

Streamlining drug development and clinical trials with biomarkers

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Anti-atherosclerotic drug development

- ◆ Failures late in drug development, withdrawals and controversies about some marketed drugs underscore the importance of assessing the effects of interventions on clinical outcomes.
- ◆ Effects of new drugs need to be assessed when added to the best standards-of-care, resulting in large and long clinical trials.
- ◆ Conducting outcomes trials for every new drug in development is not likely to be economically viable given the current costs, with potentially negative effects on translating innovations to practice.
- ◆ Rationale for selecting drugs that are moved to phase 3 may involve the judicious use of soluble and imaging biomarkers.

IVUS assessment - Atherosclerosis regression

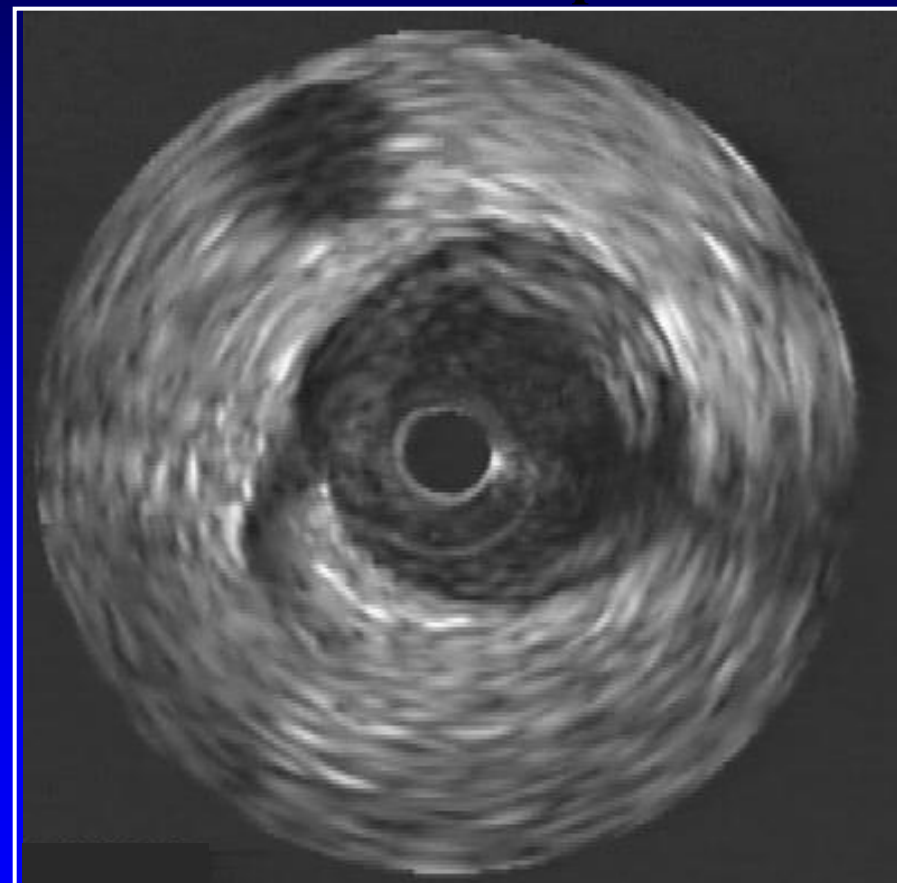
20% reduction in plaque burden

Baseline



Plaque volume (mm³): 272.9
EEM volume (mm³): 609.5

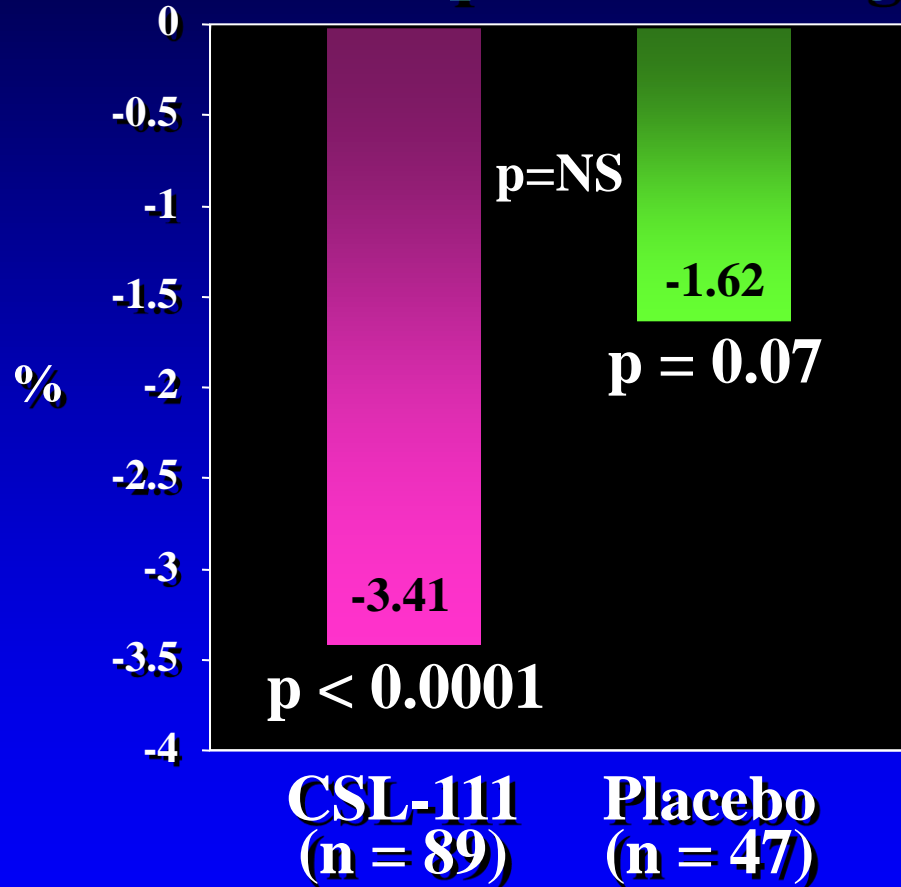
Follow-up



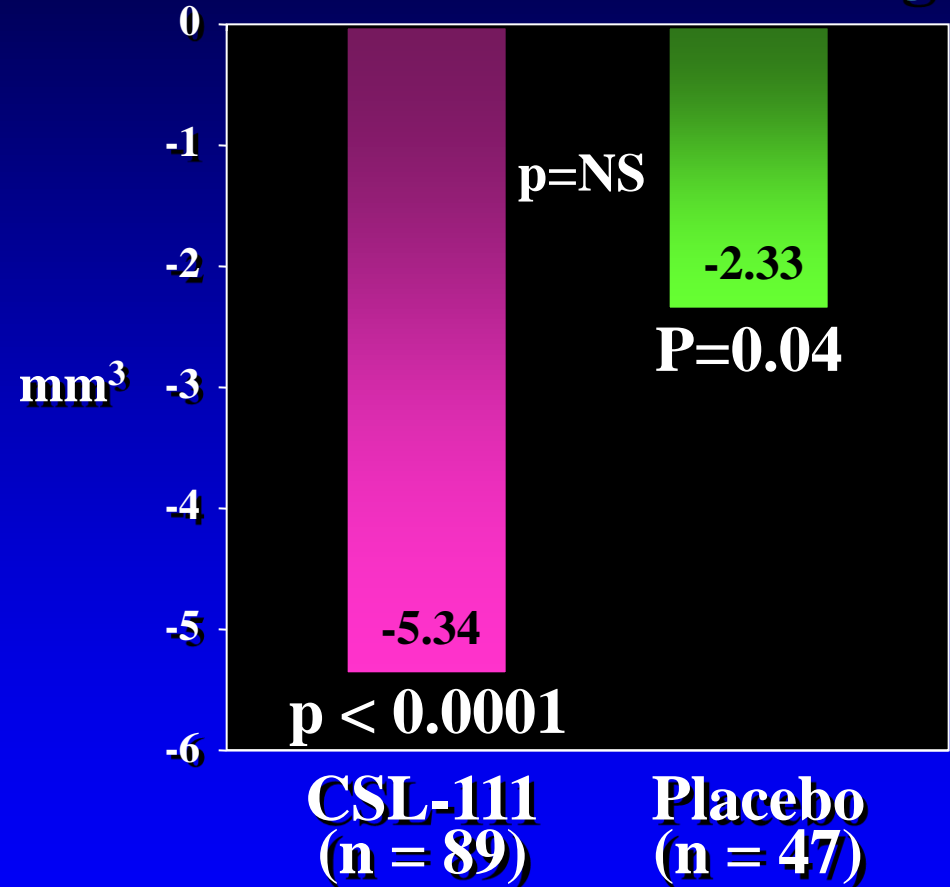
Plaque volume (mm³): 197.3
EEM volume (mm³): 445.9

