Emerging Therapies – Drugs in the Pipeline

Paul Ziajka MD, PhD, FNLA
Director, The Florida Lipid Institute
Immediate Past President, SELA
Paul Ziajka - Disclosures

• Research Support:
  – Merck, Genzyme, Regeneron, Kowa, Catabase

• Speakers Bureau / Consultant:
  – AZ, Abbott, Merck, Kowa, Aegerion, GSK, Amarin, Hunter Heart Lab
Evolving Therapies

- ACAT inhibitors
- ApoA1 mimetics
- CETP inhibitors
- Chol. Absorption blockers
- DGAT inhibitors
- IBAT inhibitors
- MTP inhibitors
- Non-iodinated T4 analogs
- Omega-3 f.a.’s
- PCSK9 inhibitors
- PLA2 inhibitors (Lp, S & C)
- ppar δ agonists
- RXR agonists
- Squalene synthetase inhibitors
- Synthetic HDL
- VCAM inhibitors
Presentation Outline

- PCSK9 inhibitors
- CETP inhibitors
- Lp-PLA2 inhibitors
- History and basic science
- Mechanism(s) of action
- Review of agents in the class
- Clinical study results
Proprotein Convertase Subtilisin / Kexin Type 9 (PCSK9) Inhibitors
PCSK9

- PCSK9 is a serine protease (one of 9 mammalian subtilases known as proprotein convertase) expressed in highest concentrations in the liver, intestines and kidney
  - 63kD protein; gene located on chromosome 1p32
- PCSK9 acts a “chaperone” to escort the LDL-R/LDL complex from the cell surface to the liposome for degradation
- Over activity leads to increased LDL-R destruction and increases in TC and LDL

Austin; Am J Epid 2004;160:407
Lambert; Athero 2009;203:1
Horton; Trends Biochem Sci 2007;32:71
Cohen; NEJM 2006;354:1264
PCSK9

- Activity regulated by intra-cellular cholesterol concentration via SREBP-2
- Statins and fibrates up regulate LDL-R and PCSK9 activity
  - effect not seen with cholesterol absorption inhibitors

Horton; Trends Biochem Sci 2007;32:71
Cohen; NEJM 2006;354:1264
Lambert; Curr Opin Lipid 2007;18:304
Kawashiri; ACC Meeting 2011;Poster 1113-282
Costet; Athero 2010 PMID: 20619837
PCSK9 Mutations

- 3 missense “gain in function” mutations are associated with autosomal dominant hypercholesterolemia
  - D374Y (aka Asp374Tyr)
    - most common in Europe and the USA
  - S127R
  - F216L
- Patients with PCSK9 gain of function mutations have more severe ↑TC than LDL-R mutations

Horton; Trends Biochem Sci 2007;32:71
Hooper; Exp Opin Biol Ther 2013;13:429
PCSK9 Mechanism of Action
Strategies to Inhibit PCSK9

- Inhibiting antibodies
  - human monoclonal Abs that bind to PCSK9 and inhibit its interaction with the LDL-R
- Therapeutic gene silencing / antisense oligonucleotides
  - all trials so far terminated early
- Small molecules that inhibit PCSK9 interactions with the LDL-R
  - all are in preclinical development

Giugliano; Lancet 2012;380:2007
Duff; Exp Opin Ther Target 2011; 10.1517/14728222.2011.547480
Specific PCSK9 Inhibitors

- AMG145 (Amgen)
  - LAPLACE-TIMI 57
  - MENDEL
  - GAUSS
- REGN727 / SAR236553 (Regeneron / Sanofi)
  - R727 Trial
  - Odessey series
- PF04950615/RN316 (Pfizer)
- LGT209 (Novartis)
- RG7652 (Roche)
AMG145 – LAPLACE – TIMI 57

• Randomized, placebo controlled dose ranging study
• n=631 patients with ↑TC on a stable dose of a statin +/- EZ
• AMG145: 70 mg, 105 mg, 140 mg or placebo given sq every 2 and every 4 weeks
• 1º endpoint: ΔLDL-C at week 12

Giugliano; Lancet 2012;380:2007
AMG145 LAPLACE TIMI 57
Conclusions

• AMG145 reduced LDL-C by up to an additional 66% in patients already on a statin +/- EZ

• During the trial there were no treatment related serious adverse events reported

Giugliano; Lancet 2012;380:2007
AMG145 MENDEL

• Randomized, placebo controlled phase II study
• n=406 patients with low CVD risk who did not require LDL lowering and were not on statins
• AMG145: 70 mg, 105 mg, 140 mg or placebo or EZ every 2 and every 4 weeks
• 1º endpoint: ΔLDL-C at week 12

