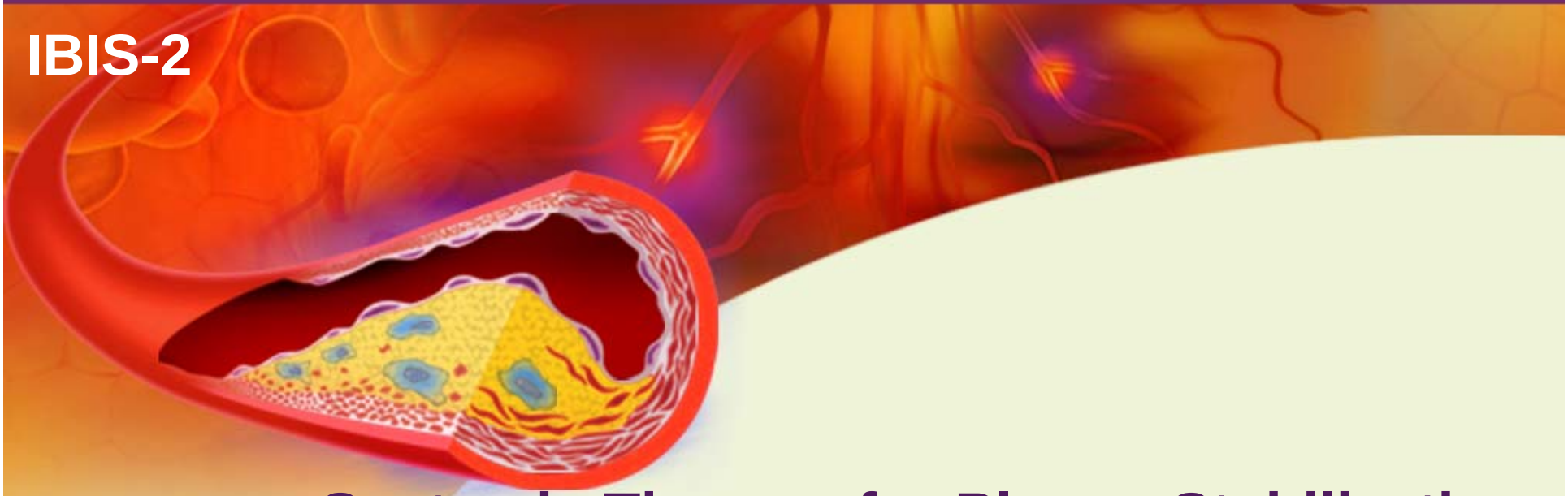
IBIS-2



Systemic Therapy for Plaque Stabilization: New Drugs Targeting LP-PLA2

Patrick W. Serruys, MD, PhD

on behalf of the IBIS-2 study investigators

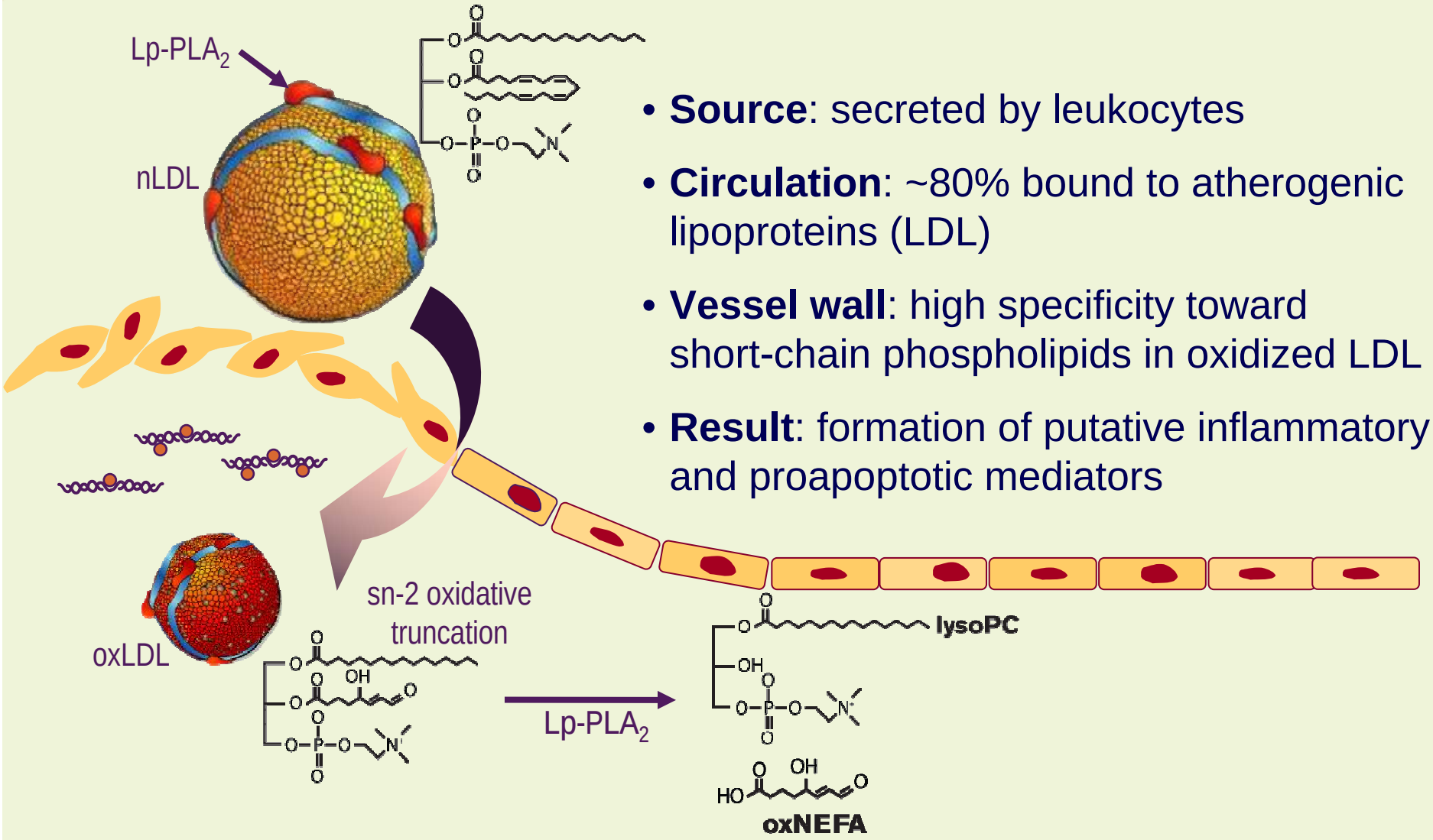
13:30-13:45, April 22, Symposium Arena, Level 3