Change in atheroma volume on IVUS

Median percent change



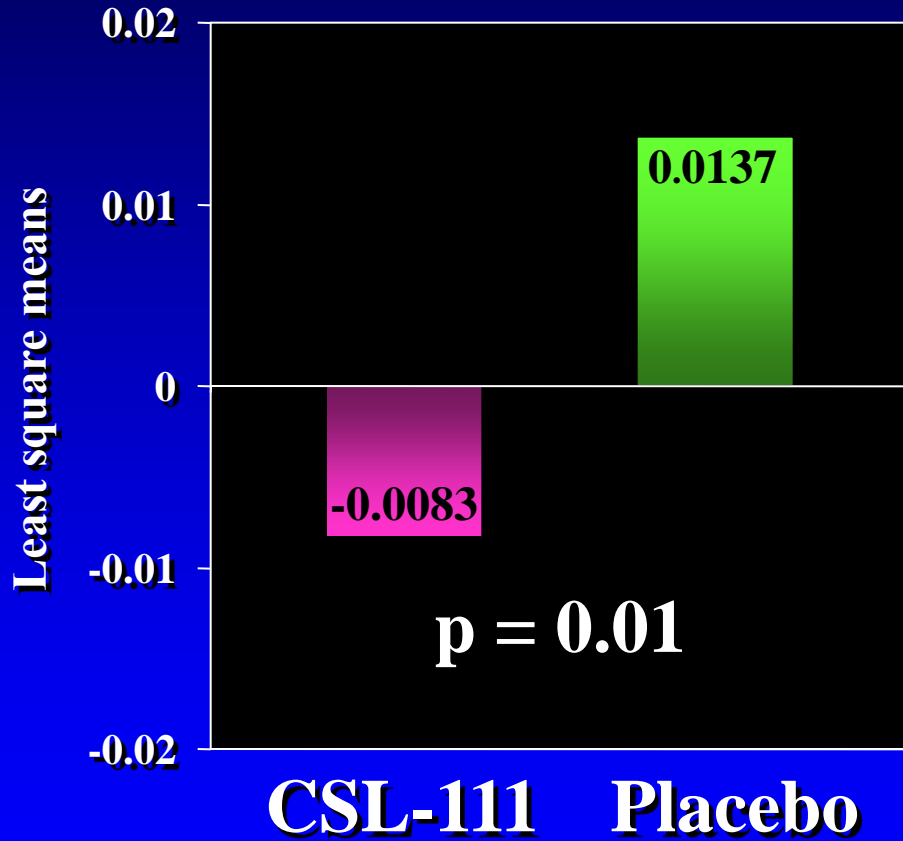
Median nominal change



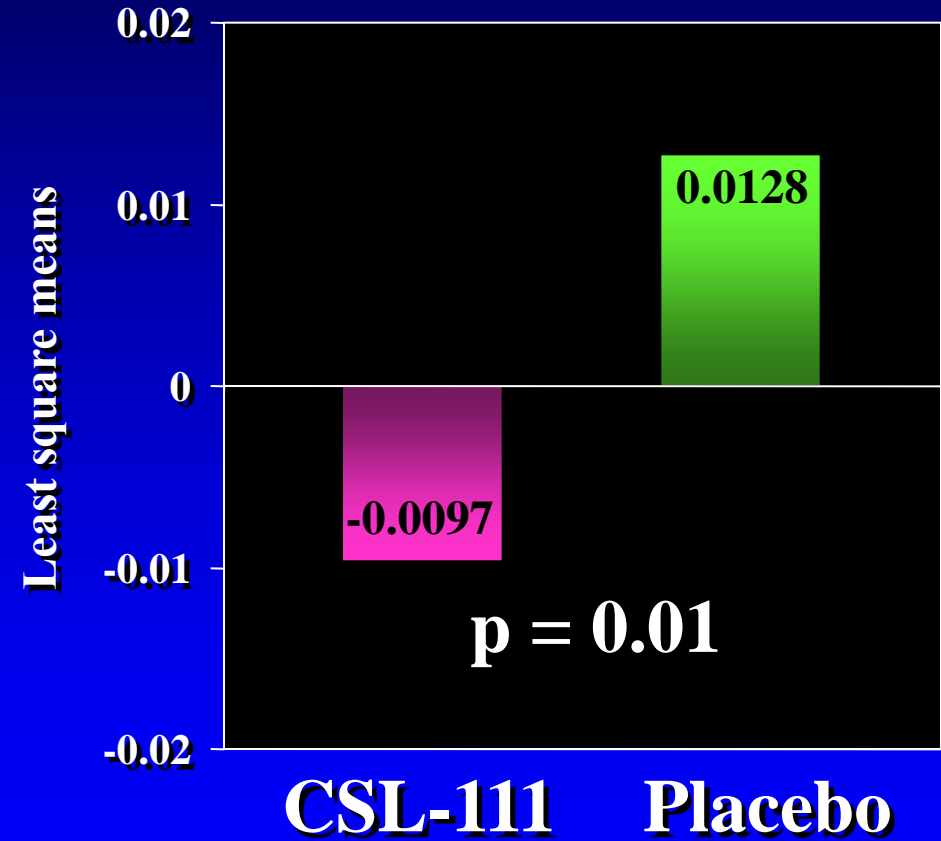
- ◆ Plaque volume at baseline: 146.0 mm³ for CSL-111, 151.4 mm³ for placebo
- ◆ Interval between IVUS examinations : 43 ± 6 days in both groups