Koren; Lancet 2012;380:1995
AMG145 MENDEL: Results

Koren; Lancet 2012;380:1995
AMG145 MENDEL
Conclusions

• AMG145 reduced LDL-C at least 48% in patients not on a statin

• Injection site reactions occurred in 6% of the AMG145 group and 4% of the placebo group

Koren; Lancet 2012;380:1995
AMG 145 GAUSS

• Randomized, double-blind placebo and EZ controlled dose ranging study
• n=160 patients with ↑TC and known statin intolerance
  – baseline LDL=193 mg%
  – <age> = 62 yrs
  – 24% had known CVD
• AMG145: 280 mg, 350 mg, 420 mg, 420 mg + EZ or EZ +placebo every 4 weeks
• 1º endpoint: ∆LDL-C at week 12

Sullivan; JAMA 2012;308:2497
AMG145 GAUSS: Results

Sullivan; JAMA 2012;308:2497
AMG145 GAUSS: Conclusions

• Overall LDL-C reductions of 42 to 63%

• Lp(a) reduction of 20 to 26%

• Modest increases of 5 to 12% in HDL-C and apo-AI

Sullivan; JAMA 2012;308:2497
REGN727

- Double blind randomized placebo controlled dose ranging study
- n=183 patients with ↑TC on atorva (10, 20 or 40 mg) but not at their ATP-III LDL-C goal
- REGN727: 150 mg or placebo every q2 or q4 weeks

McKenney; presented at the 2012 ACC Annual Mtg
REGN727 Results

• REGN727 150 mg q4weeks dropped LDL-C an additional 29%
• REGN727 150 mg q2weeks dropped LDL-C an additional 72%
  – Lp(a) dropped 27%
  – apoB dropped 50%
  – nonHDL-C dropped 63%
• No ↑ in LFTs or muscle Sx’s

McKenney; presented at the 2012 ACC Annual Mtg
REGN727 Odyssey Series

- REGN727 150 mg or placebo every 2 weeks in very high risk patients on Crestor 10 or 20 and with LDL-C not less than 70 mg%.
- REGN727 150 mg or placebo every 2 weeks in very high risk patients on Lipitor 20 or 40 and with LDL-C not less than 70 mg%.
- REGN727 150 mg or placebo every 2 weeks in very high risk patients intolerant to statins and with LDL-C not less than 70 mg%.
Cholesterol Ester Transfer Protein (CETP) Inhibitors
CETP Basic Science

- Cholesterol ester transfer protein synthesized in the liver and adipocytes
  - 476 amino acid 74 kD glycoprotein
- Exists predominantly (74%) bound to HDL
  - 83% activity associated with apo-AI particles vs. 8% activity with apo-AI/AII particles
- Mediates exchange of CE from HDL with triglyceride from apo-B containing lipoproteins (VLDL, IDL & LDL)
  - “large” VLDL are the preferred acceptors

Bishop; Am J Ther 2013;
Krauss; J Lipid Res 2012;53:540
Goff; Pharm and Ther 2004;101:17
‘I sense an element of disagreement . . . ’
CETP Deficiency

- The most common cause of hyper-α-lipoproteinemia in Asian populations – due to a mutation in the CETP gene
- Have high TC, high apoAI, CIII and E with normal apoB levels
- Have [HDL] 3 to 6 x ULN – mainly HDL2

Bishop; Am J Ther 2013; Krauss; J Lipid Res 2012;53:540
CETP: Mechanism of Action
History of CETP Inhibition
Torcetrapib

• RADIANCE 1: FH pts; ↑HDL 52%, ↓LDL 21%
  – 1º endpoint: Δ in CIMT at 2 yrs: no difference between Tor. and placebo
  – Tor group had an ↑BP and 2x as many CVD SAE’s

• RADIANCE 2: IIb pts; ↑HDL 63%; ↓LDL 18%
  – stopped early due to increased deaths in Tor group with no Δ in CIMP

Karalis; Circ 2013; 10.1161/CIRCOOUTCOMES.111.000014
Gotto; Exp Rev Cardiovasc Ther 2012;10:955
History of CETP Inhibition
Torcetrapib

- **ILLUSTRATE**: 1188 pts with CAD
  - Tor 60 mg + atorva vs atorva alone
  - ↑HDL 61%, ↓LDL 20%
  - No difference in atheroma volume at 2 years

