

Atherosclerosis

Saturday, June 18, 2011
Madrid I ~ 9:30am - 10:15am

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Objectives

- Understand the new knowledge on mechanisms of atherosclerotic plaque development and pathophysiology
- Review of results of public health outcomes related to current treatments of atherosclerosis

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**OAFP Scientific Assembly
June 18, 2011**


**SESSION 1
ATHEROSCLEROSIS AND
PLAQUE PATHOPHYSIOLOGY**

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Chief Medical Officer
INTEGRIS Heart Hospital,
Oklahoma City, OK



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




ATHEROSCLEROSIS

Where have we been?


What have we achieved?

What is next?



ATHEROSCLEROSIS


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




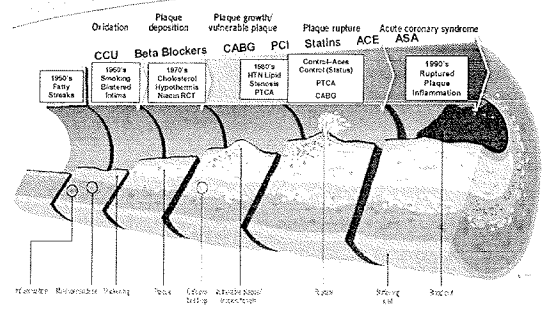
PLAQUE PROGRESSION:

**From Fatty Streak
To
Complex Plaque**

“Where have we been?”



PLAQUE PROGRESSION / TREATMENT TIMELINES



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 Mgm LDC
- > Homocystine Carbamylated LDL



1980's LIPID RESEARCH CENTERS

Increasing knowledge of Lipid particles, functions and pathophysiology.



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.



CDC


IMPACT MODEL

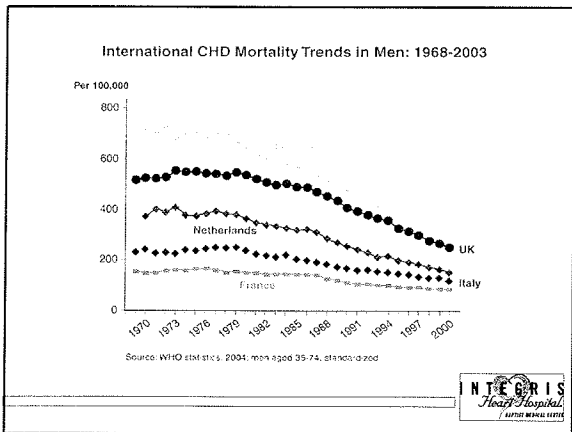
"What have we achieved?"



ATHEROSCLEROSIS
Population Trends

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






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

- Fruit and vegetable intake
- Alcohol
- Exercise
- Psychosocial

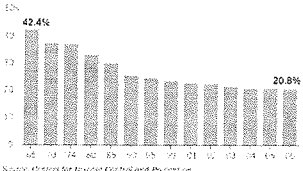


SMOKING EFFECT

Leveling off

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



Year	Percentage (%)
1965	42.4
1968	38.5
1971	36.5
1974	35.5
1977	34.5
1980	33.5
1983	32.5
1986	31.5
1989	30.5
1992	29.5
1995	28.5
1998	27.5
2001	26.5
2004	25.5
2005	20.8

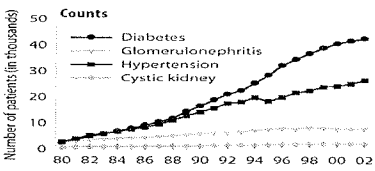
National Goal: 12%

Leveling off: November 9, 2007




HYPERTENSION AND DIABETES EFFECT

Incident Counts & Adjusted Rates, By Primary Diagnosis



Year	Diabetes (thousands)	Glomerulonephritis (thousands)	Hypertension (thousands)	Cystic kidney (thousands)
1980	5	2	3	1
1982	8	3	4	1.5
1984	12	4	5	2
1986	16	5	6	2.5
1988	20	6	7	3
1990	24	7	8	3.5
1992	28	8	9	4
1994	32	9	10	4.5
1996	36	10	11	5
1998	40	11	12	5.5
2000	43	12	13	6
2002	45	13	14	6.5



IS THE CAD REDUCTION PARTY OVER??

