FSHP Go for the Gold!

2016 ANNUAL MEETING

NEW DRUGS IN CARDIOLOGY

LORI FIALLO, PHARMD.,BCPS AQ-CARDIOLOGY

PCSK9 INHIBITORS

OBJECTIVES

- Identify recent FDA approvals in cardiology
- Describe the impact of recent FDA approvals on current practice
- Design a treatment plan utilizing new medications

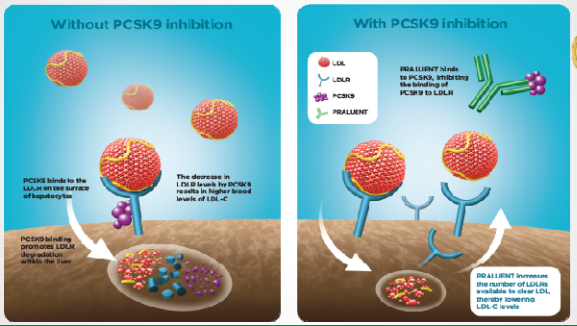
PCSK9 AND HYPERCHOLESTEROLEMIA

- PCSK9
  - Discovery reported in 2003 and 2004
- PCSK9 missense/LOF mutations- ARIC study
  - African Americans : 28% less LDL-C, 88% lower risk of developing CVD
  - Whites with less severe mutation: 15% reduction in LDL-C; 47% reduced risk of CVD
- PCSK9 – mediated cholesterol effects revealed
  - PCSK9 facilitates LDL-R degradation
    - GOF mutations lead to less LDL-R available to remove LDL-C
    - LOF mutations lead to increase LDL-R available to remove LDL-C

Abifadal M,et al.*Nat Genet*.2003:34:154-6
Cohen JC, et al.*NEJM*.2006;354:1264-72.
Horton JD,et al.*J Lipid Res*.2009;50(Suppl)S172-77

PRESENTATION OUTLINE

- Hyperlipidemia Medications
  - PCSK9 inhibitors
  - Pipeline agents
- Heart Failure Medications
  - Ivaradine (Corlanor)
  - Sacubitril/valsartan (Entresto)
- Antidotes
  - Idarucizumab (Praxbind)
  - Andexanet Alfa
  - Other Pipeline agents



PCSK9 INHIBITORS

Name	Drug Company	Stage of Development
Alirocumab (Praluent)	Renergon/Sanofi	Approved July 2015
Evolocumab (Repatha)	Amgen	Approved August 2015
Bococumab	Pfizer	Phase III trial

ALIROCUMAB (PRALUENT)

- Adverse Reactions
  - Diarrhea (5%)
  - Increased serum transaminases (2%)
  - Hypersensitivity reactions
  - Influenza (6%)
  - Injection site reactions (7%)
  - Myalgia (4%)
  - Muscle spasms (3%)
  - Cough (3%)

Praluent (alirocumab) [prescribing information]. Tarrytown, NY. Regeneron Pharmaceuticals, Inc: October 2015.

ALIROCUMAB (PRALUENT)

- Indication
  - Heterozygous familial hypercholesterolemia
    - Adjunct to diet and maximally tolerated statin therapy
  - Clinical atherosclerotic cardiovascular disease who require additional lowering of LDL-cholesterol
- Dose
  - 75 mg subcutaneously every 2 weeks
  - Titrated to a maximum dose of 150 mg subcutaneously every 2 weeks

Praluent (alirocumab) [prescribing information]. Tarrytown, NY. Regeneron Pharmaceuticals, Inc: October 2015.

ALIROCUMAB (PRALUENT) ADMINISTRATION

- Warm to room temperature for 30 to 40 minutes prior to use
- Do NOT use if it has been at room temperature for 24 hours or longer
- Administer by subcutaneous injection into the thigh, abdomen, or upper arm
- Rotate injection site with each injection
- Do NOT inject into areas of active skin disease or injury such as sunburns, skin rashes, inflammation, or skin infections
- Do NOT co-administer with other injectable drugs at the same injection site

Praluent (alirocumab) [prescribing information]. Tarrytown, NY. Regeneron Pharmaceuticals, Inc: October 2015.

ALIROCUMAB (PRALUENT)

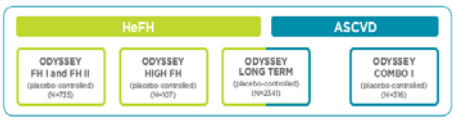
- No dosage adjustments
  - Renal Impairment
  - Hepatic Impairment
- Storage
  - Store at 2˚C to 8°C (36°F to 46°F) in the outer carton to protect from light
  - Do not freeze
  - Do not expose to extreme heat
  - Do not shake

Praluent (alirocumab) [prescribing information]. Tarrytown, NY. Regeneron Pharmaceuticals, Inc: October 2015.

