Objectives

- Identify new molecular entities approved in the last year which may be useful in the clinical care of older adults
- Identify characteristics, such as dosing, pharmacokinetics, side effects, and monitoring which may require special attention in older adults
- Recognize patients who may be candidates for these medications, taking into consideration other patient characteristics
Methods

- The FDA website (www.fda.gov) was reviewed for new molecular entity approvals from January 2015 through December 2015.
- Drugs were included according to the following criteria:
  - They had potential to be prescribed in the elderly population
  - They were expected to have a significant influence on the care of elderly patients

<table>
<thead>
<tr>
<th>Drug: Brand (generic)</th>
<th>Indication</th>
</tr>
</thead>
<tbody>
<tr>
<td>Praxbind (idarucizumab)</td>
<td>Dabigatran reversal agent</td>
</tr>
<tr>
<td>Stiolo Respimat (tiotropium bromide and olodaterol)</td>
<td>Maintenance treatment of COPD</td>
</tr>
<tr>
<td>Utibron Neohaler (indacaterol and glycopyrrolate)</td>
<td>Maintenance treatment of COPD</td>
</tr>
<tr>
<td>Entresto (sacubitril and valsartan)</td>
<td>Treatment of HFrEF</td>
</tr>
<tr>
<td>Corlanor (ivabradine)</td>
<td>Treatment of HFrEF</td>
</tr>
<tr>
<td>Praluent (alirocumab)</td>
<td>Treatment of heterozygous familial hypercholesterolemia</td>
</tr>
<tr>
<td>Repatha (evolocumab)</td>
<td>Treatment of high cholesterol</td>
</tr>
<tr>
<td>Veltassa (patiromer)</td>
<td>Treatment of hyperkalemia</td>
</tr>
</tbody>
</table>
Praxbind™ (idarucizumab)

- FDA approved (Oct 2015) for dabigatran reversal
  - Approved under accelerated approval (123 pts), with continued approval possibly contingent upon further data
    - For emergency surgery or urgent procedures
    - In patients with life-threatening or uncontrolled bleeding
- MOA: humanized monoclonal antibody fragment (Fab)
  - Binds to dabigatran and its acylglucuronide metabolites with higher affinity than the binding affinity of dabigatran to thrombin, neutralizing their anticoagulant effect

Praxbind™ (idarucizumab)

- Recommended dose: 5g IV
  - Vials include 2.5g/50mL: can give as 2 consecutive infusions or 1 bolus injection
  - Limited data support administration of additional 5g
  - Can be given with standard supportive measures
- Restart dabigatran as soon as medically appropriate
  - Can be initiated 24 hours after administration of Praxbind
CI and Warnings/Precautions

- CI: none
- Warnings/Precautions
  - Thromboembolic risk
  - Re-elevation of coagulation parameters (e.g. aPTT or ECT) in some patients between 12-24 hours after administration of 5g dose
    - If reappearance of clinically relevant bleeding or need for second emergency procedure + elevated coags = consider another 5g dose
  - Hypersensitivity reaction
  - Serious ADEs in patients with hereditary fructose intolerance due to sorbitol excipient

Praxbind™ (idarucizumab)

- Side effects: headache, hypersensitivity, thromboembolic events
- Geriatric use: mainly studied in older adults
  - 90% pts in the case series trial were ≥ 65 yrs and 60% were ≥ 75 yrs
  - No overall differences in safety or effectiveness, but greater sensitivity for some older individuals cannot be ruled out
- Cost: AWP (package 2 vials): $4200
Evidence: Interim analysis of RE-VERSE AD

- 123 patients with bleeding (n=66)/need for procedure (n=57)
  - Single cohort case series multicenter trial—study is ongoing
  - Only 90 included in the Pollack 8/2015 NEJM article

- Intervention:
  - Praxbind 5g IV
  - Patients followed until death or 1 mo after treatment
  - PK/PD assessments after infusions
  - 1° outcome: max % reversal of anticoagulation (dilute thrombin time or ECT)
  - 2° outcome: clinical outcomes (bleeding, hemodynamics, ADEs)

Change of ECT from baseline after IV Praxbind in 90 subjects
Change in aPTT from baseline after IV Praxbind in 90 subjects

Clinical Outcomes from RE-VERSE AD

- Median time to cessation of bleeding: 11.4 hours
- Normal hemostasis reported in 92% undergoing surgery
- 18 deaths reported in each group (9 in each group)
  - 10 due to vascular causes, including 5 fatal bleeding events
  - Death within 96 hrs appeared to be related to the index event (e.g. septic shock, ICH, cardiac arrest, etc)
- 5 thrombotic events (PE, DVT, atrial thrombus, NSTEMI) after not being restarted on antithrombotic tx
  - 2d, 7d, 9d, 13d, 26d
Where does Praxbind™ fit?

