Lessons from Latest Atherosclerosis Trials

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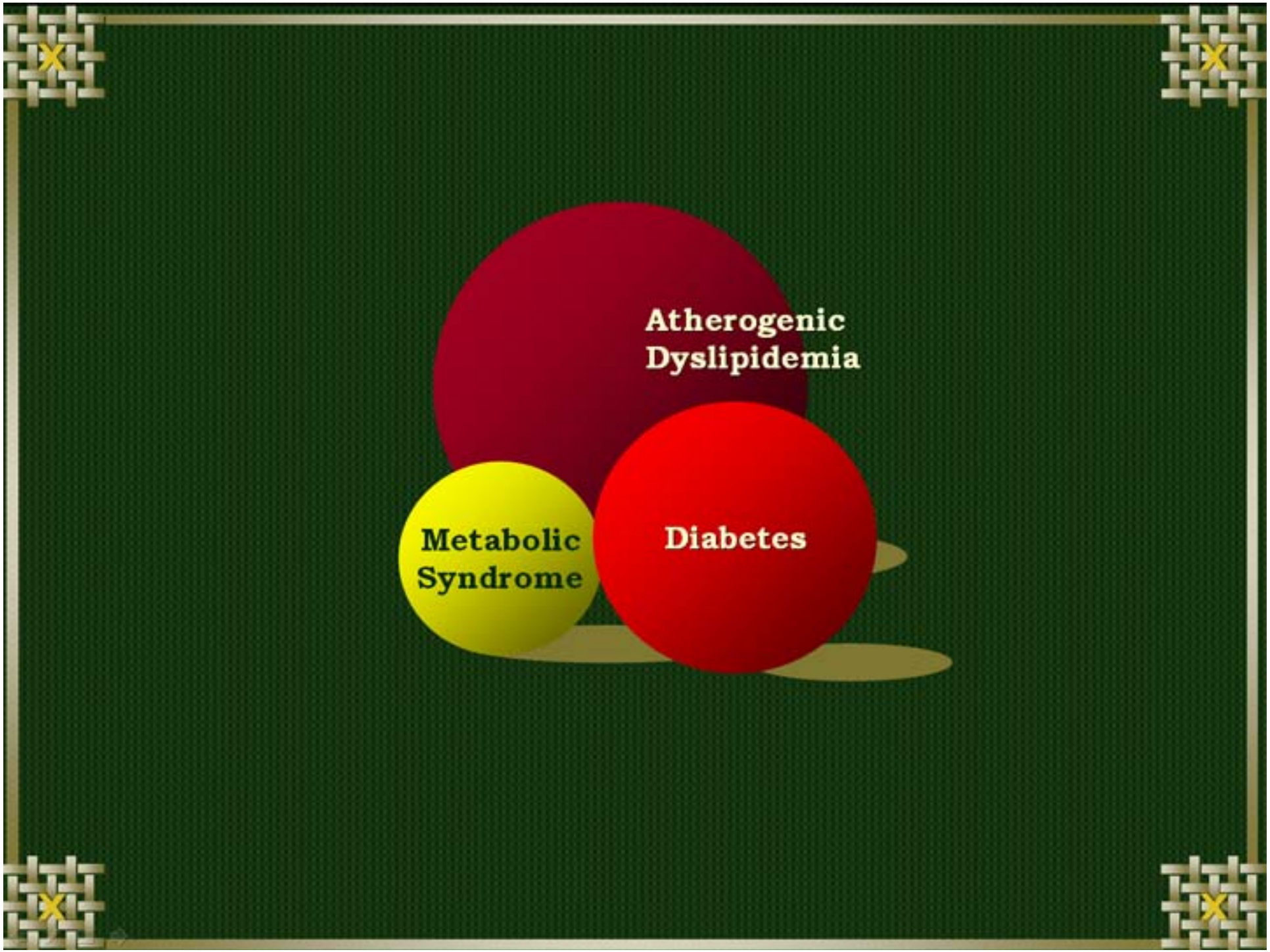
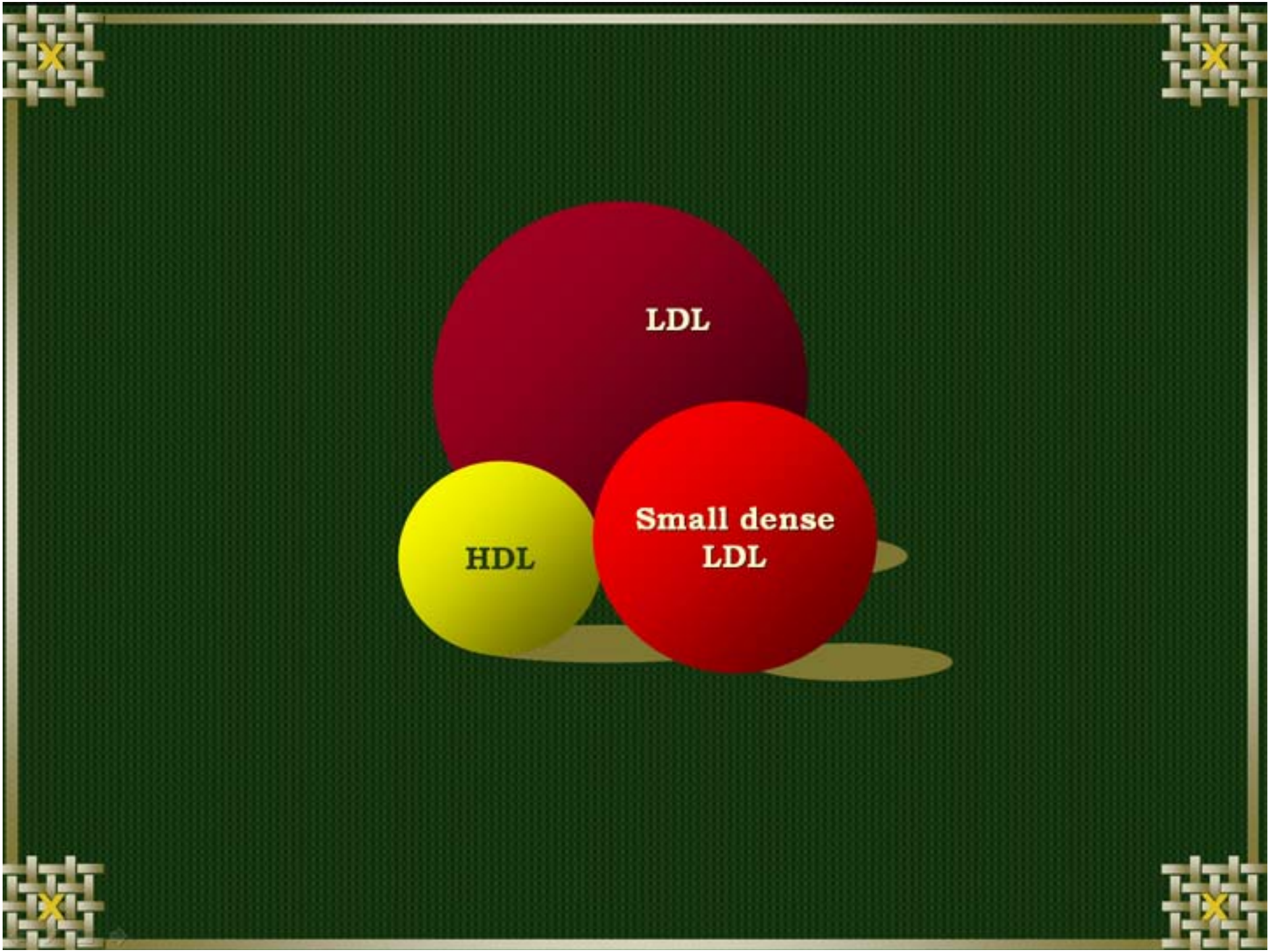
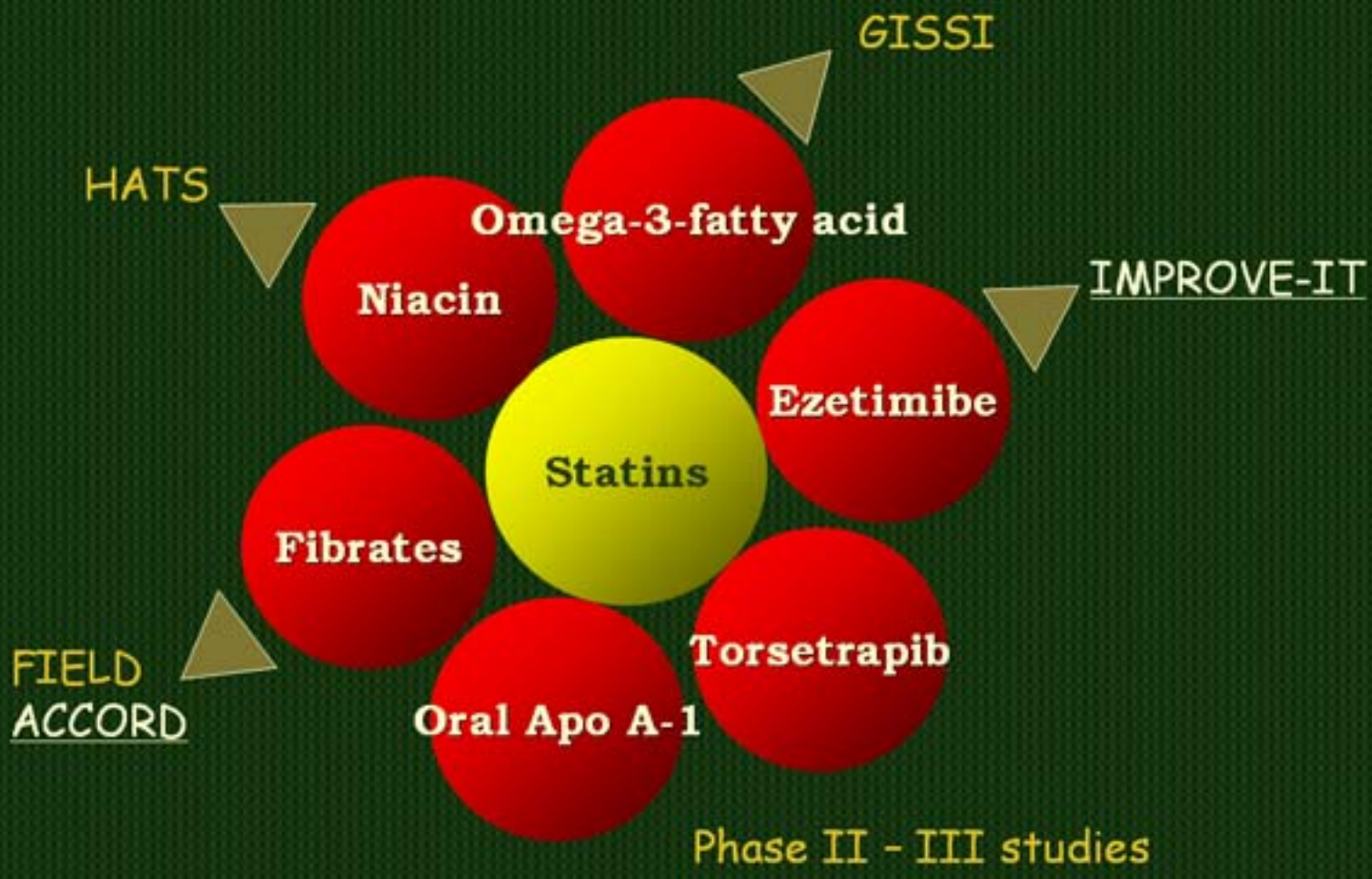
Convergence