Asian Pacific TCT

No conflict of interest to declare

Background and Rationale

targeting Lp-PLA$_2$ a key player in atherosclerosis

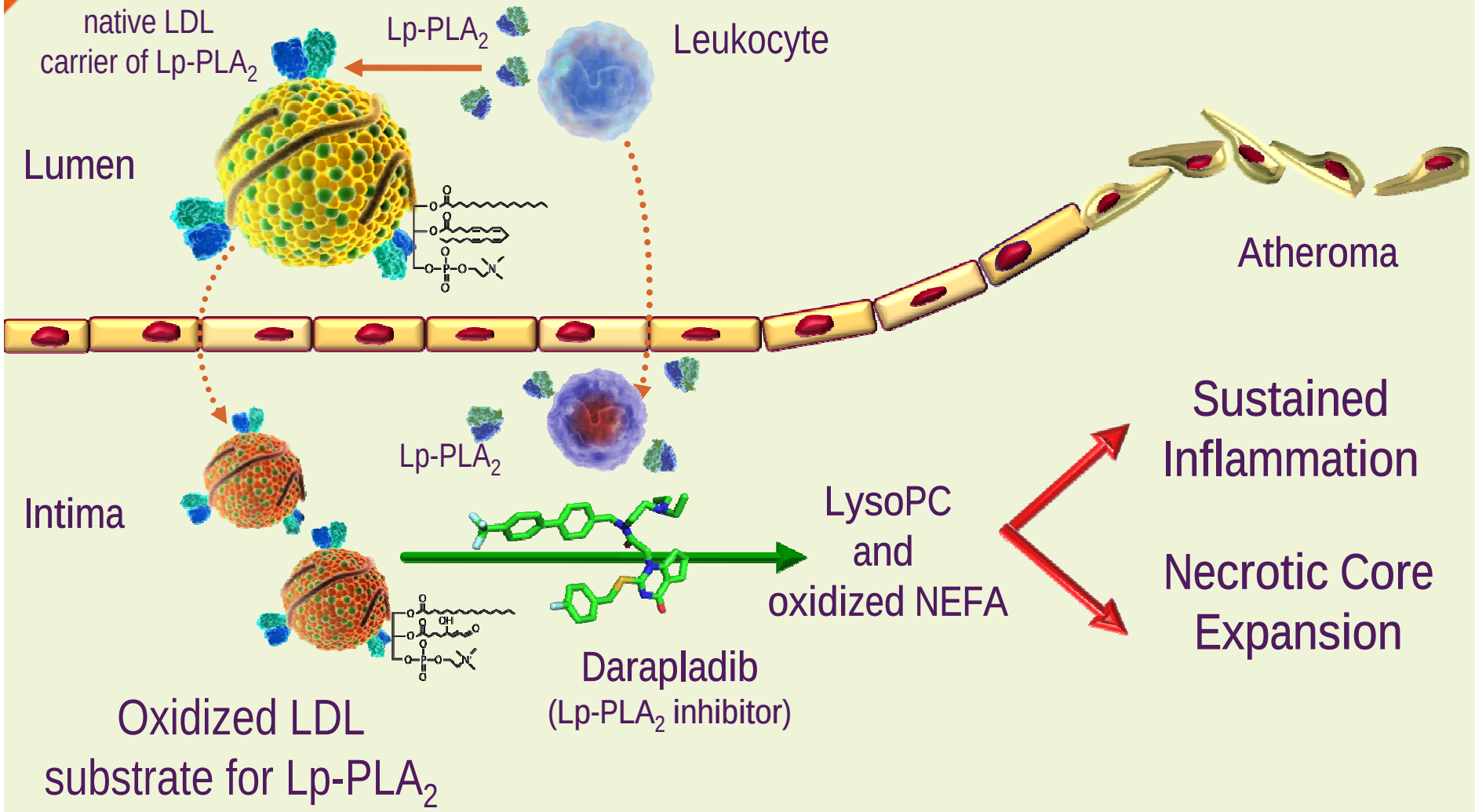


- **Source**: secreted by leukocytes
- **Circulation**: ~80% bound to atherogenic lipoproteins (LDL)
- **Vessel wall**: high specificity toward short-chain phospholipids in oxidized LDL
- **Result**: formation of putative inflammatory and proapoptotic mediators

IBIS-2

Background and Rationale

targeting Lp-PLA$_2$ a key player in atherosclerosis



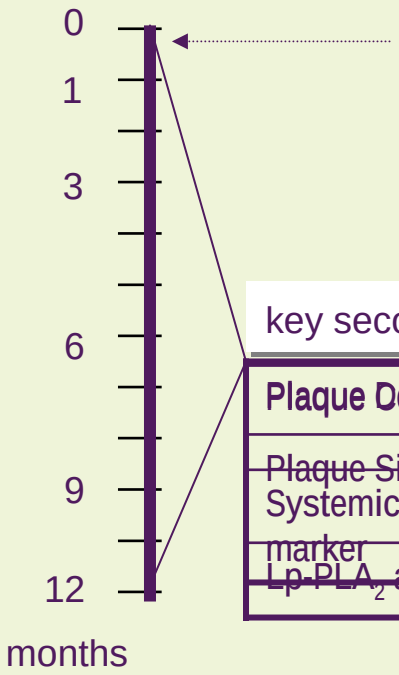
IBIS-2

Study Design and Endpoints

PATIENTS: **Acute Coronary Syndrome (ACS)** or **Chronic CAD (n=330)**

IVUS IMAGING
non-intervened segment

Randomization (1:1)
PLACEBO vs. DARAPLADIB 160 mg
stratification by ACS status



key secondary endpoints

Plaque Composition	IVUS-VH: Thin-cap fibroatheroma volume (mm³)
Plaque Deformability	IVUS-Palpography: Density of high strain
Plaque Size	IVUS-Grey Scale: Atheroma volume (mm³)
Systemic inflammatory marker	hs-CRP
Lp-PLA$_2$ activity	Percent atheroma volume (%)
	Target-related effect in plasma

IVUS IMAGING
non-intervened segment

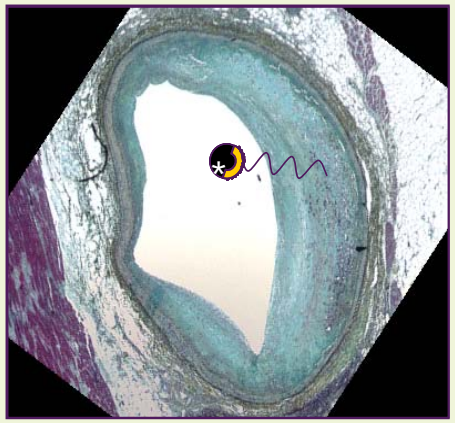
Sample size determined using an estimation approach (due to unknown effects of Lp-PLA$_2$ inhibition on novel imaging endpoints) accounting for SD of changes in IVUS-palpography from the IBIS-1pilot study