Counter trends related to:

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

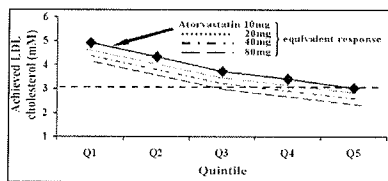
"What is next in the short-term?"



CHOLESTEROL: The Good News!




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



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




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




PRIMARY PREVENTION CONCLUSION

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



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


"What is next long-term?"



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)



Non-HDL CHOL

Total Chol – HDL = Non-HDL cholesterol


Trig < 400 due to Friedewald equation limitation



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



New pathologic LDL for Diabetes Mellitus and Smokers


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



NEW FRONTIER

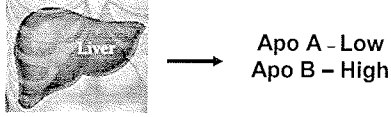
Inflammation and Progression

Atherosclerotic plaque and progression




SUMMARY OF TARGETS AND MEDS

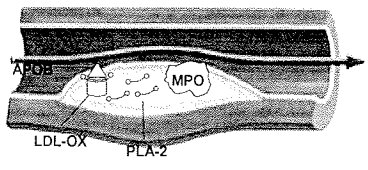
Mechanism




Apo A - Low
 Apo B - High



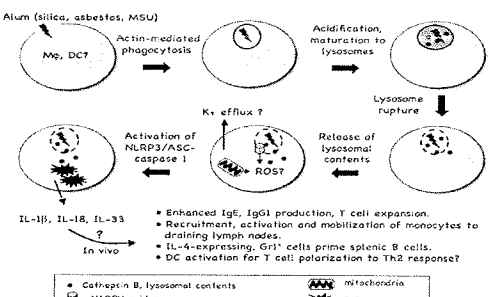
Mechanism



MPO
 Activator



INITIATING INFLAMMATION



Alum (silica, asbestos, MSU)

Mφ, DC7

Actin-mediated phagocytosis

Acidification, maturation to lysosomes

Lysosome rupture

Release of lysosomal contents

Activation of NLRP3/ASC-caspase 1

K⁺ efflux ?