Atherogenic
Dyslipidemia
Metabolic
Syndrome
Diabetes


LDL
HDL
Small dense
LDL

Era of Combination

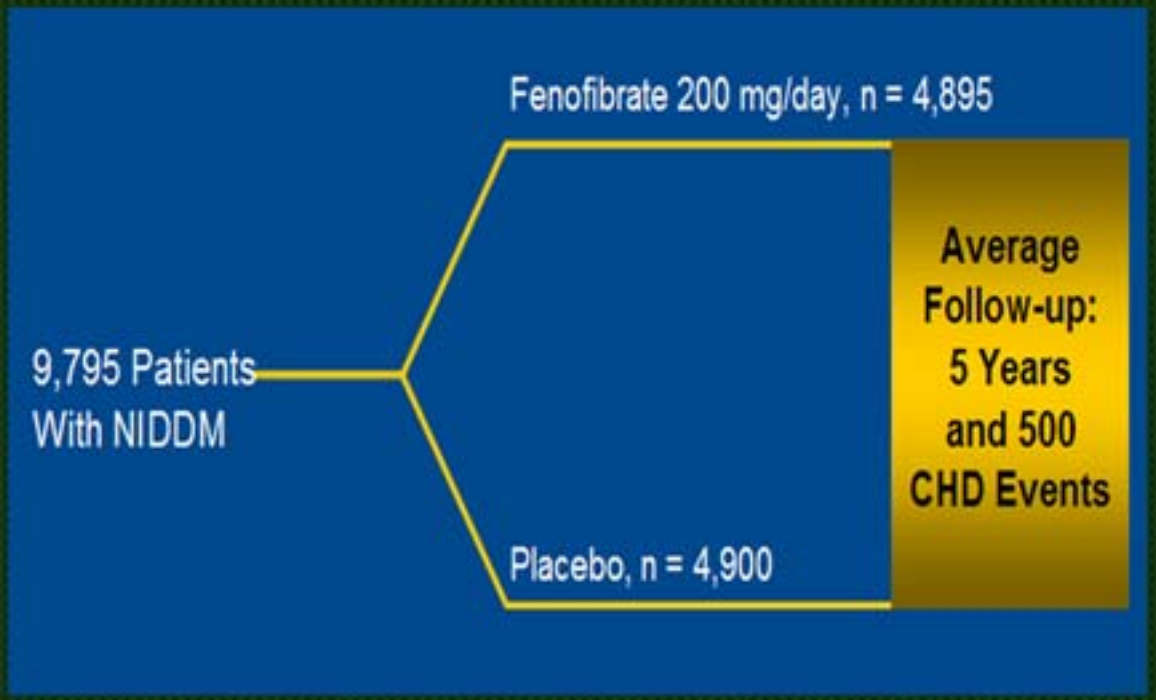


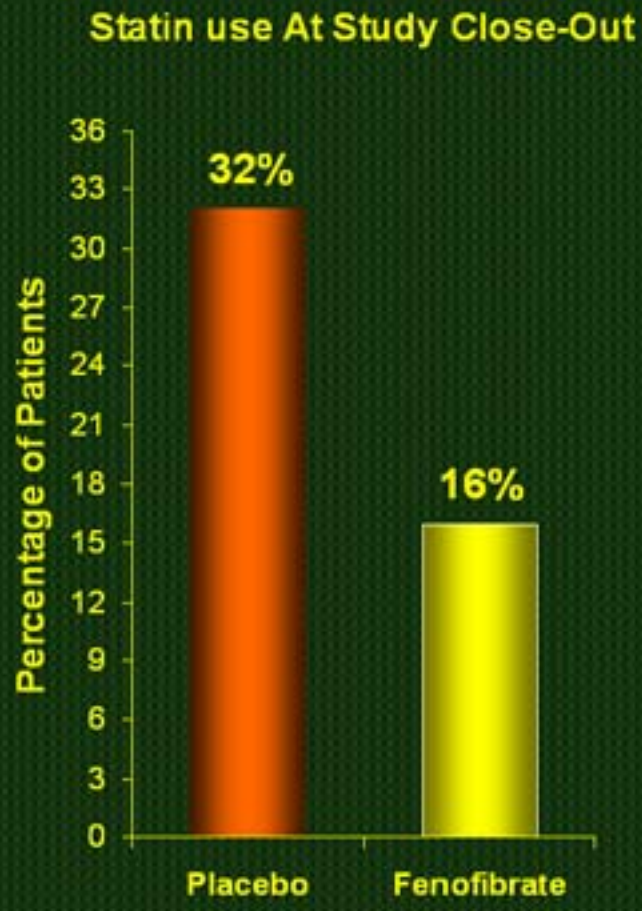
The Fenofibrate Intervention and Event Lowering in Diabetes (FIELD) Trial

Baseline Characteristics

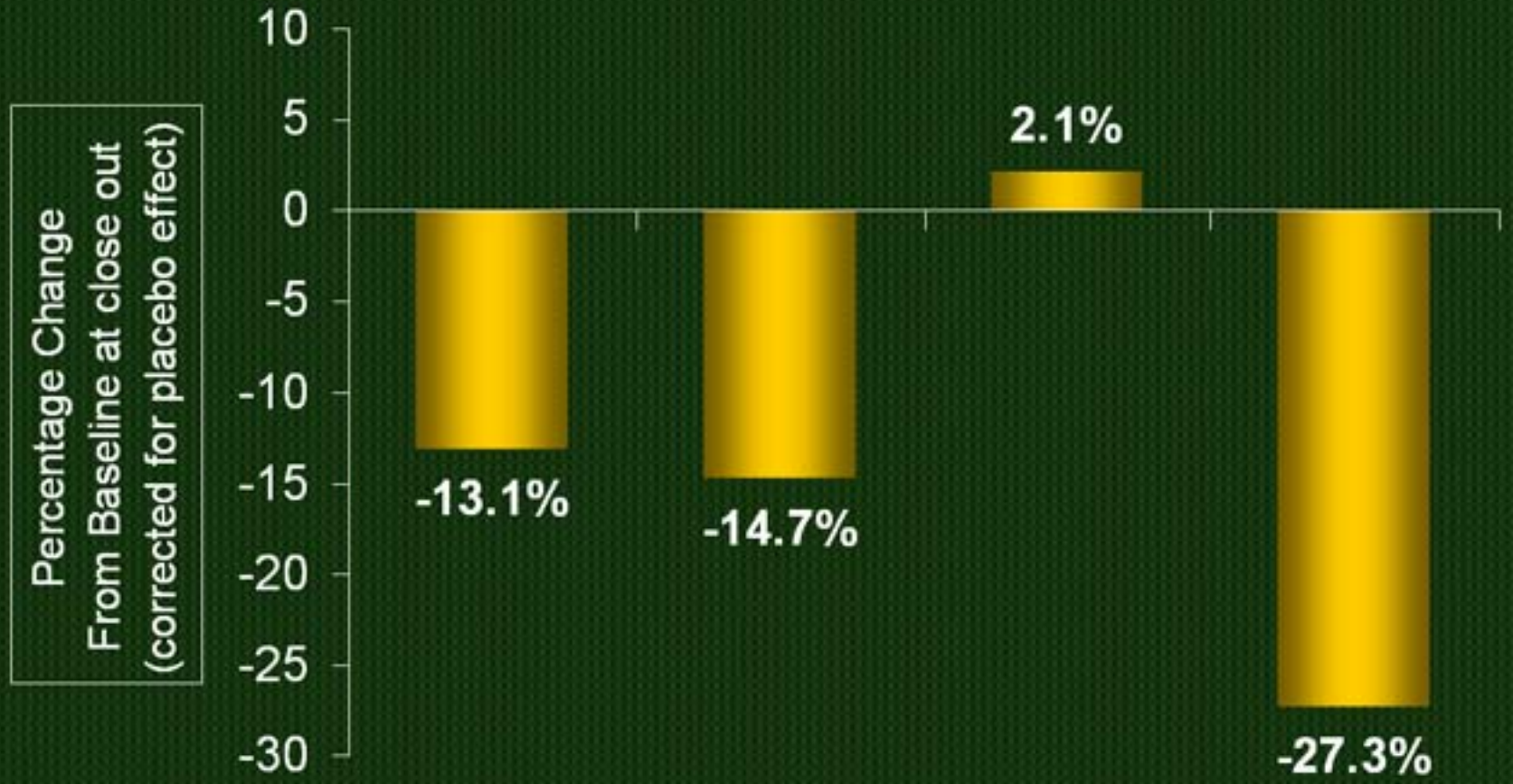
	Total Population (n = 9,795)
Male/Female, %	62.7/37.3
No Prior CVD, %	78.3
Diabetes management with diet plus one oral hypoglycemic agent %	59.5
Median duration of diabetes, years	5
Median HbA1c, %	6.9
Diabetic complications	
Retinopathy, %	8.3
Nephropathy, %	2.8
Lipid parameters, mg/dl	
TC (mean)	194
LDL-C (mean)	119
HDL-C (mean)	42
TG (median)	153
Dyslipidemic*, %	37

*TG > 150 mg/dL and HDL < 40 mg/dL for men or < 50 mg/dL for women


Fenofibrate 200 mg/day, n = 4,895
9,795 Patients
With NIDDM
Placebo, n = 4,900
Average
Follow-up:
5 Years
and 500
CHD Events


Statin use At Study Close-Out
Percentage of Patients
36
33
30
27
24
21
18
15
12
9
6
3
0
32%
16%
Placebo
Fenofibrate

Lipid Effects of Fenofibrate At Study Close (patients without statins)

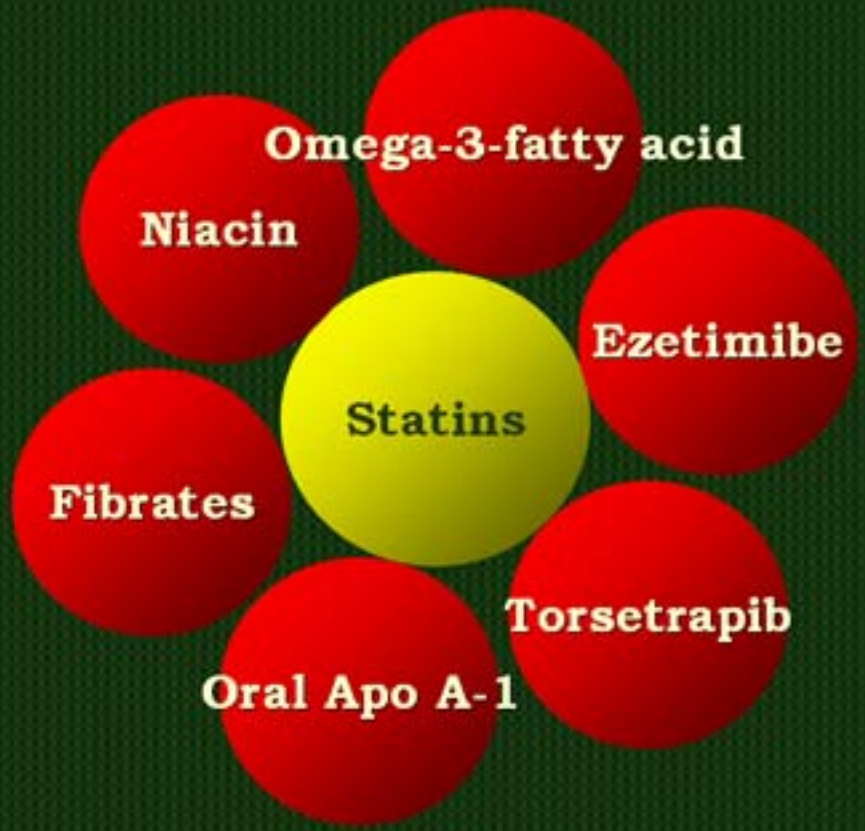


Benefit on the Primary End Point

Fenofibrate Treatment Effect	Relative Risk Reduction (95% CI)	*P*
CHD Events		
Unadjusted	11% (-5 to 25)	0.16
Adjusted for statin use*	19% (4 to 32)	0.01
Total CVD Events		
Unadjusted	11% (1 to 20)	0.035
Adjusted for statin use*	15% (5 to 24)	0.004

* Non-randomised comparison adjusting for on-study statin use

Statin is like Salt



Divergence ?

