

## Dyslipidemia (non LDL related)

Madrid I ~ 10:25am - 11:10am

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### Objectives

- Review evolving treatment strategies based on new knowledge of atherosclerotic plaque pathophysiology

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**OAFP Scientific Assembly  
June 18, 2011**

**SESSION 1  
ATHEROSCLEROSIS AND  
PLAQUE PATHOPHYSIOLOGY**

Charles F. Bethea, M.D.  
Chief Medical Officer  
INTEGRIS Heart Hospital,  
Oklahoma City, OK



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**SPECIAL THANKS**

- Cleveland Clinic for sponsoring
- New Frontiers in Anti-Atherosclerotic Therapies at ACC 4/2/11
- Dr. Nicholls            ➤ Dr. Hazen
- Dr. Libby                ➤ Dr. Kastelein
- Dr. Ridker              ➤ Dr. Rye
- Dr. Rosanson         ➤ Dr. Nissen
- Dr. Ballentyne



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**ATHEROSCLEROSIS**

Where have we been?

What have we achieved?

What is next?



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## ATHEROSCLEROSIS

- Old Pathophysiology:  
Agents of intimal injury
- New Pathophysiology:  
Intervening on agents of plaque development and initiation of inflammation




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## PLAQUE PROGRESSION:

From Fatty Streak  
To  
Complex Plaque

*"Where have we been?"*




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### PLAQUE PROGRESSION / TREATMENT TIMELINES




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### FOCUS ON THE INTIMA AND LUMEN

- Hypertension      Family History      B-100 Subtypes
- Diabetes →      LDL-C →      Triglyceride Rich Particles (IDL)
- Hyperlipidemia      HDL-2      Remnant Chylomicrons
- Smoking                              Mgm1n LDC
- Homocystine                              Carbamylated LDL



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### 1980's LIPID RESEARCH CENTERS

Increasing knowledge of Lipid particles, functions and pathophysiology.



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### 1990'S THERAPY WAS DIRECTED AT REDUCING INTIMAL INJURY

- Ace / ARB's for mechanical stress/Renin angiotensin system
- Statins – LDL-C / Low HDL
- DM – Glycemic Control (limited effect)
- Stopping Smoking
- FH – Lipid subparticle – Lp(a); B-100's small dense LDL.



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**CDC**

**IMPACT MODEL**

*"What have we achieved?"*



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**ATHEROSCLEROSIS**  
**Population Trends**

**Mortality Rate Reductions**  
(Therapies targeting intimal injury and stenotic plaque)



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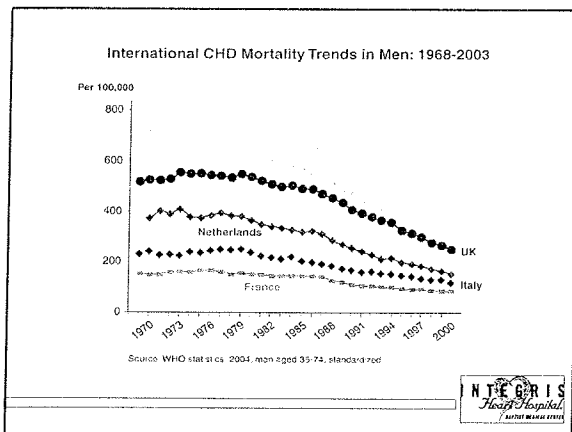
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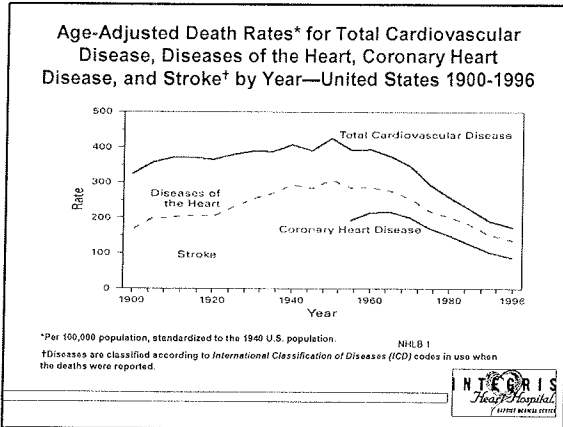
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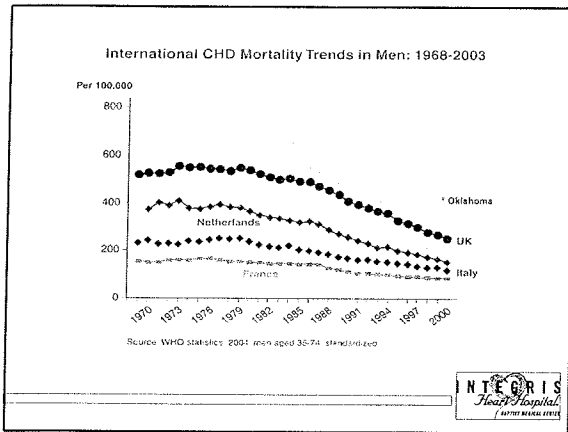
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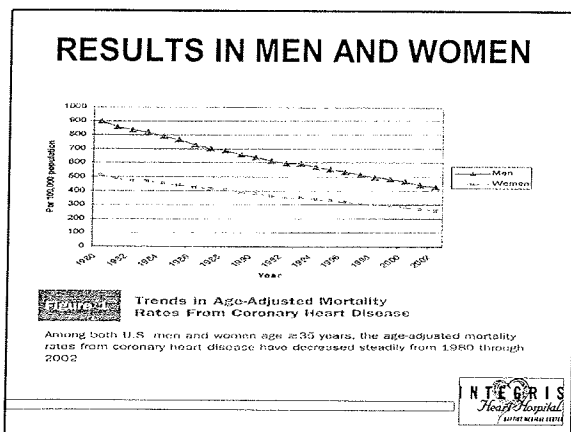
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### INTERHEART Study:

Nine Modifiable Risk Factors Account for More than 90% of the Risk of an Initial Acute Myocardial Infarction

- Smoking
- Hypertension
- Lipids (ApoB/A1 ratio)
- Abdominal obesity
- Diabetes

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- Fruit and vegetable intake
- Alcohol
- Exercise
- Psychosocial



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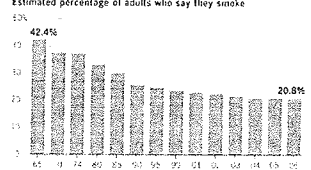
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### SMOKING EFFECT

**Leveling off**      National Goal 12%

The percentage of people in the U.S. who smoke has stopped declining, leveling off at just under 21% for the last few years. Estimated percentage of adults who say they smoke



November 9, 2007



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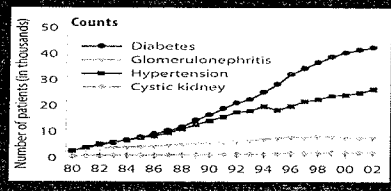
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### HYPERTENSION AND DIABETES EFFECT

**Incident Counts & Adjusted Rates, By Primary Diagnosis**





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## IS THE CAD REDUCTION PARTY OVER??

Counter trends related to:

- Body Mass Index Increase
- Sedentary Life Style
- High Fat (fast food) Diet

*"What is next in the short-term?"*




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## CHOLESTEROL: The Good News!




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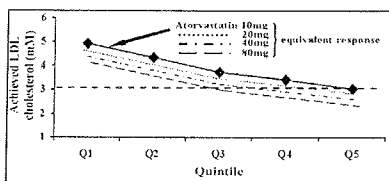
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## STRONGER STATINS



Even the most potent statins fail to achieve targets. If it is assumed that 10 mg of atorvastatin produces the same LDL cholesterol reduction as 40 mg of pravastatin, and that for each doubling of its dose there is a further 6% fall in LDL cholesterol, then even the highest recommended dose of atorvastatin (80 mg) will fail to bring the entire WOSCOPS cohort to the European LDL target value of 3.0 mmol/l. This figure should be viewed in conjunction with previous figure.




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**U.S. achieves average cholesterol  
of less than 200 (3.5 mM) in 2006  
(first time in 50 years)**



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- Much more can be achieved for major risk factors.
- Momentum has slowed for major risk factor reduction.
- Obesity and DM pose a threat.



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**PRIMARY PREVENTION  
CONCLUSION**

- Achieved a lot.
- Approaching practical limits.
- Undermined by obesity and diet.
- Future gains will be slow and difficult.



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➤ New role for inflammation, DM and lipid sub-particle management.

*“What is next long-term?”*



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### LDL SUBTYPES

Any patient with marked FH or CAD with normal lipids.