ALIROCUMAB (PRALUENT)

PRALUENT® (alirocumab) was investigated in 5 double-blind, placebo-controlled trials

- 3499 patients enrolled: 36% with heterozygous familial hypercholesterolemia (HeFH) and 64% non-FH patients with clinical atherosclerotic cardiovascular disease (ASCVD)
- All patients were receiving a maximally tolerated dose of statin, with or without other lipid-modifying therapies (LMTs)

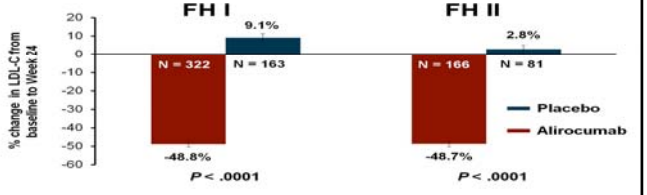


Praluent (alirocumab) [prescribing information]. Tarrytown, NY. Regeneron Pharmaceuticals, Inc: October 2015.

ODYSSEY FH I + II

Alirocumab Significantly Reduced LDL-C From Baseline to Week 24 vs Placebo

All patients on background max-tolerated statin ± other lipid-lowering therapy



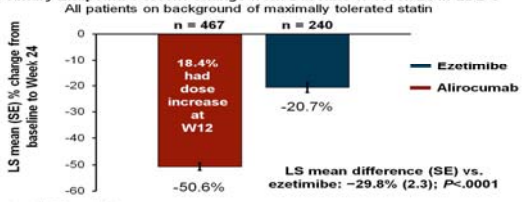
Kastelein JP, et al. 2014 ESC Congress 2014, August 31, 2014.[16]

ODYSSEY Combo

Alirocumab Significantly Reduced LDL-C From Baseline to Week 25 vs Ezetimibe

Primary Endpoint: Percent Change from Baseline to Week 24 in LDL-C

All patients on background of maximally tolerated statin



Intent-to-treat (ITT) analysis
Cannon C, et al. 2014 ESC Congress, August 31, 2014.[17]

Safety Analysis (Pooled Data From FH I and FH II)

All Data Collected Until Last Patient Visit at Week 52

% (n) of patients All patients on background of max tolerated statin ± other lipid-lowering therapy	Alirocumab, % (N = 489)	Placebo, % (N = 244)
TEAEs	74.8 (366)	75.4 (184)
Treatment-emergent SAEs	10.0 (49)	9.0 (22)
TEAEs leading to death	0.8 (4)	0
TEAEs leading to discontinuation	3.1 (15)	3.7 (9)
Adverse Events of Interest		
Adjudicated CV events†	1.6 (8)	1.2 (3)
Injection-site reactions	11.5 (56)	9.0 (22)
Neurocognitive disorders	0.2 (1)	1.2 (3)
ALT >3 x ULN	2.1 (10/488)	1.2 (3/244)
Creatine kinase >3 x ULN	3.5 (17/483)	6.2 (15/243)

4 TEAE-related deaths were all in alirocumab arm, 2 due to metastatic cancer (non-small cell lung and pancreatic), 2 due to MI (1 acute, 1 sudden cardiac death)

†Adjudicated CV events include all CV AEs positively adjudicated. The adjudication categories are the following: CHD death, non-fatal MI, fatal and non-fatal ischaemic stroke, unstable angina requiring hospitalisation, congestive heart failure requiring hospitalisation, ischaemia-driven revascularisation procedure (PCI, CABG).
Statistical analyses have not been performed.

Kastelein JP, et al. 2014 ESC Congress 2014, August 31, 2014.[16]

EVOLOCUMAB (REPATHA) INDICATIONS

- Primary hyperlipidemia
  - Heterozygous familial hypercholesterolemia (HeFH)
    - adjunct to diet and maximally tolerated statin therapy
  - Clinical atherosclerotic cardiovascular disease (CVD) who require additional lowering of LDL
- Homozygous familial hypercholesterolemia (HoFH)
  - Adjunct to diet and other LDL-lowering therapies

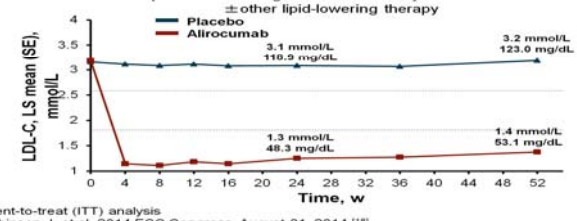
Repatha (evolocumab) [prescribing information]. Thousand Oaks, CA: Amgen Inc: August 2015.

ODYSSEY LONG TERM

Alirocumab Maintained Consistent LDL-C Reduction Over 52 Weeks

Achieved LDL-C Over Time

All patients on background of maximally tolerated statin ± other lipid-lowering therapy



Intent-to-treat (ITT) analysis
Robinson J, et al. 2014 ESC Congress, August 31, 2014.[18]

EVOLOCUMAB (REPATHA) DOSING

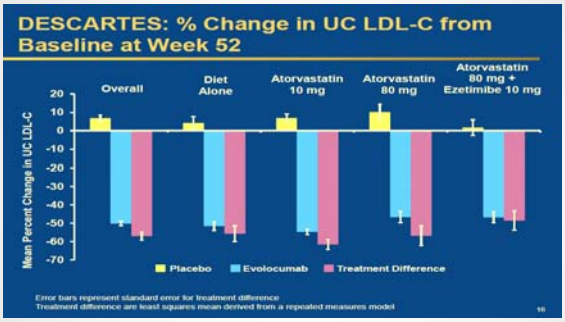
- Primary Hyperlipidemia
  - 140 mg SUBQ every 2 weeks
    OR
  - 420 mg SUBQ monthly
- Homozygous familial hypercholesterolemia (HoFH)
  - 420 mg SUBQ monthly
- Renal Impairment
  - No adjustment in Mild to moderate
  - Not studied in est GFR < 30mL/minute/1.73m^2
- Hepatic Impairment
  - No adjustment in mild to moderate
  - Not studied in severe

Repatha (evolocumab) [prescribing information]. Thousand Oaks, CA: Amgen Inc: August 2015.