Risk Evolution

CHD and equivalent

" CHD " or " CHD equivalents "

- Diagnosed CHD
- **Vascular disease in noncoronary vascular beds** (symptomatic carotid disease, aortic aneurysm, peripheral arterial disease)
- **Diabetes**

CHD ; coronary heart disease

Major Risks

5 Major Risks (NCEP-III; 2002)

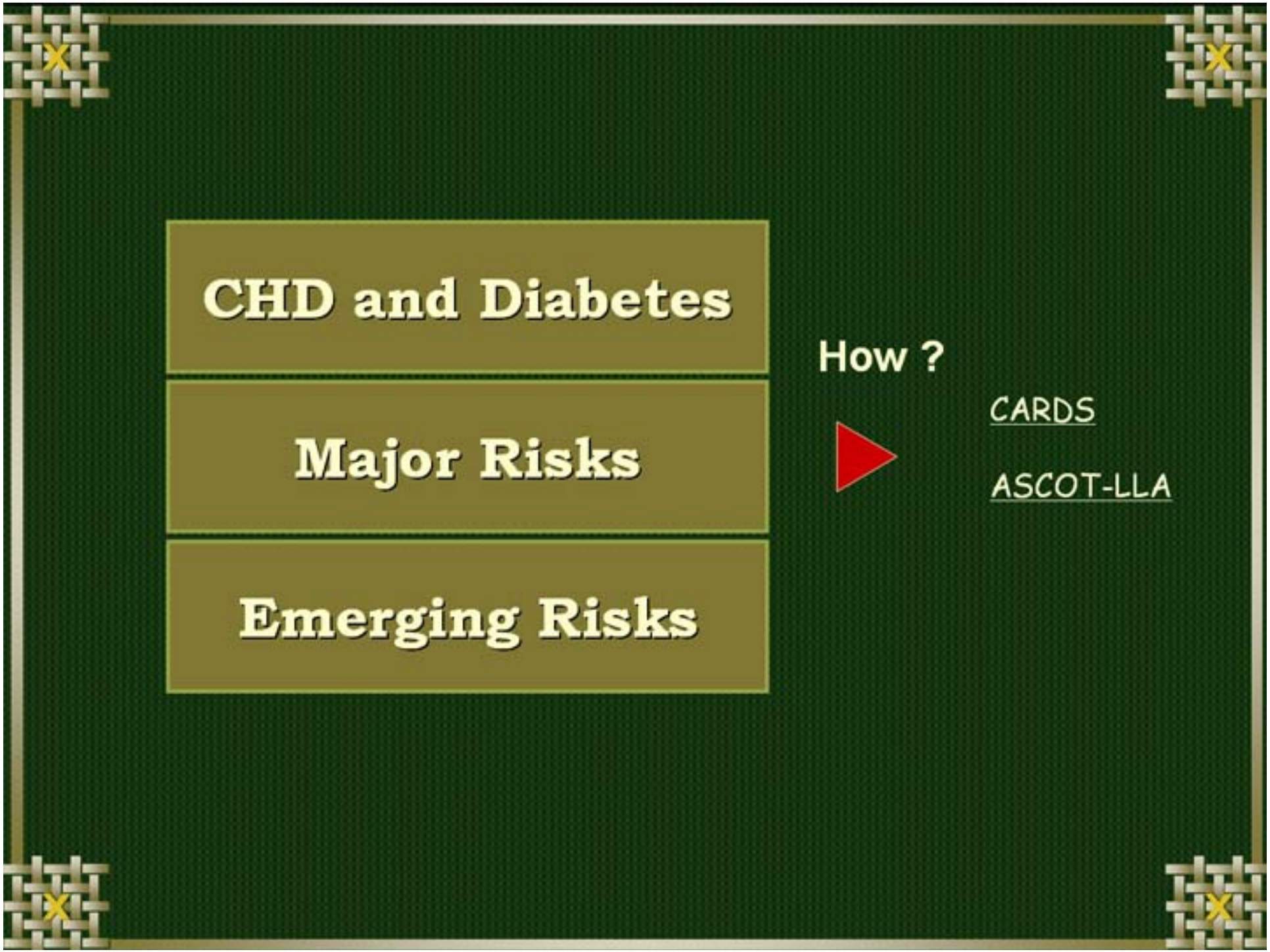
Major Risk Factors That Modify LDL Goals *
(Exclusive of LDL Cholesterol)

- **Cigarette smoking**
- **Hypertension**
  (blood pressure ≥ 140/90 mmHg
  or on antihypertensive medication)
- **Low HDL cholesterol**
  (< 40 mg/dL)†
- **Family history of premature CHD**
  (CHD in male first-degree relative < 55 years
  ; CHD in female first-degree relative < 65 years)
- **Age (men ≥ 45 years; women ≥ 55 years)**

***Diabetes** is regarded as a coronary heart disease (CHD) risk equivalent.
†**HDL cholesterol** ≥ 60 mg/dL counts as a "negative" risk factor; its presence removes 1 risk factor from the total count.

Emerging Risks

Metabolic syndrome
Inflammation etc.


CHD and Diabetes
Major Risks
Emerging Risks
How ?
CARDS
ASCOT-LLA

CARD Study ; diabetes

2838 with NIDDM 40-75 years
atorvastatin 10 mg/day vs. placebo for 4 yrs
LDL-C reduction by 40 % in atorva group

	No. of patients with an event (%)		Hazard ratio (95% CI)	*P* value
	Placebo	Atorvastatin 10 mg		
Primary end point	127 (9.0%)	83 (5.8%)	0.63 (0.48-0.83)	0.001
Acute coronary events	77 (5.5%)	51 (3.6%)	0.64 (0.45-0.91)	
Coronary revascularization	34 (2.4%)	24 (1.7%)	0.69 (0.41-1.16)	
Stroke	39 (2.8%)	21 (1.5%)	0.52 (0.31-0.89)	
Secondary end point				
Death from any cause	82 (5.8%)	61 (4.3%)	0.73 (0.52-1.01)	0.059
Any acute CVD event	189 (13.4%)	134 (9.4%)	0.68 (0.55-0.85)	0.001

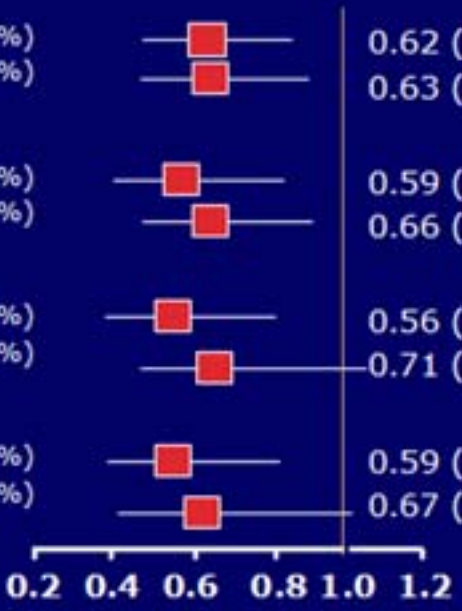
Note: Only the first acute coronary event, revascularization, or stroke is included in the primary end point.
Symbol size is proportional to amount of statistical information.

CARDS=Collaborative Atorvastatin Diabetes Study.

Colhoun HM et al. *Lancet*. 2004;364:685-696.

CARDS: Effect of Treatment on Primary End Point by Lipid Level

Median baseline lipids	No. of patients with an event (%) Placebo	Atorvastatin	Hazard ratio (95% CI)	*P* value
LDL-C (mg/dL)				
≥120	66 (9.5%)	44 (6.1%)	0.62 (0.43-0.91)	
<120	61 (8.5%)	39 (5.6%)	0.63 (0.42-0.94)	0.96
HDL-C (mg/dL)				
≥54	62 (8.5%)	36 (5.2%)	0.59 (0.39-0.89)	
<54	65 (9.6%)	47 (6.4%)	0.66 (0.45-0.95)	0.70
TG (mg/dL)				
≥151	67 (9.6%)	40 (5.5%)	0.56 (0.38-0.82)	
<151	60 (8.4%)	43 (6.1%)	0.71 (0.48-1.05)	0.40
TC (mg/dL)				
≥209	71 (10.1%)	44 (6.2%)	0.59 (0.41-0.86)	
<209	56 (7.9%)	39 (5.5%)	0.67 (0.45-1.01)	0.67



Symbol size is proportional to amount of statistical information.
P values are for test of heterogeneity.

CARDS=Collaborative Atorvastatin Diabetes Study.

