Session 4: Highlights from the Medical Literature: Part 1

Learning Objectives

1. Incorporate the findings of two recent studies into your assessment and management of patients who require long-term antithrombotic therapy.

2. Apply the findings of recent studies to your management of male patients with urologic symptoms relating to benign prostatic hyperplasia or overactive bladder.
Session 4

Highlights from the Medical Literature: Part 1

Faculty

Scott C. Litin, MD, MACP
Professor of Medicine
Division of General Internal Medicine
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John B. Bundrick, MD, FACP
Assistant Professor of Medicine
Mayo Clinic College of Medicine
Consultant in Medicine
Mayo Clinic
Rochester, Minnesota

Dr Scott Litin is a practicing general internist at Mayo Clinic, and a professor of medicine. He is a native of Rochester, Minnesota, did his undergraduate training at Rice University in Houston, Texas, and was a member of the second class to enter Mayo Medical School.

A distinguished practitioner, lecturer, and teacher, Dr Litin has served in numerous leadership positions at Mayo Clinic and nationally. He is a recipient of many awards, including the Distinguished Clinician Award from Mayo Clinic. The American College of Physicians has recognized him as a Master of the College.

He is actively involved in continuing education programs for practicing physicians and is frequently an invited speaker at medical gatherings. He now spends a portion of his time teaching and tutoring medical students, residents, and faculty physicians in ways to improve their presentation skills.

He has a special interest in atrial fibrillation, clotting disorders, and DVT treatment, and has written extensively in these areas. He is one of the founding members of the anticoagulation consulting service at his institution.

John B. Bundrick, MD, FACP, is a native of Louisiana and received his MD from LSU School of Medicine in Shreveport, followed by an internal medicine residency at the Mayo Clinic. He has practiced as a consultant in internal medicine at Mayo Clinic, Rochester, MN for over 20 years.

He has received numerous teaching awards at Mayo and has been inducted into the Mayo Clinic Teacher of the Year Hall of Fame.
Dr Bundrick has a strong commitment to education at all levels, particularly in the realm of continuing medical education. He is a frequent speaker at the Annual Session of the ACP, and his signature presentation, “Clinical Pearls in General Internal Medicine,” is consistently highly rated. He has chaired the annual scientific session of the MN ACP Chapter since 2007 and was on the scientific program committee for the 2011 ACP Annual Session meeting in San Diego. In addition he has directed numerous local and regional educational meetings for physicians and health care professionals.

**Faculty Financial Disclosure Statements**

The presenting faculty reports the following:

Dr Litin has no financial relationships to disclose.

Dr Bundrick has no financial relationships to disclose.
Highlights From the Medical Literature – Part I
Scott C. Litin, MD, MACP
John B. Bundrick, MD, FACP

Session 4: 1:00 PM -2:00 PM

Disclosures
• Dr Litin has no financial relationships to disclose.
• Dr Bundrick has no financial relationships to disclose.

Learning Objectives
• Incorporate the findings of 2 recent studies into your assessment and management of patients that require long-term antithrombotic therapy
• Apply the findings of recent studies to your management of male patients with urologic symptoms relating to benign prostatic hyperplasia or overactive bladder

1. Pre-Activity Question
Based on a recent study, which of the following is TRUE regarding patients with pacemakers who have subclinical atrial fibrillation?
1. Their risk of stroke is similar to that found in prior studies of patients with clinical atrial fibrillation
2. Their risk of stroke is independent of their CHADS2 score
3. Their risk of stroke is not influenced by the duration of the episodes of atrial fibrillation
4. They have an increased risk of developing clinical atrial fibrillation

2. Pre-Activity Question
In patients with moderate to severe Alzheimer’s dementia, a recent study demonstrated that combining memantine with donepezil was associated with:
1. Clinically significant improvement in cognitive function
2. Statistically (but not clinically) significant improvement in cognitive function
3. No improvement in cognitive function
4. Mild worsening of cognitive function

