GAMECHANGERS IN PHARMACY
SUNDAY/11:00AM-12:30PM

ACPE UAN: 0107-9999-17-013-L01-P  0.15 CEU/1.5 hr
0107-9999-17-013-L01-T  0.15 CEU/1.5 hr

Activity Type: Application-Based

Learning Objectives for Pharmacists & Pharmacy Technicians: Upon completion of this CPE activity participants should be able to:
1. List selected Gamechangers that affect your practice
2. Describe reasons the selected Gamechangers were chosen and how they affect the way pharmacists care for patients
3. Describe possible solutions to the clinical problems listed
4. Assess the clinical trials used to support this presentation
5. Apply the information presented to your specific practice

Speaker: Geoffrey C. Wall, PharmD, FCCP, BCPS, CGP
Dr. Geoffrey C. Wall is a Professor with the Department of Clinical Sciences, College of Pharmacy at Drake University and Director of the Drake Drug Information Center. His clinical practices include the Internal Medicine and Medical Intensive Care Teaching Services at Iowa Methodist Medical Center in Des Moines, IA. Dr. Wall received his Bachelor of Science in Pharmacy from the University of Utah in 1992 and his Doctor of Pharmacy from Idaho State University in 1998. He completed an ASHP-accredited Internal Medicine Specialty Residency at Scott and White Memorial Hospitals and Clinics in 1999. He is Board-Certified in Pharmacotherapy and is a Certified Geriatric Pharmacist. He is a Fellow of the American College of Clinical Pharmacy. Dr. Wall has written a number of peer-reviewed papers and textbook chapters on a variety of topics, and has designed or participated in several clinical trials. His research interests include drug treatment of gastrointestinal disorders, clinical evaluation of drug allergy and rheumatologic disorders.

Speaker Disclosure: Geoffrey Wall reports that he is on a speaker’s bureau for The Medicines Company, Boehringer Ingelheim, and Janssen. Off-label use of medications will be discussed during this presentation.
Gamechangers in Pharmacy: 2016

Geoffrey C. Wall, Pharm.D., FCCP, BCPS, CGP
Professor of Pharmacy Practice, Drake University
Internal Medicine Clinical Pharmacist
Iowa Methodist Medical Center
Des Moines, IA

Disclosure

• Geoff Wall reports he is:
  • A Speaker’s bureau member for Janssen, Boehringer Ingelheim, The Medicines Company

• Geoff Wall has indicated that off-label use of medication will be discussed during this presentation
Learning Objectives

• 1. List selected Gamechangers that affect your practice
• 2. Describe reasons the selected Gamechangers were chosen and how they affect the way pharmacists care for patients
• 3. Describe possible solutions to the clinical problems listed
• 4. Assess the clinical trials used to support this presentation
• 5. Apply the information presented to your specific practice:

What Are Gamechangers?

- Facets of clinical medicine that directly impact the everyday practice of the majority of “boots on the ground” pharmacists
- Some Gamechangers are specific to practice site
  - IV drug shortages, oral blockbuster drug goes generic
- Others are more general in scope
  - Affordable Care Act changes, landmark study published
Examples of Gamechangers

- New, first-in-class drug released
- Vanguard or seminal study published
- Wide-impact practice guidelines
- Reported ADRs of widely used medications
- FDA regulations/warnings
- New or changing laws/policies
- Economic changes

Problem: How to determine a Gamechanger

- Any one practitioner will always have bias of putting weight on the factors that influence THEIR practice
- May be unaware of a fundamental change in another area of practice
- Evaluation of potential Gamechanger may be out of area of expertise
Solution: Gamechanger Panel

- Representatives from hospital, community, long-term care with oversight by a pharmacist with expertise in regulatory affairs
- Independently select list of Gamechangers
- Meet and determine the top contenders via Modified Delphi Method
- Peer-reviews presentation data

Gamechanger 2016 Panel

- Brian Benson, PharmD
  - Exec. Director of Pharmacy, Unity Point Health
- Jennifer Moulton, RPh
  - CEO, The Collaborative Education Institute
- Kristin Meyer, PharmD
  - Clinical Pharmacist, Iowa Veterans Home
- Cheri Schmit, RPh
  - Clinical Coordinator, GRX Holdings
- Sarah Derr, PharmD
  - Executive Fellow, Iowa Pharmacy Association

- Kristin Stover, PharmD
  - Additional peer-review
Gamechanger Ground Rules

- This list was compiled by the Panel
- Your Gamechanger may not have been included
- Every effort made to be up-to-date
- This presentation does not have “all the answers” in controversial areas
- Not listed in perceived order of importance

Gamechanger #1

- The 2016 IDSA Hospital and Ventilator Associated Pneumonia Guidelines

- “Kill HCAP! Kill it with Fire!!”

Background

- Nosocomial pneumonia is the 2nd most common hospital-acquired infections after UTI (accounting for 31% of all nosocomial infections)
- Nosocomial pneumonia is the leading cause of death from hospital-acquired infections
- The incidence of nosocomial pneumonia is highest in ICU
- BUT are all these patients at risk of multi-drug resistant pathogens that require super broad-spectrum coverage??


2016 Guidelines

- New guidelines eliminate the term Health-Care Associated Pneumonia (HCAP)
- WHY?
  - “There is increasing evidence from a growing number of studies that many patients defined as having HCAP are not at high risk for MDR pathogens”
  - “Coverage for MDR pathogens among community-dwelling patients who develop pneumonia would likely be based on validated risk factors for MDR pathogens, not solely on whether or not the patient had previous contacts with the healthcare system”
  - So bottom line: lots of patients getting broad spectrum ABX WHO DO NOT NEED IT
So what do the new guidelines do?

- Do NOT say everyone gets the same ABX
- DO NOT select a specific ABX regimen
  - In fact a key point is that specific health-systems should develop their OWN empiric regimens based on antibiogram data
- downplay use of “Double-coverage” for Pseudomonas infections unless local resistance is high (which it really is not at UP-DSM)
- Like most recent medical organizational guidelines they take an “answer a specific clinical question approach” instead of trying to be a complete primer

A Summary of the Executive Summary

<table>
<thead>
<tr>
<th>Question Asked</th>
<th>Answer (level of evidence)</th>
</tr>
</thead>
<tbody>
<tr>
<td>VAP Diagnosis?</td>
<td>Non-invasive sampling with semi-quantitative cultures (Weak, Low)</td>
</tr>
<tr>
<td>Procalcitonin to initiate therapy in HAP?</td>
<td>NO--use clinical criteria (Strong, Moderate)</td>
</tr>
<tr>
<td>Treat Ventilator-Associated Tracheobronchitis?</td>
<td>NO (Weak, Low)</td>
</tr>
<tr>
<td>Empiric treatment of VAP?</td>
<td>Cover PSA, S. Aureus, Enteric Gram Neg (Strong, Low)*</td>
</tr>
<tr>
<td>Empiric Treatment of HAP?</td>
<td>Assess Risk Factors for MDR pathogen and using local Antibiogram craft therapy (Strong, Low)**</td>
</tr>
<tr>
<td>Procalcitonin to Discontinue therapy?</td>
<td>Yes BUT WITH clinical criteria (Weak, Low)</td>
</tr>
<tr>
<td>Duration of VAP/HAP Therapy?</td>
<td>7 Days for ALL (Strong, Low)</td>
</tr>
</tbody>
</table>
Pearls for the Summary of the Executive Summary

