

**Primary and Secondary Prevention of  
Coronary Artery Disease: What is the role  
of non statin drugs (fenofibrates, fish oil,  
niacin, folate and vitamins)?**

**Janet B. Long, MSN, ACNP, CLS, FAHA, FNLA  
Rhode Island Cardiology Center**

# Objectives

- Discuss current evidence supporting or refuting the value of non statin agents in the primary and secondary prevention of occlusive coronary disease
  - Fenofibrates
  - Fish oil
  - Niacin
  - Folate
  - Vitamins

# Fibrates

# Fibrates

- ↑ HDL (5-15%)
- ↓ Triglycerides (30-50%)
- ↓ VLDL
- ↓ Small dense LDL particles
  - Shift to larger buoyant particles
- Improved endothelial function
- Anti-inflammatory response
- ↓ fibrinogen
- ↓ CRP

# Summary of Key Studies Involving Fibrate therapy

| Study                                       | Treatment                   | Total Subjects        | Primary end point                    | Findings                              |
|---|-----------------------------|-----------------------|--------------------------------------|---------------------------------------|
| <b>Primary Intervention</b>                 |                             |                       |                                      |                                       |
| Helsinki Heart Study<br>1998 <sup>(1)</sup> | Gemfibrozil                 | 4,081 men             | Non-fatal MI/CHD death               | ↓34% vs placebo p<0.05                |
| <b>Secondary Intervention</b>               |                             |                       |                                      |                                       |
| Stockholm IHD<br>1988 <sup>(2)</sup>        | Clofibrate + Nicotinic acid | 555 post MI men/women | Total mortality<br><br>IHD mortality | ↓26% vs placebo/p<0.05<br>↓36% p<0.01 |
| VA-HIT<br>1999 <sup>(3)</sup>               | Gemfibrozil                 | 2,531 men with CHD    | Non-fatal MI/CHD death               | ↓22% vs placebo p=0.006               |

1. NEJM 1987. Nov 12;317 (20) 1237-45 2. ACTA Med Scand 1988;223 (5):405-18 3. NEJM 1999:341:410

# Summary of Key Studies Involving Fibrate therapy

| Study  | Treatment   | Total Subjects              | Primary end point           | Findings  |
|--|-------------|-----------------------------|-----------------------------|---|
| <b>Primary/<br/>Secondary</b>                                |             |                             |                             |   |
| DAIS<br>2001<br><br>Diabetes Care 2002.<br>Vol25 (3) 627-628 | Fenofibrate | 418<br>men/women<br>with DM | Angiographic<br>measurement | <b>42% ↓ in<br/>progression<br/>in focal<br/>stenosis</b> |

# Summary of Key Studies Involving Fibrate therapy

| Study                         | Treatment   | Total Subjects   | Primary end point         | Findings  |
|-------------------------------|-------------|--|---------------------------|---|
| <b>Primary/<br/>Secondary</b> |             |  |                           |   |
| FIELD<br>2005                 | Fenofibrate | 9,795<br>men/women<br>2,131 hx of<br>CVD and<br>type II DM | CHD death/<br>nonfatal MI | No signif diff<br>vs placebo<br>↓ <b>25% vs pl.<br/>in pts w/out<br/>CVD</b> ; no sig.<br>diff vs pl. in<br>pts w/h CVD |
| Lancet 2005;<br>366:1849      |             |  |                           |   |

# ACCORD Trial

| Study  | Treatment   | # Subjects | Primary End Point   | Findings  |
|--|---|------------|---|---|
| ACCORD Trial<br><br>NEJM 2010, Mar 14<br>Lancet 2010 June 29 | 60% taking statin prior to enrollment<br>Simvastatin + Fenofibrate<br>Simvastatin + Placebo | 5,518      | Primary: 1 <sup>st</sup> nonfatal MI, CVA or death from CV cause<br>Second: Combination primary + revascularization or hosp/CHF, fatal cor. Event, nonfatal MI, USA or CVA, death any cause | <b>Primary: no significant difference</b><br><br><b>Subgroup: TG <math>\geq</math> 204 mg/dL; HDL <math>\geq</math> 34</b><br><b>12.4% vs 17.3%</b> |