3. Pre-Activity Question
Based on a recent study, the FDA approved which of the following regimens for the treatment of BPH symptoms and erectile dysfunction?
1. Sildenafil 50 mg daily
2. Tadalafil 5 mg daily
3. Vardenafil 10 mg daily
4. Finasteride 1 mg daily
Rocket-AF Trial

Background:
• New anticoagulants are being developed because of the disutility of using warfarin.
• Dabigatran has been approved for stroke prevention in AF.
• In Nov 2011 rivaroxaban (direct Xa inhibitor) was approved for same indication mostly based on this trial

Issue:
• The use of warfarin reduces the rate of ischemic stroke in patients with atrial fibrillation but requires frequent monitoring and dose adjustment.
• Rivaroxaban, an oral factor Xa inhibitor, may provide more consistent and predictable anticoagulation than warfarin, without monitoring

Rocket-AF Trial

Study Design
• In a double-blind trial, 14,264 patients (1178 participating sites in 45 countries) with NVAF who were at increased risk for stroke (CHADS2 score ≥ 2) were randomly assigned to receive either rivaroxaban 20 mg daily or dose-adjusted warfarin.
• High risk group, 90% CHADS ≥ 3
• Primary outcome stroke or systemic embolism

Risk of Stroke in AF Patients

<table>
<thead>
<tr>
<th>Clinical Parameter</th>
<th>Points</th>
</tr>
</thead>
<tbody>
<tr>
<td>Congestive Heart Failure</td>
<td>1</td>
</tr>
<tr>
<td>Hypertension</td>
<td>1</td>
</tr>
<tr>
<td>Age &gt; 75 years</td>
<td>1</td>
</tr>
<tr>
<td>Diabetes</td>
<td>1</td>
</tr>
<tr>
<td>Prior Stroke or TIA</td>
<td>2</td>
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</tbody>
</table>

CHADS2 Risk Score

<table>
<thead>
<tr>
<th>CHADS2 Score</th>
<th>Annual Incidence of Stroke</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>1.9 / 100</td>
</tr>
<tr>
<td>1</td>
<td>2.8 / 100</td>
</tr>
<tr>
<td>2</td>
<td>4.0 / 100</td>
</tr>
<tr>
<td>3</td>
<td>5.9 / 100</td>
</tr>
<tr>
<td>4</td>
<td>8.5 / 100</td>
</tr>
<tr>
<td>5</td>
<td>12.5 / 100</td>
</tr>
<tr>
<td>6</td>
<td>18.2 / 100</td>
</tr>
</tbody>
</table>


Rocket-AF Trial: Results

- In the intention-to-treat primary end point:
  - Rivaroxaban group (2.1% per year)
  - Warfarin group (2.4% per year)
  - P<0.001 for noninferiority; P = 0.12 for superiority


Rocket-AF Trial: Results

- Major and non-major clinically relevant bleeding events were similar in both groups
- Intracranial Bleeding
  - Rivaroxaban group (0.5% per year)
  - Warfarin group (0.7% per year)
- Fatal Bleeding
  - Rivaroxaban group (0.2% per year)
  - Warfarin group (0.5% per year)


Rocket-AF Trial: Conclusion

- In patients with atrial fibrillation, rivaroxaban was non-inferior to warfarin for the prevention of stroke or systemic embolism
- No significant differences in bleeding risk between rivaroxaban and warfarin


Rocket-AF Trial: Caveats

- In Rocket-AF, the warfarin-treated patients spent just 57.8% of time in therapeutic range which was lower than in other trials
- In the 28-day period after rivaroxaban was stopped (end of study) in Rocket-AF and patients were transitioned back to warfarin, there was an increased risk of stroke.
- Investigators attributed this to the drug’s short half-life and the lack of dual anticoagulation during the overlap period in this high risk group.