- Expensive, but effective in many patients at reversing dabigatran in setting of uncontrolled bleeding or for emergency surgery or urgent procedures
- Easier than dialysis
- May increase clinician comfort level with using dabigatran
- Not effective at reversing other NOACs
  - Andexanet alfa is being studied to reverse other agents

New Combination LAMA/LABAs for COPD

FDA approval for the long term, maintenance treatment of COPD: Stiolto May 2015; Utibron Oct 2015

<table>
<thead>
<tr>
<th>Stiolto Respimat™</th>
<th>Strength: 2.5 mcg/2.5 mcg per actuation</th>
</tr>
</thead>
<tbody>
<tr>
<td>(tiotropium bromide &amp; olodaterol)</td>
<td>Dose: Inhale 2 puffs once daily</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Utibron Neohaler™</th>
<th>Strength: 27.5 mcg/15.6 mcg per capsule</th>
</tr>
</thead>
<tbody>
<tr>
<td>(indacaterol &amp; glycopyrrolate)</td>
<td>Dose: Inhale the powder from 1 cap BID</td>
</tr>
</tbody>
</table>
Combination Bronchodilator Adverse Effects

- **Most common side effects:**
  - Nasopharyngitis (S-12%; U-4%)
  - Cough (S-4%)
  - Back pain (S-4%; U-2%)
  - Hypertension (U-2%)

- **Geriatric use:** no differences in effectiveness or ADRs or dosing

---

CI, Warnings/Precautions, DDIs (typical)

- **Contraindications/BBW:** not indicated for asthma, LABAs increase risk for asthma-related deaths

- **Warnings/Precautions:** not to treat acute symptoms or acutely deteriorating COPD; do not use with other LABAs; discontinue use with bronchospasm or hypersensitivity; use with caution in patients with CAD, seizures, hyperthyroidism, narrow-angle glaucoma, BPH, DM, CrCl < 60 mL/min; may cause hypokalemia or hyperglycemia

- **DDIs:** use caution if also taking adrenergic drugs, steroids, theophylline, diuretics, MOAIs, TCAs, BB, anticholinergics
Stiolto™ Evidence

- Two 52-wk active controlled trials + 8 additional studies
- Overall elderly: 40% of subjects 65-74 years; 9.3% 75-84 years; 1 subject was ≥ 85 years

<table>
<thead>
<tr>
<th>Population</th>
<th>Intervention</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>-COPD dx</td>
<td>Stiolto (n=1029)</td>
<td>Compared to monotherapy, patients taking Stiolto:</td>
</tr>
<tr>
<td>-73% men</td>
<td>Tiotropium (n=1033)</td>
<td>• Had significant improvements in FEV1</td>
</tr>
<tr>
<td>-71% Caucasian</td>
<td>Olodaterol (n=1038)</td>
<td>• Used less rescue medication</td>
</tr>
<tr>
<td>-Mean age 64 yrs</td>
<td></td>
<td></td>
</tr>
<tr>
<td>-Mostly GOLD 2, 3</td>
<td></td>
<td></td>
</tr>
<tr>
<td>-47% on ICS</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Utibron™ Evidence

Two 12-wk efficacy trials (v. PBO, active) + one 52-wk study
Overall elderly: 45% of subjects ≥ 65 years; 11% ≥ 75 years

<table>
<thead>
<tr>
<th>Population</th>
<th>Intervention</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>-COPD dx</td>
<td>Utibron (n=507)</td>
<td>Compared to monotherapy and placebo, patients taking Utibron:</td>
</tr>
<tr>
<td>-63% men</td>
<td>Indacaterol (n=511)</td>
<td>• Had significant improvements in FEV1</td>
</tr>
<tr>
<td>-91% Caucasian</td>
<td>Glycopyrrolate (n=511)</td>
<td></td>
</tr>
<tr>
<td>-Mean age 63 yrs</td>
<td>Placebo (n=506)</td>
<td></td>
</tr>
<tr>
<td>-46% on ICS</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Insurance Coverage and Alternatives

Insurance coverage for agents:
- Stiolto™: Tricare, Humana (Tier 2/3), PA with CO Medicaid
- Utibron™: not on Tricare, not on Humana, not on CO Medicaid
- Cash: $330 for one month