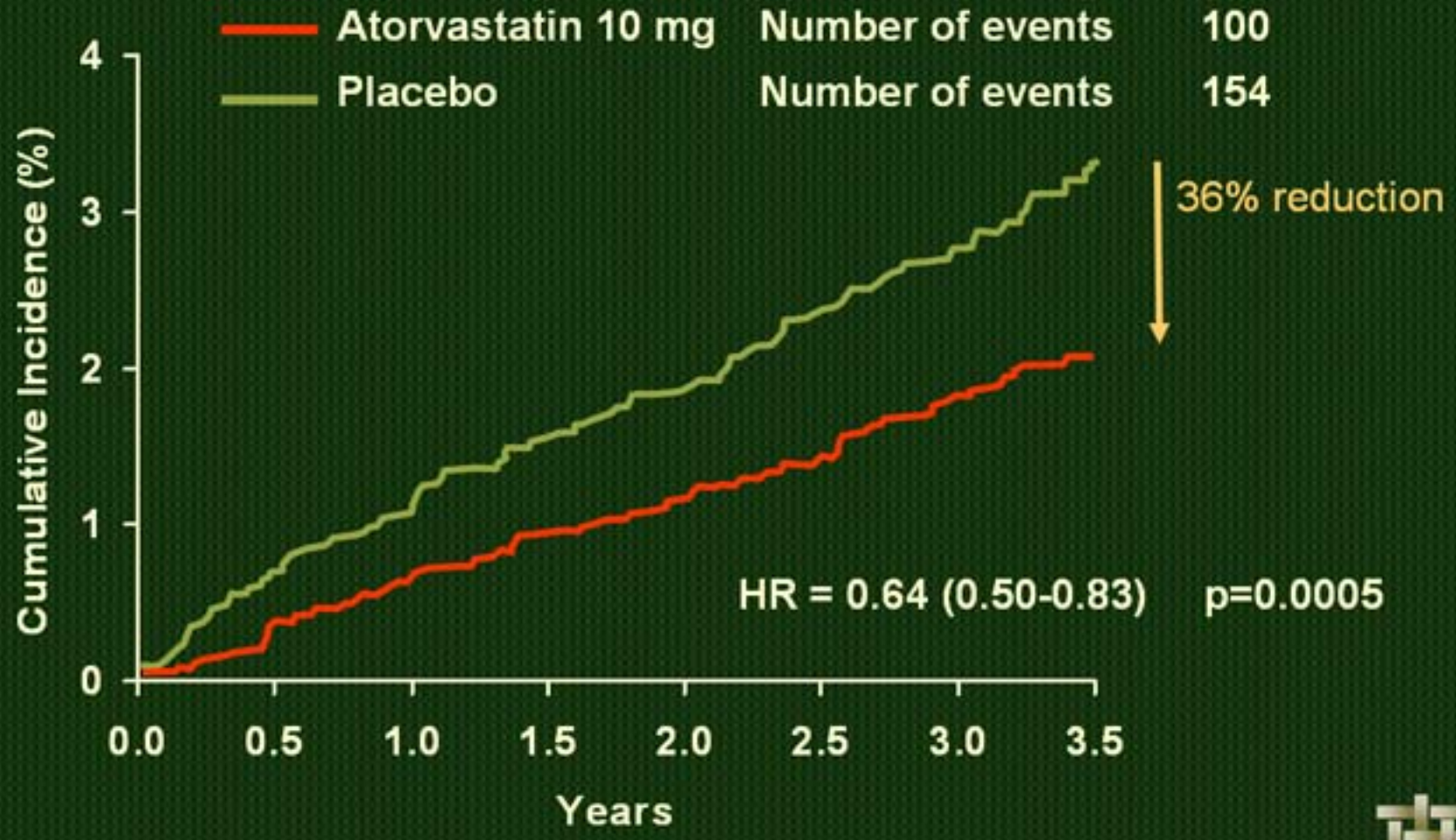
Colhoun HM et al. *Lancet*. 2004;364:685-696.

ASCOT-LLA ; hypertension

19342 with hypertension with at least 3 other RFs
40 - 79 yrs, LDL-C 132 mg/dl
Atorvastatin 10 mg, for 3.3 yrs – LDL-C reduction; 29 % 42 mg/dl

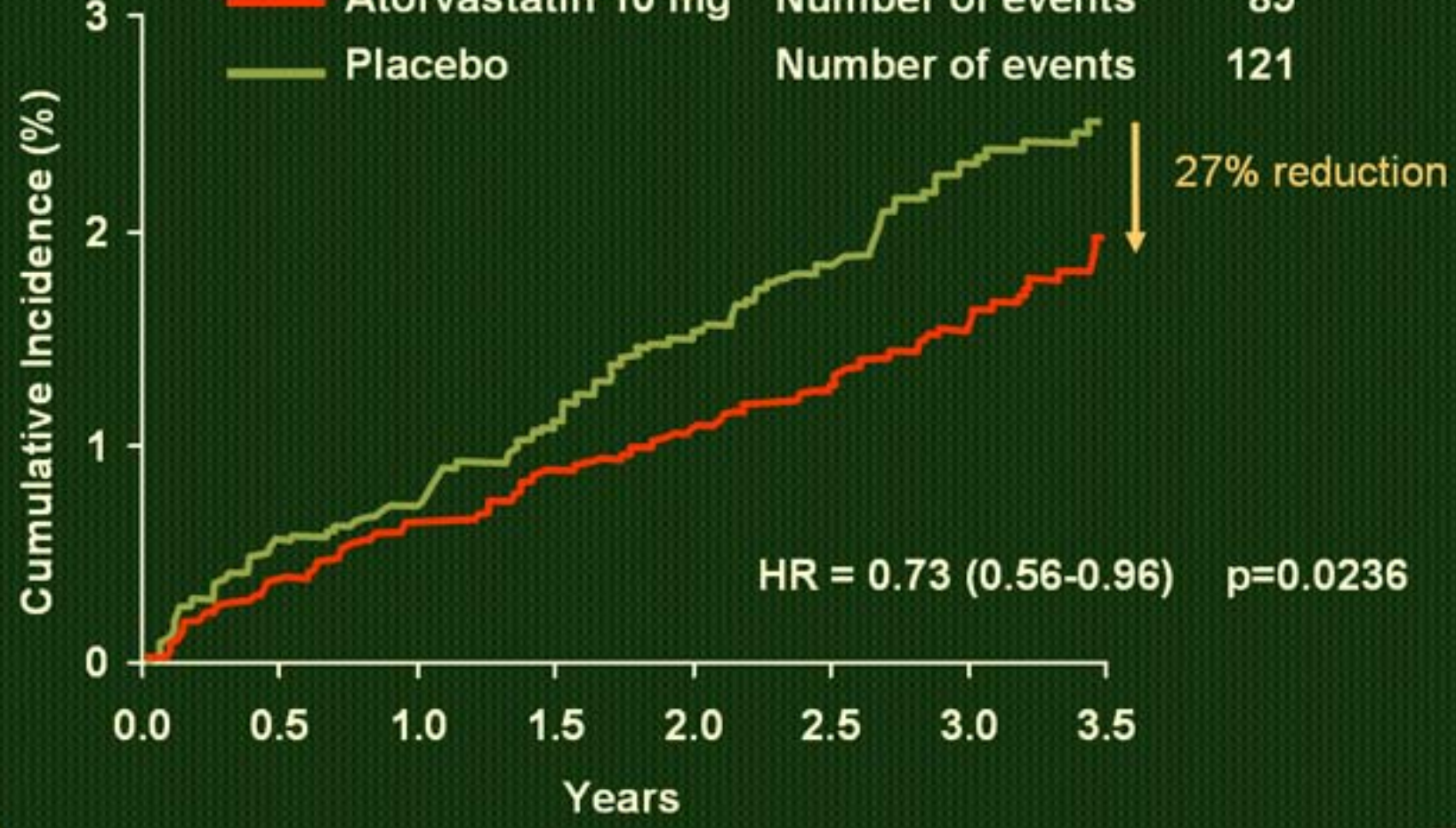
- Benefits – reducing
  - Stroke by 27 %
  - Total cardiovascular events by 21 %
  - Total coronary events by 29 %

Primary End Point: Nonfatal MI and Fatal CHD



Sever PS, Dahlöf B, Poulter N, Wedel H, et al, for the ASCOT Investigators. Lancet. 2003;361:1149-58

Secondary End Point: Fatal and Nonfatal Stroke



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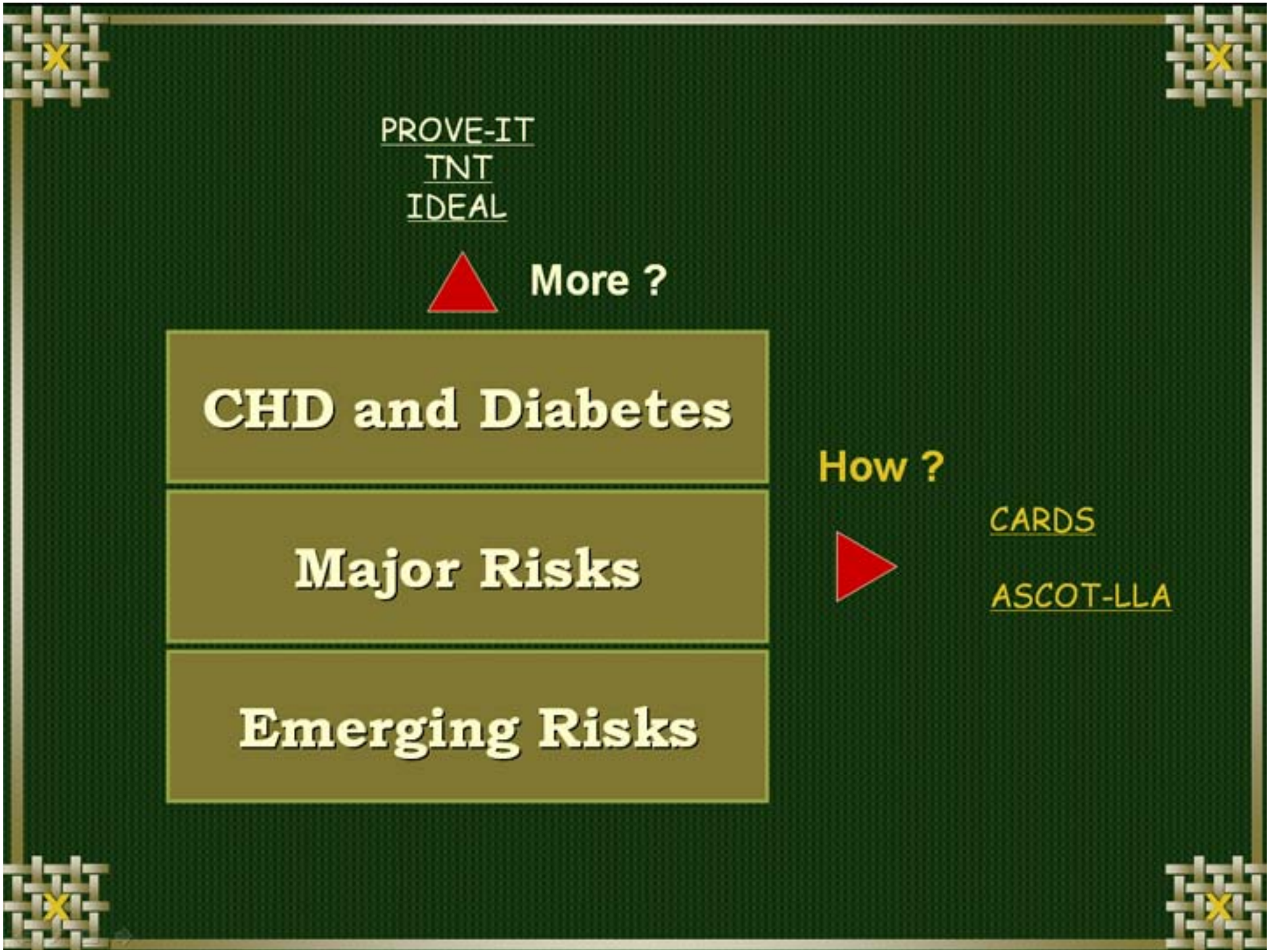

PROVE-IT
TNT
IDEAL
More ?
CHD and Diabetes
Major Risks
Emerging Risks
How ?
CARDS
ASCOT-LLA