Changes in plaque characterization indexes

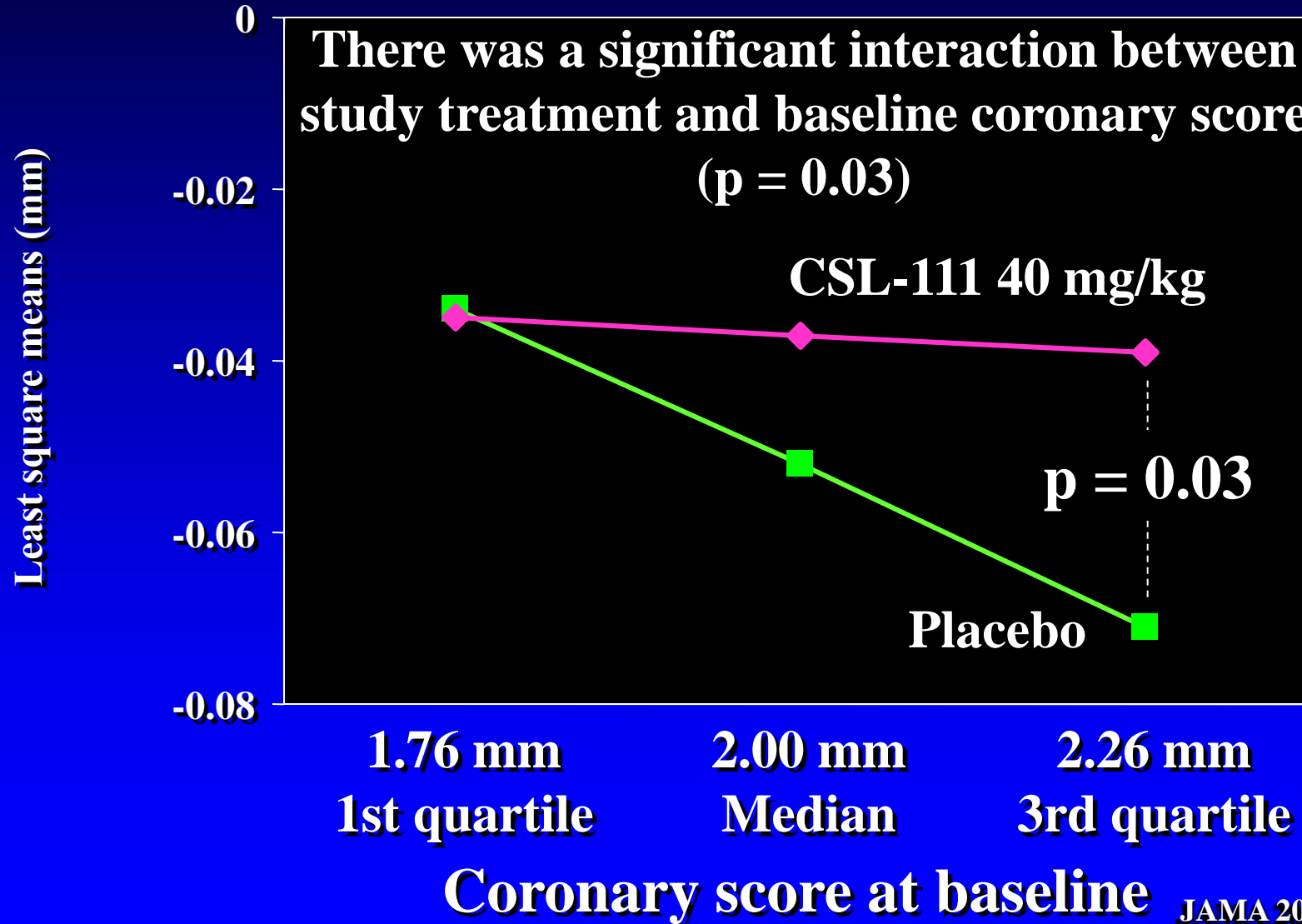
Arc index



Inner perimeter index

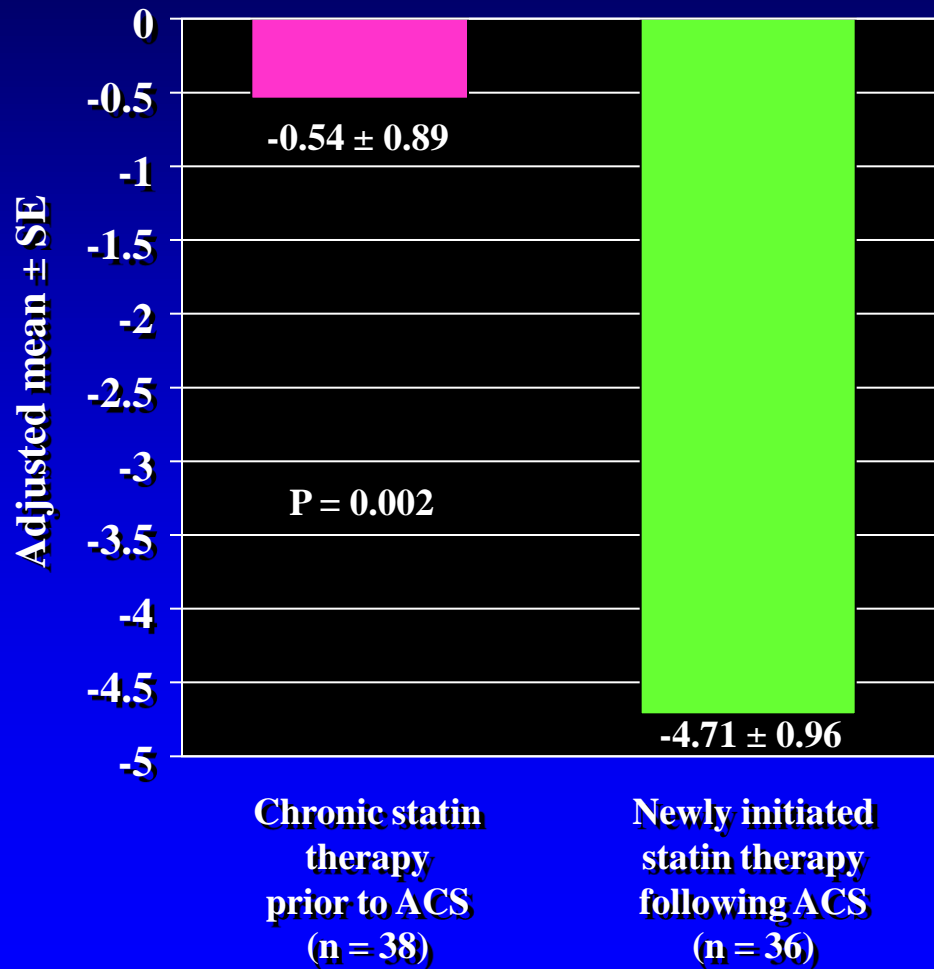


Changes in coronary score on QCA

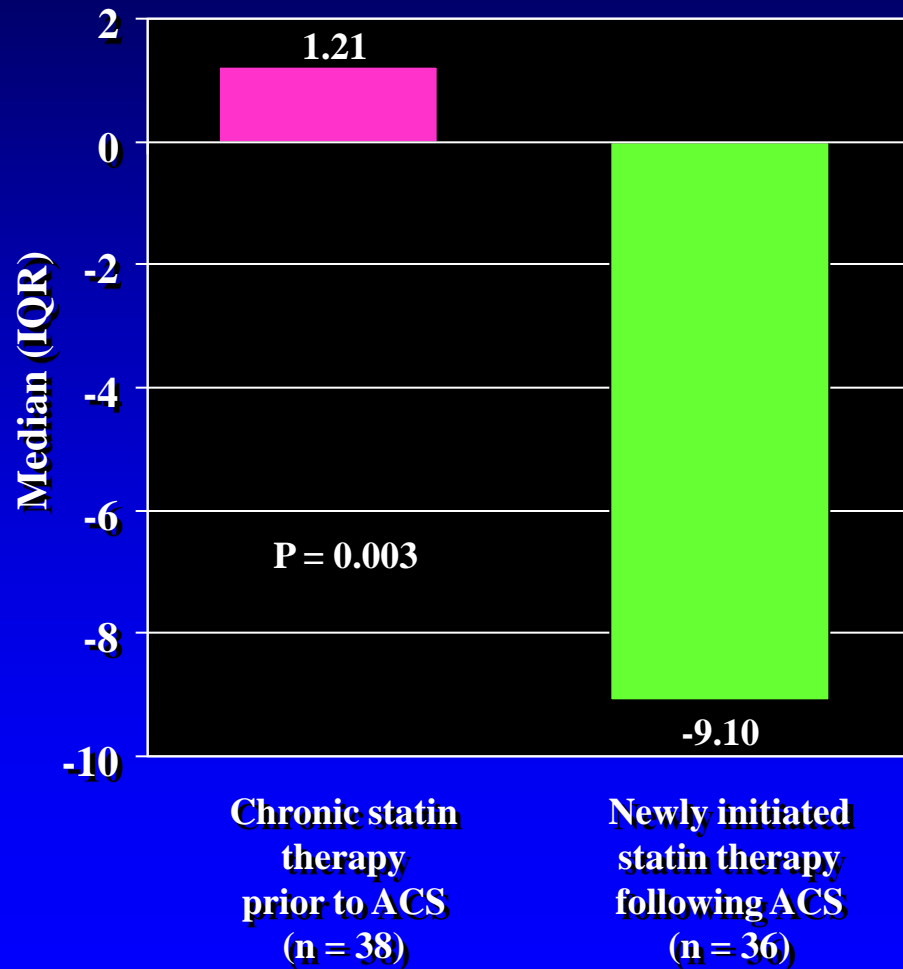


Change in atheroma volume in 6 weeks in statin-naïve patients

Relative change



Nominal change



Canadian Atherosclerosis Imaging Network

CAIN – one imaging network for one entire country

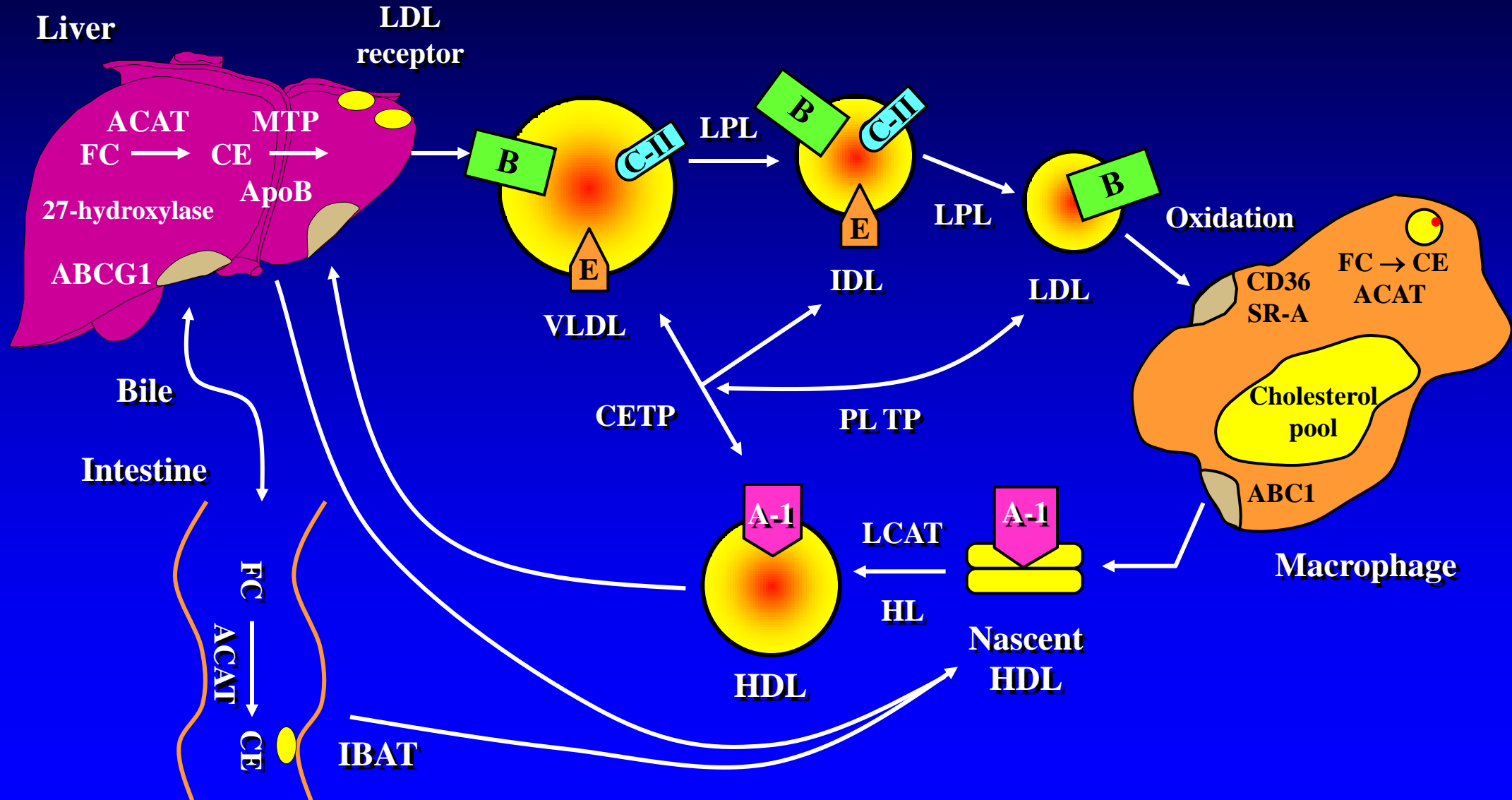
- ◆ **Imaging Core Analysis Laboratories (vascular)**
 - ◆ **IVUS, 3-D US, QCA, MDCT, MRI, PET/CT, SPECT**
- ◆ **Imaging Core Analysis Laboratories (end-organ)**
- ◆ **Network of 45 recruiting sites**
- ◆ **Data coordinating center (MHICC)**
- ◆ **Genetic, pharmacogenomic and biomarker biobanks**
- ◆ **Proteomic and metabolomic analyses**
- ◆ **Tissue samples**

Canadian Atherosclerosis Imaging Network

Clinical Translation and Practice

- ◆ **Correlation of coronary and carotid atherosclerosis and their changes over time and links with clinical outcomes**
 - ◆ **2000 patients undergoing coronary angiography, IVUS (with virtual histology) and carotid ultrasound (IMT and plaques) at baseline and 24 months**
 - ◆ **5-year follow-up for cardiovascular/cerebrovascular events**
 - ◆ **NIRS, PET/CT, MRI and microvascular substudies**
 - ◆ **Genomic (including miRNAs) and biomarker biobanks**
 - ◆ **Proteomic and metabolomic analyses**
- ◆ **Application of this knowledge and framework in randomized clinical trials of novel anti-atherosclerotic agents**

