

**D I S T A N C E   L E A R N I N G   S Y M P O S I U M**

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# **Integrating Lp-PLA<sub>2</sub> into Advanced Cardiovascular Risk Reduction**

**Richard Lanman, MD**  
**Chief Medical Officer**  
**diaDexus, Inc.**

November 3rd, 10th, & 16th, 2005



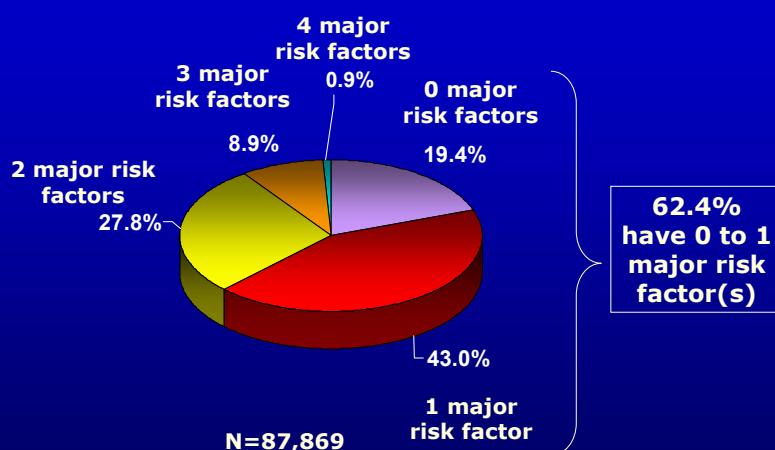
## **Integrating Lp-PLA<sub>2</sub> into Advanced Cardiovascular Risk Reduction**

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## **Advances in the Early Detection of Rupture-Prone Plaque**



## Prevalence of Major Risk Factors in CHD



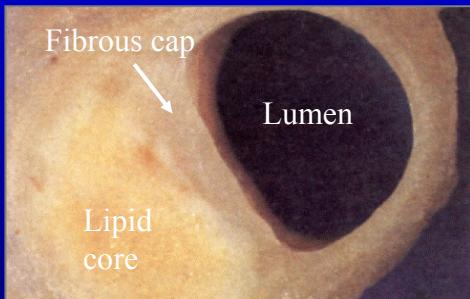
62.4%  
have 0 to 1  
major risk  
factor(s)

4 Major modifiable risk factors: hypertension,  
smoking, hypercholesterolemia, diabetes

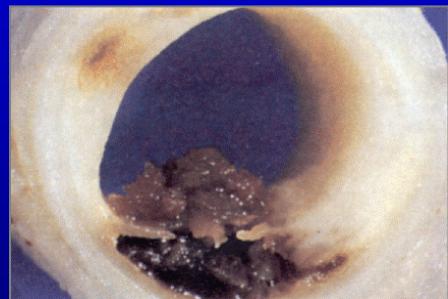
Khot, et al. JAMA. 2003

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## Plaque Rupture- and Not Stenosis- Causes Most Acute Myocardial Infarctions

