New Drugs Update: The Top 15 of 2015

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Program Objectives

By the end of the presentation, the pharmacist or pharmacy technician participant will be able to:

- Discuss trends in new drug approvals over the past five years.
- Identify at least five new medications and their indications as approved by the FDA in 2015 that will have a significant impact on patient care.
- Discuss key clinical trials and the outcomes that led to approval of at least two new medications in 2015.
- Identify medications approved in 2015 that represent a new class of medications.

I have no conflicts of interest to disclose in regards to this presentation.
FDA Drug Approval Process

New Drug Application (NDA) Chemical Types

1. New molecular entity (NME) – new to the USA market
2. New ester, new salt, or other noncovalent derivative
3. New formulation
4. New combination
5. New manufacturer
6. New indication
7. Drug already marketed, but without an approved NDA
8. OTC (over-the-counter) switch

Review Classifications

P - Priority review drug: A drug that appears to represent an advance over available therapy
S - Standard review drug: A drug that appears to have therapeutic qualities similar to those of an already marketed drug
O - Orphan drug - a product that treats a rare disease affecting fewer than 200,000 Americans
2015 NDA Approvals (NMEs/BLAs)

- Savaysa (edoxaban)
- Cosentyx (secukinumab)
- Natpara (parathyroid hormone)
- Ibrance (palbociclib) P
- Lenvima (lenvatinib) P, O
- Farydak (panobinostat) P
- Avycaz (avibactam sodium/ceftazidime) P
- Zarxio (filgrastim-sndz) B
- Cresemba (isavuconazonium sulfate) P, O
- Unituxin (dinutuximab)
- Cholbam (cholic acid) P, O
- Corlanor (ivabradine hydrochloride) P
- Kybella (deoxycholic acid)
- Viberzi (eluxadoline) P
- Kengreal (cangrelor)
- Orkambi (lumacaftor/ivacaftor) P
- Entresto (sacubitril/valsartan) P
- Rexulti (brexpiprazole)
- Praluent (alirocumab)
- Odomzo (sonidegib phosphate)
- Daklinza (daclatasvir dihydrochloride) P
- Addyi (flibanserin)
- Repatha (evolocumab)
- Varubi (rolapitant)
- Xuriden (uridine triacetate) P, O
- Vraylar (cariprazine)
- Lonsurf (trifluridine; tipiracil)
- Triseba (insulin degludec)
- Aristada (aripiprazole lauroxil)
- Praxbind (idarucuzumab)
- Veltassa (patiromer)
- Stremsiq (asfotase alfa)
- Yondelis (trabectedin) P
- Nucala (mepolizumab)
- Genvoya (cobicistat, elvitegravir, emtricitabine, tenofovir alafenamide)
- Cotellie (cobimetinib) P, O
- Tagrisso (osimertinib) P, O
- Darzalex (daratumumab) P, O
- Ninlaro (ixazomib) P, O
- Portrazza (necitumumab) O
- Empliciti (elotuzumab) O
- Kanuma (sebelipase alfa)
- Alecensa (alectinib) P
- Bridion (sugammadex) P
- Uptravi (selexipag) O
- Zurampic (lesinurad)

O = Orphan; P = Priority Review; Red = BLA  B = Biosimilar
Annual FDA Approvals
2015 Top 15 FDA Approvals

Anticoagulation-related Agents
- Edoxaban (Savaysa)
- Cangrelor (Kengreal)
- Idarucizumab (Praxbind)

Anti-infectives
- Ceftazidime/Avibactam sodium (Avycaz)
- Isavuconazol (Cresemba)
- Daclatasvir dihydrochloride (Daklinza)

Hypercholesterolemia
- Alirocumab (Praluent)
- Evolocumab (Repatha)

Cardiology
- Ivabradine hydrochloride (Corlanor)
- Sacubitril/valsartan (Entresto)

Oncology
- Necitumumab (Portrazza)
- Palbociclib (Ibrance)

Electrolyte Imbalance
- Patiromer Sorbitex Calcium (Veltassa)

Reversal Agent
- Sugammadex (Bridion)

Biosimilar
- Filgrastim-sndz (Zarxio)
NEW ANTICOAGULATION-RELATED AGENTS

EDOXABAN – Direct factor Xa inhibitor

IDARACIZUMAB – dabigatran reversal agent

CANGRELOR – IV P2Y$_{12}$ platelet inhibitor
Edoxaban (Savaysa®)

- Direct factor Xa inhibitor
  - Indications
    - Prevention of stroke and systemic embolism with NVAF
    - Treatment of DVT and PE after 5-10 days of parenteral anticoag
  - Dose
    - 60 mg PO once daily (CrCl > 50 mL/min)
    - 30 mg PO once daily if any of the following
      + CrCl 15-50 mL/min
      + Body weight < 60 kg
      + Concomitant P-gp inhibitors (e.g. verapamil, quinidine, dronedarone)
  - Available as 15 mg, 30 mg and 60 mg tablets
  - Tablets are $9.24 each (all strengths)
Edoxaban (Savaysa®)

Clinical Trial – Stroke Prevention in NVAF

- ENGAGE AF-TIMI 48 trial - *NEJM 2013;369:2093-2104*
  - R,DB,DD trial in 21,105 patients with mod-to-high risk of NVAF; median follow-up 2.8 years