IBIS-2

IBIS-2 Imaging Methodology

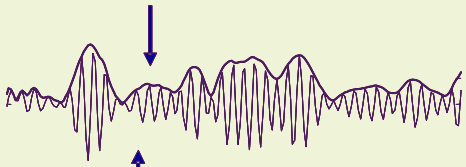
Imaging beyond measurement of plaque size

1

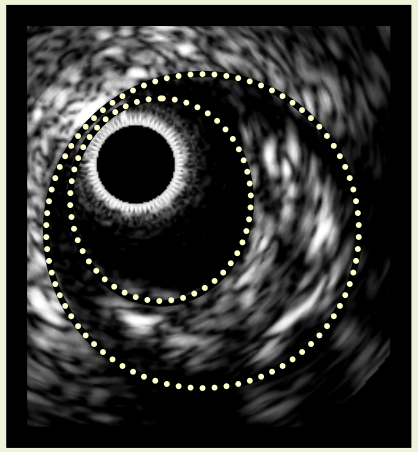


Only the amplitude (echo intensity)
is used to construct the IVUS - greyscale image

2



Frequency (beneath the amplitude)
of echo signal can vary
depending on tissue content

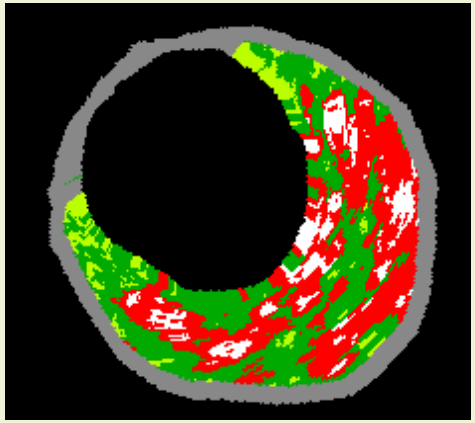


3

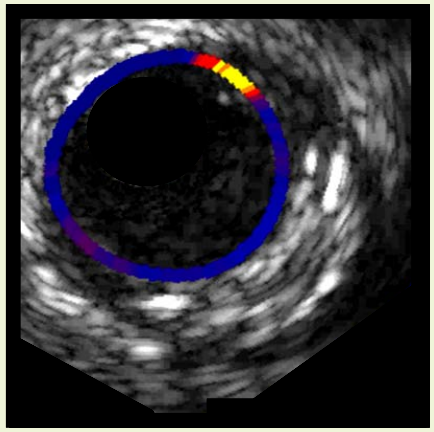
IVUS- Virtual Histology

IVUS- Palpography

4



5



- Necrotic Core
- Dense Calcium
- Fibro-fatty
- Fibrous

High

STRAIN

Low

IBIS-2

Baseline Characteristics
Safety Population

	Placebo n=151	Darapladib n=172
Demographics		
Age: mean (SD)	57 (11)	59 (10)
Gender: male (%)	83	81
Risk Factors (%)		
Diabetes	15	13
Hypertension	59	67
Hypercholesterolemia	63	63
HDL (<40 mg/dL)	26	26
Current smoker	38	37
Index hospitalization (%)		
ACS	49	51
PCI	81	76
Medications (%)		
Any anti-platelet therapy	>99	99
Statins	89	91
ACE inhibitors or ARBs	58	59
Beta-blockers	79	80

IBIS-2

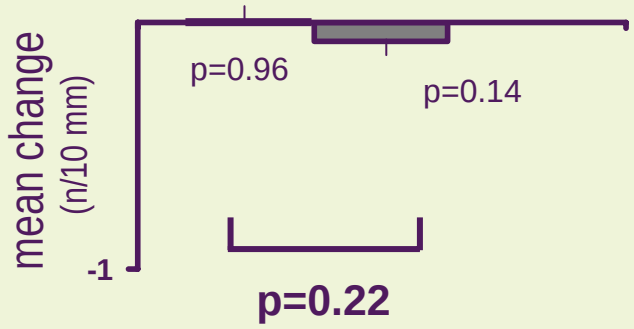
Plaque Deformability

by IVUS - Palpography

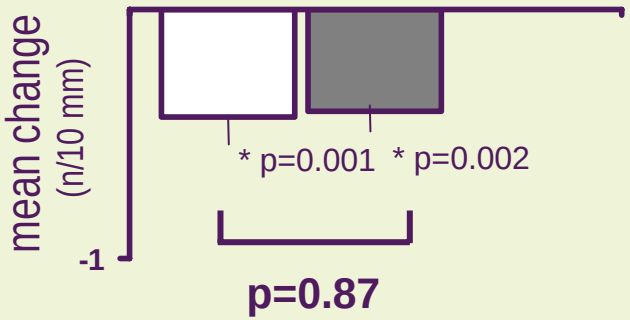
change from baseline in high strain density

entire region of interest [mean 49 mm]

