Lessons from Recent Atherosclerosis Trials

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Change of concept

- Primary vs. secondary prevention

- Low risk vs. High risk

High Risk

CHD and equivalents

CHD ; coronary heart disease

“ 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)

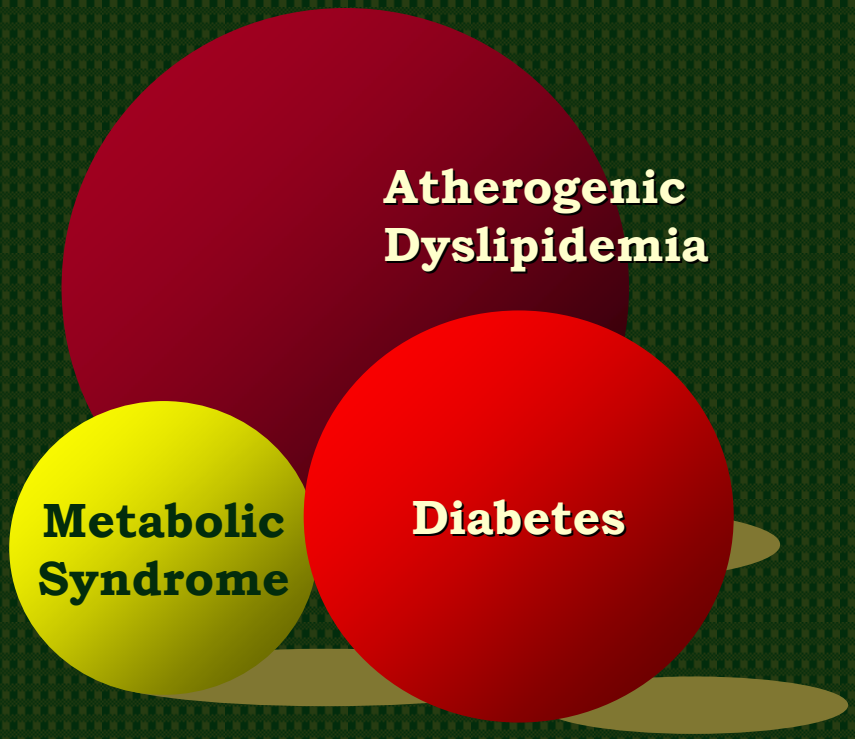
Major Risk Factors That Modify LDL Goals *
(Exclusive of LDL Cholesterol)

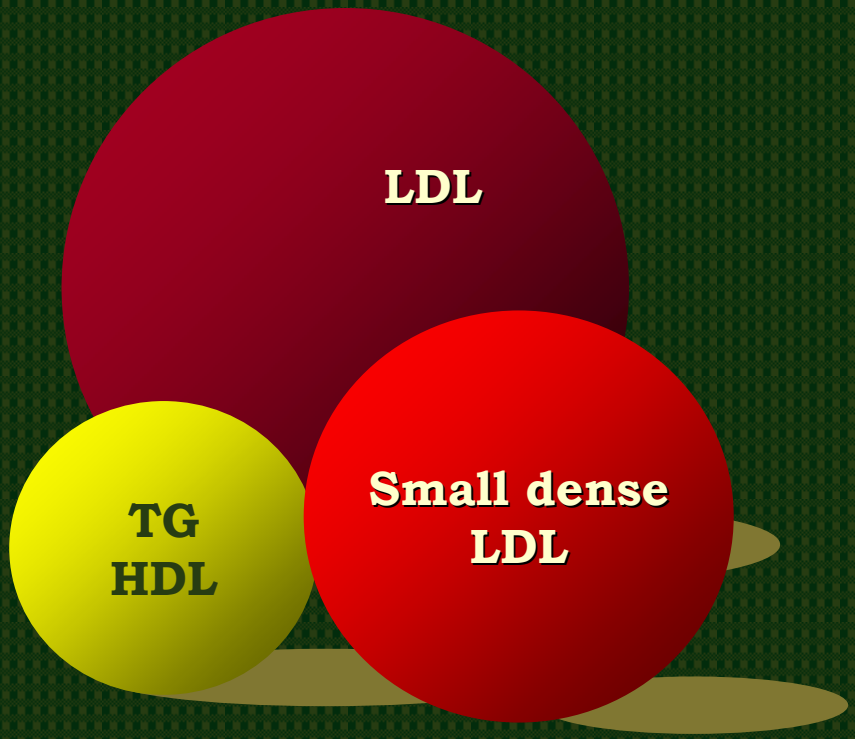
- **Cigarette smoking**
- **Hypertension**
  (blood pressure ≥ 140/90 mmHg
  or on antihypertensive medication)
- **Low HDL cholesterol**
  (< 40 mg/dL)†
- **Family history of premature CHD**
  (CHD in male first-degree relative < 55 years
  ; CHD in female first-degree relative < 65 years)
- **Age (men ≥ 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 pres ence removes 1 risk factor from the total count.

Emerging Risks

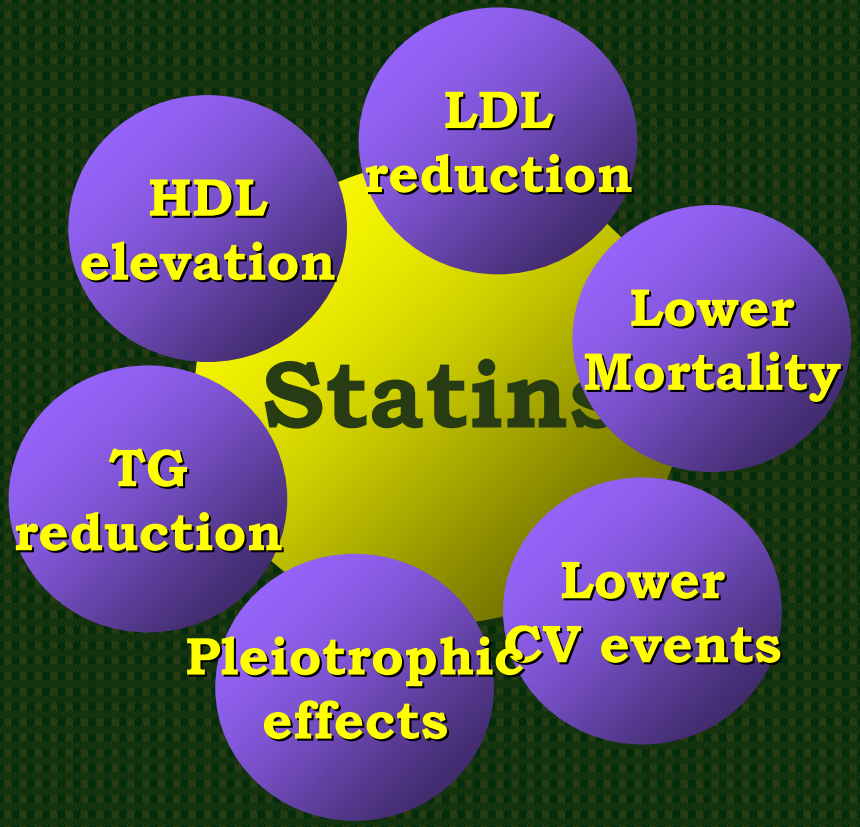
Metabolic syndrome
Inflammation


Atherogenic
Dyslipidemia
Metabolic
Syndrome
Diabetes


LDL
TG
HDL
Small dense
LDL

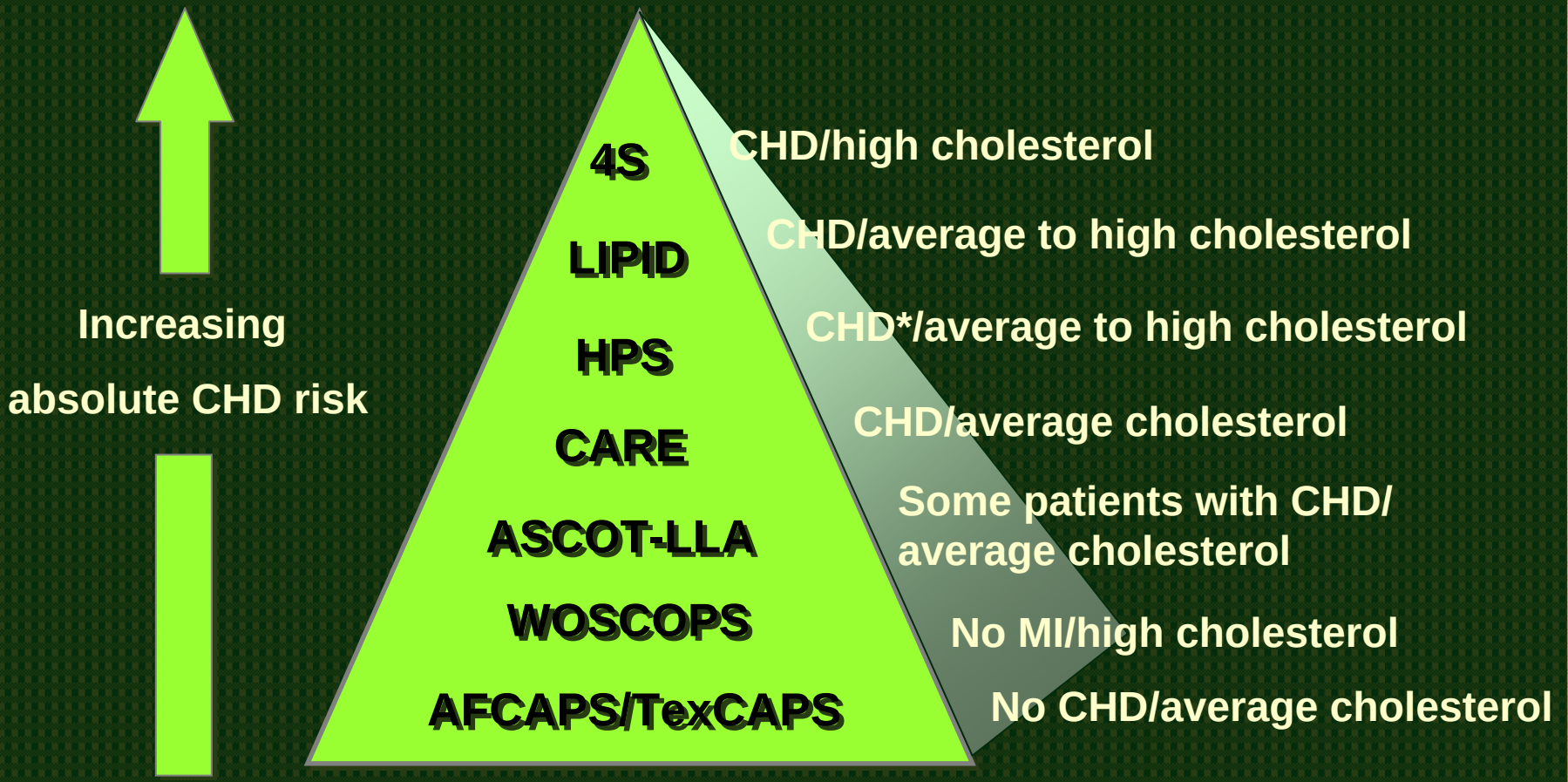
Convergence To Statin

Statin


LDL reduction
HDL elevation
Lower Mortality
Statins
TG reduction
Lower CV events
Pleiotrophic effects