<table>
<thead>
<tr>
<th></th>
<th>Warfarin (INR 2-3)</th>
<th>Edoxaban 30 mg QD</th>
<th>Edoxaban 60 mg QD</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Efficacy:</strong></td>
<td></td>
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<tr>
<td>Incidence of</td>
<td>1.5%</td>
<td>1.61% (P=0.005 for noninferiority)</td>
<td>1.18% (P&lt;0.001 for noninferiority)</td>
</tr>
<tr>
<td>stroke or systolic embolic event (annualized rate)</td>
<td></td>
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<tr>
<td><strong>Safety:</strong></td>
<td></td>
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<tr>
<td>Major bleeding (annualized rate)</td>
<td>3.43%</td>
<td>1.61% (P&lt;0.001)</td>
<td>2.75% (P&lt;0.001)</td>
</tr>
</tbody>
</table>
Edoxaban (Savaysa®)

Clinical Trial – Treatment of DVT & PE

- Treatment of Symptomatic VTE - *NEJM* 2013;369:1406-1415
  - R, DB, DD, noninferiority trial in 4921 patients with DVT and 3319 patients with PE; initial treatment with heparin or enoxaparin

<table>
<thead>
<tr>
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<th>Warfarin (INR 2-3)</th>
<th>Edoxaban 30 mg or 60 mg QD*</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Efficacy:</strong> Incidence of recurrent symptomatic venous thromboembolism</td>
<td>3.5%</td>
<td>3.2% (P&lt;0.001 for noninferiority)</td>
</tr>
<tr>
<td><strong>Safety:</strong> Major or clinically relevant nonmajor bleeding</td>
<td>10.3% (3.1% major bleeding)</td>
<td>8.5% (P=0.004 for superiority) (1.4% major bleeding)</td>
</tr>
</tbody>
</table>

*Low-dose edoxaban was administered if CrCl 30-50 mL/min or body weight ≤ 60 kg or P-gp inhibitors*
Edoxaban (Savaysa®)

➢ Is edoxaban on your hospital formulary?
A. Yes, in addition to the other DOACs
B. Yes, as the only DOAC
C. No, we only use warfarin
D. No, but patients can use their own medication
Idarucizumab (Praxbind®)

- Monoclonal antibody fragment (humanized)
  - Indication: reversal of dabigatran (direct thrombin inhibitor)
    - First in class – reversal agent
  - Dose
    - 5 gram IV dose - two 2.5 gram vials
      - Administer as two consecutive infusions, or two bolus IV injections
      - Single dose; limited data supports a second dose
      - $3500/package (WAC)

Figure 1: Recommended dose of PRAXBIND provided as two vials.
Idarucizumab (Praxbind®)

Clinical Trial

  - Multicenter, prospective cohort study
  - 90 adult patients on dabigatran for stroke prevention with NVAF
    + Group A: 51 with bleeding requiring reversal agent
    + Group B: 39 required surgery or procedure that could not be delayed
  - Results
    + Reversal
      › Median maximal reversal was 100% based on dilute thrombin time and ecarin clotting time
      + Group A - median time of bleeding cessation = 11.4 hours
      + Group B – 92% had normal intraoperative hemostasis
Idarucizumab (Praxbind®)

- **Clinical Trial**
  - **Safety**
    - 18 deaths – 5 due to fatal bleeds
    - Thrombotic events in 5 patients – DVT, PE, left atrial thrombus, NSTEMI, ischemic stroke between 2-26 days after reversal
      + Patients were not receiving antithrombotic therapy
    - Serious adverse events in 21 patients – death (n=18), thrombotic events (n=5), GI hemorrhage (n=2), post-op wound infection, delirium, right ventricular failure, pulmonary edema (each in 1 patient)

- **Other reversal agents nearing approval**
  - Aripazine – universal anticoag reversal agent in Phase II trials
Idarucizumab (Praxbind®)

Has idarucizumab been used at your hospital?

A. Yes, successfully reversed bleeds due to dabigatran at our institution
B. Yes, but it was not successful when used
C. No, but we have it on formulary
D. No, and it is not on formulary
Cangrelor (Kengreal®)

- **First IV direct-acting P2Y<sub>12</sub> platelet inhibitor**
  - **Indication:** for adult patients undergoing percutaneous coronary intervention
    - To prevent myocardial infarction, repeat vascularization and stent thrombosis
    - For patients who have not been receiving a P2Y<sub>12</sub> inhibitor
    - For patients not receiving a glycoprotein IIb/IIIa inhibitor
  - **Dosing:**
    - 30 mcg/kg IV bolus prior to PCI, followed by:
    - 4 mcg/kg/min IV infusion for at least 2 hours or the length of the procedure (whichever is longer)
    - After infusion, an oral P2Y<sub>12</sub> inhibitor should be administered
      - Strategies for starting PO agent (*Coron Arter Dis* 2016;27(1):65-69)
        - Clopidogrel – begin after cangrelor infusion is stopped
        - Prasugrel – begin prior to d/c of cangrelor infusion, up to 30 minutes before end of infusion
        - Ticagrelor – can be admin during cangrelor infusion (no interaction)
Cangrelor (Kengreal®)

PK/PD

- Platelet inhibition

- Distribution: VD = 3.9 L; 97-98% bound to plasma proteins
- Metabolism and elimination: dephosphorylated to an inactive metabolite in circulation; t½ = 3-6 minutes
- PK are not affected by age, renal or hepatic function

Cost - $749/50 mg vial
Cangrelor (Kengreal®)