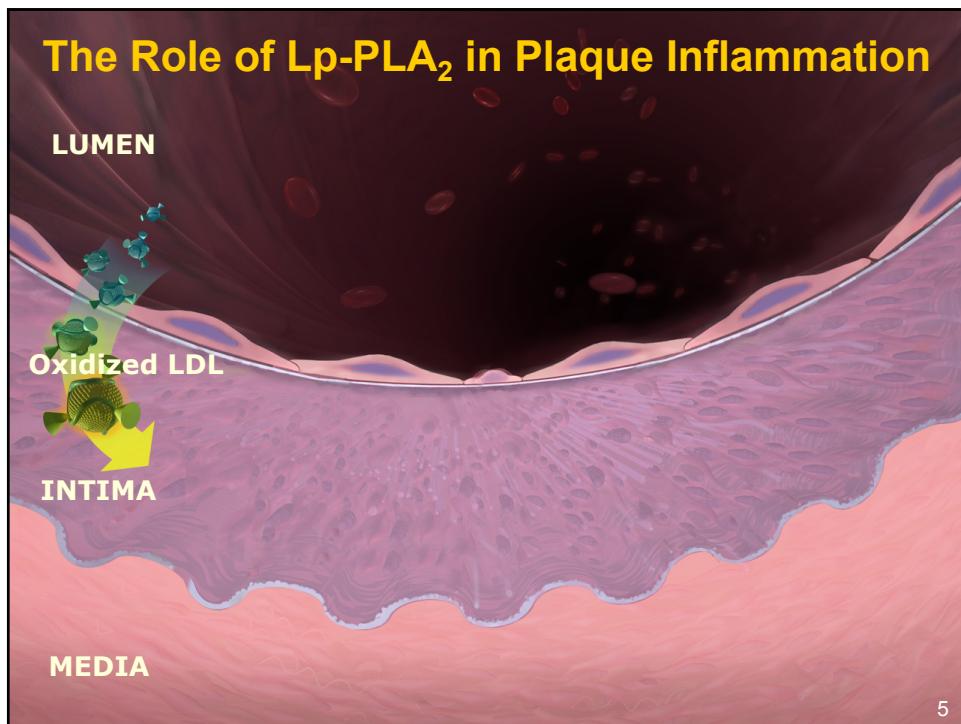


Lumen stenotic but plaque stable

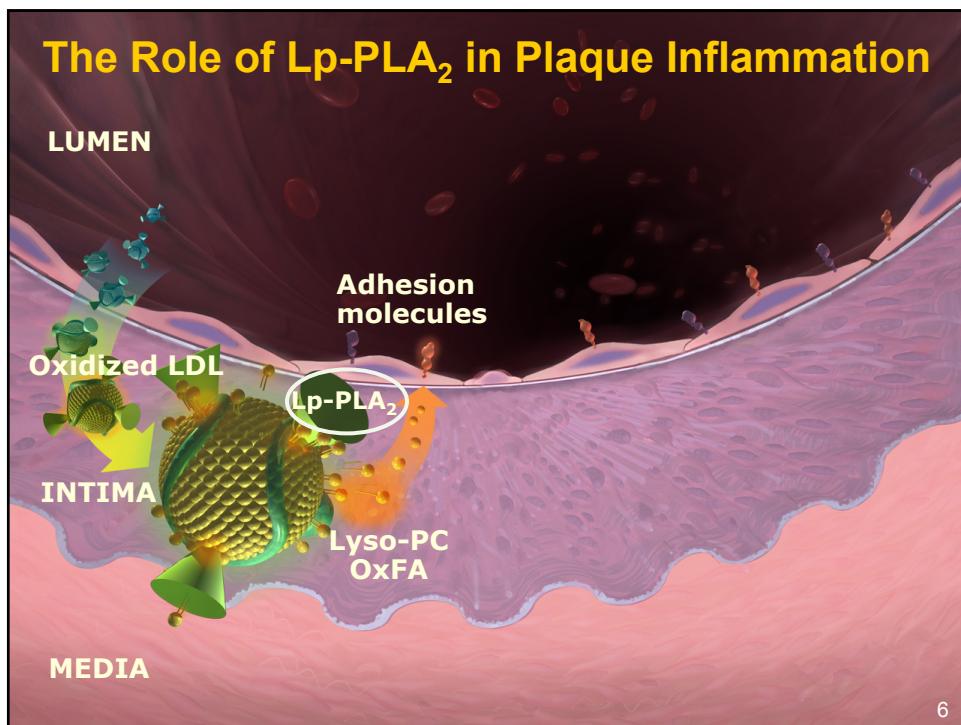


Lumen not stenotic but inflamed, thin  
fibrous cap ruptured, leading to  
thrombus formation