co-primary endpoint



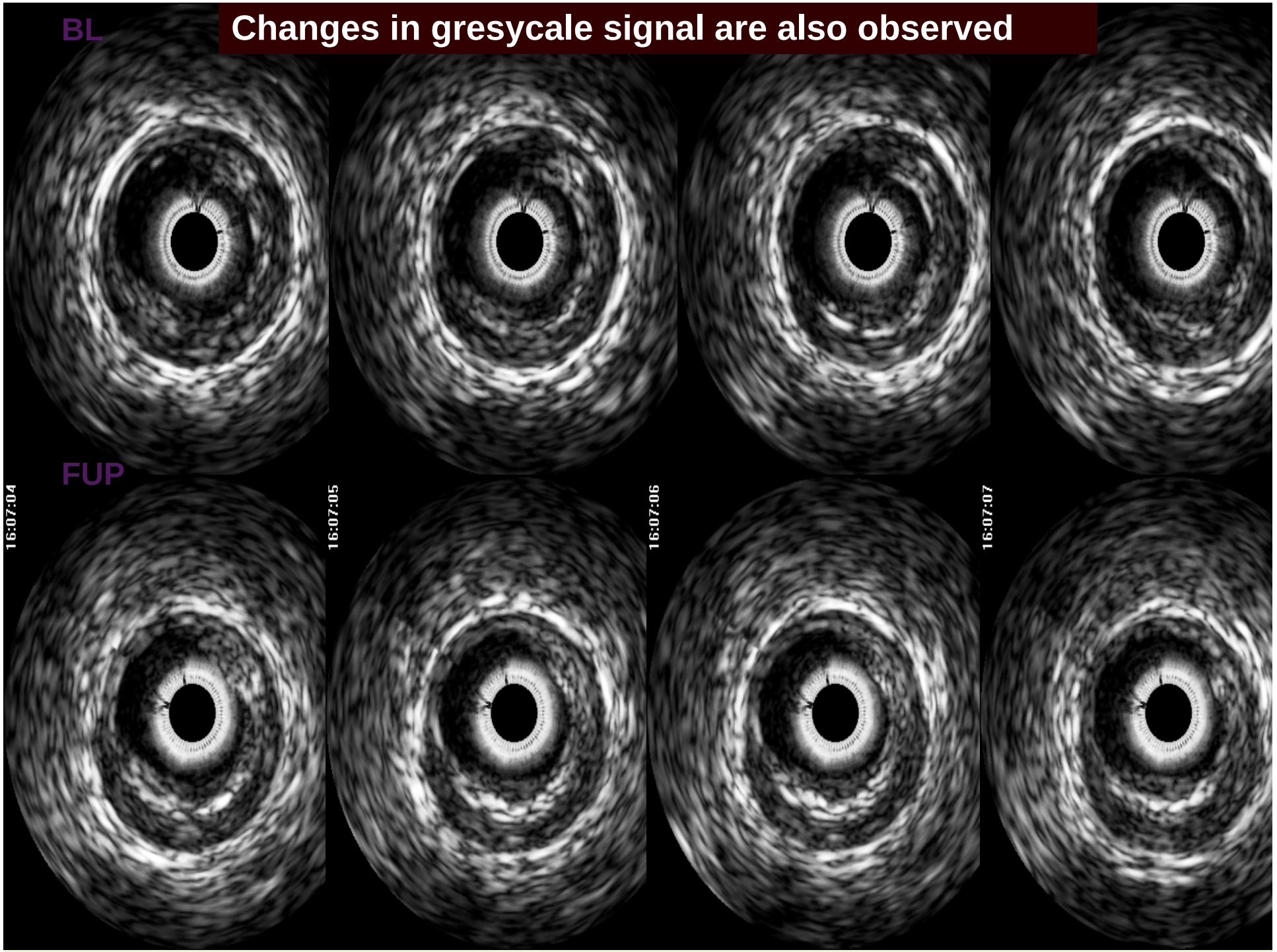
the worst 10 mm subsegment

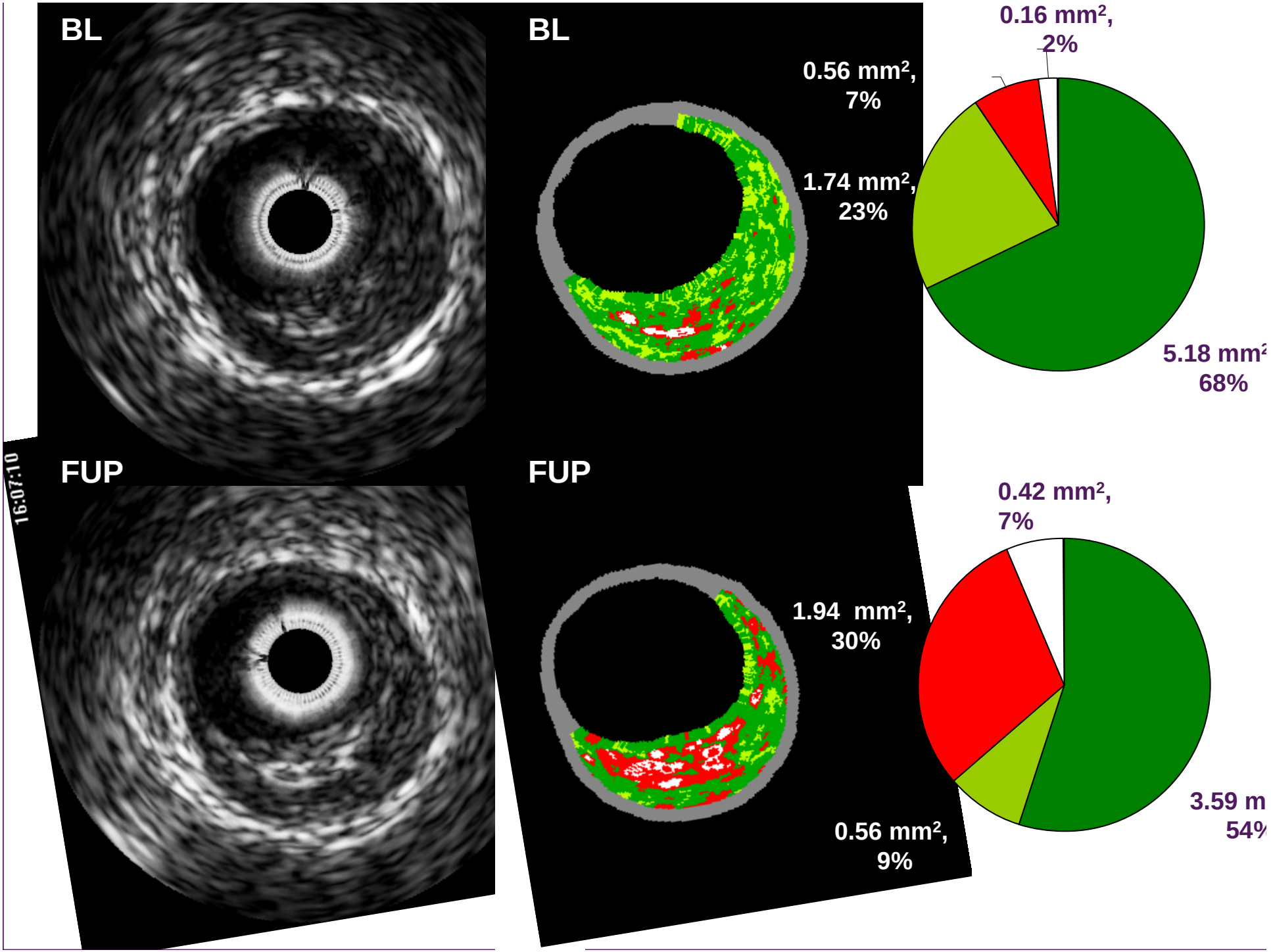


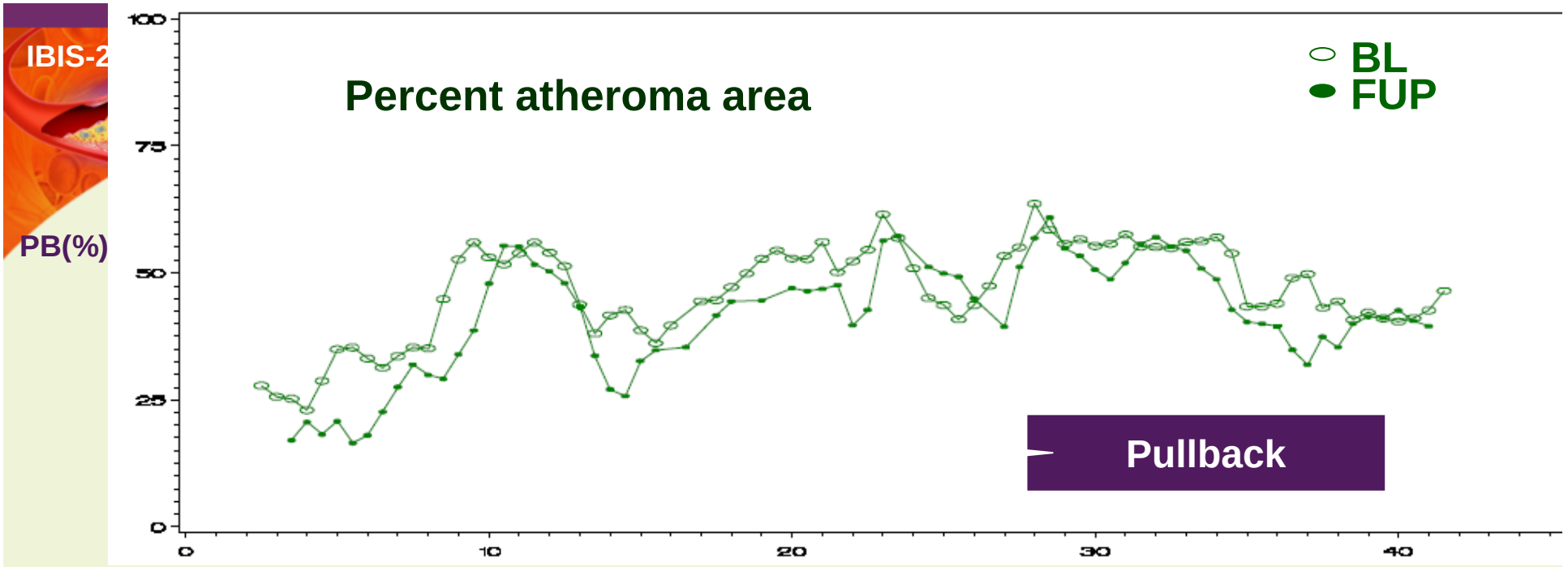
placebo (plus standard of care) n=115

darapladib 160 mg (plus standard of care) n=131

Between groups comparison: ANCOVA adjusted for ACS, pooled country, baseline