ROST

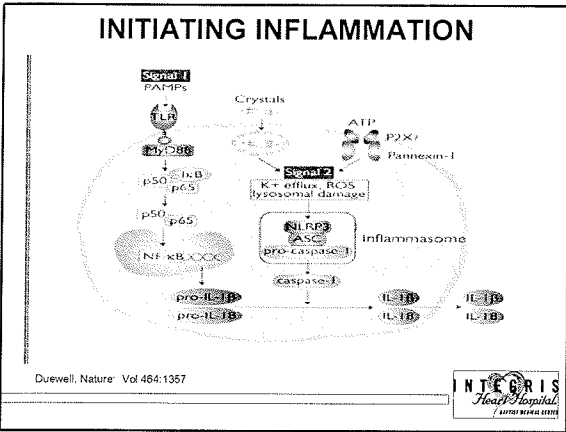
IL-1β, IL-18, IL-33

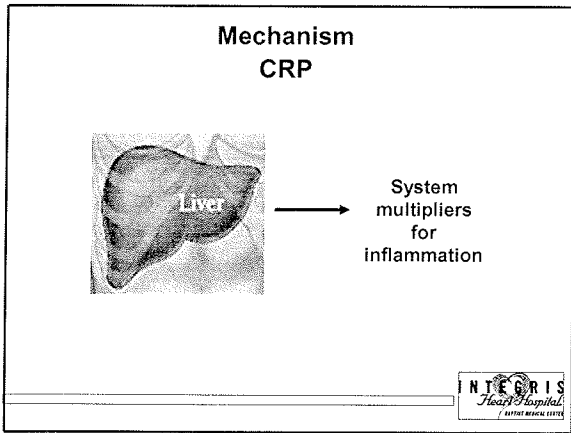
In vivo

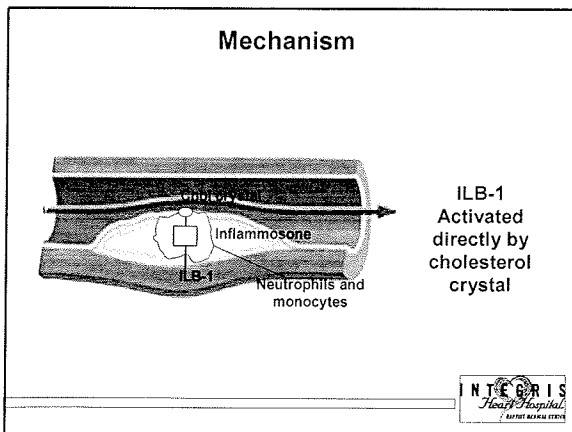
- Enhanced IgE, IgG1 production, T cell expansion.
- Recruitment, activation and mobilization of monocytes to draining lymph nodes.
- IL-4-expressing, Gr1⁺ cells prime splenic B cells.
- DC activation for T cell polarization to Th2 response?

• Cathepsin B, lysosomal contents Mitochondria
 □ NADPH oxidase Inflammasome

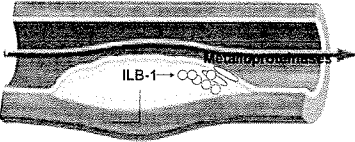









Mechanism Activated Proteinases



ILB-1 → Metalloproteinases


Metalloproteinase
II – Matrix
Imaging marker
for unstable
plaque



UNSTABLE PLAQUE


Stable plaques progression to
instability:

Mechanisms are better understood



MARKERS VS. MECHANISMS

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



SUMMARY

Links

Myocardial Injury
Expression of Atheroma
Substrate and Inflammation
(oxidative stress)

Dysfunctional HDL
Formation of bioactive lipids
Oxidative chemistry
Oxidative effects of atherogenic LDL
Oxidation of ApoB lipoproteins

VLDL/Triglyceride Metabolism
Production, oxidation
CO-oxidation

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SESSION 2:

BEYOND STATINS AND LDL

PATHOPHYSIOLOGY RESEARCH AND PROSPECTIVE NEW TREATMENTS

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CREDITS

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

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ATHEROSCLEROSIS II

New focus on plaque pathophysiology rather than endothelial injury.




MULTIPLE NEW TREATMENTS IN DEVELOPMENT

New agents are directed at plaque development or inhibiting inflammation.



SUMMARY OF TREATMENT GOALS OR MARKERS

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



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.



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



- 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.



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



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)



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.



2. INFLAMMATION AND CRP PAUL RIDKER, MD, MPH



**CRP (Hepatic multiplier of
inflammation)**

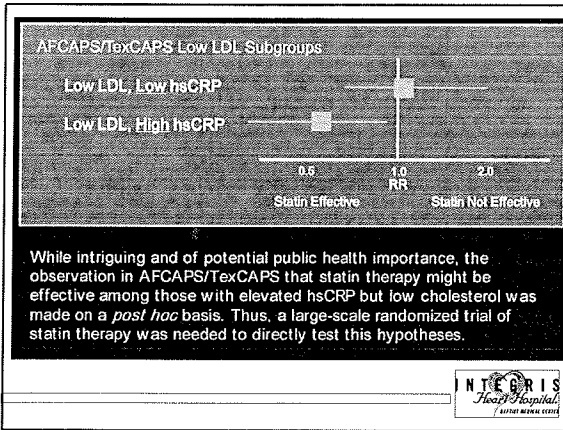
**CRP stimulates MPO and the
inflammatory response Tissue
Factor and matrix
metalloproteinase.**