Clinical Trials

  - Efficacy outcomes (mITT, N=24,910)
    + Primary: All-cause death, MI, ischemia-driven revascularization, or stent thrombosis at 48 hr
      › 3.8% cangrelor vs 4.7% control (OR 0.81, p=0.0007)
    + Secondary:
      › Stent thrombosis at 48 hr: 0.5% cangrelor vs 0.8% control (OR 0.59, p=0.0008)
      › Triple composite: all-cause death, MI, ischemia-driven revascularization at 48 hr: 3.6% cangrelor vs 4.4% control (OR 0.81, p=0.014)
  - Safety outcomes (N=25,107)
    + Primary: severe bleeding at 48 hr after PCI (GUSTO criteria): no signif difference between cangrelor vs control
NEW ANTI-INFECTIVES

- **Intravenous:** Ceftazidime/Avibactam
- **Intravenous and Oral:** Isovuconazonium sulfate
- **Oral:** Daclatasvir dihydrochloride

**Complete HIV Regimen in Oral Tablet:** Elvitegravir, cobicistat, emtricitabine, tenofovir alafenamide
Ceftazidime/Avibactam (Avycaz®)

- **3rd generation cephalosporin + beta-lactamase inhibitor**
  - Given FDA priority review as a QIDP under GAIN Act
  - Avibactam = novel beta-lactamase inhibitor
  - Active against multi-drug resistant gram-negative bacteria
    - Class A & C beta-lactamases, including extended-spectrum beta-lactamases, AmpC and KPC
    - Ceftaz and carbapenem-resistant Enterobacteriaceae and *P. aeruginosa*
  - Dose: 2.5 gm (ceftazidime 2 gm + avibactam 0.5 gm) IV q8h infused over 2 hours
    - Reduce dose with CrCl < 50 mL/min - 83% renal elimination of ceftazidime; 97% of avibactam dose is excreted unchanged in urine in 12 hours
    - t ½ is 2.7 hours for each component
Ceftazidime/Avibactam (Avycaz®)

3rd generation cephalosporin + beta-lactamase inhibitor

- Indications
  - Complicated intra-abdominal infections (with metronidazole)
    - *E.coli, K.pneumoniae, P.mirabilis, P.stuartii, E.cloacae, K.oxytoca, P.aeruginosa*
    - 5-14 days treatment duration
    - RECLAIM-1 and RECLAIM-2 – non-inferiority vs meropenem 1 gm IV q8h (*Clin Infect Dis 2016;Mar 8*)
  - Complicated urinary tract infections, including pyelonephritis
    - *E.coli, K.pneumoniae, C.koseri, E.aerogenes, E.cloacae, C.freundii, Proteus spp., P.aeruginosa*
    - 7-14 days treatment duration
    - RECAPTURE 1 and 2 – non-inferiority vs doripenem 500 mg IV q8h (not yet published)
Ceftazidime/Avibactam (Avycaz®)

**Safety**
- ADE: well-tolerated; GI adverse effects slightly higher than with comparator antibiotics in trials
- Labeling confusion
  - Initially 2 grams ceftazidime + 0.5 grams avibactam, with dose recommendation based on sum of 2.5 grams
  - Now labeled 2.5 grams (equivalent to ceftazidime 2 grams and avibactam 0.5 gram)

**Cost**
- $285 per 2.5 gm vial
- $8550 for treatment course of 2.5 mg IV q8h x 10 days
Isovuconazonium sulfate (Cresemba®)

**Triazole antifungal agent**

- Prodrug of isavuconazole – inhibits a key enzyme (Erg11p) that synthesizes ergosterol (the predominant sterol in membranes of fungi, e.g. *Aspergillus*, *Candida* and Mucorales)

**Dosing:**
- Loading dose: 372 mg (equiv. to 200 mg isavuconazole) q8h x 6 doses
  + 2 oral capsules per dose
  + 1 vial per dose administered by IV infusion over 1 hour, with in-line filter
- Maintenance dose: 372 mg q24h as 2 PO capsules or IV infusion
  + Begin @ 12-24 hours after last loading dose
Isovuconazonium sulfate (Cresemba®)

**Triazole antifungal agent**

- **Indications**
  - Invasive aspergillosis
    - SECURE Trial (NCT00412893)
    - Isovuconazole vs voriconazole treatment continued for at least 7 days after resolution of symptoms (max 84 days)
    - Noninferiority demonstrated for all-cause mortality at day 42 (18.6% for isovuconazole; 20.2% for voriconazole)
  - Invasive mucormycosis
    - VITAL Trial (NCT00634049) – 37 patients with proven or probable Mucorales
    - All-cause mortality: 37.8% @ day 42 and 43.2% @ day 84
    - Response at end of therapy: 14.3% (complete response) and 17.1% (partial response)
  - Phase III (ACTIVE) trial may validate indication for treatment of candidemia and invasive candidiasis
Isovuconazonium sulfate (Cresemba®)

PK/PD
- > 99% bound to serum proteins
- Very large Vd – approx. 450L
- Elimination via hepatic metabolism; no dose adjustments with mild/moderate hepatic impairment or renal impairment
- t ½ is 80-130 hours

Safety
- ADEs were less with isovuconazole than comparator drugs in trials
- Drug interactions – contraindicated with strong CYP3A4 inhibitors (rifampin, carbamazepine, St John’s wort, long-acting barbiturates)
- Rapid approval, therefore, post-marketing surveillance for ADEs

Cost
- Loading dose therapy: $1428 (IV) or $840 (PO)
- Maintenance therapy: $238/day (IV) or $140/day (PO)
Daclatasvir dihydrochloride (Daklinza®)