# Should we stop using Fibrates?

- No
- Fibrates have favorable effects on lipid parameters with previous trials
- ATP III Guidelines suggest lifestyle changes, adding fibrates, niacin or omega 3 when triglycerides are 200 mg/dL or greater.
- 2011 Scientific Statement from AHA “In summary the aggregate data suggest that statin or fibrate monotherapy may be beneficial in patients with high triglyceride levels, low HDL-c or both.” “What remains to be seen is whether these modalities favorably influence CVD outcomes beyond proven therapies (eg. Statins). Therefore additional clinical outcome trials are necessary.”

Circulation. 2011;123:2292-2333.

Grundy S, et. al. *Circulation*. 2005;112:2735

*JAMA* 2001;285:2486-97

# Fish Oil

# Fish Oil

- ↓ Triglycerides 25 to 45%
- ↑ LDL 0 – 30%

# Omega 3 Fatty Acids

- Two types

- $\alpha$ -linolenic acid plant derived
- EPA, DHA marine derived

# Omega 3 Fatty Acids

- $\alpha$ -linolenic acid
- Decreases arrhythmias
- Decrease platelet aggregation

# Omega 3 Fatty Acids

- Fish Oil – DHA, EPA
  - Lower triglycerides – 4 gm – 25-45%
  - Cardioprotective intakes 1 gm/day
  - Small effect on blood pressure
  - Decrease platelet aggregation
  - Reduces arrhythmias
  - Reduces resting HR
  - Improves endothelial function
  - Decreases inflammation
  - Decreases vasoconstriction

# Omega 3 Trials

|   |   |  |  |
|---|---|--|--|
| <p>GISSI-<br/>Prevention Trial</p> <p>Lancet 1999;354:447-455</p> | <p>11,232<br/>post MI</p>   | <p>EPA/DHA 850 mg/d<br/>Vitamin E<br/>Both or<br/>No treatment</p>   | <p><b>EPA/DHA prevented<br/>deaths by ↓<br/>arrhythmias</b></p>  |
| <p>JELIS study</p> <p>Lancet 2007;369:1090-<br/>1098</p>          | <p>18,000<br/>men and<br/>women<br/>with or<br/>without<br/>CAD</p> | <p>Statin (Pravastatin<br/>10 or Simvastatin 5<br/>mg/d) alone<br/>or<br/>statin plus EPA<br/>1,800 mg/d</p> | <p>After 5 years, <b>CAD pts<br/>had 19% lower rate of<br/>coronary event in<br/>EPA group</b><br/><b>Combination tx. May<br/>↓coronary events</b></p> |

# Omega 3 Trials

|                            |               |  |   |
|----------------------------|---------------|--|---|
| Alpha Omega Trial          | 4,837 post MI | Placebo margarine<br>Margarine with 400 mg EPA/DHA<br>Margarine with 2 g ALA | <b>Neither EPA/DHA nor ALA were better than placebo</b> |
| NEJM<br>2010;363:2015-2026 |               |  |   |

# Niacin

# Nicotinic Acid

- ↓ LDL  $\geq 2$  gm
- ↓ Triglycerides  $\geq 2$  gm
- ↑ HDL occur at dose of  $\geq 1$  gm

# Nicotinic Trials

|   |                            |                                |  |
|---|----------------------------|--------------------------------|--|
| <b>Coronary Drug Project (CDP)<br/>1986</b> | 8,341 men with previous MI | Nicotinic Acid 3 gm vs placebo | Treatments stopped after 6 yrs. Modes, non-signif ↓ mortality among pts on niacin          |
| JACC 1986;8:1245-1255                       |                            |                                | <b>9 yrs after tx. Stopped, statistically significant ↓ mortality in nicotinic acid pt</b> |