Alternatives:
- Stiolto: tiotropium (Spriva) + olodaterol (Striverdi)
- Utibron: indacaterol (Arcapta) + different LAMA
- Anoro Ellipta: umeclidinium/vilanterol, 1 DPI once daily

Where do the drugs fit: GOLD Guidelines 2015

<table>
<thead>
<tr>
<th>Patient Group</th>
<th>Recommended 1st Choice</th>
<th>Alternative Choice</th>
<th>Other Possible Treatments</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>SAMA PRN, SABA PRN</td>
<td>LAMA, LABA, Combivent/Duonebs</td>
<td>Theophylline</td>
</tr>
<tr>
<td>B</td>
<td>LAMA, LABA</td>
<td>LAMA/LABA</td>
<td>SABA and/or SAMA, Theophylline</td>
</tr>
<tr>
<td>C</td>
<td>ICS + LABA, LAMA</td>
<td>LAMA/LABA, LAMA + Daliresp, LABA + Daliresp</td>
<td>SABA and/or SAMA, Theophylline</td>
</tr>
<tr>
<td>D</td>
<td>ICS + LABA or LAMA, ICS + LABA/LAMA</td>
<td>ICS + LABA/LAMA, ICS + LABA + Daliresp, LAMA/LABA, LAMA + Daliresp</td>
<td>Carbocysteine, N-acetylcysteine, SABA and/or SAMA, Theophylline</td>
</tr>
</tbody>
</table>

HTTP://WWW.GOLDCOPD.ORG/UPLOADS/USERS/FILES/GOLD_POCKET_2015_FEB18.PDF
Entresto™ (sacubitril and valsartan)

- FDA approved (July 2015) for treatment of class II-IV HFrEF
  - To reduce the risk of cardiovascular death and hospitalization
  - Used in place of other ACE/ARB therapy
- MOA: Angiotensin receptor neprilysin inhibitor (ANRI)
Entresto™ (sacubitril and valsartan)

- **Strengths (sacubitril/valsartan):** 24/26 mg, 49/51 mg, 97/103 mg
- **Initial dose:** 49/51 mg BID
- **Target dose:** 97/103 mg BID
  - Double the dose after 2-4 wks as tolerated
- **Dose reduction in starting dose to 24/26 mg BID:**
  - Patients not currently taking an ACEI or ARB or on low doses
  - Patients with severe renal impairment or moderate hepatic impairment
  - Same target dose: DBL the dose every 2-4 weeks as tolerated

CIs, Warnings/Precautions, and DDIs

- **Contraindications:** history of angioedema from ACEI/ARB, concomitant use with ACEIs or aliskiren
- **Warnings/Precautions:** monitor for angioedema, hypotension, K+, and renal function
- **DDIs:** no CYP issues
  - Use with potassium-sparing diuretics \(\rightarrow\) increased serum potassium
  - Use with NSAIDs \(\rightarrow\) increased risk of renal impairment
  - Use with lithium \(\rightarrow\) increased risk of lithium toxicity
  - ? Atorvastatin
Evidence: PARADIGM-HF

Randomized, double-blind RCT: stopped early at median of 27 mo

<table>
<thead>
<tr>
<th>Population (n=8442)</th>
<th>Intervention</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>-NYHA class II-IV</td>
<td>Entresto 200 mg BID + standard of care</td>
<td>1°: composite of CV death or HF hosp 21.8% vs. 26.5%; HR 0.80, CI 0.73-0.87, p&lt;0.001</td>
</tr>
<tr>
<td>-LVEF ≤ 40%</td>
<td>Entresto 200 mg BID + standard of care</td>
<td>CV death by 20%</td>
</tr>
<tr>
<td>-BNP ≥ 100-150 pg/mL</td>
<td>Enalapril 10 mg BID + standard of care</td>
<td>HF hosp by 21%</td>
</tr>
<tr>
<td>-Taking ACEI/ARB</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ex: SBP &lt;100 mm/Hg</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ex: eGFR &lt;30 mL/min</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ex: K+ &gt; 5.2 mmol/L</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Entresto™ (sacubitril and valsartan)

- Side effects (v enalapril): hypotension (18% v 12%), hyperkalemia (12% v 14%), cough (9% v 13%), dizziness (6% v 5%), renal failure (5% v 5%), angioedema (0.5% v 0.2%, AA 2.4%)

- Cognitive effects--Neprilysin is one of multiple enzymes involved in the clearance of amyloid-β (Aβ) from the brain/CSF

- 2 week study of 194 mg sacubitril/206 mg valsartan once-daily in healthy subjects was associated with an increase in CSF Aβ1-38 compared to placebo; there were no changes in CSF Aβ1-40 or CSF Aβ1-42.
Entresto™ (sacubitril and valsartan)

- Geriatric use: no PK differences observed for patients >65 years or ≥75 years
- Cost: $400 (cash)
- Insurance coverage:
  - Covered: Tricare, Anthem, CO Medicaid
  - Not covered: Humana

Where does Entresto™ fit?

