Clinical Pearls in Geriatric Drug Treatment: Case Studies

21st Annual Clinical Update in Geriatric Medicine Conference
Pittsburgh, PA
Zachary A. Marcum, PharmD, MS, BCPS
Assistant Professor
Department of Medicine (Geriatrics)
University of Pittsburgh
Areas to be Covered

• Using a case-based approach, review clinical pearls for geriatric drug treatment related to the following topics:

  – Novel drug therapy for atrial fibrillation
  – NSAID toxicity
Mrs. AF is a 76 year old female who presents to the Emergency Department with complaints of feeling “dizzy and fluttering in my chest” for the past 24 hours. PMH significant for knee OA, GERD, CKD (CrCl ~30 mL/min) and HTN x 21 years. Current medications include: HCTZ 25 mg PO daily, lisinopril 20 mg PO daily, APAP 500 mg PO TID, omeprazole 20 mg PO daily, and a MVI PO daily. EKG shows *irregularly irregular* rhythm; patient is admitted with a new diagnosis of atrial fibrillation.

*In terms of oral anticoagulation, what are the treatment options for chronic anticoagulation once Mrs. AF is discharged?*

*What are the pros/cons of each agent?*
Atrial Fibrillation

Prevalence of AF ranges from 0.1% among adults less than 55 years to over 10% among adults over 80 years of age.

Oral Anticoagulant Options

- ASA/Clopidogrel
- Warfarin
- Dabigatran (da BIG a tran)
  - Direct thrombin inhibitor
- Rivaroxiblan (riv a ROX a ban)
  - Factor Xa inhibitor
- Apixaban (a PIX a ban)
  - Factor Xa inhibitor
Coagulation Cascade

Potential Therapeutic Targets

Vitamin K Antagonists in AF

- Meta-analysis has shown that warfarin prevents 64% of strokes and that aspirin alone reduces the risk by about 20%

- Increase in hemorrhage vs ASA
  - 70% increase extra-cranial
  - 128% increase intra-cranial

- Recommended for high-risk patients
  - Monitoring required
  - Drug interactions
  - Often not used appropriately

Challenges of Oral Anticoagulation Therapy: Warfarin

Narrow efficacy window + complex kinetics + multiple interactions = hard to use/take

Quality of Warfarin Management

<table>
<thead>
<tr>
<th>Study</th>
<th>Time in Therapeutic Range (TTR)</th>
</tr>
</thead>
<tbody>
<tr>
<td>21 LTCFs (n=2587 residents)</td>
<td>51%</td>
</tr>
<tr>
<td>5 VA NHs (n=160 residents)</td>
<td>55%</td>
</tr>
<tr>
<td>RE-LY (dabigatran)</td>
<td>64%</td>
</tr>
<tr>
<td>ROCKET-AF (rivaroxaban)</td>
<td>55%</td>
</tr>
<tr>
<td>ARISTOTLE (apixaban)</td>
<td>62%</td>
</tr>
</tbody>
</table>

### Pros and Cons of Warfarin and New OACs in Prevention of Stroke in AF

<table>
<thead>
<tr>
<th>Agent</th>
<th>PROS</th>
<th>CONS</th>
</tr>
</thead>
</table>
| Warfarin | ✓ Oral administration  
✓ Antidote (Vitamin K)  
✓ Wide clinical experience | ✓ Unpredictable response  
✓ Slow onset/offset action  
✓ Multiple drug/diet interactions  
✓ Requires routine INR monitoring  
✓ Narrow therapeutic window |
| New OACs | ✓ Predictable effect  
✓ Rapid onset/offset action  
✓ Low potential for drug interactions  
✓ No dietary precautions  
✓ No coagulation monitoring  
✓ Wide therapeutic window  
✓ Specific coagulation factor target | ✓ Lack of antidote  
✓ High cost  
✓ Long-term safety not clear                                                  |
Comparison of Warfarin with New OACs in AF

