

## Treatment of Atherosclerosis in 2007

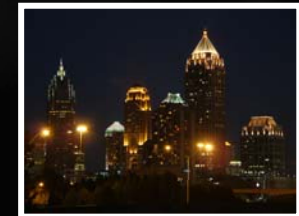
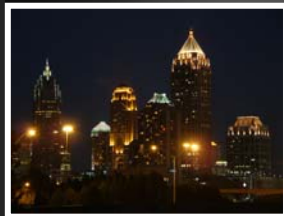
Szilard Voros, M.D.

Medical Director

Cardiovascular MR and CT

Fuqua Heart Center of Atlanta

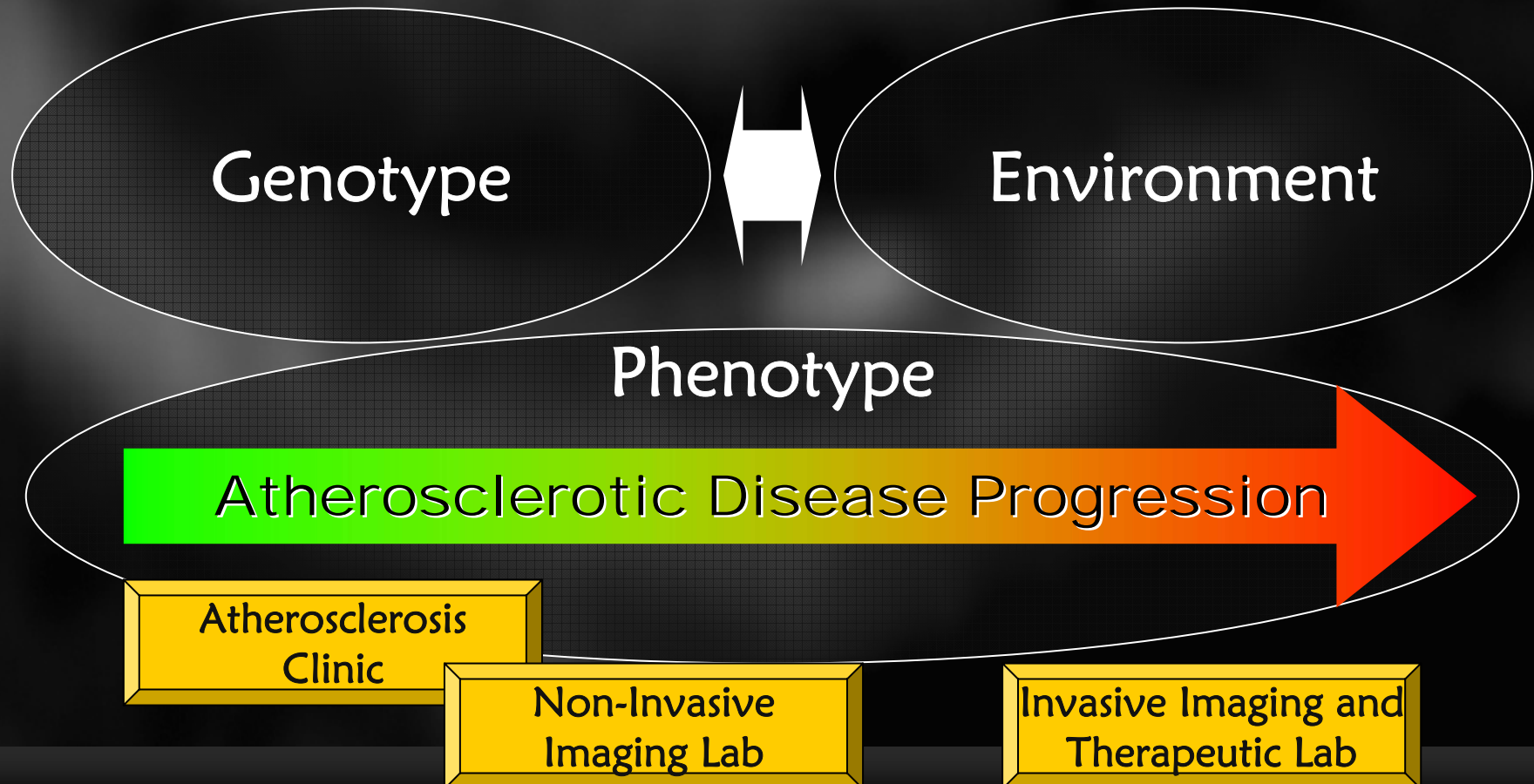
Piedmont Hospital





# Our Paradigm..

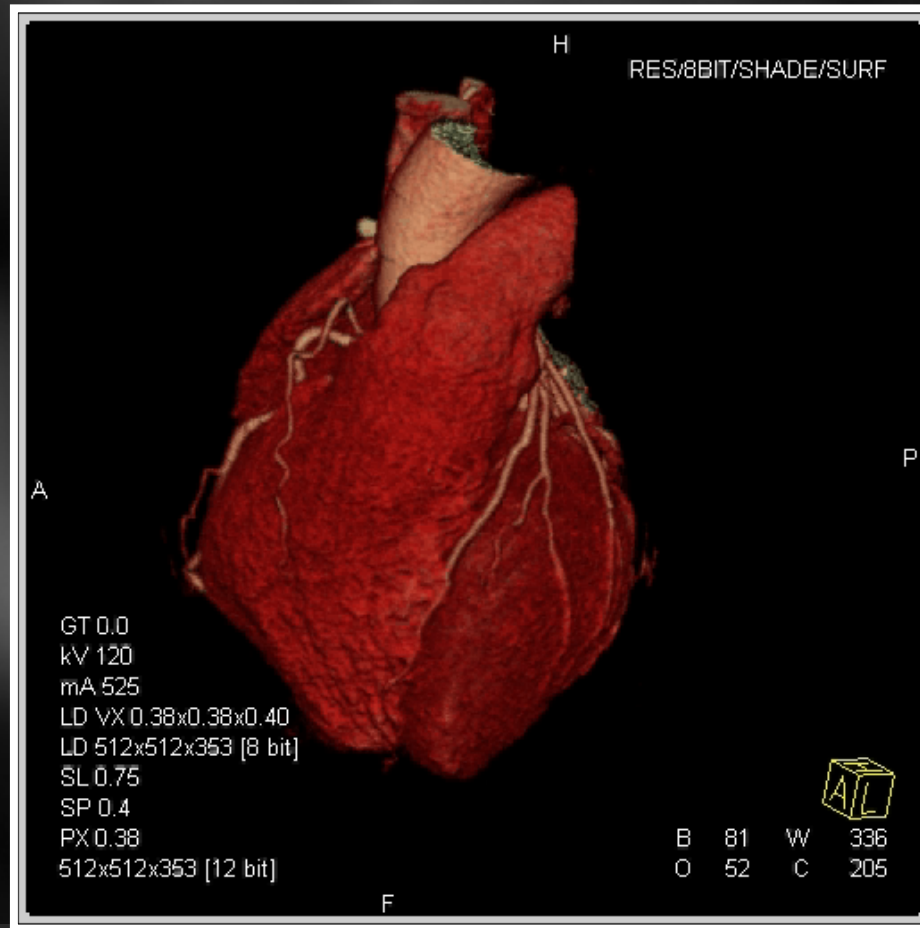
Fuqua Heart Center of Atlanta





## Introduction My Perspective

Fuqua Heart Center of Atlanta

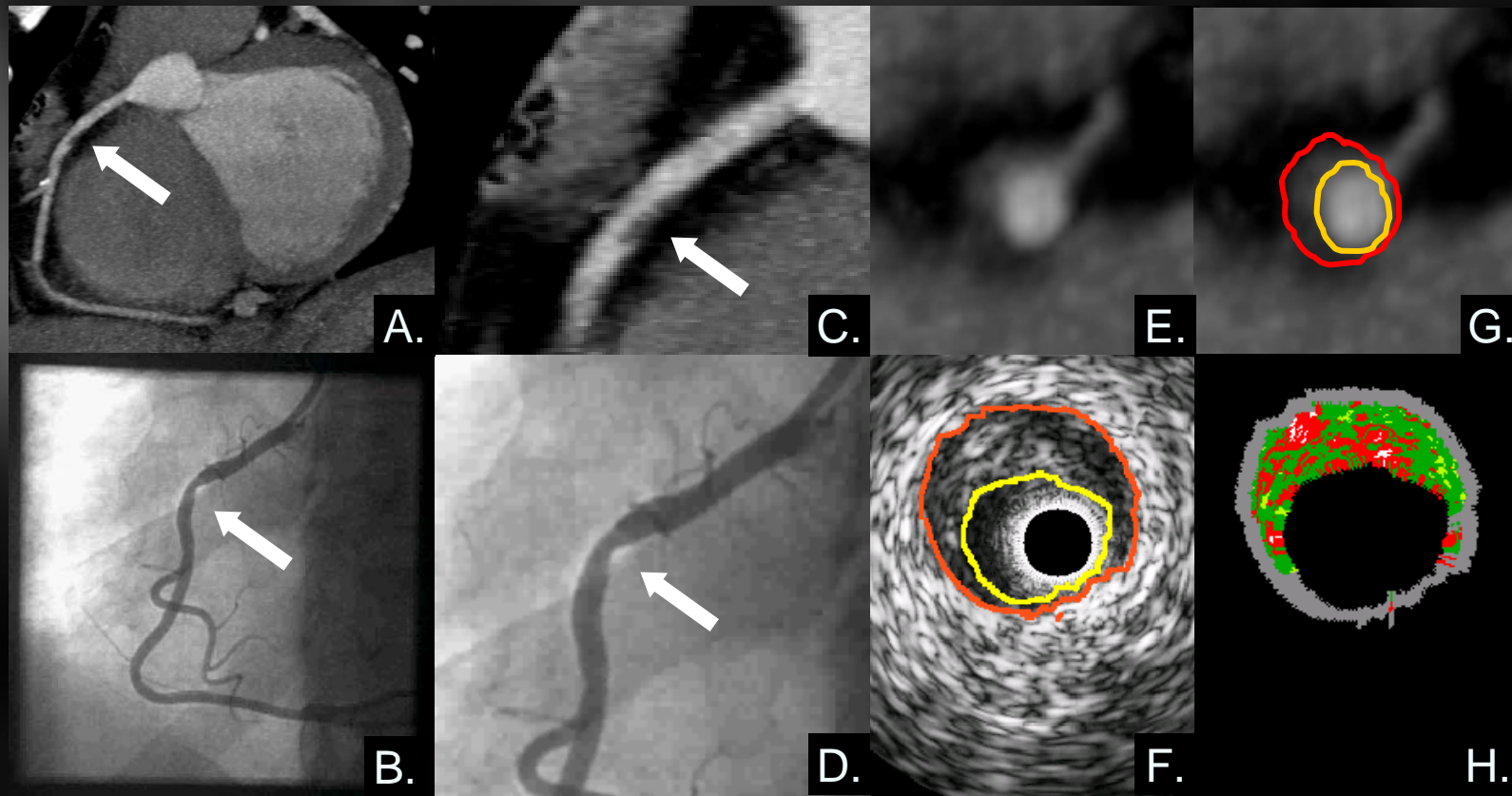




# Introduction

## My Perspective

Fuqua Heart Center of Atlanta



Superko, Voros. In PK Shah 2006.



## New Paradigm

### Dual Inhibition of Cholesterol Metabolism

Dual inhibition of cholesterol metabolism is becoming first-line therapy in the treatment of dyslipidemias



# New Paradigm

## Dual Inhibition of Cholesterol Metabolism

*Dual inhibition of cholesterol metabolism is becoming first-line therapy in the treatment of dyslipidemias*

### 1. LDL Argument

1. To reach LDL < 70, dual inhibition is needed for LDL > 140

### 2. Biological Argument

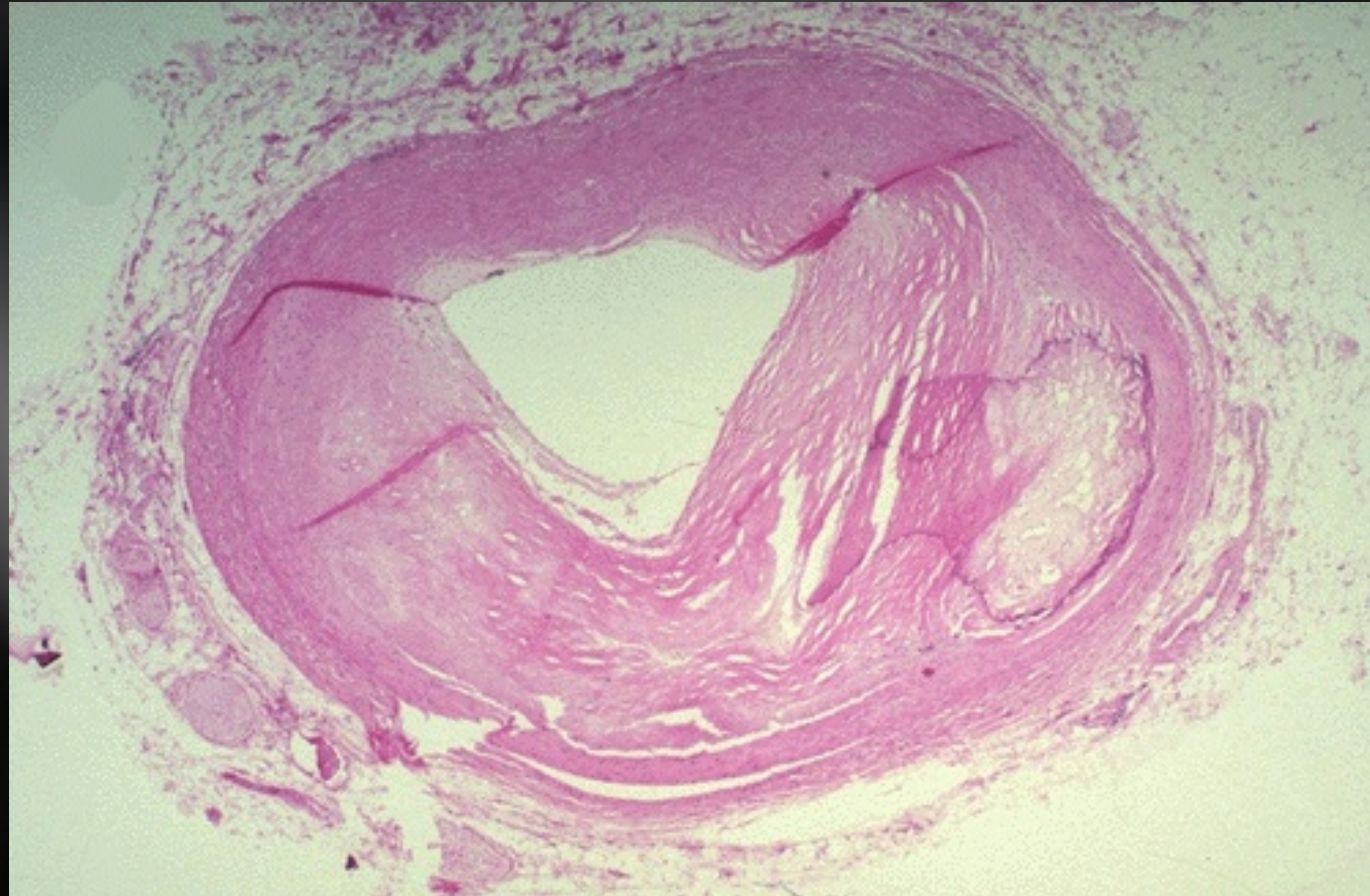
1. Cholesterol in plaque comes from two sources
2. Treatment of one pathway upregulates the other
3. Dual-inhibition is synergistic for inflammation



# Biological Arguments

## The Disease: Atherosclerosis

Fuqua Heart Center of Atlanta

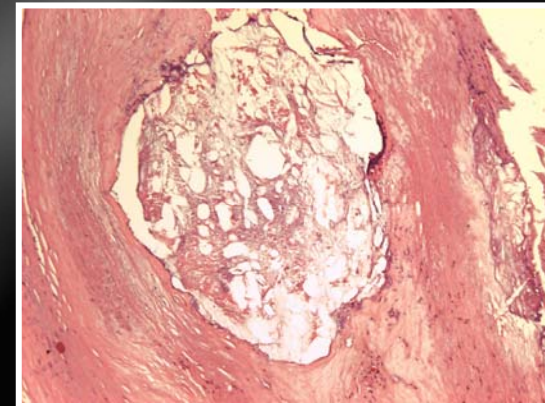
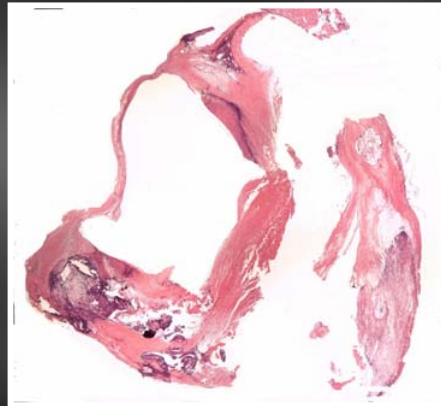
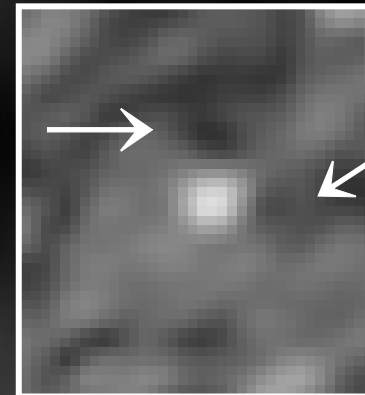
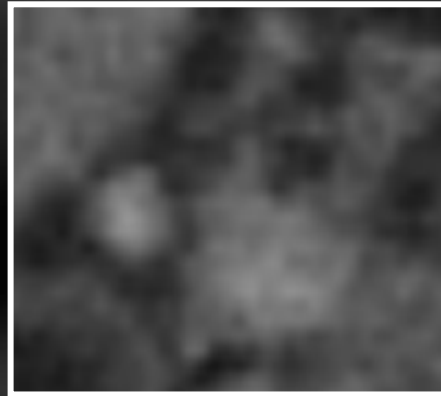
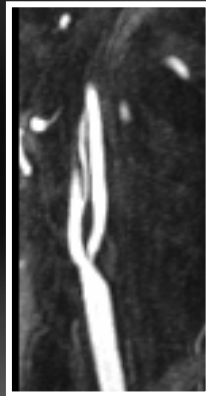




## Biological Arguments

### The Disease: Atherosclerosis

Fuqua Heart Center of Atlanta



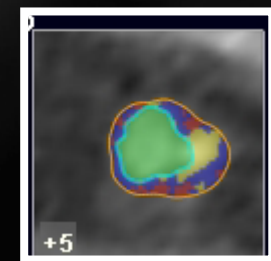
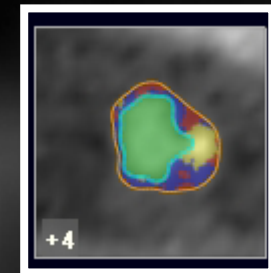
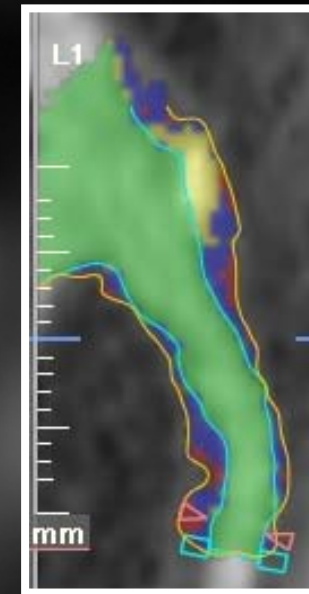
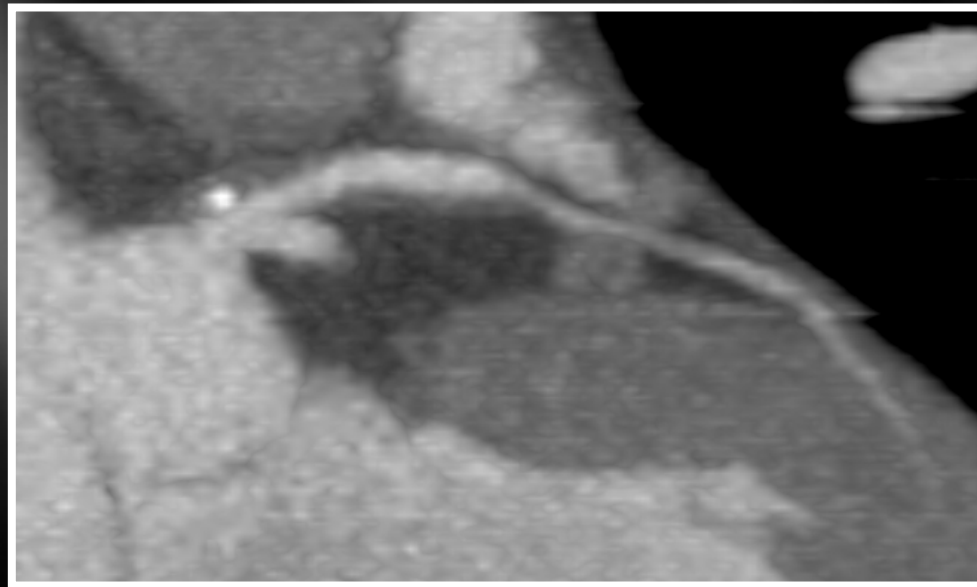




