:
  - Stop 1-2 days (CrCl ≥ 50 mL/min) or 3-5 days (CrCl <50 mL/min) before elective surgery or invasive procedures

- **Rivaroxaban**:
  - Stop ≥24 hrs before elective surgery or invasive procedures; longer if renal dysfunction or if very high risk surgery (48-72 hrs)
  
Bridging therapy usually not required

Consider longer discontinuation times (5-7 days) in patients undergoing major surgery, spinal procedures, or placement of a spinal or epidural catheter or port, in whom complete hemostasis may be required

Restart post op when safe

Food and Drug Administration Drugs
FDA-Apixaban or Dabigatran or Rivaroxaban
Available at http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm
TO BRIDGE OR NOT TO BRIDGE?

• BRIDGE TRAIL
  - Specifically, with Warfarin treated patients with AF
    - undergoing elective surgery or invasive procedure
    - perioperative bridging with LMWH was not associated with a reduction in stroke, systemic embolism, or transient ischemic attack
    - compared with NO BRIDGING
    - However, IT DID significantly increase the risk of bleeding

CERTAIN HIGH-RISK PATIENTS

• A patient who needs to stop warfarin for surgery but who has had a stroke with in the past 6 months
• Might be best bridged
• The vast majority of patients will no longer be bridged
• The BRIDGE TRIAL results are likely to have an impact on the clinical guidelines for managing patients treated with warfarin who require surgery or an invasive procedure

BRIDGING ANTICOAGULATION DURING INTERRUPTION OF WARFARIN

• Considerations in bridge therapy include balancing the risk of thromboembolism against the risk of bleeding
• Enoxaparin has never been proven to decrease risk of stroke when bridging therapy
• In fact, there is evidence for higher risk for bleeding with bridging
RISK STRATIFICATION FOR PERIOPERATIVE THROMBOEMBOLISM

<table>
<thead>
<tr>
<th>Risk Category</th>
<th>Mechanical Valve</th>
<th>Atrial Fibrillation</th>
<th>VTE</th>
</tr>
</thead>
<tbody>
<tr>
<td>High</td>
<td>Any AVR</td>
<td>CHADS2 score 5-6</td>
<td>VTE &lt;3 months ago</td>
</tr>
<tr>
<td></td>
<td>Older Aortic valve</td>
<td>Stroke or TIA &lt;6 months</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Rheumatic Valve disease</td>
<td></td>
</tr>
<tr>
<td>Moderate</td>
<td>Bileaflet AVR with additional stroke risks</td>
<td>CHADS2 score 3-4</td>
<td>VTE in past 3-12 months</td>
</tr>
<tr>
<td>Low</td>
<td>Bileaflet AVR without additional stroke risks</td>
<td>CHADS2 score 0-2</td>
<td>Single VTE</td>
</tr>
</tbody>
</table>

BLEEDING COMPLICATIONS WITH DUAL ANTIPLATELET THERAPY

CASE STUDY 3

- 70 yr old gentleman who has a history of permanent atrial fibrillation, coronary artery disease, PTCI with drug eluding stents 11/2014, COPD, OSA, DM, depression, and anxiety
- Patient complains of feeling weak and dizzy for the past few days
- He also complained of dyspnea on exertion with walking and near-syncope
- He denied chest pain, palpitations, syncope, lower extremity edema
- He had hem positive stools and anemia
- He was diagnosed with a gastrointestinal bleed
PATIENT MEDICATIONS

- Aspirin 81mg daily
- Bumex 2 mg BID
- Coumadin 3 mg daily
- Cyclobenzaprine 10 mg TID PRN
- Digoxin 0.25 mg daily
- Fenox 180 mg 2 tablets daily
- Glimepiride 4 mg daily
- Hydralazine 50 mg TID
- Isosorbide 60 mg daily
- Klor Con 30 meq BID
- Posaagel 30 mg daily
- Metoprolol 75 mg BID
- Prilosec 40 mg daily
- Simvastatin 20mg q hs
- Omega 3 1000mg daily

WHAT ARE SOME INITIAL QUESTIONS OR THOUGHTS YOU MIGHT CONSIDER WITH HIS HISTORY AND NEW DIAGNOSIS?

