Introduction

- 62 y/o man admitted to ED with
  - 2 week history epigastric pain, mild nausea
  - 1 day history of intermittent melena
  - Now complaining of lightheadedness
  - Denies vomiting

- Medical history
  - Type 2 diabetes mellitus for 6 years
  - HTN for 12 years
  - CAD with angina; coronary stent placed 6 weeks ago for 90% LAD lesion
John A. Martin, MD

Introduction

- Current medications
  - Metformin
  - Metoprolol
  - Hydrochlorothiazide
  - ASA 81 mg
  - Clopidogrel

- Exam
  - VS T 37, P 120 reg, RR 12, BP 105/78 supine, 85/60 standing
  - Abdo normal; rectal melena, heme +

Introduction

- Antithrombotic agents: used to reduce risk of thromboembolic events in patients with conditions including
  - Atrial fibrillation
  - Acute coronary syndromes
  - DVT
  - Hypercoagulable states
  - Endoprostheses

- The most common site of bleeding in patients on oral anticoagulation: GI tract
Introduction

- Antithrombotic agents
  - Anticoagulants
    - Warfarin
    - Heparin, LMWH
    - NOACs/DOACs*
  - Antiplatelet agents
    - ASA / NSAIDs
    - Thienopyridines
      - Clopidogrel
      - Ticlopidine
        » TTP, neutropenia
    - Glycoprotein IIb/IIIa receptor inhibitors
      - Prevent plt aggregation: eptifibatide, abciximab, tirofiban

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*Caution: Can cause severe hypotension and anaphylaxis.
Endoscopy and Antithrombotic Agents

- Details to consider
  - Urgency of endoscopic procedure
  - Risk of bleeding due to antithrombotic therapy
  - Risk of bleeding due to endoscopic intervention while on antithrombotic therapy
  - Alternative, less invasive studies (VCE, radiology)
  - Potential thrombotic / thromboembolic events that may occur if antithrombotic medication(s) are withdrawn

- Major caveat to consider: stroke or scope?
  - Severity of thrombotic / thromboembolic sequelae that may occur if antithrombotic therapy is withdrawn, vs
  - Severity of bleeding and sequelae that may occur as a result of a high-risk endoscopic procedure in a high-risk patient
What is known

- There are no clinical trials demonstrating increased incidence of bleeding in patients undergoing EGD or colonoscopy with or without biopsy on ASA or clopidogrel
- Gerson, et al., Am J Gastroenterol 2000
  - 104 patients underwent 171 low-risk endoscopic procedures on therapeutic warfarin (EGD/Colonoscopy with/without biopsy)
  - No clinical bleeding seen

**Endoscopy on Antithrombotics**

- What is known: polypectomy
  - Shiffman et al., GIE 1994, found <1% increased bleeding risk of postpolypectomy bleeding in 694 patients
  - Finding not replicated in other retrospective series
  - No RCTs for polypectomy on antithrombotic agents
  - Small series with hemostatic clip application show low rates of bleeding with polypectomy on coumadin (0-3%)
  - *polypectomy is always elective*

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**Elective Endoscopy on Antithrombotics**

- Common sense: when antithrombotic therapy is temporary, elective procedures should be delayed until anticoagulation is no longer indicated
  - Coronary stent patient is an excellent example: significant risk of spontaneous stent occlusion causing acute coronary syndrome and death
  - Need to stop / reverse agents should be individualized
Elective Endoscopy on Antithrombotics

- 2006 AHA / ACC guidelines
  - Patients on warfarin with low risk of thrombosis
    - Warfarin should be held without bridge therapy
    - Absolute risk of embolic event with 4-7 day anticoagulation interruption is ~1%
  - Restarting antithrombotic therapy: no consensus on optimal timing
    - Benefits of immediate re-initiation of therapy must be weighed against risk of hemorrhage
      - Depends on procedure-specific details and circumstances

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TABLE 5. Preprocedural management of warfarin for patients with atrial fibrillation or valvular heart disease undergoing elective endoscopy