<table>
<thead>
<tr>
<th>Comparison</th>
<th>Warfarin</th>
<th>DABI</th>
<th>RIVAROX</th>
<th>APIX</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dose</td>
<td>Once daily, per INR</td>
<td>150mg BID</td>
<td>20mg/d</td>
<td>5mg BID</td>
</tr>
<tr>
<td>Renal</td>
<td>Not contra- indicated</td>
<td>75mg BID if CrCl 15-30</td>
<td>15mg/d if CrCl 15-50</td>
<td>Lower dose (2.5mg BID)</td>
</tr>
<tr>
<td>Hepatic</td>
<td>Extreme caution</td>
<td>Not contra- indicated</td>
<td>Avoid in mod/severe</td>
<td>Avoid in severe</td>
</tr>
<tr>
<td>Half-life, hours</td>
<td>20-60</td>
<td>12-17 (normal renal function)</td>
<td>11-13 (elderly)</td>
<td>9-14</td>
</tr>
<tr>
<td>CYP450</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Elimination</td>
<td>Hepatic</td>
<td>Renal (80%)</td>
<td>Renal and hepatic</td>
<td>Renal and hepatic</td>
</tr>
<tr>
<td>Drug interactions</td>
<td>Multiple</td>
<td>P-glycoprotein</td>
<td>P-glycoprotein and CYP3A4</td>
<td>P-glycoprotein and CYP3A4</td>
</tr>
</tbody>
</table>

Phase 3 RCTs of Novel OACs vs. Warfarin

- **RE-LY**
  - Dabigatran
  - Approved 10/19/10
- **ROCKET-AF**
  - Rivaroxaban
  - Approved 7/1/11
- **ARISTOTLE**
  - Apixaban
  - Approved 12/28/12

**Efficacy Outcome:**
- STROKE/
- SYSTEMIC EMBOLISM

**Safety Outcome:**
- MAJOR BLEEDING

### RR (95% CI)
- **All-cause stroke/systemic embolism**
  - **RR (95% CI):** 0.78 (0.67-0.92)
  - **Study:** RE-LY, ROCKET AF, ARISTOTLE
  - **Subtotal (I-squared = 55.9%, p = 0.104)**

- **Ischemic and unspecific stroke**
  - **RR (95% CI):** 0.87 (0.77-0.99)
  - **Study:** RE-LY, ROCKET AF, ARISTOTLE
  - **Subtotal (I-squared = 0.0%, p = 0.522)**

- **Hemorrhagic stroke**
  - **RR (95% CI):** 0.45 (0.31-0.68)
  - **Study:** RE-LY, ROCKET AF, ARISTOTLE
  - **Subtotal (I-squared = 52.2%, p = 0.124)**

RR (95% CI)

0.88 (0.71-1.09)  

0.49 (0.36-0.66)  

1.25 (0.91-1.72)  

Major bleeding

Intracranial bleeding

GI bleeding

### Event Rates of New OACs vs. Warfarin

<table>
<thead>
<tr>
<th>Event</th>
<th>WARF</th>
<th>DABI</th>
<th>NNT</th>
<th>RIVAROX</th>
<th>NNT</th>
<th>APIX</th>
<th>NNT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stroke/ syst emb</td>
<td>Ref</td>
<td>down</td>
<td>172</td>
<td>up</td>
<td>333</td>
<td>down</td>
<td>300</td>
</tr>
<tr>
<td>Hemor stroke</td>
<td>Ref</td>
<td>down</td>
<td>357</td>
<td>down</td>
<td>555</td>
<td>down</td>
<td>434</td>
</tr>
<tr>
<td>Isch/ unspec stroke</td>
<td>Ref</td>
<td>down</td>
<td>357</td>
<td>up</td>
<td>--</td>
<td>up</td>
<td>1250</td>
</tr>
<tr>
<td>Major hemor</td>
<td>Ref</td>
<td>down</td>
<td>400</td>
<td>up</td>
<td>--</td>
<td>down</td>
<td>104</td>
</tr>
<tr>
<td>Intracra hemor</td>
<td>Ref</td>
<td>down</td>
<td>227</td>
<td>down</td>
<td>500</td>
<td>down</td>
<td>212</td>
</tr>
<tr>
<td>Mortality</td>
<td>Ref</td>
<td>down</td>
<td>204</td>
<td>down</td>
<td>294</td>
<td>down</td>
<td>238</td>
</tr>
</tbody>
</table>

CHEST Update 2012

Guidance or Misguided?

Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines
Loading Dose Initiation

- **2012**: Initiate at 10mg dose of warfarin x 2 days then estimated maintenance dose
- **2008**: Initiate between 5mg and 10mg x 2 days then subsequent dosing based on INR
- Grade 2C
Antithrombotic Tx for AF

- **2012**: For patients with AF, we suggest dabigatran 150mg twice daily rather than dose-adjusted warfarin
- **2008**: Warfarin has always been first line
- Grade 2B
Mrs. AF

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*In terms of oral anticoagulation, what are the treatment options for chronic anticoagulation once Mrs. AF is discharged?*

*What are the pros/cons of each agent?*
Warfarin

- Remains drug of choice for stroke prophylaxis in older adults with AF
- Comparability of study populations in the clinical trials of new agents vs. real world
  - Frail LTC patients with multiple co-morbid conditions
- Cost, convenience, and safety
- Medication benefits and harms
  - Long-term?
Areas to be Covered

• Using a case-based approach, review clinical pearls for geriatric drug treatment related to the following topics:

  – Novel drug therapy for atrial fibrillation

  – NSAID toxicity
Mr. WS

WS is a 72 yo male with chronic OA, HTN, CAD (s/p MI) and type II DM. He presents to his PCP for a routine follow-up appointment. Of note, he has previously failed acetaminophen 1000mg QID and is now receiving the follow medications:

- Metformin 500mg by mouth BID
- Glipizide XL 10mg by mouth once daily
- Celecoxib 100mg by mouth BID
- ASA 81mg by mouth once daily
- MVI by mouth once daily
- HCTZ 12.5mg by mouth once daily
- Lisinopril 20mg by mouth once daily
- Metoprolol 50mg by mouth twice daily

What are the major concerns regarding NSAID toxicity in this patient?
NSAIDs

• Not 1st line treatment for persistent pain
• 70% of older adults use NSAIDs weekly, accounting for 90% of NSAID prescriptions
• Wide range of adverse drug events (ADE)
  1) Gastrointestinal (GI)
  2) Renal
  3) Cardiovascular (CV)

NSAIDs & GI Risk

• Wide range of GI ADEs
  – Symptoms of dyspepsia, heartburn, nausea, vomiting and abdominal pain
    • Most common, affecting 15-40% of users
  – Mucosal lesions and endoscopic ulcers with unclear clinical significance
  – GI bleeding (mostly upper), ulcer perforation and obstruction
  – Mortality
    • 16th most common cause of death in the US

Gastroprotective Agents

- H2 Receptor Antagonists (H2RAs)
- Misoprostol
- Proton Pump Inhibitors (PPIs)
Are All NSAIDs Equal?

• COX-2 Selective vs. COX-non-selective
  – COX-2 inhibitors have a ↓ risk of GI bleeding vs. non-selective NSAIDs but ↑ vs. placebo
  – Any potential gastroduodenal sparing effect with selective COX-2 inhibitors may be abolished when used with low dose ASA for primary/secondary prevention of CV disease

• AGS Pain Guidelines
  – COX-2 inhibitor + ASA should use a PPI or misoprostol for gastrointestinal protection

## Patients at Increased Risk for NSAID GI Toxicity

<table>
<thead>
<tr>
<th>High Risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. History of a previously complicated ulcer, especially recent</td>
</tr>
<tr>
<td>2. Multiple (&gt;2) risk factors</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Moderate Risk (1-2 risk factors)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Age &gt;65 years</td>
</tr>
<tr>
<td>2. High dose NSAID therapy</td>
</tr>
<tr>
<td>3. A previous history of uncomplicated ulcer</td>
</tr>
<tr>
<td>4. Concurrent use of aspirin (including low dose), corticosteroids or</td>
</tr>
<tr>
<td>anticoagulants</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Low Risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. No risk factors</td>
</tr>
</tbody>
</table>
## ACG 2009 Practice Guidelines