EVOLOCUMAB (REPATHA) ADVERSE REACTIONS

- Nasopharyngitis (6% – 11%)
- Hypertension (3%)
- Dizziness (4%)
- Fatigue (2%)
- Gastroenteritis (3% - 6%)
- Nausea (2%)
- UTI (5%)
- Influenza (8 – 9%)
- Injection site reaction (6%)
- Myalgia (4%)
- Upper respiratory tract infection (9%)
- Sinusitis (4%)
- Skin rash (1%)

Repatha (evolocumab) [prescribing information]. Thousand Oaks, CA: Amgen Inc: August 2015.

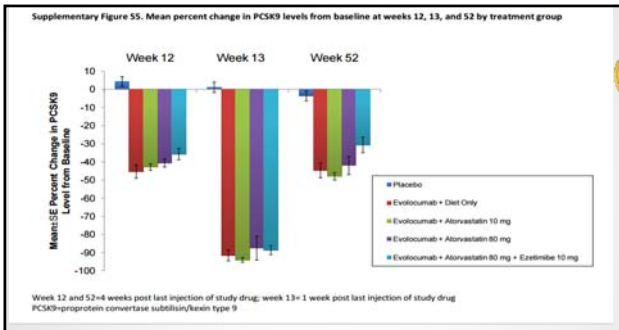


Bloom DJ, et al. A 52 Week Placebo-controlled Trial of Evolocumab in Hyperlipidemia. N Engl J Med 2014; 370: 1809-19.

EVOLOCUMAB (REPATHA) ADMINISTRATION

- Administer by subcutaneous injection into the thigh, abdomen, or upper arm
  - Rotate injection site with each injection
  - Do NOT inject into areas of active skin disease or injury such as sunburns, skin rashes, inflammation, or skin infections
  - Do NOT co-administer with other injectable drugs at the same injection site
- Dose of 420 mg
  - 3 injections of 140 mg consecutively within 30 minutes

Repatha (evolocumab) [prescribing information]. Thousand Oaks, CA: Amgen Inc: August 2015.

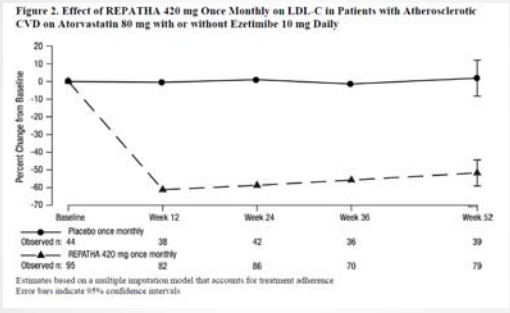


Bloom DJ, et al. A 52 Week Placebo-controlled Trial of Evolocumab in Hyperlipidemia. N Engl J Med 2014; 370: 1809-19.

EVOLOCUMAB (REPATHA)

- Storage
  - Refrigerator
    - Warm to room temperature for 30 to 40 minutes prior to use
  - Room Temperature in original carton
    - Must be used within 30 days

Repatha (evolocumab) [prescribing information]. Thousand Oaks, CA: Amgen Inc: August 2015.



Bloom DJ, et al. A 52 Week Placebo-controlled Trial of Evolocumab in Hyperlipidemia. N Engl J Med 2014; 370: 1809-19.

DESCARTES: TREATMENT EMERGENT ADVERSE EVENTS

N (%)	Placebo N = 302	Evolocumab N = 599
Any Treatment Emergent Adverse Event	224 (74.2)	448 (74.8)
Serious	13 (4.3)	33 (5.5)
Adjudicated events	2 (0.7)	6 (1)
Death	0 (0)	2 (0.3)
Leading to discontinuation of study drug	3 (1)	13 (2.2)

Bloom DJ, et al. A 52 Week Placebo-controlled Trial of Evolocumab in Hyperlipidemia. N Engl J Med 2014; 370: 1809-19.