Statin Pyramid

Key Statin Trials and Spectrum of Risk



*CHD or CHD risk equivalent, e.g. diabetes

Diabetes

Major Risks

Emerging Risks

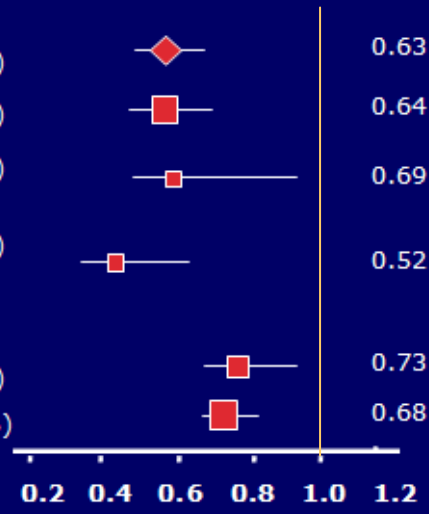
CARDS

FIELDS

CARD Study ; diabetes

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



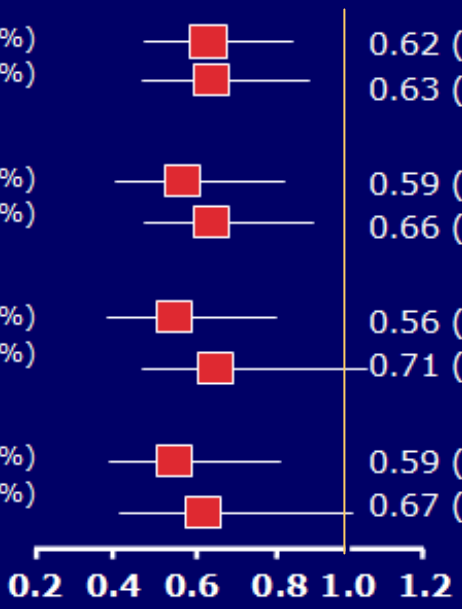
Note: Only the first acute coronary event, revascularization, or stroke is included in the primary end point.
Symbol size is proportional to amount of statistical information.

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.

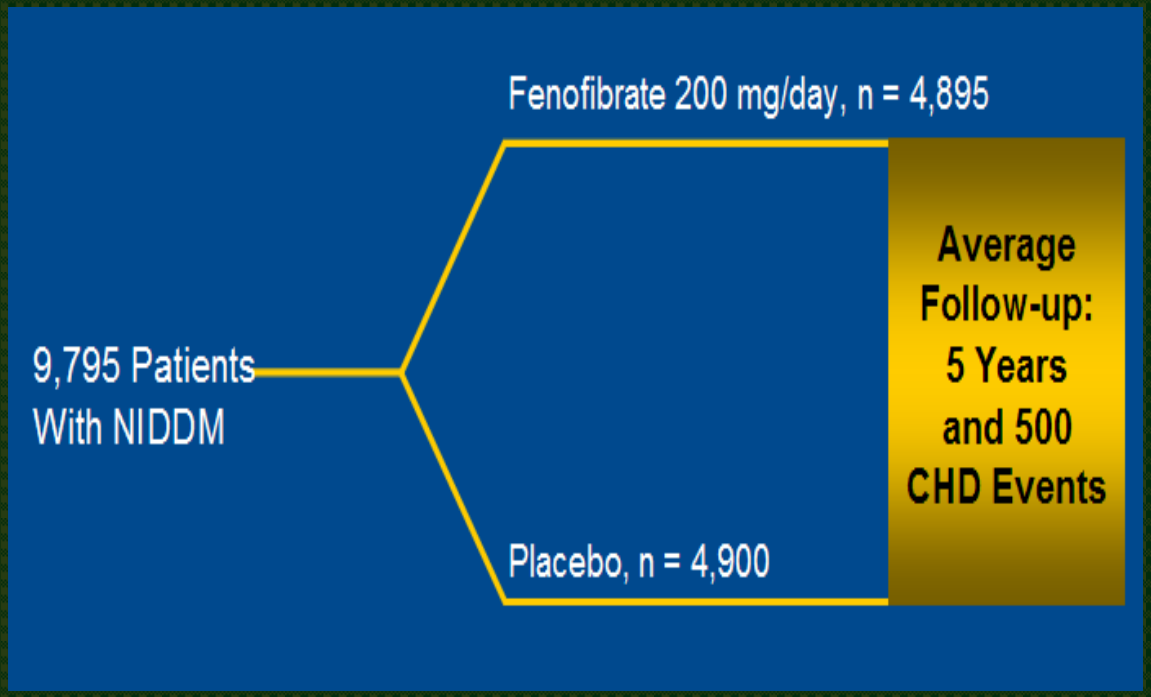
Colhoun HM et al. *Lancet*. 2004;364:685-696.

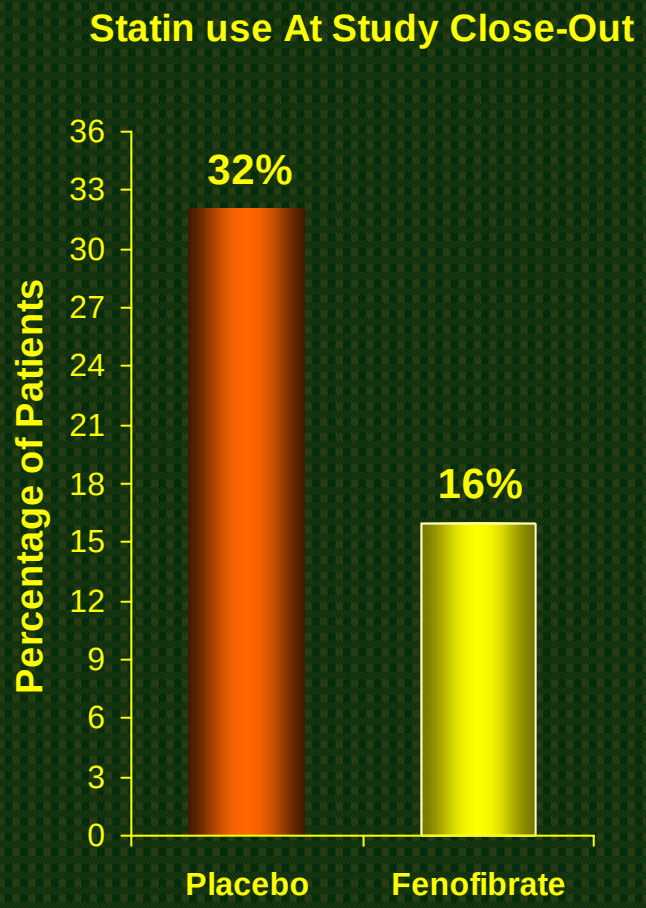
The Fenofibrate Intervention and Event Lowering in Diabetes (FIELD) Trial

Baseline Characteristics

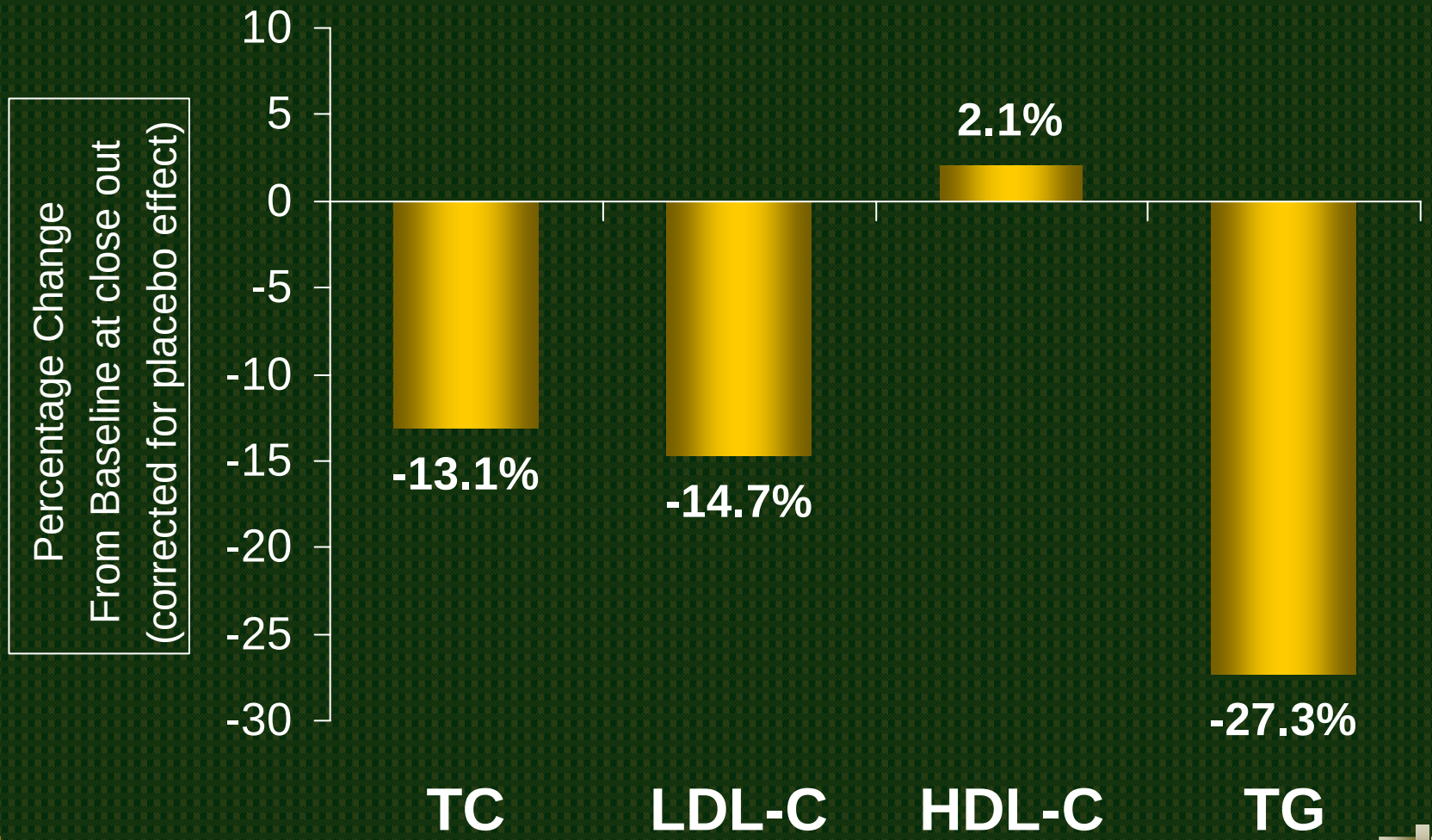
	Total Population (n = 9,795)
Male/Female, %	62.7/37.3
No Prior CVD, %	78.3
Diabetes management with diet plus one oral hypoglycemic agent %	59.5
Median duration of diabetes, years	5
Median HbA1c, %	6.9
Diabetic complications	
Retinopathy, %	8.3
Nephropathy, %	2.8
Lipid parameters, mg/dl	
TC (mean)	194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