• * = VAP Treatment: 2 Anti-PSA Antibiotics should be used if PSA Resistance rate to first agent is > 10%, MRSA should be covered if MRSA rate is >20%. AVOID AMINOGYLCOSIDES unless needed

• ** = HAP Treatment (At UP-DSM where MRSA rate > 20%):
  • Low Risk of Mortality, AND No IV ABX in last 90 days:
    • 1 Drug for PSA/Gram Negatives, + Vancomycin
  • Septic shock OR Ventilatory Support for Pneumonia OR IV ABX within last 90 days
    • 2 drugs for PSA/Gram Negatives + Vancomycin
  • Previous IV ABX in the last 90 days is a major risk factor for MDR pathogens—if not present the Zosyn/Levaquin/Vanco Cha Cha is usually NOT NEEDED

ICU Antibiogram 2015
Locking the Barn After the Horse has been Stolen

- [05-12-2016] The U.S. Food and Drug Administration is advising that the serious side effects associated with fluoroquinolone antibacterial drugs generally outweigh the benefits for patients with acute sinusitis, acute bronchitis, and uncomplicated urinary tract infections who have other treatment options. For patients with these conditions, fluoroquinolones should be reserved for those who do not have alternative treatment options.

- An FDA safety review has shown that fluoroquinolones when used systemically (i.e. tablets, capsules, and injectable) are associated with disabling and potentially permanent serious side effects that can occur together. These side effects can involve the tendons, muscles, joints, nerves, and central nervous system.

- As a result, we are requiring the drug labels and Medication Guides for all fluoroquinolone antibacterial drugs to be updated to reflect this new safety information. We are continuing to investigate safety issues with fluoroquinolones and will update the public with additional information if it becomes available.


Gamechanger #2

- Naloxone dispensing and administration to prevent opioid overdose deaths
43,982 Drug Overdose Deaths in 2013

- Non-Prescription: 21,215
- Prescription: 22,767
- Opioid: 16,235
- Other: 6,532


Source: NCHS Data Brief, December, 2011, updated with 2009 mortality data
Naloxone

• Routes of administration
  • Intravenously
  • Intramuscularly
  • Subcutaneously
  • Intranasally
  • Nebulizer

Naloxone. Lexi comp. 2015
Kaleo, Evzio. 2015.

WHY??

• 1. Most opioid abusers do not use or live alone—bystanders can administer
• 2. High risk patients can be identified
• 3. Hypoxic brain injury is time-dependent: the sooner naloxone given the better
• 4. Bystanders may fear calling EMTs for fear of law enforcement

Endorsed by:
• American Medical Association
• American Pharmacists Association
• World Health Organization
• And many others

Naloxone Rescue Kits

OD Education and Naloxone Distribution (OEND) Programs in U.S.

<table>
<thead>
<tr>
<th>Number (#)</th>
<th>2007*</th>
<th>2010†</th>
</tr>
</thead>
<tbody>
<tr>
<td>States w/ OENDs</td>
<td>9</td>
<td>16</td>
</tr>
<tr>
<td>Programs</td>
<td>42</td>
<td>155</td>
</tr>
<tr>
<td>People enrolled</td>
<td>20,950</td>
<td>53,339</td>
</tr>
<tr>
<td>Reported OD reversals</td>
<td>2,642</td>
<td>10,194</td>
</tr>
</tbody>
</table>

* Knox, 2008 † Wheeler, E. NOPE Working Group–Harm Reduction Coalition, 2010

Example of Naloxone Rescue Program

1. Pain Diagnosis
   - Opioid prescription
   - Identify high risk patient
   - Prescribe naloxone
2. Substance Abuse Treatment
   - Prescribe naloxone

Watch video
- doctor’s office

Get naloxone kit
- pharmacy

Tell your family + friends
- home
Community Pharmacist Attitudes Towards Naloxone Co-presentation

- Study done in Australia in 2015
- 595 community pharmacists surveyed from different types of community practice

**General results:**
- Dispense naloxone via prescription: 90.3%
- Dispense with standing order for opioids: 53%
- Dispense OTC: 48%
- Educate patients on effectiveness and use of naloxone: 78.4%
- Moral or ethical concerns associated with drug abuse and overdose: 22.9%
- Concerns about litigation: 38%


The Massachusetts Experience

- Public health program in Mass. From 2004-06
- 19 communities with multiple opioid OD deaths
- Dept. of Public Health provided naloxone training to friends/family/bystanders of opioid users
- Time series analysis of results

What Can Pharmacists Do?

- Get trained! - Multiple Programs exist
  - CEI has a great program for Pharmacists:
    - [http://gotocei.org/Home/Index#FeaturedEvents)
  - Get involved at the legislative level
- Aid prescribers to identify high risk patients
- Administer yourself??

- Remember:
  - Opioids are a high risk medication similar to insulin
    - Glucagon for insulin patients?
    - Naloxone for opioid patients

Gamechanger #3

- Anticoagulation Update: Reversal agents and the new 2016 ACCP guidelines for the treatment of venous thromboembolism
New ACCP VTE Guidelines

- First since 2012
- No longer a “tome” of numerous guidelines for antithrombotic therapy but periodic releases like other medical practice guidelines
- Uses standard system of clinical questions of high import to practitioners and evidence-based answers that are graded
  - Questions examined involve:
    - Cancer-associated vs No cancer
    - Provoked vs Unprovoked
    - Proximal vs Distal DVT
    - Upper extremity vs Lower extremity DVT
    - Subsegmental PE


VTE and No Cancer

- Use NOAC – Now preferred over warfarin! (Grade 2B)
  - Rivaroxaban, apixaban
    - No bridging needed
  - Dabigatran, edoxaban
    - Start with parenteral anticoagulation x5 days
- If contraindications to NOAC, then use VKA therapy (warfarin) (Grade 2C)
  - Overlap with parenteral anticoagulation x5 days,
  - And INR >2 for 24 hours
Provoking Transient Risk Factors for VTE

- Surgery
- Estrogen therapy
- Pregnancy
- Leg injury
- Flight >8h

Location of VTE

- Lower extremity DVT
  - Proximal – Popliteal or more proximal veins
  - Distal – Calf veins
- Upper extremity DVT
  - Proximal – Axillary or more proximal veins
  - Catheter-associated
### Duration of Therapy