Guidelines to Manage Dyslipidemia

2013 ACC/AHA Guidelines[a,c]		2011 ESC/EAS Guidelines[b,c]	
Category	Recommendation	Category	Recommendation
Clinical ASCVD	• High-intensity statin • Combination therapy if 50% LDL-C lowering not reached	CVD	• LDL-C < 70 mg/dL or 50% reduction in LDL-C
Primary LDL-C ≥ 190 mg/dL	• High-intensity statin	Familial dyslipidemia (FH, FCH)	• LDL-C < 100 mg/dL or maximal LDL-C reduction with drug combination and LDL apheresis
Diabetes (type 1 or 2) without clinical ASCVD but LDL-C = 70-189 mg/dL	• Low risk: moderate-intensity statin • High risk: high-intensity statin	Diabetes mellitus or type 1 with target organ damage	• LDL-C < 70 mg/dL or 50% reduction in LDL-C
None of the above but estimated 10-y risk ≥ 7.5%	• Moderate- to high-intensity statin	None of the above but estimate 10-y risk (SCORE)	• Very high risk (SCORE > 10%) LDL-C < 70 mg/dL or 50% reduction • High risk (SCORE 5% to 0%) LDL-C < 100 mg/dL • Moderate risk (SCORE 1% to 5%) LDL-C < 120 mg/dL

a. Stone NJ, et al. *J Am Coll Cardiol*. 2014;63(25 Pt B):2889-2934[11]; b. European Association for Cardiovascular Prevention & Rehabilitation, et al. *Eur Heart J* 2011;32:1769-1818[12]; c. Ray KK, et al. *Eur Heart J*. 2014;35:960-968.[13]

BOCOCIZUMAB PHASE III ONGOING

- *The Evaluation of Bococizumab in Reducing the Occurrence of Major Cardiovascular Events in High Risk Subjects*
- *Study Arms*
  - *Bococizumab 150mg subcutaneously every 2 weeks*
  - *Placebo subcutaneously every 2 weeks*
- *Primary Endpoint*
  - *Time from randomization to first occurrence of a major cardiovascular event*
    - *Composite endpoint of CV death, non-fatal MI, non-fatal stroke, and hospitalization for unstable angina needing urgent revascularization*
    - *Time frame: 60 months*

ClinicalTrials.gov

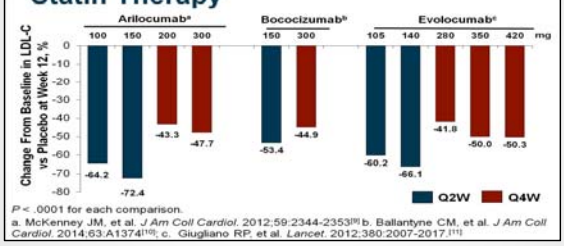
Statin Therapy

Intensity	Dose
High	Daily dose lowers LDL-C, on average, by approximately ≥ 50% • Atorvastatin (40)*-80 mg • Rosuvastatin 20 (40)* mg
Moderate	Daily dose lowers LDL-C, on average, by approximately 30% to < 50% • Atorvastatin 10 (20)* mg • Rosuvastatin (5)* 10 mg • Simvastatin 20-40 mg • Pravastatin 40 (80)* mg • Lovastatin 40 mg • Fluvastatin XL 80 mg • Fluvastatin 40 mg twice daily • Pitavastatin 2-4 mg
Low	Daily dose lowers LDL-C, on average, by < 30% • Simvastatin 10 mg • Pravastatin 10-20 mg • Lovastatin 20 mg • Fluvastatin 20-40 mg • Pitavastatin 1 mg

* Dosage used in randomized controlled studies and reviewed by panel

Stone N, et al. *J Am Coll Cardiol*. 2014;63:2889-2934.[1]

PCSK9 Inhibition in Patients With Hypercholesterolemia Receiving Statin Therapy



P < .0001 for each comparison.

a. McKenney JM, et al. *J Am Coll Cardiol*. 2012;59:2344-2353[9] b. Ballantyne CM, et al. *J Am Coll Cardiol*. 2014;63:A1374[10]; c. Giugliano RP, et al. *Lancet*. 2012;380:2007-2017.[11]

IMPROVE-IT

Table 2. Primary, Secondary, and Individual End Points.[a]

Outcome	Simvastatin Monotherapy (N = 9077)	Simvastatin-Ezetimibe (N = 9067)	Hazard Ratio (95% CI)	P Value
	no. of patients (%)			
Primary end point: death from cardiovascular causes, major coronary event, or nonfatal stroke	2742 (34.7)	2572 (32.7)	0.936 (0.89–0.99)	0.016
Secondary end points				
Death from any cause, major coronary event, or nonfatal stroke	3246 (40.3)	3089 (38.7)	0.95 (0.90–1.0)	0.03
Death from coronary heart disease, nonfatal MI, urgent coronary revascularization ≥30 days	1448 (18.9)	1322 (17.5)	0.91 (0.85–0.98)	0.02
Death from cardiovascular causes, nonfatal MI, hospitalization for unstable angina, all revascularization ≥30 days, nonfatal stroke	2869 (36.2)	2716 (34.5)	0.95 (0.90–1.0)	0.04

Cannon CP, et al. Ezetimibe Added to Statin Therapy after Acute Coronary Syndromes. N Engl J Med 2015; 372: 2387-97.