Rocket-AF Trial: Clinical Implications

- There are now FDA approved alternatives to warfarin available to prevent strokes in patients with AF

On the Horizon in US: DVT & PE Treatment
(Rivaroxaban not yet approved indication)

Einstein DVT Study
Rivaroxaban

- Rivaroxaban 15 mg BID X 21 days, then 20 mg daily vs.
- Enoxaparin 1mg/kg BID > 5d, bridge to warfarin INR 2.0-3.0
- Followed for 3, 6, 12 mos.
- End Point: recurrent symptomatic DVT
- Rivaroxaban 2.1%  Enox/warfarin 3.0%


Clinical Implications

Consider the future possibility:
- Patient with a DVT could potentially be diagnosed and treated from your office with 3 months of oral therapy and with no need for lab monitoring

Other Issues

- Can’t assess adherence or failure without assay to monitor
- Can’t easily reverse anticoagulant effect
- Renal excretion – long term safety issues
- Possible ↑ MI risk
- Cost

Other Issues

New drugs…..use them quickly, while they are still felt to be effective
And before the side effect profile becomes well known

An antidote for new anticoagulants?

Your resident mentions that he heard there may be antidotes for the new anticoagulants.

What do you tell him?
1. Dabigatran effect may be reversed with FFP
2. Dabigatran effect may be reversed with prothrombin complex concentrate (PCC)
3. Rivaroxaban effect may be reversed with FFP
4. Rivaroxaban effect may be reversed with PCC
Reversal of Rivaroxaban and Dabigatran by Prothrombin Complex Concentrate


Anticoagulation Reversal: Background

• Traditional anticoagulants (heparin and warfarin) have drawbacks, e.g. narrow therapeutic window, interactions, need for frequent monitoring, etc.
• Newer anticoagulants, approved in atrial fibrillation, provide added options with promise of similar or better efficacy, less interactions, and no monitoring

• Dabigatran (direct thrombin inhibitor)
• Rivaroxaban (direct Xa inhibitor)

Anticoagulation Reversal

Question:
Could prothrombin complex concentrate (PCC) reverse the anticoagulant effect of dabigatran and rivaroxaban?

Anticoagulation Reversal

PCC studied:
• A human prothrombin complex product from the Netherlands, derived from human plasma
• It contains a large amount of the procoagulation factors II, VII, IX, and X, as well as the natural anticoagulants protein C and S and antithrombin

Anticoagulation Reversal

Study design:
• Randomized, double-blind, placebo- controlled study
• 12 healthy male volunteers received rivaroxaban 20 mg twice daily (n=6) or dabigatran 150 mg twice daily (n=6) for 2 1/2 days
• This followed by either a single bolus of 50 IU/kg PCC or a similar volume of saline

Anticoagulation Reversal

After a washout period, this procedure was repeated with the other anticoagulant

- Rivaroxaban 20mg BID (n=6)
- Dabigatran 150mg BID (n=6)

PCC or Placebo

2.5 days Washout Period (11 days) 2.5 days


Anticoagulation Reversal: Results

Rivaroxaban

The PT was significantly prolonged by rivaroxaban
Immediately after the infusion of PCC, the PT completely normalized

Anticoagulation Reversal: Conclusions

- Prothrombin complex concentrate (PCC) neutralized the anticoagulant effect of rivaroxaban, a factor Xa inhibitor.
- PCC had no effect on dabigatran, a direct thrombin inhibitor at PCC study dose (50 U/kg).

Anticoagulation Reversal: Caveats

- The study population all young healthy men with normal renal function
- The particular PCC product studied might yield different results from other PCC products
- The effect of PCC has yet to be confirmed in patients with bleeding events who are treated with rivaroxaban

Anticoagulation Reversal: Clinical Implications

- Although serious bleeding is rare with the use of the new anticoagulants, the lack of an antidote has been an issue for clinicians
- Supportive strategies have been advocated in such situations while waiting for these short half-life drugs to clear
- Clinicians might feel more confident using rivaroxaban, if safe antidote is available
Case: 67-year-old Male on Warfarin

Your 67-year-old male patient is on warfarin for stroke prevention in atrial fibrillation. His dose has been the same for the past 12 months. He doesn’t like coming in for blood work every 4 weeks. You recall a study that suggests it might be safe in his situation to move his INR recheck appointments to:

1. Every 6 weeks
2. Every 8 weeks
3. Every 10 weeks
4. Every 12 weeks
5. Every 16 weeks

Warfarin Dose Assessment Every 4 Weeks Versus Every 12 Weeks in Patients With Stable International Normalized Ratios


INR Testing Frequency

- Background:
  - Clinical guidelines differ on the optimal interval for prothrombin monitoring (limited data)
  - A 1998 British guideline suggests that PT monitoring can be done up to every 12 weeks for very stable patients
  - Underpowered Italian study stated no difference between 4 and 6 week testing

INR Testing Results

Outcomes measured:

- Percentage of time in the therapeutic range (primary outcome)
- Number of extreme INRs, changes in maintenance dose, major bleeding events, objectively verified thromboembolism, and death (secondary outcomes)

The percentage of time in the therapeutic range:

- 74.1% in the 4-week group
- 71.6% in the 12-week group
- This met the requirement for noninferiority
- Secondary outcomes:
  - No difference between groups
INR Testing Results

Patients whose warfarin dose was assessed every 12 weeks:
- Fewer dosage changes, and fewer extreme INRs that were >4.5 or <1.5
- These results demonstrate that the frequency of assessing warfarin dosing can be substantially reduced in stable patients


INR Testing Conclusions

Assessment of warfarin dosing every 12 weeks seems to be safe and noninferior to assessment every 4 weeks


INR Testing Clinical Implications

- Interval of testing in very stable patients on warfarin can be safely extended
- This might reduce the hassle factor for AF patients who consider switching to one of the “newer” anticoagulants to avoid testing

Case: 76-year-old Male with Pacemaker

Patient had a dual chamber pacemaker placed 3 months ago for sinus-node disease and has since been asymptomatic.

- Meds: Lisinopril for HTN and metformin for DM
- His pulse is 72, regular rhythm.

Patient with Pacemaker

- On a routine check of his pacemaker yesterday, he was incidentally noted to have experienced 6 episodes of atrial rate >190 since it was placed three months ago.
- These ranged in duration from 8 minutes up to a maximum of 16 hours

What is his risk of stroke in the next year?
1. 0.5%
2. 1.2%
3. 3.8%
4. 6.6%
Subclinical atrial fibrillation and the risk of stroke


Question

In patients with pacemakers or ICDs, does the detection of subclinical atrial tachyarrhythmia signify an increased risk of stroke?

Background

• 25% of all ischemic strokes are cryptogenic, and subclinical atrial fibrillation is suspected to be a possible cause in many of these
• The prevalence and prognosis of subclinical atrial fibrillation has been difficult to assess

Background

• More than 400,000 pacemakers and ICDs implanted each year in North America
• These have the capacity to record episodes of atrial tachyarrhythmia
• The significance of pacemaker detected subclinical atrial fibrillation is unknown

Subclinical Atrial Fib

• 2,580 patients with HTN who had pacemaker (95%) or ICD (5%) placed
• Episodes of atrial rate >190 lasting at least six minutes recorded for 1st three months → followup for 2.5 years for ischemic stroke or systemic embolism

Subclinical Atrial Fibrillation

Results

• By 3 months, subclinical atrial tachy had occurred in 10.1% of patients.
• Over the next 2.5 years, the risk of stroke was doubled in these patients (and the risk of clinical atrial fib increased 5 fold) compared to those without atrial tachy.
Subclinical Atrial Fibrillation
Results

The risk increased by CHADS Score

<table>
<thead>
<tr>
<th>CHADS Score</th>
<th>Stroke risk %/yr</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>0.56</td>
</tr>
<tr>
<td>2</td>
<td>1.29</td>
</tr>
<tr>
<td>≥ 3</td>
<td>3.78</td>
</tr>
</tbody>
</table>


Subclinical Atrial Fibrillation
Results

However, the risk was not as great as in studies of clinical atrial fibrillation:

<table>
<thead>
<tr>
<th>CHADS2 Score</th>
<th>Stroke risk %/yr in this study</th>
<th>Stroke risk %/yr in clinical AF study</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>0.56</td>
<td>2.8</td>
</tr>
<tr>
<td>2</td>
<td>1.29</td>
<td>4.0</td>
</tr>
<tr>
<td>≥ 3</td>
<td>3.78</td>
<td>&gt;6.4*</td>
</tr>
</tbody>
</table>

* The risk of stroke is 6.4%/yr for CHADS score of 3 (higher for scores >3)


Subclinical Atrial Fibrillation
Results

Those who had episodes lasting >17.7 hours had a higher risk of stroke (4.89% per year) than those in lower quartiles of duration


Caveats

- Although the risk of stroke is increased in patients with subclinical atrial tachy in this study, it is not as high as that in other studies with clinical atrial fibrillation.
- There are currently no randomized trials of anticoagulation in this group.

Blood Pressure Goal after Stroke

A 67-year-old female with HTN presents to your office 2 weeks after a small lacunar infarct. She has mild residual weakness on her right side but is otherwise well.

- Meds include ASA, lisinopril, and HCTZ
- BP is 134/74

Clinical Implications

Patients who exhibit atrial tachy on quarterly pacemaker reports should be followed more carefully for:

a) progressive ↑ in frequency/duration of events or,

b) clinical atrial fibrillation.

In those with CHADS of 3 or greater and episodes over 17 hrs, it would be reasonable to consider anticoagulation
Female s/p Stroke

How would you manage her BP to best reduce her risk of recurrent stroke?

1. Increase meds to get systolic BP <120
2. Increase meds to get systolic BP <130
3. No change in meds

Level of systolic blood pressure within the normal range and risk of recurrent stroke


Poststroke Blood Pressure Target

Background:
• National guidelines suggest a target BP of <120/80 poststroke, but limited data to support this level of reduction

Poststroke BP Target

Question:
• What is the relationship between systolic BP in the high-normal vs. low-normal range with clinical outcomes in patients who have had a stroke?

Poststroke BP

Methods:
Post-hoc observational analysis of PROFESS trial
> 20,000 patients with stroke randomized 2 x 2 to:

ASA / extended release dipyridamole vs clopidogrel; and
telmisartan vs. placebo

Mean age 65 years; 36% female

Excluded: hemorrhagic stroke, severe disability poststroke

Almost all were non-cardioembolic: about half small vessel, 30% large vessel, and most of the remainder cryptogenic

**Poststroke BP**

- Baseline BP was checked at hospital discharge or in clinic at 1 week, then at 1, 3, and 6 months and q 6 months
- Mean follow-up 2.5 years

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**Poststroke BP**

The first SBP after the baseline was used to classify the patients:

<table>
<thead>
<tr>
<th>BP Range</th>
<th>Stroke %/yr</th>
<th>Composite Endpoints %/yr</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;120</td>
<td>8.0</td>
<td>12.5</td>
</tr>
<tr>
<td>120-129</td>
<td>7.2 *</td>
<td>11.4</td>
</tr>
<tr>
<td>130-139</td>
<td>6.8</td>
<td>10.2</td>
</tr>
<tr>
<td>140-149</td>
<td>8.7</td>
<td>13.1</td>
</tr>
<tr>
<td>&gt; 150</td>
<td>14.1</td>
<td>19.8</td>
</tr>
</tbody>
</table>

*not significant difference from 130-139

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**Poststroke BP**

- **Primary outcome:**
  - First recurrence of stroke
- **Secondary outcome:**
  - Composite of stroke, MI, Vascular death

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**Poststroke BP**

The four randomized treatment groups did not differ in outcome, thus were combined for this analysis

- The groups differed slightly at baseline (more DM, HTN, use of HTN rx in the higher BP groups), and outcomes were thus adjusted for these and other variables

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**Poststroke BP Results**

These differences in outcome persisted after adjustment for age, DM, CHF, and multiple other variables
Poststroke BP Results

The J-shaped relationship between BP and outcome was most prominent within the first 180 days (but persisted thereafter).