**Proximal DVT or PE**
- **Provoked**
  - 3 months (Grade 1B)
- **Unprovoked**
  - Low bleeding risk
  - Extended therapy (first VTE - Grade 1B, second VTE - Grade 1B)
  - 3 months (first VTE - Grade 1B, second VTE - Grade 2B)
  - Mild symptom s or high bleeding risk
  - Anticoagulate (Grade 2C)
  - Severe symptoms or risk for extension
  - Anticoagulate (Grade 2C)
  - Serial imaging x2 weeks (Grade 2C)
  - Extending thrombus
  - Anticoagulate (Grade 1B, 2C)

**Isolated Distal DVT**
- Mild symptom s or high bleeding risk
- Anticoagulate (Grade 2C)
- Severe symptoms or risk for extension
- Anticoagulate (Grade 2C)
- Extended therapy (Grade 1B)

**Cancer-associated**
- Anticoagulate (Grade 2C)
- Upper extremity DVT
- Anticoagulate (Grade 2C)

### Special Considerations for Upper Extremity DVT

**Proximal**
- Anticoagulate

**Catheter-associated**
- Catheter functional?
  - Yes
  - Anticoagulate
  - No
  - No

**Catheter still needed?**
- Yes
  - Leave catheter in and anticoagulate
- No
  - Remove and anticoagulate x3 months
Provoking Risk Factors for VTE and Risks for bleeding

- Age >65
- Recent surgery
- Cancer
- Previous stroke
- Known thrombophilia

- Age >75
- Poor anticoagulant control
- Comorbidity and reduced functional capacity
- Frequent falls
- Alcohol abuse
- NSAID/Antiplatelet use
- Renal/liver failure
- Thrombocytopenia
- SSRI Use?

<table>
<thead>
<tr>
<th>Low risk</th>
<th>0 risk factors</th>
</tr>
</thead>
<tbody>
<tr>
<td>Moderate risk</td>
<td>1 risk factor</td>
</tr>
<tr>
<td>High risk</td>
<td>≥2 risk factors</td>
</tr>
</tbody>
</table>

Risk Factors for Extension of Distal DVT—consider longer treatment!

- Positive D-dimer
- Extensive thrombus
  - >5cm long, involves multiple veins, >7mm diameter
- Thrombus close to proximal veins
- No reversible provoking factor
- Active cancer
- History of VTE
- Inpatient status

Role of Aspirin?

- Aspirin is better than nothing but worse compared to anticoagulation for extended therapy (Grade 2B)

### Duration of Therapy

- **Proximal DVT or PE**
  - Provoked
  - Unprovoked
    - Low to moderate bleeding risk
    - High bleeding risk
    - 3 months
    - Extended therapy
  - 3 months

- **Isolated Distal DVT**
  - Mild symptoms or high bleeding risk
  - Severe symptoms or risk for extension
  - Serial imaging x2 weeks
  - Anticoagulate
  - Anticoagulate

- **Cancer-associated**
  - Extended therapy
  - Anticoagulate

- **Upper extremity DVT**
  - Anticoagulate
Idarucizumab

- Humanized monoclonal antibody fragment (Fab) that binds to dabigatran and its acylglucuronide metabolites with an affinity higher than that of thrombin
- Indicated in patients treated with dabigatran (not other NOACs) that require anticoagulation reversal in cases of:
  - Emergency Surgery or Urgent Procedure
  - Life Threatening Bleeding
- Dosing: 5 g infusion: provided as two 2.5g/50 mL vials. There is limited data to support a second 5 g infusion
- Cost about $7K


RE-VERSE AD Trial

- Interim analysis of a large prospective cohort study
  - First 90 patients out of a planned 300
  - Two groups: A-Life-threatening bleed, B-Urgent surgery or procedure required
- Outcomes
  - Primary: Maximum percentage reversal (using aPTT, Thrombin Time)
  - Secondary: Proportion with normalization of dilute thrombin time
  - Safety assessed

Results

- **Primary:**
  - Maximum percentage reversal in Groups A and B was 100%
  - Reversal was evident on first sample taken after infusion
- **Secondary:**

<table>
<thead>
<tr>
<th>Normalization of clotting time</th>
<th>Dilute Thrombin Time</th>
<th>Ecarin Clotting Time</th>
</tr>
</thead>
<tbody>
<tr>
<td>Group A</td>
<td>98%</td>
<td>89%</td>
</tr>
<tr>
<td>Group B</td>
<td>93%</td>
<td>88%</td>
</tr>
</tbody>
</table>

Andexanet Alfa

- Recombinant, modified human factor Xa decoy protein that binds factor Xa inhibitors but **does not** have intrinsic catalytic activity
- Should reverse ALL direct and indirect Factor Xa drugs
  - Rivaroxaban, Abixaban, Edoxaban, LMWHs, fondaparinux, and heparin
- Initial studies showed rapid return Factor Xa levels to baseline in healthy volunteers

ANNEXA-4 Trial

- Similar to REVERSE-AD study
  - First report of an ongoing multicenter, prospective, open-label, single-group study of andexanet in patients with acute major bleeding (first 67 patients)
  - History of taking Factor Xa drugs and major or life-threatening bleed
- Dose based on drug and time from last dose

Outcomes
- Anti-Factor Xa activity after administration
- Clinical signs or radiologic signs of "excellent hemostasis"
- Rates of thrombosis


However, thrombotic events occurred in 18% of patients
Bottom Line

- New guidelines for VTE published
  - Emphasize duration of treatment
  - NOACs over warfarin
  - CAN defer treatment in certain cases
- Reversal agents for NOACs
  - Data on the safety of agents is lacking
  - Andexanet is not approved by FDA
  - Costly drugs
  - Remember as a class, all NOAC cause less fatal and intracranial bleeding compared to warfarin

Gamechanger #4

- Update on Biosimilars
  - Who said anything about big savings??
Biologics may be “miracle drugs” but they come at a price

**Biosimilar Vs. Interchangeable**

- **Biosimilar**
  - *Highly similar* to the U.S. licensed reference biological product notwithstanding minor differences in clinically inactive components
  - No clinically meaningful differences from the reverence product in terms of safety, purity, and potency