# Biological Arguments

## The Disease: Atherosclerosis

Fuqua Heart Center of Atlanta

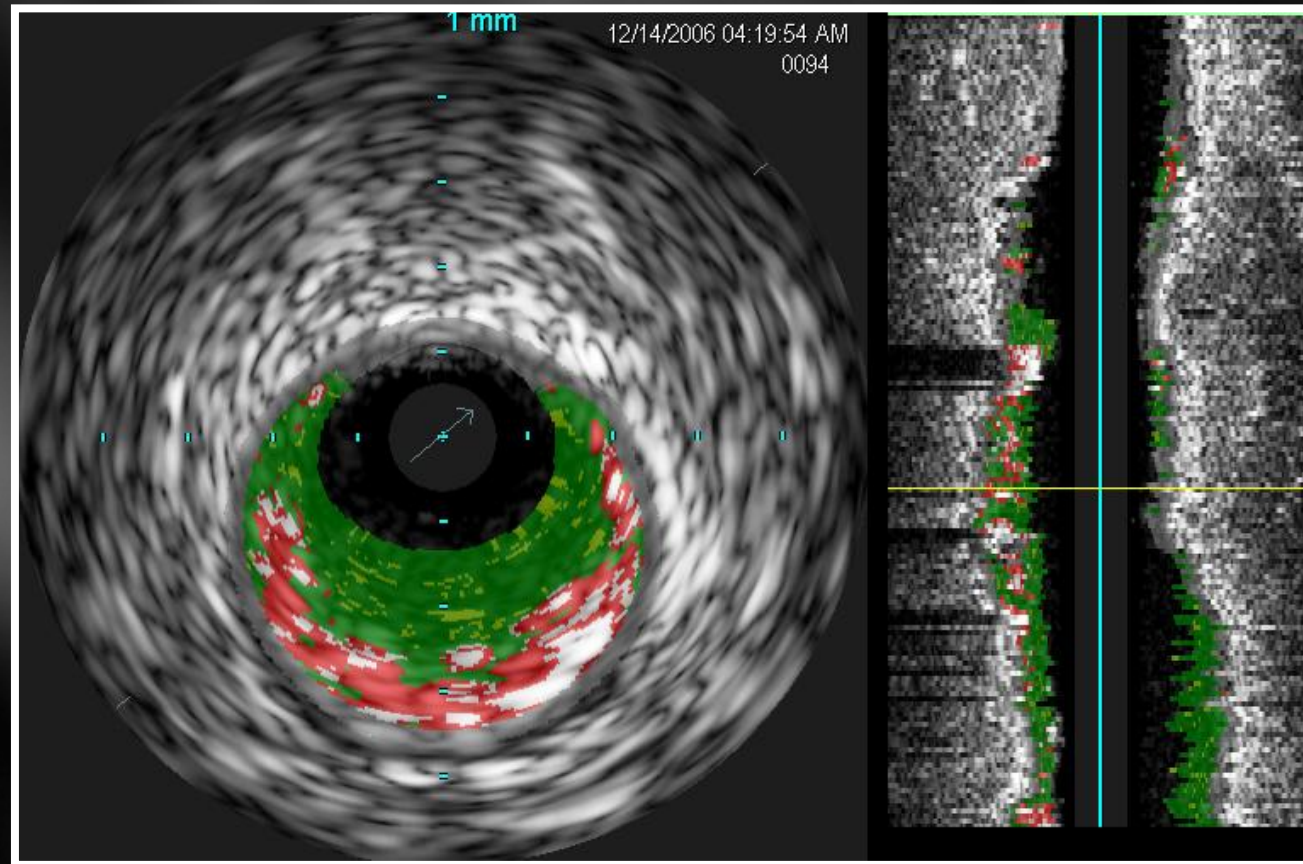




# Biological Arguments

## The Disease: Atherosclerosis

Fuqua Heart Center of Atlanta



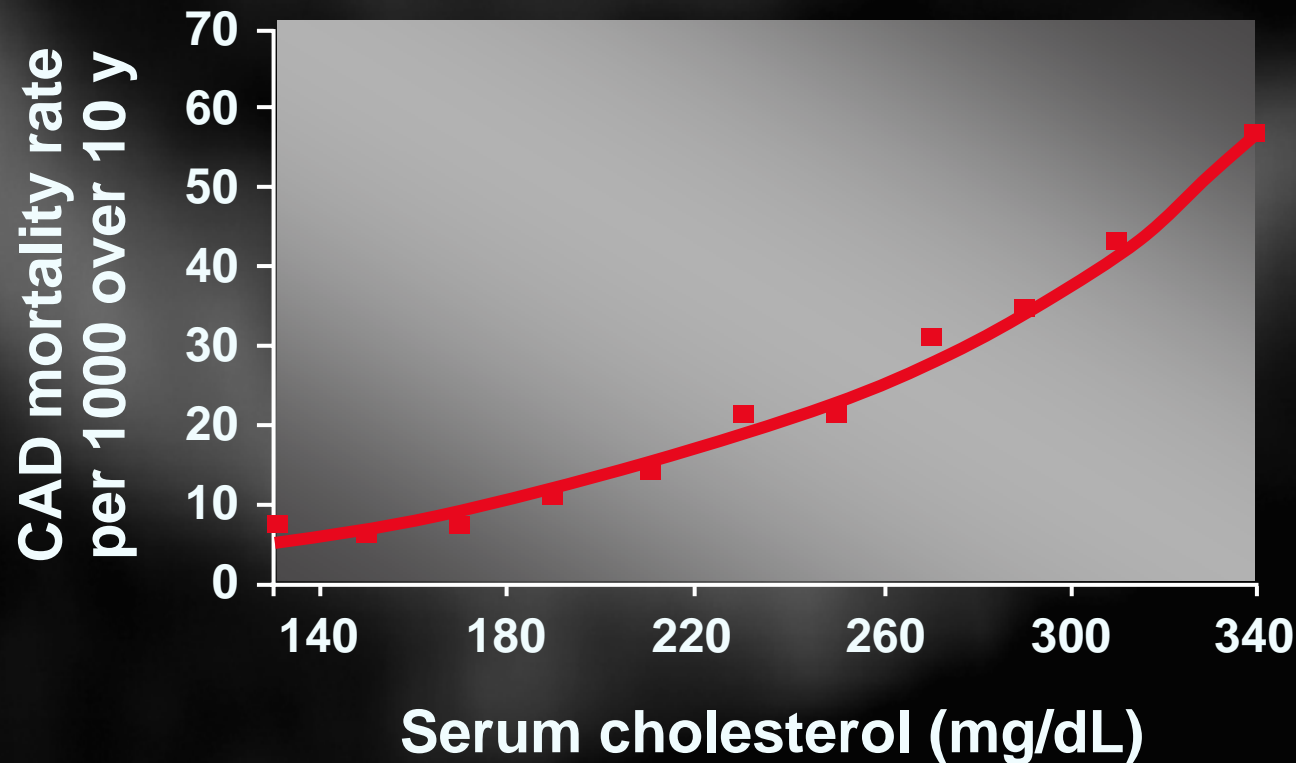


# Biological Arguments

## Role of Cholesterol in CAD

Fuqua Heart Center of Atlanta

MR-FIT (N=316,099)

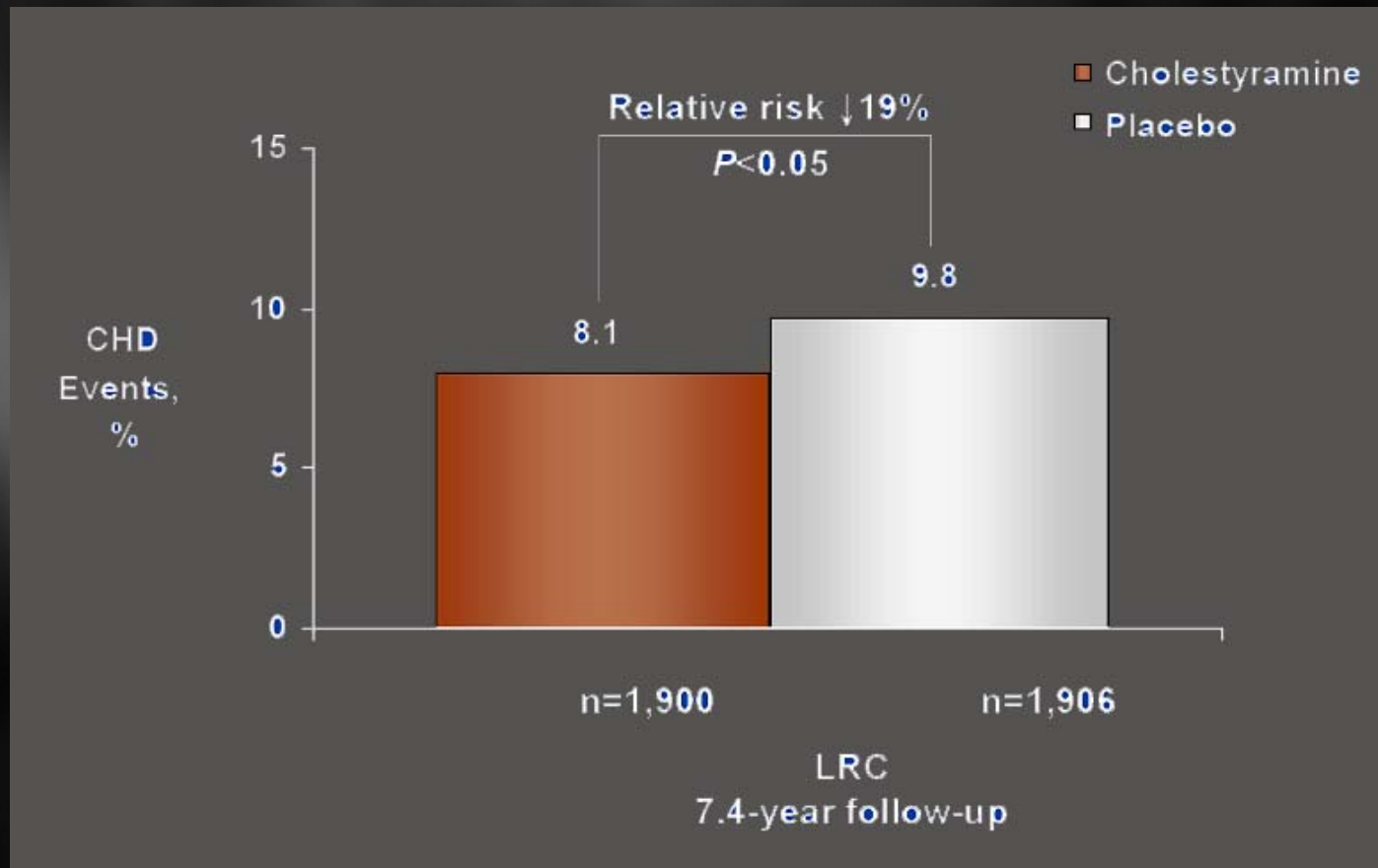




# Biological Arguments

## Role of Cholesterol in CAD

Fuqua Heart Center of Atlanta



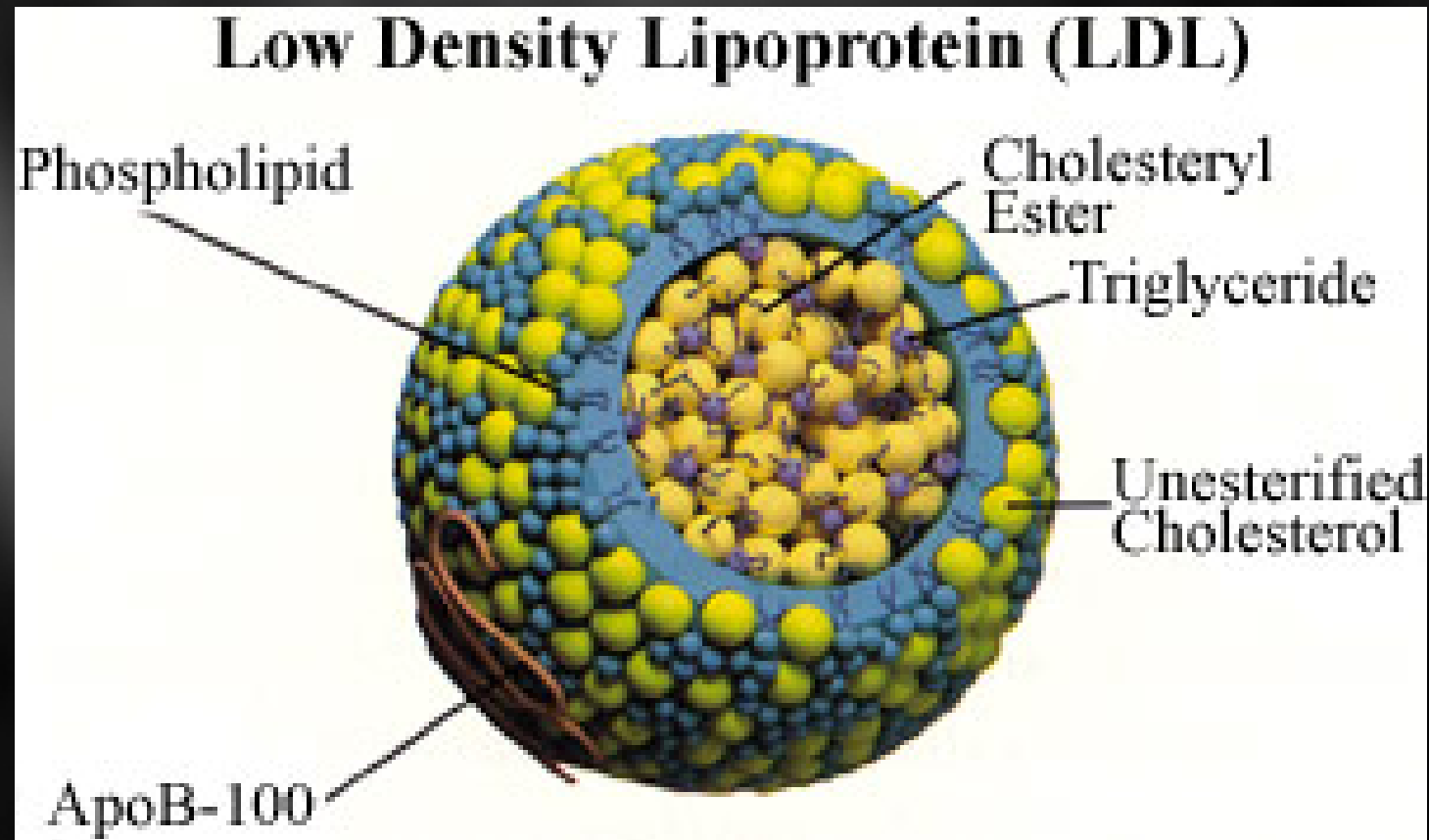
JAMA 1984;251:351-364.