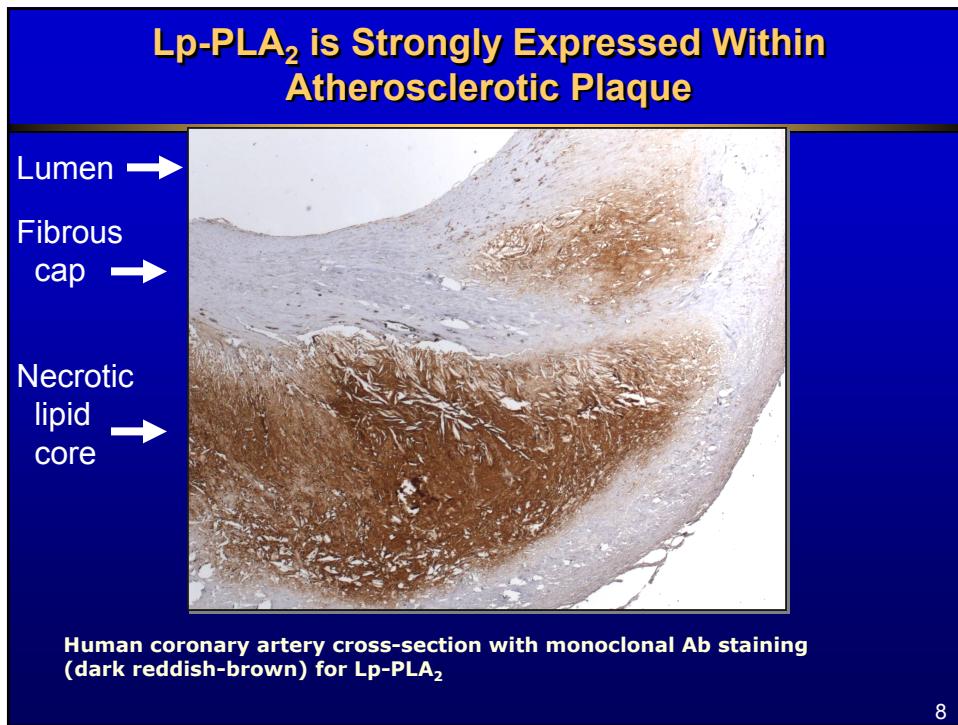
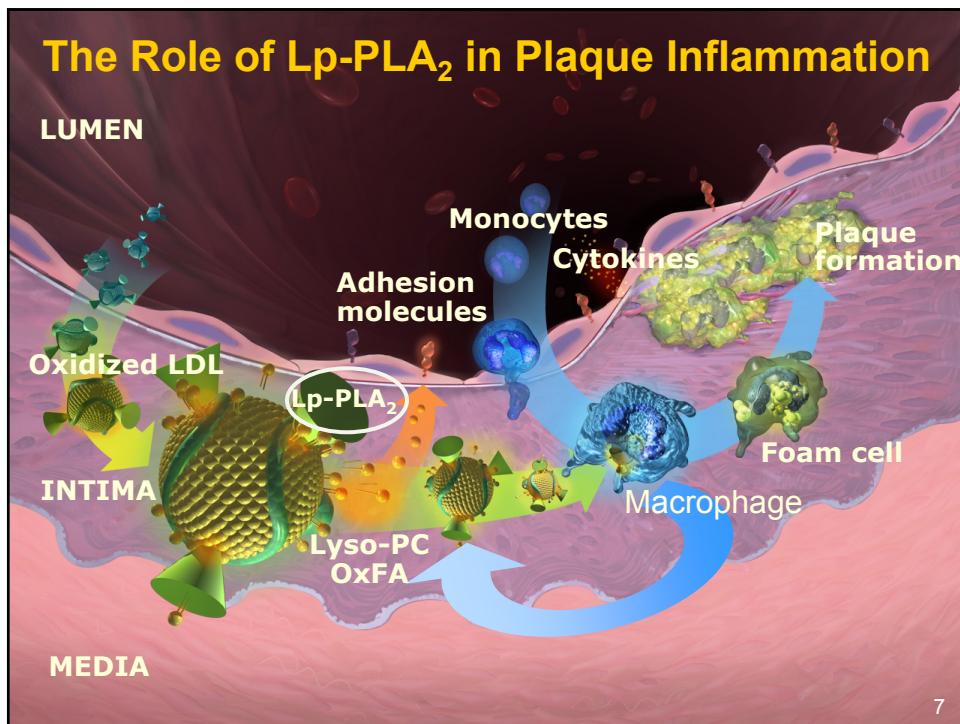
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## Lp-PLA<sub>2</sub> is Most Strongly Expressed Within Thin Cap Rupture-Prone Lesions

\*Lp-PLA<sub>2</sub> staining (%)

Lesion Type	SMCs	Macro-phage	Lipid Pool	Necrotic Core	Fibrous Cap
DIT N=5	7.8	0.0	--	--	--
PIT N=5	1.3	31.6	32.0	--	--
FA N=8	2.7	48.1	--	51.8	10.6
TCFA N=7	1.2	45.0	--	43.6	47.9**

DIT= diffuse intimal thickening; PIT= pathologic intimal thickening;  
FA= fibrous cap atheroma; TCFA= vulnerable plaques with fibrous caps <65 µm.