- **Hepatitis C virus NS5A inhibitor**
  - Indication: first-line treatment of chronic hepatitis C virus genotype 3 infection
    - Use in combination with sofosbuvir 400 mg PO once daily
  - Dosing:
    - 60 mg PO once daily for 12 weeks
    - Adjust dose with CYP3A inhibitors/inducers:
      + Strong CYP3A inhibitors – 30 mg once daily
      + Moderate CYP3A inducers – 90 mg once daily
  - Clinical Trials
      + Open-label, two-cohort trial in 152 adult patients with chronic Hep C gen 3 (treatment naïve or experienced with HCV-RNA levels >10,000 IU/mL)
      + Overall SVR12 of 89% ; HCV-RNA undetectable at end of treatment in ≥ 99% of patients
Daclatasvir dihydrochloride (Daklinza®)

Safety

- ADEs > 10%: headache (30%); fatigue (29%); nausea (18%); diarrhea (13%)
- Bradycardia – avoid use of amiodarone with daclatasvir/sofosbuvir

Place in Therapy

- Other oral Hepatitis C direct-acting antivirals and their Hep C indications:
  - ledipasvir/sofosbuvir (G1;12 weeks)
  - ombitasvir/paritaprevir/ritonavir/dasabuvir (G1;12 or 24 weeks)
  - ombitasvir/paritaprevir/ritonavir (G4;12 weeks)
  - Simeprevir (G1 or G4 in combination; 12 or 24 weeks)
  - sofosbuvir (G1, G2, G3, or G4 in combination; 12, 24 or 48 weeks)

Cost

- $750/60 mg or 30 mg tablet
- Total cost of therapy x 12 weeks= $147,000
  - Daclatasvir 60 mg per day x 12 weeks = $63,000
  - Sofosbuvir 400 mg per day ($1000/day) x 12 weeks = $84,000
New Antimicrobial Agents

Which have you added to formulary in 2015?

A. Only ceftaz/avibactam
B. Both ceftaz/avibactam and isovuconazonium
C. All 3 – ceftaz/avibactam, isovuconazonium and daclatasvir
D. None of the above
E. Other combination not shown above
### NEW CARDIOVASCULAR MEDICATIONS

<table>
<thead>
<tr>
<th>Indication</th>
<th>New Medication</th>
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<tbody>
<tr>
<td>Familial Hypercholesterolemia</td>
<td>Alirocumab</td>
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<tr>
<td></td>
<td>Evolocumab</td>
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<tr>
<td>Chronic Heart Failure</td>
<td>Ivabradine hydrochloride</td>
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<td></td>
<td>Sacubitril/valsartan</td>
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Alirocumab (Praluent®) and Evolocumab (Repatha®)

- **PCSK9 inhibitors**
  
  - **Indications**
    - Alirocumab – heterozygous familial hypercholesterolemia (HeFH)
      - Adjunct to diet and maximally tolerated statin therapy
      - Affect on cardiovascular morbidity and mortality is unknown
    - Evolocumab
      - HeFH or atherosclerotic CV disease, after max tolerated statin therapy
      - Homozygous familial hypercholesterolemia (HoFH), as adjunct to other LDL-lowering therapies
  
  - **Dose**
    - Alirocumab – 75 mg SC every two weeks; adjust dose if LDL-C response is inadequate; max dose 150 mg SC every two weeks
    - Evolocumab
      - HeFH: 140 mg SC every two weeks or 420 mg once monthly
      - HoFH: 420 mg SC once monthly
Alirocumab (Praluent®) and Evolocumab (Repatha®)

- PCSK9 inhibitors – Mechanism of Action

![Diagram showing the mechanism of action of PCSK9 inhibitors](image)

- Binding of PCSK9 to LDLR promotes lysosomal degradation of LDLR
- Degradation of LDLR
- Lysosome
- LDLR recycling
- LDL-C uptake
- Uptake of LDL-C by the cell
- Statin action
- Upregulation of plasma PCSK9 level
Clinical Trials

- Alirocumab – 5 clinical trials demonstrating reduction in the surrogate endpoint, LDL-C
  - 3 trials evaluated use in HeFH; 2 trials in non-FH patients with atherosclerotic CV disease
  - ODYSSEY LONG TERM trial (N=2341) in HeFH – mean change in LDL-C at week 24 -61.9% vs placebo
    - *NEJM 2015:372:1489-1499*
  - ADEs: injection site reactions, diarrhea, fatigue, headache
  - Morbidity and mortality data, and long-term safety data, is lacking

Alirocumab (Praluent®) and Evolocumab (Repatha®)
Alirocumab (Praluent®) and Evolocumab (Repatha®)

Clinical Trials

- Evolocumab – 4 clinical trials: 2 with primary hypercholesterolemia and atherosclerotic CVD, 1 with HeFH and 1 with HoFH patients
- Results of OSLER-1 AND OSLER-2 trials (N=4465) in *N Engl J Med* 2015;372:1500-1509
## Alirocumab (Praluent®) and Evolocumab (Repatha®)

<table>
<thead>
<tr>
<th>PK/PD</th>
<th>Alirocumab</th>
<th>Evolocumab</th>
</tr>
</thead>
<tbody>
<tr>
<td>Time to max serum conc</td>
<td>3-7 days</td>
<td>3-4 days</td>
</tr>
<tr>
<td>Time to max suppression of PCSK9</td>
<td>4-8 hours</td>
<td>4 hours</td>
</tr>
<tr>
<td>Distribution</td>
<td>0.04-0.05 L/kg</td>
<td>3.3 L</td>
</tr>
<tr>
<td>Elimination</td>
<td>Via saturable binding to target PCSK9 and a non-saturable proteolytic pathway (No changes needed for renal or hepatic impairment)</td>
<td></td>
</tr>
<tr>
<td>Half-life</td>
<td>17-20 days</td>
<td>11-17 days</td>
</tr>
</tbody>
</table>

### Available as

- **Alirocumab**: 75 mg pen or syringe; 150 mg pen or syringe ($560 each)
- **Evolocumab**: 140 mg pen or syringe ($542 each)
PCSK9 Inhibitors – Alirocumab and Evolocumab

Which of the following is true?