# Biological Arguments

## Role of Cholesterol in CAD

Fuqua Heart Center of Atlanta

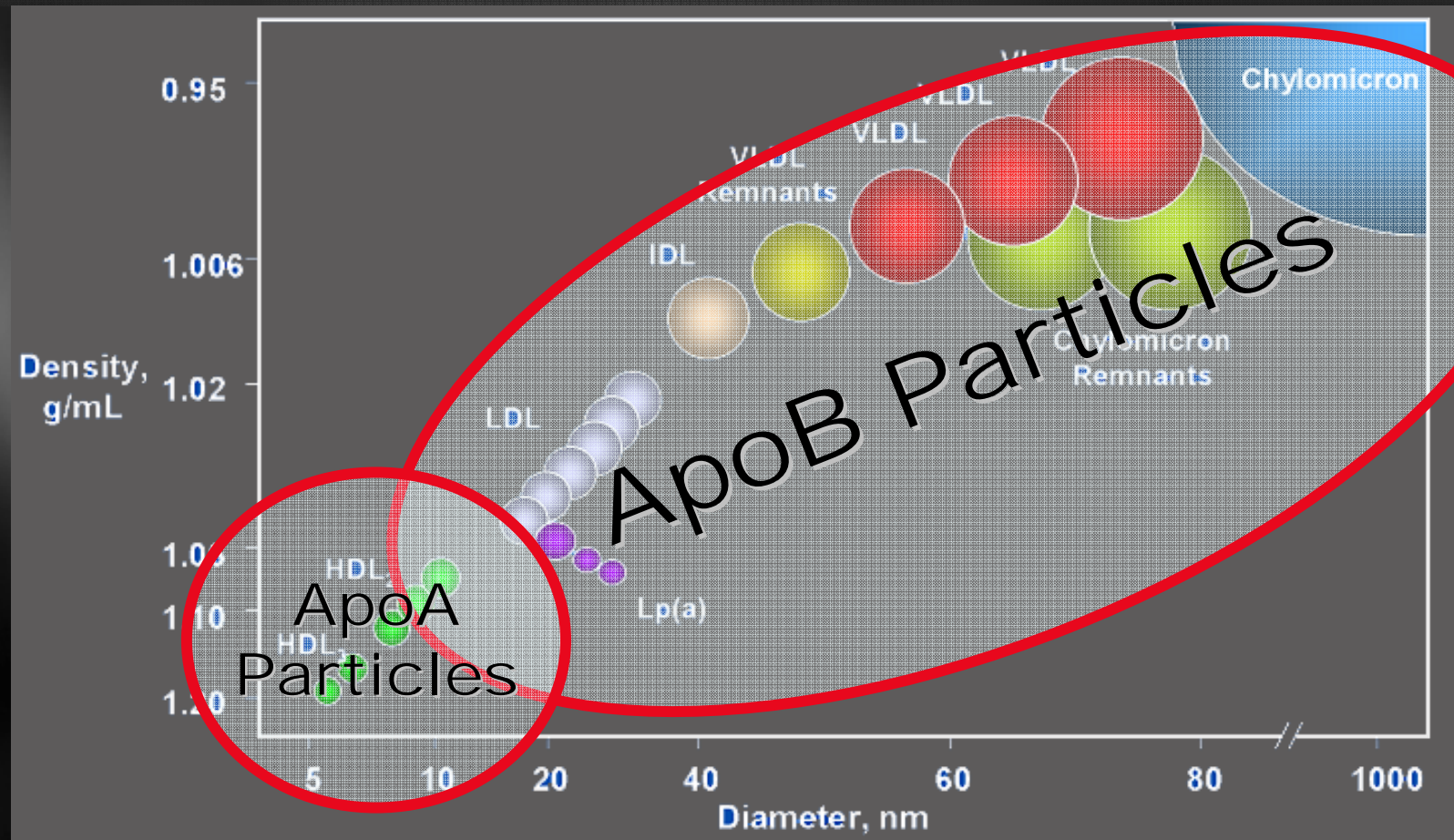




# Biological Arguments

## Role of Cholesterol in CAD

Fuqua Heart Center of Atlanta

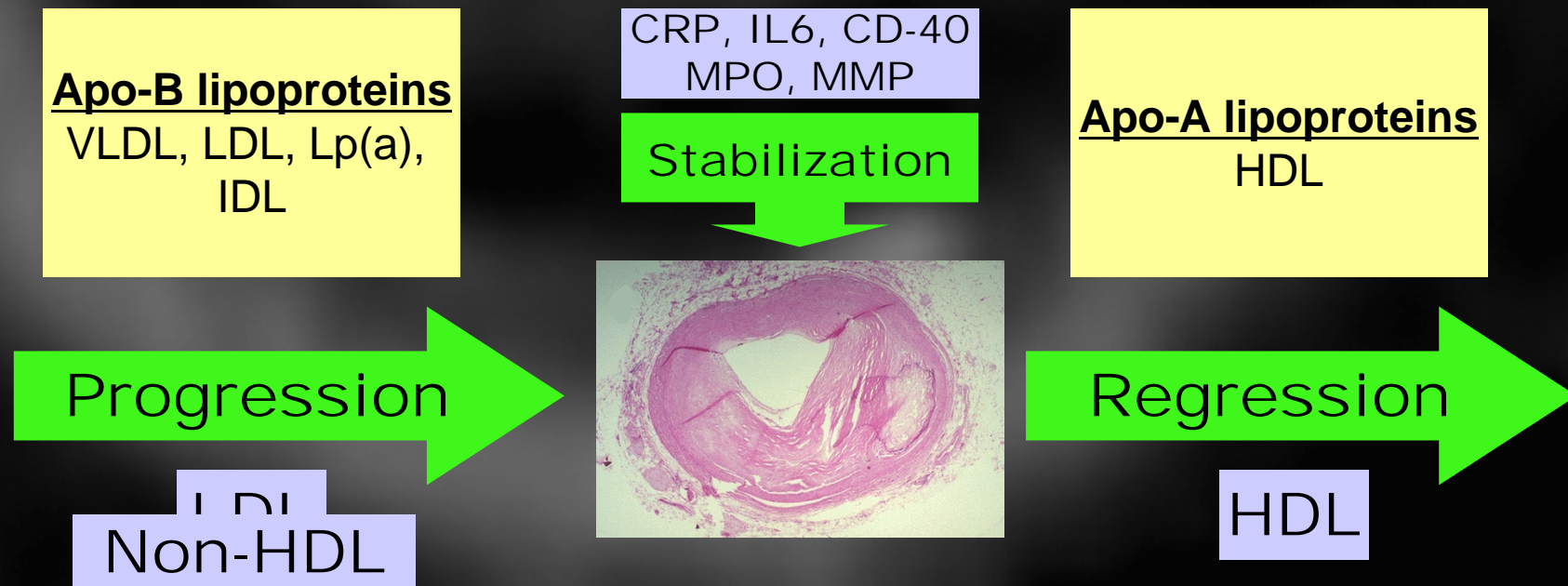




# Biological Arguments

## Atherosclerosis Progression and Regression

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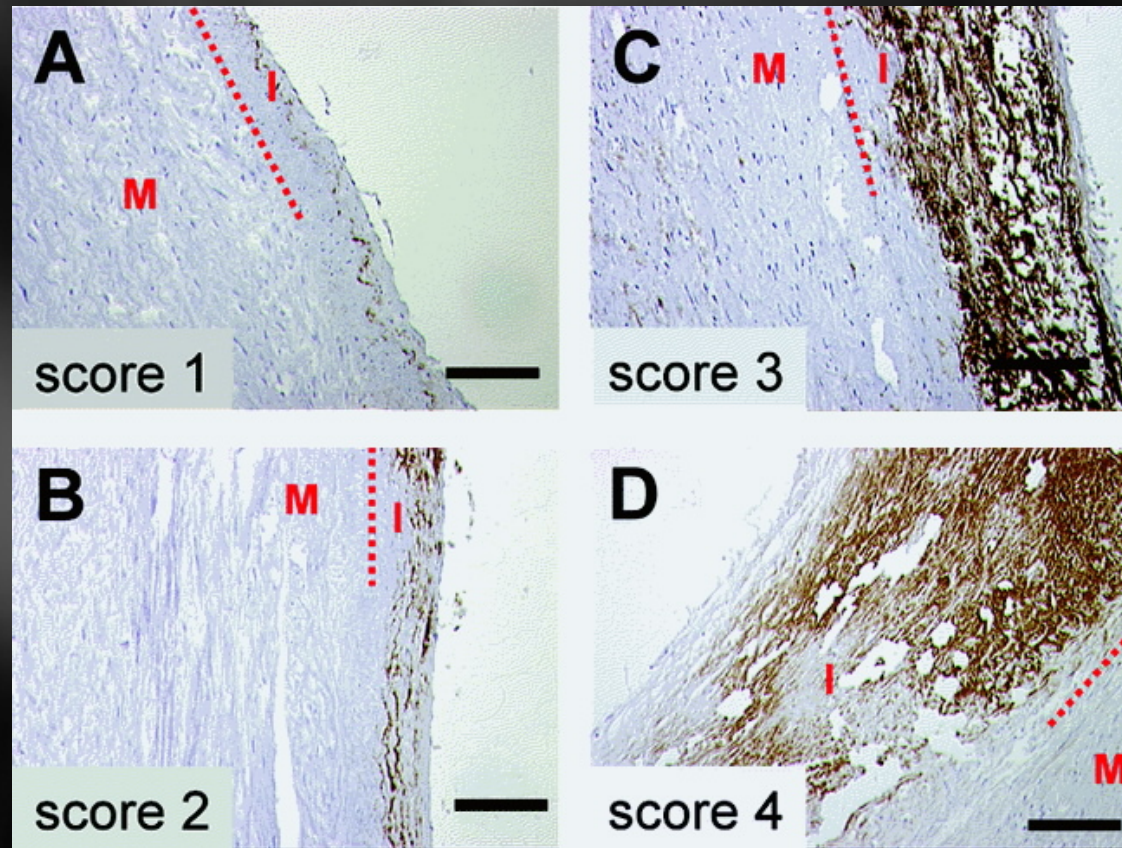




# Biological Arguments

## Atherosclerosis Progression: ApoB

Fuqua Heart Center of Atlanta







# New Paradigm

## Dual Inhibition of Cholesterol Metabolism

*Dual inhibition of cholesterol metabolism is becoming first-line therapy in the treatment of dyslipidemias*

### 1. LDL Argument

1. To reach LDL < 70, dual inhibition is needed for LDL > 140

### 2. Biological Argument

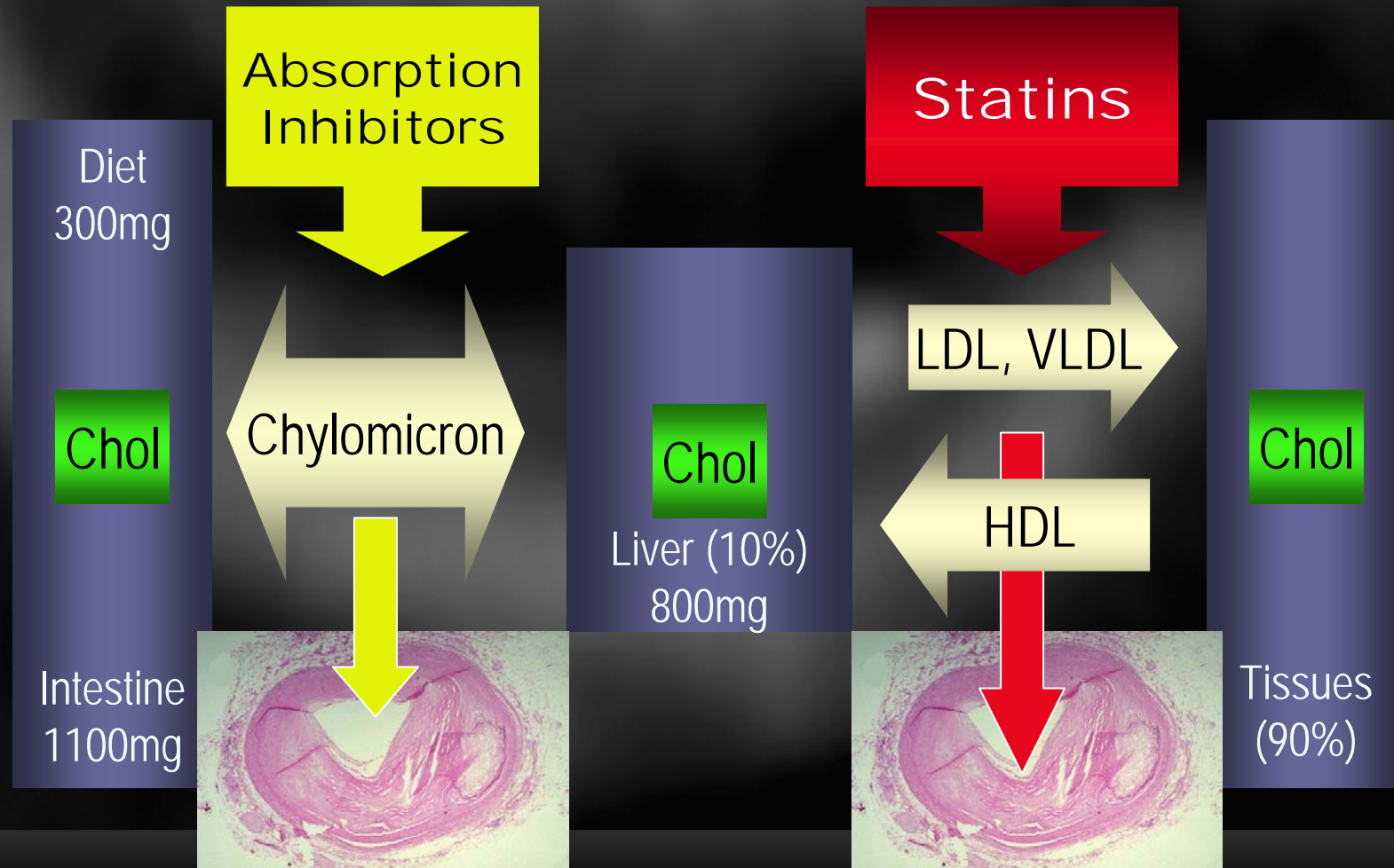
1. Cholesterol in plaque comes from two sources
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# Biological Arguments

## 1. Cholesterol in Plaque from Two Sources

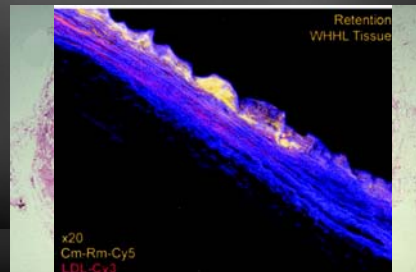
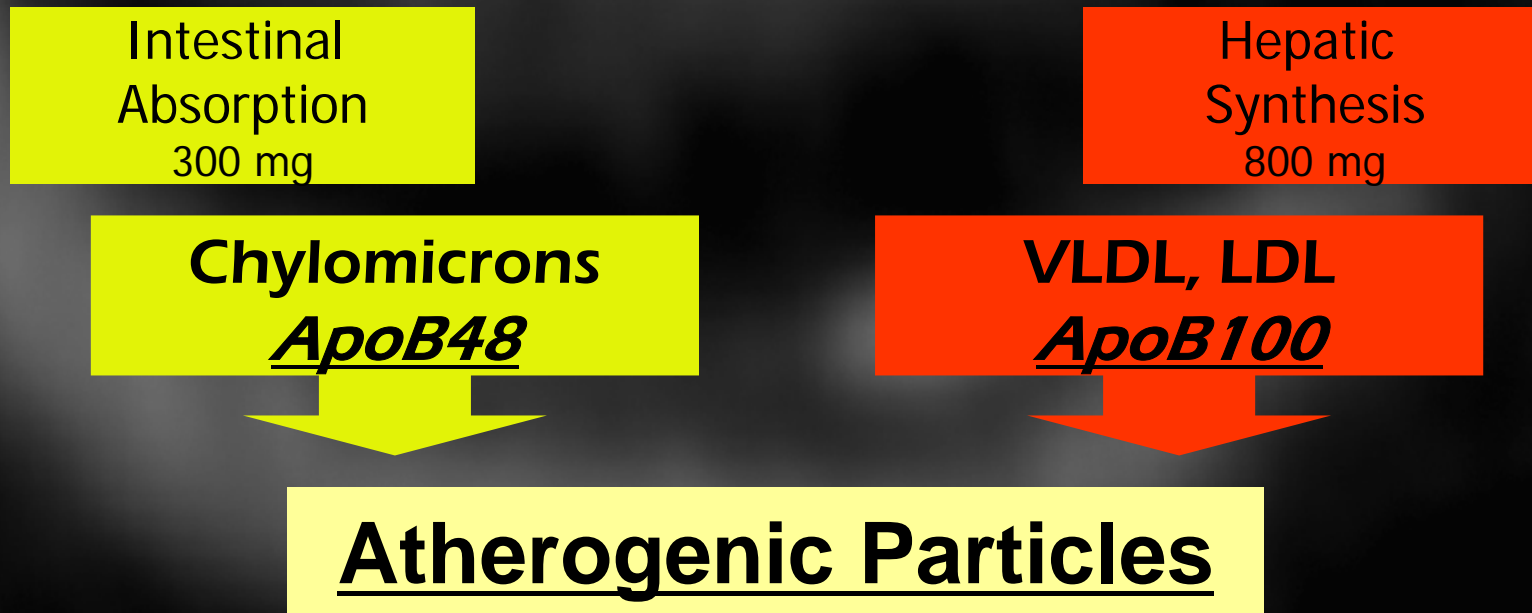
Fuqua Heart Center of Atlanta





# Biological Arguments

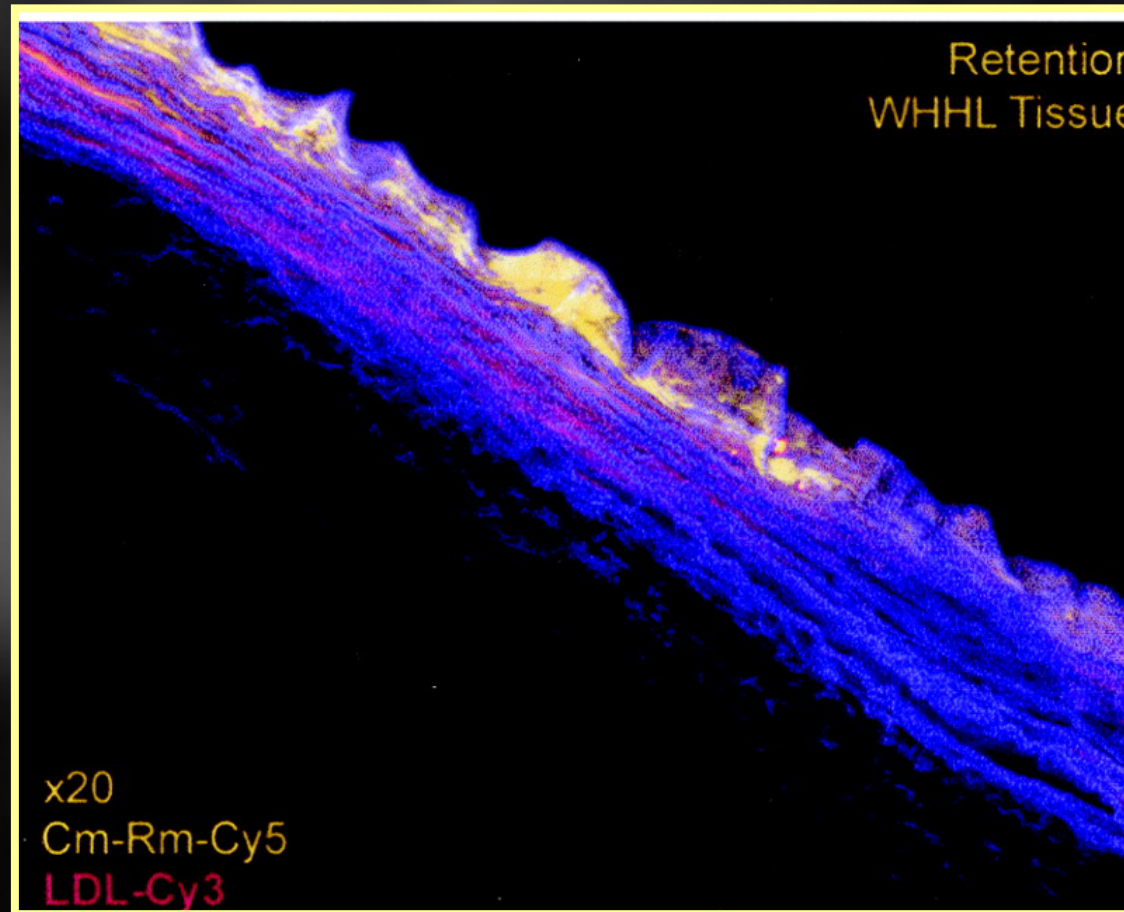
## 1. Cholesterol in Plaque from Two Sources





# Biological Arguments

## 1. Cholesterol in Plaque from Two Sources



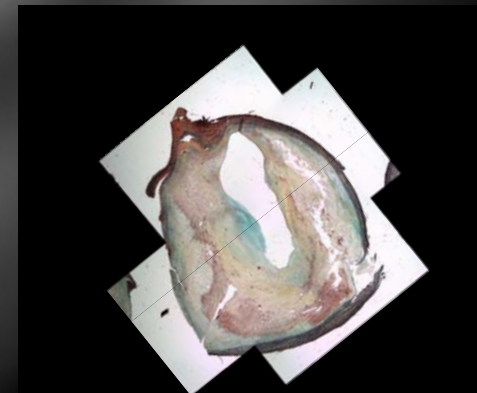
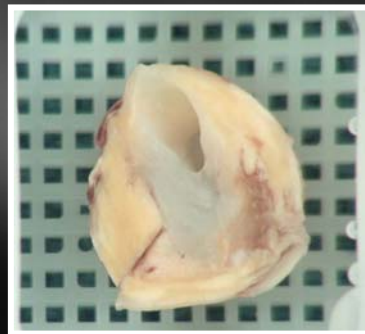
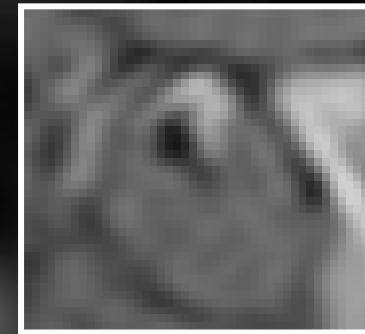
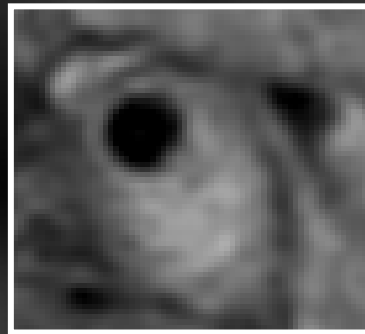
Proctor et al. ATVB 2003;23:1595.