Lp (a)  
Small LDL (ApoB)  
Non-HDL-cholesterol

? Berkely screen – (IDL) Female with PAD (not advised)



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### Non-HDL CHOL

Total Chol – HDL = Non-HDL cholesterol

Trig < 400 due to Friedewald equation limitation



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### TREATMENT GOALS

CAD RISK	LDL	NON-HDL CHOL
Very high risk	< 70	< 100
High risk	< 100	< 130
Moderate risk	< 130	< 160
Low risk	< 160	< 190

Bitner, Vero Proceedings: 2007



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### New pathologic LDL for Diabetes Mellitus and Smokers

- Mg min LDL
- Metformin modifies abnormal sugars
- Carbamylated LDL – smokers and renal failure



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### NEW FRONTIER

Inflammation and Progression

Atherosclerotic plaque and progression



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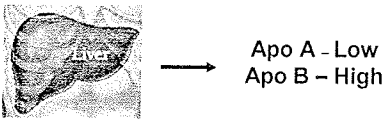
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### SUMMARY OF TARGETS AND MEDS

Mechanism



Apo A - Low  
 Apo B - High




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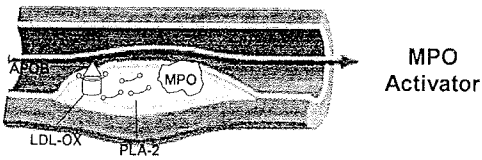
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### Mechanism



MPO  
 Activator




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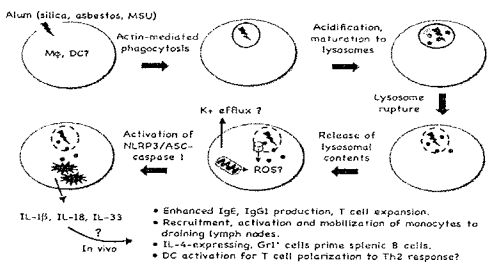
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### INITIATING INFLAMMATION



Alum (silica, asbestos, MSU)

Mφ, DC7

Actin-mediated phagocytosis

Acidification, maturation to lysosomes

Lysosome rupture

Release of lysosomal contents

ROS?





K<sup>+</sup> efflux?


Activation of NLRP3/ASC-caspase 1

IL-1 $\beta$ , IL-18, IL-33

In vivo

- Enhanced IgE, IgG1 production, T cell expansion.
- Recruitment, activation and mobilization of monocytes to draining lymph nodes.
- IL-4-expressing, Gr1<sup>+</sup> cells prime splenic B cells.
- DC activation for T cell polarization to Th2 response?

 Cathepsin B, lysosomal contents  
 NADPH oxidase  
 mitochondria  
 Inflammasome




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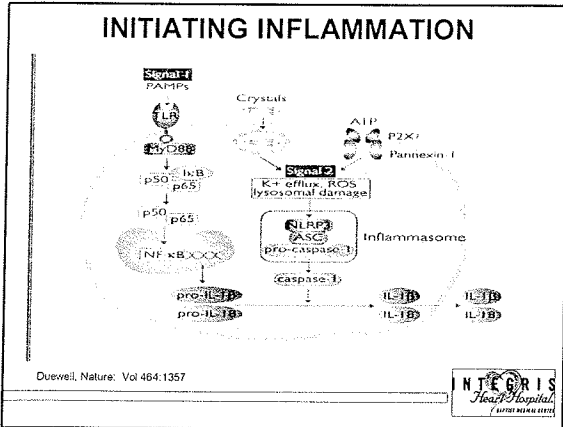
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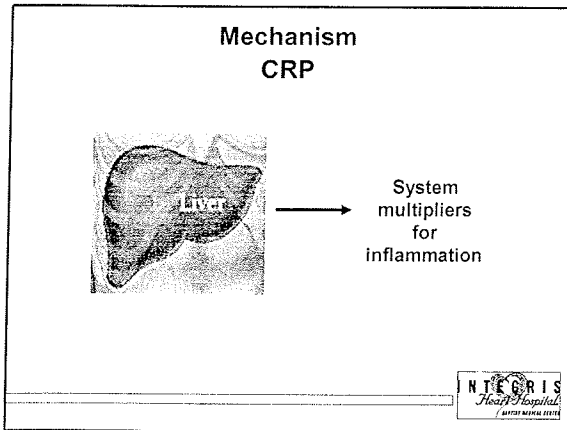
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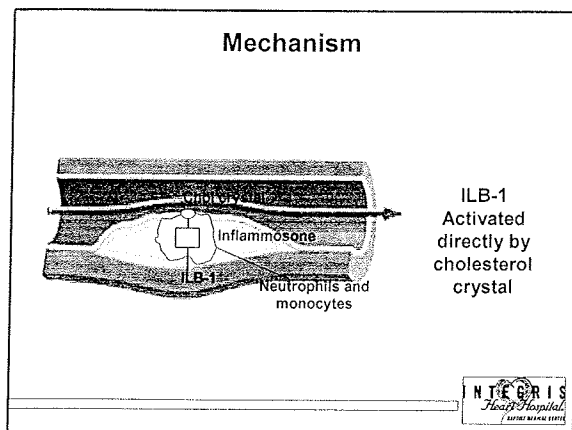
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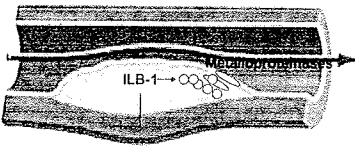
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### Mechanism Activated Proteinases