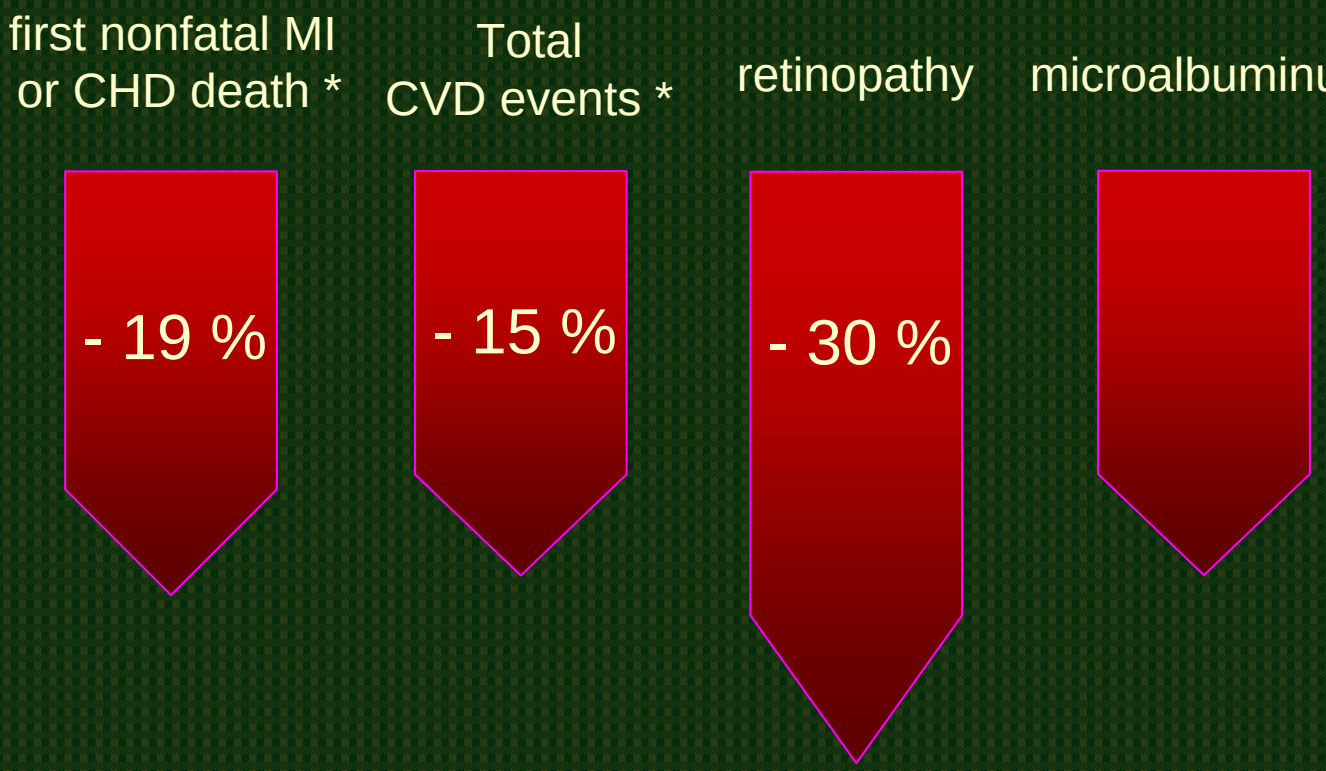


Benefit on the Primary End Point

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

Fibrate as a shield



- * ; Adjusted for statin use
- Fenofiibrate shows more effect to the patients without prior cardiovascular event

CHD and Diabetes

Major Risks

Emerging Risks

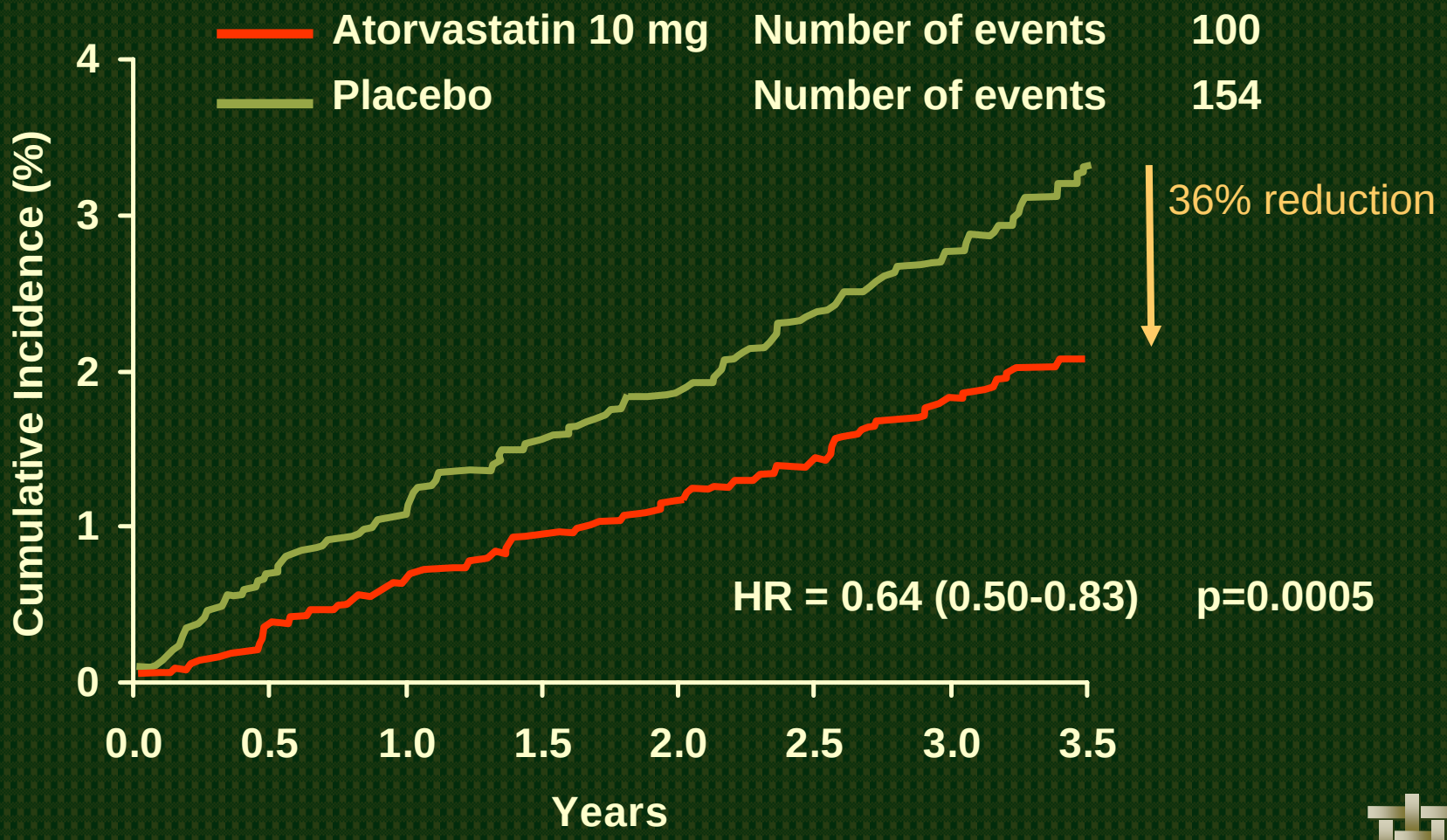
ASCOT

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

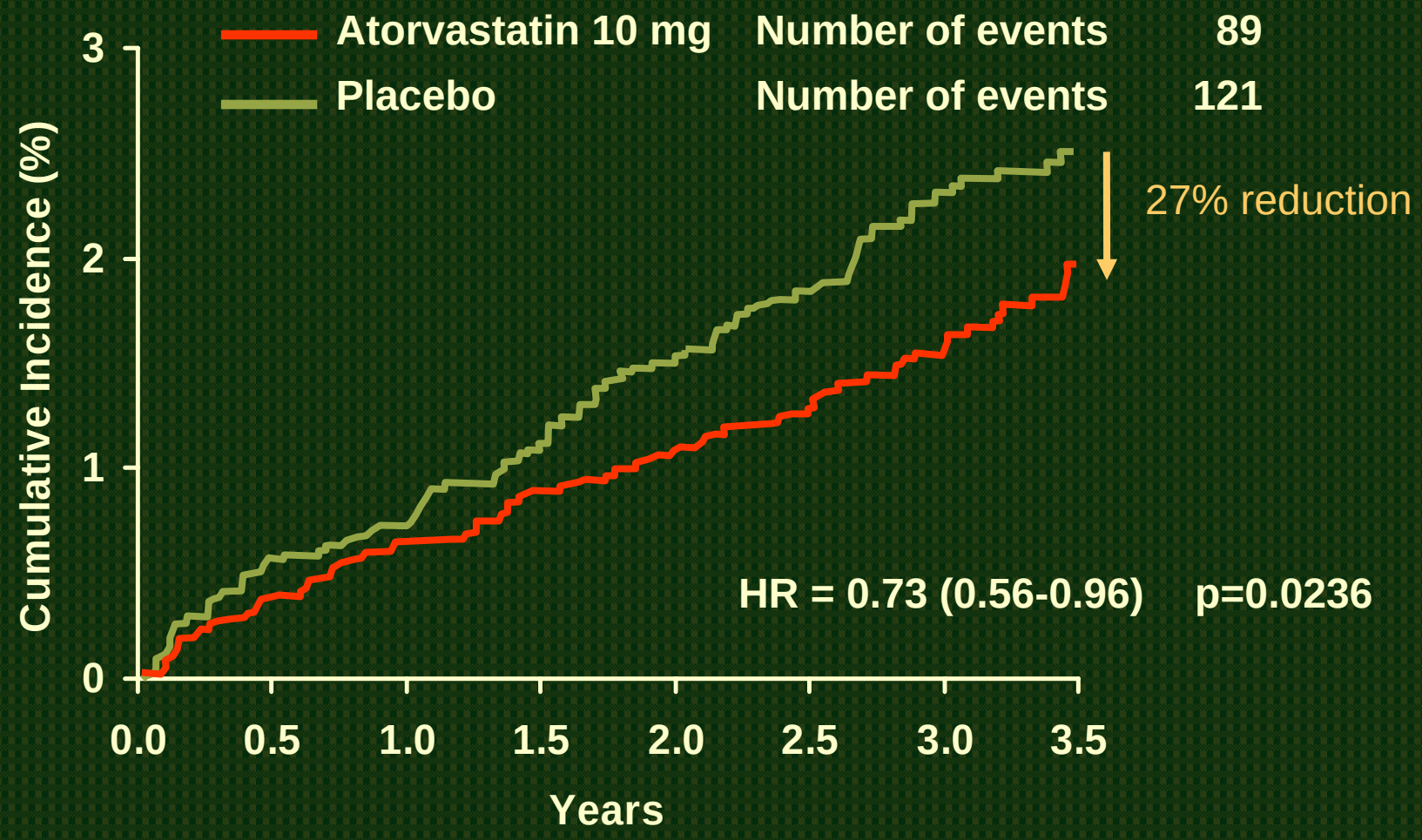
- Benefits – reducing
  - Stroke by 27 %
  - Total cardiovascular events by 21 %
  - Total coronary events by 29 %