### Summary of recommendations for prevention of NSAID-related ulcer complications

<table>
<thead>
<tr>
<th>Gastrointestinal risk</th>
<th>Low CV risk (low dose ASA)</th>
<th>High CV risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low CV risk</td>
<td>NSAID alone</td>
<td>Naproxen (ibuprofen) + PPI/misoprostol</td>
</tr>
<tr>
<td>Low CV risk</td>
<td>NSAID + PPI/misoprostol</td>
<td>Naproxen (ibuprofen) + PPI/misoprostol</td>
</tr>
<tr>
<td>High CV risk</td>
<td>Alternative therapy if possible or COX-2 inhibitor + PPI/misoprostol</td>
<td></td>
</tr>
</tbody>
</table>
Health ABC Study

- Longitudinal cohort study
- Community-dwelling elders: Pittsburgh & Memphis
- Design: Pre-post study @ 02/03 and 06/07 visits
- Participants: 404 and 172 daily users of NSAIDs
- Outcome: UNDERUSE OF GI PROTECTION
  - Non-selective NSAID users NOT taking a PPI or misoprostol with 2+ risk factors (age 65+, current warfarin use, current steroid use, or hx of PUD)
  - COX-2 selective NSAID users taking ASA NOT taking a PPI or misoprostol with 2+ risk factors
- Stats: GEE

Marcum ZA et al. AGS Abstract 2013.
Health ABC Study

• Results:
  – Daily NSAID use decreased from 17.6% to 11.3%
  – Underuse of GI protection was 23.5% and 15.1% at the two visits (p=0.008)
  – Likelihood of underuse was significantly lower in the post (06/07) period vs. the pre (02/03) period
    • AOR 0.43, 95% CI 0.25-0.73
    • Controlled for age, gender, race, education, site, marital status, medical insurance, and self-reported health

• Conclusions:
  – Among high-risk older daily NSAID users, underuse of GI protective agents decreased over time

Marcum ZA et al. AGS Abstract 2013.
NSAIDs & Renal Risk

• Wide range of renal ADEs
  – Decreased glomerular perfusion
  – Decreased glomerular filtration rate
  – Acute renal failure

• Estimated 2.5 million individuals in the US experience adverse renal effects from NSAID use annually

• Drug-disease Interaction
  – NSAIDs and CKD Stages III/IV
    • Rationale: May increase risk of kidney injury
    • Recommendation: AVOID
    • Quality of Evidence: Moderate
    • Strength of Evidence: Strong
NSAIDs with Antihypertensives

- Objective: To assess whether double or triple therapy combination consisting of diuretics, ACE-I, or ARB with the addition of an NSAID is associated with an increased risk for AKI
- Design: Retrospective cohort study using nested case-control
- Setting: UK Clinical Practice Research Datalink linked to Hospital Episodes Statistics data
- Outcome: AKI as 1\textsuperscript{o} hospital diagnosis (PPV 94%)

Lapi F et al. *BMJ* 2013;epub online.
NSAIDs with Antihypertensives

• Results:
  – 487,372 antihypertensive users (mean age ~77)
  – Mean follow-up of 5.9 (SD 3.4) years
  – Triple therapy (two of either diuretics or ACE-I or ARB with an NSAID) was associated with ↑ AKI risk (RR 1.31, 95% CI 1.12-1.53)
    • Highest risk in first 30 days (RR 1.82, 1.35-2.46)

• Conclusion:
  – Vigilance warranted for concurrent use of NSAIDs and antihypertensives

Lapi F et al. BMJ 2013;epub online.
NSAIDs & CV Risk

• Wide range of CV ADEs
  – MI, HTN, HF

• American Heart Association (2007)
  – Published focused update discouraging the use of NSAIDs for patient with established cardiovascular disease

• Yet, many patients with CV disease still receive NSAIDs

Marcum ZA, Hanlon JT. *Ann Longterm Care* 2010;18:24-7.
• Drug-disease Interaction
  – NSAIDs and HF
    • Rationale: Potential to promote fluid retention and exacerbate heart failure
    • Recommendation: AVOID
    • Quality of Evidence: Moderate
    • Strength of Evidence: Strong
Long-Term CV Risk of NSAIDs after First-Time MI