value and segment length; within groups comparison: paired t test

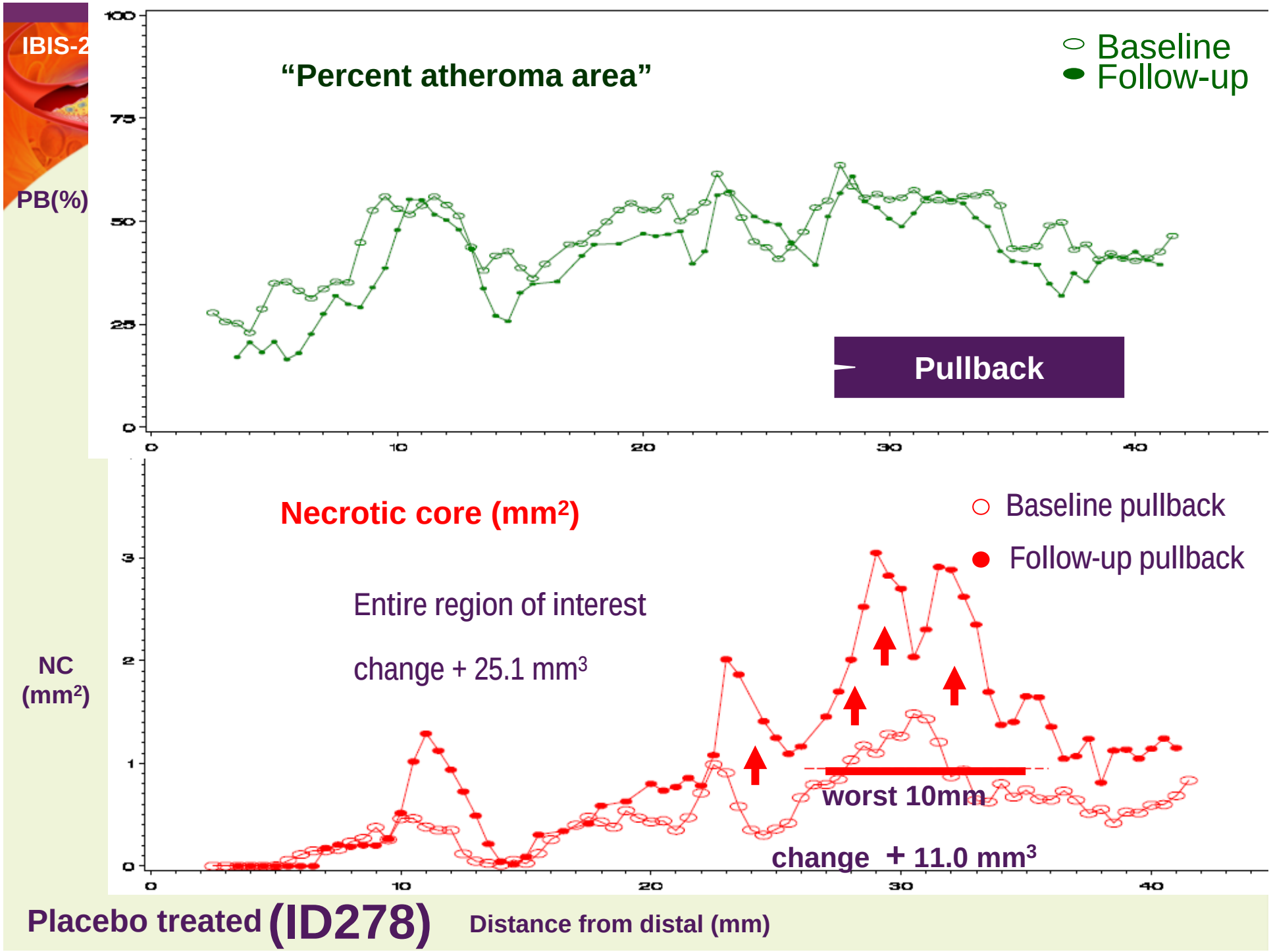

BL
Changes in gresycale signal are also observed
FUP
16:07:04
16:07:05
16:07:06
16:07:07


BL
BL
0.56 mm², 7%
1.74 mm², 23%
0.16 mm², 2%
5.18 mm² 68%
FUP
FUP
16:07:10
1.94 mm², 30%
0.56 mm², 9%
0.42 mm², 7%
3.59 m 54%