Primary End Point: Nonfatal MI and Fatal CHD

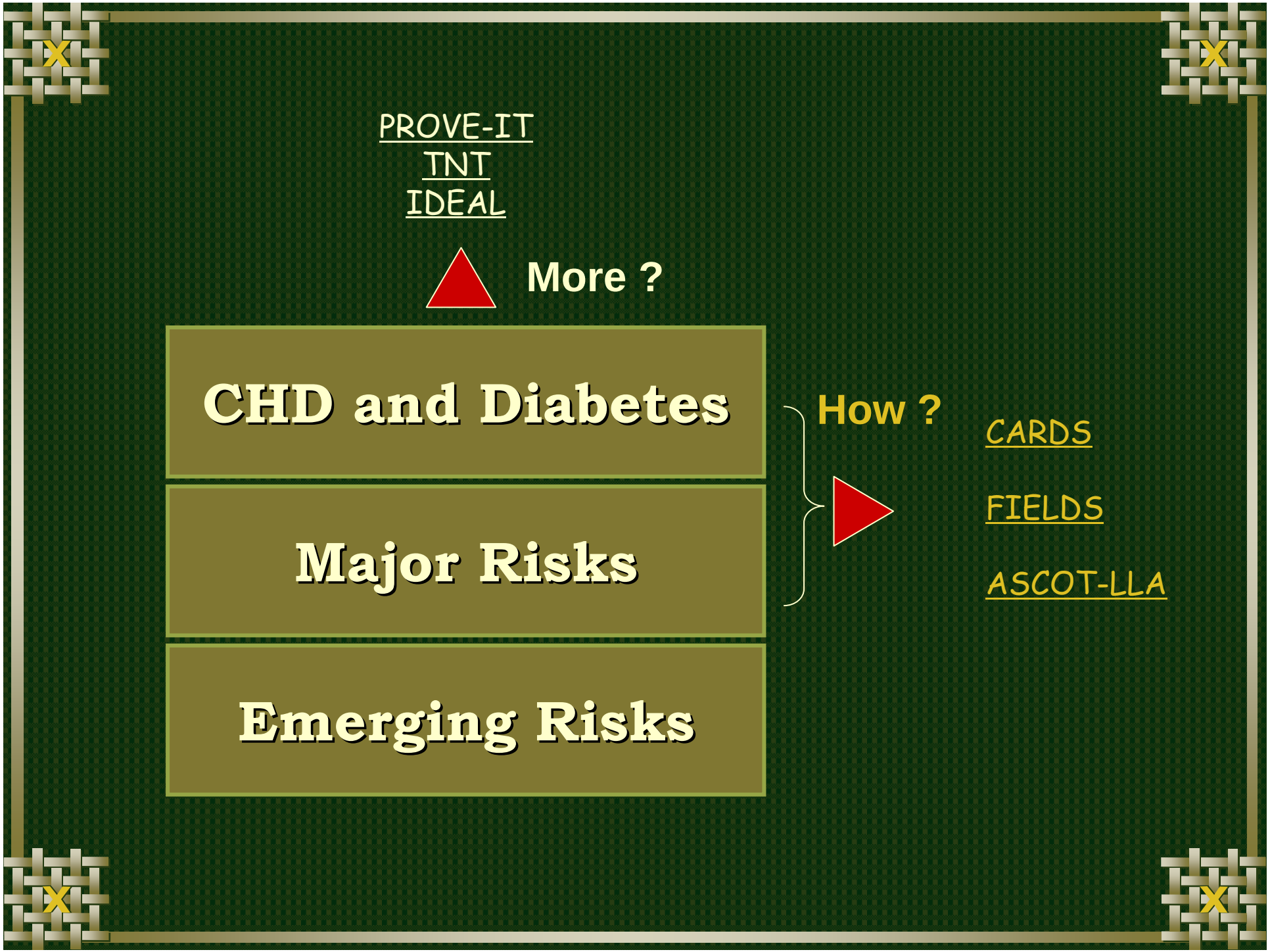


Sever PS, Dahlöf B, Poulter N, Wedel H, et al, for the ASCOT Investigators. Lancet. 2003;361:1149-58

Secondary End Point: Fatal and Nonfatal Stroke



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


PROVE-IT
TNT
IDEAL
More ?
CHD and Diabetes
Major Risks
Emerging Risks
How ?
CARDS
FIELDS
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 ;

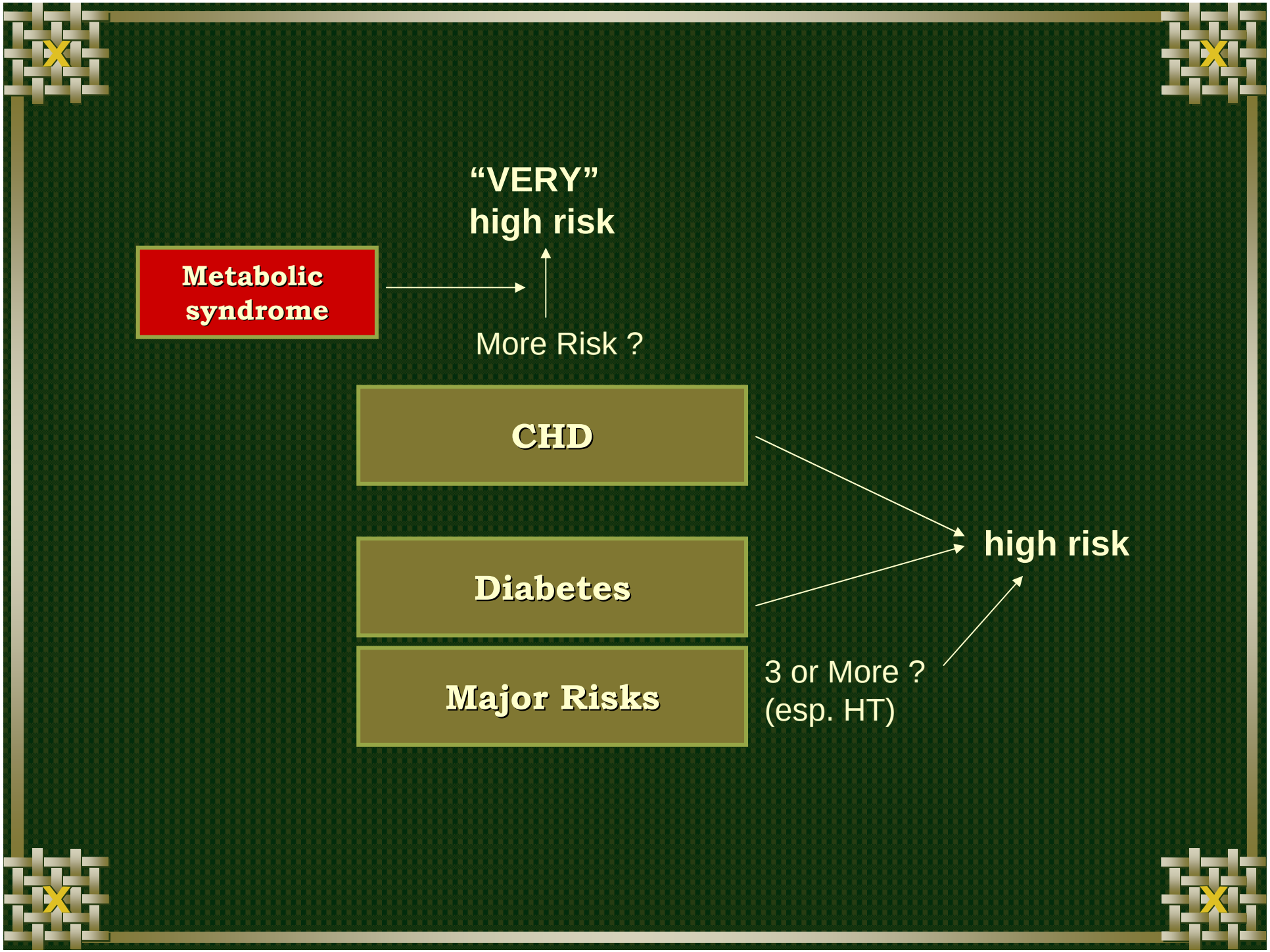
  <100 mg/dl as a ‘minimal’ goal with ‘standard’ statin dose