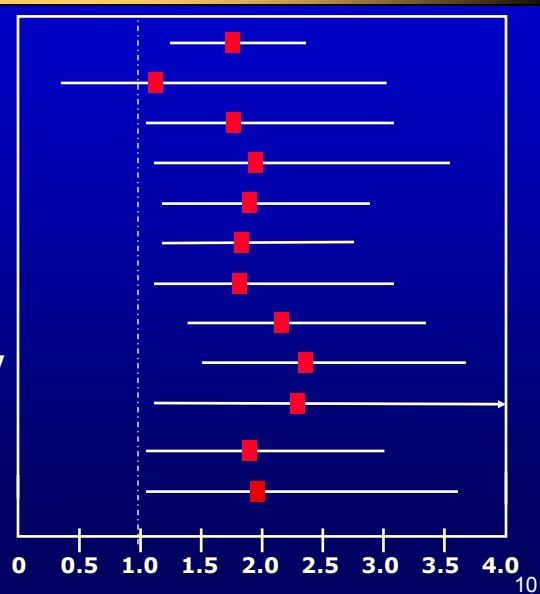
\*Lp-PLA<sub>2</sub> was expressed as a percentage of lesional SMC's, macrophage, lipid pool, necrotic core, or fibrous cap area; n=number of cross sections \*\*p=0.0001 TCFA vs FA

Kolodgie F, et al. AHA 2004.

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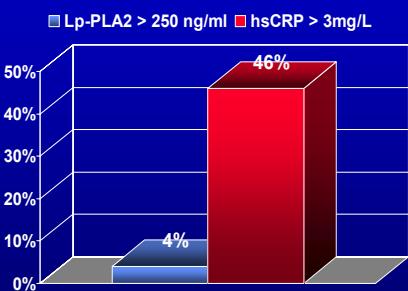
## Elevated Lp-PLA<sub>2</sub> is Associated With a Doubling of Risk for CHD and Stroke Events

- WOSCOPS (2000) CHD**
- WHS – Ridker (2001) CHD**
- AtheroGENE (2003) CHD**
- ARIC (2004) CHD LDL<130**
- Rotterdam Study (2005) CHD**
- LURIC CV Study (2005) CHD**
- HELICOR (2005) Chronic CHD**
- KAROLA (2005) CV**
- Intermountain Health (2005) CV**
- Mayo Heart Study (2005) CV**
- ARIC (2005) Stroke**
- Rotterdam Study (2005) Stroke**



## Lp-PLA<sub>2</sub> is Specific to Vascular Inflammation

**Lp-PLA<sub>2</sub> is not typically elevated in healthy individuals**



Blood from 90 healthy heart disease free individuals

**Lp-PLA<sub>2</sub> has Minimal Biovariability**

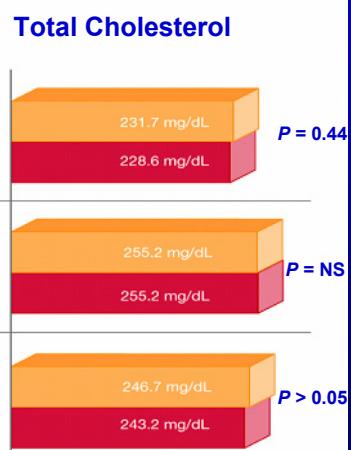
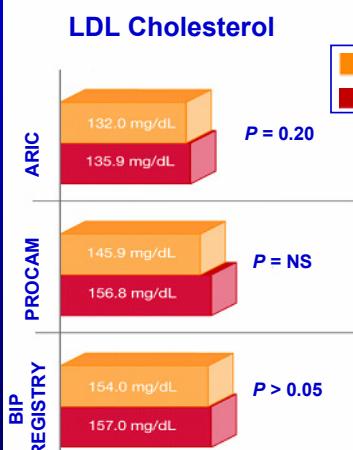