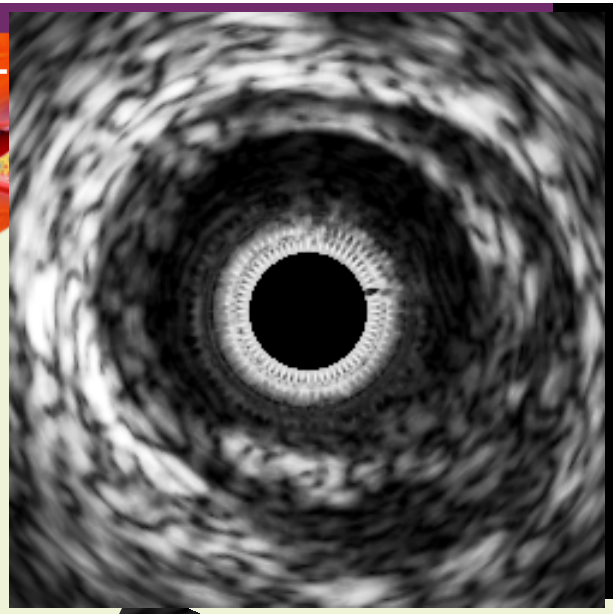
Placebo treated

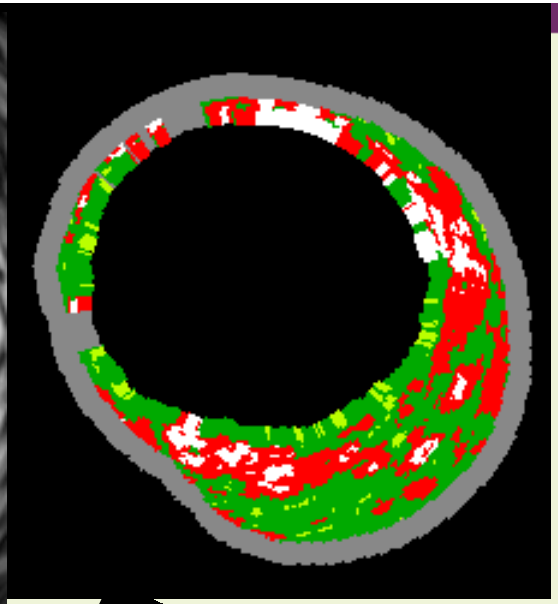
Consistent mild decrease in percent atheroma area throughout the coronary vessel

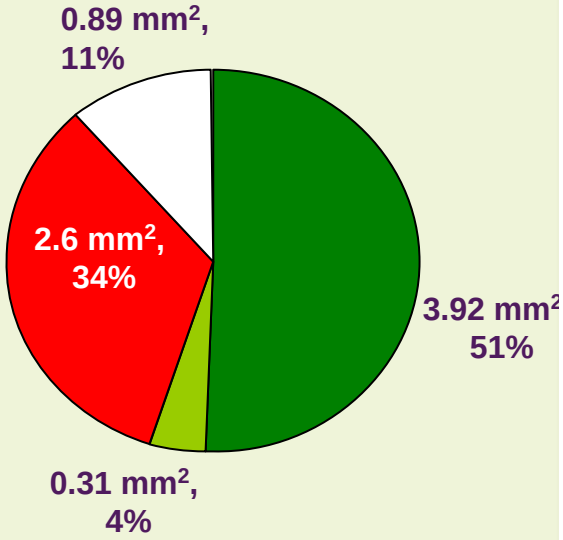

IBIS-2
PB(%)
"Percent atheroma area"
Baseline
Follow-up
Pullback
Necrotic core (mm²)
Baseline pullback
Follow-up pullback
Entire region of interest
change + 25.1 mm³
worst 10mm
change + 11.0 mm³
NC (mm²)
Placebo treated (ID278)
Distance from distal (mm)