A. These new oral medications are first line therapy for hypercholesterolemia
B. The long-term mortality and safety benefits of PCSK9 inhibitors have yet to be proven
C. The adverse effects of these meds will significantly limit their use
D. These SC medications significantly reduce morbidity and mortality with hypercholesterolemia
Ivabradine hydrochloride (Corlanor®)

Sinoatrial node blocking agent

- Indication: chronic heart failure with reduced ejection fraction (≤35%) on max tolerated beta-blockers
  - For patients in sinus rhythm with heart rate > 70 beats per minute
  - NYHA class II-IV
  - Reduces heart rate (target range = 50-60 bpm) but no effect on contractility, conductivity or blood pressure
  - Reduces the risk of hospitalization
Ivabradine hydrochloride (Corlanor®)
Ivabradine hydrochloride (Corlanor®)

- **Sinoatrial node blocking agent**
  - Dose: 5 mg PO twice daily
    - Adjust dose to 2.5 mg twice daily if sensitive to bradycardia
    - Adjust dose after 2 weeks, based on heart rate
    - Max dose is 7.5 mg twice daily
  - **PK/PD**
    - Take with food to increase bioavailability by 20-40%
    - 70% protein binding; Vd approx 100L at steady state
    - Hepatic metabolism by CYP3A4;
    - t ½ = 6 hours
  - **Drug interactions**
    - Caution with negative chronotropic agents
    - Caution with CYP3A4 inhibitors and inducers (avoid with strong inhibitors)
Ivabradine hydrochloride (Corlanor®)

Clinical Studies

- **SHI_FT** trial - *Lancet 2010;376:875-885*
  - Iva vs Plc for CHF with sxs, LVEF <35%, heart rate ≥70 bpm, hospitalized in past year, stable background meds including beta blocker (N=6505)
  - Iva signif reduced:
    + CV death or hosp adm for worsening CHF (24% vs 29%) (median follow up of 22 months)(P<0.0001)
    + Death from heart failure (3% vs 5%)(P=0.014)

- **BEAUTI_FUL** trial - *Lancet 2008;372:807-816*
  - Iva vs Plc for CAD and LVEF <40% (N=10,917); 87% on beta blockers
  - Iva did not reduce 1° composite endpoint: CV death or hosp adm for MI or worsening heart failure; did not reduce hosp adm for heart failure (median follow up of 19 months)
  - Iva *did reduce* hosp adm for MI, unstable angina in subgroup with heart rate of ≥70 bpm

- **SIGNI_F_Y** trial - *NEJM 2014;371:1091-1099*
  - Iva vs Plc for stable CAD without CHF, and heart rate of ≥70 bpm (median follow up of 27.8 months)
  - No improvement in patient outcomes
Ivabradine hydrochloride (Corlanor®)

- **Adverse effects:**
  - Visual disturbances, headache, dizziness, bradycardia, atrial fibrillation, AV block

- **Warnings:**
  - Monitor for bradycardia and atrial fibrillation
    - Avoid use in patients with 2nd degree AV block
    - Contraindicated in patients with demand pacemakers set to rates $> 60$ beats per minute

- **Cost:**
  - Available as 5 mg and 7.5 mg tablets - $6.25$ each
  - $375$ per month (both strengths)
Sacubitril/valsartan (Entresto®)

- **Dual inhibitor of neprilysin (sacubitril) and angiotensin II receptors (valsartan)**
  - Indication: Chronic heart failure (NYHA Class II-IV) and reduced EF
    - To reduce risk of hospitalization for heart failure
    - To reduce risk of CV death
  - Dosing:
    - Available as 24/26 mg, 49/51 mg and 97/103 mg tablets
    - Starting dose: 49/51 mg twice daily
      - Reduce to 24/26 mg twice daily if CrCl < 30 mL/min or mod hepatic impairment or if new to ACE or ARB therapy
    - Double the dose every 2-4 weeks to obtain target dose of 97/103 mg twice daily
Sacubitril/valsartan (Entresto®)

LCZ696: A First-in-Class Angiotensin Receptor Neprilysin Inhibitor

- Natriuretic Peptide System
  - pro BNP
  - BNP
  - NT-pro BNP
- Heart Failure
  - Angiotensinogen (liver secretion)
  - Angiotensin I
  - Angiotensin II
  - AT₁ receptor

- Inactive fragments
- Neprilysin

- Vasodilation
  - ↓ blood pressure
  - ↓ sympathetic tone
  - ↓ aldosterone levels
  - ↓ fibrosis
  - ↓ hypertrophy
  - ↓ natriuresis/diuresis

- AHU377
- LBQ657

- Vasoconstriction
  - ↑ blood pressure
  - ↑ sympathetic tone
  - ↑ aldosterone
  - ↑ fibrosis
  - ↑ hypertrophy

Heart failure

The heart.org
Medscape Education
Sacubitril/valsartan (Entresto®)