# Biological Arguments

## 1. Cholesterol in Plaque from Two Sources

Fuqua Heart Center of Atlanta

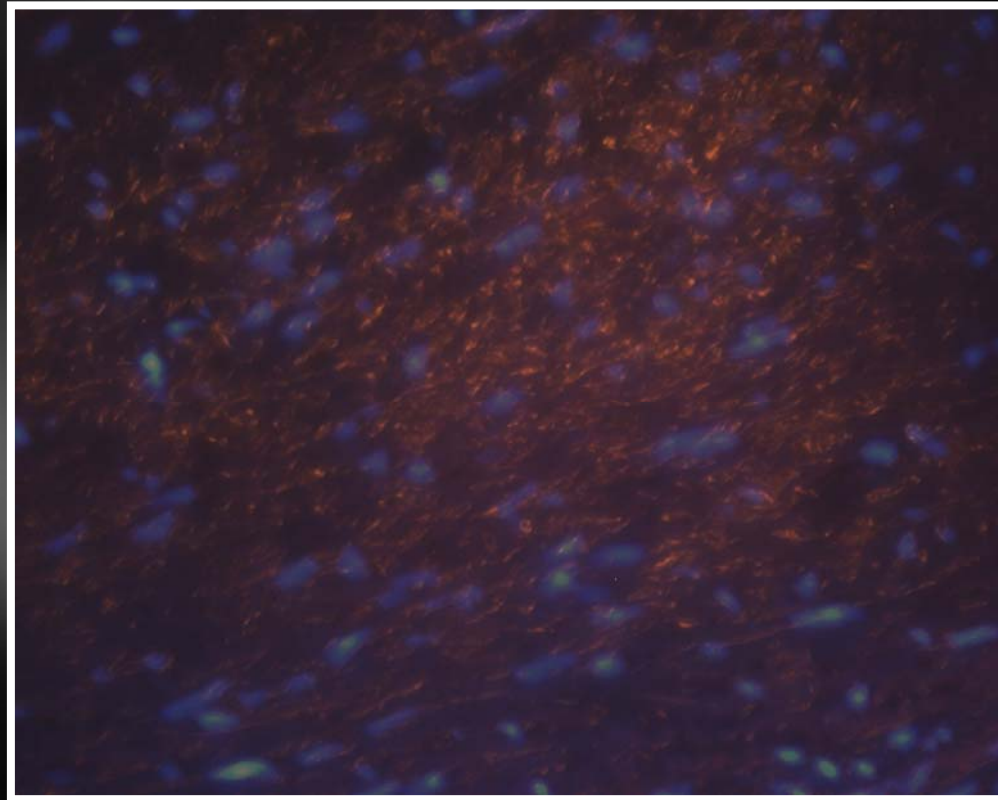




# Biological Arguments

## 1. Cholesterol in Plaque from Two Sources

Fuqua Heart Center of Atlanta

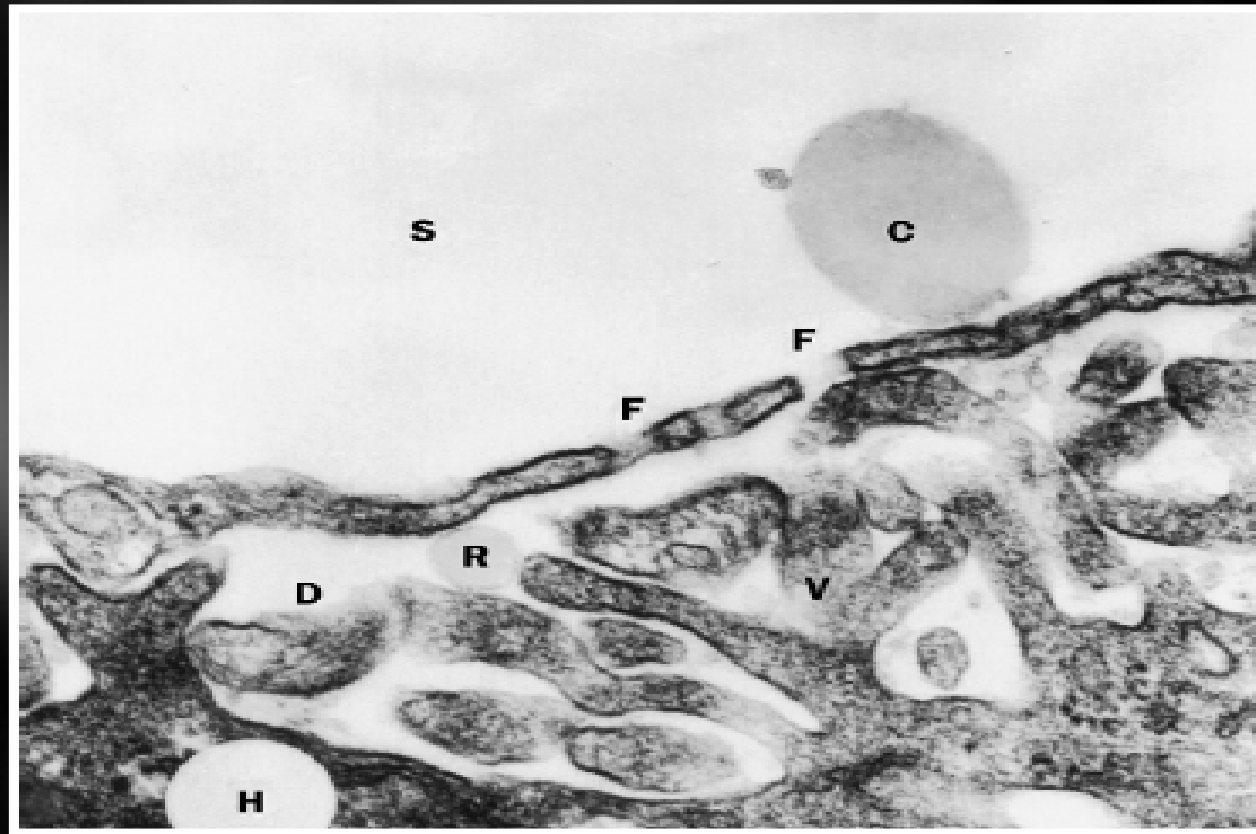


Voros et al. 2006.