IBIS-

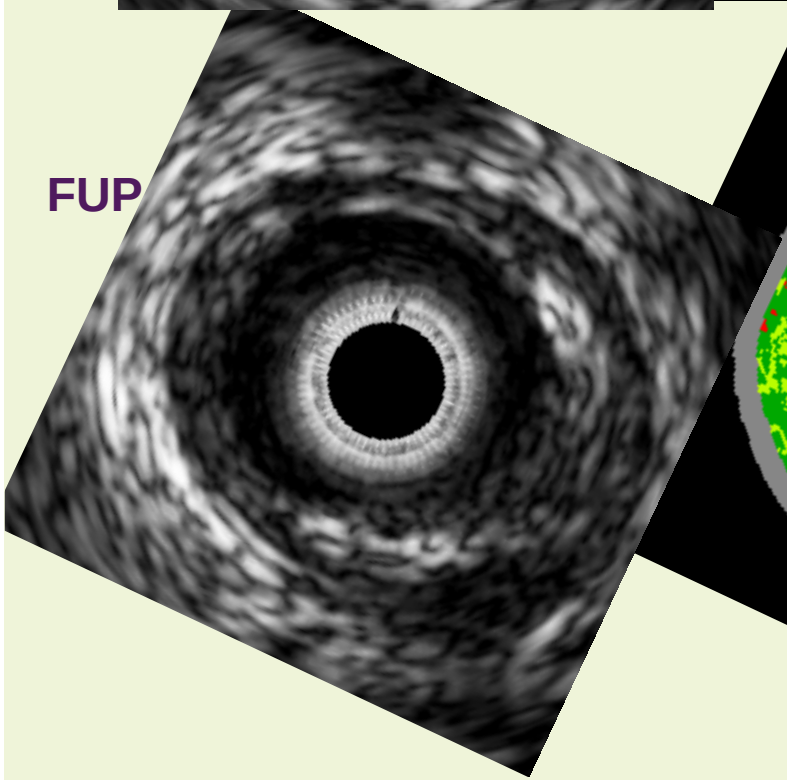
BL

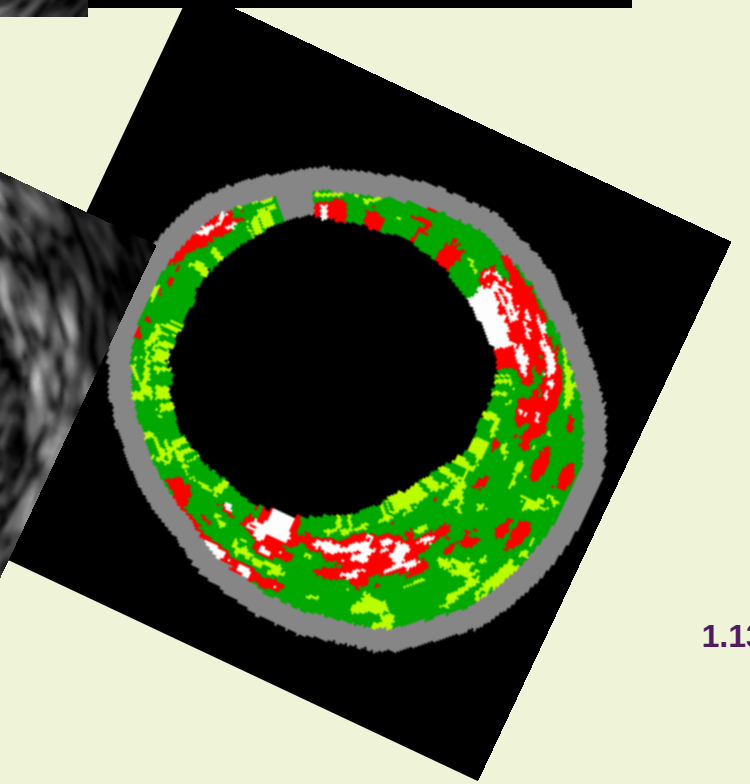


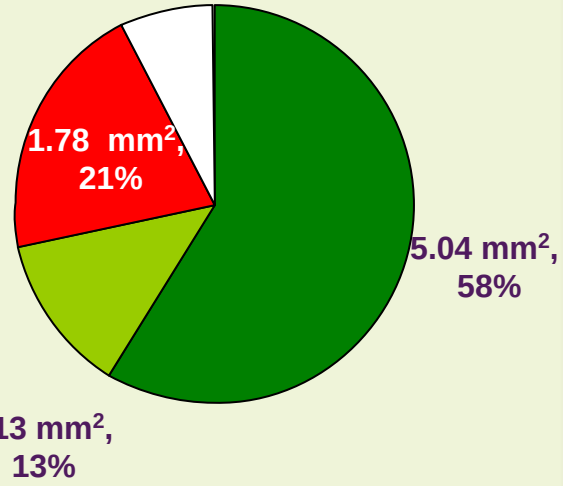




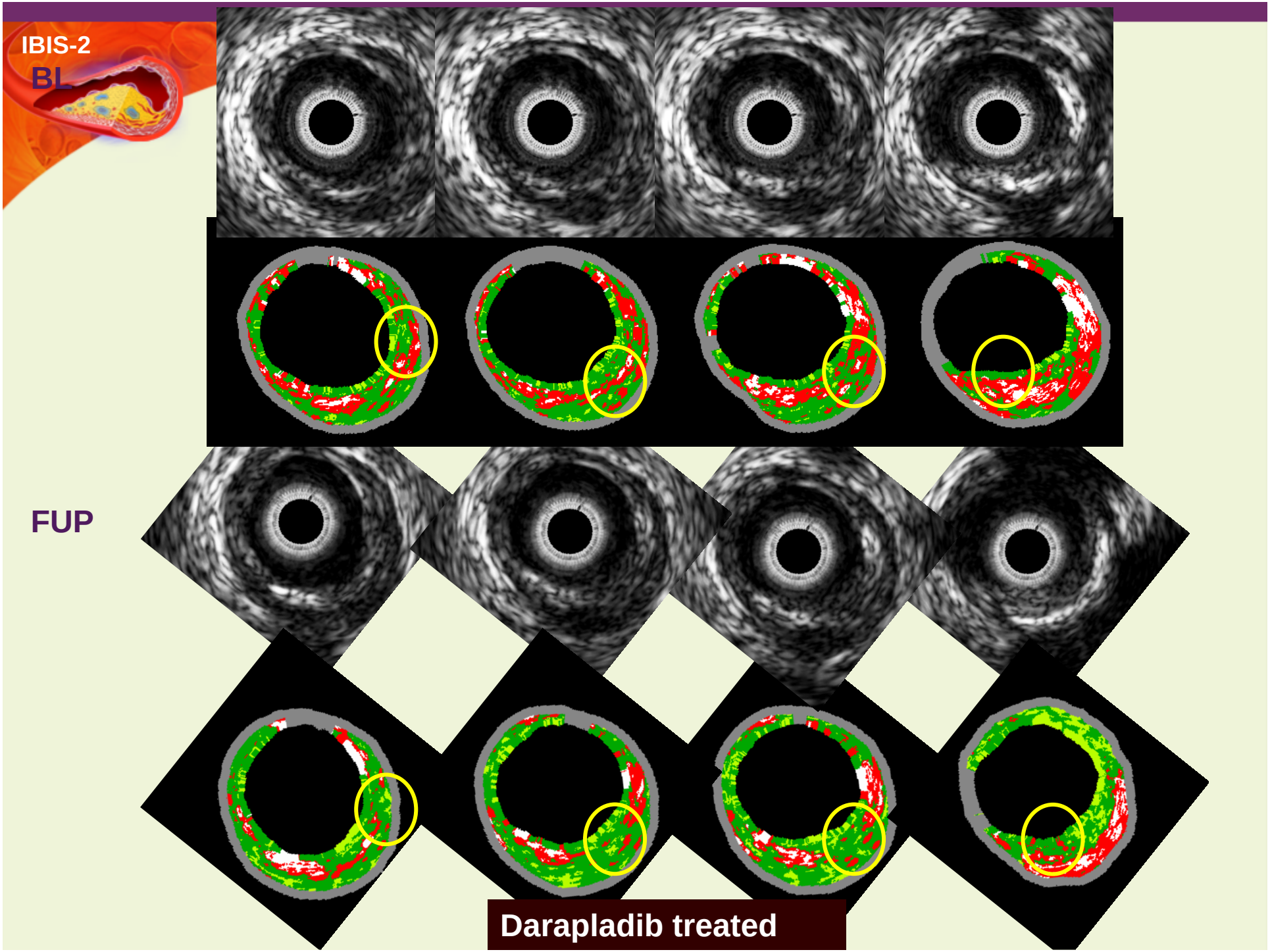
FUP





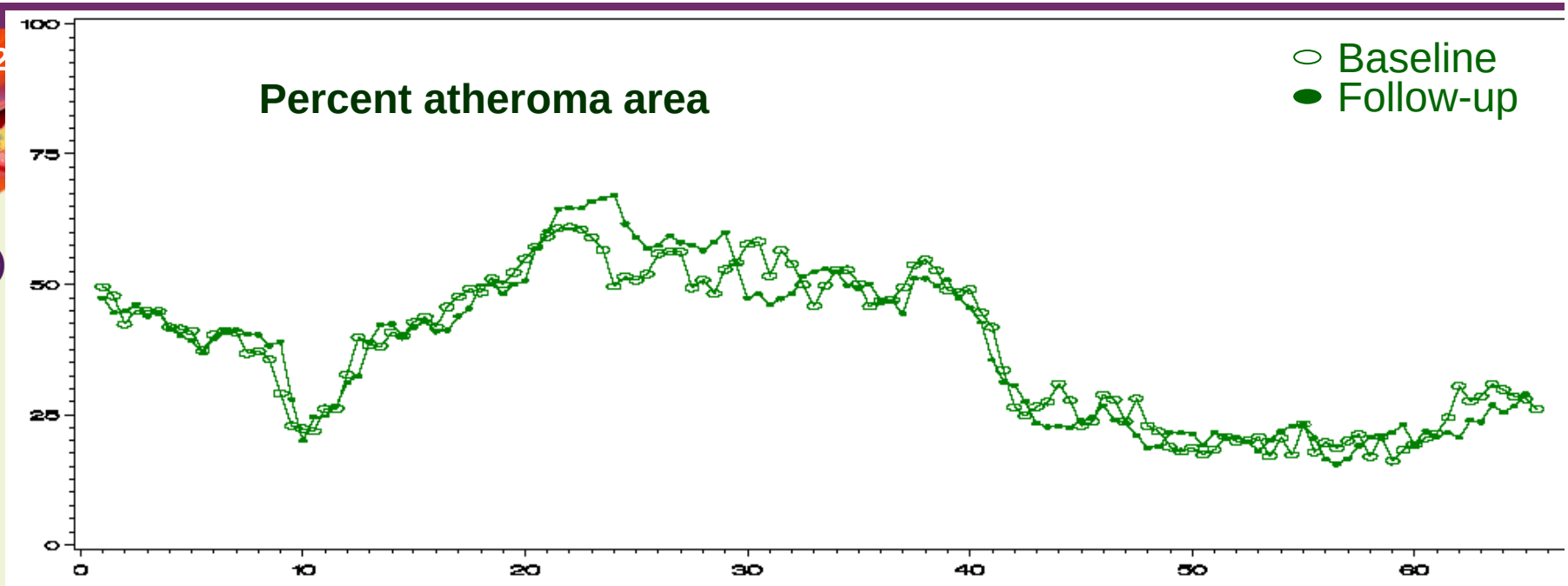


Darapladib treated


IBIS-2
BL
FUP
Darapladib treated

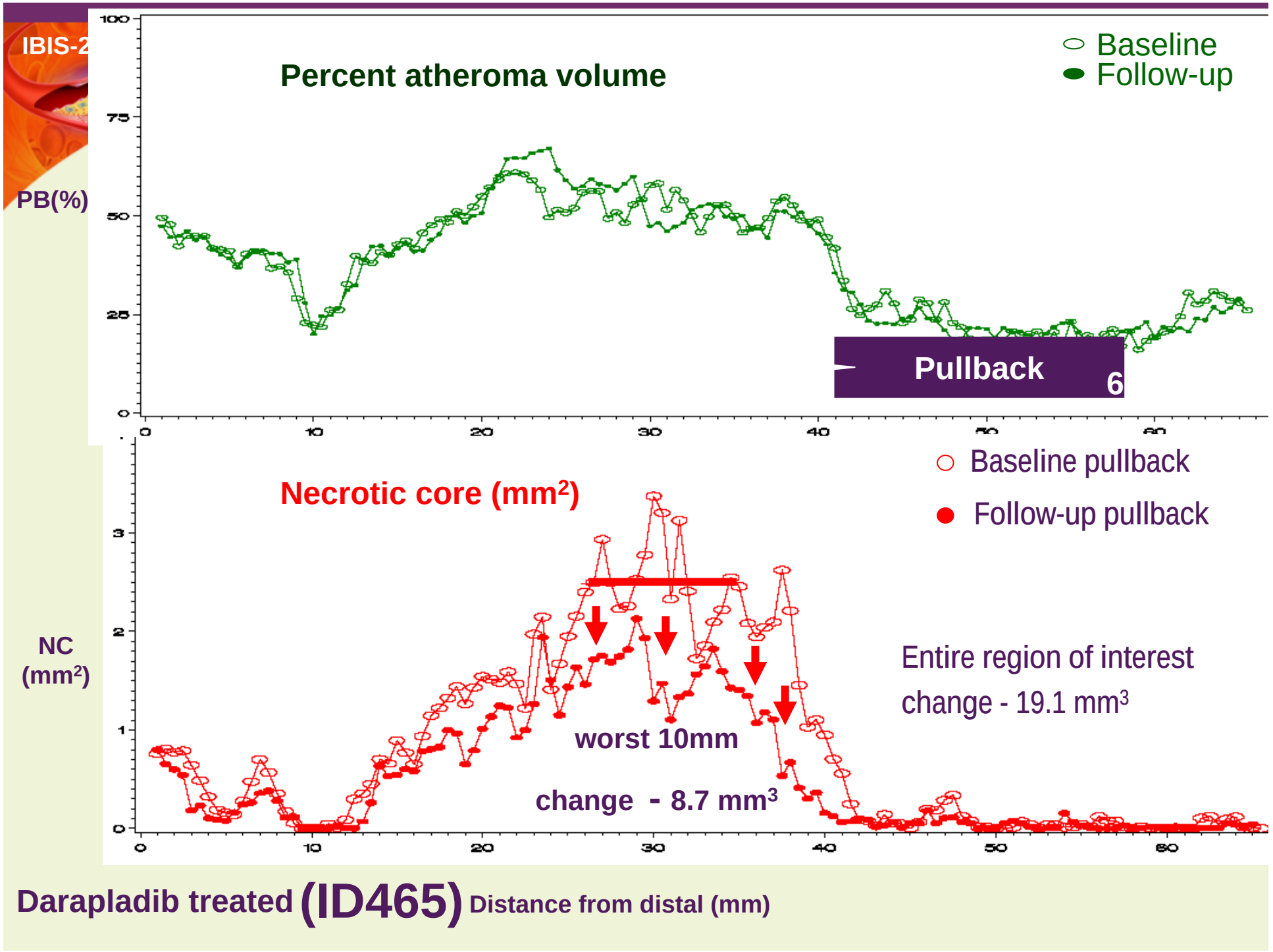
IBIS-2

PB(%)



Darapladib treated