- **ILLUMINATE**: 15,000 high risk pts.
  - Tor 60 mg + atorva vs. atorva alone
  - ↑HDL 72%
  - Tor group: 25% ↑CVD deaths and 58% ↑ all cause mortality

Karalis; Circ 2013; 10.1161/CIRCOOUTCOMES.111.000014
Gotto; Exp Rev Cardiovasc Ther 2012;10:955
Torcetrapib development was stopped in 2007
History of CETP Inhibition
Dalcetrapib

• dal-PLAQUE: 130 pts with CVD
  – dal 600 vs placebo x 2 years
  – ↑HDL 31%; no change in LDL
  – No difference in CIMT endpoint

• dal-VESSEL: 472 pts with CAD
  – dal 600 vs placebo x 36 weeks
  – ↑HDL 31%; no change in LDL
  – No difference in endothelial function

Karalis; Circ 2013; 10.1161/CIRCOOUTCOMES.111.000014
Gotto; Exp Rev Cardiovasc Ther 2012;10:955
History of CETP Inhibition
Dalcetrapib

• dal-OUTCOMES: 15,871 pts with ACS
  – dal 600 vs placebo (plus usual care)
  – ↑HDL 31%; no change in LDL
  – Study stopped early due to “futility

Karalis; Circ 2013; 10.1161/CIRCOUICOMES.111.000014
Gotto; Exp Rev Cardiovasc Ther 2012;10:955
Dalcetrapib development was stopped in 2012
Current Status of CETP Inhibition

- Anacetrapib (aka MK-0859) – by Merck
- Evacetrapib – by Lilly
Anacetrapib: DEFINE

- Double blind randomized controlled safety study
- n=1623 pts with CAD or CHD equivalent on a statin
- Randomized to ana 100 vs placebo
- 1º outcome: Δ in LDL after 24 wks and 76 wks f/u
- Safety: no difference in BP, electrolytes, or SAE’s

Gotto; Exp Rev Cardiovasc Ther 2012;10:955
Cannon; NEJM 2010;363:2406
Bishop; Am J Thera 2013
DEFINE

Effects on LDL-C and HDL-C

**LDL-C**

-39.8% (p<0.001)

**HDL-C**

+138.1% (p<0.001)

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DEFINE – Safety Data

• Pre-defined adjudicated CV events and mortality

• Anacetrapib arm: n=808
  – 16 events (2.0%)

• Placebo arm: n=804
  – 21 events (2.6%)
30,000 patients with occlusive arterial disease in North America, Europe and Asia

Background LDL-lowering with atorvastatin

Randomized to anacetrapib 100 mg vs. placebo

Scheduled follow-up: 4 years

Primary outcome: Coronary death, myocardial infarction or coronary revascularization

www.revealtrial.org
Evacetrapib: Dose Ranging Study

• Double blind randomized controlled
• n=398 pts randomized to eva 30 mg, 100mg, 500 mg or placebo plus simva 40, atorva 20 or rosuva 10
• 1º endpoint: Δ in LDL and HDL at 12 weeks
• Results:
  – @ 500 mg: ↑HDL 129%; ↓LDL 36%
  – lower the baseline HDL, greater the increase
  – no changes in BP

Bishop; Am J Therap 2013
Evacetrapib: ACCELERATE

- Randomized, double blind placebo controlled
- \( n=11,000 \) pts with CAD, CVD or PAD
- f/u x 4 years
- 1ºendpoint: CVD events
- Expected completion date: 2015

Karalis; 2013; DOI:10.1161/CIRCOOUTCOMES.111.000014
Lipoprotein Associated Phospholipase A2 (Lp-PLA2) Inhibitors
Phospholipase A

• “Super family” of calcium independent lipase enzymes

• 5 classes:
  – Lipoprotein-associated (Lp-PLA)
  – Secreted (sPLA)
  – Cytosolic (cPLA)
  – Lysosominal (IPLA)
  – Platelet factor acetohydrolases

Lonn; Can J Card 2010;26(S):27A
Suckling; Athero 2010;212:357
Phospholipase A2

- All hydrolyze sn-2 ester bonds in phospholipids
- Lp-PLA and sPLA involved in the atherosclerotic process

Lonn; Can J Card 2010;26(S):27A
Suckling; Athero 2010;212:357
Lp-PLA2 Basics

- Lp-PLA₂ = Lipoprotein Associated Phospholipase A2
- Enzyme responsible for the hydrolysis of (only) oxidized phospholipids on LDL
- 80% circulates on LDL particles and requires apo-B100 for activity
  - especially active on small, dense LDL
  - remaining 20% on HDL and remnant particles
Lp-PLA$_2$ Basics