---

**Top 10 U.S. Drugs, 2010 vs. 2016E**

<table>
<thead>
<tr>
<th>Product</th>
<th>Sales ($B)</th>
<th>Product</th>
<th>Sales ($B)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Plavix</td>
<td>6.2</td>
<td>Rituxan</td>
<td>3.6</td>
</tr>
<tr>
<td>Lipitor</td>
<td>5.3</td>
<td>Humira</td>
<td>3.5</td>
</tr>
<tr>
<td>Seeretide/Advair</td>
<td>4.0</td>
<td>Avastin</td>
<td>3.5</td>
</tr>
<tr>
<td>Seroquel</td>
<td>3.7</td>
<td>Januvia</td>
<td>3.4</td>
</tr>
<tr>
<td>Epogen/Procrit</td>
<td>3.6</td>
<td>Advair</td>
<td>3.3</td>
</tr>
<tr>
<td>Actos</td>
<td>3.6</td>
<td>Revlimid</td>
<td>2.9</td>
</tr>
<tr>
<td>Abilify</td>
<td>3.3</td>
<td>Lantus</td>
<td>2.8</td>
</tr>
<tr>
<td>Enbrel</td>
<td>3.3</td>
<td>Enbrel</td>
<td>2.8</td>
</tr>
<tr>
<td>Singularair</td>
<td>3.2</td>
<td>Remicade</td>
<td>2.6</td>
</tr>
<tr>
<td>Remicade</td>
<td>3.1</td>
<td>Atripla</td>
<td>2.6</td>
</tr>
<tr>
<td><strong>Top 10 Total</strong></td>
<td><strong>$39.4</strong></td>
<td><strong>Top 10 Total</strong></td>
<td><strong>$31.0</strong></td>
</tr>
</tbody>
</table>

Source: *Hem Preview 2010, EvaluatePharma, June 2011*

Interchangeable Definitions

- Interchangeable
  - *Biosimilar* to the U.S. licensed reference product
  - Expected to produce the same clinical result to the reference product in any given patient
  - If a product is indicated for multiple administrations, then the product must be able to be alternated with the reference product without any loss of efficacy or change in risk of adverse events
  - May be substituted at the pharmacy level without the intervention of a healthcare provider

Biosimilar 351(k) Application

- In order to be granted biosimilar status by the FDA, the biological product must show clinical data derived from:
  - Analytical studies that demonstrate that the biological product is highly similar to the reference product notwithstanding minor differences in clinically inactive components;
  - Animal studies (including the assessment of toxicity); and
  - A clinical study or studies (including the assessment of immunogenicity and pharmacokinetics or pharmacodynamics) that are sufficient to demonstrate safety, purity, and potency in one or more appropriate conditions of use for which the reference product is licensed and intended to be used and for which licensure is sought for the biological product.
How Biologics are Made “The Patent is the Process”

- First application under the new biosimilar pathway brought to an FDA advisory committee
- On January 7th, 2015, the FDA Oncologic Drugs Advisory Committee unanimously voted that Sandoz’s EP2006 (Zarxio) should be licensed as biosimilar to the reference product, Neupogen
  - Includes all 5 indications for which Neupogen is approved
  - Zarxio (filgrastim-sndz) was approved March 6, 2015 as a biosimilar, not an interchangeable
  - Route of administration, indications and side effects are the same as Neupogen
  - Launched September 3, 2015
  - 15 percent wholesale list price discount

First Marketed Biosimilar: Filgrastim

- First application under the new biosimilar pathway brought to an FDA advisory committee
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Other Currently Approved Biosimilars

<table>
<thead>
<tr>
<th>Drug</th>
<th>Inflectra® (infliximab-dyyb)</th>
<th>Erelzi® etanercept-szzs</th>
<th>Amjevita® adalimumab-atto</th>
</tr>
</thead>
<tbody>
<tr>
<td>Biosimilar to:</td>
<td>Remicade®</td>
<td>Enbrel®</td>
<td>Humira®</td>
</tr>
<tr>
<td>Approval (NOT Release) Date:</td>
<td>April 2016</td>
<td>August 2016</td>
<td>September 2016</td>
</tr>
</tbody>
</table>

**Indications:**
- Moderate-to-severe Crohn’s disease
- Moderate-to-severe ulcerative colitis
- Moderate-to-severe rheumatoid arthritis in combination with methotrexate
- Active ankylosing spondylitis
- Active psoriatic arthritis
- Chronic severe plaque psoriasis.
- Rheumatoid arthritis
- Polyarticular juvenile idiopathic arthritis (JIA)
- Psoriatic arthritis
- Ankylosing spondylitis
- Plaque psoriasis.

**Table 1. Selected Biosimilars Under Investigation**

<table>
<thead>
<tr>
<th>Reference Product (Brand, Manufacturer)</th>
<th>Est. Patent Expiration (U.S.)</th>
<th>Indication</th>
<th>Biosimilar</th>
<th>Manufacturer</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adalimumab (Humira, AbbVie)</td>
<td>2022</td>
<td>RA, psoriatic arthritis, AS, UC, Crohn’s disease, psoriasis, HS, IA</td>
<td>GP-017</td>
<td>Sanofi Plurica Bocad</td>
</tr>
<tr>
<td>Bevacizumab (Avastin, Genentech)</td>
<td>2019</td>
<td>Colorectal, lung and renal cancers</td>
<td>BICD-031</td>
<td>Biocad Pfizer Amgen</td>
</tr>
<tr>
<td>Certolizumab (Cimzia, Eli Lilly)</td>
<td>Expired (2016)</td>
<td>Colorectal, head and neck cancers</td>
<td>ABI 264</td>
<td>Amgen</td>
</tr>
<tr>
<td>Daraparparat (Kynaos, Amgen)</td>
<td>2018</td>
<td>Anemia due to CKD or chemotherapy</td>
<td>BICD-030</td>
<td>Biocad</td>
</tr>
<tr>
<td>Epoetin alfa (Epogen, Amgen)</td>
<td>Expired (2016)</td>
<td>Anemia due to CKD or chemotherapy</td>
<td>I0575</td>
<td>Sanofi</td>
</tr>
<tr>
<td>Galsamer acetate (Copaxone, Teva)</td>
<td>Expired (2014)</td>
<td>Multiple sclerosis</td>
<td>BICD-063</td>
<td>Biocad</td>
</tr>
<tr>
<td>Infliximab (Remicade, Johnson &amp; Johnson)</td>
<td>September 2018</td>
<td>Autoimmune diseases including RA, psoriatic, UC, Crohn’s disease</td>
<td>GP-1111</td>
<td>Sanofi Pfizer Amgen</td>
</tr>
<tr>
<td>Pegfilgrastim (Neulasta, Amgen)</td>
<td>Expired (October 2015)</td>
<td>Chemotherapy-induced neutropenia</td>
<td>LA-2006</td>
<td>Sanofi</td>
</tr>
<tr>
<td>Rituximab (Mabthera, Genentech)</td>
<td>September 2016</td>
<td>Lymphoma</td>
<td>GP-0210</td>
<td>Sanofi Bocad Pfizer Amgen</td>
</tr>
<tr>
<td>Trastuzumab (Herceptin, Genentech)</td>
<td>June 2019</td>
<td>Breast cancer</td>
<td>BCD-022</td>
<td>Biocad Pfizer Amgen</td>
</tr>
</tbody>
</table>

**Published Data:**
- Phase III trial under way
- Phase I trial under way
- Phase III (2017)
- Phase III trial completed
- Preclinical phase I trials completed
- Phase III trials under way
- Phase III trials completed
- Phase III trials completed
- Phase II and II trials under way
- Phase III trials completed
- Preclinical phase I trials completed
- Phase III trials completed
- Phase III trials completed
- No data available
- File accepted by FDA at the end of 2015
- Phase III trials completed
- Preclinical phase I trials completed
- Phase III trials completed
- Phase III trials completed
- No data available
- Phase III trials completed
- Preclinical phase I trials completed

**Notes:**
State Board Rules?

Biosimilar Pharmacovigilance

Constant Monitoring to Identify and Characterize Safety Risk

Pharmacovigilance
- Define methods
- Real-time data
- Ensure monitoring parameters
- Easy reporting traceability

Risk minimization
- Healthcare provider feedback and communication
- Recalls and alerts
- REMS?