ILB-1 → Metalloproteinases

Metalloproteinase II - Matrix  
Imaging marker for unstable plaque



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### UNSTABLE PLAQUE

Stable plaques progression to instability:

Mechanisms are better understood



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### MARKERS VS. MECHANISMS

HSCRIP	F2-	Isoprostanes -
Apo A		Gold standard for
Apo B		oxydative stress
Pla-2	ILB-1	
MPO	Metalloproteinase	



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### SUMMARY

**Links**

- Myocardial Injury
- Exposure to oxidized lipids
- Altered lipoprotein remodeling
- Heart Failure

**Normal Artery**

- LPL
- HDL
- ABCA1
- ABCG1
- ABCG5
- ABCG8
- ABCA2
- ABCA3
- ABCA4
- ABCA5
- ABCA6
- ABCA7
- ABCA8
- ABCA9
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- ABCA98
- ABCA99
- ABCA100

**Dysfunctional HDL**

- Formation of dysfunctional HDL
- Lipid modification
- Generation of atherogenic LDL
- Oxidation of lipoproteins

**Vulnerable Plaque**

- Inflammation
- Lipid accumulation
- Fibrous cap formation
- Rupture

**Ruptured Plaque**

- Thrombosis
- Myocardial infarction

**INTEGRIS Heart Hospital**  
A HCA HEALTH SYSTEM

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### SESSION 2:

#### BEYOND STATINS AND LDL

#### PATHOPHYSIOLOGY RESEARCH AND PROSPECTIVE NEW TREATMENTS

**INTEGRIS Heart Hospital**  
A HCA HEALTH SYSTEM

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### CREDITS

- ACC: Risks Beyond Lipid Profile – 2011
- Cleveland Clinic – New Frontiers in Anti-atherosclerotic Therapies

**INTEGRIS Heart Hospital**  
A HCA HEALTH SYSTEM

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**ATHEROSCLEROSIS II**

New focus on plaque pathophysiology rather than endothelial injury.



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**MULTIPLE NEW TREATMENTS IN DEVELOPMENT**

New agents are directed at plaque development or inhibiting inflammation.



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**SUMMARY OF TREATMENT GOALS OR MARKERS**

1. B-100 particle counts
2. C Reactive Protein
3. MPO levels
4. PLA-2
5. HDL
6. Inflammasone – ILB- 1
7. Proteinase cascade and metalloproteinase inhibitors



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## 1. B-100 PARTICLES

- Lipoproteins can be characterized by Lipid content – e.g. cholesterol or triglyceride

Or

Protein content – Apoprotein B

- Total amount of Apoprotein B is best predictor of atherosclerosis.



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## SMALL LDL

- If the LDL is partially oxidized (LDL-ox) then the Lipo proteins are smaller and are more toxic to the endothelium.
- Hepatic Lipase
- CETP - rarely overactive



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- Measuring B-100 (\$85) gives you a reliable number of B particles and a better measure of atherogenicity.
- Alternatively, it is cheaper but less accurate to simply calculate the non-HDL cholesterol from lipid profile.



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### Normal For Non-HD LDL

CAD RISK	LDL	NON-HDL CHOL
Very high risk	< 70	< 100
High risk	< 100	< 130
Moderate risk	< 130	< 160
Low risk	< 160	< 190



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### LDLB: ATHEROGENIC VARIANTS

- The B-100 or particle counts can be high for multiple reasons. (e.g. LDL, Lpla)
- For all types of abnormal B-100 particles, everyone seems to have fewer events if LDL less than 70. (Consider statin and Niacin)
- It is not necessary to follow specific levels (i.e. Lpla levels)



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### STATIN INTOLERANCE

- A new treatment for increased B-100 or particle count elevation is mipromersin missense.
- It is an injectable MRNA missense therapy that blocks B-100 particles production.
- Injected through 1 gauge higher than an insulin syringe, it has had no side effects – Phase II trial.