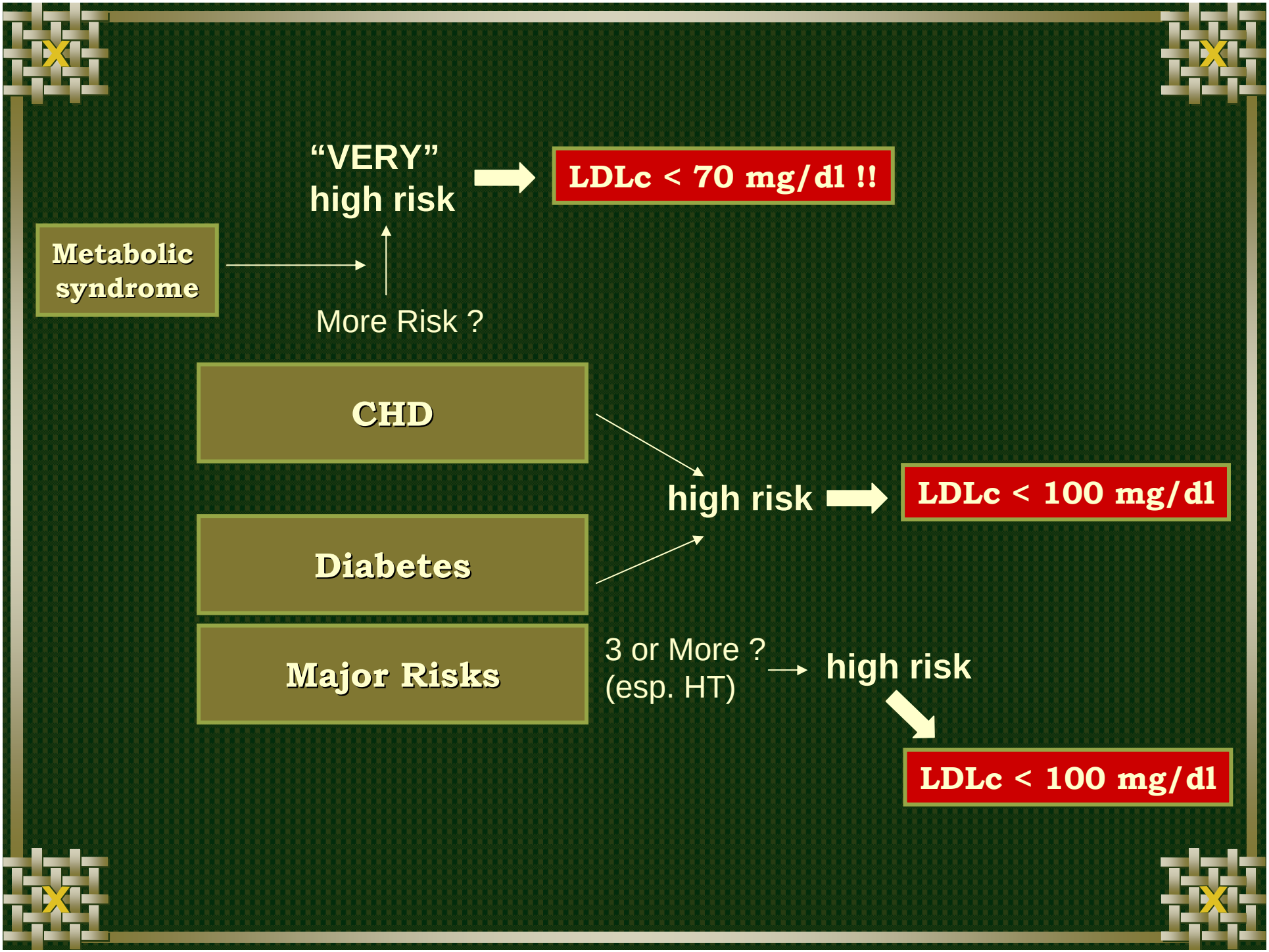
- **“Very high”** risk patients ;

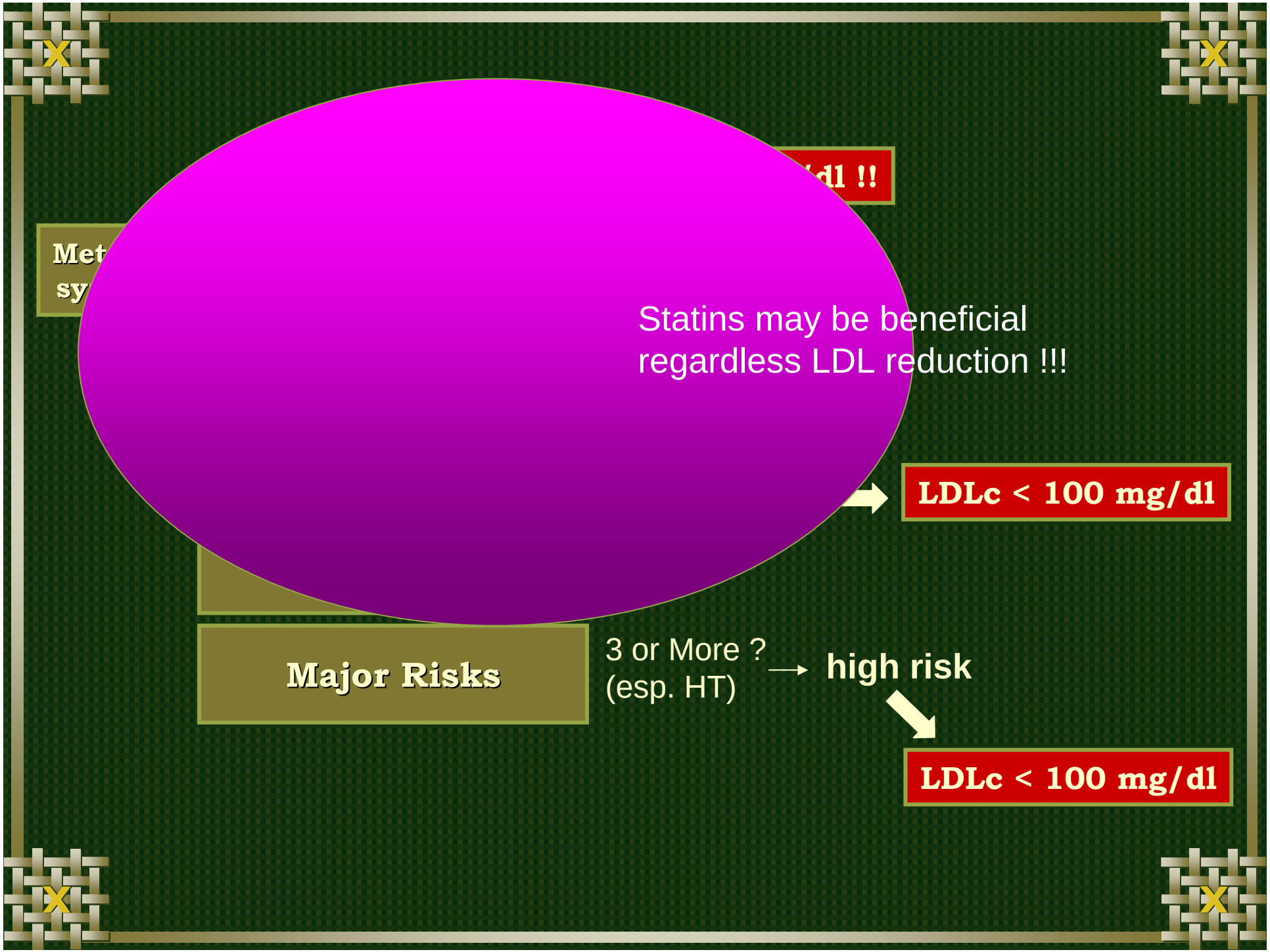
  <70 mg/dl is favored (and CRP <2 mg/L)

  - very high ; CVD with

    1. multiple RFs (esp. DM)
    2. poorly controlled RFs (esp. smoking)
    3. multiple factors of the Metabolic syndrome
       (high TG $\geq$ 200 plus nonHDL-C $\geq$ 130 with low HDL-C $\leq$ 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


dl !!
Met
sy
Statins may be beneficial
regardless LDL reduction !!!
LDLc < 100 mg/dl
Major Risks
3 or More ?
(esp. HT)
high risk
LDLc < 100 mg/dl

More High Risks ?

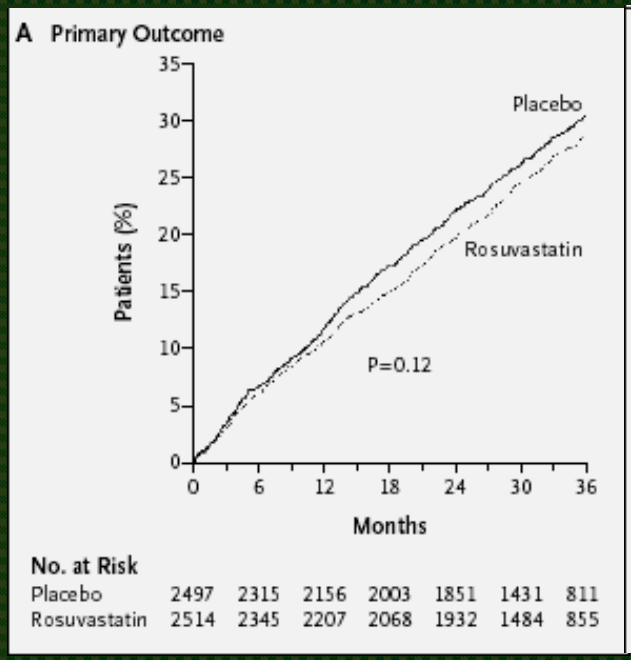
GALAXY outcome trials

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**

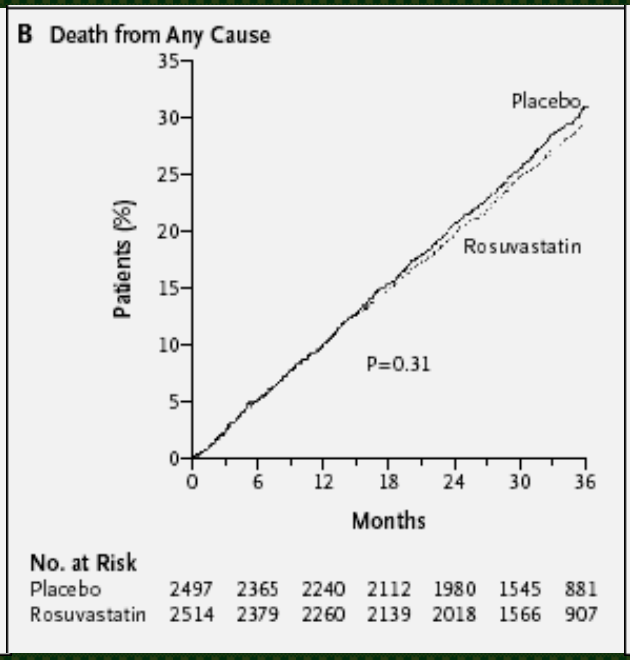
1. Fellström B et al. Curr Control Trials Cardiovasc Med 2005;6:9;e-pub ahead of print. 2. Ridker P. Circulation 2003;108:2292-2297

CORONA – Heart Failure

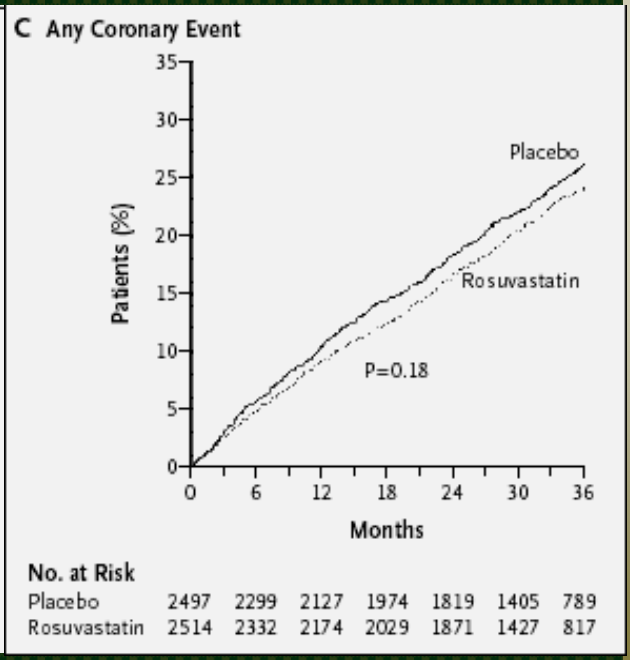
5011 with HF (II or higher) with at least 60 years old
LDL-C around 130 mg/dl
Rosuvastatin 10 mg, for 32.8 mos – LDL-C reduction; 45 %



HR = 0.92



HR = 0.95



HR = 0.92

Lowering LDL- Not only how low, But how long ?

