New Cardiovascular Drugs 2015

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MERCY CARDIOLOGY

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Disclosures

Financial: None

Personal: Married, 4 children, 2 grandchildren, 1 grandchild on the way

Trivia: I have sailed twice from New Zealand to Tahiti and I am an internet ordained minister having officiated 5 weddings and 1 funeral

Objectives

1. Understand breakthrough drug categories of the 2010's.
2. Review 4 important new drugs that were FDA approved in 2015

Big Decades for CV drugs and Bands

Decade	CV Drugs	Bands
1960’s	Furosemide	Beatles, Motown
1970’s	Beta blockers	Stones, AC/DC, Bee Gees
1980’s	Statins	Bon Jovi, Guns N’ Roses
	ACE-I	
1990’s	Anti-Platelet agents	Back Street Boys, NSYNC
	CCB’s	Nirvana, Red Hot Chili Peppers
2000’s	Drug coated stents	U2, Linkin Park
2010’s	NOAC’s	Black Eyed Peas, Cold Play
	PCSKP9 Inhibitors	
	Neprilysin Inhibitors	

NOAC Agents

Pradaxa-Dabigatran

Xarelto-Rivaroxaban

Eliquis-Apixaban

Savaysa-Edoxaban

- 1. Savaysa-Edoxaban indications are for nonvalvular afib and DVT/PE treatment AFTER 5 days of parental anti-coagulation.
- 2. Non-inferior to warfarin therapy for prevention of stroke with less bleeding than warfarin
- 3. Once daily

NOAC Concerns

- No Reversal Agent

First NOAC reversal Agent

Praxbind-Idarucizumab

- 1. Antidote for Pradaxa-Dabigatran only
- 2. Fab. Fragment anti-body that binds to Pradaxa. Works much like Digibind for antidote for Digoxin toxicity.

Praxbind-Idarucizumab

- FDA approval based upon 3 trials
- 283 volunteers that did not need Pradaxa received Pradaxa followed by Praxbind. The reversal agent lasts approximately 24 hours
- 123 patients that were taking Pradaxa and then either had uncontrolled bleeding or needed emergent surgery. Based on lab tests the anticoagulation effect of Pradaxa was reversed in 89% of patients within 4 hours of receiving Praxbind
- 39 patents that were taking Pradaxa and needed urgent surgery received Praxbind. 36 went on to have surgery. 33/36 or 92% had normal hemostasis during surgery.

Cholesterol Management

- Agents to block GI absorption
  - Zetia-Ezetimibe
  - Questran-Cholestyramine
  - Welchol-Colesevecam
- Agents to block production
  - Statins
- Agents to increase destruction
  - PCSK9 Inhibitors

PCSK9 Inhibitors-How do they work?

- We all have a PCSK9 gene that affects LDL receptors
- LDL receptors sit on the cell surface and remove LDL from the blood stream
- When PCSK9 binds to the LDL receptor, that LDL receptor is then broken down and not available for removing LDL from the blood stream
- Too little PCSK9 means more LDL receptors and lower LDL serum levels
- Too much PCSK9 means fewer LDL receptors and higher LDL levels. HeFH and HoFH patients.
- Thus, by inhibiting levels of PCSK9 with drug therapy, one can increase the LDL receptors and lower LDL serum values

Ways to Lower PCSK9 Levels

- Monoclonal antibodies
  - Praluent-Alirocumab
  - Repatha-Evolocumab
  - Bococizumab
- Peptide mimics
  - Peptides that mimic LDL receptor to bind up circulating PCSK9
- Gene silencing
  - Block the gene that makes PCSK9
- Vaccination
  - Vaccine that makes IgG antibodies to PCSK9. Mice and monkeys
- Naturally occurring inhibitors
  - Plant based products to inhibit PCSK9 gene transcription. In Vitro only

Currently Available PCSK9 Inhibitors

- Praluent-Alirocumab
- Repatha-Evolocumab

PCSK9 Indications

- Treatment of patients with clinical atherosclerosis CV disease who require additional LDL lowering. This may include statin intolerant patients
- Adjunct therapy for patients with HoFH who need additional therapy
- Can be used with or without statin therapy. In patients with clinical documented CV disease and LDL >130 on maximally tolerated statin therapy, can add Zetia to a statin or consider PCSK9 inhibitor

PCSK9 Outcome data

- None
- Preliminary data appears to decrease CV events comparable with statin data
- Long term outcome data is pending