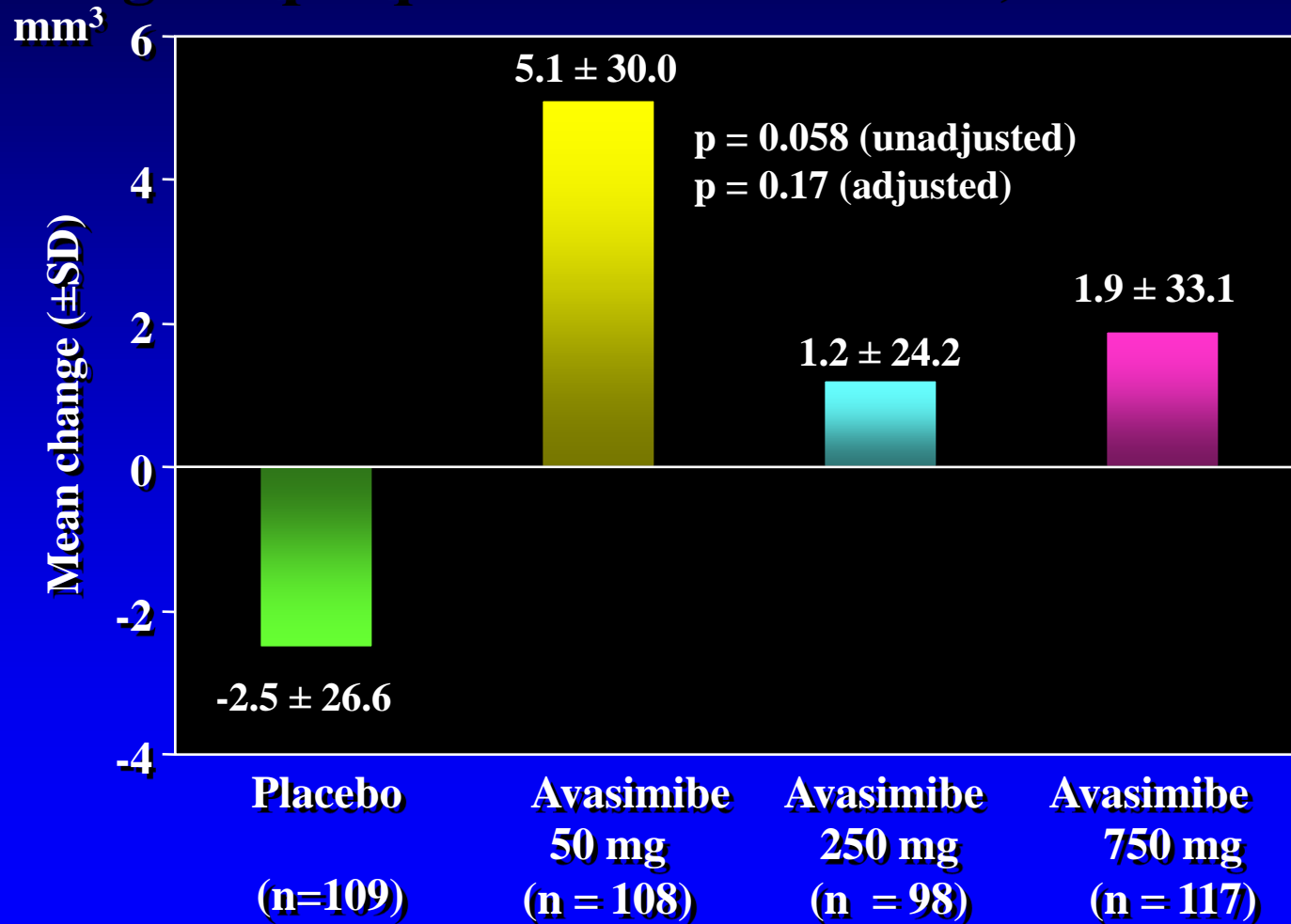
Lipoprotein metabolism



Biomarkers to stop development of NCE early in drug development

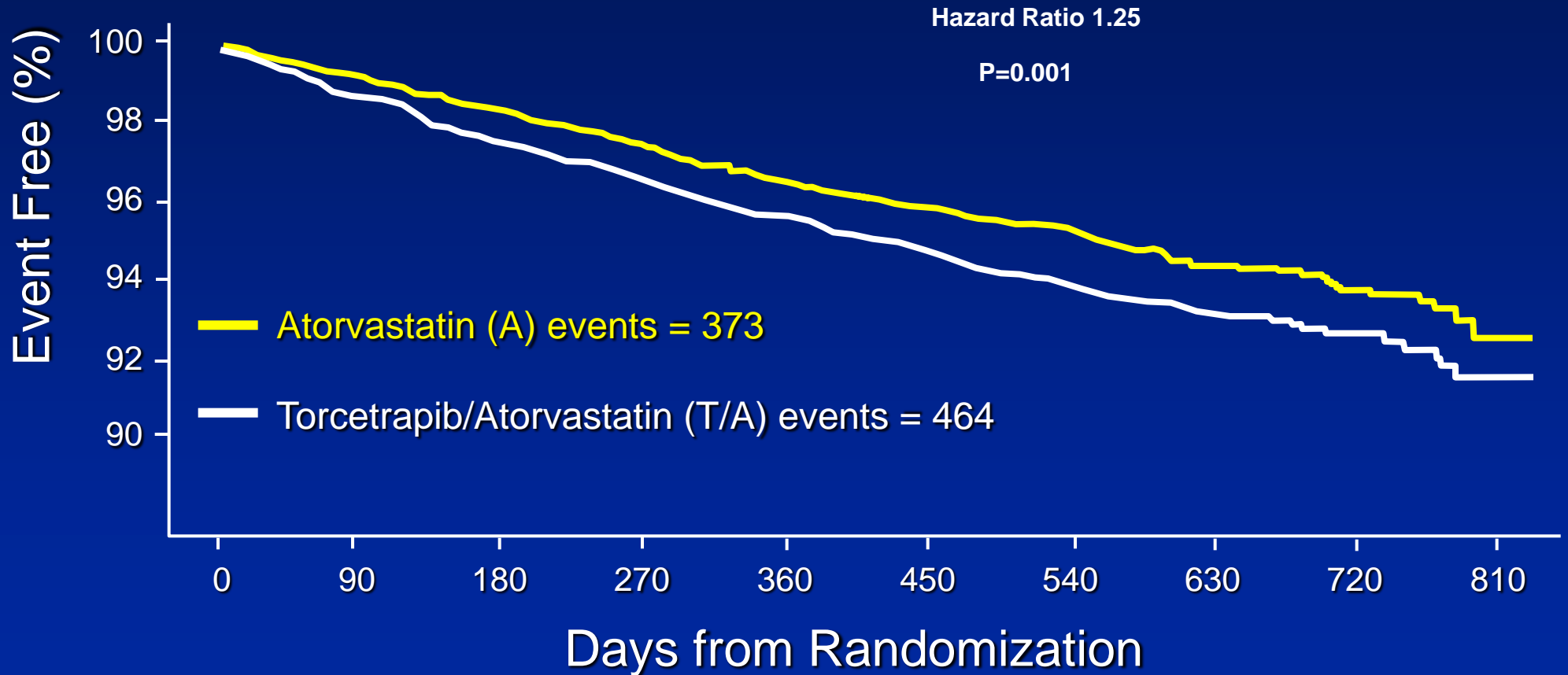
A+

Change in plaque volume on IVUS, 30-mm segment



ILLUMINATE - Primary Endpoint

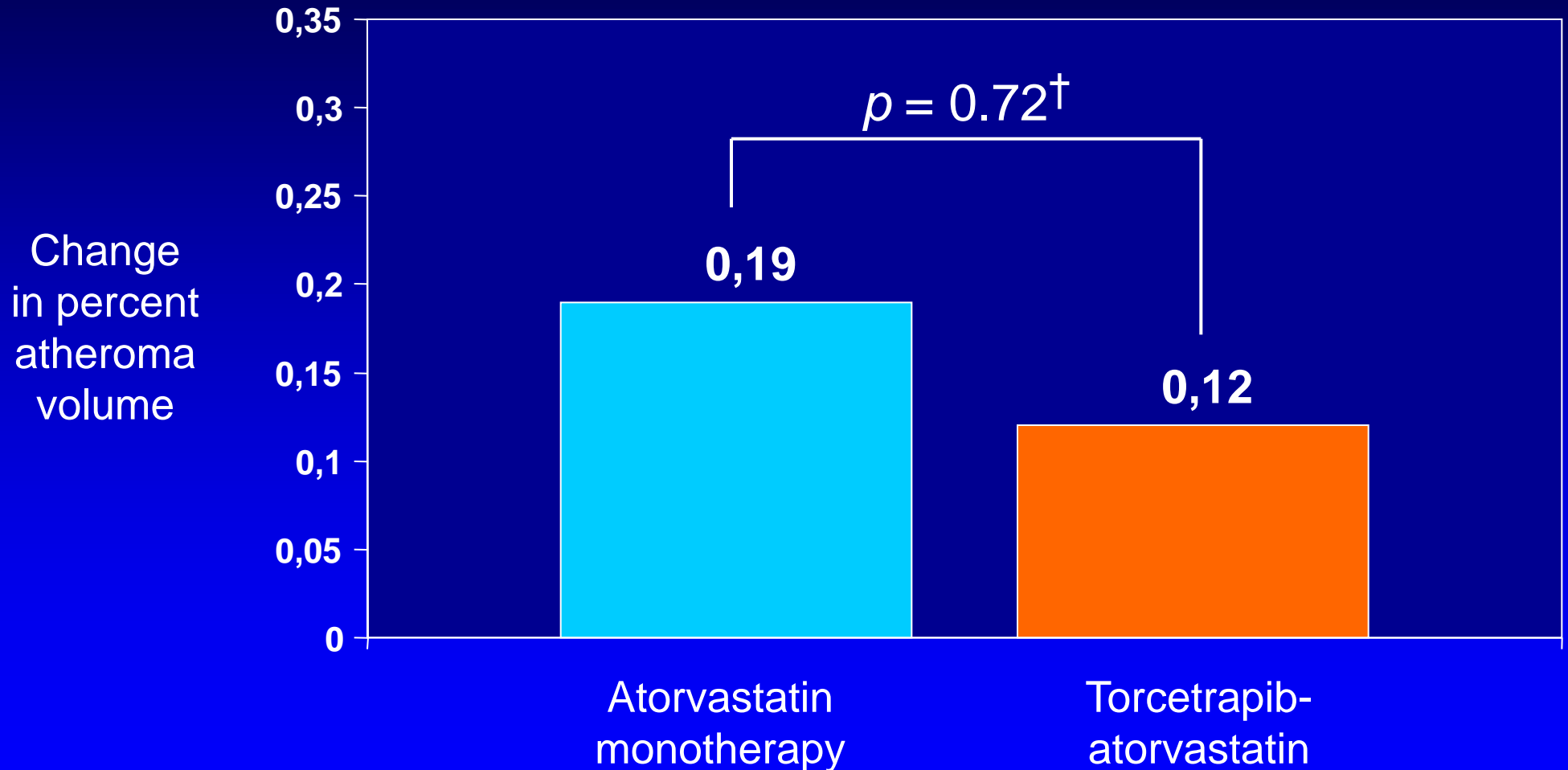
Time to First MCVE*: Kaplan-Meier Plot



*Major cardiovascular event: CHD death, non-fatal MI, stroke or hospitalization for unstable angina