PROVE-IT

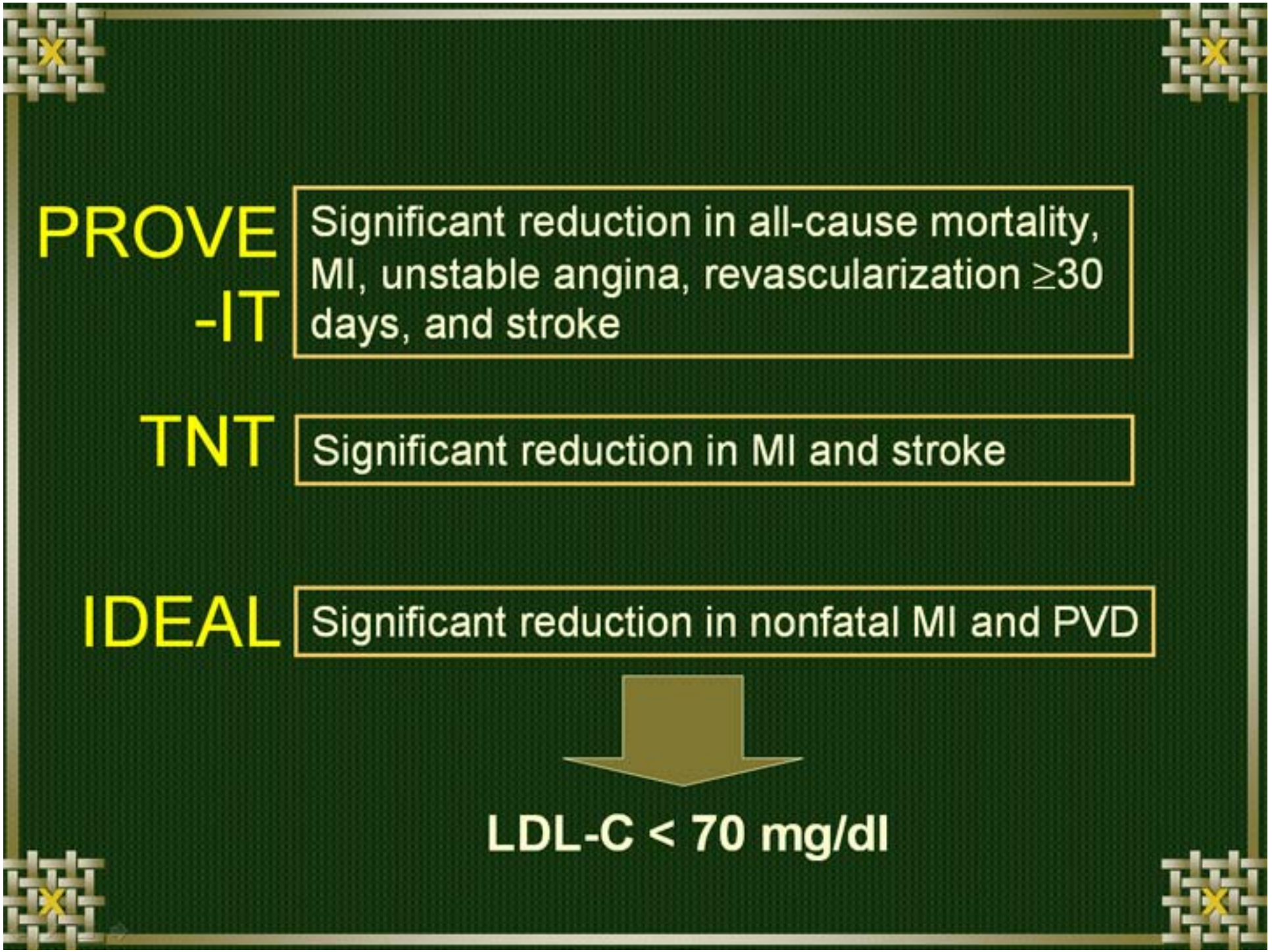
4162 Acute coronary syndrome
Atorva 80 mg vs. prava 40 mg, for 2 yrs
LDL-C in atorva 80 mg/d; 67 mg/dl
LDL-C, in prava 40mg/d; 97 mg/dl

TNT

15464 Stable chronic angina
Atorva 80 mg vs. 10 mg, for 4.9 yrs
LDL-C 130-250mg/dl, TG<600 mg/dl
LDL-C in atorva 80 mg/d; 70 mg/dl, in 10mg/d ; 100 mg/dl

IDEAL

8888 Old myocardial infarction
Atorva 80 mg vs. simva 20 mg, for 4.8 yrs
Age <80 yrs. LDL-C 130-250mg/dl, TG<600 mg/dl
LDL-C in atorva 80 mg/d; 80 mg/dl, in simva 20mg/d ; 99.8 mg/dl


PROVE-IT
Significant reduction in all-cause mortality, MI, unstable angina, revascularization ≥30 days, and stroke
TNT
Significant reduction in MI and stroke
IDEAL
Significant reduction in nonfatal MI and PVD
LDL-C < 70 mg/dl

ATP-III update (2004)
Modified LDL Goal ; absolute LDL-C levels

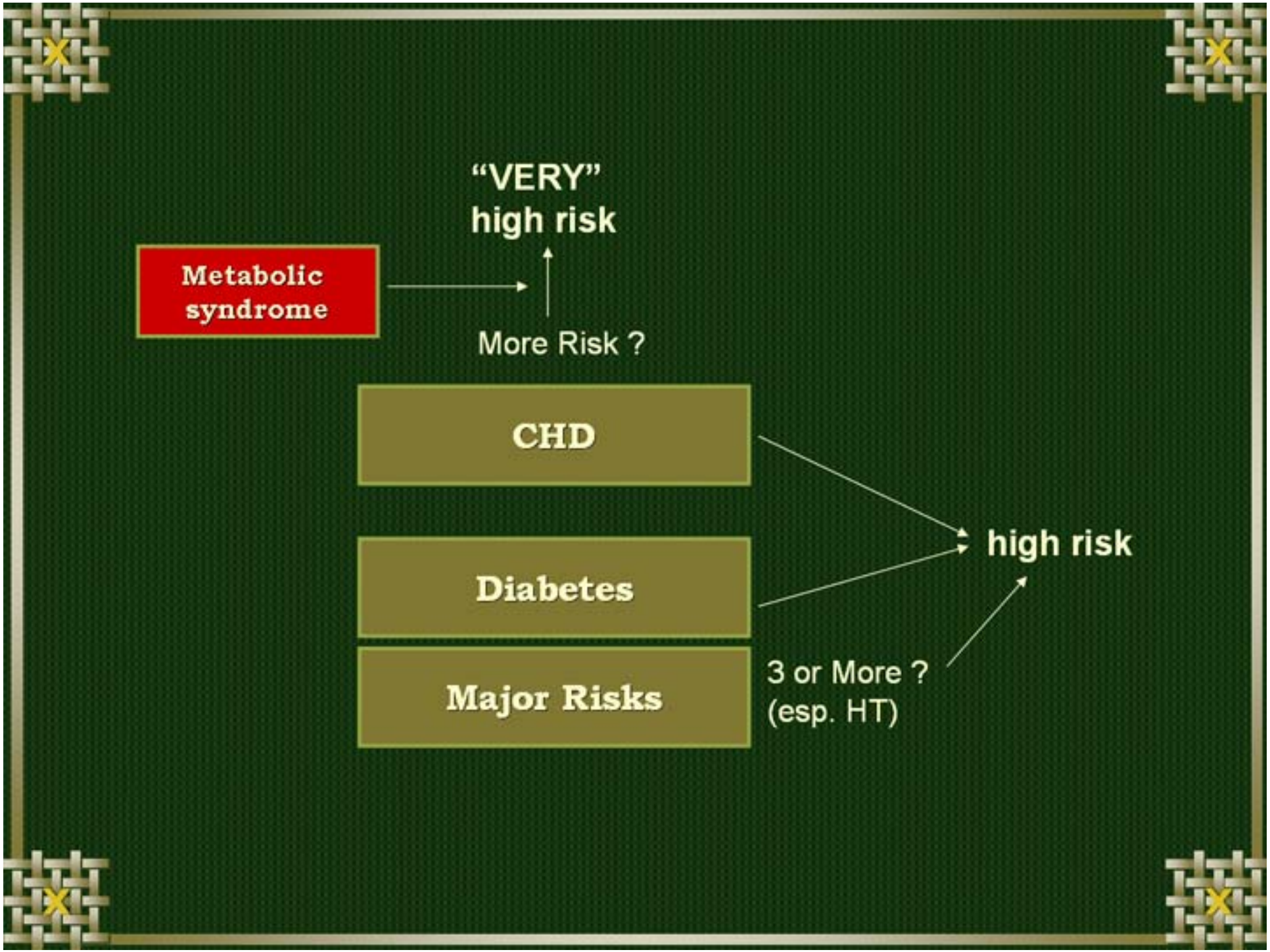
- High risk patients ;

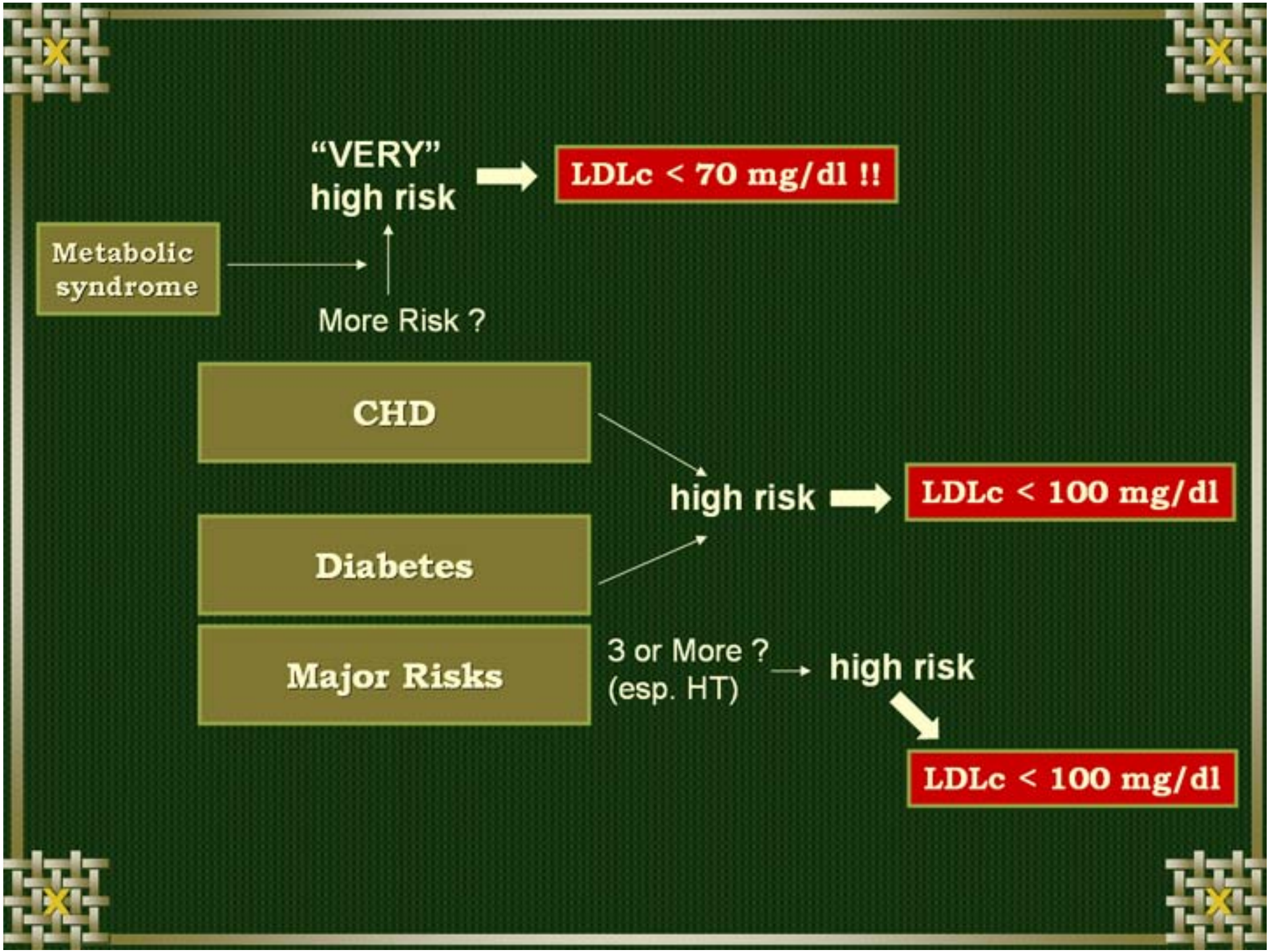
  <100 mg/dl as a 'minimal' goal with 'standard' statin dose