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**2. INFLAMMATION AND CRP**  
**PAUL RIDKER, MD, MPH**



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**CRP (Hepatic multiplier of inflammation)**

**CRP stimulates MPO and the inflammatory response Tissue Factor and matrix metalloproteinase.**



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**PRELIMINARY CLINICAL TRIALS OF INFLAMMATION**

- There is a suggestion that low LDL patients with elevated HSCRP's might benefit from statin for inflammation.
- It is possibly due to an anti-inflammatory effect as well as low LDL.



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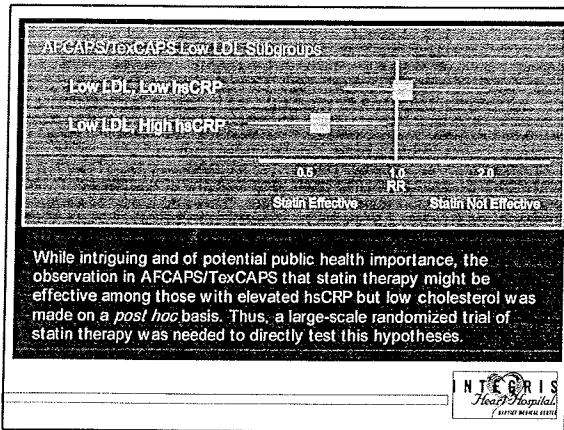
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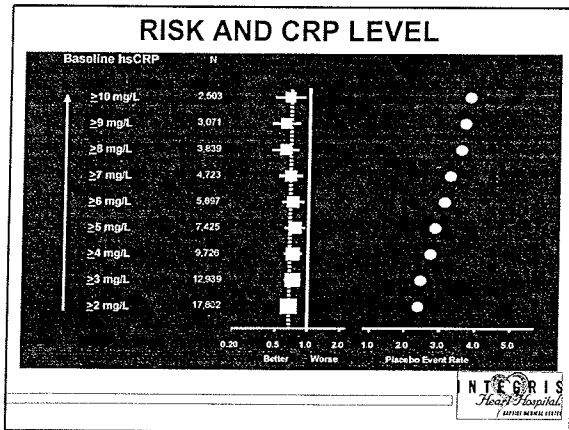
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**CANDIDATE TREATMENTS FOR INFLAMMATION**

Aspirin / Statins	Leukotriene blockade
Direct CRP Inhibitors	Salsalate
DMARDs/ MTX	CCR2/CCR5
TNF / IL-6 Inhibitors	Lp-PLA2 Inhibition
IL-1 antagonism	spLA Inhibition
5-LO Inhibitors	RNAi / anti-sense
	Immunization strategies

**INTEGRIS**  
 Heart Hospital  
 A SAFETY NET FOR LIFE

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### DIABETES / NSAID'S: SPECIAL CASE

Randomized trial of salsalate (Disalcid) vs placebo on the change in coronary artery plaque volume as assessed by MDCT from baseline to 30 months of therapy

Secondary endpoints: improvement in metabolic syndrome, lipids, abdominal adiposity, markers of inflammation, NASH, HOMA-IR

Targeted Sample Size 278, Targeted Completion 2012

Joslin Diabetes Center – Allison Goldfine / Steve Schoelson

NCT00624923



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Is there evidence that individuals with elevated levels of inflammatory biomarkers are at high vascular risk even when other risk factors are acceptable? YES

Is there evidence that individuals identified at increased risk due to inflammation benefit from a therapy they otherwise would not have received? YES

Is there evidence that reducing inflammation per se will reduce vascular events? WE NEED TO FIND OUT



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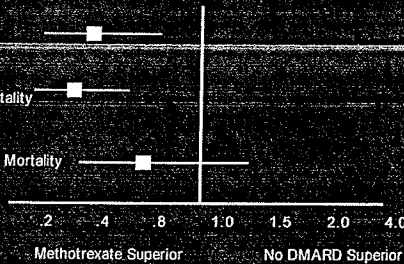
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All Cause Mortality

Cardiovascular Mortality

Non-Cardiovascular Mortality



Choi et al, Lancet 2002;359:1173-77



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## TRIALS

- **CIRT Trial:** Low dose Methotrexate lowers CRP vs. clinical events.
- **TINSEL CVD:** Salsalate (Dicalcid) vs. MDCT measurement of plaque burden.



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## WHY DICALCID IN DM?

- Lowers blood sugar (since 1876)
- Lowers inflammation
- ?? Thromboxane: RCT is anatomic study



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## 3. MPO LEVELS

- Lowering MPO has a double edge.
- Inhibitors may increase risk of infection (sepsis).
- Niacin, fish oil, Actos, and statins all decrease it. No trial planned.