Blood from 43 healthy adults at least 7 times in 4 weeks

Wolfert, AHA Abstract 2004 Manuscript in preparation

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## Cholesterol is Not a Reliable Predictor for Stroke



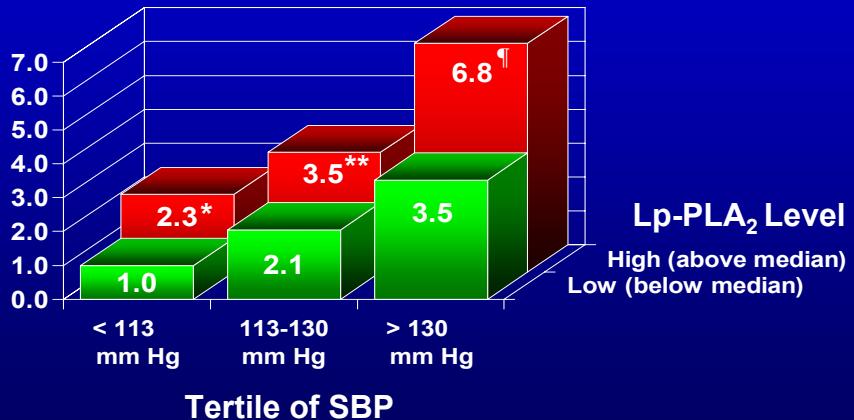
1. Ballantyne CM, et al. *AHA 2004*
2. Berger K, et al. *Stroke 1998*
3. Tanne D, et al. *Circ.2005*

4. Bowman TS, et al. *Stroke 1998*
5. Oei HH, et al. *Circ. 2005*
6. Wannamethee SG, et al. *Stroke 2000*

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## The Lp-PLA<sub>2</sub> Test Identifies Stroke-Prone Hypertensive Patients in ARIC

Risk Ratios for Ischemic Stroke Based on Lp-PLA<sub>2</sub> Level and SBP

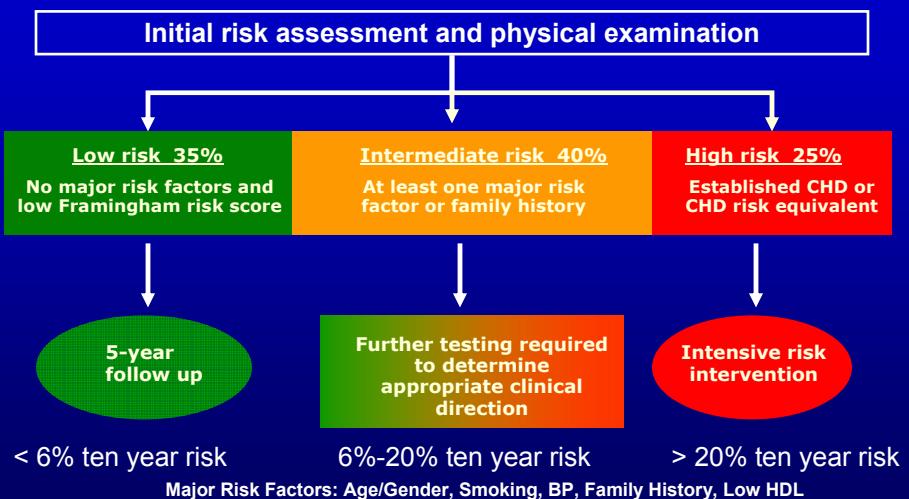


\*p=0.03, \*\*p≤ 0.005, †p<0.0001

(Data on file with FDA)

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## Consider Using the Lp-PLA<sub>2</sub> Test in the Intermediate Risk or “≥ 1 Risk Factor” Patient