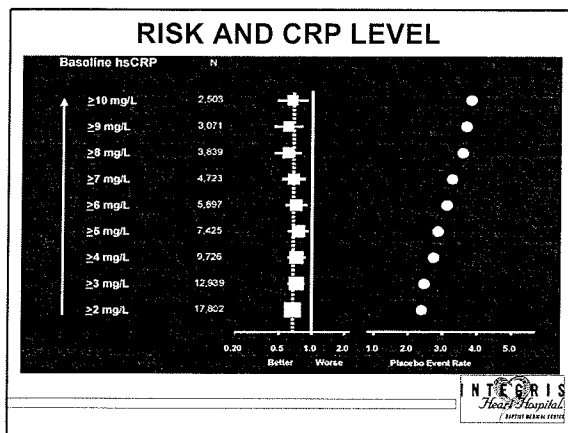


PRELIMINARY CLINICAL TRIALS OF INFLAMMATION

- 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.







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

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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

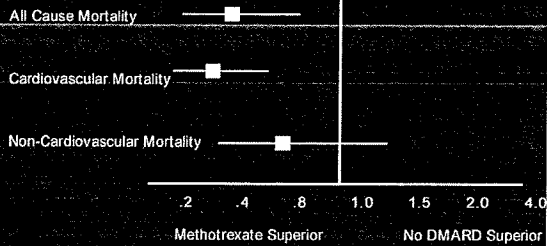


Is there evidence that individuals with elevated levels of inflammatory biomarkers are at high vascular risk even when other risk factors are acceptable? YES

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

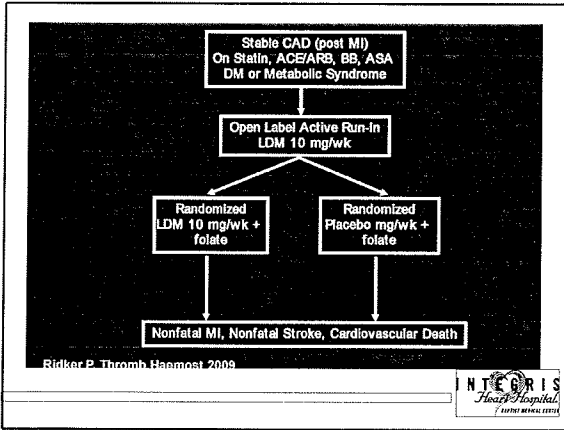
Is there evidence that reducing inflammation per se will reduce vascular events? WE NEED TO FIND OUT

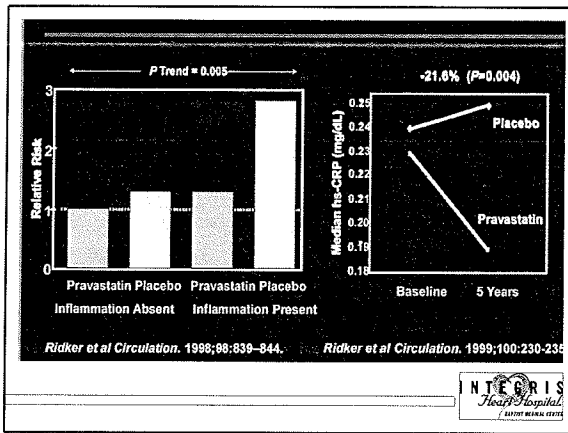


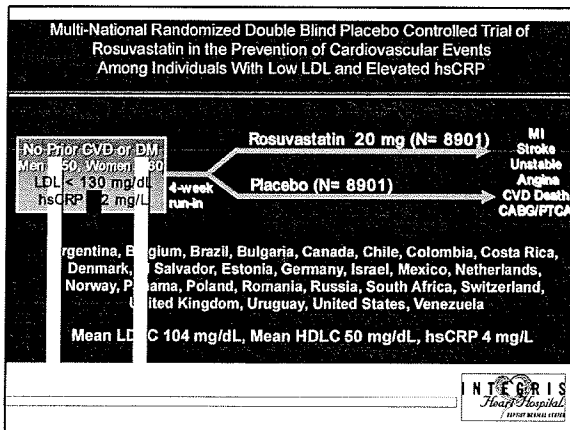


Choi et al, Lancet 2002;359:1173-77









TRIALS

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



WHY DICALCID IN DM?