<table>
<thead>
<tr>
<th>Condition</th>
<th>Associated diagnosis</th>
<th>Management</th>
</tr>
</thead>
<tbody>
<tr>
<td>Atrial fibrillation</td>
<td>None</td>
<td>Hold warfarin 3-5 days before procedure; Restart warfarin within 24 h.*</td>
</tr>
<tr>
<td></td>
<td>Mechanical valve(s) and/or history of cerebrovascular accident, transient ischemic attack, or systemic embolism</td>
<td>Hold warfarin and start UFH when INR ≤ 2.0. Stop UFH 4-6 h before procedure and restart after procedure. Resume warfarin on the evening of the procedure and continue both agents until INR ≥ therapeutic.* Therapeutic doses of SQ UFH or LMWH may be considered in lieu of IV UFH.</td>
</tr>
<tr>
<td>Valvular heart disease</td>
<td>Mechanical baffle, aortic valve</td>
<td>Hold warfarin 48-72 h before procedure for a target INR &lt; 1.5. Restart warfarin within 24 h.*</td>
</tr>
<tr>
<td></td>
<td>Mechanical mitral valve or mechanical aortic valve plus any of the following: atrial fibrillation, previous thromboembolic event, left ventricular dysfunction, hypercoagulable condition, mechanical tricuspid valve or &gt; 1 mechanical valve</td>
<td>Hold warfarin and start UFH when INR ≤ 2.0. Stop UFH 4-6 h before procedure and restart after procedure. Resume warfarin on the evening of the procedure and continue both agents until INR ≥ therapeutic.* Therapeutic doses of SQ UFH or LMWH may be considered in lieu of IV UFH.</td>
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Many patients with ACS with recently placed (< 1 year) vascular stents receive multiple antithrombotic agents:

- 1-3% will develop GI bleeding during index hospitalization.
  - These patients will have 4- to 7-fold increased risk of in-hospital mortality.
  - Risk of complications with EGD in setting of acute cardiac event is 1-2%.
  - Most diagnoses were PUD-related.


Decision analysis in patients undergoing EGD prior to cardiac catheterization to evaluate GIB in the setting of acute MI:

- EGD was beneficial in patients presenting with overt GIB in setting of ACS.
- Overall reduction in deaths from 600 to 97 per 10,000 patients.
- Not beneficial in patients presenting with occult GIB and acute MI.

Management of antithrombotics in the elective endoscopic setting

- Aspirin/NSAID
  - Low Bleeding Risk: Continue
  - High Bleeding Risk: Consider Discontinuing

- Thienopyridines (e.g. Clopidogrel)
  - Low Bleeding Risk: Continue
  - High Bleeding Risk: Consider Discontinuing

- Warfarin
  - Low Bleeding Risk: Continue
  - High Bleeding Risk: Consider Discontinuing

In patients with high thromboembolic risk: In patients with high thromboembolic risk, consider discontinuing antithrombotic therapy for 7-10 days prior to procedure.

Management of antithrombotics in the urgent endoscopic setting

- Aspirin/NSAID
  - Low Bleeding Risk: Continue
  - High Bleeding Risk: Consider Discontinuing

- Thienopyridines (e.g. Clopidogrel)
  - Low Bleeding Risk: Continue
  - High Bleeding Risk: Consider Discontinuing

- Warfarin
  - Low Bleeding Risk: Continue
  - High Bleeding Risk: Consult Cardiologist

In patients with high thromboembolic risk: In patients with high thromboembolic risk, consider discontinuing antithrombotic therapy for 7-10 days prior to procedure.
Endoscopy on Antithrombotics: Summary

- ASGE 2009 guidelines recommend
  - Patients on temporary anticoagulation therapy have elective endoscopic procedures deferred until antithrombotic therapy is completed
  - ASA / NSAIDs may be continued for all endoscopic procedures
  - Elective procedures should be deferred in patients with recently placed vascular stent or ACS until antithrombotic therapy has been given for the minimum recommended time

- ASGE 2009 guidelines (continued)
  - Clopidogrel and ticlopidine may be continued for low-risk procedures, but should be discontinued 7-10 days before higher-risk procedures
  - Consultation of patient’s cardiologist is highly recommended to aid in optimal decision-making regarding urgent endoscopy in patients on thienopyridines at high-risk for thrombotic / thromboembolic events undergoing high-risk endoscopic procedures
Getting back to our patient…

- 62 y/o M HTN DM2 CAD s/p recent LAD stent presenting with epigastric pain, melena, evidence of acute hypovolemic hypotension
- What would you do?

What’s new?
NOACs and DOACs: new agents

- New / direct oral anticoagulants
  - Dabigatran (Pradaxa)
  - Apixaban (Eliquis)
  - Rivaroxaban (Xarelto)
  - Edoxaban (Lixiana)
- Renally cleared
- Predictable pharmacokinetic and pharmacodynamic profiles
- Reach peak levels quickly
- Short half life


Alternatives to warfarin
NOACs and DOACs: new agents

Intrinsic pathway
- XIa → IXa
- VIII complex → IXa
- VIII and von Willebrand factor

Extrinsic pathway
- Tissue factor → VIIa
- VIIa → Xa
- X → Va
- Prothrombin
- Thrombin
- Fibrinogen → Fibrin


NOACs and DOACs: new agents

Intrinsic pathway
- Factor Xlla
- Factor Xlla
- Factor IXa

Extrinsic pathway
- Factor VIIa
- Tissue factor
- Factor Va
- Direct factor Xa inhibitors
- Thrombin inhibitors
- Fibrin

