Session 6:
Highlights from the Medical Literature: Part 2

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 6

Highlights from the Medical Literature: Part 2

Faculty

Scott C. Litin, MD, MACP
Professor of Medicine
Division of General Internal Medicine
Mayo Clinic College of Medicine
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.

Kelly Anne Spratt, DO, FACP, FACC
Clinical Associate Professor of Medicine
University of Pennsylvania
Philadelphia, Pennsylvania

Kelly Anne Spratt, DO, FACC, is a clinical associate professor of medicine at the University of Pennsylvania and an integral part of the Preventive Cardiology Cardiovascular Risk Intervention Program, a program designed to include outstanding prevention strategies and enrollment in clinical trials. Her practice includes noninvasive cardiology, with a strong emphasis on preventive aspects of cardiovascular disease as well as heart disease in women. She has been a co-chair and member of the Executive Leadership Team for Go Red for Women, the AHA national campaign for promoting awareness of and treatment for heart disease in women. She is board certified in both internal medicine and cardiovascular disease.
Dr Spratt has authored journal articles and chapters in cardiology textbooks and lectures regionally and nationally. She is involved in teaching medical students and house staff and is also actively involved in patient education in several media, including radio, television, and the internet. She has served as a consultant for “Ask the Doctor” for the Better Homes and Gardens health website, a resource for patients with a variety of health concerns. She is a CME section editor at Journal Watch, where she has helped develop website-based CME.

Dr Spratt received her medical degree at the Philadelphia College of Osteopathic Medicine and completed her residency in internal medicine and a fellowship in cardiology at Hahnemann University Hospital in Philadelphia. She has been at the University of Pennsylvania since that time.

**Faculty Financial Disclosure Statements**
The presenting faculty reports the following:

Dr Litin has no financial relationships to disclose.

Dr Spratt has no financial relationships to disclose.
Evaluation of stethoscopes as vectors of *Clostridium difficile* and methicillin-resistant *Staphylococcus aureus*


**Stethoscopes as Vectors**

**Background:**
- Past studies have shown stethoscope diaphragms may be contaminated with pathogens such as *Clostridium difficile* and methicillin-resistant *Staphylococcus aureus* (MRSA).
- However the risk for transmission of *C. difficile* and MRSA by stethoscopes had not been quantified

**Stethoscopes as Vectors**

**Study:**
- Stethoscope diaphragms were contaminated with *C. difficile* and MRSA.
- They were easily able to transmit these disease causing agents to agar plates.

**Study Design:**
- To assess indirect transfer from infected patients to stethoscopes, skin surfaces were contaminated with *C. difficile* and MRSA. Then simulated exams were performed.
- For *C. difficile*, the skin site was the forearm of a human volunteer. For MRSA, a processed pig skin surface was used.
- Then the diaphragms were pressed on agar plates
**Stethoscopes as Vectors**

**Study Results:**
Simulated examination of colonized patients showed rate of transfer by stethoscope of *C. difficile* to be 14% and for MRSA 19%.

**Removing the Pathogens:**
- The data suggested direct contact with friction (gauze with saline) was sufficient to remove more than 90% of *C. difficile* spores.
- Pads or gauze containing alcohol removed 100% of MRSA.


**Study Conclusion:**
- These findings suggest that stethoscopes may be an underappreciated vector for transmission of pathogens.
- Perhaps we should not only wash our hands, but also wash our stethoscopes between patients.

**Alzheimer’s Disease**

A concerned daughter asks your opinion about her father who has progressive dementia due to Alzheimer’s. He has been on donepezil for 18 months. She has heard the addition of memantine is helpful.

Would you add memantine to the donepezil?
1. Yes
2. No

**Donepezil and Memantine for Moderate-to-Severe Alzheimer’s Disease**


**Background:**
- Cholinesterase inhibitors (CI) have been shown to decrease progression of mild-moderate disease
- Memantine suggested to also be helpful
- One non-reproducible study showed that combination therapy with memantine and a CI was more effective than therapy with a CI alone

**Study question:**
- Would community-living patients with Alzheimer’s disease, who have moderate-to-severe disease and are already receiving (CI) donepezil, benefit from continuing treatment?
- Is initiating memantine at this point in the course of the disease beneficial?
Alzheimer's Disease Study

Study design:
- Multicenter, double-blind, placebo-controlled, clinical trial with a two-by-two factorial design
- Eligible patients had mod-severe dz and had been on donepezil for ≥ 3 mos
- Physician considering change in treatment plan