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



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.

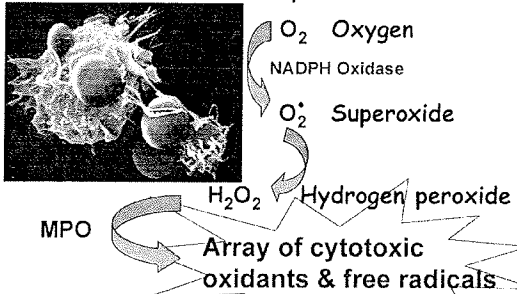


MPO LEVEL AS A MARKER

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.



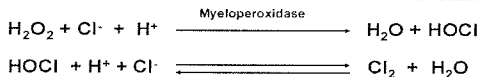
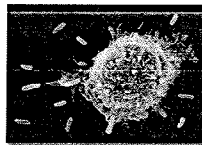
Neutrophils, Monocytes and some Macrophages
 Use MPO to Generate Cytotoxic Oxidants



MPO as Friend in the Immune System

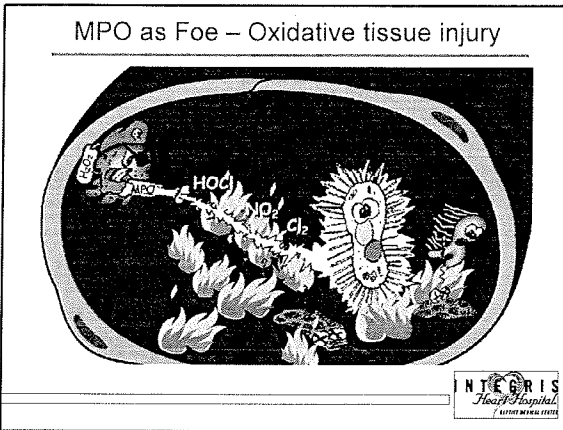
MPO produces HOCl and other reactive chlorinating species

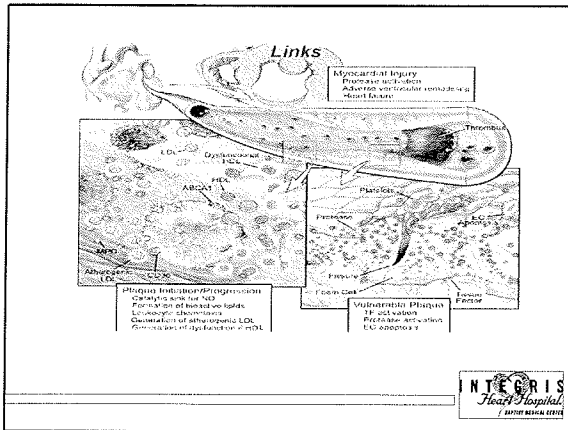
HOCl is antimicrobial, killing invading parasites and pathogens