PCSK9 CV OUTCOMES TRIALS

- FOURIER
  - Further Cardiovascular Outcomes Research with PCSK9 Inhibition in Subjects with Elevated Risk (Evolocumab)
    - Estimated enrollment: 22,500 patients
- ODYSSEY Program
  - Evaluation of Cardiovascular Outcomes After an Acute Coronary Syndrome During Treatment with Alirocumab
    - Estimated enrollment: 18,000 patients
- SPIRE-1/SPIRE-2
  - The Evaluation of Bococizumab in Reducing the Occurrence of Major Cardiovascular Events in High Risk Subjects
    - Estimated enrollment: 18,300 patients

ClinicalTrials.gov

PIPELINE CHOLESTEROL LOWERING AGENTS

BEMPEDOIC ACID (ETC-1002)

- Orally available
- Inhibits ACL
  - enzyme that supplies substrate for cholesterol and fatty acid synthesis in the liver
- Enrolling in Phase III trial

ANACETRAPIB

- CETP- inhibitor
  - 3 previous CETP-inhibitors have failed in trials
- Phase III trial
  - Concludes Jan. 2017

ClinicalTrials.gov

PCSK9 INHIBITORS

- Cost
  - Evolocumab(Repatha) 140 mg: $650.77 per dose
    - 140 mg every 2 weeks: annual cost $16,920.02
    - 480 mg monthly: annual cost $23,427.77
  - Alirocumab (Praluent) 75 mg/ 150mg : $672 per dose
    - Every 2 weeks administration: annual cost $17,472

SUMMARY

- PCSK9 inhibitors
  - Two currently on the market and one in phase III trials
  - Decrease LDL significantly
  - Morbidity and mortality data unknown at this time
  - Indication as adjunct therapy
- Two novel medications in phase III trials

HOW LOW IS TOO LOW?

- No clear data in human studies
- JUPITER trial
  - Rosuvastatin treated patients
  - Median LDL-C 55 mg/dL
- IMPROVE-IT trial
  - Median LDL-C 53.7 mg/dL

Cannon CP, et al. Ezetimibe Added to Statin Therapy after Acute Coronary Syndromes. N Engl J Med 2015; 372: 2387-97.

Ridker PM,et al. Rosuvastatin to Prevent Vascular Events in Men and Women with Elevated C-Reactive Protein. N Engl J Med 2008; 359: 2195-2207.

HEART FAILURE NEW MEDICATIONS

Corlanor (ivabradine) 5mg 7.5mg tablets

IVABRADINE

IVABRADINE (CORLANOR)

- Dosage
  - 5 mg twice daily with meals
  - 2.5 mg twice daily with meals
    - History of conduction defects
    - Or patients with concern of bradycardia
  - Titrate up in 2 weeks for resting heart rate of 50-60bmp
  - Maximum dose of 7.5 mg twice daily

Corlandor (ivabradine) [prescribing information]. Thousand Oaks, CA: Amgen Inc; April 2015.

IVABRADINE (CORLANOR)

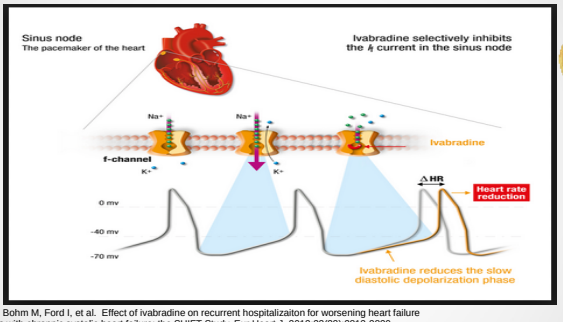
- Indication
  - Reduce risk of hospitalization for worsening heart failure (HF)
  - LVEF less than 35%
  - Resting heart rate above 70 bpm
  - Taking maximally tolerated doses of beta blockers or contraindicated to beta blockers

Corlandor (ivabradine) [prescribing information]. Thousand Oaks, CA: Amgen Inc; April 2015.

IVABRADINE (CORLANOR)

- Adverse Reactions
  - Bradycardia
  - Hypertension
  - Atrial Fibrillation
  - Heart block
- Contraindications
  - Acute decompensated HF
  - BP less than 90/50 mmHg
  - Sick sinus syndrome, sinoatrial block, or third-degree AV block
  - Resting HR less than 60 bpm
  - Severe hepatic impairment
  - Pacemaker dependence
  - Concomitant use with strong CYP 3A4 inhibitors

Corlandor (ivabradine) [prescribing information]. Thousand Oaks, CA: Amgen Inc; April 2015.



Borer JS, Bohm M, Ford I, et al. Effect of ivabradine on recurrent hospitalizaiton for worsening heart failure in patients with chronnic systolic heart failure: the SHIFT Study. Eur Heart J. 2012;33(22):2813-2820.

SHIFT STUDY

	Ivabradine group (n=3241)	Placebo group (n=3264)	HR (95% CI)	p value
Primary endpoint				
Cardiovascular death or hospital admission for worsening heart failure	793 (24%)	937 (29%)	0·82 (0·75–0·90)	<0·0001
Mortality endpoints				
All-cause mortality	503 (16%)	553 (17%)	0·90 (0·80–1·02)	0·092
Cardiovascular mortality	449 (14%)	491 (15%)	0·91 (0·80–1·03)	0·128
Death from heart failure	113 (3%)	151 (5%)	0·74 (0·58–0·94)	0·014
Other endpoints				
All-cause hospital admission	1231 (38%)	1356 (42%)	0·89 (0·82–0·96)	0·003
Hospital admission for worsening heart failure	514 (16%)	672 (21%)	0·74 (0·66–0·83)	<0·0001
Any cardiovascular hospital admission	977 (30%)	1122 (34%)	0·85 (0·78–0·92)	0·0002
Cardiovascular death, or hospital admission for worsening heart failure, or hospital admission for non-fatal myocardial infarction	825 (25%)	979 (30%)	0·82 (0·74–0·89)	<0·0001

Data are number of first events (%), hazard ratio (HR; 95% CI), and p values.