**Clinical Trials**

- **PARADIGM-HF Trial** - *NEJM 2014;371:993-1004*
  - Study drug (200 mg twice daily) vs enalapril (10 mg twice daily) in DB/R/MC international clinical trial
  - Patients with class II, III, IV heart failure, EF \(\leq\) 40% on standard regimens
  - Primary Outcomes:
    - Composite of death from CV causes
    - First hospitalization for heart failure
  - Secondary Outcomes:
    - Time to death from any cause
    - KCCQ change from baseline to 8 months
    - Time to new onset of atrial fibrillation
    - Time to first occurrence of decline in renal function
  - Expected 8000 patients for 34 months to detect 15% decrease in risk of death with study drug

**TRIAL STOPPED EARLY**
Sacubitril/valsartan (Entresto®)

Clinical Trials

- PARADIGM-HF Trial - *NEJM 2014;371:993-1004*

<table>
<thead>
<tr>
<th>Outcome</th>
<th>LCZ696 (N=4187)</th>
<th>Enalapril (N=4212)</th>
<th>Hazard Ratio or Difference (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary composite outcome — no. (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Death from cardiovascular causes or first hospitalization</td>
<td>914 (21.8)</td>
<td>1117 (26.5)</td>
<td>0.80 (0.73–0.87)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>hospitalization for worsening heart failure</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Death from cardiovascular causes</td>
<td>558 (13.3)</td>
<td>693 (16.5)</td>
<td>0.80 (0.71–0.89)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>First hospitalization for worsening heart failure</td>
<td>537 (12.8)</td>
<td>658 (15.6)</td>
<td>0.79 (0.71–0.89)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Secondary outcomes — no. (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Death from any cause</td>
<td>711 (17.0)</td>
<td>835 (19.8)</td>
<td>0.84 (0.76–0.93)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Change in KCCQ clinical summary score at 8 mo†</td>
<td>-2.99±0.36</td>
<td>-4.63±0.36</td>
<td>1.64 (0.63–2.65)</td>
<td>0.001</td>
</tr>
<tr>
<td>New-onset atrial fibrillation‡</td>
<td>84 (3.1)</td>
<td>83 (3.1)</td>
<td>0.97 (0.72–1.31)</td>
<td>0.83</td>
</tr>
<tr>
<td>Decline in renal function‡</td>
<td>94 (2.2)</td>
<td>108 (2.6)</td>
<td>0.86 (0.65–1.13)</td>
<td>0.28</td>
</tr>
</tbody>
</table>
Sacubitril/valsartan (Entresto®)

Safety

<table>
<thead>
<tr>
<th>Event</th>
<th>LCZ696 (N = 4187)</th>
<th>Enalapril (N = 4212)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypotension</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Symptomatic</td>
<td>588 (14.0)</td>
<td>388 (9.2)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Symptomatic with systolic blood pressure &lt;90 mm Hg</td>
<td>112 (2.7)</td>
<td>59 (1.4)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Elevated serum creatinine</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥2.5 mg/dl</td>
<td>139 (3.3)</td>
<td>188 (4.5)</td>
<td>0.007</td>
</tr>
<tr>
<td>≥3.0 mg/dl</td>
<td>63 (1.5)</td>
<td>83 (2.0)</td>
<td>0.10</td>
</tr>
<tr>
<td>Elevated serum potassium</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt;5.5 mmol/liter</td>
<td>674 (16.1)</td>
<td>727 (17.3)</td>
<td>0.15</td>
</tr>
<tr>
<td>&gt;6.0 mmol/liter</td>
<td>181 (4.3)</td>
<td>236 (5.6)</td>
<td>0.007</td>
</tr>
<tr>
<td>Cough</td>
<td>474 (11.3)</td>
<td>601 (14.3)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Angioedema†</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No treatment or use of antihistamines only</td>
<td>10 (0.2)</td>
<td>5 (0.1)</td>
<td>0.19</td>
</tr>
<tr>
<td>Use of catecholamines or glucocorticoids without hospitalization</td>
<td>6 (0.1)</td>
<td>4 (0.1)</td>
<td>0.52</td>
</tr>
<tr>
<td>Hospitalization without airway compromise</td>
<td>3 (0.1)</td>
<td>1 (&lt;0.1)</td>
<td>0.31</td>
</tr>
<tr>
<td>Airway compromise</td>
<td>0</td>
<td>0</td>
<td>—</td>
</tr>
</tbody>
</table>

Cost

- $6.25/tab (all strengths); $375 per month
New Agents for Heart Failure

Which of the following do you think is true?

A. Sacubitril/valsartan is a breakthrough drug that will be considered first-line in HF
B. Ivabradine is a breakthrough drug that will be considered first-line in HF
C. More evidence is needed to prove the value of these two new medications
D. We need to wait 6 months or longer to see if any adverse effects arise that weren’t captured in the trials
E. Other
# NEW AGENTS FOR ONCOLOGY

<table>
<thead>
<tr>
<th>New Medication</th>
<th>Type of Cancer</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alectinib</td>
<td>Non-small Cell Lung Cancer</td>
</tr>
<tr>
<td>Cobimetinib</td>
<td>Melanoma</td>
</tr>
<tr>
<td>Daratumumab</td>
<td>Multiple Myeloma</td>
</tr>
<tr>
<td>Dinutuxumab</td>
<td>Neuroblastoma</td>
</tr>
<tr>
<td>Elotuzumab</td>
<td>Multiple Myeloma</td>
</tr>
<tr>
<td>Ixazomib</td>
<td>Multiple Myeloma</td>
</tr>
<tr>
<td>Lenvatinib</td>
<td>Thyroid Cancer</td>
</tr>
<tr>
<td>Necitumumab</td>
<td>Non-small Cell Lung Cancer</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>New Medication</th>
<th>Type of Cancer</th>
</tr>
</thead>
<tbody>
<tr>
<td>Osimertinib</td>
<td>Non-small Cell Lung Cancer</td>
</tr>
<tr>
<td>Palbociclib</td>
<td>Breast Cancer</td>
</tr>
<tr>
<td>Panobinastat</td>
<td>Multiple Myeloma</td>
</tr>
<tr>
<td>Sonidegib phosphate</td>
<td>Basal Cell Carcinoma</td>
</tr>
<tr>
<td>Trabectedin</td>
<td>Liposarcoma or Leiomyosarcoma</td>
</tr>
<tr>
<td>Trifluridine/Tipiracil</td>
<td>Colorectal Cancer</td>
</tr>
</tbody>
</table>
Necitumumab (Portrazza®)