Alzheimer's Disease Study

Outcome Measures:
- The co-primary outcomes were scores on the SMMSE (0-30) and on the caregiver-rated Bristo Activities of Daily Living Scale (BADLS, range from 0 to 60, with higher scores indicating greater impairment)
- Assessment at several intervals during 52 wk study


Results:
- All participants showed decline over the 52 weeks
- Those who continued donepezil did slightly better than those who discontinued
- Memantine changes did not reach study significance
- There were no significant benefits of combining donepezil with memantine over donepezil alone


Conclusions:
In patients with moderate-severe Alzheimer's disease, continued treatment with donepezil was associated with cognitive benefits that exceeded the minimum clinically important difference and with significant functional benefits over the course of 12 months.

Alzheimer's Disease Study

Caveats:

• All participants showed progressive decline during study

• Though statistically significant, a difference of 2 points (4 of 30 vs 6 of 30; off vs on donepezil at 52 weeks) in a mini-mental status test is not clinically significant


Alzheimer's Disease Study

Clinical Significance:

• Treatments for Alzheimer's disease currently are dismal

• Treatment effects with donepezil are small and must be balanced against cost and side effects

• There is no benefit of combining donepezil with memantine over donepezil alone

Colonoscopic Polypectomy and Long-Term Prevention of Colorectal Cancer Deaths


Prevention of Colon Cancer Deaths

Background:

• One in 20 Americans will develop colorectal cancer

• In 2012
  – New cases: 103,170 (colon); 40,290 (rectal)
  – Combined deaths: 51,690

• National Polyp Study (NPS), showed polypectomy decreased future colon cancer diagnosis


Prevention of Colon Cancer Deaths

Study:

• Patients referred for initial colonoscopy (between 1980 and 1990) at NPS clinical centers who had polyps included

• 2,602 patients were followed for median 15.8 yrs

• 80% continued periodic follow-up scopes

• Compared their colon cancer death rate with the expected rate from cancer tracking (SEER) data


Newspaper Headlines

Feb 22, 2012

Colonoscopy Cuts Cancer Deaths in Half
Prevention of Colon Cancer Deaths

Results:
• Through 2003, 1,246 of the patients who had adenomas removed died
• Only 12 of those deaths were from colon cancer
• Expected 25.4 colon cancer deaths in similar people in the general population (SEER)
• Risk of death cut by 53%


Clinical Implications:
• Evidence that colon cancer screening saves lives
• Half of eligible candidates will decline screening
• May encourage more to undergo colonoscopy

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What about CT Colonography?

Would patients be more apt to consider screening?
Burden of colonoscopy compared to non-cathartic CT-colonography in a colorectal cancer screening program: randomized controlled trial


Colonoscopy or CT Colonography

Study:
• 8,844 Dutch citizens (50-74 yrs) randomly invited for CRC screening with colonoscopy (n=5924) or CT-colonography (n=2920)
• Completed burden questionnaire before and 14 days after study

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Colonoscopy or CT Colonography

Results:
• Colonoscopy invitees expected the screening procedure and bowel preparation to be more burdensome than CT-colonography invitees
• CT colonography actually scored more burdensome than colonoscopy 14 days later
• Over 90% of each group would undergo study again

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Colonoscopy or CT Colonography

Why surprise results?
• CT participants expected little burden in advance
• Oral contrast produced watery diarrhea
• CO2 insufflations produced cramping
• No sedation in CT colonography
• Sedation in colonoscopy likely decreased expected burden

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Colonoscopy or CT Colonography

Clinical Implications:
Explaining results to patients more likely to help them accept CRC screening colonoscopy

Screening for Ovarian Cancer

A 63-year-old woman asks your advice about early detection of ovarian cancer. She has heard about screening with cancer antigen 125 (Ca-125) and transvaginal ultrasound (TVUS). You tell her:

1. Ca-125 is helpful because it can pick up ovarian cancer at an earlier stage and improve survival slightly
2. TVUS is helpful because it can pick up ovarian cancer at an earlier stage and improve survival slightly
3. If used together the tests can pick up ovarian cancer at an earlier stage and improve survival slightly
4. If used together they can do more harm than good

Effect of Screening on Ovarian Cancer Mortality The Prostate, Lung, Colorectal and Ovarian (PLCO) Cancer Screening Randomized Controlled Trial