PCSK9 Cost

- To be cost effective the PCSK9 drugs would need to cost ~$2,400/year
- Using a “willingness to pay” threshold of $50,000/year quality adjusted life-year (QALY), the PCSK9 drugs would need to cost $2,100 for FH, $2,400/year for secondary prevention not at goal therapy on statin drugs, and $2,600/year for statin intolerant patients with known CV disease
- Even at a generous QALY of $150,000/year the drugs are cost effective at $5,200/year
- Current US PCSK9 drug pricing is $14,000-$14,600/yr.
- EU PCSK9 cost for Repatha-Evolocumab is $6,800/year in UK, $8,200/year in Austria, and $8,800/year in Finland

Estimated US PCSK9 Costs

- It is estimated that ~2.6 million US individuals could potentially receive a PCSK9 inhibitor in the next 5 years
- 19 billion dollar impact for treatment of FH
- 15 billion dollar impact for treatment of the CVD/statin intolerant
- 74 billion dollar impact for treatment of the CVD/not at goal target subpopulation

New CHF Medication

- Entresto-Sacubitril/Valsartan
- Neprilysin Inhibitor/ARB

Neprilysin Inhibition

- Natriuretic peptides (NPs) are hormones responsible for Na and fluid homeostasis
- NPs are increased with increased LV filling pressures
- NP benefits are to increase GFR, indirect vasodilation, decreased renin, and diuresis
- In CHF, NPs are increased b/o hypervolemia, but are ineffective at relieving excess volumes
- NPs are broken down by neprilysin, which also helps to decrease angiotensin II
- By inhibiting neprilysin, the NPs are increased to then help improve GFR etc.

Neprilysin Inhibition

- Because neprilysin decreases angiotensin II, inhibiting neprilysin must be combined with an inhibitor of the renin-angiotensin-aldosterone (RAAS) system
- Neprilysin inhibition and ACE-I had increased angioedema
- Neprilysin inhibition and ARB did not have significantly increased angioedema rates
- Neprilysin is not to be used with an ACE-I

PRARADIGM-HF Trial

- Used Entresto-Sacubitril/Valsartan
- 8,000 patient study with class II-IV HFrEF (LVEF<40%)
- Reduced CV death and HF hospitalizations by 20% compared with Enalapril alone
- Decreased all cause mortality by 16%

Entresto-Sacubitril/Valsartan Indications

- If patients with NYHA class II-IV with HFrEF remain symptomatic on ACE-I and optimal medical therapy
- Not yet indicated for first line therapy to replace ACE-I

Entresto-Sacubitril/Valsartan Dosing

- Start with 49mg/51mg PO BID
- Target or maintenance dose: after 2-4 weeks increase dose to 97mg/103mg PO BID as tolerated

Entresto-Sacubitril/Valsartan dosing Concerns

- If patient is on an ACE-I, allow a 36 hour washout between drugs
- If not an ACE-I or ARB therapy then start at 24mg/26mg PO BID
- If eGFR is <30 start with lower dose of 24mg/26mg PO BID
- Do not use with an ACE-I

New CHF Medication

- Corlanor-Ivabradine

Corlanor-Ivabradine Mechanism of Action

- Hyperpolarization-activated cyclic nucleotide gated channel blocker. AKA ”funny channel” blocker
- This channel is responsible for regulating heart rate
- There is a higher mortality in patients with HFrEF who are in sinus rhythm and HR>70

SHIFT Trial Using Corlanor-Ivabradine

- Published in 2010
- >6500 patients with NYHA class II-IV HF with LVEF<35% and sinus rhythm with HR>70 with a hospitalization for CHF in the past year and on stable meds including BB therapy if tolerated
- There was an 18% decrease in CV death or hospitalization from worsening CHF over a 23 month period compared with placebo (29% to 25%)

Indications for Corlanor-Ivabradine

- Indicated to reduce the risk of hospitalization for worsening CHF in patients with stable symptoms, NYHA class II-IV CHF, with LVEF <35% who are sinus rhythm with a HR >70 bpm AND who are on maximally tolerated BB therapy or have a contra-indication to BB therapy

Corlanor-Ivabradine dosing

- Start with 5mg PO BID and then after 2 weeks adjust dose to achieve a HR of 50-60bpm but not to exceed a dose of 7.5mg PO BID

Summary of 2015 Important New CV drugs

- Praxbind-Idarucizumab
- PCSK9 Inhibitors: Praluent-Alirocumab and Repatha-Evolocumab
- Entresto-Sacubitril/Valsartan
- Corlanor-Ivabradine

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