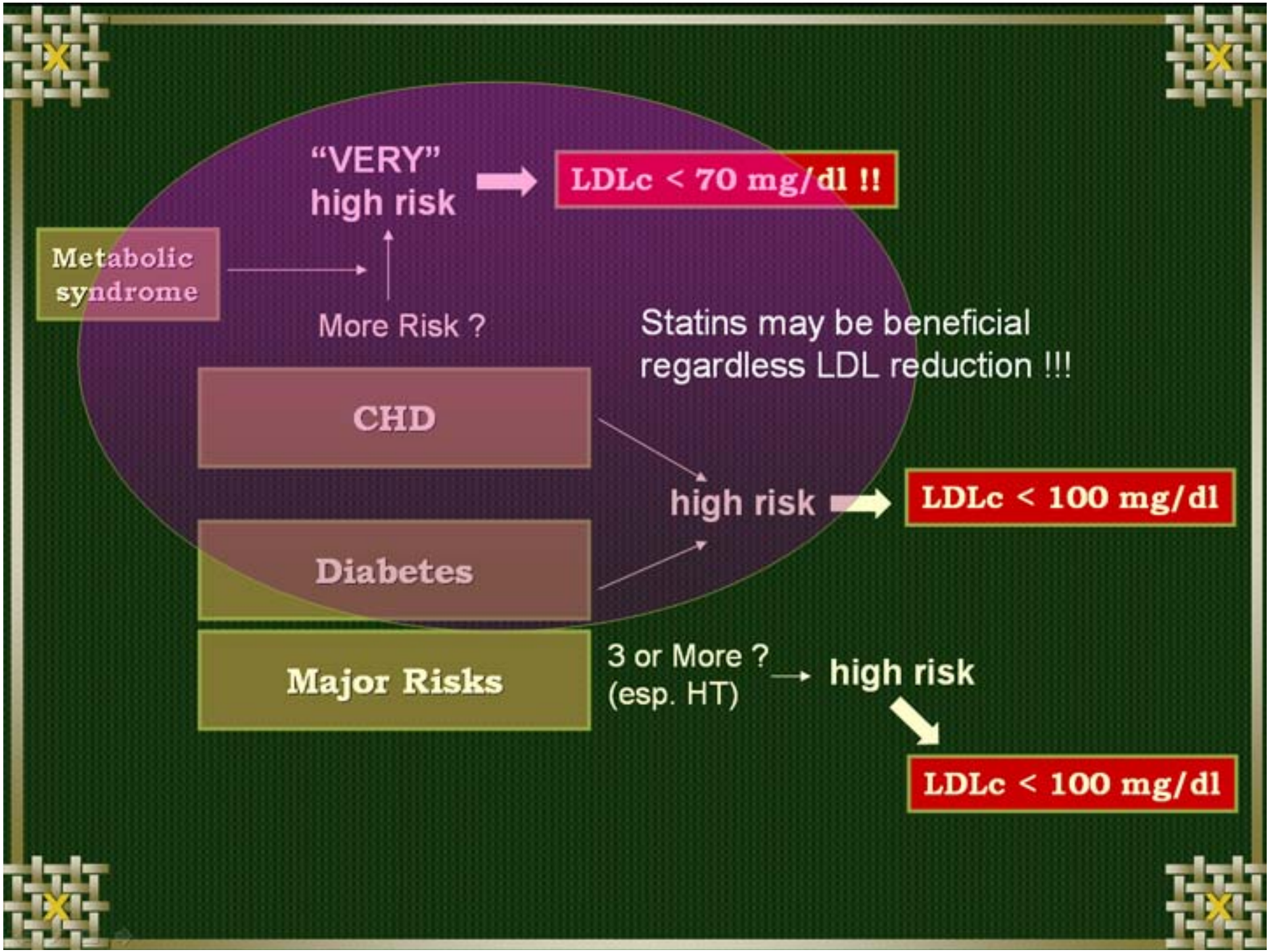
- "Very" high risk patients ;

  <70 mg/dl is favored (and CRP <2 mg/L)

- very high ; CVD with
  1. multiple RFs (esp. DM)
  2. poorly controlled RFs (esp. smoking)
  3. multiple factors of the Metabolic syndrome
     (high TG ≥ 200 plus nonHDL-C ≥ 130 with low HDL-C ≤ 40)
  4. with ACS


"VERY"
high risk
Metabolic syndrome
More Risk ?
CHD
Diabetes
Major Risks
high risk
3 or More ?
(esp. HT)


"VERY" high risk
LDLc < 70 mg/dl !!
Metabolic syndrome
More Risk ?
CHD
Diabetes
Major Risks
high risk
LDLc < 100 mg/dl
3 or More ? (esp. HT)
high risk
LDLc < 100 mg/dl


"VERY"
high risk
LDLc < 70 mg/dl !!
Metabolic
syndrome
More Risk ?
Statins may be beneficial
regardless LDL reduction !!!
CHD
high risk
LDLc < 100 mg/dl
Diabetes
Major Risks
3 or More ?
(esp. HT)
high risk
LDLc < 100 mg/dl

More High Risk ?

GALAXY outcomes studies

STUDY	OVERVIEW
AURORA	A long-term, randomised, double-blind, placebo-controlled study to evaluate the effects of CRESTOR 10mg on survival and major cardiovascular events in 2775 subjects with **end-stage renal disease on chronic haemodialysis**[1]
JUPITER	A long-term, randomised, double-blind, placebo-controlled study to assess CRESTOR 20mg in the primary prevention of cardiovascular events in 15000 subjects with **low LDL-C levels and elevated levels of C-reactive protein (CRP)**[2]
CORONA	A long-term, randomised, double-blind, placebo-controlled study to evaluate CRESTOR 10mg on cardiovascular mortality and morbidity and overall survival in 5016 patients with **chronic symptomatic systolic heart failure (NYHA II-IV) of ischaemic aetiology receiving standard treatment**

1. Fellström B et al. Curr Control Trials Cardiovasc Med 2005;6:9;e-pub ahead of print. 2. Ridker P. Circulation 2003;108:2292-2297

Low Risk Abandoned ? No

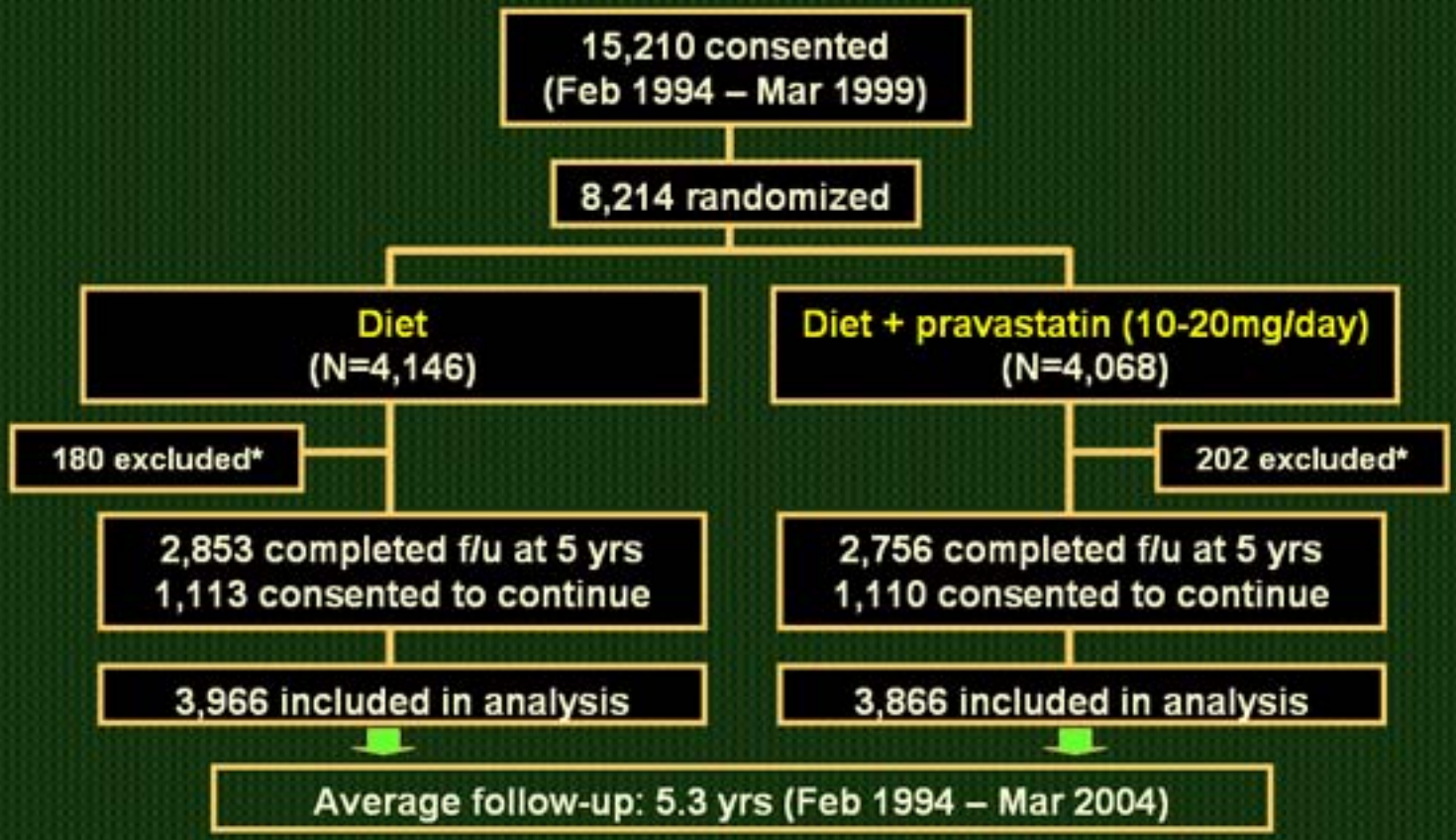
MEGA study

Low dose statin
to
Low risk patients

MANAGEMENT OF ELEVATED CHOLESTEROL IN THE PRIMARY PREVENTION GROUP OF ADULT JAPANESE

Primary prevention of cardiovascular disease in Japan. Results of the randomized MEGA Study with pravastatin.

H. Nakamura et. al. AHA2005 (Dallas) MVL-04SL-0206



*Excluded patients were selected under blinding, based on information of pre-randomization by data reviewing committee before end of study.

