Reducing Cardiovascular Risk with New Pharmacotherapeutic Strategies

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March 23, 2018

Objectives

- Review new cardiovascular drugs, including indications, dosing, side effects, and pertinent research
- Discuss future directions of cardiovascular care and research

Novel mechanisms for reducing Cardiovascular Risk

- New drugs targeting new pathways
  - Developed for this purpose
  - Subsequent findings/benefits
- Review the "What, When, How" in the areas of:
  - Heart failure management
  - Hyperlipidemia management
  - Anticoagulation reversal
  - Diabetes management leading to CV reduction
Heart Failure Management

- Gold standard of ACE-i/ARB, cardioselective beta blocker plus others in heart failure with reduced ejection fraction (HFrEF) (aka: systolic dysfunction)
- Changed with the publication of PARADIGM-HF in 2014
  - A novel mechanism with superior outcomes
  - Resulted in focused update to ACC/AHA heart failure guidelines

![Diagram of Renin-Angiotensin-Aldosterone System (RAAS)]


![Diagram of Neprilysin Inhibition]
**What?**
- Nephrilysin inhibitor + ARB → FDA approval July 2015
- **Entresto** (sacubitril/valsartan)
  - Available in three strengths: 24/26 mg, 49/51 mg, and 97/103 mg
  - Dosed po BID
- Side effects: hypotension (14% symptomatic), hyperkalemia, angioedema (rare)

**PARADIGM-HF**
- Composite of CV death or hospitalization for heart failure: 21.8% of Entresto group vs. 26.5% of the enalapril group (p < 0.001)
- CV death: 13.3% vs. 16.5% (p < 0.001)
- Hospitalization for HF: 12.8% vs. 15.6% (p < 0.001)

**When?**
- HF hospitalization or symptomatic despite TARGET doses of gold standard medications
- Entresto is used in place of ACE-i or ARB
- Avoid duplication of therapy

**How?**
- Typically outpatient start by cardiology
- Ensure patient affordability/prior authorization process
  - Trial cards, copay cards, patient assistance programs
  - Cash price: ~ $550/month
- Patient education for appropriate transition of therapy
  - Starting dose is dependent on current ACE-i or ARB dose
  - To avoid adverse drug events → angioedema
  - Stop ACE-i, wait 36 hours then initiate Entresto
  - If on ARB, no waiting period
  - Uptitrate every 2-4 weeks as tolerated to target maximal dose
  - Target 97/103 mg po BID
Hyperlipidemia

- 2013 ushered in a change in the management of hyperlipidemia
- ACC/AHA guidelines were released:
  - removed specific LDL treatment targets
  - New risk calculator
  - Statins as primary therapy and dosed based on intensity
  - Non-statin options = not preferred

- Then new drugs with unique mechanisms joined the conversation…

PCSK9 and its role in hyperlipidemia

- Humanized monoclonal antibody resulting in > 60% reduction in LDL

- Praluent (alirocumab) – FDA approved 7/24/15
  - 75 mg subcutaneously every 2 weeks (prefilled pen)
  - Can increase to 150 mg subcutaneously every 2 weeks
  - Can start at 300 mg subcutaneously every 4 weeks (given as 2 injections)

- Repatha (evolocumab) – FDA approved 8/27/15
  - 140 mg subcutaneously every 2 weeks (prefilled pen)
  - 420 mg via on-body infusor every 4 weeks
  - Adverse effects: injection site reactions, nasopharyngitis
When?