Poststroke BP Conclusion

Among patients with recent non-cardioembolic stroke, systolic BP levels in the 120-139 range are associated with lower risk of recurrent stroke as compared to BP levels outside of this range.


Poststroke BP: Clinical Implications

• In patients with a recent non-cardioembolic ischemic stroke, a systolic BP in the range of 120-139 seems to be an optimal target.

• There does not seem to be any advantage to lower BP levels within this range (and certainly not for <120), especially within the first six months.

Case: Female Undergoes DXA Screening

• A 67-year-old female undergoes osteoporosis screening with DXA and is found to have osteopenia. Her T-scores at the femur neck and total hip are both -1.6.

• She is on appropriate vitamin D and calcium and has no other osteoporosis risk factors.

• Relevant PMH: TAH age 46, ERT for four years after menopause at age 50.

DXA Screening

How long would you wait before retesting her bone density?

1. 1 year
2. 2 years
3. 3 years
4. 5 years
5. 10 years

Bone-Density Testing Interval and Transition to Osteoporosis in Older Women

**Bone Density Testing Intervals**

**Question:**
At what rate do women with varying degrees of osteopenia on bone mineral density (BMD) testing progress to osteoporosis?

**Background:**
• Current osteoporosis screening guidelines advise BMD screening for women aged 65 and older.
• None of these specify a screening interval for repeating the BMD which is based on data from a longitudinal cohort.

**Methods:**
• 4,957 women aged 67 and older recruited from four sites in US
• BMD checked at baseline and years 2, 6, 8, 10, and 16
• Excluded: Hip replacements, osteoporosis on baseline study

**Outcome of interest was time required for 10% of women to transition to a BMD of osteoporosis (T < -2.5) before:**
1. Incident hip/clinical vertebral fx or
2. Receiving treatment for osteoporosis

<table>
<thead>
<tr>
<th>T-Score</th>
<th>Normal</th>
<th>Mild osteopenia</th>
<th>Moderate osteopenia</th>
<th>Advanced osteopenia</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>&gt; -1.00</td>
<td>-1.01 to -1.49</td>
<td>-1.50 to -1.99</td>
<td>-2.00 to -2.49</td>
</tr>
</tbody>
</table>

Bone Density Testing Intervals

Time required for 10% of women to reach BMD T-score -2.5 or less:

- Normal BMD: 17.4 years
- Mild osteopenia: 16.5 years
- Moderate osteopenia: 4.6 years
- Advanced osteopenia: 1.0 years

Unadjusted Cumulative Incidence of Osteoporosis According to Baseline T-Score Range


BMD Testing Intervals Results

- 121 women (2.4%) had a hip/clinical vertebral fx prior to reaching osteoporosis on BMD.
- Time required for 2% of women to experience fx was >15 yrs in those with normal BMD/mild osteopenia and about 5 yrs for those with moderate/advanced osteopenia.

BMD Testing Intervals Conclusions

- In women at average risk for osteoporosis with an initial BMD T-score > -1.5, it appears safe to wait up to 15 years before rechecking the BMD.
- Women with greater degrees of osteopenia at baseline will need more frequent testing (5 years for moderate, 1 year for advanced).

BMD Testing Intervals Results

- Age was a factor in determining the testing intervals.
- For example, although the overall testing interval was around 5 years for those with moderate osteopenia, for women aged 85 and older it was closer to 3 years.

BMD Testing Intervals Caveats

- The data was limited to women aged 67 and older (although within the study cohort, relatively younger women had a slower rate of BMD decline).
- BMD is only one factor in determining risk of fracture. Treatment decisions should be based on overall risk assessment (e.g. FRAX). Women at higher risk (e.g. steroid use) will need more frequent testing.
BMD Testing Intervals
Clinical Implications

• In most women who are at average risk of osteoporosis, the decision of when to retest the BMD may be based upon the initial BMD result.
• Longer intervals may be appropriate for many of these women.

Questions
?

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