Table 3: Effects on primary and major secondary endpoints

Swedberg K, et al. Effect of ivabradine on recurrent hospitalizaiton for worsening heart failure in patients with chronnic systolic heart failure: the SHIFT Study. Eur Heart J. 2012;33(22):2813-2820.

HF GUIDELINES UPDATE

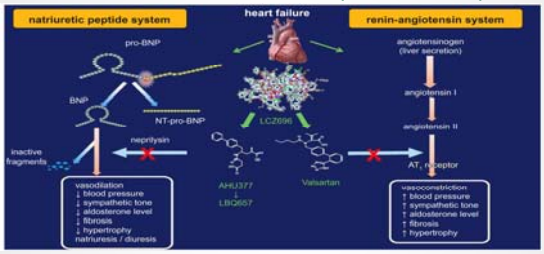
COR	LOE	RECOMMENDATION
IIa	B-R	**Ivabradine** can be beneficial to reduce HF hospitalization for patients with symptomatic (NYHA class II-III) stable chronic HFrEF (LVEF <35%) who are receiving GDEM including a beta blocker at maximum tolerated dose and who are in sinus rhythm with a heart rate of 70 bpm or greater at rest

Corlandor (ivabradine) [prescribing information]. Thousand Oaks, CA: Amgen Inc; April 2015.

Entresto™ (sacubitril/valsartan) tablets
24/26 mg · 49/51 mg · 97/103 mg

SACUBITRIL/VALSARTAN

SACUBITRIL/VALSARTAN (ENTRESTO)



Solomon SD, Zile M, Pieske B, et al; Prospective comparison of ARNI with ARB on Management Of heart failure with preserved ejection fraction (PARAMOUNT) Investigators. Lancet; 2012;380:1387-95

SACUBITRIL/VALSARTAN (ENTRESTO)

- Indication
  - Reduce the risk of cardiovascular death and hospitalizations in patients with chronic Heart Failure (HF) and reduced ejection fraction
- Dosing
  - Starting dose of 49/51 mg twice daily
  - Target maintenance dose of 97/103 mg twice daily
    - Increase in 2 to 4 weeks
  - Reduce starting dose to 24/25 mg twice daily
    - Not currently taking ACEi/ARB or low doses
    - eGFR less than 30ml/min/1.73m^2
    - Moderate hepatic impairment

Entresto (sacubitril/valsartan) [prescribing information]. East Hanover, NJ: Novartis; August 2015.

SACUBITRIL/VALSARTAN (ENTRESTO)

- Contraindications
  - Hypersensitivity to sacubitril or valsartan
  - History of angeioedema related to previous ACE inhibitor or ARB therapy
  - Concomitant use or use within 36 hours of ACE inhibitors
  - Concomitant use of aliskiren in patients with diabetes
- Black Box Warning
  - Pregnancy
    - Can cause injury and death to the developing fetus
    - When pregnancy is detected, discontinue sacubitril/valsartan as soon as possible

Entresto (sacubitril/valsartan) [prescribing information]. East Hanover, NJ: Novartis; August 2015.

SACUBITRIL/VALSARTAN (ENTRESTO)

- Adverse Reactions
  - Hypotension (18%)
  - Hyperkalemia (12%)
  - Increase serum creatinine (up to 16%)
  - Renal failure (5%)
  - Cough (9%)
  - Angioedema (black patients: 2%; others: <1%)
  - Dizziness (6%)

Entresto (sacubitril/valsartan) [prescribing information]. East Hanover, NJ: Novartis; August 2015.

SUMMARY

- Ivabradine (Corlanor)
  - HFrEF
  - Decrease hospitalizations
  - Maximally tolerated beta-blockers or unable to take beta-blockers
- Sacubitril/valsartan (Entresto)
  - HFrEF
  - Replace ACEi or ARBs
  - Decrease morbidity and mortality
  - Monitor potassium and blood pressure

PARADIGM-HF

Table 2. Primary and Secondary Outcomes.*

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

McMurray JJV, Packer M, Desai AS, et al. Angiotensin-neprilysin inhibition versus enalapril in heart failure. N Engl J Med. 2014;371:993-1004.