Ovarian Cancer Screening

A leading cause of cancer death among women

Study Design:
- Enrollment from 1993-2001 with 13 yr planned follow-up
- Women were considered eligible if they were aged 55 to 74 years and had no previous diagnosis of lung, colorectal, or ovarian cancer
- Women were randomized to either the intervention group (Ca-125 and US) or the usual care group (34,000 each group)
- Intervention: Ca-125 at entry and annually 5 yrs, TVUS at entry and annually 3 yrs
Ovarian Cancer Screening

Results:
• Compliance 85% in screening group
• Contamination in control group 2-4%

Incidence during follow-up:
• 212 ovarian cancer cases (5.7 per 10,000 person years) in screened group
• 176 ovarian cancer cases (4.7 per 10,000 person years) in usual care group

Ovarian Cancer Screening

Results:
• No difference in tumor characteristics, ovarian cancer, or all-cause mortality, between groups

False Positives Screened Group:
• 5% each screened round, most from TVUS
• False positives often resulted in surgery
• Oophorectomies in 33% of false positive patients
• Resulting in higher costs and medical complications

Ovarian Cancer Screening

Conclusions:
• Annual screening of average risk women with Ca-125 and TVUS does not result in a decrease of disease-specific mortality
• However, it does result in more invasive procedures and harms

Ovarian Cancer Screening

Clinical Implications:
• One third of surveyed physicians felt Ca-125 and/or TVUS were effective screening tests
  • Jan. 27 2012 Morbidity and Mortality Weekly Report
• USPSTF: Ovarian cancer screening incurs more risk than benefit
• Currently no proven screening interventions to decrease the morbidity or mortality of ovarian cancer in low- and medium-risk women

Bedtime dosing of antihypertensive medications reduces cardiovascular risk in chronic kidney disease


Nocturnal Dosing BP Rx

Background:
• Previous studies with ambulatory BP monitoring (ABPM) have demonstrated that the mean sleep-time BP is a better predictor of CV events than is the mean daytime or 24-hr BP.
• BP Rx has traditionally been dosed primarily in the morning.
Nocturnal Dosing BP Rx

Background:
• Some recent studies have suggested that restoration of the normal circadian “dipping” pattern of nocturnal BP by giving some of the antihypertensive rx at bedtime may lead to lower CV risk
• Nocturnal hypertension common in CKD

Question:
In hypertensive patients with CKD, does giving at least one of the HTN medications at bedtime reduce CV risk compared to giving all medications upon waking?

Methods:
• 661 hypertensive patients with mild CKD (about ½ with Cr Cl >60 ml/min but + microalbuminuria)
• About 2/3 were “nondippers” (BP did not exhibit normal circadian drop at night)

All patients were on once daily BP Rx.
• They were randomized to take at least one BP rx at bedtime or to continue taking them all upon awaking.
• ABPM was done for 48 hours at baseline and at least yearly.

Results:
• The adjusted hazard ratio for major CV events was 0.28 for nocturnal vs morning dosing
• Major CV events were 1.45%/yr for the AM dosing vs 0.51%/yr for bedtime dosing
• This gives an NNT of 100 patients (to prevent one major CV event/yr)
Results:

- The awake BP mean was no different between the groups.
- However, the sleep systolic BP mean was 6 mmHg lower in the bedtime dose group, and a greater number reverted to a "dipping" pattern (59% vs 29% in AM dose group at end of study).

Conclusions:

In hypertensive patients with mild CKD on once daily BP medications, moving at least one of the doses to bedtime reduces CV morbidity.

Caveats:

- Clinic BPs in both groups at end of study were above accepted targets (mean 146/80).
- It is unclear if the magnitude of benefit would be as great if all patients had been more aggressively treated.

Clinical Implications:

- In patients with mild CKD (and possibly others), it's reasonable to switch at least one of their BP rx to bedtime dosing (unless the patient is at high risk for falls in the night or for decreased compliance).
- While changing dose to bedtime on an empiric basis is of benefit, periodic ambulatory BP monitoring may be needed in practice to target the control of sleep BP more precisely.

Case: Male with Overactive Bladder

- A 62 yo male presents to your office with continued symptoms of mild urgency, frequency (9x per day), and nocturia (2x).
- Evaluation unrevealing for a structural cause. Some dry mouth and mild constipation, ROS otherwise negative.

No response to one month of tamsulosin. Flow is 11 mL/sec; post void residual (PVR) is 100 mL.

What would you do next?

