Challenging Lipid Cases

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Disclosures

- None
- IMPROVE-IT not yet published
- PCSK9 inhibitors not currently available

Case 1

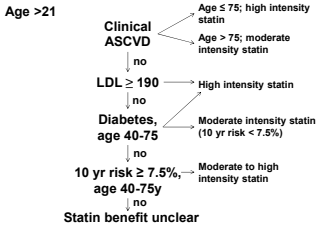
49 ♀ type 2 DM with no known CVD
- DM2 x 16 years
- Nonsmoker,
- Hypertension controlled

Meds:
- Metformin
- Glipizide
- Sitagliptin
- Levothyroxine
- Lisinopril
- ASA
- Atorvastatin 40mg/d

Labs (on statin)
- TC 143 (3.7)
- HDL-c 28 (0.73)
- LDL-c 115 (2.99)
- TG 283 (3.2)
- HbA1c 8.7%
- TSH 1.2

What is the next best step?
A. Add a fibrate
B. Add niacin
C. Add ezetimibe
D. Add fish oil
E. Add insulin

ASCVD Statin benefit groups



Current ADA Guidelines for Lipid Lowering Therapy in Diabetes

Age	CVD or RFs	Statin Therapy intensity
<40 years	No RFs +RFs Overt CVD	None Moderate or High High
40-75 years	No RFs + RFs Overt CVD	Moderate High High
> 75 years	No RFs + RFs Overt CVD	Moderate Moderate or High High

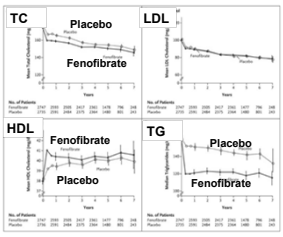
RFs: LDL ≥ 100 mg/dl, HTN, smoking, overweight

Diabetes Care, 2015

Add a Fibrate? ACCORD Study

- 5518 Type 2 diabetics, HbA1c 8.3%, with known CVD or high risk
- 31% female; 60% on simvastatin prior to enrollment
- Patients on simvastatin (avg 20 mg/d) randomized to fenofibrate (160 mg/d) or placebo

Statin + Fibrate: Lipid Effects

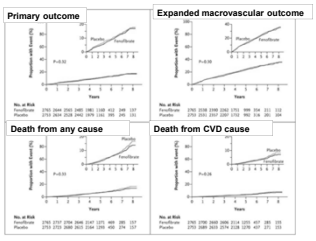


ACCORD Study

Type 2 DM pts on simvastatin randomized to fenofibrate or placebo

ACCORD study group; NEJM 2010

Statin + Fibrate: Outcomes



ACCORD study group; NEJM 2010

Statin + Fibrate: Safety

- CK > 10 x ULN in 19 pts (equal between fibrate and placebo)
- Creatinine ↑ from 0.93 to 1.1 mg/dl in fibrate group, then stabilized (placebo from 0.93 to 1.04)
- Study drug d/c rate 2.4% in fibrate, 1.1% in placebo due to GFR, no difference in ESRD rates

Add a Fibrate?

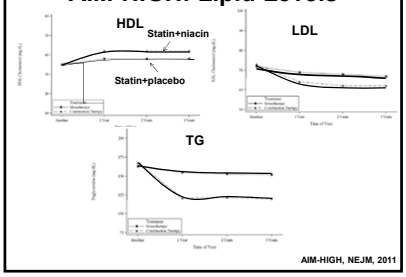
- **ACCORD subgroup analysis suggested possible benefit for those with high TG (>200) and low HDL (<31)**
- **Safety: no increased risk of rhabdo or renal failure in trial settings**
- **Adding a fibrate may be an option**

Add Niacin? AIM-HIGH

- **3414 patients with known CVD randomized to simvastatin + placebo or simvastatin + ER niacin**
  - **ezetimibe if needed for LDL 40-80 on therapy**
- **76% were on statin > 1 year pre-trial**

AIM-HIGH, NEJM, 2011

AIM-HIGH: Lipid Levels



AIM-HIGH, NEJM, 2011

AIM-HIGH: No effect on CVD

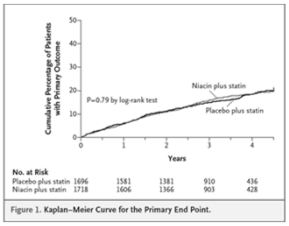
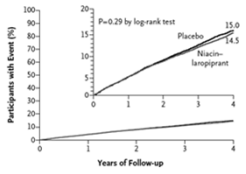


Figure 1. Kaplan–Meier Curve for the Primary End Point.