ANTIDOTES

HF GUIDELINES UPDATE

COR	LOE	RECOMMENDATIONS
I	A	The use of **ACE inhibitors** is beneficial for patients with prior or current symptoms of chronic HFrEF to reduce mortality and morbidity
I	A	The use of **ARBs** to reduce morbidity and mortality is recommended in patients with prior or current symptoms of chronic HFrEF who are intolerant to ACE inhibitors because of cough or angioedema
I	B-R	In patients with chronic symptomatic HFrEF NYHA class II or III who tolerate ACE inhibitors or ARB, replacement by an **ARNI** is recommended to further reduce morbidity and mortality

New Oral Anticoagulants	Classification	Reversal Agent Available
Rivaroxaban	Factor Xa inhibitor	No
Apixiban	Factor Xa inhibitor	No
Edoxaban	Factor Xa inhibitor	No
Dabigatran	Direct Thrombin Inhibitor	Yes

IDARUCIZAMAB (PRAXBIND)

- Indication
  - Reversal of the anticoagulant effects of dabigatran
    - Emergency surgery/urgent procedures
    - Life-threatening or uncontrolled bleeding
- Dosing
  - 5 grams
    - Administered as 2 doses of 2.5 g no more than 15 minutes apart
  - No adjustments for renal or hepatic impairment

Praxbind (idarucizumab) [prescribing information]. Ridgefield, CT: Boehringer Ingeleim Pharmaceuticals, Inc: October 2015.

IDARICIZUMAB (PRAXBIND)

- Warnings/Precautions
  - Re-evaluation of coagulation parameters
  - Hypersensitivity reactions
  - Thromboembolic risk
  - Hereditary fructose intolerance
- Adverse Reactions
  - Delirium (7%)
  - Headache (5%)
  - Hypokalemia (7%)
  - Constipation (7%)
  - Hypersensitivity
  - Pneumonia (6%)
  - Fever (6%)

Praxbind (idarucizumab) [prescribing information]. Ridgefield, CT: Boehringer Ingeleim Pharmaceuticals, Inc: October 2015.

IDARUCIZAMAB (PRAXBIND)

- **Mechanism of action**
  - Humanized monoclonal antibody fragment (Fab)
  - Binds to dabigatran and its acyl glucuronide metabolites neutralizing their anticoagulant effect
  - Almost 350 times greater affinity than the binding affinity of dabigatran to thrombin

Praxbind (idarucizumab) [prescribing information]. Ridgefield, CT: Boehringer Ingeleim Pharmaceuticals, Inc: October 2015.

IDARICIZUMAB (PRAXBIND)

- Cost
  - 5 gram dose: $4,200
- Resume anticoagulant
  - Dabigatran can be re-initiated 24 hours after idarucizumab administration

IDARUCIZAMAB (PRAXBIND)

- Administration
  - Intravenously administer the dose of 5 grams (2 vials containing 2.5 g each)
    - Two consecutive infusion
    - Bolus injection consecutively
  - Once removed from vial
    - Administration should begin within 1 hour
  - Do not mix with other medicinal products
  - Aseptic technique
  - Flush IV line with normal saline prior to infusion

Figure 1 Recommended dose of PRAXBIND provided as two vials.
Figure 2 Two consecutive infusions by hanging vials.
Figure 3 Inject both vials consecutively via syringe.

Praxbind (idarucizumab) [prescribing information]. Ridgefield, CT: Boehringer Ingeleim Pharmaceuticals, Inc: October 2015.

REVERSE-AD

Prospective cohort study to determine safety and ability to reverse anticoagulant affects of patients receiving dabigatran with :

- Group A
  - Overt, uncontrollable or life-threatening bleeding
- Group B
  - Required surgery or other invasive procedure that could not be delayed for at least 8 hours

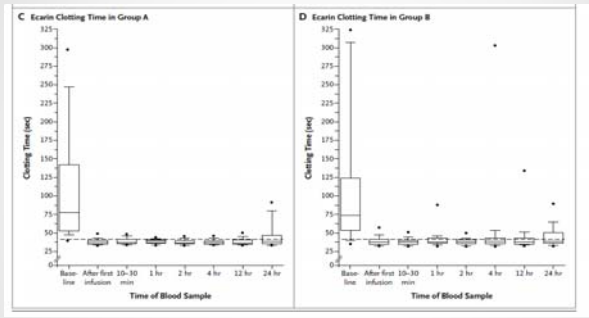
Pollack *et al.* Idarucizumab for Dabigatran Reversal. *New England Journal of Medicine*. 373:511-520.DOI: 10.1056 2014

REVERSE-AD

Interim analysis results

$$\text{Reversal} = \frac{\text{predose coagulation test} - \text{minimum postdose coagulation test}}{\text{predose coagulation test} - 110\%\ \text{ULN}} \times 100\%$$

Pollack *et al.* Idarucizumab for Dabigatran Reversal. *New England Journal of Medicine*. 373:511-520.DOI: 10.1056 2014



Pollack *et al.* Idarucizumab for Dabigatran Reversal. *New England Journal of Medicine*. 373:511-520.DOI: 10.1056 2014

REVERSE-AD

- Interim analysis results of primary outcomes

	Group A	Group B
Median maximum percentage reversal	100%	100%
dTT normalization	98%	93%
ECT normalization	89%	88%

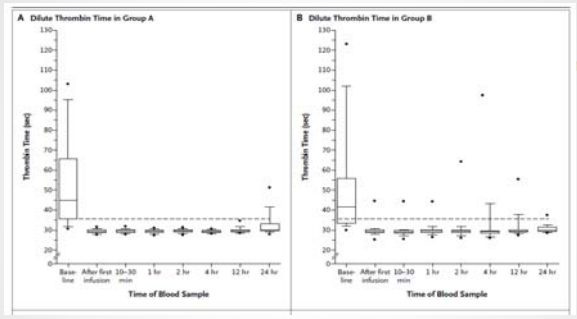
Pollack *et al.* Idarucizumab for Dabigatran Reversal. *New England Journal of Medicine*. 373:511-520.DOI: 10.1056 2014