ILLUSTRATE – Primary endpoint

Change in Percent Atheroma Volume



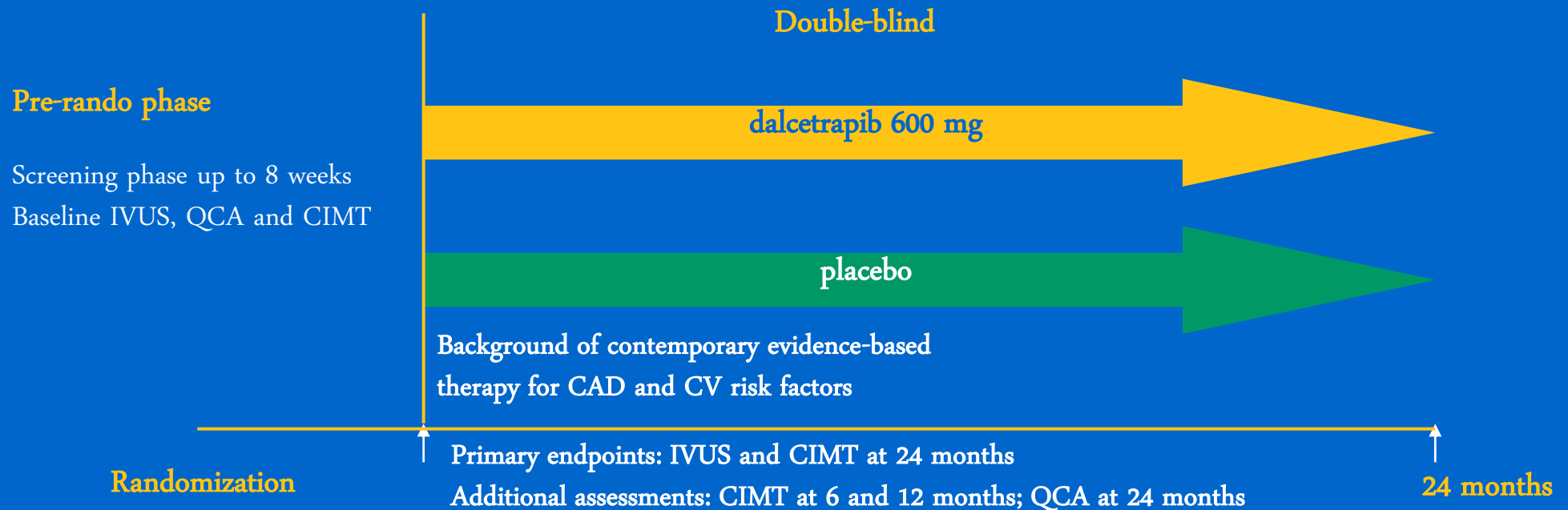
*LS Mean change

[†] p value from ANCOVA

Nissen, Tardif, et al. N Engl J Med 2007; 356:1304-16

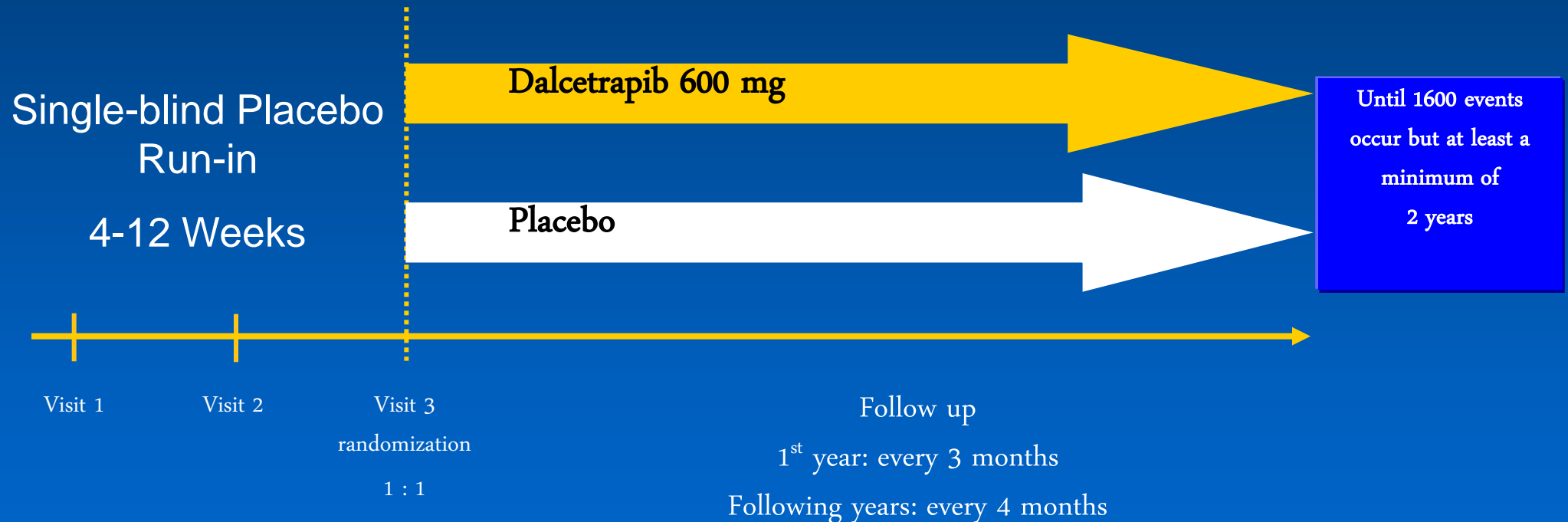
dal-PLAQUE-2: Study Design

- **Objective:** to assess the effect of dalcetrapib *versus* placebo on atherosclerotic disease progression in patients with CAD
- A double-blind, randomized, placebo-controlled, parallel-group multicenter study in 900 patients with CAD