- Epidermal growth factor receptor (EGFR) antagonist
  - Indication: Non-small cell lung cancer (NSCLC)
    - Second generation EGFR antag – binds with very high affinity
    - Administer in combination with gemcitabine and cisplatin
    - NOT for non-squamous NSCLC
  - Dosing:
    - 800 mg IV infusion on days 1 and 8 of each 3-week cycle
      + Admin over 60 minutes
  - Cost:
    - $4000 per 50 mL vial of 800 mg
    - $8000 per cycle is above the “willingness-to-pay threshold” estimated as $1300 per cycle for necitumumab
      + Am Health & Drug Benefits 2015; 8:11.
Necitumumab (Portrazza®)

- Epidermal growth factor receptor (EGFR) antagonist

- Clinical Trials
    - Stage IV squamous NSCLC
    - Six 3-week cycles of Necitumumab(D1&D8)/Gemcitabine(D1 &D8)/Cisplatin(D1) vs Gemcitabine(D1&D8)/Cisplatin(D1)
  - Results:
    - median duration of follow-up (mo) = 25.2 (N/G/C) and 24.8 (G/C)
    - Overall survival (mo) = 11.5 (N/G/C) vs 9.9 (G/C) (p=0.01)
    - Serious ADEs (Grade 3-4 rash; hypomagnesemia, etc.) = 48% (N/G/C) vs 38% (G/C)
Necitumumab (Portrazza®)

- Epidermal growth factor receptor (EGFR) antagonist

**Clinical Trials**

  - Stage IV non-squamous NSCLC
  - 6 cycles of Necitumumab(D1&D8)/Cisplatin(D1)/ Pemetrexed (D1) vs Cisplatin(D1)/Pemetrexed(D1)
  - Results: no difference in overall survival; higher incidence of ADEs
  - Not recommended to add N to C/P

**Safety:**

- Grade 1-3 ADE in trials: hypomagnesemia, skin reactions including rash, conjunctivitis, venous thromboembolic events
- Addition of necitumumab was well tolerated overall
Palbociclib (Ibrance®)

- **Kinase inhibitor**
- **Indication:** Advanced breast cancer
  - Administer in combination with letrozole
  - Only for ER-positive, HER2-negative breast cancer
  - First-line endocrine-based therapy for metastatic disease
- **Dosing:**
  - 125 mg PO once daily with food
    + 21 day cycle with 7 days off
- **Cost:**
  - $469 each - 75 mg capsule (orange); 100 mg capsule (peach); 125 mg capsule (caramel)
  - $9849 per 28-day cycle
Palbociclib (Ibrance®)

- **Kinase inhibitor**
  - Clinical Trials
      + ER+, HER2- advanced breast cancer – treatment naive
      + Palbociclib 125mg daily/Letrozole 2.5mg daily vs Letrozole 2.5mg daily; 3 weeks on, 1 week off therapy
      + Results:

![Graph](image)
Palbociclib (Ibrance®)

**Kinase inhibitor**

- **Clinical Trials**
    - ER+, HER2- advanced breast cancer with relapse or progression with prior endocrine therapy
    - Palbociclib/Fulvestrant vs Placebo/Fluvestrant in 2:1 ratio plus goserelin in pre/peri-menopausal women
    - Results:
      - Median duration of follow-up = 5.6 months (interim analysis)
      - Primary endpoint met (P<0.001)
        - Median Progression Free Survival (mo): 9.2 (Palb/F) vs 3.8 (P/F)
      - Adverse Events – neutropenia (79%); leukopenia (45%); fatigue (38%); anemia (26%); thrombocytopenia (19%); alopecia (15%), stomatitis (12%)
New Oncology Agents

Which of the following is a false statement?

A. Necitumumab is indicated for squamous and non-squamous NSCLC
B. Palbociclib is the first in a new line of kinase inhibitors
C. Palbociclib and Necitumumab are now considered first-line oncology agents
D. Palbociclib’s approval is contingent on further positive study results
NEW MEDICATIONS FOR ELECTROLYTE IMBALANCE

ASFOTASE ALFA for Hypophosphatemia

PATIROMER for Chronic Hyperkalemia

PARATHYROID HORMONE for Hypocalcemia with Hypoparathyroidism
Patiromer sorbitex calcium (Veltassa®)

- **Potassium binder for chronic hyperkalemia**
  - Active moiety is patiromer – a non-absorbed potassium-binding polymer
  - Binds potassium in GI lumen
  - Delayed onset – not for emergency treatment of hyperkalemia

- **Dosing:**
  - 8.4 grams orally once daily with food
    - Increase dose at weekly intervals if necessary
    - Powder is mixed with water for administration
    - Do not add to heated foods or liquids
  - Store in refrigerator or up to 3 months at room temperature