• Naming standards
• Integration into electronic medical record (EMR)
• Drug codes: HCPCS, NDC, etc.
• Prospective registries

Gamechanger #5

- DIR fees and financial implications for community pharmacists—another blow to the financial viability of community pharmacy

A fee by any other name.....

Rising Fees Pinch Some Pharmacies

A sharp rise in fees associated with a popular type of drug plan is chipping away at pharmacists’ profits across the U.S.

Michael DeRanger, owner of three pharmacies in Indiana, initially pocketed a profit of $9.48 after he sold a 5-colliliter bottle of Bepanthen ointment presciption—this case of oc initial cost $15.99. At the time of sale, Mr. DeRanger said he received $7.75.

**DIR Fees**

- DIR = “direct and indirect remuneration”
- Originally designed by Medicare Part D plans to assess/manage gross costs for drugs not seen at point of sale (e.g. manufacturer rebates, etc)
- NOW a catch-all term for fees charged by payers to pharmacies AFTER the point of sale
  - “Pay to play” fees for network participation
  - An “inducement” to meet metrics determined by PBM
  - “Reimbursement adjudication”
- This added fee has resulted in serious difficulties for community pharmacy—especially independent pharmacies


**DIR Example**

- Product X cost the independent pharmacist $15.00/30 day dispensing
- “Standard” reimbursement from patient’s PBM is AWP – 30% + $0.65 = $18.00, net profit from this Rx = $3.00
- BUT PBM informs pharmacist 4 months later they are instituting a DIR fee on their scripts of 5.5%. In this case the DIR fee for this Rx is $1.00, profit drops to $2.00.
- With the razor thin margins most Rx are filled on, the DIR fee can mean the difference between net profit or loss on an Rx
  - Several pharmacies report net lost on between 20 and 40% of Rxs
Or, perhaps a visual example

Basis

• Often stated the DIR fees are based on performance
  • Problem:
    • Even meeting 100% performance metrics may not eliminate fee
    • Performance criteria are often vague
    • A whole chain can have fees taken for individual stores that are “not meeting metrics”
    • Metrics can change
Solutions for Independent Pharmacy?

- Pharmacy Services Administrative Organizations (PSAOs)
  - Group independent pharmacies together via contract and negotiate with MCOs and PBMs to gain the best reimbursement terms
  - PSAOs often act literally as the “attorney-in-fact” for independent pharmacies, actually entering into contracts with PBMs on behalf of pharmacies.
  - PSAOs also “bind” independent pharmacies to other contracts that the independents may not know about
  - Often collect accounts receivable on behalf of the pharmacy, and frequently hold onto the monies for a few days before paying them over to the pharmacy
  - Concerns about bias in the larger PSAOs


Is this even legal?

- For the most part, yes
  - With numerous and complicated reimbursement structures in process difficult to convince lawmakers of the danger this poses to patients and access
  - S. 3308/H.R. 5951, the Improving Transparency and Accuracy in Medicare Part D Spending Act, would prohibit retroactive "DIR fees" on pharmacies in Medicare Part D
    - Bipartisan, but only addresses Part D plans
  - Various state legislation efforts as well, based on state insurance rules

What should all pharmacists do?

• For community pharmacists
  • Examine PSAO terms and rights under their contracts
  • Process to deal with issues via the PSAO and the PBM itself
    • Make sure the process is transparent

• For ALL pharmacists
  • Contact your legislative representative at the state and federal level
  • Support bills that protect community pharmacy and thereby protect the access of medications to patients

Gamechanger #6

• The PATHWAY-2 study: Spironolactone for difficult to control hypertension
  • Cheap and effective?
Study Criteria

- Inclusion criteria
  - 18–79 years with seated clinic SBP 140 mm Hg or greater (or ≥135 mm Hg for patients with diabetes) and home systolic blood pressure 130 mm Hg or greater, despite treatment for at least 3 months with maximally tolerated doses of three drugs (ACEI or ARB + CCB + Thiazide)

- Select exclusion criteria
  - DM Type 1, CrCl < 45 ml/min, serum potassium disturbances, Afib, cardiac adverse event within 6 months, need for study drugs for other indications, active cancer, absolute contraindications to study drugs

Methodology

Double blind, Randomised, Placebo-Controlled, Cross-over Study

- Screening for Resistant Hypertension
  - Rx A + C + D
  - DOT* to exclude non-compliance
  - Home BP to exclude white coat hypertension
  - Secondary hypertension excluded

- Randomisation
- 4 Week Single blind placebo run in Treated with A+C+D
- Doxazosin MR 4 – 8mg o.d.
- Spironolactone 25 – 50mg o.d.
- Home Systolic BP measured at 6 and 12 weeks
- Bisoprolol 5 – 10mg o.d.
- Placebo
- Amlodipine Open-label Run-out 10-20mg o.d.

- 12 weeks per treatment cycle
- Forced titration, lower to higher dose at 6 weeks
- No washout period between cycles
Outcomes

- Hierarchical Primary End-point:
  1. Difference in average home systolic BP (HSBP) between spironolactone and placebo followed, if significant by;
  2. HSBP difference between spironolactone and the average of the other two active drugs (bisoprolol and doxazosin) followed, if significant by
  3. HSBP difference between spironolactone and each of the other two active drugs

Patient Disposition

436 screened

335 randomised

314 with any follow up (ITT Analysis)
  285 for spironolactone
  282 for doxazosin
  285 for bisoprolol
  274 for placebo

230 completed all treatment cycles

88 excluded
  13 took no study drug

21 no follow up for any drug
### Selected Baseline Characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Mean (SD) or N (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yrs.)</td>
<td>61.4 (9.6)</td>
</tr>
<tr>
<td>Male</td>
<td>230 (68.7%)</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>93.5 (18.1)</td>
</tr>
<tr>
<td>Smoker</td>
<td>25 (7.8%)</td>
</tr>
<tr>
<td>Home BP (mmHg)</td>
<td></td>
</tr>
<tr>
<td>Systolic</td>
<td>147.6 (13.2)</td>
</tr>
<tr>
<td>Diastolic</td>
<td>84.2 (10.9)</td>
</tr>
<tr>
<td>Clinic BP (mmHg)</td>
<td></td>
</tr>
<tr>
<td>Systolic</td>
<td>157.0 (14.3)</td>
</tr>
<tr>
<td>Diastolic</td>
<td>90.0 (11.5)</td>
</tr>
<tr>
<td>Blood electrolytes</td>
<td></td>
</tr>
<tr>
<td>Sodium (mmol/L)</td>
<td>140 (3.0)</td>
</tr>
<tr>
<td>Potassium (mmol/L)</td>
<td>4.1 (0.47)</td>
</tr>
<tr>
<td>eGFR (mL/min)</td>
<td>91.1 (26.8)</td>
</tr>
<tr>
<td>Diabetic</td>
<td>46 (13.7%)</td>
</tr>
</tbody>
</table>