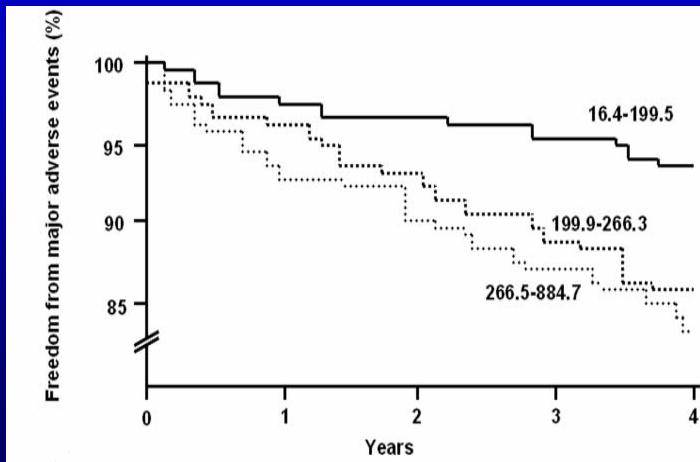


Greenland P, et al. Improving CHD Risk Assessment in Asymptomatic People. *Circ.* 2001.  
Pearson TA, et al. AHA/CDC Scientific Statement “Markers of Inflammation & CVD” *Circ.* 2003.

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## Lp-PLA<sub>2</sub> Predicts Major CV Events in CHD Patients: Mayo Heart Study

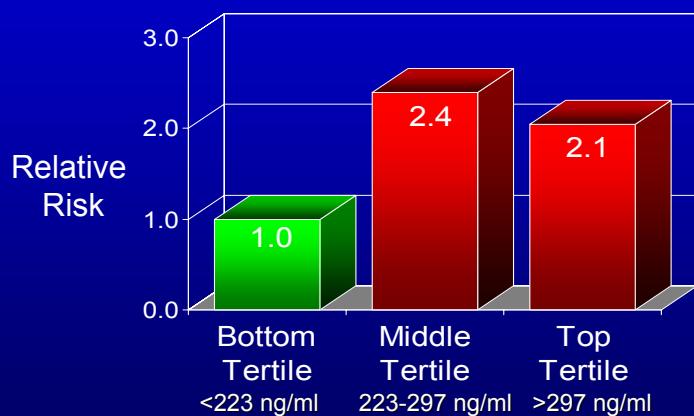
95% of patients with Lp-PLA<sub>2</sub> < 200 ng/ml were Event Free at 4 years



Brilakis ES et al. Mayo Heart Study. Euro J Card 2005

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## Lp-PLA<sub>2</sub> in Rehab Pts S/P AMI Doubles Risk of Recurrent NFMI/CVA/Cardiac Death



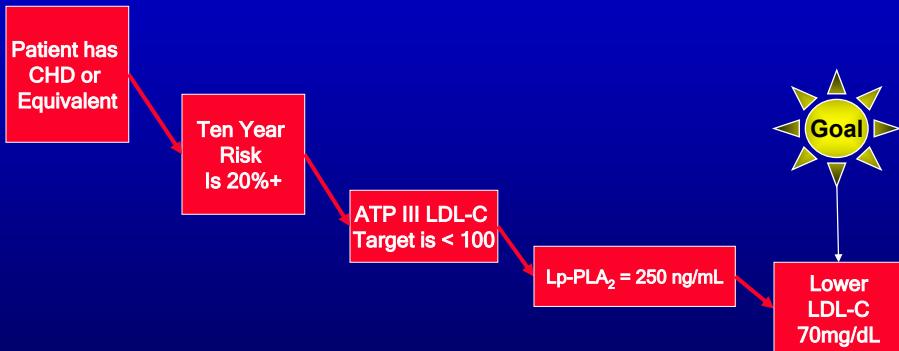
Fully adjusted for traditional risk factors, LDL and HDL, statin Rx, CRP, age, BMI, etc.