REVERSE-AD

- Interim analysis results of secondary (clinical) outcomes

	Group A	Group B
Median investigator-reported time to cessation of bleeding	11.4 hours	____
Normal intra-operative hemostasis	____	92%

Pollack *et al.* Idarucizumab for Dabigatran Reversal. *New England Journal of Medicine*. 373:511-520.DOI: 10.1056 2014



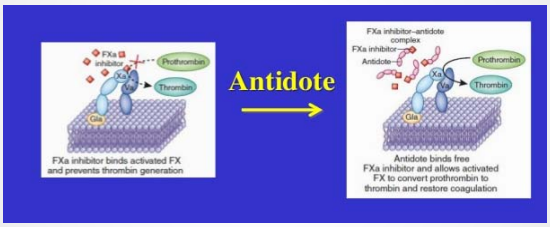
Pollack *et al.* Idarucizumab for Dabigatran Reversal. *New England Journal of Medicine*. 373:511-520.DOI: 10.1056 2014

ANDEXANET ALFA

- Novel agent currently in Phase III trials
- Reversal of factor Xa inhibitors
  - Rivaroxaban
  - Apixiban
- Mechanism of Action
  - Recombinant modified human factor Xa decoy protein
  - Binds and sequesters factor Xa inhibitors
  - Decoy of factor Xa molecule
    - Bind with high affinity to anti-factor Xa

Siegal *et al. Andeanet Alfa for the Reversal of Factor Xa inhibitor activity*. New England Journal of Medicine. 373:2413-24.

ANDEXANET ALFA

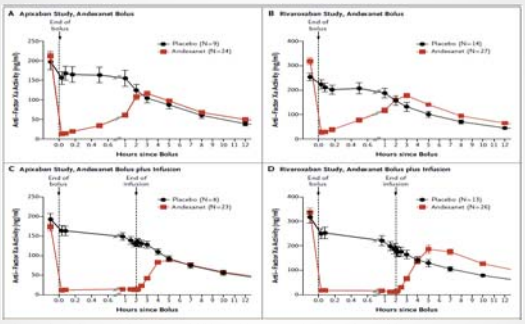


I

ANDEXANET ALFA

fXa Inhibitor	IV bolus	IV infusion
Apixiban Last dose of rivaroxaban greater than 7 hours	400 mg at a target rate of 30 mg/min	480 mg at 4 mg/min for 120 minutes
Enoxaparin Last dose of rivaroxaban less than 7 hours or at an unknown time Received anti-fXa but unknown which one	800 mg at a target rate of 30 mg/min	960 mg at 8 mg/min for 120 minutes

ClinicalTrials.gov



Siegal *et al. Andeanet Alfa for the Reversal of Factor Xa inhibitor activity*. New England Journal of Medicine. 373:2413-24.

PER977 (CIRAPARANTAG)

- Currently in Phase II clinical trials
- Broad spectrum reversal agent
  - Low molecular weight heparin
  - Unfractionated heparin
  - Edoxaban
  - Dabigatran
  - Rivaroxaban
  - Apixiban
- Single IV bolus

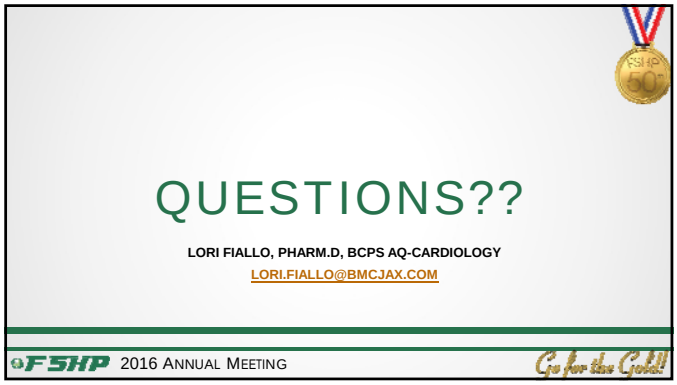
ANDEXANET ALFA

- Phase III trial ongoing
  - Prospective, open label study of andexanet alfa in patients receiving a factor Xa inhibitor who have acute major bleeding
  - Primary outcome
    - Demonstrate the decrease in anti-fXa activity following andexanet treatment
    - Evaluate hemostatic efficacy of andexanet in patients receiving a fXa inhibitor who have acute major bleeding and reduced fXa activity
  - Secondary outcome
    - Assess the relationship between decrease in anti-fXa activity and achievement of hemostatic efficacy in patients receiving a fXa inhibitor who have acute major bleeding and reduced fXa activity

ClinicalTrials.gov

SUMMARY

- Idarucizumab
  - Approved for reversal of dabigatran
- Andexanet alfa
  - Currently in phase III trials
  - Reversal agent for rivaroxaban and apixiban
- PER977
  - Currently in phase II trials
  - Broad spectrum reversal agent


QUESTIONS??
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FSHP 2016 ANNUAL MEETING
Go for the Gold!