NOACs and DOACs: new agents

- Once daily treatment; peak levels 2-4 hrs
  - Primary/secondary stroke prevention in a-fib
  - Venous thromboembolism (DVT, PE)
  - Lower extremity orthopedic prophylaxis
  - Post-acute coronary syndrome after PCI or revascularization surgery with a-fib (usually with ASA and thienopyridine anti-platelet agent)

- Already being used widely in medicine and cardiology practice


Advantages

- Easy to use
  - Therapeutic effect without delay
  - No lab monitoring
  - As good or better than warfarin in preventing stroke or systemic embolism
  - Renal excretion
  - Short half-lives

Disadvantages

- No specific reversal agent
- Limited data

NOACs and DOACs: new agents

Pharmacokinetic profiles and metabolism of the new oral anticoagulants

<table>
<thead>
<tr>
<th>Feature</th>
<th>Dabigatran</th>
<th>Rivaroxaban</th>
<th>Apixaban</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prodrug</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Mode of action</td>
<td>Thrombin inhibition</td>
<td>Factor Xa inhibition</td>
<td>Factor Xa inhibition</td>
</tr>
<tr>
<td>Bioavailability</td>
<td>6%–8%</td>
<td>80%</td>
<td>50%</td>
</tr>
<tr>
<td>Time to peak</td>
<td>1.5–2 hours</td>
<td>2–3 hours</td>
<td>3 hours</td>
</tr>
<tr>
<td>Half-life</td>
<td>14–17 hours</td>
<td>7–11 hours</td>
<td>8–14 hours</td>
</tr>
<tr>
<td>Excretion</td>
<td>Renal (unchanged) &gt; 80%</td>
<td>Renal (half inactive) 66%</td>
<td>Renal 25%–30%</td>
</tr>
<tr>
<td></td>
<td>Bile 5%–10%</td>
<td>Feces 33%</td>
<td>Feces 56%</td>
</tr>
<tr>
<td>Plasma protein binding</td>
<td>35%</td>
<td>95%</td>
<td>87%</td>
</tr>
</tbody>
</table>


Endoscopy with NOACs & DOACs: a work in progress...

- Treatment differs from VIT K-associated GI bleeding (for now: paucity of data)
  - Acute bleeding
    - Holding doses
    - *Volume resuscitation to promote renal clearance
    - Timely use of focused hemostatic endotherapy
    - Administering coagulation factors (FFP, prothrombin complex concentrates, recomb activated factor VII) more likely to reverse FXa's
  - Non-acute bleeding: consider supportive care, interim observation, reevaluation

Elective endoscopic evaluation & therapy
- Consider drug half-life and CrCl
  - Dabigatran: peak level 2-3 hr, half-life 12-14 hr
  - Pre-procedure:
    - Obtain CrCl (determines timing of discontinuation)
      » Impaired CrCl can double half-life
    - Consider risk of procedure and interventions
    - Obtain PTT day before endoscopy: if nl, no drug effect
- Dabigatran example (reasonable to extrapolate)
  - NI CrCl, hold: proc risk mod 1-1.5 d prior, high 2-3 d
  - CrCl 30-50: proc risk mod 1.5-2 d prior, high 3-4 d
  - CrCl <30: proc risk mod 2-3 d prior, high 4-6 d


In general:
- Preventing bleeding in the first place makes the most sense
- A normal thrombin time and normal activated partial thromboplastin time will, in many cases, imply no hemostatic dysfunction due to dabigatran
- A normal prothrombin time or an undetectable anti-factor Xa activity would exclude hemostatic dysfunction due to rivaroxaban or apixaban in many cases

Endoscopy with NOACs & DOACs

**what to do...**

- **General measures:**
  - “wait a day...” (*remember—the half life is short*)
  - Assess vital signs and resuscitate as appropriate
  - Withdraw the anticoagulant (hold the drug)
  - Take advantage of renal clearance
  - Periodically assess blood count and coagulation cascade
    - No standard calibration of various clotting factor assays with these agents


- **If bleeding is severe or life-threatening:**
  - Consider multidisciplinary team care in an intensive care unit
  - Urgent endoscopic interventions as appropriate
  - Mechanically compressive hemostasis
  - Hemodialysis (only dabigatran—only 35% plasma protein bound; others ~90% bound)
  - PRBCs
  - FFP (not yet evidence-based)
  - Nonspecific prohemostatic agents
    - Activated prothrombin complex concentrate 50–100 U/kg intravenously (preferred)
    - Prothrombin complex concentrate 50 U/kg
    - Recombinant factor VIIa 120 U/kg

Conclusion

- Antithrombotic agents and combinations are being used increasingly in thromboembolic diseases and after coronary and orthopedic intervention.
- These impact the endoscopist in both the elective procedure and in acute intervention, though differently.
- Peri-endoscopic algorithms pertaining to newer pharmacologic agents and combinations are evolving rapidly.
- Evidence-based guidelines incorporating the newest agents still await the arrival of additional data on which to base algorithms.