AIM-HIGH, NEJM, 2011

HPS2-THRIVE: No CVD Benefit



LDL was 10 mg/dl lower and HDL was 6 mg/dl higher in niacin group c/w placebo group

- **25,673 patients with known CVD were randomized to simvastatin + placebo or simvastatin + ER niacin, ezetimibe added if needed**

NEJM, 2014

Add Niacin?

- **Increased SAEs:**
  - **Increased serious infections**
  - **Worse diabetes control**
  - **Increased diabetes incidence**
  - **Increased GI, MSK and skin complaints**
- **No clear benefit to any subgroup**
  - **Possible benefit in those with higher baseline LDL**
  - **No benefit in those with low HDL /high TG**

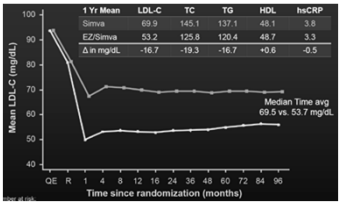
Adding Niacin not the best choice

Add Ezetimibe? IMPROVE-IT

- **18,144 ACS subjects were randomized to simvastatin 40 mg/d or simvastatin 40mg + ezetimibe 10 mg/d**
- **35% had prior lipid therapy**
- **27% diabetic**
- **25% female**

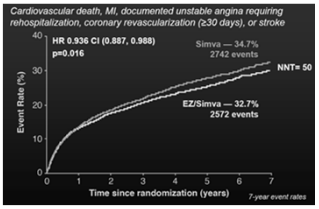
Note – not yet published, so this data is from the web

IMPROVE-IT: LDL Effects



http://www.eas-society.org/fileArchive/IMPROVE%20IT%20-%20PRESENTATION%202014-11-17.pdf

IMPROVE-IT: CVD Effects



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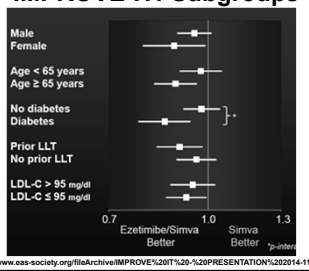
IMPROVE-IT: Subgroups



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Add Ezetimibe?

- Relatively safe, and appears to be efficacious
- Adding ezetimibe may be an option

Add Fish oil?

- Diet studies fairly consistently report high fish intake associated with low CVD and vv
- Treatment with fish oil has had inconsistent results

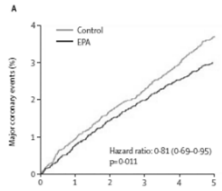
Fish Oil + Statin

- Alpha Omega Trial randomized post-MI patients to EPA-DHA or placebo (via diet supplements)
  - no overall effect on CVD
  - Trend to ↓CVD in statin non-users only
- ORIGIN randomized patients with diabetes/pre-diabetes to omega-3 or placebo; 50% were on statins
  - No effect on CVD

Fish Oil + Statin: JELIS

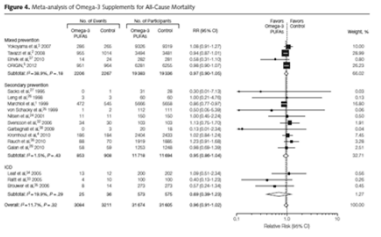
- 18,645 Japanese patients were randomized to 1800 mg EPA + statin or statin alone
  - Prava 10-20mg/d or Simva 5-10 mg/d
  - Baseline LDL >169 (4.4) (average = 181)
  - Overall CVD mortality much lower than other studies
  - 2/3 study population were women

JELIS: CVD outcomes



Yokoyama et al, Lancet 2007, 1090-98

Omega-3 Effect on All-Cause Mortality



Rizos et al, JAMA, 2012

Add Fish Oil?

- Still remains controversial
- Possible benefit, but may not be as good as alternate agents

Add Insulin?

- UKPDS – suggested CVD benefit from improved glycemic control
- ADVANCE, ACCORD, VADT – confused the issue
- Meta-analyses overall suggest limited benefit of intensive glucose control on all cause and CVD mortality, but microvascular benefits

Case 1

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- DM2 x 16 years
- Nonsmoker,
- Hypertension controlled

Meds:
- Metformin
- Glipizide
- Sitagliptin
- Levothyroxine
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What is the next best step?
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Case 2

38 ♂ with known CVD
- MI age 32, 36
- Nonsmoker
- BP controlled

Meds:
- Lisinopril
- HCTZ
- ASA
- Rosuvastatin 40mg/d

Labs (on statin)
- TC 348 (9.0)
- HDL-c 42 (1.09)
- LDL-c 285 (7.4)
- TG 98 (1.1)