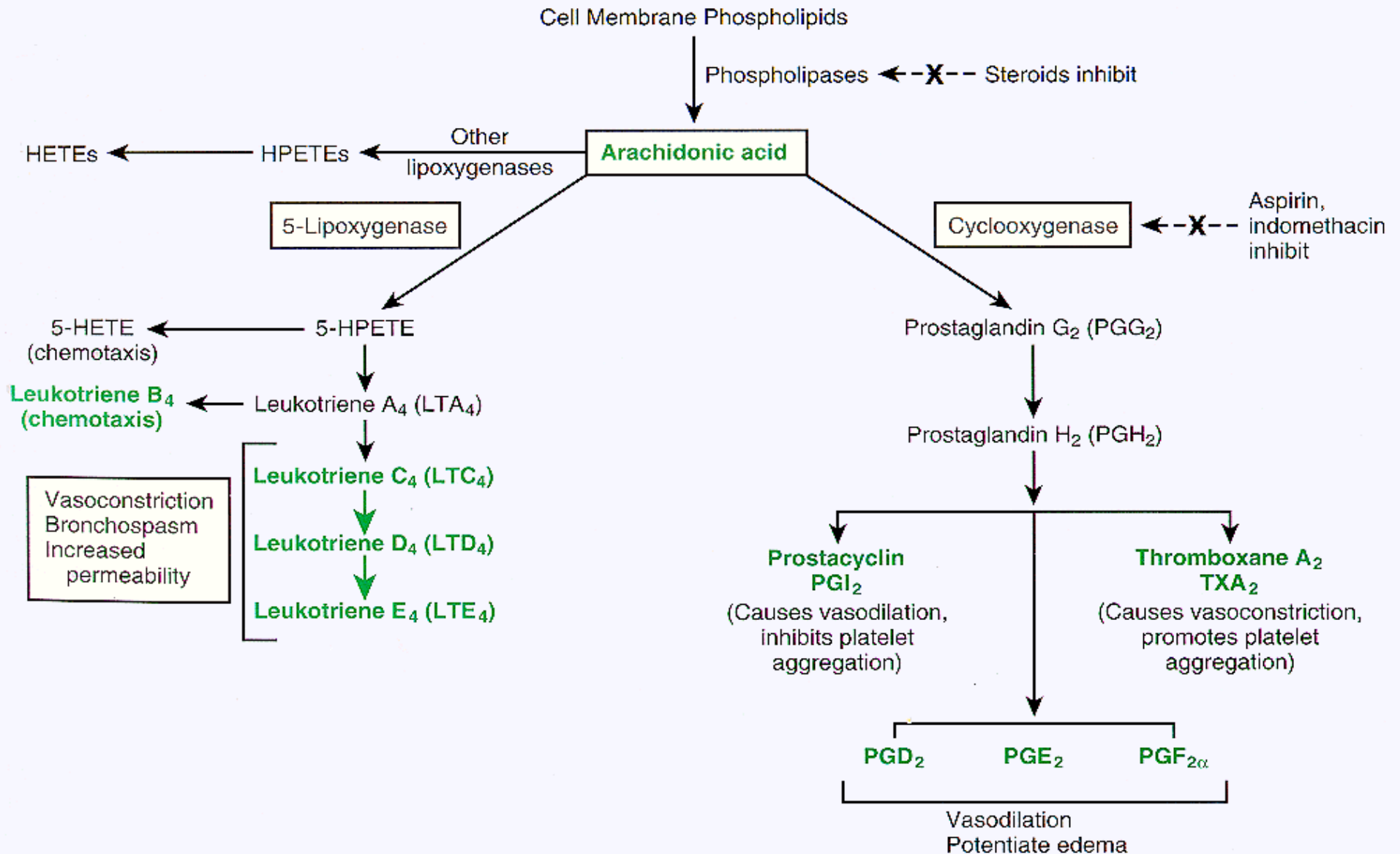


Vital importance of developing and validating biomarkers of HDL composition and cholesterol efflux

DAL-OUTCOMES Study Design (n=15,600)



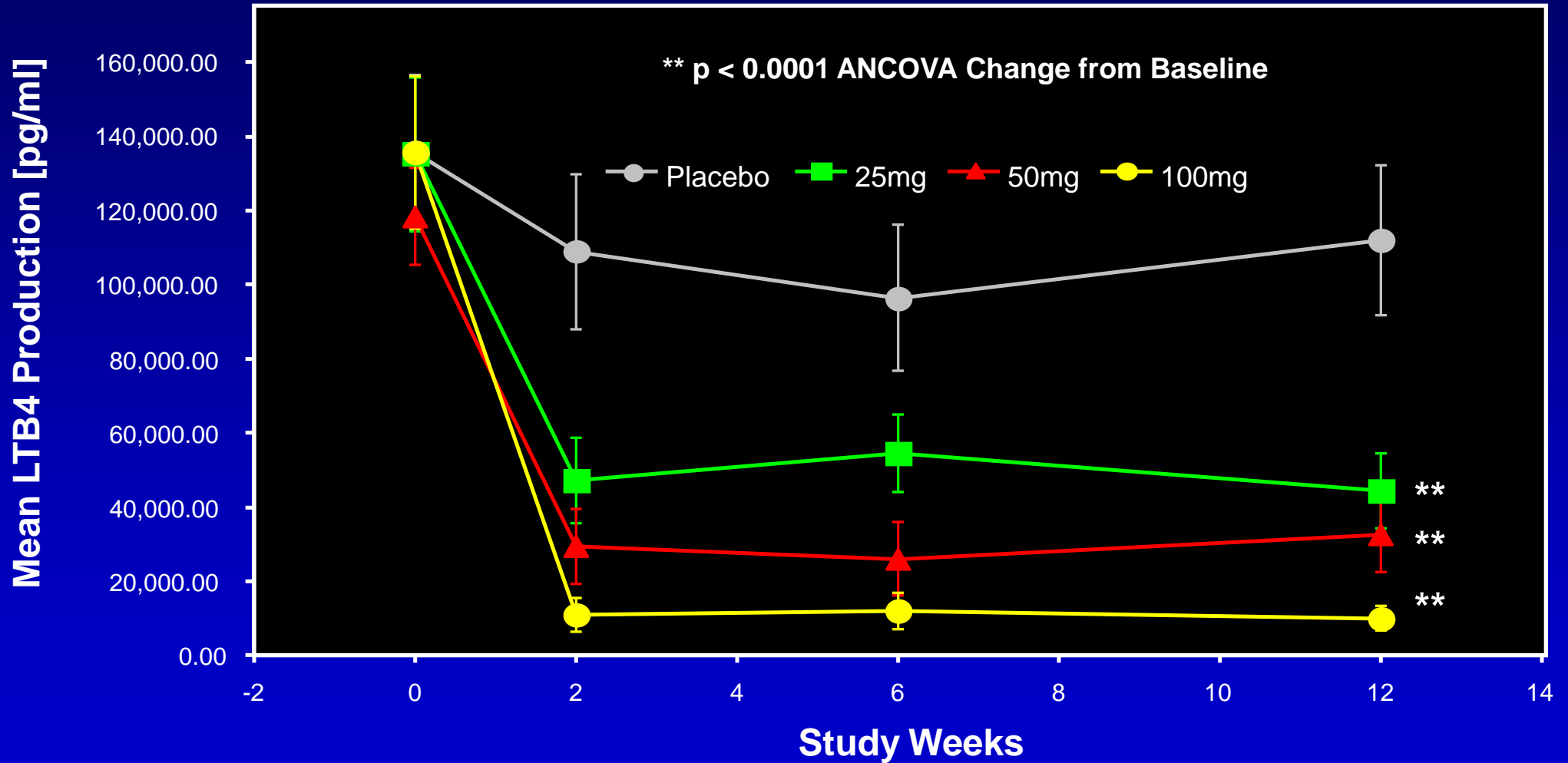
5-LO as a potential therapeutic CV target