1. Behavioral training
2. Start oxybutynin
3. Start finasteride
4. Double the dose of tamsulosin
Behavioral versus drug treatment for overactive bladder in men: The Male Overactive Bladder Treatment in Veterans (MOTIVE) trial


Overactive Bladder in Men

Question:
What is the comparative effectiveness of behavioral treatment with that of antimuscarinic therapy in men without bladder outlet obstruction who continue to have overactive bladder (OAB) symptoms with alpha-blocker therapy?

Methods:
• 143 men mean age 64 with urge and >8 voids/day after 4 weeks of tamsulosin
• All had clinical eval and uroflow with ultrasound residual (PVR)
• Four weeks tamsulosin run-in (to eliminate mild obstruction as a factor)

Excluded:
• Flow <5ml/s (baseline) or <10ml/s (post tamsulosin run-in)
• PVR >250 ml (baseline) or >150 ml (post tamsulosin run-in)

Background:
• Antimuscarinic is most common therapy in women with OAB and men without obstruction, but has side effects
• Behavioral therapy is well established in women with OAB, but little studied in men

Interventions:
• Behavioral therapy: pelvic floor training, delayed voiding, bladder diaries, urge suppression techniques
• Antimuscarinic therapy: extended-release oxybutynin 5 → 30 mg daily (titrated to max tolerated dose =10 mg for most patients in the study)
Overactive Bladder in Men

**Primary outcome** at end of the 8 weeks tx period was post-therapy 24 hr voiding frequency (on a 7 day diary)

**Secondary outcomes:**
1. Global satisfaction ratings
2. Nocturia, urgency, side effects
3. AUA score

Overactive Bladder in Men

**Results:**
• Both groups had reduced voiding frequency (from around 11 per day to 9)
• Both also reported reduced nocturia and urgency, with high satisfaction scores (>90% “completely” or “somewhat” satisfied)
• [No significant differences between the groups on the above measures]

Overactive Bladder in Men

**Results:**
Differences between the groups:
– Urgency scores better in oxybutynin group
– Bothersome side effects worse in oxybutynin group (29% vs only 13% for the behavioral tx)

Overactive Bladder in Men

**Conclusions:**
• Behavioral therapy is at least as effective as antimuscarinic drug therapy for managing symptoms of OAB in men without significant outlet obstruction who have not responded to 4 weeks of an alpha-blocker
• Bothersome side effects greatly reduced with this approach

Overactive Bladder in Men

**Clinical Implications:**
• In many men with OAB symptoms, behavioral therapy would be reasonable to try as a first line therapy
• Reserve antimuscarinics for those who have persistent bothersome urgency

Tadalafil 2.5 or 5 mg Administered Once Daily for 12 Weeks in Men with Both Erectile Dysfunction and Signs and Symptoms of Benign Prostatic Hyperplasia

**Tadalafil for ED and BPH-LUTS**

**Background:**
- ED and BPH-LUTS commonly coexist in older men
- Medical therapy for BPH-LUTS consists of α1-adrenergic blockers and/or, a 5α-reductase inhibitor
- Side effects including sexual dysfunction
- Previous studies showed 5α-reductase inhibitors decreased BPH-LUTS

**Study Design:**
- Men were ≥45 years old, sexually active, and experiencing ED for ≥3 months and BPH-LUTS for ≥6 months
- 4-week washout and 4-week placebo followed by random assignment based on ED and BPH-LUTS severity
- Random assignment 2.5 mg, 5.0 mg, placebo for 12 weeks

**Outcomes:**
- Change from baseline (randomization) to 12 week end point for the IIEF-EF domain score and total IPSS vs. placebo
- Tadalafil 2.5 mg (N = 198) and 5 mg (N = 208) significantly improved IIEF-EF domain scores (both P < 0.001) vs. placebo (N = 200) at end point
- For IPSS and other measures of BPH-LUTS, improvements were significant with tadalafil 5 mg (P < 0.001), but not 2.5 mg
- Tadalafil was well tolerated with no clinically adverse changes in orthostatic vital signs or uroflow parameters

**Conclusions:**
- Tadalafil 5 mg significantly improved both ED and BPH-related outcomes through 12 weeks and was well tolerated

**Clinical Implications:**
- Tadalafil 5 mg was FDA approved for treatment of men with ED and BPH-LUTS
- Now well tolerated single drug option available to treat men with these 2 disorders
New Drug Creation
Attempts at combining tadalafil with finasteride to help balding men with ED halted due to unintended reaction

1. Post-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. Post-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. Post-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

Questions?