What is the next best step?
A. Add lomitapide
B. Add mipomersen
C. Refer for PCSK9 research study
D. Refer for LDL apheresis
E. No further benefit to adding therapy

Case 2

- Excess LDL cholesterol due to
  - Loss of function mutations in LDL receptor
  - Loss of function mutations in apoB
  - Gain of function mutations in PCSK9
  - Loss of function mutations in LDLRAP1
- Causes premature CVD
  - Homozygotes can have CVD in childhood
  - Heterozygotes present in early adult years
- Response to statins dependent upon LDL receptor levels

Statin Intensity

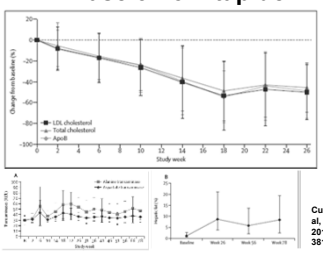
High intensity statin
- ↓LDL >50%
- Atorva 40, 80
- Rosuva 20, 40

Moderate intensity statin
- ↓LDL 30-50%
- Atorva 10, 20
- Fluva 80
- Lova 40
- Pitava 2, 4
- Prava 40, 80
- Rosuva 5, 10
- Simva 20, 40

Lomitapide

- Juxtapid®: MTP (microsomal triglyceride transfer protein) inhibitor, decreases LDL
- Indication for homozygous FH (only)
- 5, 10, or 20 mg po daily (max 60 mg/d)
- ↓LDL 40%, ↓TG 45%, ↓HDL 7%
- SE: liver toxicity, hepatic steatosis, decreased fat soluble vitamin levels (add supplements)
- Use is restricted due to hepatotoxicity

Phase 3 Lomitapide



Cuchel et al, Lancet 2013, 381;40-46

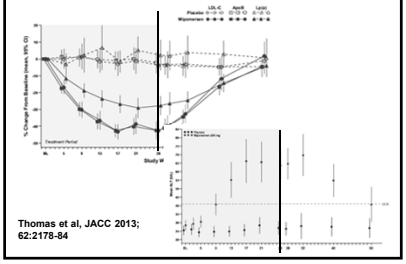
Mipomersen:

- Kynamro®: anti-sense oligonucleotide (ASO) of apoB100 - blocks synthesis
- Indicated for homozygous FH (only)
- 200 mg SC weekly
- ↓LDL 25%, ↓TG 18%, ↑HDL 15%
- SE: liver toxicity (12%), injection site reactions (84%), flu-like symptoms (30%)
- Use is restricted due to hepatoxicity

Mipomersen Data

- 157 patients with hypercholesterolemia (not FH) with or high risk for CVD receiving maximally tolerated lipid therapy
- Patients randomized 2:1 to mipomersen or placebo

Mipomersen



Thomas et al, JACC 2013; 62:2178-84

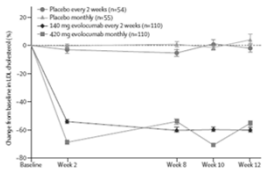
PCSK9 Drugs

- In Phase 3 trials: evolucamab, alirocumab
- PCSK9 binds to the LDLR and induces LDLR degradation, thus causing ↑LDL
- Gain of function mutations cause ↑LDL (resembles FH); loss of function mutations cause ↓LDL
- Drugs (monoclonal antibodies) to inhibit PCSK9 are in development, can lower LDL > 50% and are additive to statins, outcomes studies ongoing
- SC injections, monthly
- Will probably be marketed for htzFH, statin resistance

PCSK9 Inhibitor Evolocumab

- 331 patients with htz FH on lipid lowering therapy randomized to evolocumab (140 mg q2 weeks or 420 mg qmo) or placebo (q2 weeks or qmo)
- Baseline LDL > 100 (2.6) on statins

PCSK9 Inhibition



Additional longer term studies have shown LDL reductions are stable for up to 52 weeks with no additional safety or tolerability issues; PCSK9 has additive effects to statin & ezeitimibe therapy

Raal et al, Lancet 2015, 385:331-40

LDL apheresis

- Several small imaging studies have reported atherosclerosis regression with 1-3 years of LDL apheresis
- Seems to increase life expectancy
- LDL apheresis generally performed weekly, expensive, time-consuming
- Lowers LDL 30-60% each session
  - Also lowers lp(a), VLDL (TG)
- Indicated for hmzFH, htz FH with LDL > 300 mg/dl or LDL>200 mg/dl and CAD

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