- Products of the reaction are oxidized fatty acids and lysophosphatidyl choline
  - both of which trigger an inflammatory cascade and induce endothelial dysfunction
- Intimal macrophages / foams cells are the primary source of Lp-PLA$_2$ production
- Lp-PLA$_2$ production is highly up-regulated in active (unstable) plaques
Elevated Lp-PLA\textsubscript{2} is Consistently Associated With a Doubling of Risk for Cardiovascular Disease

Blake (WHS), *J Am Coll Cardiol* 2001 – CHD
Blankenberg (AtheroGENE), *J Lipid Res* 2003 – CAD
Ballantyne (ARIC), *Circulation* 2004 – CHD LDL < 130
Oei (Rotterdam), *Circulation* 2005 – CHD
Brilakis (Mayo Heart), *Eur Heart J* 2005 – CHD
Ballantyne (ARIC), *Arch Intern Med* 2005 – Stroke
Oei (Rotterdam), *Circulation* 2005 – Stroke
Winkler (LURIC), *Circulation* 2005 – CHD
Khuseynova (HELICOR), *Atherosclerosis* 2005 – CHD
Koenig (KAROLA), *Arterioscler Thromb Vasc Biol* 2005 – CVD
May (Intermountain Heart), *Am Heart J* - CHD
Jenny (CHS), *AHA-EPI Abstract* 2006 – MI
Elkind (NOMAS), *Arch Intern Med* 2006 – Stroke
O’Donoghue (PROVE IT), *Circulation* 2006 – CVD
Corsetti (THROMBO), *Clinical Chemistry* 2006 – CHD
Gerber (Olmsted County), *ATVB* 2006 - Death S/P MI
Oldgren (GUSTO / FRISC), *Eur Heart J* 2007 - Acute ACS
Sabatine (PEACE), *AHA-Scientific Sessions* 2006 – CVD
Persson (Malmo), *Arterioscler Thromb Vasc Biol* 2007 - CVD
Mockel (NOBIS-II), *Clin Res Cardiol* 2007 – CVD
Hatoum (Nurse’s Health Study), *Circ Suppl* 2007 – MI
Daniels (Rancho Bernardo), *JACC* 2008 – CHD

Lp-PLA2 Inhibitor - Darapladib

• Selective, reversible oral inhibitor of Lp-PLA2 that targets the serine residue

Quang; Expert Opin Invest Drugs 2010;19:161
Darapladib – IBIS 1

- DBPC dose ranging study
- n=959 pts with CHD or a CHD equivalent
- Randomized to atrova 20 vs 80 with dara 40, 80 160 or placebo
- 1º endpoint: reduction in Lp-PLA2 activity
- Results:
  - placebo: no effect
  - 40 mg: ↓43%
  - 80 mg: ↓55%
  - 160 mg: ↓66%

Quang; Expert Opin Invest Drugs 2010;19:161
Darapladib – IBIS 2

- DBPC study of n=330 pts with angiographically proven CAD on usual care
- Randomized to dara 160 mg vs placebo
- 1º outcome: IVUS Δ’s over 12 months
- Results:
  - Placebo group: LRNC ↑’d
  - Dara group: LRNC stabilized – no changes

Quang; Expert Opin Invest Drugs 2010;19:161
Darapladib: STABILITY

- DBRC ongoing outcomes study
- n=15,828 pts with known CHD on usual care
- Randomized to dara 160 vs placebo
- 1<sup>o</sup> outcome: MACE at 3 yrs
- Was fully enrolled as of April 2010

Quang; Expert Opin Invest Drugs 2010;19:161
White; Am H J 2010;160:655
Darapladib: STABILIZE

STABILITY TRIAL Study Design

High risk patients with chronic CHD

Additional entry criteria
- Continue/modify guideline-mandated treatment
  - e.g., Aspirin, statin unless contraindicated
  - e.g., adjust anti-hypertensive medications

Randomization

Darapladib  Placebo

n = ~15,828

1st Endpoint: composite MACE (CV death, MI, stroke)
2nd Endpoints: Major Coronary Events/Total coronary events/All-cause Mortality

1 patients <60 years of age will require additional enrichment criteria:
diabetes mellitus, low HDL, current smoking, CKD (eGFR <60 ml/min/1.73 m2), polyvascular disease

Quang; Expert Opin Invest Drugs 2010;19:161
White; Am H J 2010;160:655
Summary Slide

• Over the next few years several new drugs and drug classes will be available to treat a variety of lipid and atherosclerosis related disorders
Questions?