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## MPO LEVEL AS A MARKER

It is specific to plaque inflammation unlike CRP.  
 However, it's lack of sensitivity and specificity resulted in Biosite discontinuing it as a marker for ACS.




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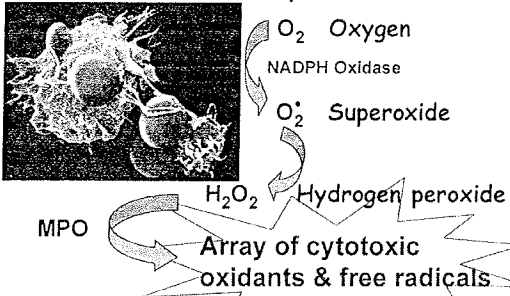
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Neutrophils, Monocytes and some Macrophages Use MPO to Generate Cytotoxic Oxidants




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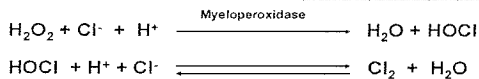
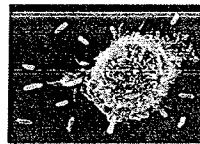
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## MPO as Friend in the Immune System

MPO produces HOCl and other reactive chlorinating species

HOCl is antimicrobial, killing invading parasites and pathogens



Klebanoff S.J. *J. Leuk Biol* 2005  
 Hazen SL et al. *JCI* 1996




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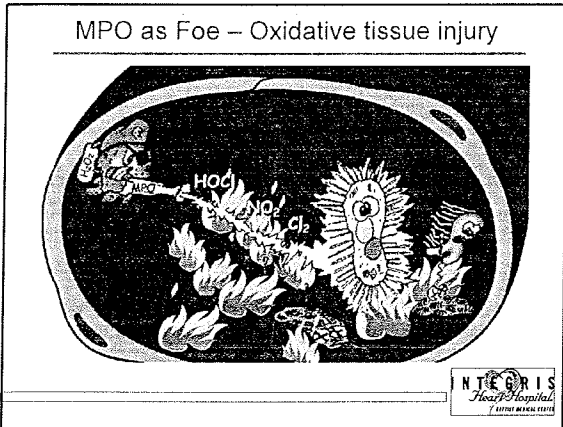
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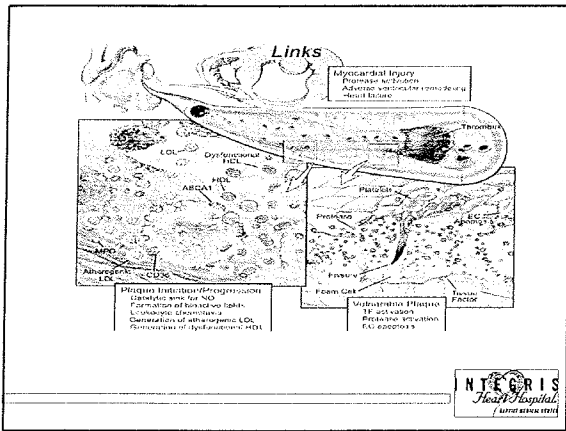
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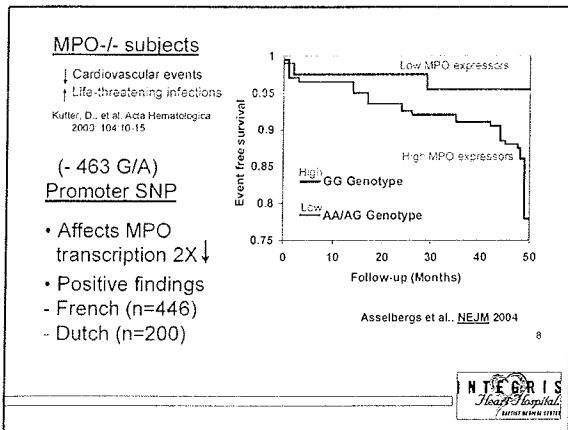
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MPO predicts risk in subgroups otherwise associated with low risk

Future CAD Events (MI and Death)

	MPO < 600 pM	MPO ≥600 pM
LDL < 130 mg/dL	1	1.77 (1.24 - 2.53)
LDL > 130 mg/dL	1.71 (1.25 - 2.34)	2.14 (1.58 - 2.90)
HDL > 50 mg/dL	1	1.57 (1.26 - 1.97)
HDL < 50 mg/dL	1.98 (1.54 - 2.55)	2.21 (1.75 - 2.78)
CRP < 2 mg/dL	1	1.24 (1.00 - 1.53)
CRP > 2 mg/dL	1.89 (1.49 - 2.41)	2.39 (1.95 - 2.93)