- Effective in those <75 yrs, but with only ≈1600 patients ≥ 75 yrs knowledge of benefits in the very elderly is limited
- Standard of Care
  - BB + ACEI/ARB +/- aldosterone antagonist
  - Unknown if Entresto should replace ACEI/ARB prior to initiating aldosterone antagonist
- No data for those with eGFR <30 mL/min/1.73m²
- Unknown cognitive effects
- Expensive
Corlanor™ (ivabradine)

- FDA approved (April 2015) for treatment of HFrEF
- MOA: selective and specific inhibitor of HCN channels within the SA node → prolonging diastolic depolarization and reducing heart rate
Corlanor™ (ivabradine)

- Approved dosing:
  - 5 mg BID or 2.5 mg BID (conduction defects or bradycardia risks)
  - After 2 weeks, titrate to resting HR 50-60 bpm (max= 7.5 mg BID)
  - Administer with meals
  - CrCl <15 ml/min use with caution

Warnings and Precautions

- **Contraindications**: severe hepatic impairment, acute decompensated HF, BP <90/50 mmHg, resting HR <60 prior to treatment, use with strong CYP3A4 inhibitors

- **Warnings/Precautions**: Atrial fibrillation, bradycardia or conduction disturbances, visual function (phosphenes)
Corlanor™ (ivabradine)

- **Side effects:** bradycardia, hypertension, atrial fibrillation, phosphenes
- **Geriatric use:** no PK differences observed for patients >65 years; Only 11% of patients in studies were ≥75 years
- **Cost:** $450

### Evidence: SHIFT

- **Randomized, double-blind trial**

<table>
<thead>
<tr>
<th>Population (n=6558)</th>
<th>Intervention</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>- NYHA class II-IV</td>
<td>Corlanor 5 mg</td>
<td>1º: composite of first occurrence of hosp. for worsening HF or CV death</td>
</tr>
<tr>
<td>- LVEF ≤ 35%</td>
<td>BID + standard of care</td>
<td>- Corlanor reduced 1º 24.5% vs. 28.7% [CI] 0.75-0.9, p&lt;0.0001</td>
</tr>
<tr>
<td>- Resting HR ≥ 70</td>
<td>Placebo +</td>
<td></td>
</tr>
<tr>
<td>- 2500 ≥ 65 years</td>
<td>standard of care</td>
<td></td>
</tr>
<tr>
<td>- Stable regimen x 4 wks</td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Hospitalized in last yr</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Where does Corlanor™ fit?

- LVEF ≤ 35%
- Patients with HR > 70 bpm who are on maximum tolerated dose of a beta blocker
- CI to beta blockers

Lipid Update

- PCSK9 inhibitors
  - Monoclonal antibodies
  - Increase LDL-C clearance and lowers LDL-C levels in the blood
PCSK9 Inhibitors

<table>
<thead>
<tr>
<th>PCSK9 Inhibitor</th>
<th>Dosage and Details</th>
</tr>
</thead>
</table>
| Repatha™ (evolocumab) | Single use pen dosed 140 mg every 2 weeks or 420 mg monthly  
Half-life: 11-17 days |
| Praluent™ (alirocumab) | Single use pen dosed 75 mg every 2 weeks; may increase to 150 mg  
Half-life: 17-20 days; 12 days with statin |

- Can lower LDL levels up to 70%

Warnings and Precautions

- **Contraindications**: previous hypersensitivity reactions

- **Warnings/Precautions**: Allergic reactions (rash, urticaria) have been reported

### PCSK9 Inhibitor Comparison

**Repatha™**

- Side effects ≥5%: Nasopharyngitis, influenza, URI, back pain, injection site reactions
- No dosing adjustments
- Geriatric use: no differences in response observed
- **Cost**: AWP = $650.77

**Praluent™**

- Side effects ≥5%: Nasopharyngitis, injection site reactions
- No dosing adjustments
- Geriatric use: no differences in response observed
- **Cost**: AWP = $672
Repatha™ Evidence: OLSER-1 and OLSER-2