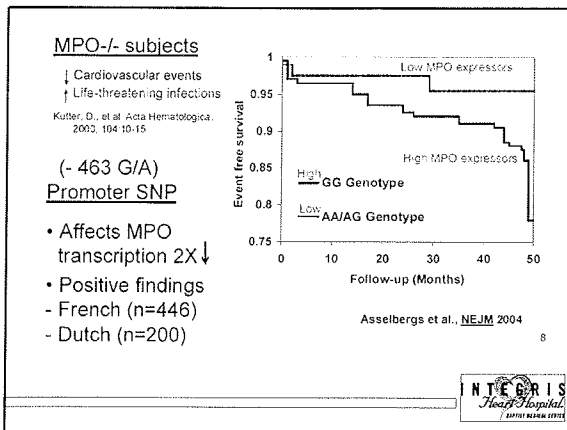


Klebanoff S.J. *J Leuk Biol* 2005
 Hazen SL et al. *JCI*. 1996



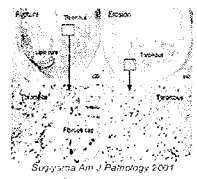






MPO RAP SHEET

- MPO is found in atherosclerotic plaques
Bischoff-Grethe et al. J Lipid Res 1994; 35: 237-47
- MPO oxidizes LDL in the artery wall
Bischoff-Grethe et al. J Lipid Res 1994; 35: 237-47
- MPO oxidized LDL is atherogenic
Wolfe et al. J Lipid Res 1994; 35: 237-47
- MPO initiates lipid oxidation in vivo
Bischoff-Grethe et al. J Lipid Res 1994; 35: 237-47
- MPO consumes nitric oxide as substrate
Chen et al. J Biol Chem 1999; 274: 8552-6
- MPO is enriched in culprit lesions
Yoshida et al. Am J Pathol 2001; 158: 2012S
- MPO promotes endothelial dysfunction
Reiss et al. Science 2002; 296: 3392
Gina et al. Circulation 2001; 103: 1113
Winkler et al. JAMA 2001; 285: 3082
- Unstable coronary plaque triggers MPO release
Wolfe et al. JAMA 1992; 267: 273
Winkler et al. JAMA 2001; 285: 1595
Baldus et al. Circulation 2001; 103: 1440
- MPO renders HDL "dysfunctional" in vivo
Wolfe et al. JAMA 1992; 267: 273
Bischoff-Grethe et al. J Lipid Res 1994; 35: 237-47
Winkler et al. JAMA 2001; 285: 1595
- MPO mediated carbamylation in human atherosclerotic plaque is proatherogenic
Baldus et al. Nature Medicine 2003; 9: 1176

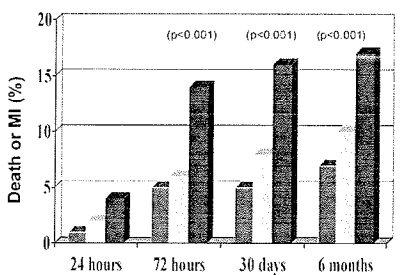


Sequential patients presenting to ER with chest pain

	MPO Quartile				
	(pM)	Q1 <119	Q2 119 - 198	Q3 198 - 394	Q4 > 394
MI at Evaluation					
All patients	1.0	1.2 (0.7-2.3)	2.1 (1.2-3.8)*	3.9 (2.2-6.8)**	
MACE, 30 days					
All patients	1.0	1.7 (1.1-2.9)*	3.3 (2.0-5.5)**	4.9 (3.0-8.1)**	
Troponin negative	1.0	2.2 (1.5-3.1)**	3.7 (2.5-6.1)**	5.7 (2.9-8.6)**	
MACE, 6 months					
All patients	1.0	1.6 (1.0-2.7)*	3.6 (2.2-5.8)**	4.7 (2.9-7.7)**	
Troponin negative	1.0	2.5 (1.7-3.6)**	3.8 (2.4-6.5)**	5.8 (2.4-9.3)**	

* p<0.05 relative to Q1
 ** p<0.01 relative to Q1
 Adapted from Brennan et al, NEJM, (2003)





Baldus, et al. Circulation 2003;108: 1440-5.



MPO predicts risk in subgroups otherwise associated with low risk

Future CAD Events (MI and Death)