Brown MS and Goldstein JL
Science 2006,311:1721

- Statins ; lowering LDL–C by 80 mg/dl
  reducing heart attack only by 40%
- Loss of function of PCSK9 ;
  lowering LDL–C by only 20 mg/dl
  reducing heart attack by 80%

- Time really matters.

High Risk ?

Lower is Better

Earlier is Better

Low Risk Abandoned ? No

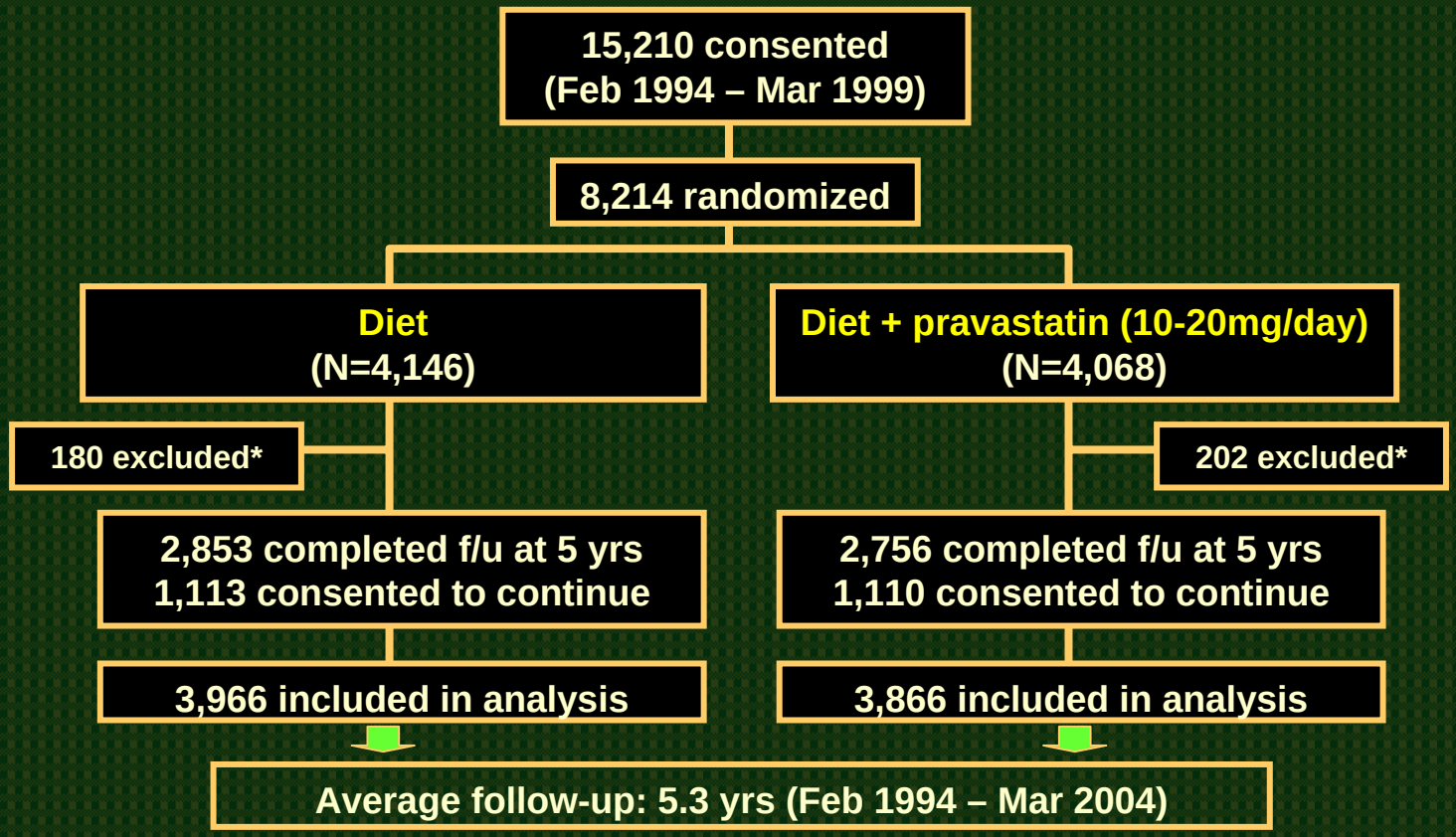
MEGA study

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 makes the game

Changing Concept

Retard the plaque growth

Stabilize the plaque

ORION

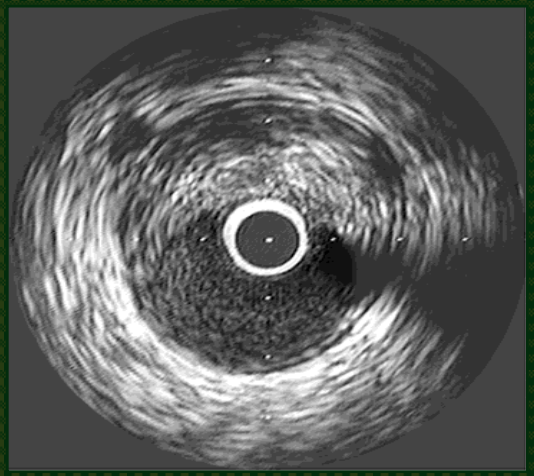
Regress the plaque

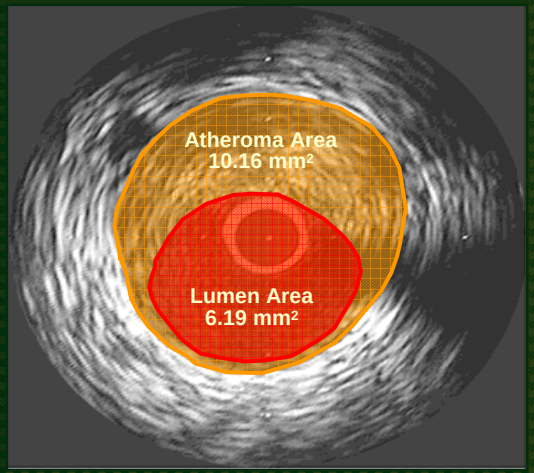
ASTEROID

REVERSAL

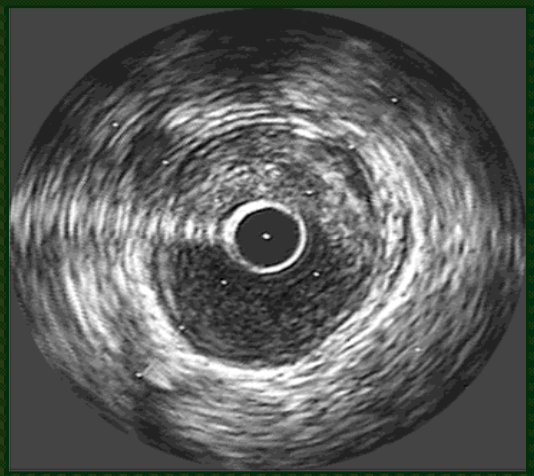
Example of regression of atherosclerosis (ASTEROID, measured by IVUS)

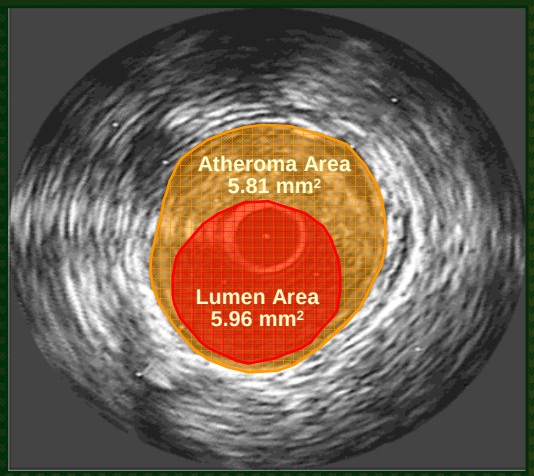
Baseline IVUS





Follow-up IVUS 24 months statin





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

ASTEROID – a 2-year study

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

Patients (n=507)