Population (n=4465) | Intervention | Results
--- | --- | ---
-Varying CV risks
-Mean LDL 120 mg/dL
-Mean age: 57
-1420 ≥ 65 years
-171 ≥ 75 years | 140 mg every 2 weeks OR 420 mg/mo + standard therapy | 1°: AE incidence 69.2% vs. 64.8%
 | Standard therapy only | 2°: LDL reduction 73 mg/dL

Praluent™ Evidence: ODYSSEY LONG TERM

Population (n=2341) | Intervention | Results
--- | --- | ---
-Heterozygous familial hypercholesterolemia (18%) or CHD (68%)
-Mean LDL 123 mg/dL
-Mean age: 59 years
-1158 ≥ 65 years
-241 ≥ 75 years | 150 mg SQ every 2 weeks x 78 weeks | 1°: LDL reduction 61.9% compared to placebo (absolute 70)
 | Placebo | 2°: AEs
Where do these fit in?

- At UCH, patients have to go to the Lipid or Endocrine clinic
- Insurance coverage for agents:
  - Repatha™: United (commercial), CVS Caremark, BCBS, Cigna
  - Praluent™: United (medicare), Humana
  - Both: Aetna, Medicaid, Express Scripts

Veltassa™ (patiromer)

- FDA approved (October 2015) for treatment of hyperkalemia
- MOA: ↑ fecal K+ excretion by binding K+ in the lumen of the GI tract → to reduced free K+ in GI and reduction of serum K+
Veltassa™ (patiromer)

- Approved dosing
  - 8.4 g daily
  - May titrate up to 25.2 g daily
  - Monitor serum potassium daily if titrating dose
  - Doses are in single use packets for oral suspension
  - Do not heat or add to heated foods or liquids
  - No dosing adjustments necessary

---

Veltassa™ (patiromer)

- Administration Instructions
  - Add 1 ounce of water to an empty cup
  - Empty packet into cup
  - Stir mixture
  - Add additional 2 ounces to cup
  - Stir mixture (mixture should look cloudy)
  - Drink mixture immediately
  - **Bottom line: difficult administration instructions**
Warnings and Precautions

- Binding to orally administered medications
  - Administer medications 6 hours before or after Veltassa

- Worsens GI motility
  - Avoid use in patients with severe constipation, bowel obstruction or impaction

- Hypomagnesemia
  - Binds to magnesium in colon, leading to hypomagnesemia (5.3%)

Veltassa™ (patiromer)

- Side effects ≥ 2%: constipation, hypomagnesemia, diarrhea, nausea, abdominal discomfort, flatulence

- Geriatric use: 59.8% age 65 and older with 19.8% 75 and older. Only difference was increased GI effects compared to younger patients.

- Cost: AWP= $714
Evidence

- Two-part study, randomized 243 patients
  - CKD with at least 1 RAAS inhibitor
- Baseline:
  - Mean age 64 years, 58% men, 97% HTN, 57% DM, 42% CHF
- Intervention:
  - Baseline K+: 5.1 to <5.5 mEq/L → Veltassa 8.4 g per day
  - Baseline K+: 5.5 to <6.5 mEq/L → Veltassa 16.8 g per day
  - Target K+: 3.8 – 5.5 mEq/L

---

Evidence

- Primary endpoint: change in K+, baseline to week 4

<table>
<thead>
<tr>
<th>Baseline Potassium</th>
<th>5.1 to &lt;5.5 mEq/L (n=90)</th>
<th>5.5 to &lt;6.5 mEq/L (n=147)</th>
<th>Overall population (n=237)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serum Potassium (mEq/L)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline, mean (SD)</td>
<td>5.31 (0.57)</td>
<td>5.74 (0.4)</td>
<td>5.58 (0.51)</td>
</tr>
<tr>
<td>1st endpoint, mean ± SE (95% CI)</td>
<td>-0.65 ± 0.05 (-0.74, -0.55)</td>
<td>-1.23 ± 0.04 (-1.31, -1.16)</td>
<td>-1.01 ± 0.03 (-1.07, -0.95)</td>
</tr>
<tr>
<td>p-value</td>
<td>---</td>
<td>---</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>
Where does Veltassa™ fit?

- Difficult instructions for administration
- Should not use in patients with GI motility issues
- Should be given at least 6 hours from other medications
- Potential role for patients on RAAS inhibitors who struggle with hyperkalemia

Conclusions

- Praxbind
- Stiolto
- Entresto
- Veltassa
- PCSK9 inhibitors
- Utibron