### Results

#### Comparators (N=314)

<table>
<thead>
<tr>
<th>Comparator</th>
<th>Home Systolic BP difference (mmHg)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Spironolactone vs placebo</td>
<td>-8.70 (-9.72,-7.69)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Spironolactone vs mean Bisoprol/Dox</td>
<td>-4.26 (-5.13,-3.38)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Spironolactone vs Doxazosin</td>
<td>-4.03 (-5.04,-3.02)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Spironolactone vs Bisoprolol</td>
<td>-4.48 (-5.50,3.46)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

#### Treatments

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Home Systolic BP (mmHg)</th>
<th>Change from baseline</th>
</tr>
</thead>
<tbody>
<tr>
<td>Spironolactone</td>
<td>134.9 (134.0,135.9)</td>
<td>-12.8 (-13.8,-11.8)</td>
</tr>
<tr>
<td>Doxazosin</td>
<td>139.0 (138.0,140.0)</td>
<td>-8.7 (-9.7,-7.7)</td>
</tr>
<tr>
<td>Bisoprolol</td>
<td>139.4 (138.4,140.4)</td>
<td>-8.3 (-9.3,-7.3)</td>
</tr>
<tr>
<td>Placebo</td>
<td>143.6 (142.6,144.6)</td>
<td>-4.1 (-5.1,-3.1)</td>
</tr>
</tbody>
</table>
Results

- Serious adverse effects
  - 2-3% for all groups including placebo (p = 0.8)
  - Dizziness, fatigue, and diarrhea were the most common ADRs across the three medications
  - Potassium increased 0.42 mEq and sodium decreased 1.9 mEq over course of study
  - eGFR decreased slightly in all three drug groups

<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>Final</th>
<th>Patients (n)</th>
<th>Met target</th>
<th>Least Squares Estimates</th>
<th>Odds ratio</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Home Systolic BP (mmHg)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Spironolactone</td>
<td>148.3</td>
<td>133.9</td>
<td>282</td>
<td>163</td>
<td>57.8</td>
<td>58.0 (52.0, 63.7)</td>
<td>0.52 (0.37, 0.73)</td>
</tr>
<tr>
<td>Doxazosin</td>
<td>147.8</td>
<td>138.9</td>
<td>276</td>
<td>115</td>
<td>41.7</td>
<td>41.5 (35.8, 46.5)</td>
<td>0.55 (0.39, 0.78)</td>
</tr>
<tr>
<td>Bisoprolol</td>
<td>147.7</td>
<td>139.6</td>
<td>280</td>
<td>122</td>
<td>43.6</td>
<td>43.3 (37.5, 49.2)</td>
<td>0.55 (0.39, 0.78)</td>
</tr>
<tr>
<td>Placebo</td>
<td>147.8</td>
<td>143.5</td>
<td>270</td>
<td>66</td>
<td>24.4</td>
<td>23.9 (19.1, 29.4)</td>
<td>0.23 (0.16, 0.33)</td>
</tr>
</tbody>
</table>

Safety
Authors’ Conclusions

• Spironolactone 25-50mg daily is superior to other treatments for resistant hypertension
• Nearly 60% of patients receiving spironolactone achieved their goal BPs in this study
• Spironolactone was well tolerated but electrolytes should be periodically monitored
• Spironolactone is cost effective

Reviewer’s Analysis

• Pros
  • Well done RCT
  • Broad inclusion criteria
  • Excellent safety evaluation
  • Used ambulatory and clinic BP readings

• Cons
  • No washout in a cross over study might have allowed for “bleeding” of effects between arms
  • Study not long enough to evaluate one of the more common ADRs of spironolactone: gynecomastia
  • CKD is a big exclusion that will limit applicability of this trial
  • Given ADRs one wonders about patient blinding
Gamechanger #7

• Community pharmacy networks and their transformative effect on practice

MACRA and Community Pharmacy

• Just like medicine (and fee-for-service) the reimbursement for traditional dispensing fees pharmacies charge will not allow many pharmacies to remain profitable
  • The Medicare Access and CHIP Reauthorization Act of 2015, or MACRA, will replace the Sustainable Growth Rate (SGR) methodology, which has caused physician payment uncertainty for more than a decade
  • MACRA will increase the number of physicians participating in alternative payment models that encourage quality and efficiency. Physicians in high quality, efficient practices may benefit financially from MACRA.
• So who determines which patients are impacting the metrics of the payer?
• What pharmacy activities can optimize medical benefits?
• Can pharmacies and clinics work together?
Current Programs

- Navitus Health Solutions
  - Recognize the value of pharmacists and already reimburse for adherence monitoring, certain consultation services and pharmacist-provided patient training
  - Not organized from the PBM or individual pharmacist level
- Wisconsin Pharmacy Quality Collaborative (WPQC)
  - Works as a conduit between community pharmacy members and payers
  - Payments for pharmacies that aid in attaining quality and adherence goals
  - MTM training for members
  - To date over 55,000 patients impacted by WPQC


http://www.pswi.org/WPQC/About-WPQC/About-WPQC/Goal-of-WPQC

Community Pharmacy Enhanced Service Network

- Community Pharmacy Enhanced Service Network (CPESN)
  - Group of diverse community pharmacies across Iowa
  - Modeled after North Carolina pilot project under CMMI grant
  - Pharmacists reimbursed for quality activities
    - Comprehensive Medication Review with Disease State Management
    - Clinical Medication Synchronization
    - Medication Reconciliation
    - Immunizations
    - Adherence Packaging
- National Involvement
  - CPESN-USA which is a 50/50 joint venture between NCPA and CCNC
Wellmark High Performing Pharmacies

- Asthma
  - % on controller meds and adherence measures
- Diabetes
  - >80% on ACEi/ARB, adherence to medications
  - Glycemic and BP control according to ADA
- Hyperlipidemia
  - >80% on appropriate dose intensity statin and adherence
- Depression
  - Appropriate screening and treatment with adherence
- Total Cost of Care
- Readmission Rates
- ED visit rates

Wellmark High Performing Pharmacies

- So what’s unique about this?
  - No PBM involvement—Wellmark is paying high performing pharmacies directly
  - Standardized outcomes
  - Activities able to be completed in most community pharmacies
  - Again: the Payer is directly paying pharmacies for quality outcomes!
Bottom Line