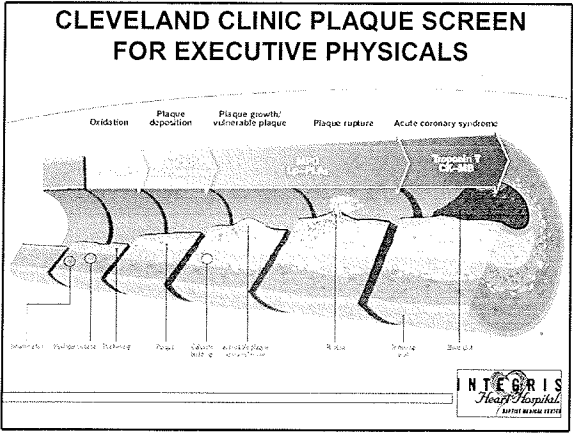
	MPO < 600 pM	MPO ≥ 600 pM
LDL < 130 mg/dL	1	1.77 (1.24 - 2.53)
LDL > 130 mg/dL	1.71 (1.25 - 2.34)	2.14 (1.58 - 2.90)
HDL > 50 mg/dL	1	1.57 (1.26 - 1.97)
HDL < 50 mg/dL	1.98 (1.54 - 2.55)	2.21 (1.75 - 2.78)
CRP < 2 mg/dL	1	1.24 (1.00 - 1.53)
CRP > 2 mg/dL	1.89 (1.49 - 2.41)	2.39 (1.95 - 2.93)

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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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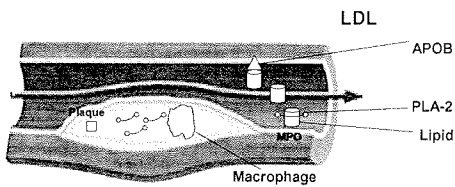


4. PLA-2

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



PLA-2 LOCATION (Plaque Test)



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.



PLA-2 INHIBITORS TRIAL STATUS

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

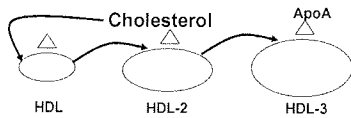


5. HDL IN CAD

HDL: AIDING CHOLESTEROL
EFFLUX



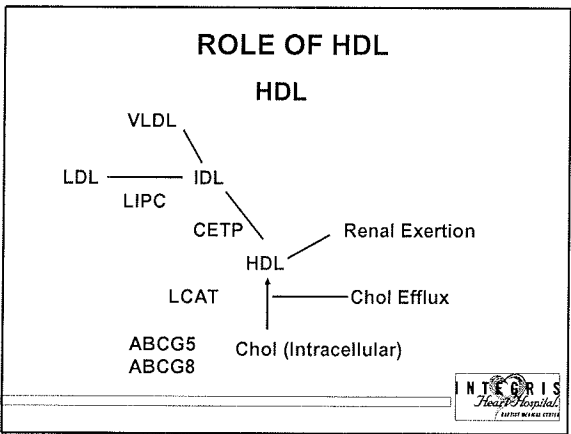
FILLING THE CHOLESTEROL CUP



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

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





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".

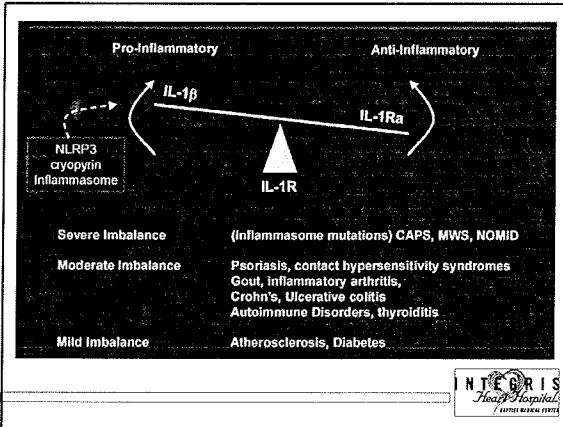
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6. INFLAMMATION