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### SUMMARY FOR MPO

- Attractive as a marker
- Mixed bag for Rx
- May have sepsis and infection if over treated
- May have niche in a biomarker screening panel



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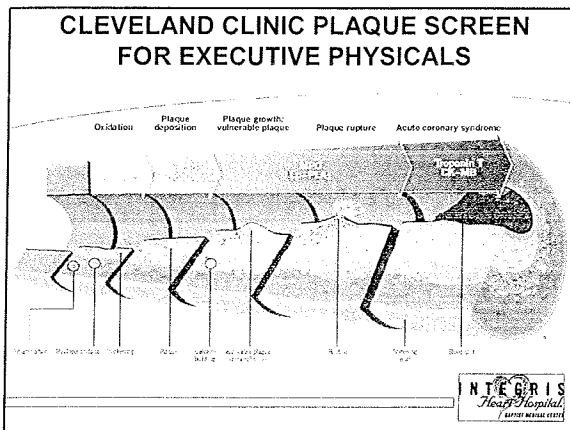
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#### 4. PLA-2

It is both a marker (plaque test)  
and a pathophysiologic agent.  
Hydrolyses LDL and initiates  
oxydative cascade by  
neutrophils and monocytes  
(foam cells).



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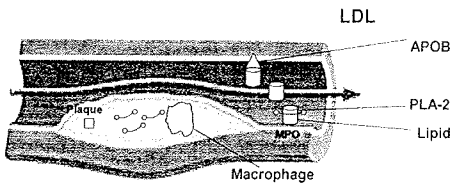
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#### PLA-2 LOCATION (Plaque Test)



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#### PLA-2 SUMMARY

- Somewhat helpful as a marker.
- It is plaque specific.
- May be better as a treatment target since it initiates the oxydative process of LDL.
- May be even better with HDL raising agents.



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### PLA-2 INHIBITORS TRIAL STATUS

- Phase 2 FRANCIS Trial → 500mg of Varespladib
- Phase 3 VISTA 16 → 80mg Lipitor + Varespladib



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### 5. HDL IN CAD

HDL: AIDING CHOLESTEROL  
EFFLUX



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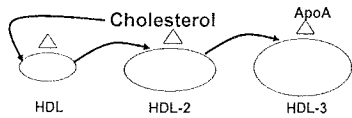
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### FILLING THE CHOLESTEROL CUP



HDL-3 is bad HDL-2 is good "is silly"

Cholesterol can not be broken down in the plaque despite oxydative agents!!!



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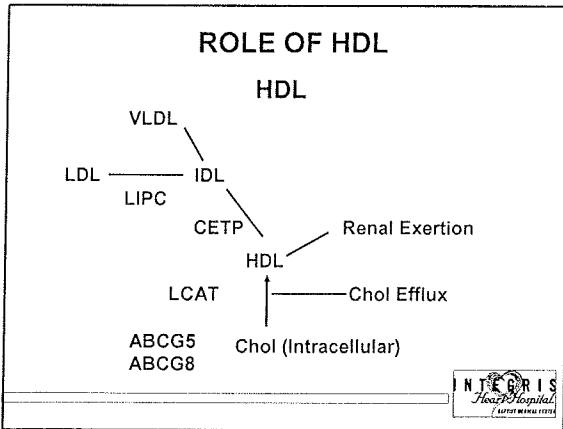
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### HDL TRIALS / GENETIC STUDIES

High HDL occurs when CETP is inhibited

1. Gene polymorphism of CETP led to longevity (HDL milano)
2. Same gene increases CAD if high triglyceride is present.
3. D4426 mutation lowers CETP and increases HDL and CAD.
4. Current trials:  
Torcetrapid – raised mortality and BP as well as HDL  
JTT 705 – investigative (weaker Torcetrapid)  
Anacetrapid – investigative, no BP increases
5. ApoA can be dysfunctional and cholesterol not "Escape to IDL by CETP".