QUESTION

- How long should a patient be on an anti-platelet drug with a Drug eluding stent (DES)?
  A. 6 months
  B. 3 months
  C. 1 month
  D. 1 year
QUESTION

- How long should a patient be on an antiplatelet drug with a bare metal stent (BMS)?
  A. 6 months
  B. 3 months
  C. 1 month
  D. 1 year

STENTS

- New generation DES’s are preferred to BMS’s
- For most patients
  - The use of BMS is limited to those patients with low risk of restenosis for whom a very short duration of triple therapy is needed [one month or less]
  - DES, low bleeding risk, average ischemic risk: 3-12 months of triple therapy
  - DES, low bleeding risk, increased ischemic risk: 6-12 months of triple therapy
  - DES, high bleeding risk: 1-6 months triple therapy
  - DES, very high bleeding risk: 12 months of OAC plus clopidogrel. [WOEST Trial]
  - BMS: One month of triple therapy irrespective of ischemic or bleeding risk


THE AMERICAN COLLEGE OF CARDIOLOGY, AMERICAN HEART ASSOCIATION AND EUROPEAN SOCIETY OF CARDIOLOGY GUIDELINE COMMITTEES HAVE BEEN CAUTIOUS IN RECOMMENDING TRIPLE THERAPY DUE TO THE LIMITED INFORMATION ABOUT EFFICACY AND SAFETY. THE ESC’S WORKING GROUP ON THROMBOSIS (TABLE) AND A NORTH AMERICAN CONSENSUS GROUP HAVE PUBLISHED TREATMENT RECOMMENDATIONS.

Summary of ESC Working Group recommendations for antithrombotic therapy in patients with AF and moderate to high thromboembolic risk who undergo PCI.

Jessica Mega, and Edward T. Carreras Hematology 2012;2012:547-552

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RECOMMENDATIONS

• Triple antithrombotic therapy is required in patients with indications for both DAPT and OAC
• The treatment goal is to minimize the exposure to triple therapy because of increased bleeding risk
• The conundrum is that OAC withdrawal may increase the risk for stroke, whereas DAPT withdrawal may increase the risk for stent thrombosis, so the duration of triple therapy depends on the balance of risks

- Patients with DVT, PE or LV thrombi should have elective PCI deferred 3 to 6 months until OAC can be discontinued
- For most patients on chronic OAC, postponing PCI is not an option
- Patients with mechanical valves should have the INR target lowered to 2.5 to 3.0
- Patients with AF at low risk for stroke (CHADS2 score 0 or 1) or high risk for bleeding (age ≥75 years, severe renal dysfunction, recent gastrointestinal bleed, prior stroke, uncontrolled hypertension) should be treated with DAPT alone after PCI
- Patients who are at high risk for stroke (CHADS2 score ≥2) without high risk for bleeding should receive triple antithrombotic therapy with an INR target of 2.0 to 2.5
- BMS should be implanted instead of DES, if possible, so that triple therapy exposure can be limited to 1 month
- If DES are implanted, triple therapy should be limited to 3 to 6 months
- It is critically important to minimize bleeding risk by using low-dose aspirin (≤100 mg/day), avoiding concomitant nonsteroidal anti-inflammatory agent use and adding a proton pump inhibitor to the treatment regimen as prophylaxis against gastrointestinal bleeding.
GASTROPROTECTIVE THERAPY

- 20% of hemorrhagic events in patients on triple therapy occur in the GI tract.
- Reducing the risk of GIB is relevant.

HOW WOULD YOU MANAGE THIS PATIENT GIVEN THE HISTORY PROVIDED?