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

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

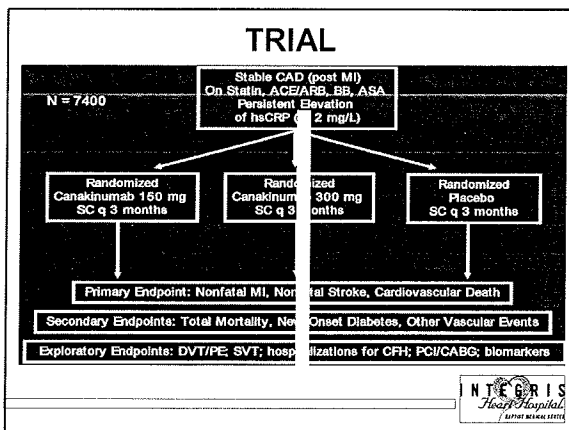
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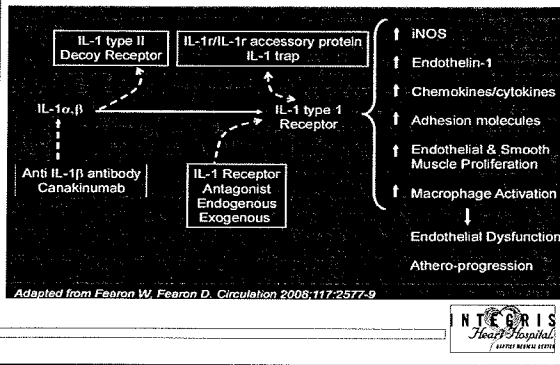
ISSUES IN ANTI-INFLAMMATION

	Statins	TNF inhibition	IL-6 Inhibition	IL-1 β inhibition	LDM
TC	↕↕	↑	↑	↔	↔
LDL	↕↕	↑	↑	↔	↔
HDL	↑	↑	↑	↔	↔
TG	↔	↑	↑	↔	↔
Chylo	↔	↑	↑	↔	↔
CRP / IL-6	↓	↕↕	↕↕	↕↕	↓

INTEGRIS Heart Hospital
UNIVERSIDAD NACIONAL AUTÓNOMA DE MÉXICO



INFLAMMASONE AND IL-1B RAP SHEET



- high-affinity human monoclonal anti-human interleukin-1β (IL-1β) antibody currently indicated for the treatment of IL-1β driven inflammatory diseases (Cryopyrin-Associated Period Syndrome [CAPS], Muckle-Wells Syndrome)
 - designed to bind to human IL-1β 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 HARVARD MEDICAL CENTER

- ### 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
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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.



SUMMARY OF TARGETS AND MEDS



Target (Elevated LDL or Particle Count)

Trial Status Phase III

RX



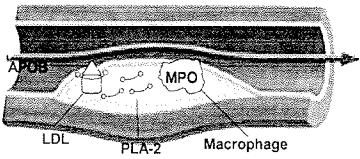
→ Apo B's Low Particle Count

Mipromersen
High dose statins/Niacin

Possible solution for statin intolerance



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




APoB
LDL
PLA-2
Macrophage
MPO

Trial Status
Phase II Francis
Trial Phase III
VISTA 16

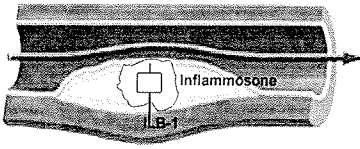
RX
Varespladib

Marker
MPO



**Target
(Inflammation)**


IL-ID



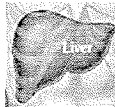
Inflammasome
IL-1

Trial Status
Cantos
Phase III
Phase II

RX
Canakinomab
SD 2291
Niacin / Actos
/ Omega 3




Target



Increased
CRP

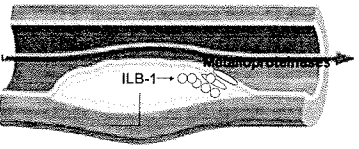
Trial Status
CIRT
C Phase III
Tinsal-CVD
Phase III

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



Target

Metalloproteinase II - Matrix




ILB-1 → Metalloproteinase II

? Identifying the vulnerable plaque

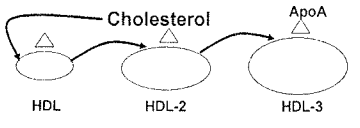
Marker
Metalloproteinase II labeled as imaging agent at target animal studies

Trial Status
Failed diastolic dysfunction trial

RX
None



CHOLESTEROL CRYSTAL EFFLUX




Cholesterol

HDL HDL-2 HDL-3

ApoA

RX
Anacetrapid
ITT 705



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.