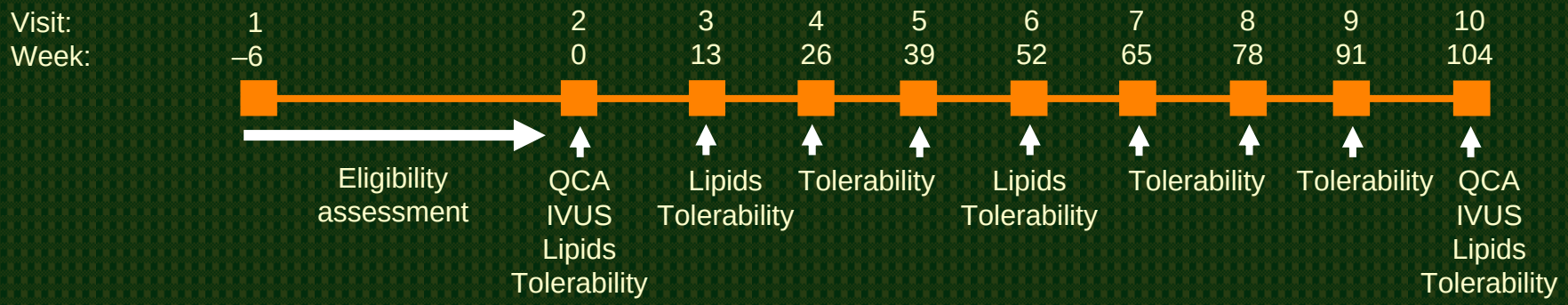
CAD, undergoing PCI

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

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

≥18 years

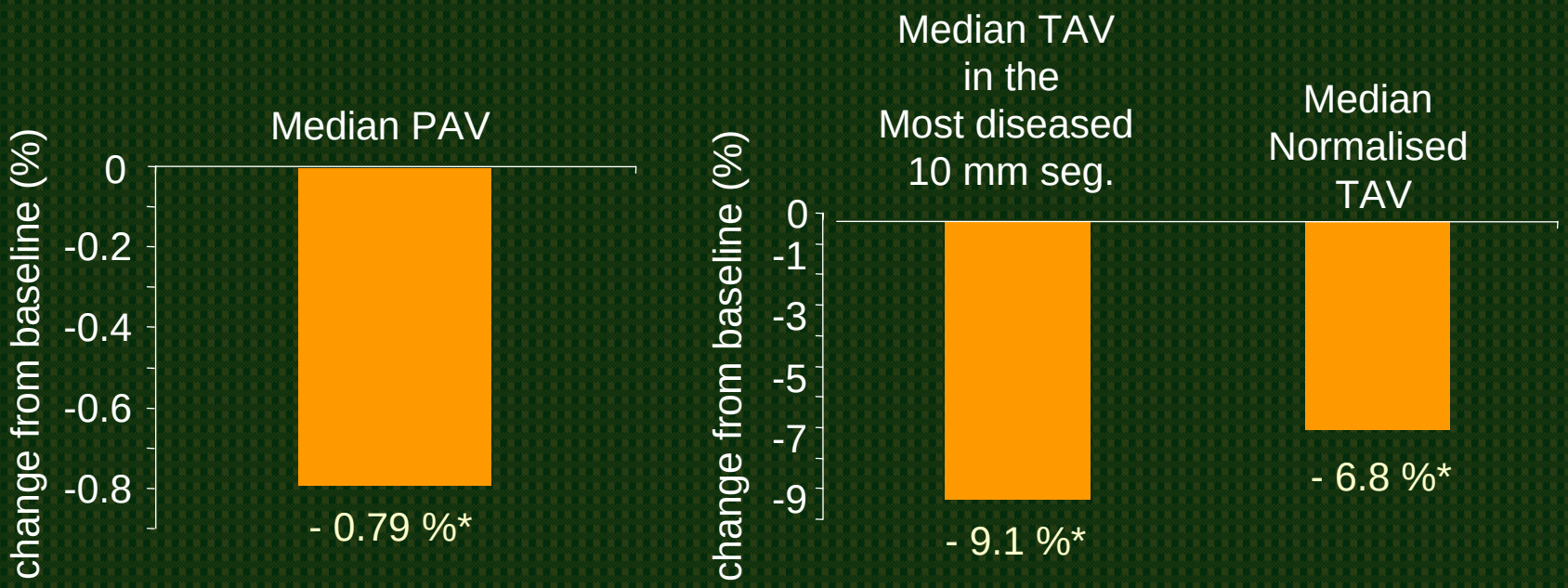
Rosuvastatin 40 mg (n=507)



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

Nissen S. ISA Sep 2003. Poster presentation

Endpoint analysis: Changes in atheroma volume

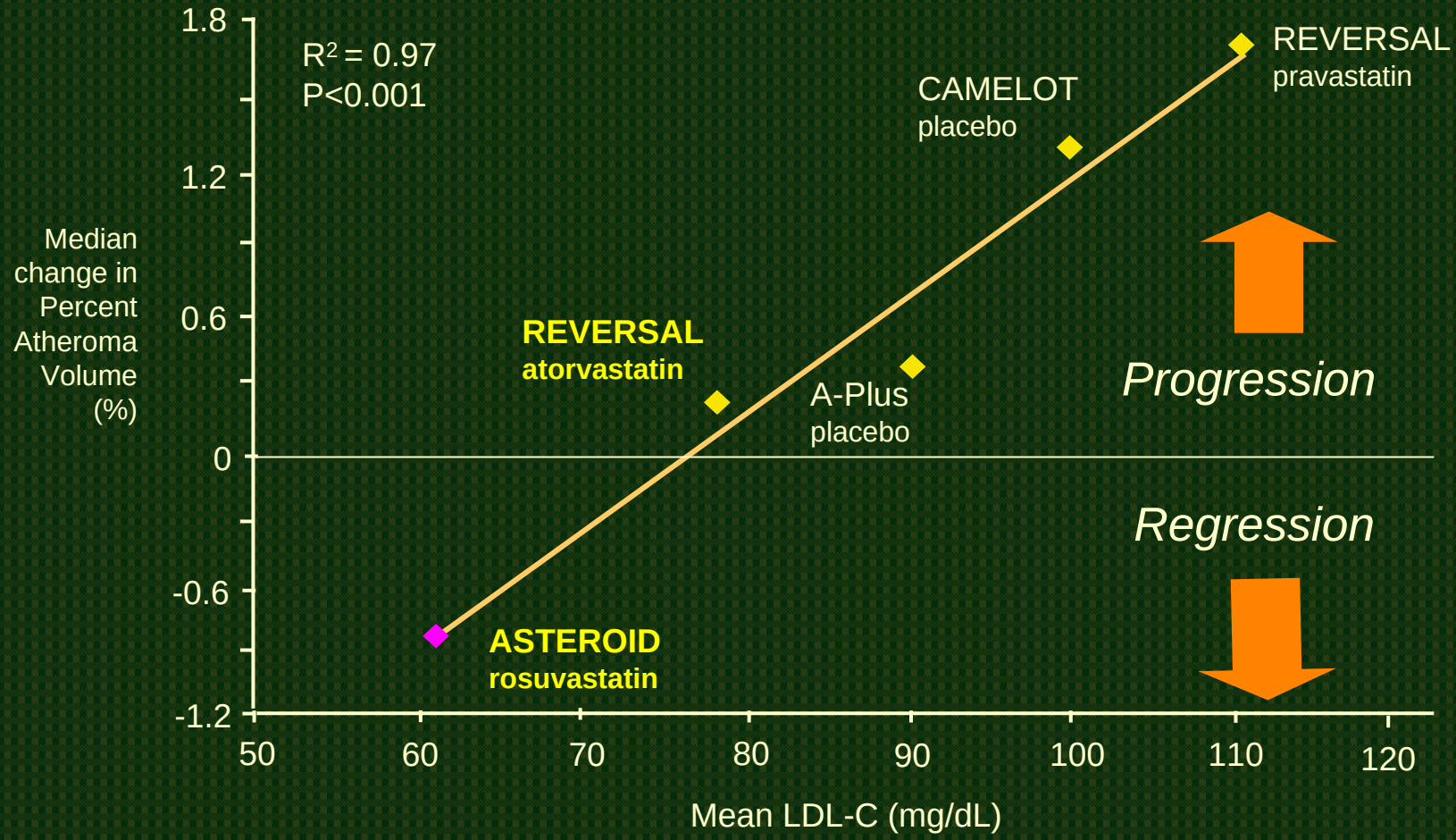


* p<0.001 for difference from baseline values. Wilcoxon signed rank test

Atherosclerosis Regression Studies

REVERSAL	ASTEROID
Atorva 80 mg/d	Rosuva 40 mg/d
For 1.6 yrs	For 2 yrs
Basal LDLc 150	130 mg/dl
LDLc down to 80	60-70 mg/dl
CRP down by 30 %	HDL up by 15 %

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

Changing Concept

Quantify the plaque mass

Qualify the plaque composition

ORION

ORION – a 2-year study

Patients (n=33)

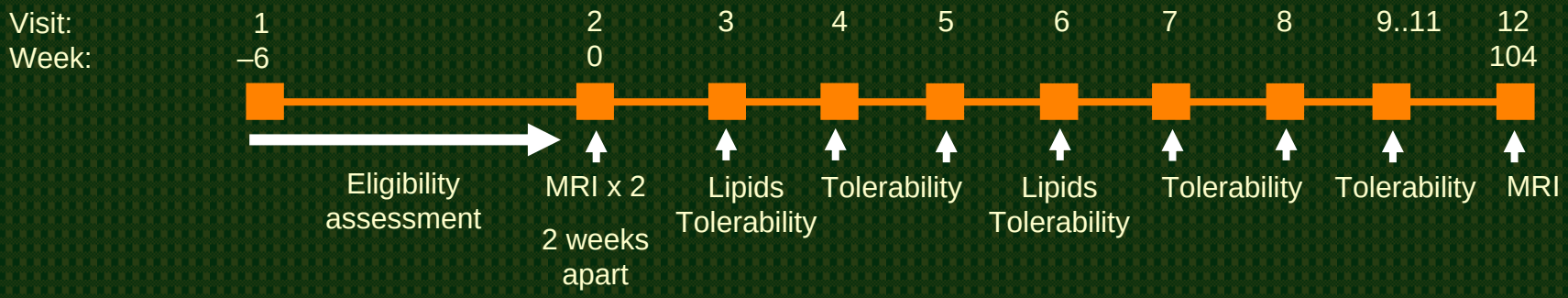
Neurologically asymptomatic

Carotid stenosis: 16-79%

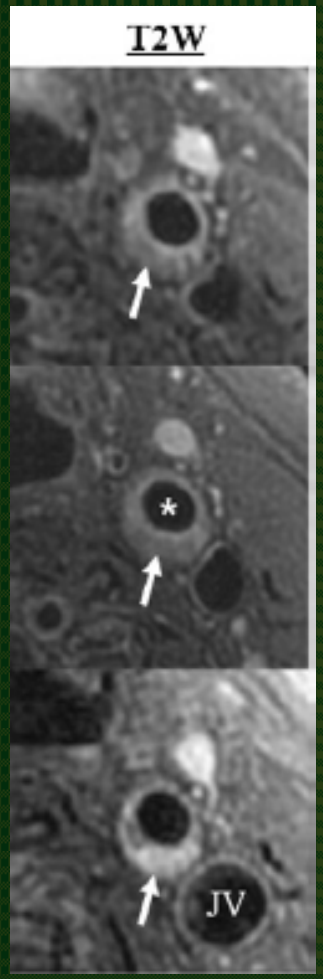
LDL; 100-250 mg/dl

TG <400 mg/dl

Rosuvastatin 40 mg or 5 mg



Changes of plaque composition



	Combined	Low-dose rosuvastatin	High-dose rosuvastatin	P*
% LRNC				
n	18	8	10	–
Baseline	10.7 ± 2.5	10.0 ± 5.3	11.3 ± 2.0	.15
End of study	8.0 ± 2.5	7.9 ± 5.2	8.1 ± 2.0	.14
Median/mean % change †	−26.7/−41.4 ± 8.1	−19.0/−46.7 ± 16.2	−19.0/−37.0 ± 7.5	.7
95% CI	−60.3 to −16.7‖	−81.5 to 16.9§	−56.8 to −10.8‖	–
P‡	.005	.1	.014	–
% Calcification				
n	14	6	8	–
Baseline	4.0 ± 1.2	4.6 ± 2.3	3.6 ± 1.3	.7
End of study	4.1 ± 1.1	3.9 ± 2.2	4.3 ± 1.1	.4
Median/mean % change †	0.7/32.4 ± 11.8	10.6/6.8 ± 21.5	16.7/56.1 ± 13.6	.5
95% CI §	−20.8 to 130.3	−68.3 to 281.5	−18.7 to 235.8	–
P‡	.3	.9	.2	–
% Fibrous tissue				
n	33	13	20	–
Baseline	92.4 ± 1.9	91.7 ± 3.9	92.9 ± 1.9	.9
End of study	93.9 ± 1.7	93.3 ± 3.6	94.2 ± 1.7	.95
Median/mean % change	0.0/1.8 ± 0.7	0.0/2.2 ± 1.0	0.0/1.6 ± 1.1	.8
95% CI ‖	0.2-5.5	−0.1 to 6.8	−1.6 to 8.3	–
P‡	.02	.1	.2	–