- 2017 ACC/AHA Focused update on non-statin therapy (Sept 2017)
  - Addition of non-statin therapies to maximally tolerated statin therapy is recommended to be considered among patients with clinical ASCVD when additional LDL lowering is desired.
  - Verbiage does not say 'statin intolerant'
- FDA label indications vary slightly between Praluent and Repatha
- Awaiting results of outcomes trials…


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FDA Approves Amgen's Repatha® (evolocumab) To Prevent Heart Attack And Stroke

Following FDA Priority Review, Repatha® is the Only PCSK9 Inhibitor Approved to Reduce Risk of Heart Attack, Stroke and Coronary Revascularization

THOUSAND OAKS, Calif., Dec. 1, 2017 /PRNewswire/ -- Amgen (NASDAQ: AMGN) today announced that the U.S. Food and Drug Administration (FDA) has approved Repatha® (evolocumab) to prevent heart attack and stroke.

development-of-amgen-repatha-evolocumab-to-prevent-heart-attack-and-stroke

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FOURIER

Trial design: Patients with established cardiovascular disease on statin therapy were randomized to evolocumab 140 mg subcutaneous every 2 weeks or 420 mg monthly (n = 13,704) versus placebo every 2 weeks (n = 13,780).

Results
- Cardiovascular death, MI, stroke, hospitalization for unstable angina, or coronary revascularization
  - 12.8% of the evolocumab group versus 14.6% of the placebo group (p < 0.0001)
- Any serious adverse event: 24.8% with evolocumab versus 24.7% with placebo

Conclusions
- Among patients with elevated cardiovascular risk on statin therapy, evolocumab was effective at reducing cardiovascular events
- Serious adverse events were similar between treatment groups


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How?

- Referred to Risk Factor Clinic
  - Teaching provided in office
- Medications are dispensed through a specialty pharmacy
- Prior authorization process initiated & reauthorized annually
  - Need to include PA forms and clinical documentation
  - Average 47% medication approval rate
    - Commercial third-party payers made up the lowest approval (24.4%)
    - Medicare had the highest (60.9%)
- Cost: ~$14,000 / year

Anticoagulation Reversal – the current state

- DOACs/TSOACs are now commonly prescribed oral anticoagulants
  - Pradaxa (dabigatran) – direct thrombin inhibitor
  - Xarelto (rivaroxaban), Eliquis (apixaban), Savaysa (edoxaban) – factor Xa inhibitors
  - Indications vary from stroke prevention in NVAF, VTE treatment & prevention, etc
- Most common adverse effect: bleeding or bruising
  - Lower risk of major bleeds, but can still occur
- Previous concern: we have vitamin K to reverse warfarin…what about these?

FDA approves Praxbind, the first reversal agent for the anticoagulant Prada
Idarucizumab (Praxbind®)
- Humanized monoclonal antibody fragment
- Binds to dabigatran with an affinity 350 times that of thrombin
- Binds free and thrombin-bound dabigatran and neutralizes the drug effects within minutes
- No pro-coagulant adverse effects
- Indication: Reversal of dabigatran in life-threatening/uncontrolled bleeding and/or emergency procedure
- Dosing: 5 gm IV administered as two separate 2.5 gm doses no more than 15 minutes apart
- Per manufacturer limited information to repeat 5 gm dose
- Warnings: contains sorbitol


Andexanet Alpha (AndexXa®)
- For the reversal of Xa inhibitors
- Recombinant modified human factor decoy protein with a high affinity for factor Xa inhibitors
- Review of Biologics Application extended by FDA until May 2018
  - Originally reviewed August 2017 → not approved, FDA-requested additional data
- Dosing: 400 mg IV Bolus or 400 mg IV bolus followed by infusion of 4mg/min for 120 minutes
  - In studies reversed anticoagulant within minutes and maintained reversal throughout the infusion (when used)
- No antibody formation or thrombotic events
- ANNEXA-4 to be presented at ACC annual meeting March 2018


When?
- Life-threatening bleeding
- Need for emergency surgery
- If possible, confirm when DOAC/TSOAC last taken
  - Keep in mind these medications have a short half-life
  - Utilize available thrombotic testing
How?