- **Safety:**
  - **Boxed Warning:** can bind, decrease absorption and effectiveness of oral medications; separate administration by at least 6 hours.
  - **ADEs:** constipation, hypomagnesemia, diarrhea, nausea, abdominal discomfort, flatulence.
Patiromer sorbitex calcium (Veltassa®)

Clinical Trials

- OPAL-HK trial - studied in CKD patients with hyperkalemia, on stable doses of one or more RAA system inhibitor (ACE-inhibitor, ARB or aldosterone antagonist) NEJM 2015;372:211-221.
  - **Part 1** (single-group, single-blind): 243 patients received 4 wks of Tx
    - Results:
      - Mean 0.65 mEq/L reduction with initial K+ level 5.1-5.5 mEq/L (Dose: 4.2 g BID)
      - Mean 1.23 mEq/L reduction with initial K+ level 5.5 to < 6.5 mEq/L (Dose 8.4 g BID)
  - **Part 2** (PC/single-blind/R): 107 patients with initial serum K+ 5.5 to < 6.5 mEq/L and achieved K+ endpoint (3.8 - < 5.1 at the end of 4 weeks) were randomized to continue patiromer or change to placebo
    - Placebo – serum potassium rose by 0.72 mEq/L by week 4; no change at week 4 if still on patiromer
Patiromer sorbitex calcium (Veltassa®)

Clinical Trials

• AMETHYST-DN Trial (JAMA 2015;314(2):151-161)
  - 304 patients in 1 year, open-label trial (CKD + type 2 DM on RAAS inhibitor therapy) – treatment effect was maintained
NEW REVERSAL AGENT

SUGAMMADEX
Sugammadex (Bridion®)

- **Modified gamma cyclodextrin**
  - 7 year history of FDA review before approval
    - 2008: FDA Advisory committee unanimously recommends approval; FDA denies approval – requests hypersensitivity study
    - 2013: FDA calls for review of a clinical site in the trials
    - 2015: December approval
  - Indication: selectively binds with and reverses neuromuscular blocking agents (NMBA) rocuronium and vecuronium
**Sugammadex (Bridion®)**

- **Modified gamma cyclodextrin**
  - **Dosing:** IV bolus injection – 2 mg/kg, 4 mg/kg, 16 mg/kg (for 3 min reversal of single dose of rocuronium)
    - Median recovery time *(Health Technology Assessment 2010;14(39). DOI:10.3310/hta14390)*
      - Moderate blockade - 1.3-1.7 min (R + S) vs. 21-86 min (R + Placebo) or 17.6 min (R + Neostigmine)
      - Profound blockade – 2.7 min (R + S) vs. 30 to > 90 min (R + Placebo) or 49 min (R + N)
    - Similar results with vecuronium
  - **Evaluations**
    - UK found sugammadex cost-effective for routine reversal of rocuronium-induced moderate blockade if reductions in recovery time are achieved in OR (not recovery room) *(Health Technology Assessment 2010;14(39). DOI:10.3310/hta14390)*
    - Most patients use 1 vial of 200 mg sugammadex (general, ortho, plastic, “other” surg); less antiemetics used in sugammadex patients *(Eur J Anaesthesiol 2014;31:423-429)*
  - **Cost:** $9.50 for 200 mg vial; $17.40 for 500 mg vial
FIRST BIOSIMILAR APPROVAL
FILGRASTIM-SNDZ
Filgrastim-sndz (Zarxio®)

- **Biosimilar - Leukocyte growth factor**
  - First biosimilar approved through the Biologics Price Competition and Innovation Act (BCPIA)
  - Prescribing information same as Neupogen®: dosing, route of administration, dilution, storage, warnings, contraindications, etc.
  - Differs from Neupogen®:
    - Lacks one of the six indications – increased survival with myelosuppressive doses of radiation
      - tbo-filgrastim (Granix®) – *only has one indication*
    - Available packaged in single-dose, prefilled syringes (no vials)
    - Specialty distribution vs wholesaler availability of Neupogen® and Granix®
  - WAC Pricing: 15% lower than Neupogen® (Granix® is 25% lower)
Filgrastim-sndz (Zarxio®)

How has your institution addressed the filgrastim agents?

A. Filgrastim-sndz was added to formulary
B. Tbo-filgrastim was added to formulary
C. Filgrastim-sndz and tbo-filgrastim are on formulary
D. Only filgrastim (Neupogen®) is on formulary
E. Other
What's In Store for 2016?

- Biologics
- Kinase Inhibitors
- Oncology Medications
- Anti-infectives
- Biosimilars

Best selling Biologics
Patent Cliff

<table>
<thead>
<tr>
<th>Company</th>
<th>Product</th>
<th>2011 Sales (billion USD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amgen</td>
<td>Enbrel</td>
<td>7.9</td>
</tr>
<tr>
<td>Novo Nordisk</td>
<td>Novolog</td>
<td>2.4</td>
</tr>
<tr>
<td>Sanofi-Aventis</td>
<td>Lantus</td>
<td>5.4</td>
</tr>
<tr>
<td>Amgen</td>
<td>Neulasta</td>
<td>3.9</td>
</tr>
<tr>
<td>Abbot</td>
<td>Humira</td>
<td>8.2</td>
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<tr>
<td>Genentech</td>
<td>Rituxan</td>
<td>6.8</td>
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<tr>
<td>Centocor</td>
<td>Remicade</td>
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<tr>
<td>Genentech</td>
<td>Avastin</td>
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<tr>
<td>Genentech</td>
<td>Herceptin</td>
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<tr>
<td>Genentech</td>
<td>Lucentis</td>
<td>3.8</td>
</tr>
</tbody>
</table>
Questions?