- **Objective:** To examine the CV risk associated with episodes of NSAID use in relation to time elapsed post-MI
- **Design:** Nationwide retrospective cohort study
- **Setting:** All residents of Denmark (mean age 69); 1997 to 2009
- **Outcomes:** 1) all-cause death; 2) CAD death or readmission for nonfatal MI

Risk of death according to the time of NSAID treatment among patients with previous myocardial infarction (MI)


Risk of death associated with NSAID treatment after MI

<table>
<thead>
<tr>
<th>NSAID</th>
<th>1 year</th>
<th>2 years</th>
<th>&gt;5 years</th>
</tr>
</thead>
<tbody>
<tr>
<td>All NSAIDs</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rofecoxib</td>
<td>1.59</td>
<td>1.84</td>
<td>1.63</td>
</tr>
<tr>
<td>Celecoxib</td>
<td>1.73</td>
<td>2.01</td>
<td>1.83</td>
</tr>
<tr>
<td>Ibuprofen</td>
<td>1.87</td>
<td>2.03</td>
<td>1.85</td>
</tr>
<tr>
<td>Diclofenac</td>
<td>1.7 [1.3, 2.2]</td>
<td>1.6 [1.2, 2.1]</td>
<td>1.65 [1.2, 2.1]</td>
</tr>
<tr>
<td>Naproxen</td>
<td>1.7 [1.3, 2.2]</td>
<td>1.6 [1.2, 2.1]</td>
<td>1.65 [1.2, 2.1]</td>
</tr>
<tr>
<td>Other NSAIDs</td>
<td>1.7 [1.3, 2.2]</td>
<td>1.6 [1.2, 2.1]</td>
<td>1.65 [1.2, 2.1]</td>
</tr>
</tbody>
</table>

(Horizontal bars indicate 95% confidence intervals)

Copyright © American Heart Association
Risk of coronary death or nonfatal MI according to the time of NSAID treatment among patients with previous MI


Copyright © American Heart Association
Mr. WS

WS is a 72 yo male with chronic OA, HTN, CAD (s/p MI) and type II DM. He presents to his PCP for a routine follow-up appointment. Of note, he has previously failed acetaminophen 1000mg QID and is now receiving the follow medications:

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What are the major concerns regarding NSAID toxicity in this patient?
<table>
<thead>
<tr>
<th>Drug</th>
<th>Initial Dosing</th>
<th>Special Considerations in Older Adults</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mild-to-Moderate Pain</td>
<td></td>
<td></td>
</tr>
<tr>
<td>APAP</td>
<td>325-500 mg every 4 h or 500-1000 mg every 6 h; maximum daily dose of 4000 mg</td>
<td>Does not interfere with platelet function; reduce maximum dose 50% to 75% in patients with hepatic insufficiency or history of alcohol abuse</td>
</tr>
<tr>
<td>Celecoxib</td>
<td>100 mg daily</td>
<td>Higher doses associated with higher incidence of GI and CV side effects; patients with indications for cardioprotection require aspirin</td>
</tr>
<tr>
<td>Ibuprofen</td>
<td>200 mg 3-4 times/day; maximum daily dose of 3200 mg</td>
<td>Risk of GI bleeding increased in persons &gt; 75 yr; misoprostol or PPI should be prescribed for long-term users</td>
</tr>
<tr>
<td>Salsalate</td>
<td>500-750 mg every 12 h; maximum daily dose of 3000 mg</td>
<td>Does not interfere with platelet function; GI bleeding and nephrotoxicity are rare</td>
</tr>
<tr>
<td>Moderate-to-Moderately Severe Pain</td>
<td></td>
<td></td>
</tr>
<tr>
<td>APAP/Codeine</td>
<td>325/30 mg every 6 h; maximum daily dose of 12 tablets</td>
<td>Monitor for constipation, confusion, and falls; same considerations for APAP as listed above</td>
</tr>
<tr>
<td>APAP/Tramadol</td>
<td>325/37.5 mg every 6 h; maximum daily dose of 8 tablets</td>
<td>Renally adjusted dose when estimated creatinine clearance &lt; 30 mL/min: maximum of 2 tablets every 12 h; treatment should not exceed 5 days; same considerations for APAP as listed above</td>
</tr>
</tbody>
</table>
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