- Consider activated charcoal if last ingestion within 2-4 hours
- Pradaxa
  - Pradaxa 5 gm IV
- Xarelto/Eliquis
  - KCenta (4-factor PCC) 50 units/kg IV

Cardiovascular disease and Type 2 Diabetes...a crossroad

- What we know:
  - Cardiovascular disease is the leading cause of death in individuals with Type 2 DM
  - Type 2 DM is a risk factor for development of CVD
- In 2008, FDA released research guidance for industry
  - Cardiovascular safety/outcomes requested
- Two medications within two newer classes now with CV labeling → not class-wide
  - SGLT2
  - GLP-1


**What?**

- Sodium-glucose co-transporter 2 (SGLT-2) inhibitor
- **Jardiance** (empagliflozin)
- Dose: 10 mg PO every morning
  - May increase to 25 mg PO every morning
  - Not approved for eGFR < 45 ml/min/1.73m²
- Most common side effects: urinary tract infection, yeast infection
  - Warnings: hypotension, ketoacidosis, hypoglycemia, increased LDL
  - Cost/month: ~ $465
- December 2016 → FDA approved for additional indication of:
  - reduce the risk of cardiovascular death in adult patients with T2DM and CVD

**Jardiance** (empagliflozin)

**What?**

- Glucagon-like peptide-1 (GLP-1)
- **Victoza** (Liraglutide)
- Dose: multi-dose pen for subcutaneous injection
  - 0.6 mg x 1 week → 1.2 mg x 1 week → 1.8 mg thereafter
- Most common side effects: GI effects (nausea/vomiting/diarrhea/constipation)
  - Urticaria
  - Warnings: thyroid tumors, pancreatitis, severe hypoglycemia, hypersensitivity reactions, acute gallbladder disease
  - Cost/month: ~ $540 (1.2 mg daily) & ~ $805 (1.8 mg daily)
- August 2017 → FDA approved for additional indication of:
  - reduce the risk of MACE (heart attack, stroke and CV death) in adults with T2DM and established CVD

**Victoza** [package insert]. Plainsboro, NJ: Novo Nordisk Inc; August 2017


**Research leading to new FDA labeling**

- **Jardiance** (empagliflozin)
  - EMPA-REG OUTCOME trial
    - Empagliflozin added to standard of care significantly reduced the composite primary outcome of death from CV causes, nonfatal MI, or nonfatal stroke
    - Decreased hospitalization due to heart failure (statistically significant)
    - Decreased CV death rates (statistically significant)
    - Decreased overall death rates (statistically significant)
    - Did not reduce the individual rates of MI or stroke.


Research leading to new FDA labeling

**Victoza (liraglutide)**

- **LEADER trial**
  - Liraglutide added to standard of care significantly reduced the composite primary outcome of death from CV causes, nonfatal MI, or nonfatal stroke
  - Decrease death from CV causes (statistically significant)
  - Decreased death from any cause (statistically significant)
  - Did not reduce individual rates of MI, nonfatal stroke, or hospitalization for heart failure.

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**When?**

- **ADA Standards of Care 2018**

  - A1C is less than 9%, consider Monotherapy
  - A1C is greater than or equal to 9%, consider Dual Therapy

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**How?**

- Not primetime in outpatient cardiology
- Available trial data and new ADA Standards of Care provide guidance on use of these medications in individuals with T2DM and underlying CVD
- New options in our diabetes toolbox with data to support their use in specific patient populations
- Medications are expensive and not without their own risks
Future Directions

- PARAGON-HF
  - Entresto in HF with preserved EF (2019)
- ODISSEY Outcomes → Praluent CV outcomes study. Completed Jan 2018
  - Evaluation of Cardiovascular Outcomes After an Acute Coronary Syndrome During Treatment With Alirocumab
  - To be presented at ACC annual meeting (March 2018)
- Ciraparantag → in development
  - Reversal agent for factor Xa inhibitors, factor IIa inhibitors, unfractionated heparin, and LMWH
- Additional anti-diabetic medications seeking CV indications

Conclusion

- New therapeutic strategies provide additional options for cardiovascular management and risk reduction
- Common theme is cost of therapy and ensuring access for appropriate patients
- More research to come