# Nicotinic acid Trials

|                                   |                          |   |  |
|-----------------------------------|--------------------------|---|--|
| <p><b>CLAS trial<br/>1990</b></p> | <p>188 men post CABG</p> | <p>Diet plus placebo/ or diet plus combined colestipol 30 g/d and nicotinic acid 3 to 12 gm/day</p> | <p><b>Regression greater in treated group at 2 and 4 yrs.</b> Progression of old lesions and development of new lesions significantly less in treated group.</p> <p><b>Most beneficial in patients with chol &gt;240 mg/dL</b></p> |
|                                   |                          |   | <p>JAMA 1990;264:30013<br/>Circulation 1996;93:34</p>  |

# Nicotinic Acid Trials

|                            |  |   |  |
|----------------------------|--|---|--|
| <b>FATS trial<br/>1990</b> | 146 Men with familial combined dyslipid with 1 coronary stenosis | Placebo + colestipol<br>Nicotinic + colestipol<br>Lovastatin + colestipol | <b>Nicotinic + and Lovastatin + were equally effective – delayed progression and ↑ likelihood of regression of coronary lesions. Also fewer endpoints death, MI or cor revascularization</b> |
| NEJM<br>1990;323:1289      |  |   |  |

# Nicotinic Acid Trials

|                            |   |   |  |
|----------------------------|---|---|--|
| <b>HATS Trial<br/>2001</b> | 160 patients with clinical and angiographic CAD | 1) Simvastatin +niacin<br>2) Antioxidants<br>3) Simvastatin + Niacin + antioxidants<br>Or<br>4) Placebo | <b>Simvastatin + niacin less likely CV event (death, MI, CVA, or revascularization) AND showed angiographic regression of most signif stenosis compared to placebo. ↓ in clinical events greater than with statins alone</b> |
| NEJM<br>2001;345:1583      |   |   |  |

# Nicotinic Acid Trials

|  |                                     |   |   |
|--|-------------------------------------|---|---|
| <p><b>ARBITER 2 Study (1)</b><br/>2004</p>                     | <p>167 patients with known CAD</p>  | <p>Niacin ER 1gm vs Placebo</p>   | <p><b>CIMT did not progress in Niacin group after 1 yr vs Placebo</b> that increased significantly.</p> |
| <p><b>Oxford Niaspan Study (2)</b><br/>2009</p>                | <p>71 patients HDL &lt;40 + CAD</p> | <p>Pts already taking Statin + increasing dose of Niaspan up to 2 gm or placebo</p> | <p><b>Pts. Treated with Niaspan had greater decrease in carotid artery wall area</b></p>                |
| <p>(1) Circulation 2004;110:3512<br/>(2) JACC 2009;54:1787</p> |                                     |   |   |

# Nicotinic Acid Trials

|   |  |  |   |
|---|--|--|---|
| <b>ARBITER<br/>6-HALTS<br/>trial<br/>2009</b> | 208 Men and women with CHD or CHD equivalent | Compared Niacin ER 2 gm/d with Ezetimibe 10 mg/d<br>All patients were taking statin and had LDL <100 mg/dL and HDL <50 mg/dL men and <55 mg/dL women | LDL was reduced better by Ezetimibe<br><b>HDL raised by niacin</b> and ↓ by Ezetimibe<br><b>Niacin ↓ CIMT compared with ezetimibe</b> at both 8 and 14 months. Trial was stopped early due to that. <b>Fewer CV events (MI, revasc, ACS death from CHD in Niacin group)</b> |
|   |  |  | NEJM 2009;361:2113  |

# Nicotinic Acid Trials

## AIM-HIGH Trial

|  |                                   |  |   |
|--|-----------------------------------|--|---|
| AIM-HIGH trial<br>May 2011   | 3414<br>CVD<br>Low HDL<br>high TG | Niacin ER 2<br>gm/d + statin<br>Vs<br>Statin alone | Stopped early<br>Niacin ER + statin did<br>not reduce fatal or non-<br>fatal MI, CVA,<br>hospitalizations for ACS<br>or revascularization |
| <a href="http://www.nih.gov/news/health/may2011/nhlbi-26.htm">www.nih.gov/news/health/may2011/nhlbi-26.htm</a> |                                   |  |   |

# Folate in the treatment of Homocysteine: Yes or No

## Folate (natural occurring in food); Folic Acid (synthetic form found in supplements)

- Elevated plasma homocysteine levels have been associated with higher risks of CVD.
- Folic acid, Vitamin B6 and B12 have been shown to reduce homocysteine levels
- Does reducing the homocysteine level, reduce CV risk?