**INTEGRIS**  
Heart Hospital  
LIPID METABOLISM

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### 6. INFLAMMATION

**NLRP3 inflammations are required for Atherogenesis and activated by cholesterol crystals.**

P. Duewell, Nature 2010; 464:1357-1362

**INTEGRIS**  
Heart Hospital  
LIPID METABOLISM

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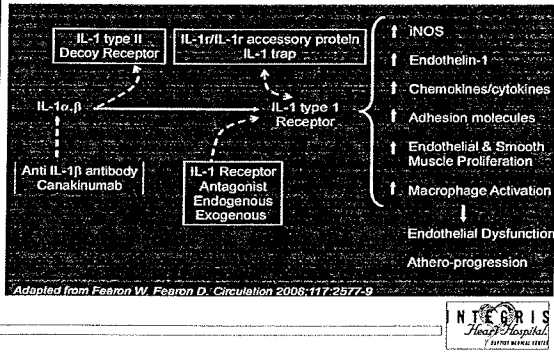
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### INFLAMMASONE AND IL-1B RAP SHEET



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- high-affinity human monoclonal anti-human interleukin-1 $\beta$  (IL-1 $\beta$ ) antibody currently indicated for the treatment of IL-1 $\beta$  driven inflammatory diseases (Cryopyrin-Associated Period Syndrome [CAPS], Muckle-Wells Syndrome)
  - designed to bind to human IL-1 $\beta$  and functionally neutralize the bioactivity of this pro-inflammatory cytokine
  - long half-life (4-8 weeks) with CRP and IL-6 reduction for up to 3 months
- INTEGRIS**  
Heart Hospital  
A BARNHART HEALTH SYSTEM

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### 7. MATRIX METALLOPROTEINASE INHIBITOR

1. Tried in diastolic dysfunction: major orthopedic problem.
2. Did poorly in early cancer trials (blocked angiogenesis)
3. New trials in anti-inflammatory disease and especially LV remodeling are pending.

**INTEGRIS**  
Heart Hospital  
A BARNHART HEALTH SYSTEM

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### TREATMENTS THAT HAVEN'T WORKED

- Zocor + Niacin for moderate risk CAD – failed.
- CETP inhibitor – Torcetrapid – failed.

#### CAVEAT

- Niacin may still be essential in high risk patients B-100 subgroups and inflammation.
- Niacin has uncertain role in Lp(a) treatment.



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### SUMMARY OF TARGETS AND MEDS



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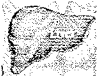
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### Target (Elevated LDL or Particle Count)

Trial Status Phase III

RX



→ Apo B's Low Particle Count

Mipromersen  
High dose statins/Niacin

Possible solution for statin intolerance



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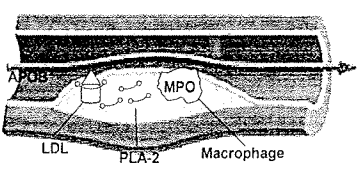
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**Target  
(PLA-2) (MPO)**



**Trial Status**  
 Phase II Francis  
 Trial Phase III  
 VISTA 16

**RX**  
 Varespladib

**Marker**  
 MPO




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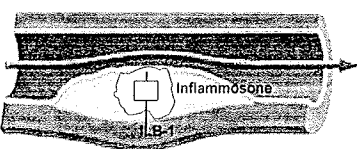
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**Target  
(Inflammation)**

**IL-ID**



**Trial Status**  
 Cantos  
 Phase III  
 Phase II

**RX**  
 Canakinomib  
 SD 2291  
 Niacin / Actos  
 / Omega 3




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**Target**



**Trial Status**  
 CIRT  
 C Phase III  
 Tinsal-CVD  
 Phase III

**RX**  
 Low dose  
 Methotrexate  
 (clinical events)  
 Salsalate -  
 Anatomical Trial  
 by MDCT




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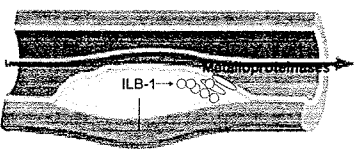
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### Target

Metalloproteins  
II - Matrix




Marker  
Metalloproteinase II  
labeled as imaging  
agent at target  
animal studies

Trial Status  
Failed diastolic  
dysfunction trial

RX  
None

? Identifying the vulnerable plaque



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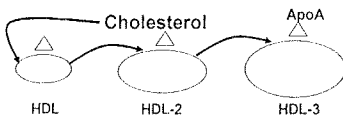
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### CHOLESTEROL CRYSTAL EFFLUX




Cholesterol

ApoA

HDL HDL-2 HDL-3

RX  
Anacetrapid  
ITT 705



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### CONCLUSION

- Evidence suggests maximizing current treatments could have lowered national CAD events by another 10-15%.
- Evidence suggests the Oklahoma event rate could be lowered 25% by improved risk factor reduction.
- We have reviewed 8 emerging pathophysiologic mechanisms to be used for either treatment targets or disease markers. The treatment goals of the future are awaiting.
- 8 promising RCT's
- 2 promising marker applications and other initiatives.



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