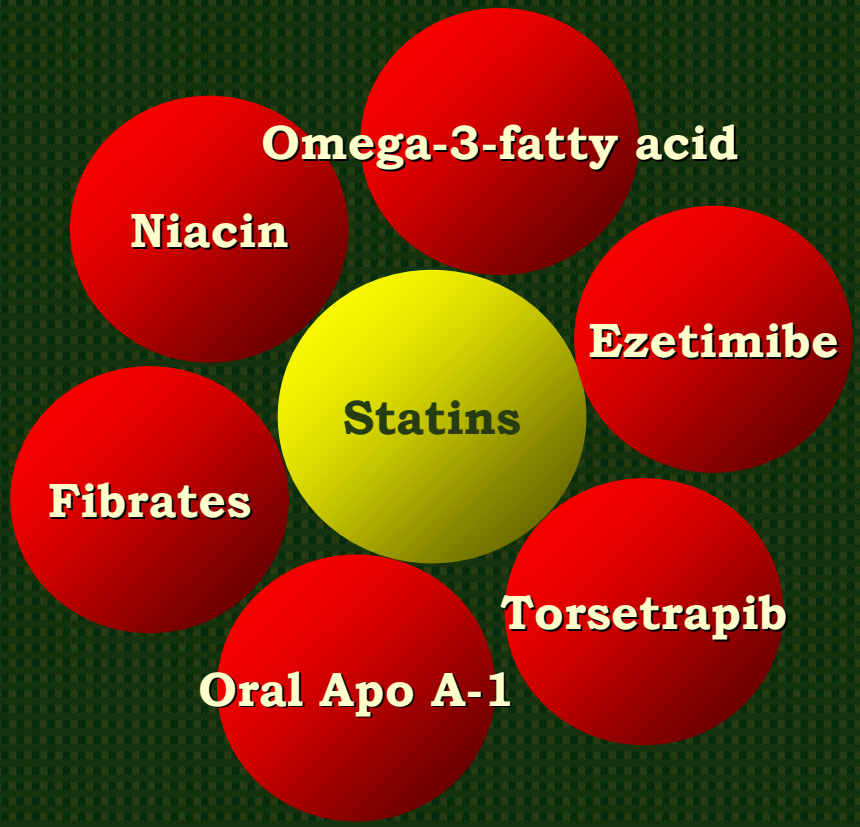
* Comparison between low- and high-dose groups.
‡ Comparison to zero of mean percent change from baseline to end of study.
† Robust percent change (SE via bootstrap).
§ 95% CI for mean percent change.
‖ 95% CI for median percent change.

Summary – statin trials

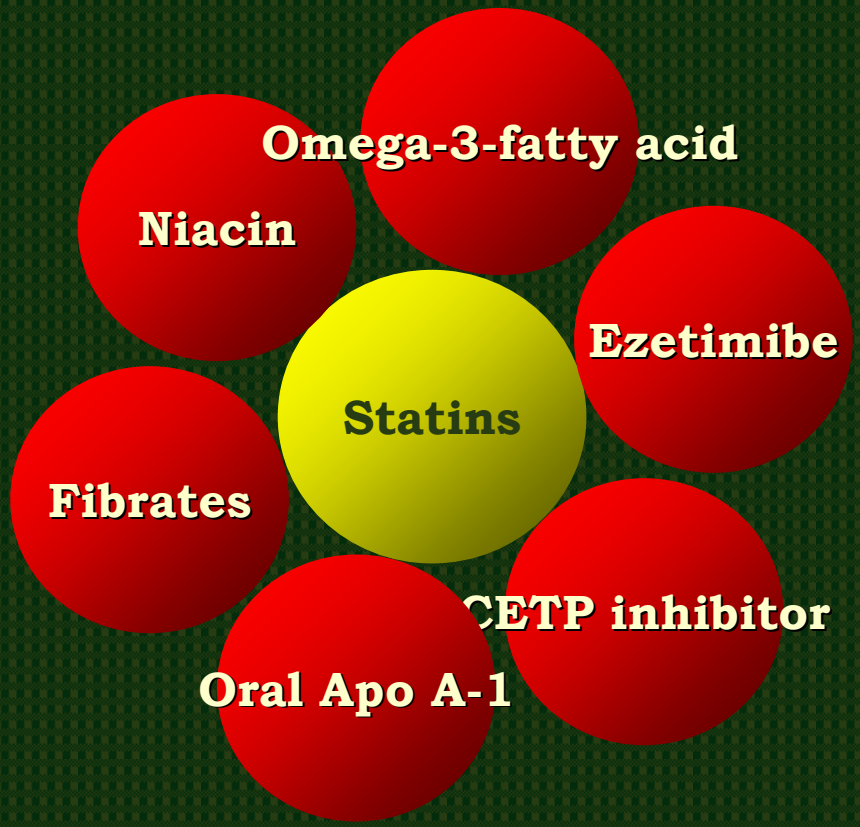
- Identification of high risk
  - Diabetes ; **CARDS, FIELD**
  - Hypertension ; **ASCOT-LLA**
  - Inflammation ; **JUPITER**
  - ESRD ? ; **AURORA**
  - CHF ? ; **CORONA**
- New classification ; 'Very' high risk
  MIRACL – PROVE-IT – TNT – IDEAL
- Statin effect in low risk
  MEGA
- Beyond prevention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

Divergence

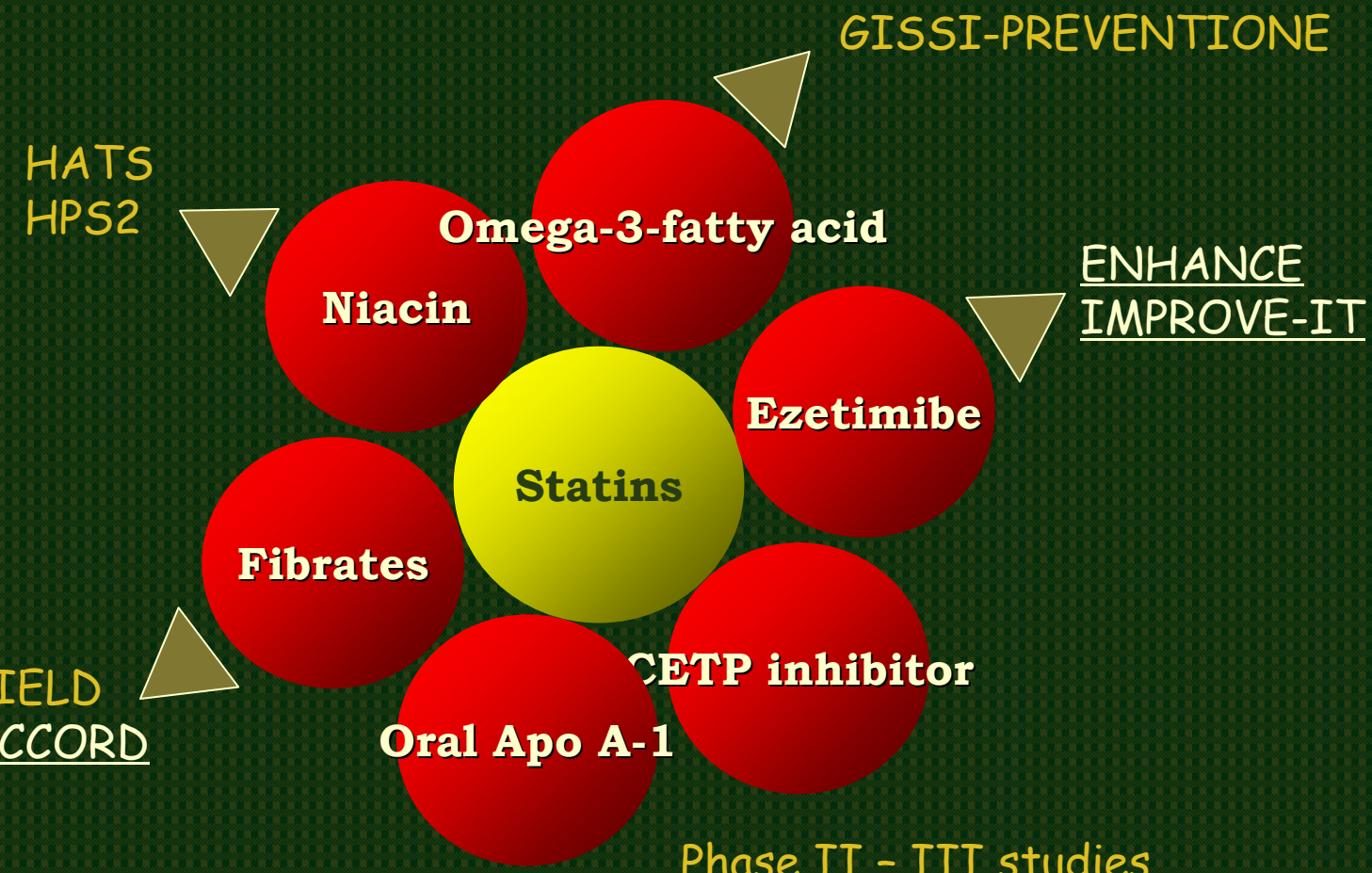
Statin is like Salt



Era of Combination



Era of Combination



Conclusion

- 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 and stabilize the atherosclerotic plaque
- More precise risk stratification is needed to find high- and very high- risk patients ; ex; Metabolic syndrome ?
- More evidence is needed to introduce combination with stain treatment in mixed dyslipidemia