CONCLUSION CASE STUDY 3

- Patient had a GIB in the setting of two antiplatelets and one anticoagulant.
- Receiving Prasugrel and Coumadin for coronary DES from November of 2014 and permanent atrial fibrillation.
- His aspirin has been held as well as the warfarin (which his INR level was supratherapeutic) until the source of the GIB has been identified.
- Since his DES was within the year this required him to remain on the Prasugrel to prevent the risk of stent thrombosis.
INDIVIDUALIZED RECOMMENDATIONS

- For all patients, recommendations need to be individualized
- Based on careful consideration of patient characteristics as well as patient preference
- Patient’s baseline ischemic and bleeding risks are particularly important in formulating an antithrombotic regimen for patients who are candidates for TOAT

NEWER ANTITHROMBOTIC DRUGS

- Prasugrel (Effient) and ticagrelor (Brilinta) are more effective antiplatelet agents than clopidogrel (Plavix) in patients with ACS. However, they also increase the risk for bleeding. Therefore, if these agents are ultimately shown to be superior to clopidogrel when included in triple antithrombotic therapy, the duration or dosing of these agents may need to be lowered to minimize bleeding risk.
- Dabigatran (Pradaxa), rivaroxaban (Xarelto) and apixaban (Eliquis) are more effective than warfarin in nonvalvular AF and cause less intracerebral hemorrhage. They should be attractive OAC options in patients requiring triple antithrombotic therapy, but this has yet to be proven in randomized trials or tested in clinical registries.
- Therefore, triple therapy should consist of aspirin, clopidogrel and warfarin until a superior strategy is proven to be safe and effective.


TOO MUCH OMEGA 3

- Bleeding Problems
  - According to the US National Library of Medicine - Medline Plus, too much omega 3 may cause clotting problems. Symptoms include easy bruising or bleeding, and may also lead to gastrointestinal bleeding, a much more serious, albeit rare, side effect. The recommended amount to prevent this problem is no more than 3 grams per day.
- Stroke
  - Bleeding in the brain can cause a stroke, and while omega 3s have been found to have a positive impact on cardiovascular health, they may also cause strokes, especially in the elderly, those with severe headaches, double vision, blurred vision and numbness, tingling or difficulty coordinating movements on one side of the body. Immediate and prompt medical attention is very important in the case of potential strokes.
<table>
<thead>
<tr>
<th>Herbal Medication</th>
<th>Uses</th>
<th>Effects on AC</th>
</tr>
</thead>
<tbody>
<tr>
<td>Garlic</td>
<td>Atherosclerosis, BP, cholesterol</td>
<td>Prevents platelet aggregation. DC 7 days perioperatively.</td>
</tr>
<tr>
<td>Ginkgo</td>
<td>Cognitive disorders, PVD, memory, skin disorders</td>
<td>Inhibits platelet aggregation. DC 7 days perioperatively.</td>
</tr>
<tr>
<td>Bloodroot</td>
<td>Excessive intraoperative bleeding</td>
<td>Inhibits platelet aggregation. DC 7 days perioperatively.</td>
</tr>
<tr>
<td>Feverfew</td>
<td>Fever (curent infection)</td>
<td>Inhibits platelet aggregation.</td>
</tr>
<tr>
<td>Fish Oil</td>
<td>Atherosclerotic disease, decreases triglycerides</td>
<td>Decreases response to warfarin.</td>
</tr>
<tr>
<td>Black Cohosh</td>
<td>Menopausal symptoms</td>
<td>Increases thromboembolism risk by reducing blood levels of warfarin.</td>
</tr>
<tr>
<td>Chamomile</td>
<td>Anxiety, depression, headache, skin issues, stomach ulcers, insomnia</td>
<td>Increases bleeding risk by interfering with coagulation.</td>
</tr>
<tr>
<td>Goldenseal</td>
<td>Antiseptic properties for mouth sores, eye sores, vaginal infections</td>
<td>Increases thromboembolism risk by opposing the effects of warfarin and heparin</td>
</tr>
<tr>
<td>St. John’s Wort</td>
<td>anxiety, depression, menopausal symptoms, dermatitis</td>
<td>Increases thromboembolism risk by opposing the effects of warfarin.</td>
</tr>
<tr>
<td>Coenzyme Q10</td>
<td>Enhance insulin sensitivity in diabetics</td>
<td>Decreases response to warfarin.</td>
</tr>
<tr>
<td>St. John’s Wort</td>
<td>Antidepressant properties for menopausal depression, anxiety</td>
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