Vascular Inflammation, Leukotrienes and 5-LO

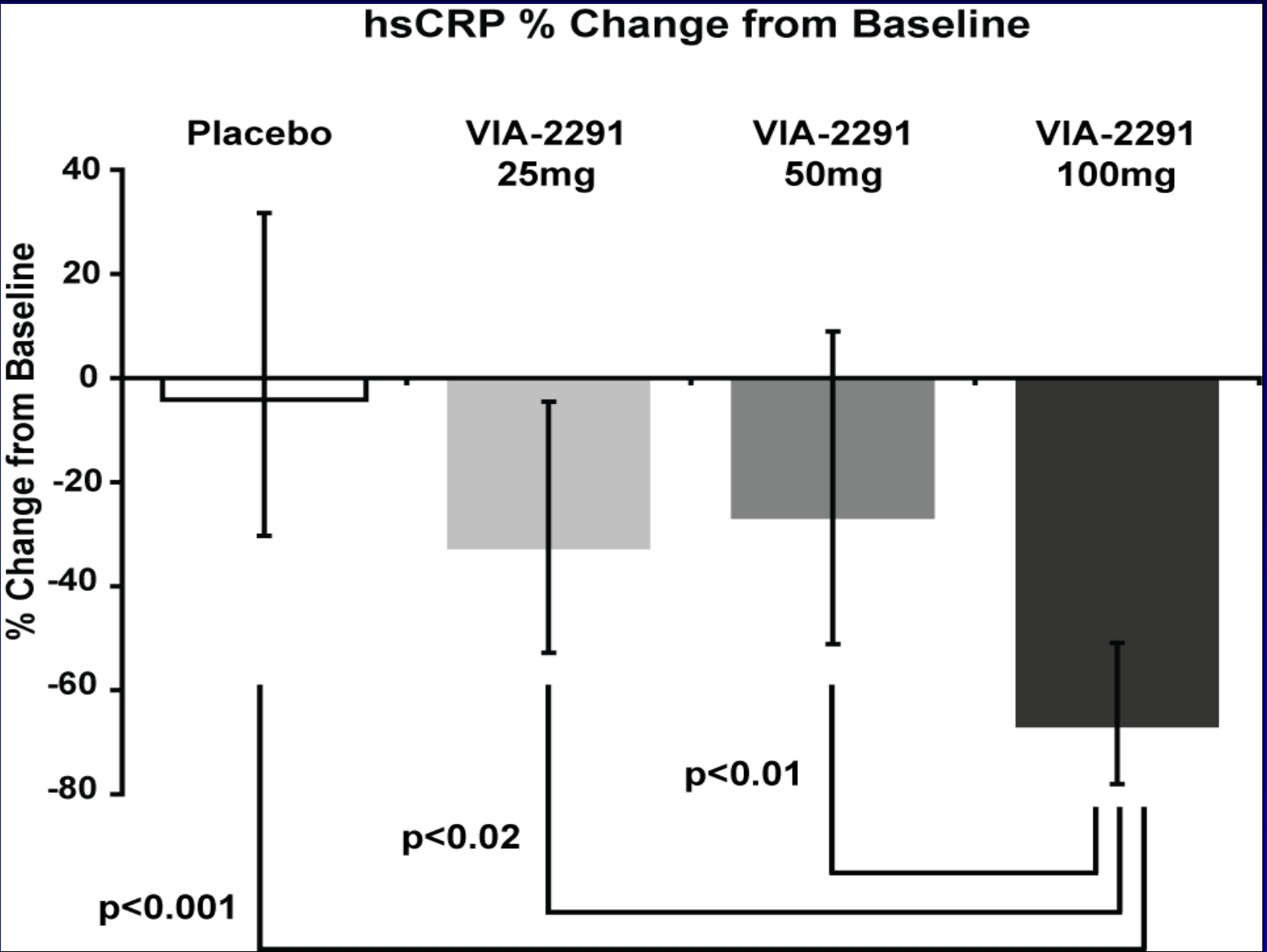
- Vascular inflammation is involved in atherosclerosis and CV events
- 5-lipoxygenase as a target in atherosclerosis
 - 5-LO is the rate-limiting enzyme in leukotriene production
 - Leukotrienes recruit/activate inflammatory cells in unstable plaques
 - Human genetic data, expression in diseased vessels, animal models
- VIA-2291 is a second generation 5-lipoxygenase inhibitor
 - Extensive clinical experience – more than 1100 patients in 29 trials in asthma with proven efficacy and extensive safety database

VIA-2291 Decreases ex Vivo Whole Blood LTB4 Production from Baseline through Week 12



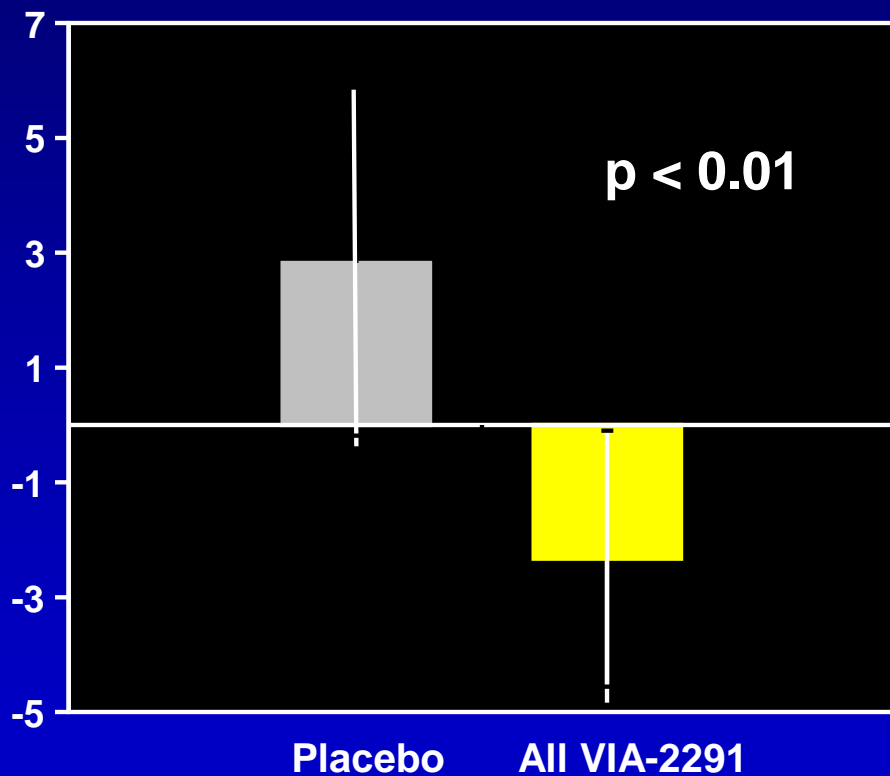
Error Bars represent 95% CI

Significant Decrease in hs-CRP in VIA-2291 100 mg Group versus Placebo at 24 Weeks

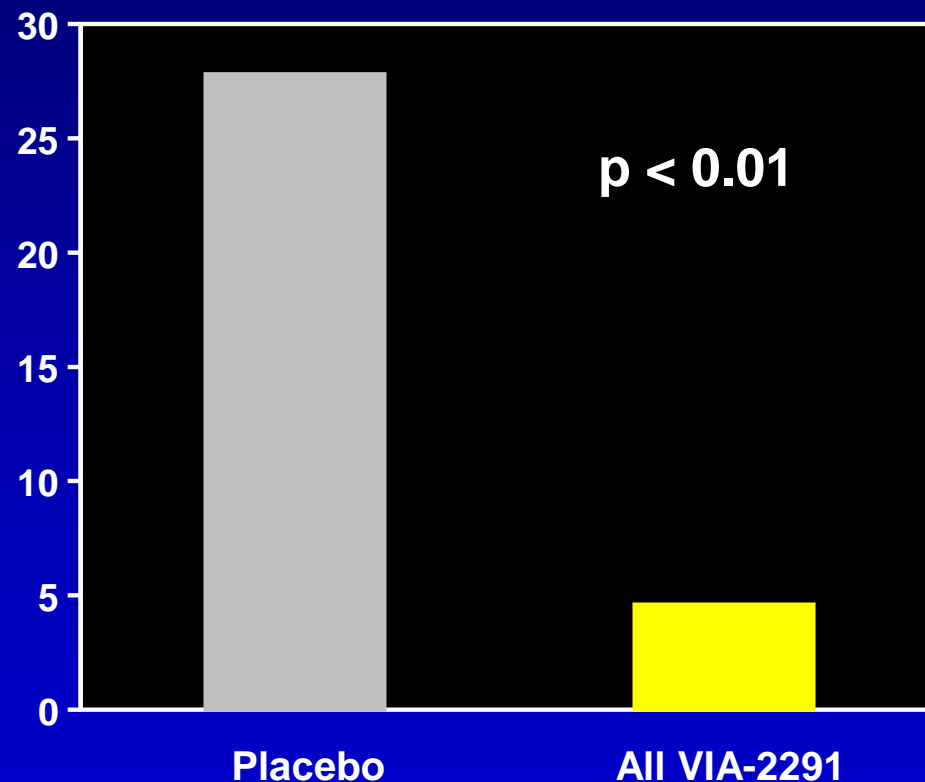


Change in non-calcified plaque volume and patients with new plaque lesions on serial coronary CT scans in the VIA-2291 groups versus placebo at 24 Weeks

Plaque volume (mm³)



Pts with new plaques (%)



Streamlining drug development and clinical trials

- ◆ **Can involve the judicious use of circulating and imaging biomarkers in phase 2, based on pathophysiology and expected drug effects.**
- ◆ **Biomarkers can be used to stop early the development of a NCE, move forward with greater confidence to phase 3, and/or enrich study population with more responsive or higher risk patients.**
- ◆ **Will benefit from collaborations between industry, regulatory agencies and academia.**