# Biological Arguments

## 1. Cholesterol in Plaque from Two Sources



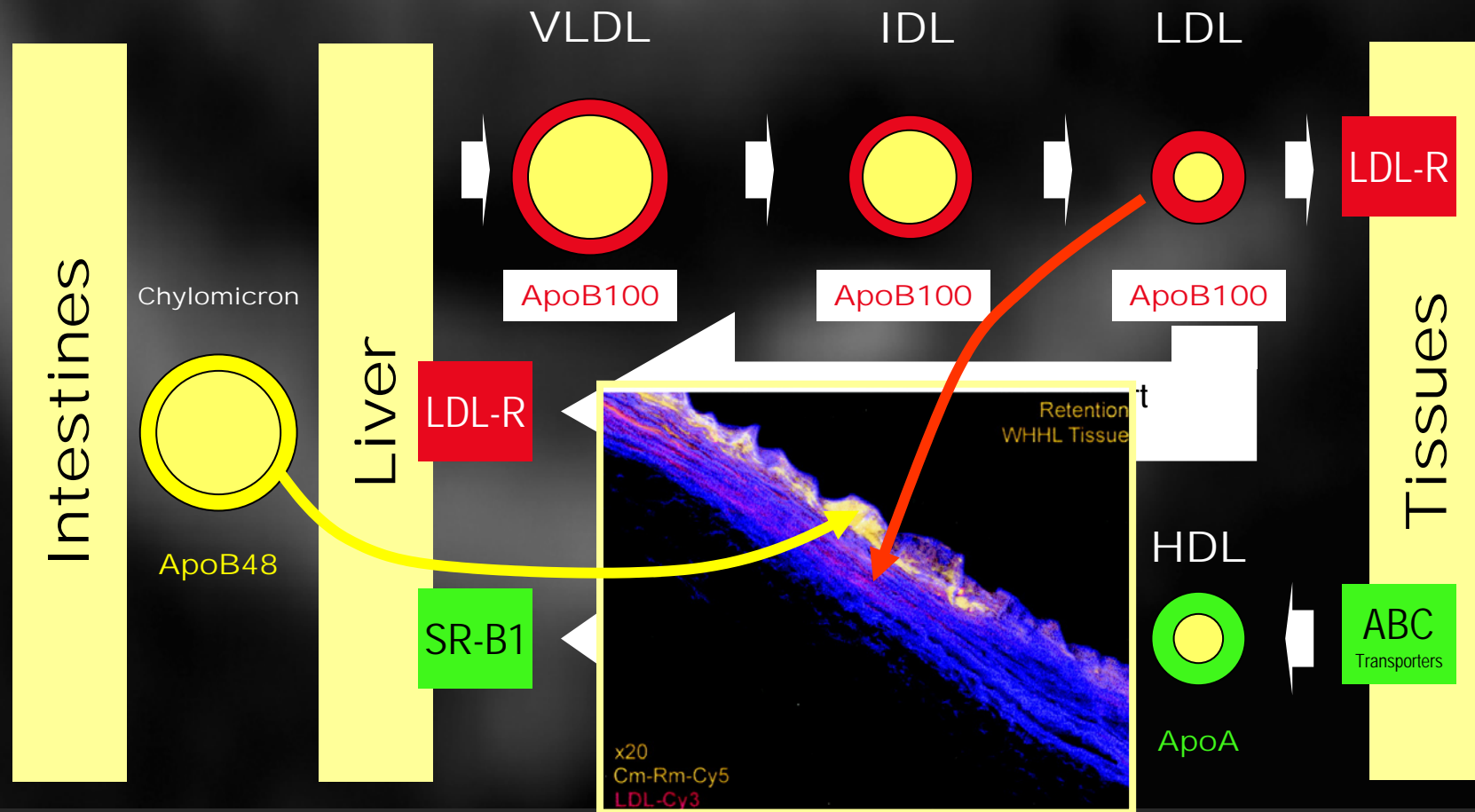
Fuqua Heart Center of Atlanta



# Biological Arguments

## Reverse Cholesterol Transport

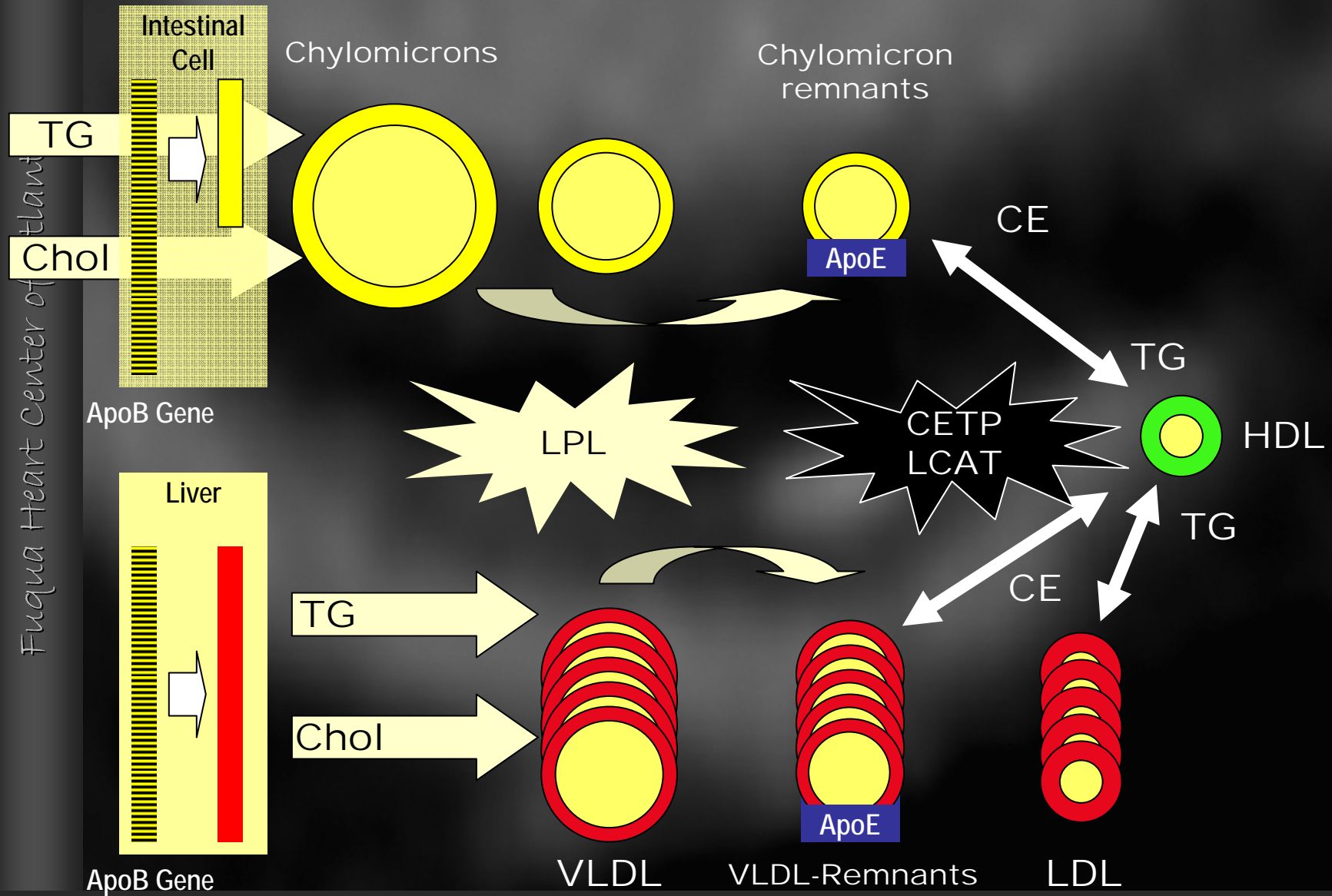
Fuqua Heart Center of Atlanta







# Atherosclerosis and Lipoproteins

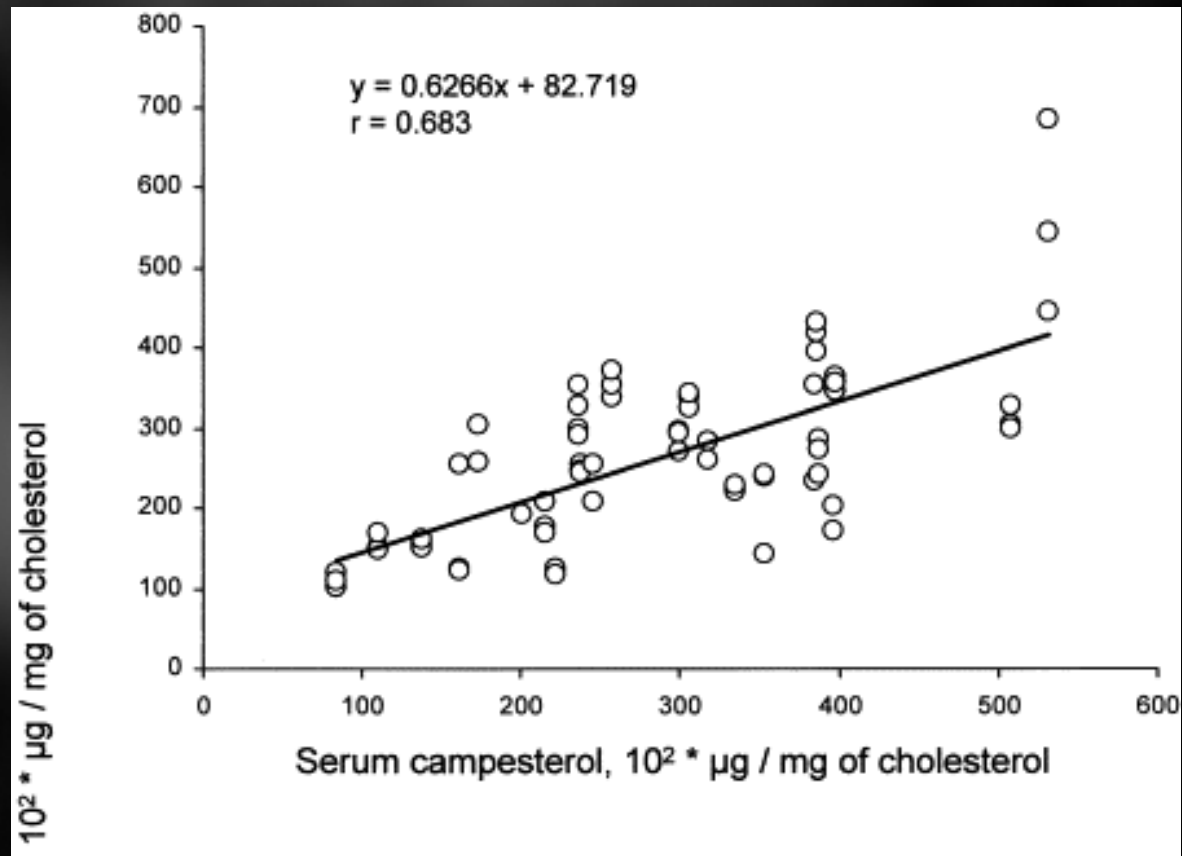




# Biological Arguments

## 1. Cholesterol in Plaque from Two Sources

Fuqua Heart Center of Atlanta

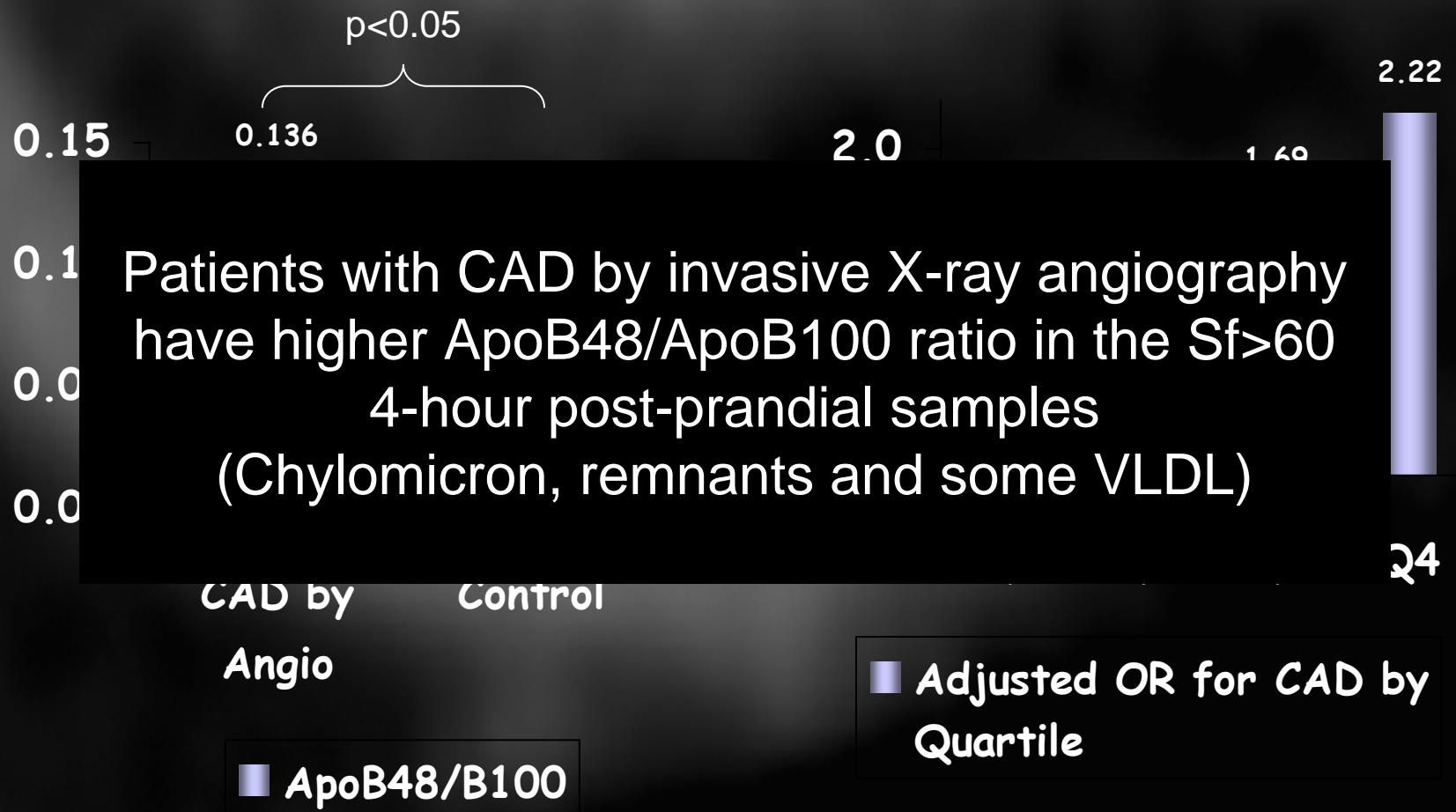




# Biological Arguments

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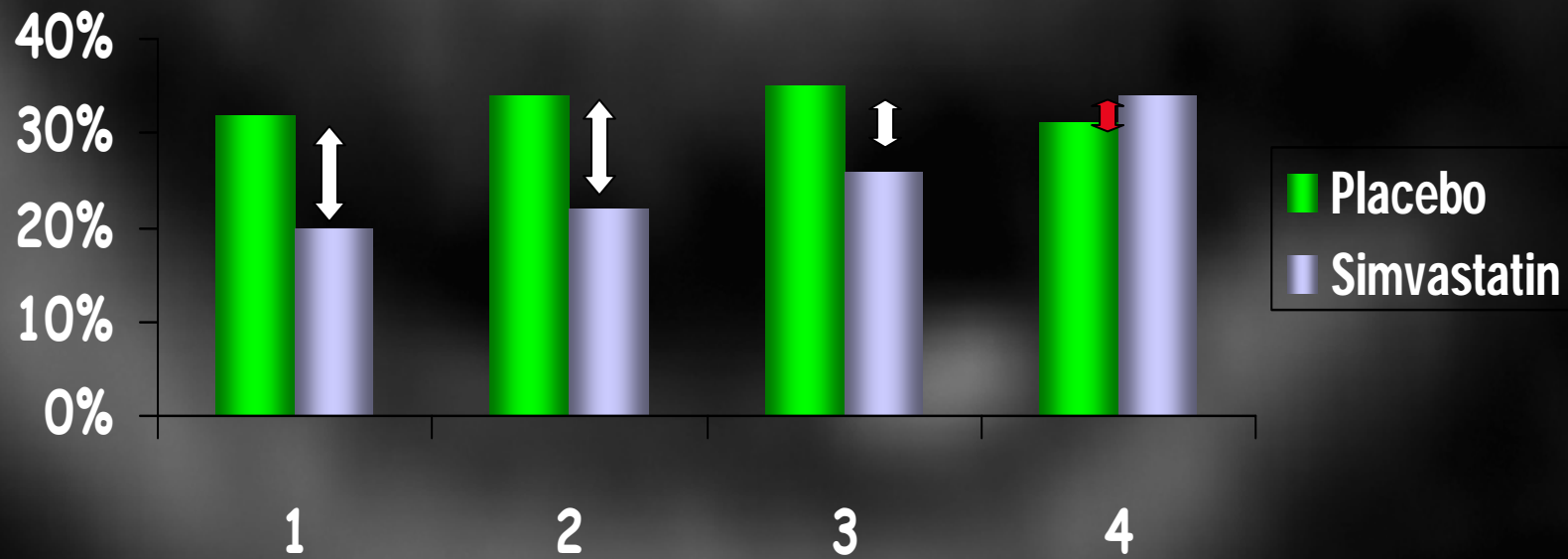
Patients with CAD by invasive X-ray angiography have higher ApoB48/ApoB100 ratio in the Sf>60 4-hour post-prandial samples (Chylomicron, remnants and some VLDL)



# Biological Arguments

## 1. Cholesterol in Plaque from Two Sources

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Quartiles of cholesterol absorption

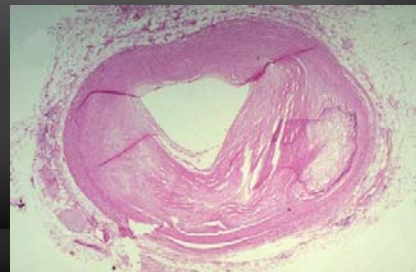
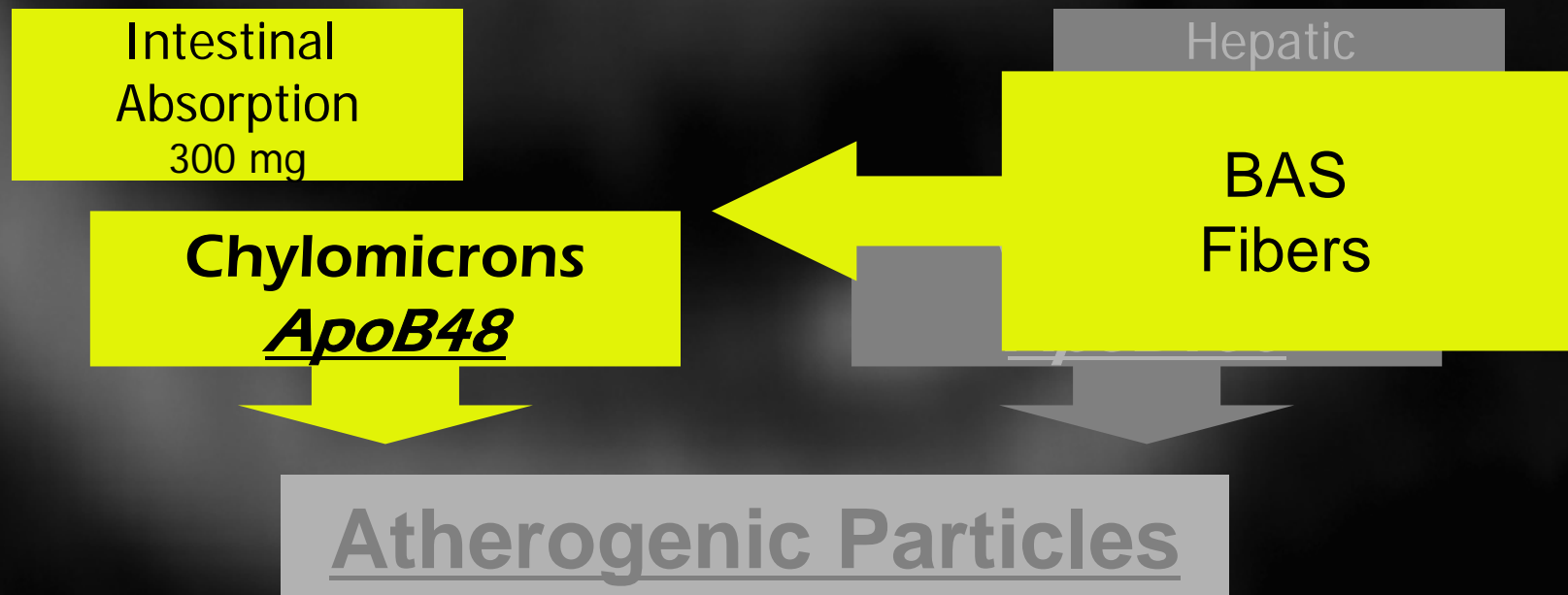
4S population



# Biological Arguments

## 1. Cholesterol in Plaque from Two Sources

Fuqua Heart Center of Atlanta

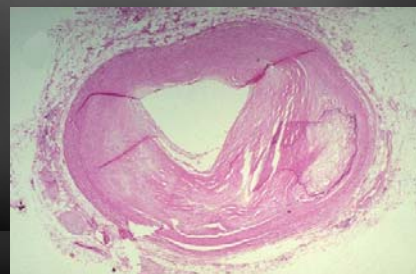
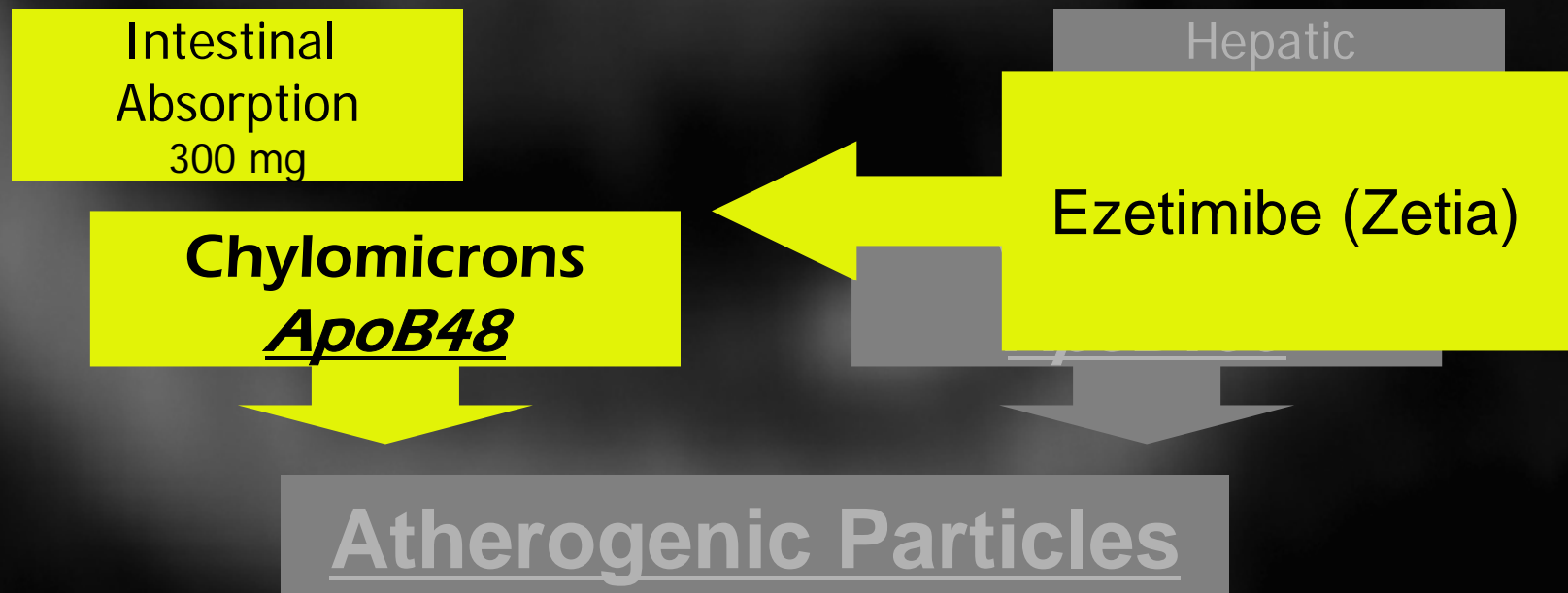




# Biological Arguments

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Fuqua Heart Center of Atlanta

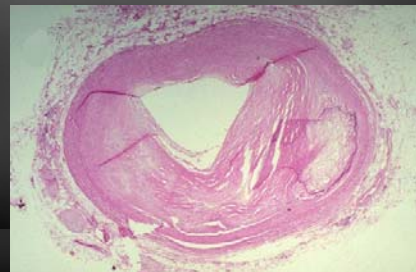
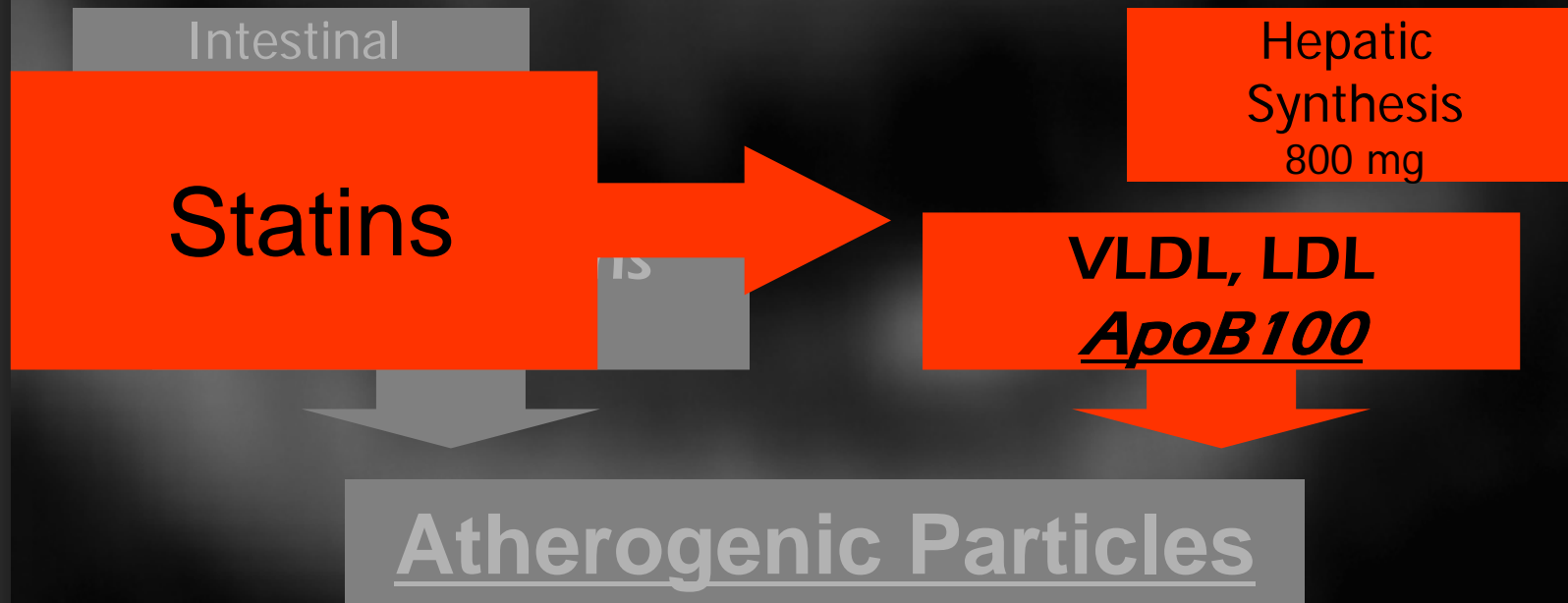




# Biological Arguments

## 1. Cholesterol in Plaque from Two Sources

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# Biological Arguments

## 1. Cholesterol in Plaque from Two Sources

Intestinal  
Absorption

300 mg

Chylomicrons

*ApoB48*

Hepatic  
Synthesis

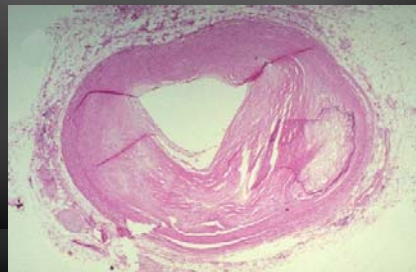
800 mg

VLDL, LDL

*ApoB100*

DUAL INHIBITION

**Atherogenic Particles**



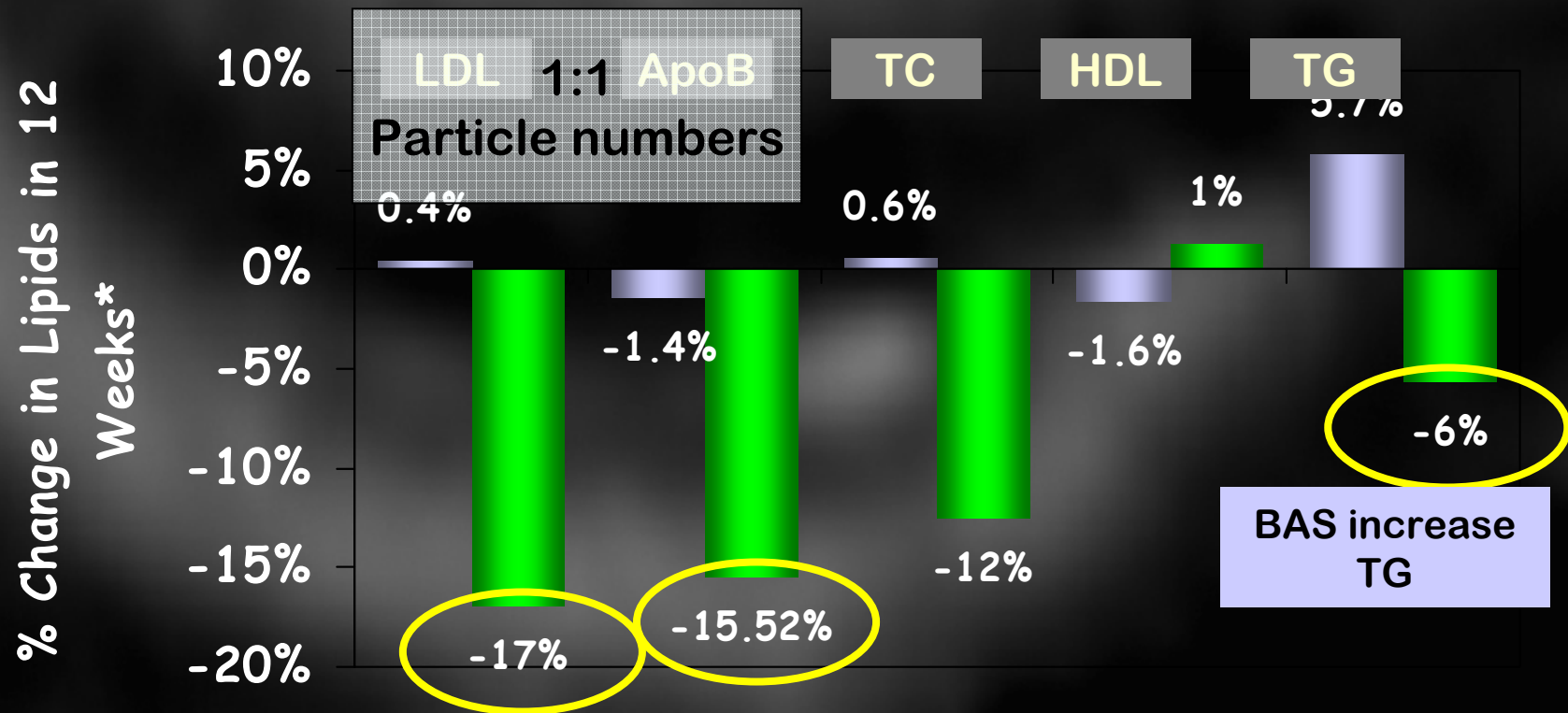




# Biological Arguments

## Ezetimibe (Monotherapy)

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\*Seen at 2 weeks and maintained at 12 weeks

■ Placebo ■ Ezetimibe

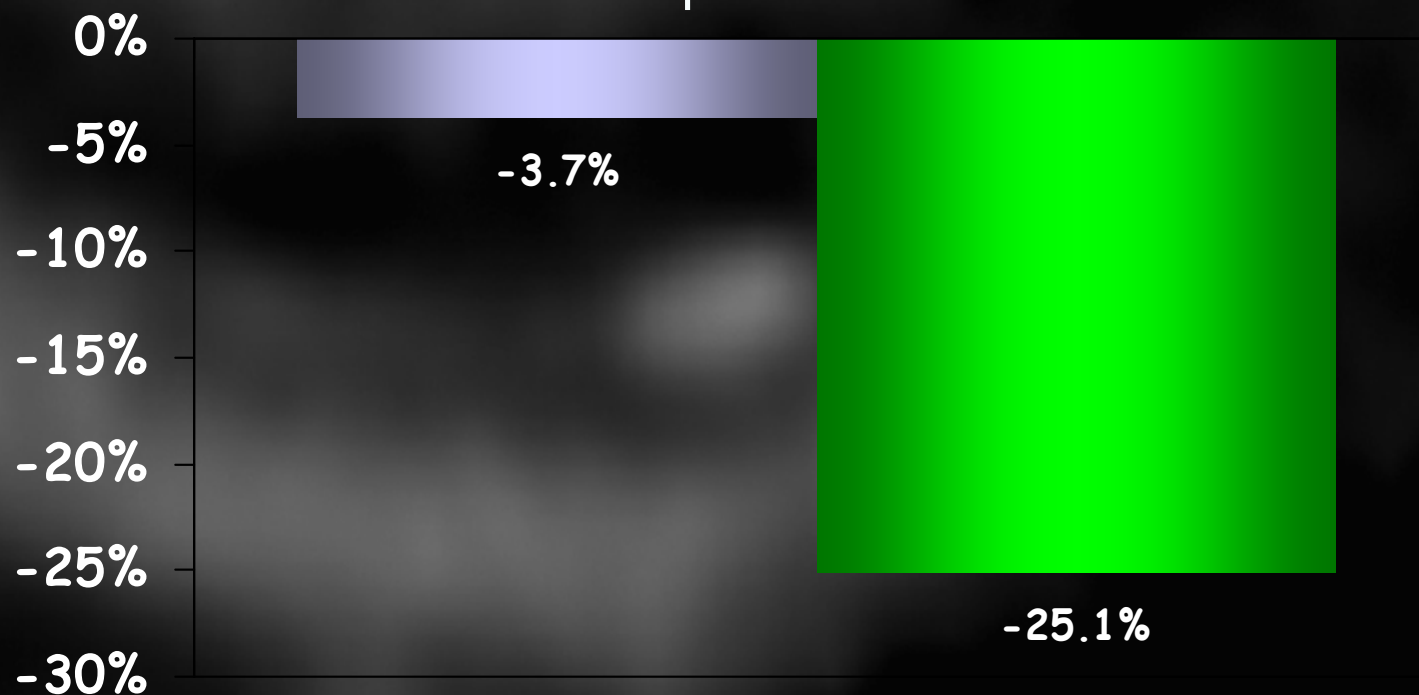


# Biological Arguments

## Ezetimibe (Add-On Therapy)

$p < 0.001$

% Change in LDL-Cholesterol  
from Statin Baseline



■ Placebo ■ Ezetimibe



# New Paradigm

## Dual Inhibition of Cholesterol Metabolism

*Dual inhibition of cholesterol metabolism is becoming first-line therapy in the treatment of dyslipidemias*