# Negative Studies

|  |  |
|--|--|
| Bazzano et al. Effect of folic acid supplementation on risk of CVD: a meta analysis. JAMA 2006;296:2720-2726   | Evaluated 12 randomized controlled trials of folic acid suppl. In pts with CVD and <b>did not find that treated pts had better outcomes.</b>   |
| Albert et al. Effect of folic acid and B vitamins on risk of CV events and total mortality among women at high risk for CVD a randomized trial. JAMA 2008;299:2027-2036          | Evaluated effect of combination pill (folic acid, Vit B6, Vit B12) on CV events in women at high risk (CAD, or $\geq 3$ RF). <b>Treatment did not ↓ CVD mortality, stroke, MI or cor. Revascularization.</b> |
| Ebbing et al. Mortality and CV events in patients treated with homocysteine lowering B vitamins after coronary angiography: a randomized controlled trial. JAMA 2008;300:795-804 | 2008 the effect of folic acid, Vit B12 and Vit B6 on risks of death from any cause and of CV events in patients undergoing cor. Angiography. <b>Outcomes no better in treated group</b>                      |

# Negative Studies

Clarke, et al. for the B-Vitamin Treatment Trialists' Collaboration. Effects of Lowering Homocysteine Levels with B Vitamins on CVD, Cancer, and Cause-Specific Mortality

Arch Intern Med Oct 11, 2010, Vol 170, No. 18

Meta-analysis of 8 randomized trials involving 37,485 individuals. Analysis involved intention to treat comparisons of first events during the scheduled treatment period.

9326 major vascular events

3,990 major coronary events

1,528 strokes

5,068 revascularizations

3010 cancers

5,125 deaths

During median f/u of 5 yrs, folic acid

**no significant effect on vascular outcomes**

# USPSTF

- Concluded that “ no evidence that treating persons with a high homocysteine level improves outcomes. In several well conducted trials, homocysteine therapy did not prevent CHD events in persons with known heart disease.”

- Ann Intern Med 2009;151:474-482

# Conclusion

- Elevated homocysteine increases CV Risk
- Folic Acid, B6, B12 lower serum homocysteine levels
- Trials have not shown that reducing the homocysteine levels decrease CV risk or events
- Most trials have included all patients regardless of whether the homocysteine level is normal or elevated.
- Recent trials showed that treatment with folic acid supplementation may ↑ cancer risk
- Further studies need to be done
- Current recommendations do not support treating elevated homocysteine levels.

# Vitamins

| <b>Supplement/<br/>Food</b>        | <b>Mechanism</b>   | <b>Lipid lowering<br/>average %<br/>change</b>           | <b>Usefulness for<br/>lipid<br/>management</b>           |
|------------------------------------|--------------------|--|--|
| <b>Vitamin E</b>                   | <b>Antioxidant</b> | No significant<br>change in<br>TC/LDL<br><br>Lowers HDL2 | <b>May have<br/>harmful effect</b>                       |
| <b>Vitamin C<br/>Beta Carotene</b> | <b>Antioxidant</b> | No significant<br>change in lipid<br>profile             | <b>No clear benefit;<br/>may have<br/>harmful effect</b> |
|                                    |                    |  |  |
|                                    |                    |  |  |
|                                    |                    |  |  |
|                                    |                    |  |  |
| Circulation.<br>2005;112:3184-3209 |                    |  |  |

## Summary

- Fibrates continue to be used as monotherapy and combination therapy
- Niaspan- Beneficial in treating cholesterol, triglycerides, HDL and LDL
- Fish Oil – Beneficial treating high triglycerides
- Folic acid – **no benefit** in reducing homocysteine levels
- Vitamins – **no cardiovascular benefit**