Koenig W. KAROLA Heart Study. ACC abstract 2005

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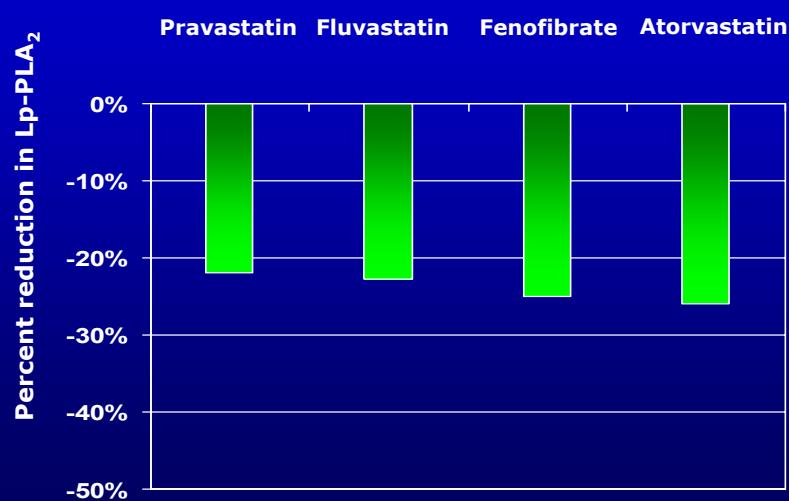
## Significance of Incorporating Emerging Risk Factors

A Case Study: Who is Very High Risk?



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## Medications that Lower the Incidence of CV Events Have Also Been Shown to Lower Lp-PLA<sub>2</sub>

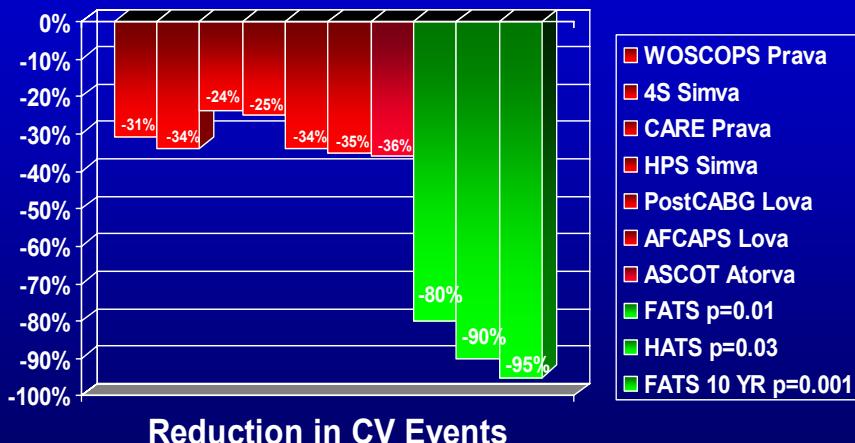


1. Albert M, et al. *Atherosclerosis* in press  
2. Winkler, et al. *JCEM* 2004

3. Tsimihodimos V, et al. *J Lipid Res.* 2003  
4. Schaefer, et al. *Am J Card* 2005

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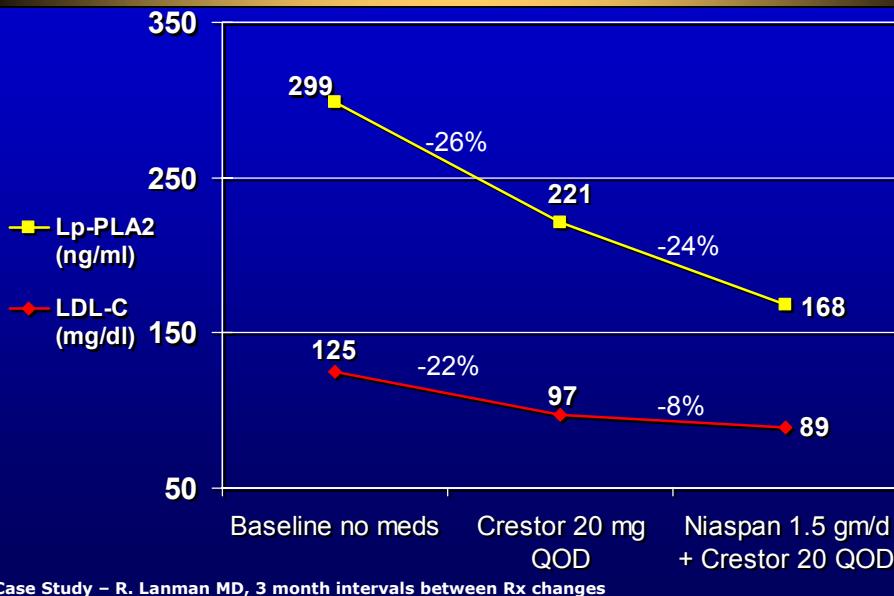
## Statin Monotherapy vs. Combination Rx