### 1. LDL Argument

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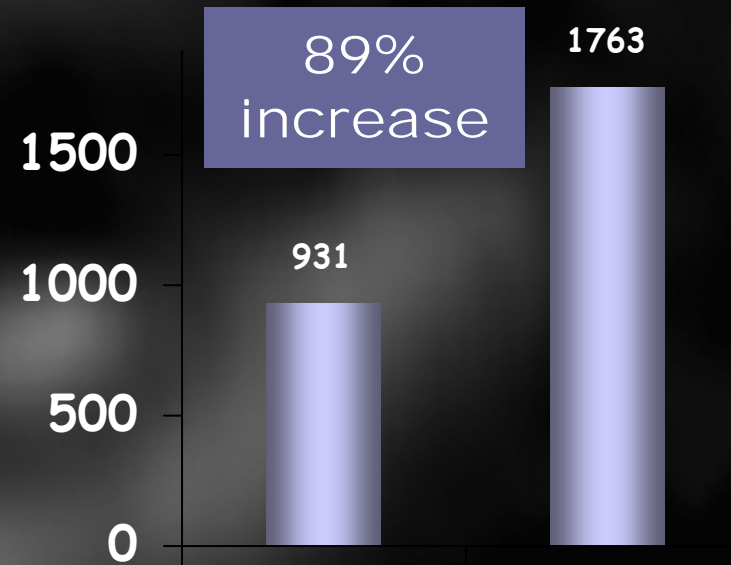
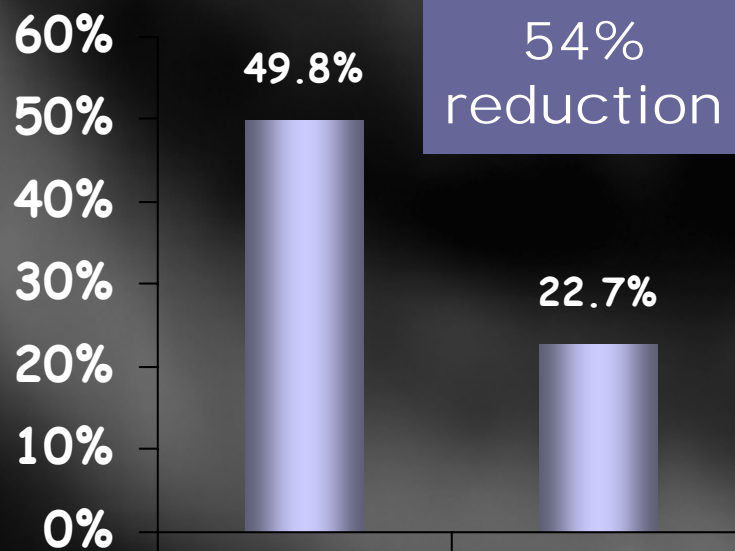
1. Cholesterol in plaque comes from two sources
2. Treatment of one pathway upregulates the other
3. Dual inhibition is synergistic for inflammation



# Biological Argument

## 2. Inhibiting One Pathway Upregulates Other

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■ Absorption

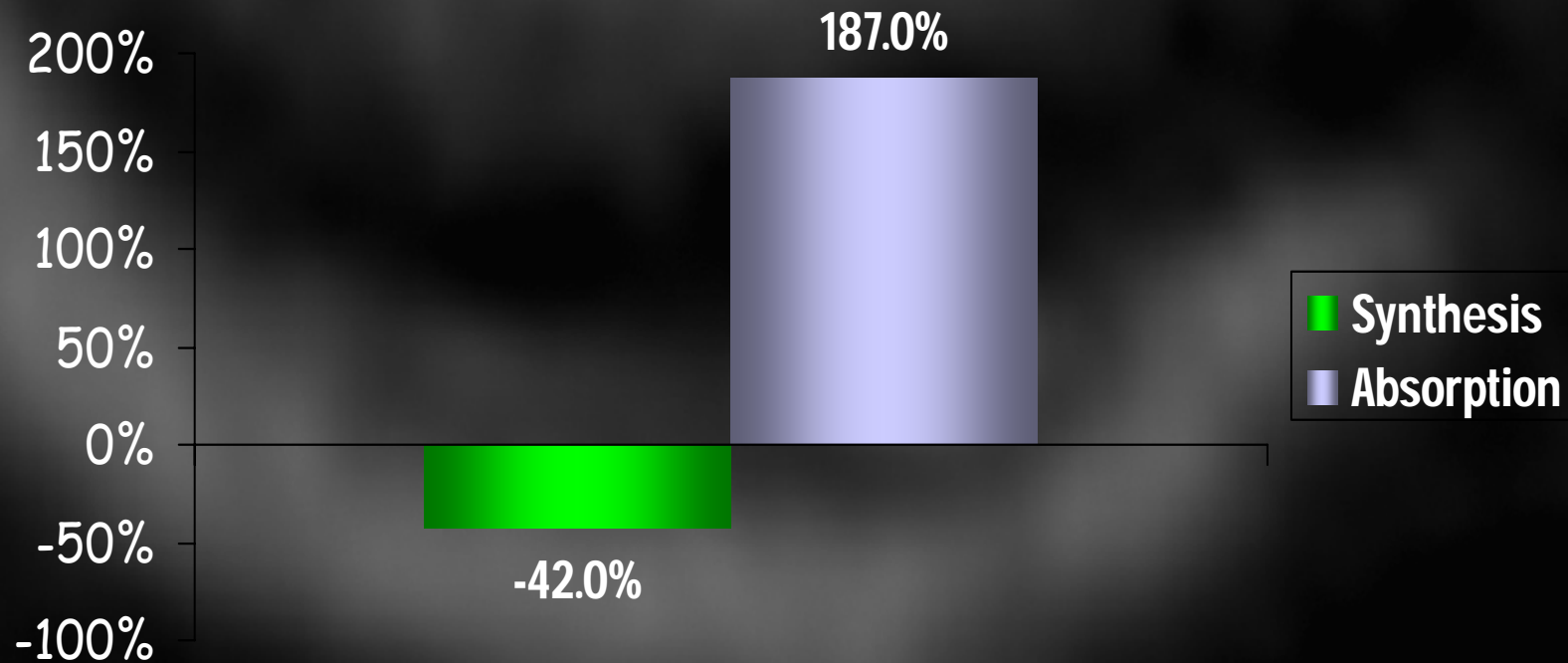
■ Cholesterol Synthesis



# Biological Argument

## 2. Inhibiting One Pathway Upregulates Other

Fuqua Heart Center of Atlanta



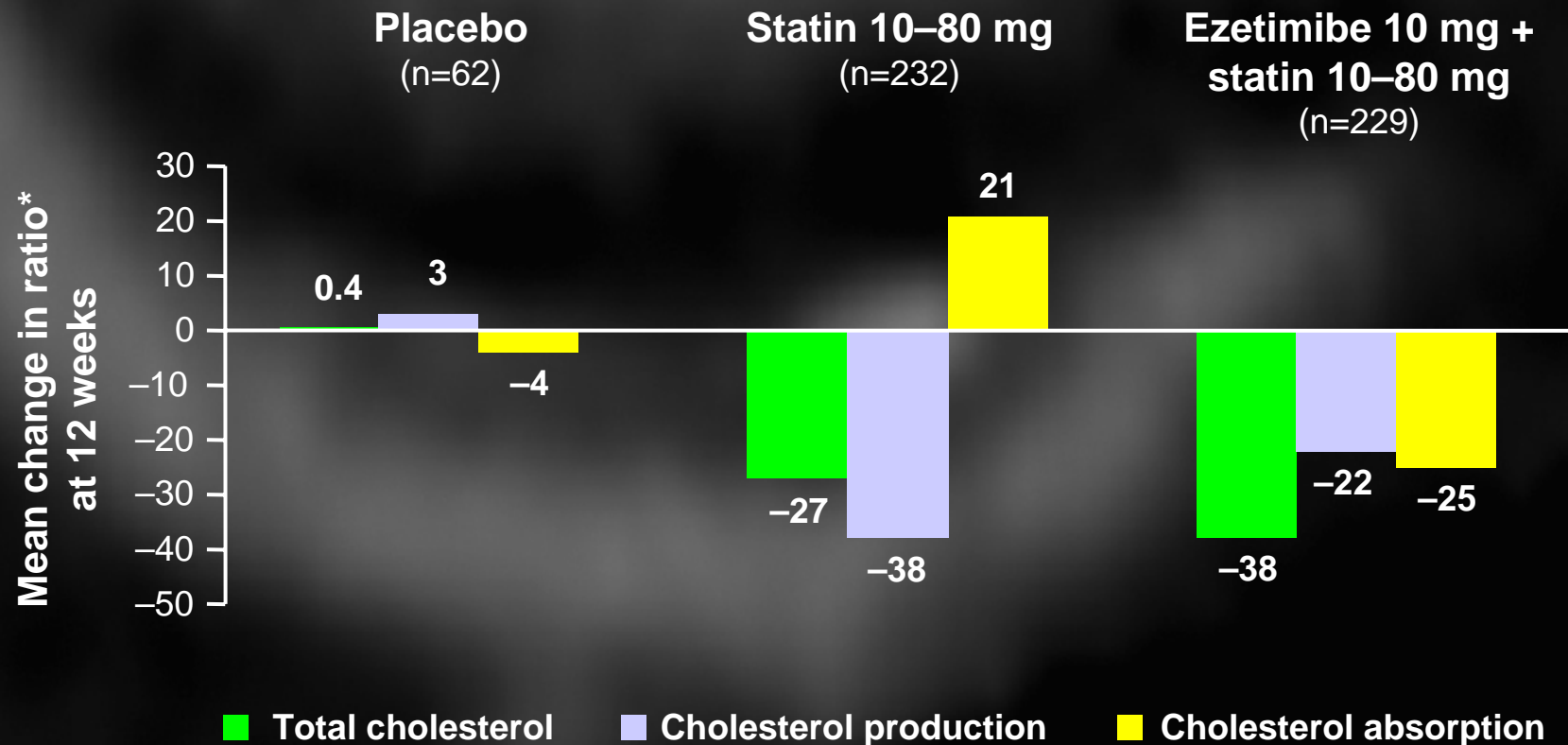
Long-term atorvastatin treatment in T2DM



# Biological Argument

## 2. Inhibiting One Pathway Upregulates Other

Fuqua Heart Center of Atlanta

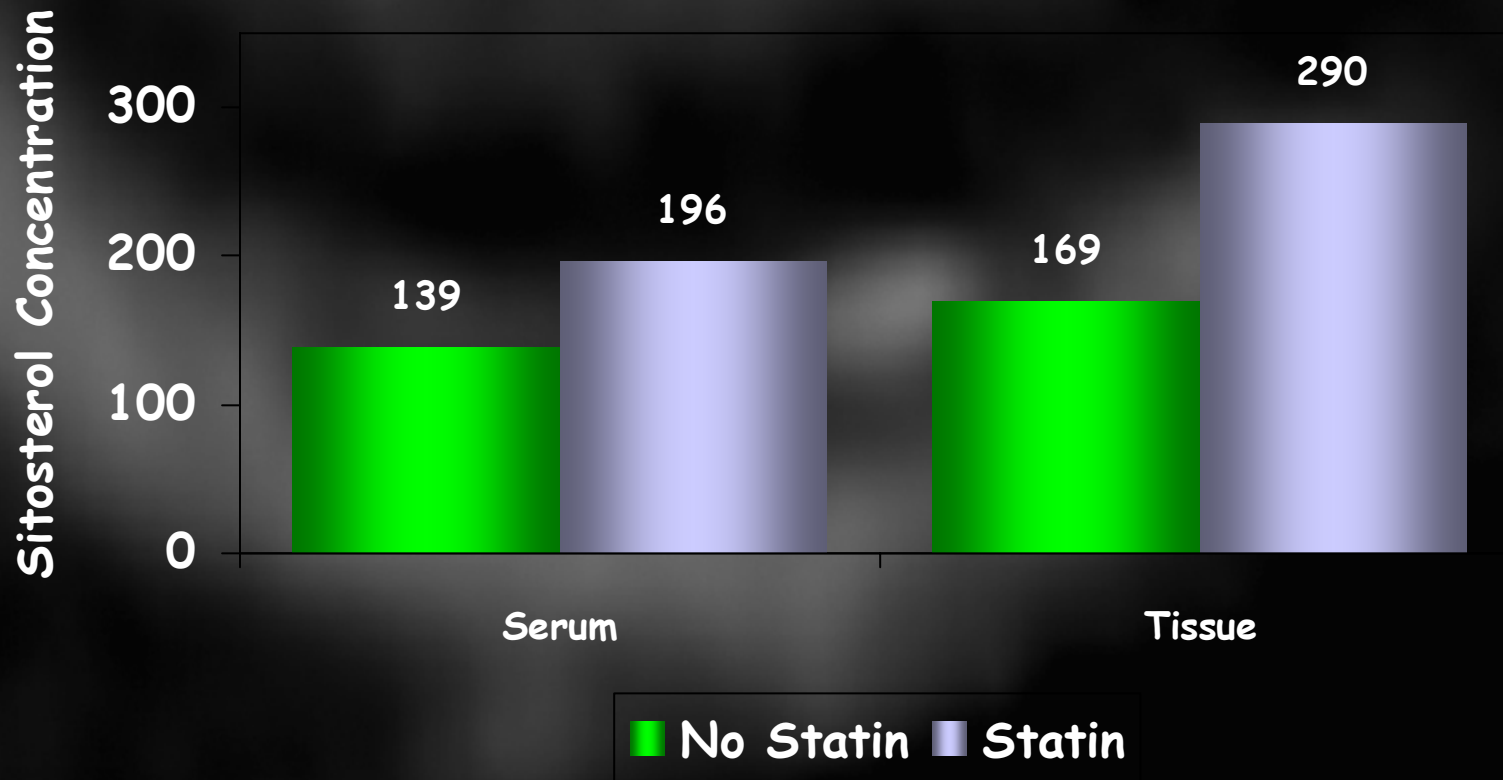




# Biological Argument

## 2. Inhibiting One Pathway Upregulates Other

Fuqua Heart Center of Atlanta





# New Paradigm

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*Dual inhibition of cholesterol metabolism is becoming first-line therapy in the treatment of dyslipidemias*

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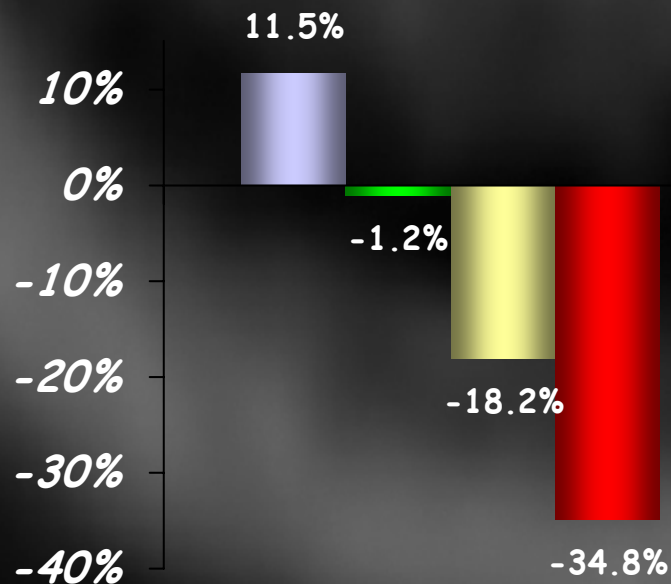




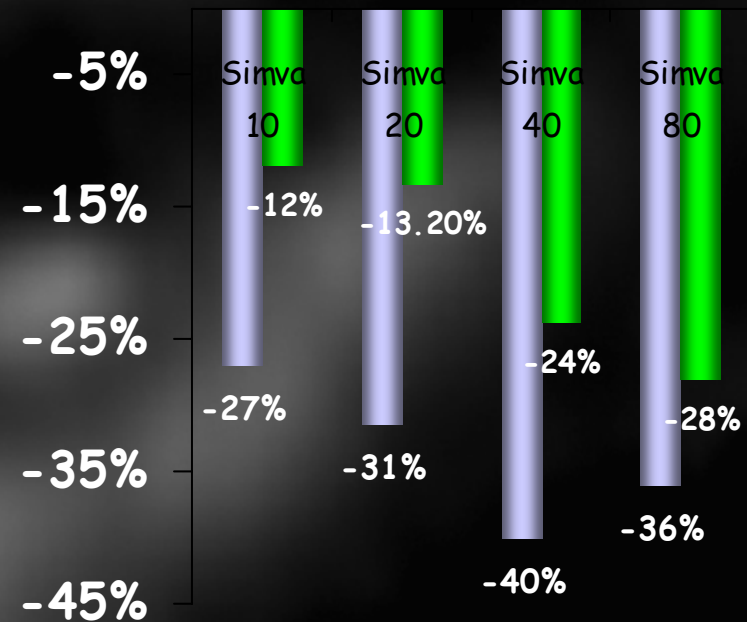
# Biological Argument

## 3. Dual-Inhibition: Synergy for Inflammation

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■ Placebo      ■ EZ alone  
■ Simva alone    ■ Simva+EZ