- The traditional “fee-for-dispensing” model is in serious jeopardy
  - Shrinking margins, DIR fees, etc.
- Community pharmacy has to find other methods of revenue
  - Partnering with payers and providers
    - Improve quality
    - Help Providers meet their MACRA goals
  - Does NOT require “super-duper” clinical experts, things like medication reconciliation, adherence targeting, and medication synchronization can do the job

Gamechanger #8

- Metformin dosing and renal function: 2016 FDA label changes
Metformin – FDA labeling changes 2016

• In patients taking metformin whose eGFR later falls below 45 mL/minute/1.73 m², assess the benefits and risks of continuing treatment
• Discontinue metformin if the patient’s eGFR later falls below 30 mL/minute/1.73 m²
  • eGFR NOT Serum Creatinine
• Discontinue metformin at the time of or before an iodinated contrast imaging procedure in patients with an eGFR between 30 and 60 mL/minute/1.73 m²; in patients with a history of liver disease, alcoholism, or heart failure; or in patients who will be administered intra-arterial iodinated contrast.
• Re-evaluate eGFR 48 hours after the imaging procedure; restart metformin if renal function is stable.


Why?

• Lactic acidosis associated with impaired renal clearance of metformin
• FDA based past serum creatinine restrictions on data from phenformin removed from market due to safety
• Most other countries less restrictive in dosing guidance
• Many studies have shown NO increase in rates of lactic acidosis in patients with mild-to-moderate CKD
• Relaxing restrictions on use:
  • >500,000 more U.S. patients would be eligible to use metformin

Inzucchi SE. JAMA. 2014;312:2668-2675
Flory JH. JAMA Intern Med. 2015;175:458-459
So how accurately does eGFR reflect ability to clear metformin??

- Remember metformin primarily cleared by active tubular secretion NOT by glomerular filtration
  - Both serum creatinine and eGFR are not linear substitutes
- What weight are we talking about?
  - The endless debate in the one HCP professional who routinely calculates this figure: Pharmacists!!
  - What formula?
  - More confusion on appropriate use??
    - Is metformin ok to use in a 41 year old man, weight 180Kg, Ht 73 in, Serum creatinine of 2.1 mg/dl??
    - How about a 94 year old female, weight 60Kg, Ht 63 in, serum creatinine of 1.1 mg/dl??
  - PCPs will need help with these assessments!!


Bottom Line

- FDA has switched the assessment tool to determine appropriate metformin use from serum creatinine to eGFR
- This means some patients are now eligible for metformin use and some who were are not anymore
- Pharmacists in a unique position to assess and calculate eGFR for providers
Gamechanger #9

• Specialty pharmacy and medication access—especially in hospitals

Specialty Pharmacy—No Single Definition

• It’s not uncommon for different stakeholders to have different definitions for “specialty” drugs:
  • Centers for Medicare & Medicaid Services define specialty drugs as those that cost more than $600
  • Food & Drug Administration, employers, and other health care stakeholders define it differently

When asked to define specialty drugs, PBMs and specialty pharmacy executives provided a number of responses
Distribution, Dispensing and Site of Care

- Specialty pharmacies provide broad-based distribution of specialty drugs in the health care delivery system
  - They are accountable for patient safety and typically provide intensive one-to-one patient education and follow-up support by a pharmacist and/or nurse
  - Safety reporting (REMS programs, etc)
  - Usually handles cost issues (i.e. patient support programs)
  - There are a limited number of specialty pharmacies in the U.S. compared to the large number of retail pharmacies
  - A specialty pharmacy typically provides more extensive care management, counseling, case management and coordination of care with other stakeholders involved in a patient’s treatment


Specialty Pharmacy Constituents

**Patients**
- Higher member satisfaction
- Care Management program support
- Education and counseling
- Insurance and coverage assistance
- Better healthcare

**Manufacturers**
- Reliable, seamless distribution
- Appropriate utilization
- Patient persistence and adherence
- Access to integrated data
- Better outcomes

**Physicians**
- Lower administrative burden
- Incentives aligned with patient care
- Assistance in patient education and follow-up
- Convenient solution with better patient services

**Payors**
- Proven cost savings
- Utilization management
- Higher patient and physician satisfaction
- Accountability and better care
- Product access and pipeline control
Access to Medications

- With fewer community pharmacies handling these medications, dispensing occurs almost exclusively from the specialty pharmacy
- Which is all well and good—until something like a hospitalization happens…
  - Especially if the specialty pharmacy is not “in-network” with the health-system

An Example

- A 67 yo patient with a history of asthma, systemic sclerosis, and pulmonary hypertension presents to her local (community) hospital with an increase of shortness of breath, pedal edema, and fatigue. An exacerbation of her pulmonary HTN and concomitant right HF symptoms is suspected. She currently takes Medication X, approved for pulmonary hypertension, that is a specialty drug. Monthly costs for the drug is $9000, and the hospital does not have it on formulary due to its cost and infrequent use. JC rules do not allow patients to bring in their own medications for use……..
- HOW does the hospital pharmacy continue to provide this medication for this patient?
What are some health-systems doing?

• Specialty drug P&T Subcommittee
  • Consists of physicians, nurses, pharmacists, patient representatives and representatives from CFO’s office
  • Standardized criteria for selecting specialty drugs the pharmacy carries
  • If a drug is absolutely needed, committee has pathway to explore working with drug manufacturer concerning costs and access
  • Track and Trace issues with “borrowing” medication from specialty pharmacy

Other Potential Solutions

• Pathway to bring in own medications that meets Joint Commission regulations
• Possible substitution for formulary product?
  • Often not practicable

• Just develop your own health-system’s specialty pharmacy!
Bottom Line

- Specialty Pharmacies
  - Specialize in dispensing, storing, safety and monitoring issues, and other components of biologics and other expensive drugs
  - However when they become the ONLY pathways to receive those medications problems can occur
- Health-systems should prospectively develop policies to prevent lack of access to specialty medications, while containing costs

Gamechanger #10

- The EMPA-Reg study: Empagliflozin and CV mortality in patients with Type 2 DM

Background

- The Diabetes epidemic rolls on: 800 million patients worldwide have DM 2
- Diabetes is a major risk factor for a number of diseases, largely grouped into
  - Macrovascular: MI/CVD, Stroke, PAD
  - Microvascular: Nephropathy, Neuropathy, Retinopathy
- Although tight blood glucose control with oral agents or insulin has been shown to reduce microvascular complications of DM, only metformin (in the UK-PDS 34 study) decreased MIs in addition to its other effects 2
- Empagliflozin is a selective inhibitor of sodium glucose cotransporter 2 (SGLT2) that has been shown to have several other physiologic effects:
  - Decreases weight and BP, BUT Increases LDL and HDL
- Can it have an effect on CV outcomes where other drugs have not?