MEGA Study

Relatively low-risk Japanese population
Majority of study subjects ; women (68%)
Baseline LDL-C ; 156 mg/dl HDL-C ; 57 mg/dl
LDL-C reduction 18 % vs. 3 %

	End Points At 5-year (35,962 person-yrs)		
	HR	Risk Reduction	P-value
CHD	0.70	30%	0.03
CHD + Cerebral Infarction	0.66	34%	0.003
Stroke	0.65	35%	0.03
Total Mortality	0.68	32%	0.05

Offense

Changing Concept !

Retard the growth

Regress the plaque

Retard the plaque growth

Regress the plaque

ASTEROID

ASTEROID

A Study To evaluate the Effect of Rosuvastatin On Intravascular ultrasound-Derived coronary atheroma burden

- **Primary objective**

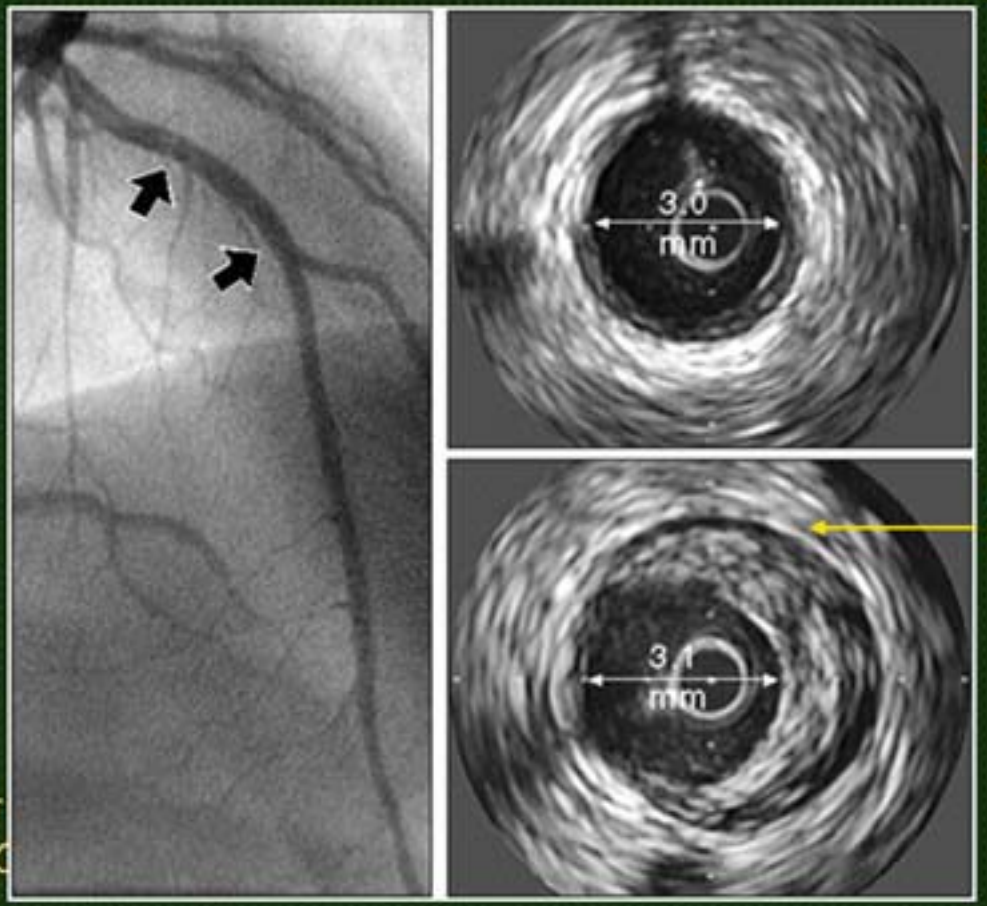
  rosuvastatin 40 mg/d for 2 years in CAD patients

  Regression of coronary artery atheroma burden, as measured by IVUS

The IVUS technique can detect angiographically 'silent' atheroma

< Angiogram >

No evidence of disease



< IVUS >

Little evidence of disease

Atheroma

IVUS=intravascular

Nissen S, Yock P. C

ASTEROID – a 2-year study

Patients (n=507)

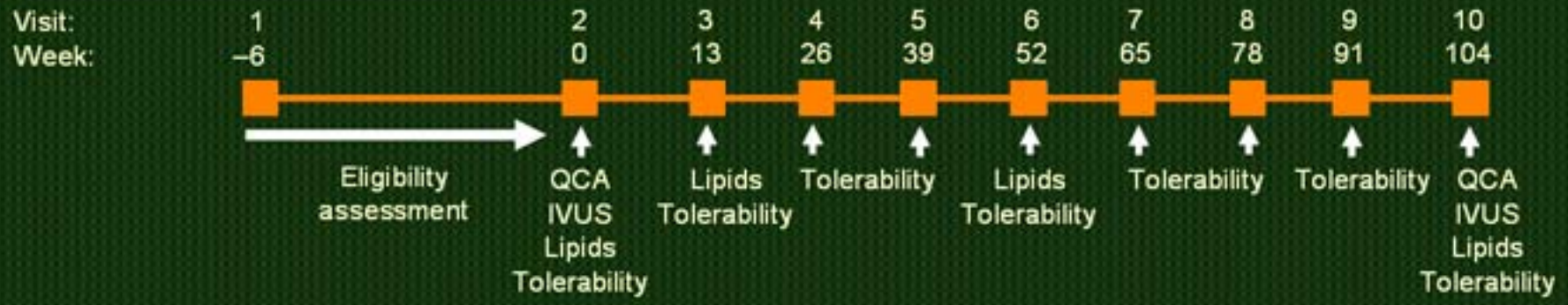
CAD, undergoing PCI

Left main coronary artery: ≤50% reduction in lumen diameter

Target coronary artery: ≤50% reduction in lumen diameter of ≥40 mm segment

≥18 years

Rosuvastatin 40 mg (n=507)



CAD=coronary artery disease; PCI=percutaneous coronary intervention; QCA=quantitative coronary angiography; IVUS=intravascular ultrasound

Nissen S. ISA Sep 2003. Poster presentation

Study endpoints

Primary

Dual endpoints assessed by IVUS:

- change in PAV in the entire segment of coronary artery assessed
- change in TAV in the most severely diseased 10mm segment of the coronary artery

Secondary

- change in TAV within the entire segment assessed by IVUS
- percentage change from baseline in lipid and lipoprotein levels

PAV = percentage atheroma volume, TAV = total atheroma volume

Baseline characteristics - demographics

Demographics	n=349
Age, y, mean (SD)	58.5 (10)
Male gender, n (%)	245 (70)
Race, % White	97
Weight, kg (SD)	85.5 (16.8)
BMI, median kg/m^2	28.4
History of hypertension, (%)	96
History of diabetes mellitus, (%)	13
History of acute coronary syndrome, (%)	17
History of prior myocardial infarction, (%)	25

Ref: Nissen S *et al.* JAMA 2006; 295: e-publication ahead of print

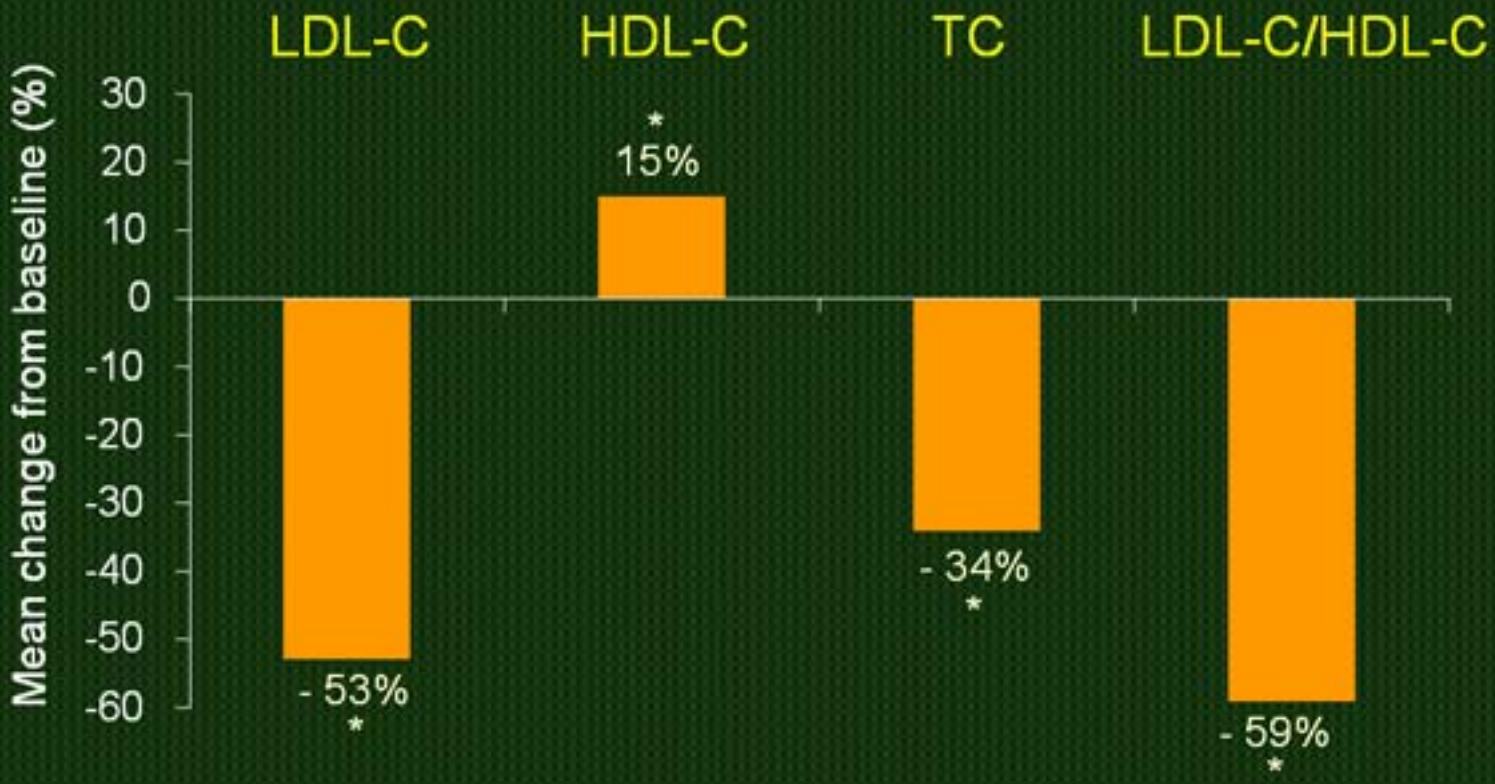
Baseline characteristics - lipids

Baseline level; total population (n=346*)	Baseline level mg/dL mean (SD)	Baseline level mmol/L mean
TC	204 (41)	5.3
LDL-C	130 (34)	3.4
HDL-C	43 (11)	1.1
Non-HDL-C	161 (40)	4.2
TG	152 (82)	1.7
ApoB	128 (29)	Not calculated
ApoA-1	139 (27)	Not calculated