■ EZ      ■ Statin alone



## New Paradigm

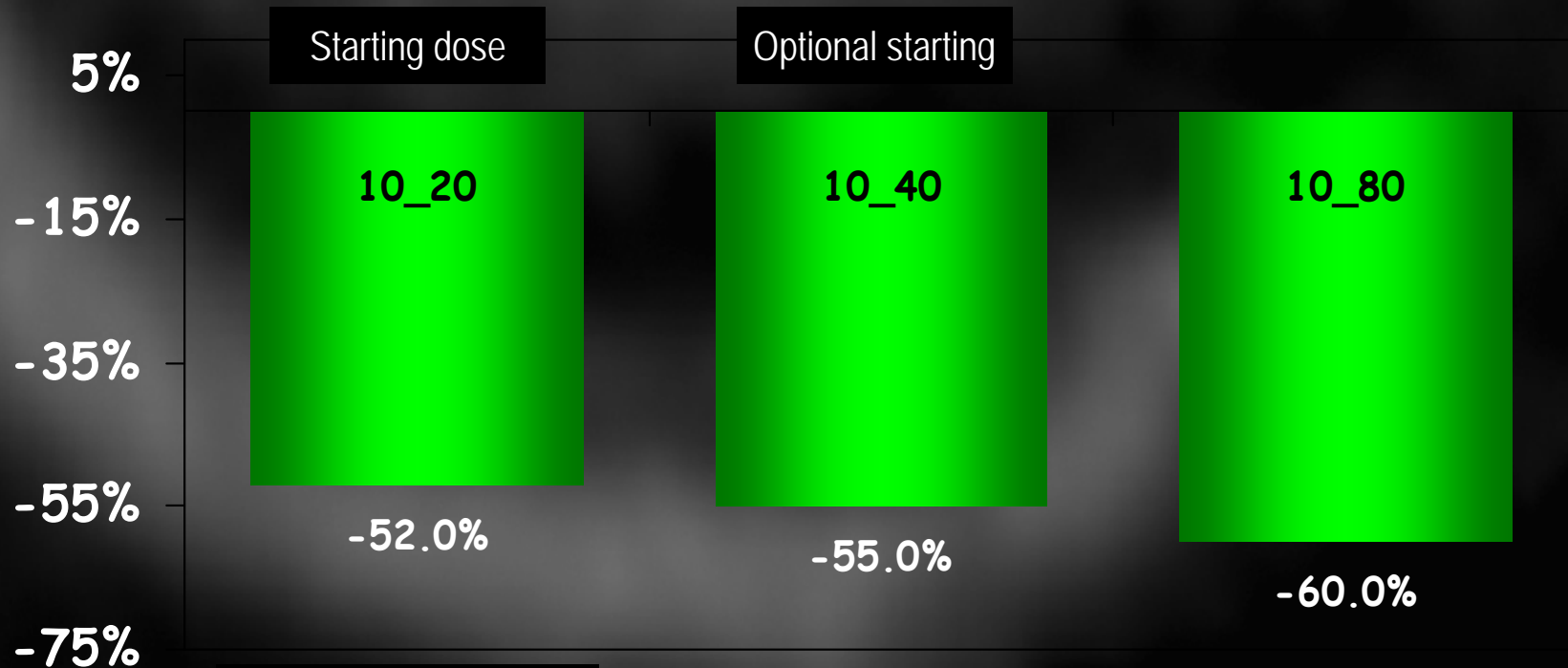
### Dual Inhibition of Cholesterol Metabolism

Dual inhibition of cholesterol metabolism is becoming first-line therapy in the treatment of dyslipidemias



# Dual Inhibition

Simvastatin+Ezetimibe (VYTORIN): LDL



1528 patients  
Double blind, RCT  
12 weeks

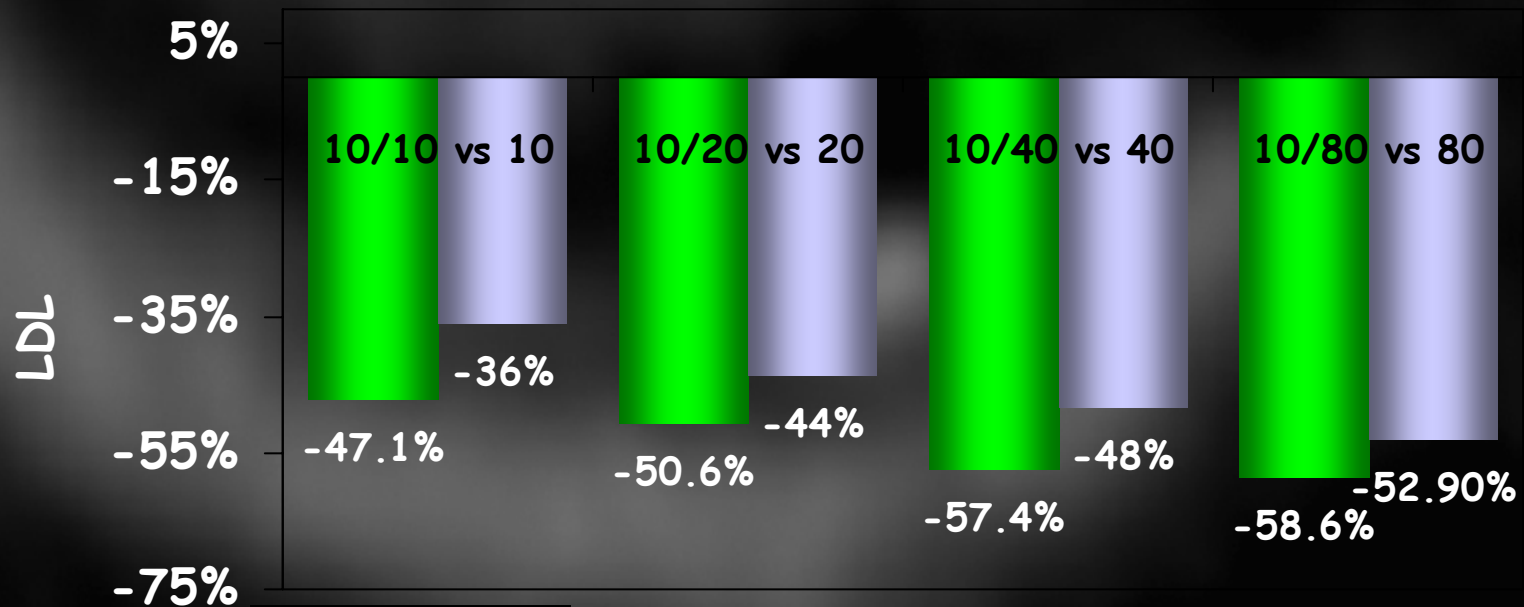
■ LDL Reduction



# Dual Inhibition

## VYTORIN Versus Atorvastatin (VYVA)

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-2000 patients  
Double blind, RCT  
6 weeks  
~ half were high risk  
(10-year risk > 20%)

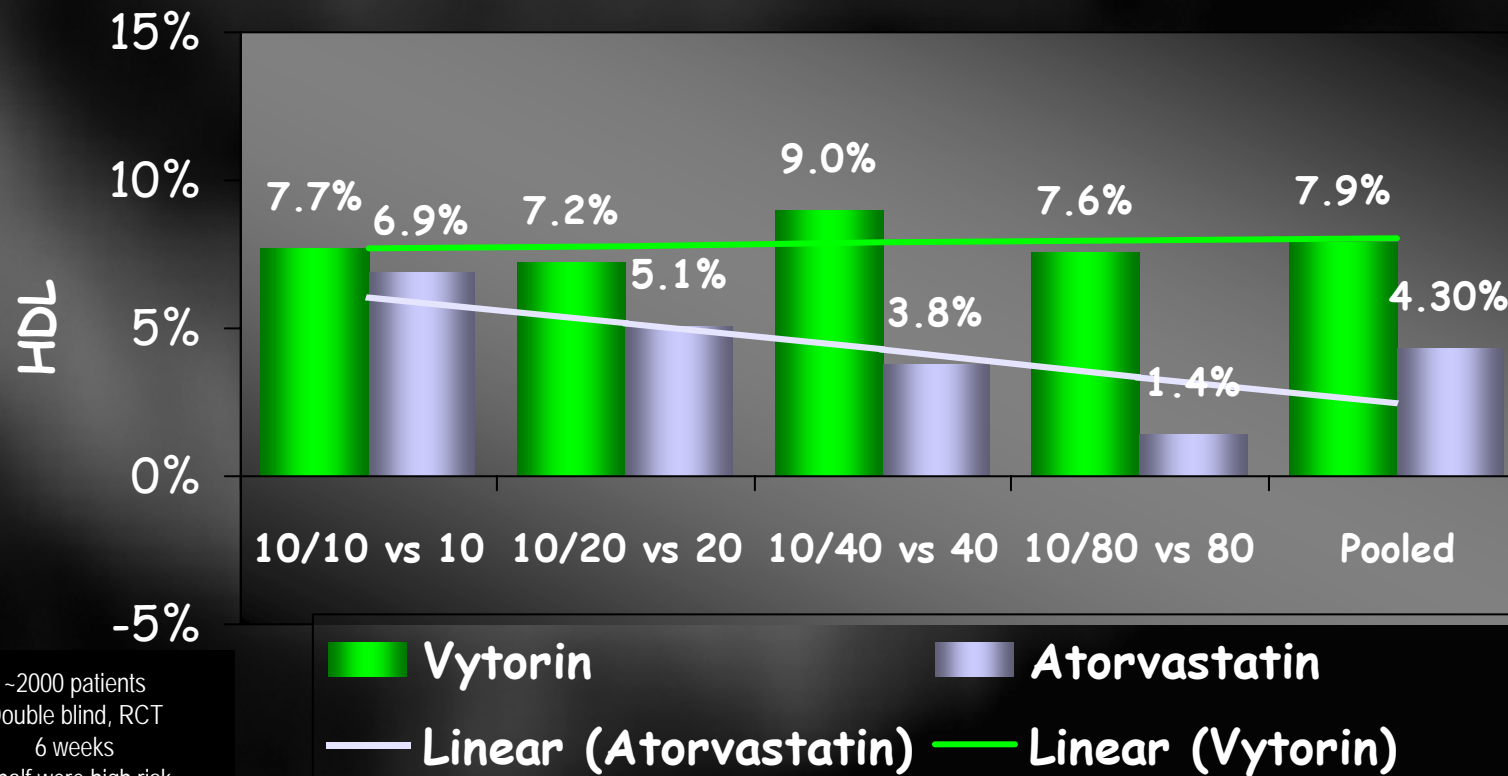
■ Vytorin ■ Atorvastatin



# Dual Inhibition

## VYTORIN Versus Atorvastatin (VYVA)

Fuqua Heart Center of Atlanta



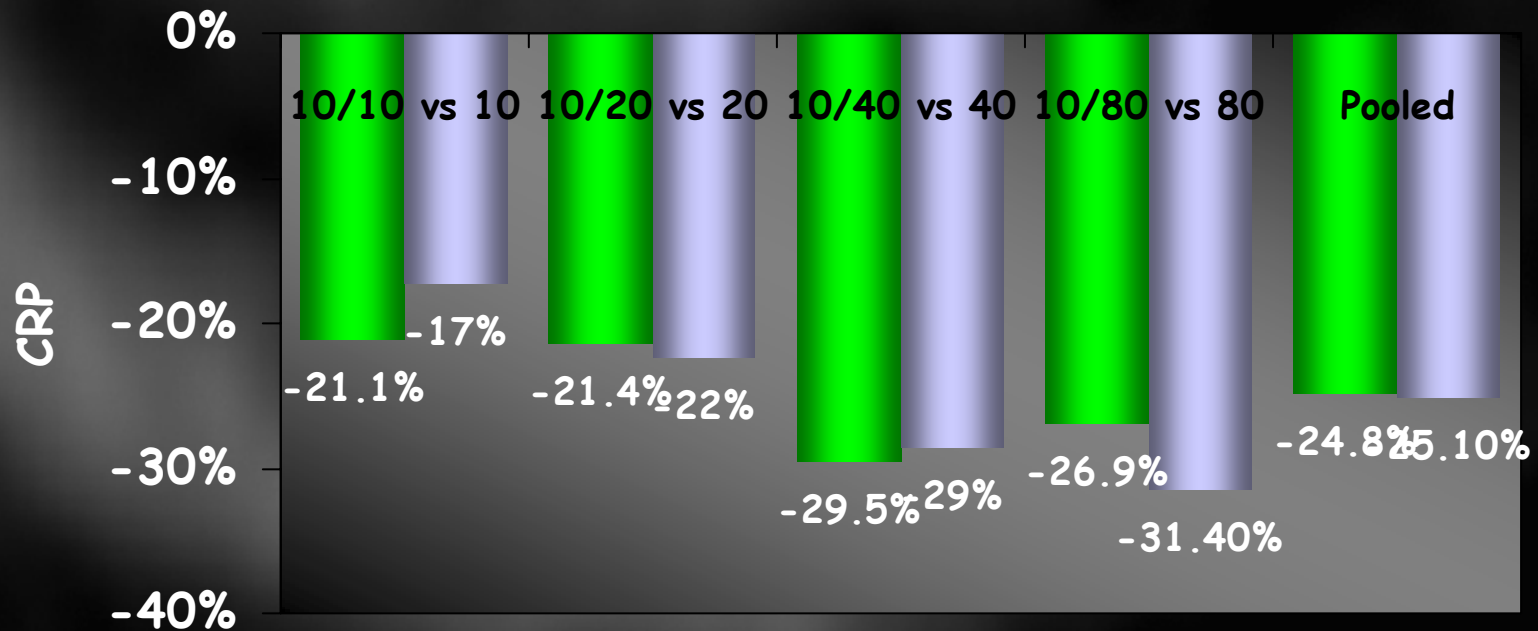
-2000 patients  
Double blind, RCT  
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# Dual Inhibition

## VYTORIN Versus Atorvastatin (VYVA)

Fuqua Heart Center of Atlanta



-2000 patients  
Double blind, RCT  
6 weeks  
~ half were high risk  
(10-year risk > 20%)

■ Vytorin ■ Atorvastatin



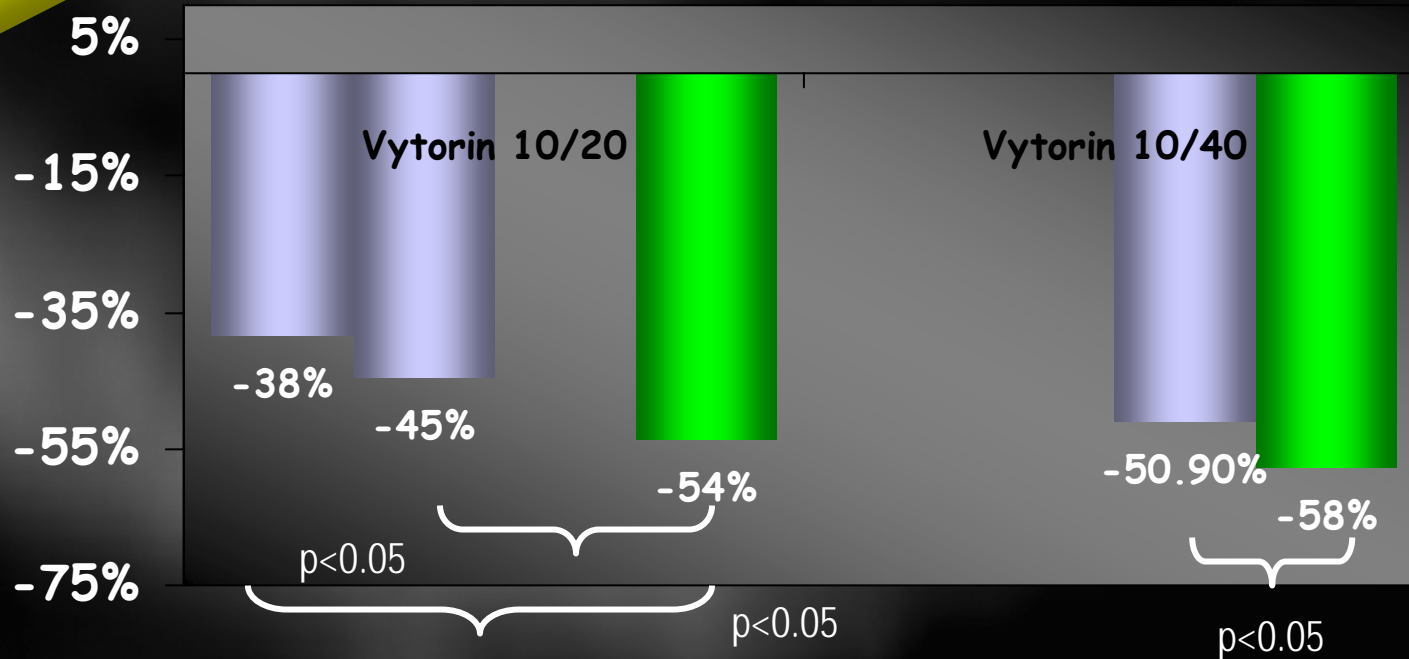
# Dual Inhibition

## VYTORIN Versus Atorvastatin in T2DM

**NEW!**

Fuqua Heart Center of Atlanta

LDL



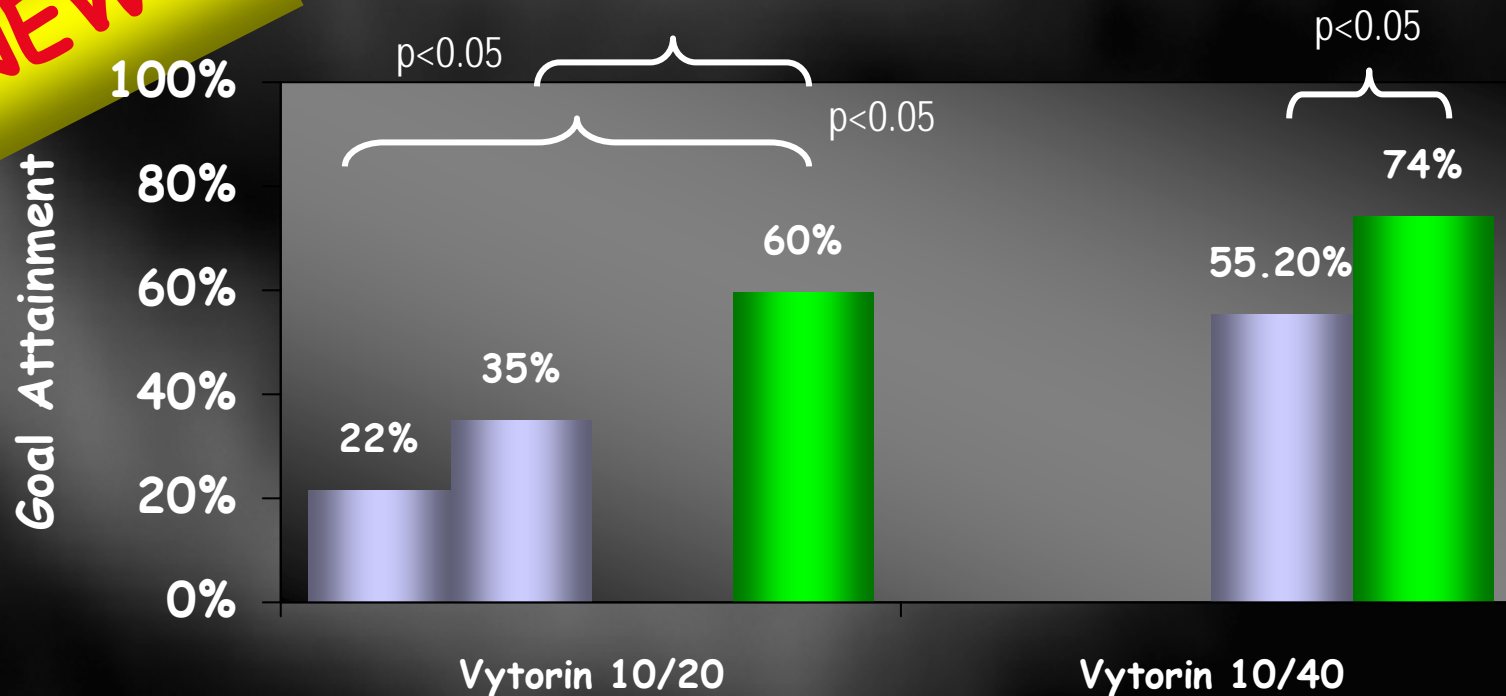
1229 patients  
Double blind, RCT  
6 weeks  
All with T2DM



# Dual Inhibition

## SYMPLECTIC INHIBITION Versus Atorvastatin in T2DM

**NEW!**



■ Atorvastatin 10 ■ Atorvastatin 20 ■ Atorvastatin 40 ■ Vytorin

Goldberg et al. ADA; June 2006.