Brown BG et al NEJM 1999; 323:1289-98  
 Brown BG et al. NEJM 2001;345(22):1583-92  
 Brown BG. Circulation Suppl 1997

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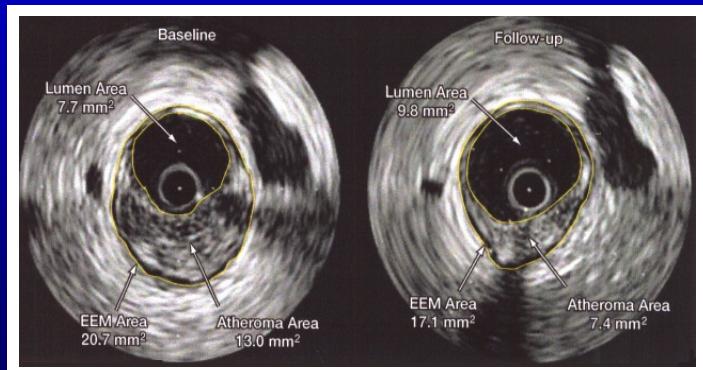
## Niaspan Further Reduces Vascular Inflammation, Additionally to Statin Rx



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## Treatment Can Stabilize Rupture Prone Plaque

Change in atheroma area seen with Coronary IVUS in REVERSAL Study  
with aggressive treatment (atorvastatin 80 mg/day)



Nissen SE, et al. JAMA 2004

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## Conclusions

Lp-PLA<sub>2</sub> is a novel risk marker that:

- Is a *specific* marker for vascular inflammation, i.e. rupture-prone plaque
- Identifies the “Intermediate risk person” who is actually “High risk” & whose LDL target should be lowered from 130 to 100
- Identifies those high-risk persons who are in fact “Very high risk” warranting an LDL target reduction from 100 to 70 and probably, evaluation for Lp(a) and small/dense LDL pattern B & consideration of combination lipid Rx
- When elevated, Lp-PLA<sub>2</sub> confers a 2-fold risk for CHD & STROKE events
- May be used every 3 months until the job is done, i.e. that rupture prone plaque has stabilized in patients after TLC and lipid Rx

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## Case study 3 - when is the job done?

**Patient history**    **50-year-old asymptomatic male, Non-smoker**  
**Family history of premature stroke**  
**↑Lp(a), pattern B before Tx despite TG 75**  
**Current Meds: Crestor 20 mg QOD**

**Physical examination**    **BP              132/80 mm Hg**  
**Waist            38 in**  
**BMI             26 kg/m<sup>2</sup>**

**Laboratory measurements**    **TC              163 mg/dL**  
**Is the Job Done?    LDL-C            97 mg/dL**  
**HDL-C            50 mg/dL**  
**TG               55 mg/dL**  
**FBG              82 mg/dL**

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hsCRP 8.2 mg/L

Lp-PLA<sub>2</sub> 95 ng/mL

Likely false positive hsCRP

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hsCRP 0.6 mg/L  
Lp-PLA<sub>2</sub> 221ng/ml  
Plaque may not be  
stable yet.

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LDL IIIa+b 25% LDL IVb 12%  
HDL2b 32% Lp(a) 60 mg/dL

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## What to do for Case Study #3?

Titrated Niaspan up to 1.5 grams/day and LDL now 89, HDL 75, TG 47,  
LDL IIIa+b 16%, LDL IVb 3%, HDL2b 35%, Lp(a) still 60 mg/dl

Looks good but IS THE JOB DONE?:

hsCRP < 0.6 mg/L  
Lp-PLA<sub>2</sub> 168 ng/ml  
**Yes!**

Other options – DON'T FORGET LIFESTYLE INTERVENTION, TOO!

BMI 26 – no more Dairy Queen (D/C sugar and trans fats), add Omega 3's  
SBP 132- PRE-HTN, review sodium intake & lose 5-10 pounds  
LDL still > 70 consider more Crestor or Zetia to lower LDL target?  
Check Homocysteine, Apo E genotyping?

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