Background

Meta-analysis of intensive glucose control in T2DM: major CV events including heart failure

<table>
<thead>
<tr>
<th>Event</th>
<th>More intensive</th>
<th>Less intensive</th>
<th>Difference in HbA1c (%)</th>
<th>HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stroke</td>
<td>378</td>
<td>370</td>
<td>-0.88</td>
<td>0.96 (0.83, 1.10)</td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>730</td>
<td>745</td>
<td>-0.88</td>
<td>0.85 (0.76, 0.94)</td>
</tr>
<tr>
<td>Hospitalisation for or death from heart failure</td>
<td>459</td>
<td>446</td>
<td>-0.88</td>
<td>1.00 (0.86, 1.16)</td>
</tr>
</tbody>
</table>

- Meta-analysis of 27,049 participants and 2,370 major vascular events from:
  - ADVANCE
  - UKPDS
  - ACCORD
  - VADT

Turnbull FM et al. Diabetologia 2009;52:2288-2298
This Paper

• Research Question:
  • Does empagliflozin, as compared with placebo, decrease cardiovascular morbidity and mortality in patients with Type 2 diabetes at high risk for cardiovascular events who were receiving standard care?

• Type: Multicenter, R, DB, PC Trial
• Funding: Boehringer Ingelheim/Eli Lilly
• Level of Evidence sought: A

• 590 sites in 42 countries worldwide

Study Criteria

• Key inclusion criteria
  • Adults with type 2 diabetes
  • BMI ≤45 kg/m2
  • HbA1c 7–10%
  • Established cardiovascular disease
    • Prior myocardial infarction, coronary artery disease, stroke, unstable angina or occlusive peripheral arterial disease

• Key exclusion criteria
  • eGFR <30 mL/min/1.73m2 (MDRD)
Methodology

- Primary Outcome
  - Time to first occurrence of CV death, non-fatal MI or non-fatal stroke

- Key Secondary Outcomes
  - Time to first occurrence of CV death, non-fatal MI, non-fatal stroke or hospitalization for unstable angina (all separate)
  - All-cause mortality

- Formal Safety Analysis
  - HbA1c, Weight, Waist circumference, BP, LDL + HDL cholesterol
  - ADR/Safety

Outcomes

- Primary Outcome
  - Time to first occurrence of CV death, non-fatal MI or non-fatal stroke

- Key Secondary Outcomes
  - Time to first occurrence of CV death, non-fatal MI, non-fatal stroke or hospitalization for unstable angina (all separate)
  - All-cause mortality

- Formal Safety Analysis
  - HbA1c, Weight, Waist circumference, BP, LDL + HDL cholesterol
  - ADR/Safety
Stats

- Power
  - 90% in noninferiority analysis
- Four-step hierarchical-testing strategy for the pooled empagliflozin group versus the placebo group noninferiority then if appropriate superiority testing for outcomes
- Cox proportional-hazards model performed, ITT
- n = 7020 over approximately 2.5 years average

### Selected Baseline Characteristics

<table>
<thead>
<tr>
<th></th>
<th>Placebo (n=2333)</th>
<th>Empagliflozin 10 mg (n=2345)</th>
<th>Empagliflozin 25 mg (n=2342)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years</td>
<td>63.2 (8.8)</td>
<td>63.0 (8.6)</td>
<td>63.2 (8.6)</td>
</tr>
<tr>
<td>HbA1c, %</td>
<td>8.08 (0.84)</td>
<td>8.07 (0.86)</td>
<td>8.06 (0.84)</td>
</tr>
<tr>
<td>Metformin (%)</td>
<td>1734 (74.3)</td>
<td>1729 (73.7)</td>
<td>1730 (73.9)</td>
</tr>
<tr>
<td>Insulin (%) MDD 70 U</td>
<td>1135 (48.6)</td>
<td>1132 (48.3)</td>
<td>1120 (47.8)</td>
</tr>
<tr>
<td>Body mass index, kg/m²</td>
<td>30.7 (5.2)</td>
<td>30.6 (5.2)</td>
<td>30.6 (5.3)</td>
</tr>
<tr>
<td>Coronary artery disease</td>
<td>1763 (75.6%)</td>
<td>1782 (76.0%)</td>
<td>1763 (75.3%)</td>
</tr>
<tr>
<td>ACE inhibitors/ARBs</td>
<td>1868 (80.1%)</td>
<td>1896 (80.9%)</td>
<td>1902 (81.2%)</td>
</tr>
<tr>
<td>Statins</td>
<td>1773 (76.0%)</td>
<td>1827 (77.9%)</td>
<td>1803 (77.0%)</td>
</tr>
</tbody>
</table>
Results: Primary Outcome

Primary outcome: 12.1% vs 10.5%, NNT = 63

Statistically driven by decreases in all cause and CV mortality
Results: Secondary Outcome

Death from ANY cause: 8.3% vs 5.7%, NNT 39

This over an average of 3 years

Safety

<table>
<thead>
<tr>
<th></th>
<th>Placebo (n=2333)</th>
<th>Empagliflozin 10 mg (n=2345)</th>
<th>Empagliflozin 25 mg (n=2342)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n (%)</td>
<td>Rate</td>
<td>n (%)</td>
</tr>
<tr>
<td>One or more drug-related* AEs</td>
<td>549 (23.5%)</td>
<td>11.33</td>
<td>666 (28.4%)</td>
</tr>
<tr>
<td>One or more AEs leading to discontinuation</td>
<td>453 (19.4%)</td>
<td>8.26</td>
<td>416 (17.7%)</td>
</tr>
<tr>
<td>Events consistent with genital infection</td>
<td>42 (1.8%)</td>
<td>0.73</td>
<td>153 (6.5%)</td>
</tr>
<tr>
<td>Urosepsis</td>
<td>3 (0.1%)</td>
<td>0.05</td>
<td>6 (0.3%)</td>
</tr>
</tbody>
</table>

Rate = per100 patient-years

No difference in hypoglycemia episodes, DKA, AKI
Among patients with type 2 diabetes at high risk for cardiovascular events, those receiving empagliflozin had a lower rate of the primary composite outcome and was driven by a significant reduction in death from cardiovascular causes.

Empagliflozin was associated with a reduction in HbA1c without an increase in hypoglycemia, reductions in weight and blood pressure, and small increases in LDL cholesterol and HDL cholesterol.

Patients were largely treated based on current standards of care.

Authors’ Conclusions

Pros
- Appropriate RCT was a large population of high risk patients
- Solid outcomes and observation
- In-depth safety follow-up

Cons
- Big question: WHY this benefit? No biologically plausible reason discussed
- Is this a class effect?
- NNH for urosepsis = 250
- Cost of course: Cash price of $350-400/month

Reviewer’s Analysis
Conclusions

• A lot of information I know
• Perhaps a Focus on:
  • Areas that impact your practice
  • Variations that may change these recommendations
  • The “bottom line” slides
• PLEASE give us feedback
  • Gamechangers for 2017?

QUESTIONS?

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