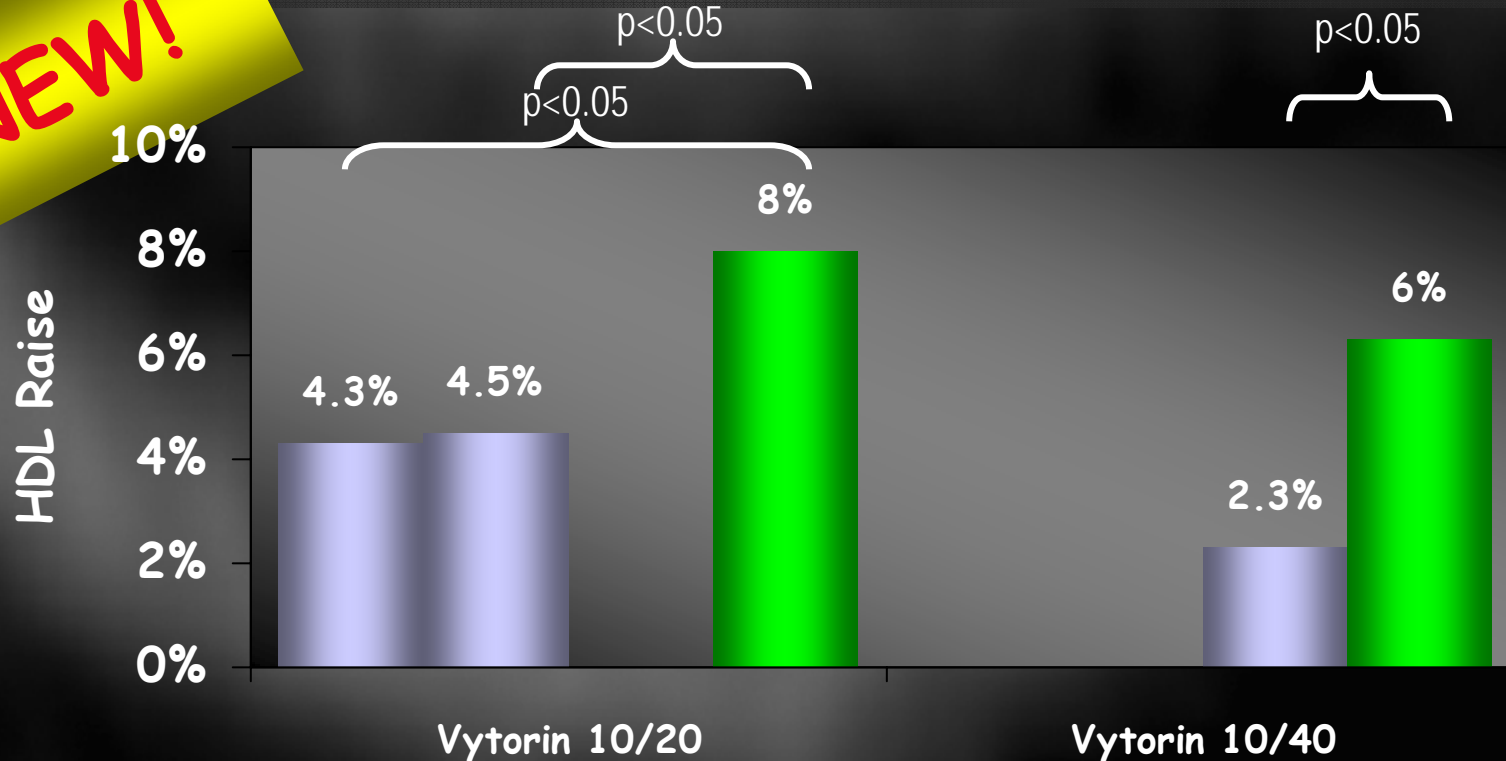




# Dual Inhibition

## VYTORIN Versus Atorvastatin in T2DM

**NEW!**



■ Atorvastatin 10 ■ Atorvastatin 20 ■ Atorvastatin 40 ■ Vytorin

Goldberg et al. ADA; June 2006.

Fuqua Heart Center of Atlanta, Piedmont Hospital



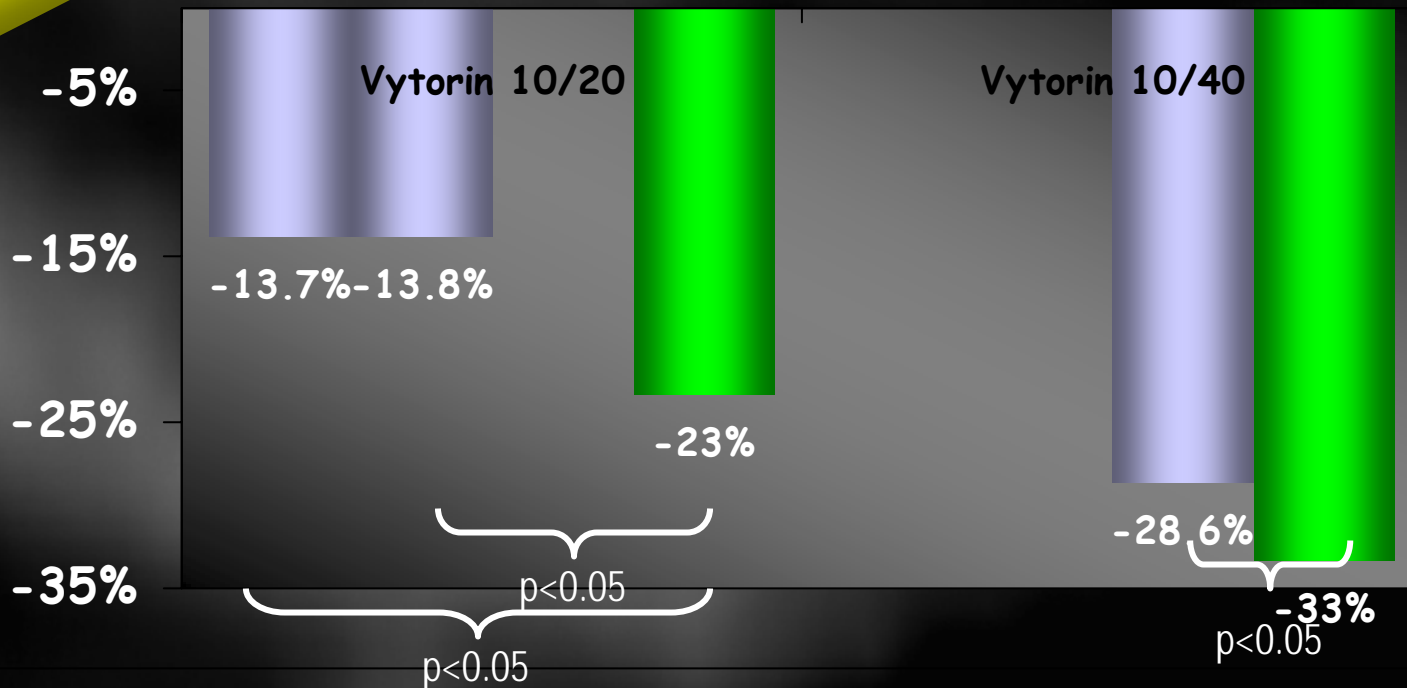
# Dual Inhibition

## VYTORIN Versus Atorvastatin in T2DM

**NEW!**

Fuqua Heart Center of Atlanta

LDL-C Change



1229 patients  
Double blind, RCT  
6 weeks  
All with T2DM

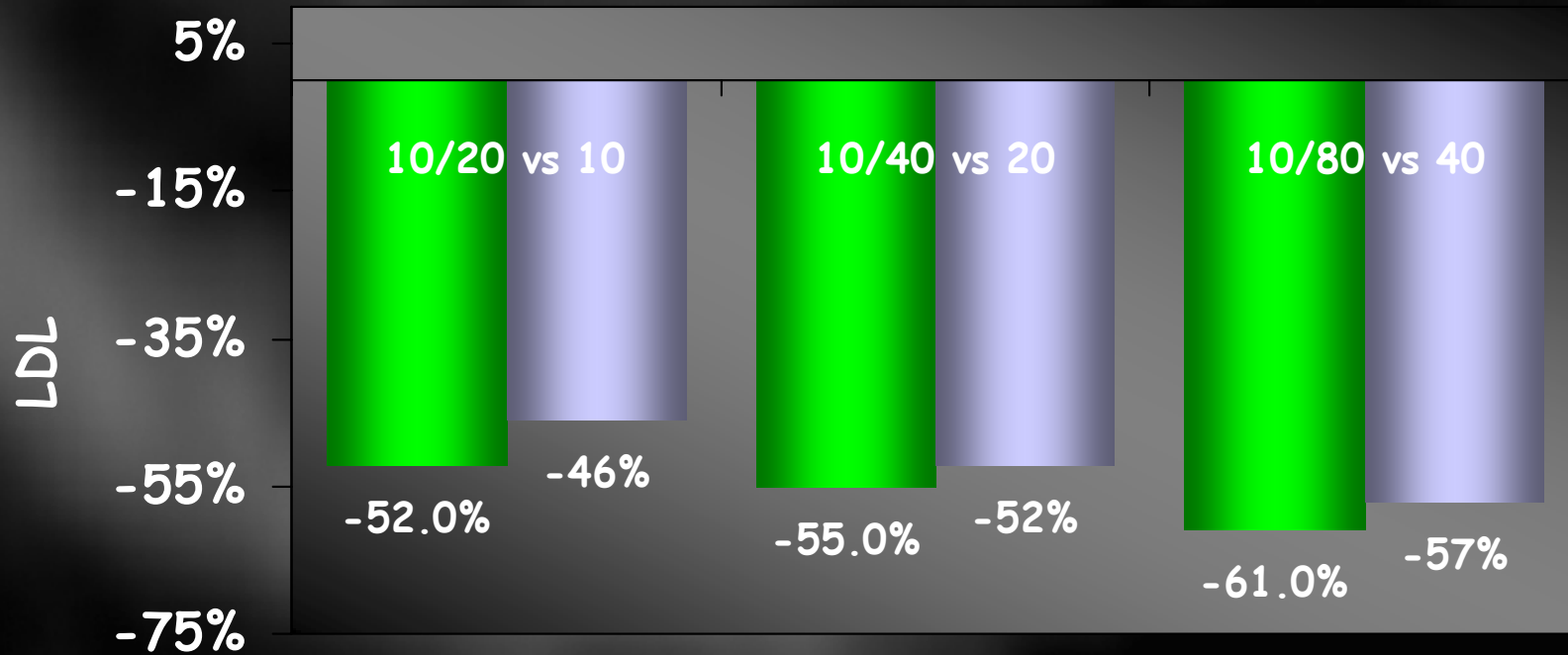
■ Atorvastatin 10 ■ Atorvastatin 20 ■ Atorvastatin 40 ■ Vytorin



# Dual Inhibition

## VYTORIN Versus Rosuvastatin

Fuqua Heart Center of Atlanta



~2855 patients  
Double blind, RCT  
6 weeks

Vytorin Rosuva

ISA Meeting; Rome, June 2006.

Fuqua Heart Center of Atlanta, Piedmont Hospital



# New Paradigm

## Dual Inhibition of Cholesterol Metabolism

*Dual inhibition of cholesterol metabolism is becoming first-line therapy in the treatment of dyslipidemias*

### 1. LDL Argument

1. To reach LDL<70, dual inhibition is needed for LDL >140

### 2. Biological Argument

1. Cholesterol in plaque comes from two sources
2. Treatment of one pathway upregulates the other
3. Dual-inhibition is synergistic for inflammation

### 3. ?Outcomes Argument?



# Dual Inhibition

## Outcomes Studies

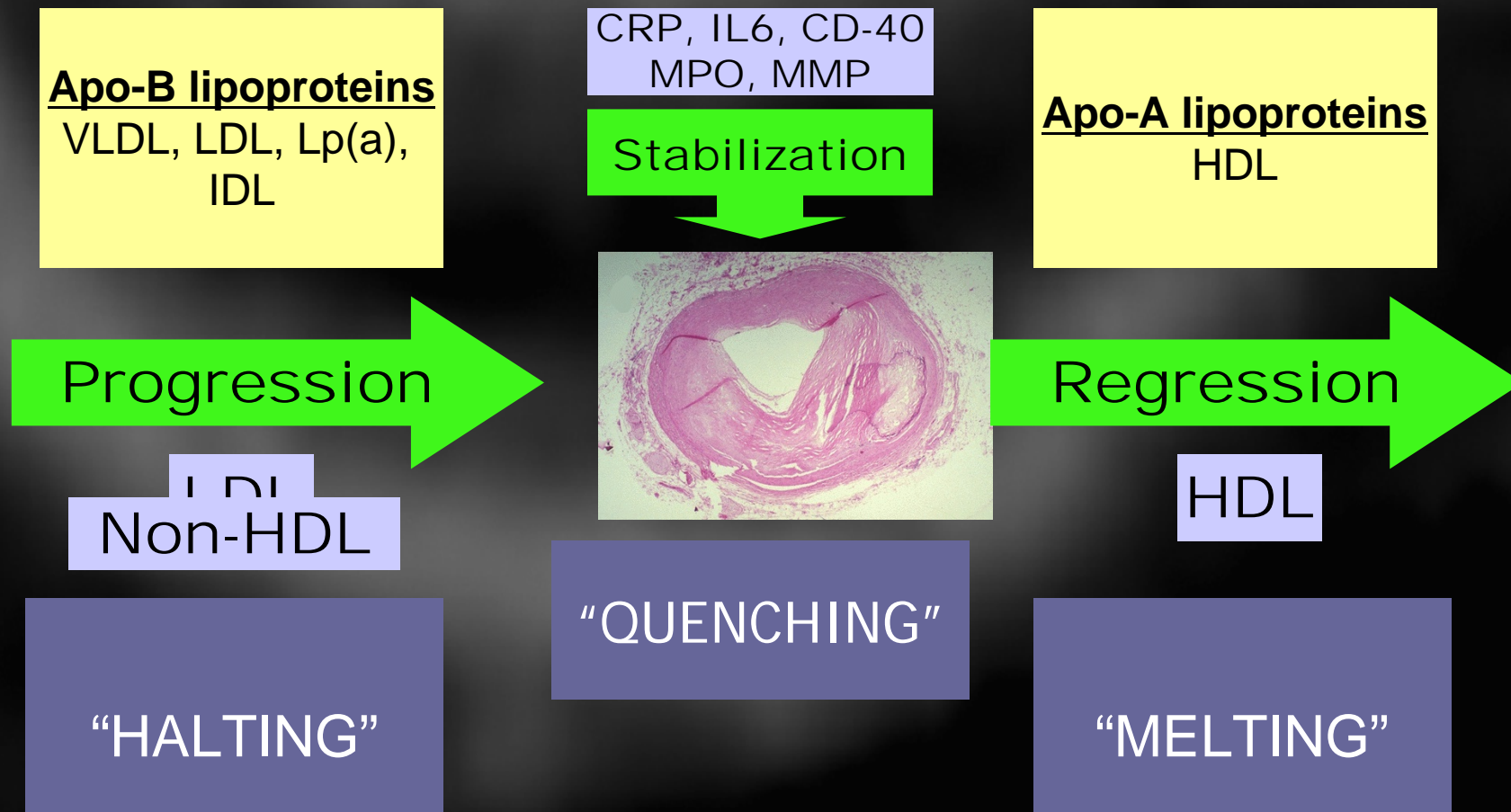
1. SEAS: Aortic stenosis (n=1400)
2. SHARP: Renal dz (n=9000)
3. ENHANCE: FH (n=725)
  
4. Im-PROVE IT (n~10,000)
  1. Simvastatin 40
  2. Vytorin 10/40



# Conclusions

Present and Future

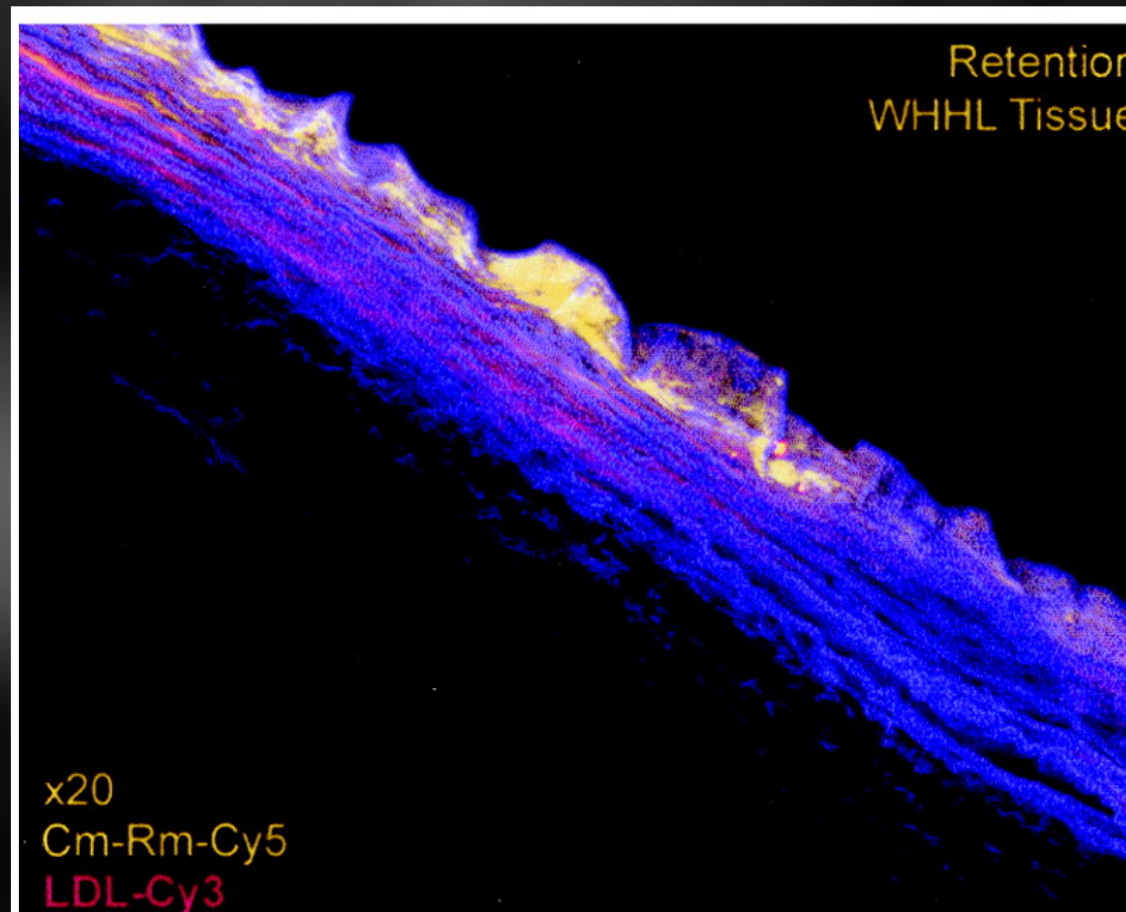
Fuqua Heart Center of Atlanta





## Conclusions

Fuqua Heart Center of Atlanta



Proctor et al. ATVB 2003;23:1595.







# Atherosclerosis and Lipoproteins

Ezetimibe

NPC1L1

ApoB48

ApoE3

ApoB100

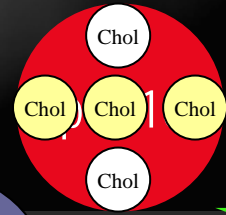
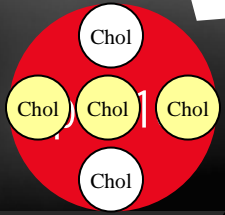
LDL-R

LDL-R

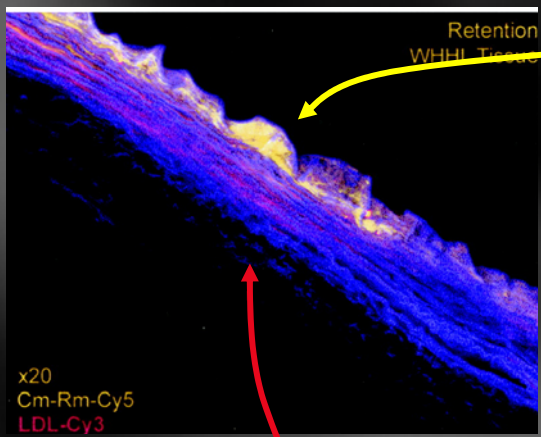
LDL-R

LDL-R

LDL-R



LDL ApoB 18%



Fuqua Heart Center of Atlanta



# Atherosclerosis and Lipoproteins

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