*3 out of 349 patients completing the trial were missing lab data

Ref: Nissen S *et al.* JAMA 2006; 295: e-publication ahead of print

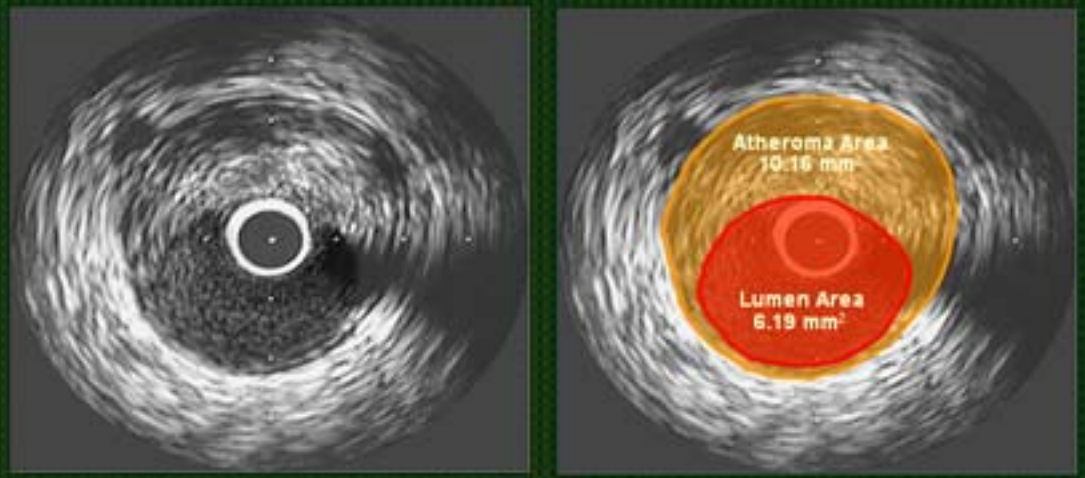
% change in LDL-C, HDL-C, TC & LDL-C/HDL-C Ratio



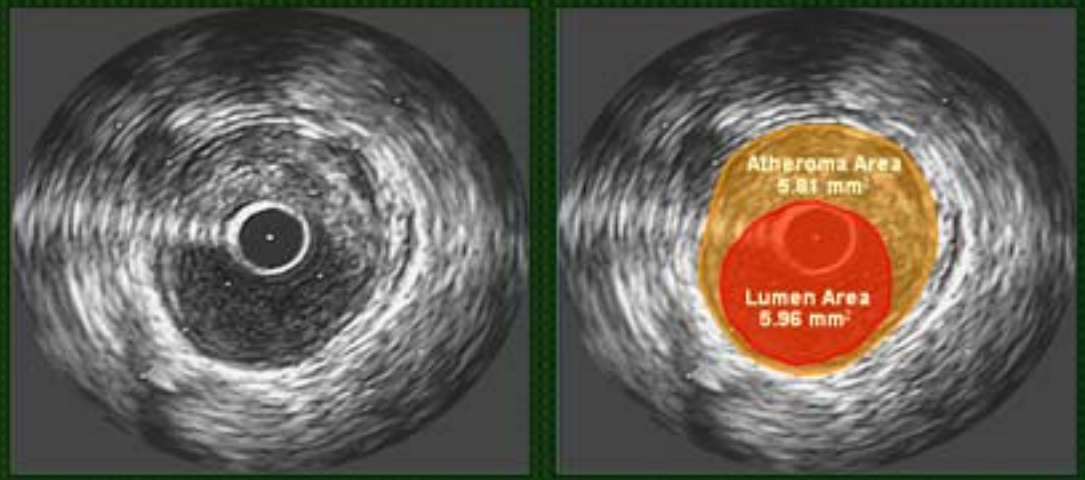
Ref: Nissen S *et al.* JAMA 2006; 295: e-publication ahead of print

Example of regression of atherosclerosis with rosuvastatin in ASTEROID, measured by IVUS

Baseline IVUS

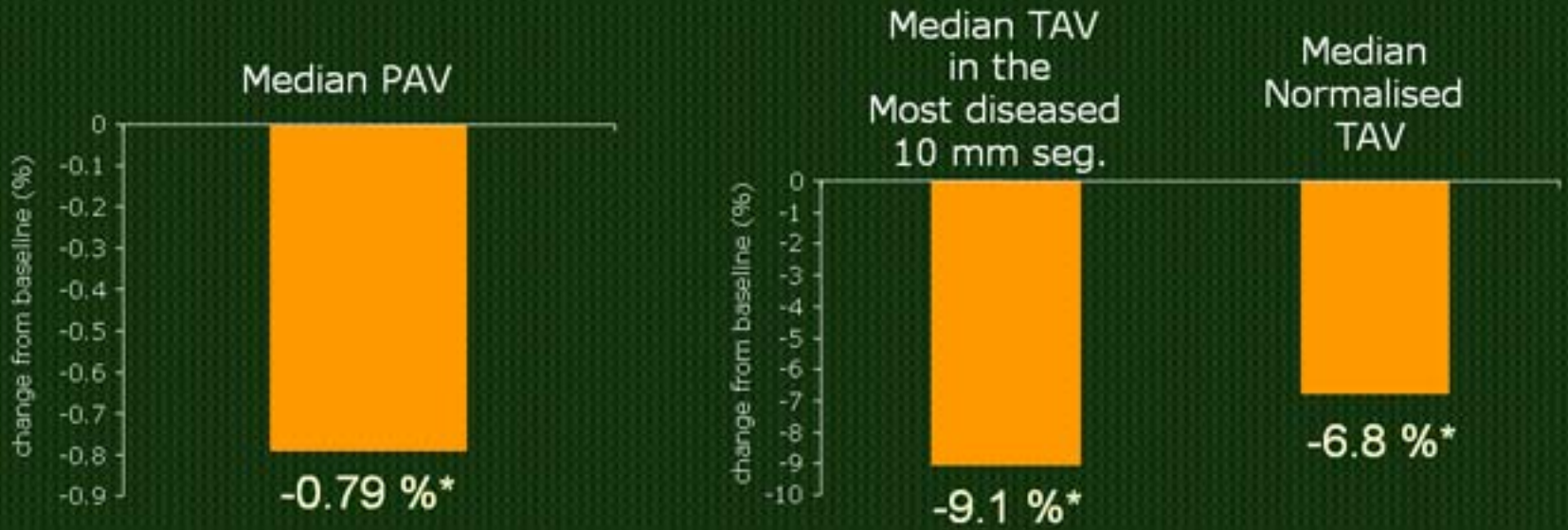


Follow-up IVUS 24 months rosuvastatin



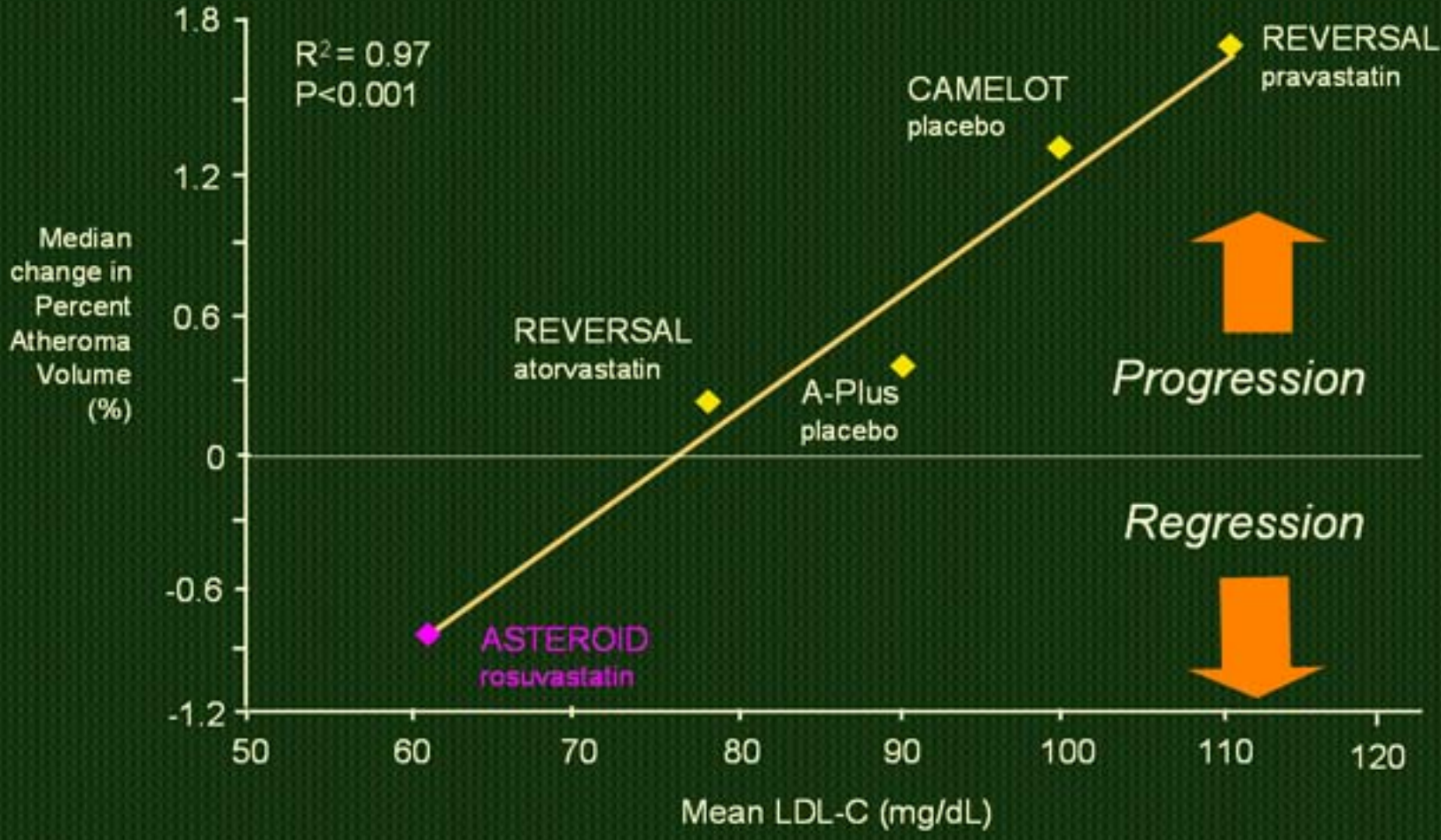
Ref: Nissen S *et al.* JAMA 2006; **295**: e-publication ahead of print

Endpoint analysis: Change in atheroma volume



* p<0.001 for difference from baseline values. Wilcoxon signed rank test

Relationship between LDL-C levels and change in percent atheroma volume for several IVUS trials



Ref: Nissen S *et al.* JAMA 2006; 295: e-publication ahead of print

Summary of ASTEROID

- Regression of atherosclerosis can be achieved with intensive statin therapy
- Regression of atherosclerosis was associated with a substantial reduction of LDL-C (-53%) combined with a significant increase in HDL-C (15%).
- Regression occurred in 4 out of 5 patients and in virtually all subgroups evaluated, including men and women, older and younger patients and in most subgroups defined by lipid levels.

Summary – statin trials

- Identification of high risk
  - Diabetes ; CARDS, FIELD
  - Hypertension ; ASCOT-LLA
  - Inflammation ? ; JUPITER
  - ESRD ? ; AURORA
  - CHF ? ; CORONA
- New classification ; 'Very' high risk
  - MIRACL - PROVE-IT - TNT - IDEAL
- Statin effect in low risk
  - MEGA
- Beyond prevention ; plaque regression
  - REVERSAL
  - ASTEROID

Conclusion

- More precise risk stratification is needed to find high- and very high- risk patients
- Statin treatment shows benefits in high- and very high risk patients regardless basal LDL cholesterol levels
- Ultimate goal of LDL lowering management to those high-risk group is to regress the atherosclerotic burden, as proven in ASTEROID study