no change in percent atheroma area throughout the coronary vessel


IBIS-2
PB(%)
Percent atheroma volume
Baseline
Follow-up
Pullback
6
NC (mm²)
Necrotic core (mm²)
Baseline pullback
Follow-up pullback
worst 10mm
change - 8.7 mm³
Entire region of interest
change - 19.1 mm³
Darapladib treated (ID465)
Distance from distal (mm)

IBIS-2

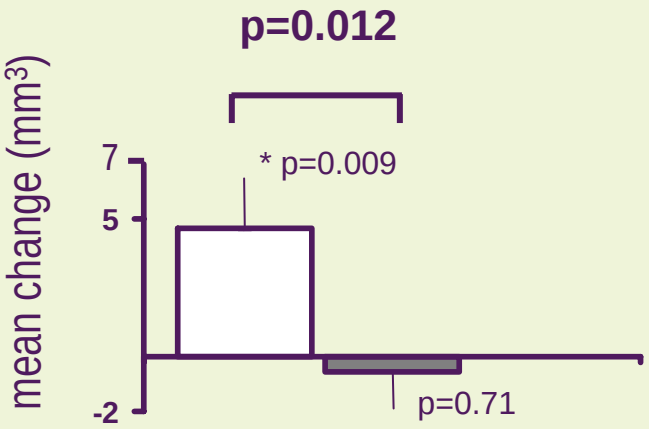
Plaque Composition

by IVUS - VH

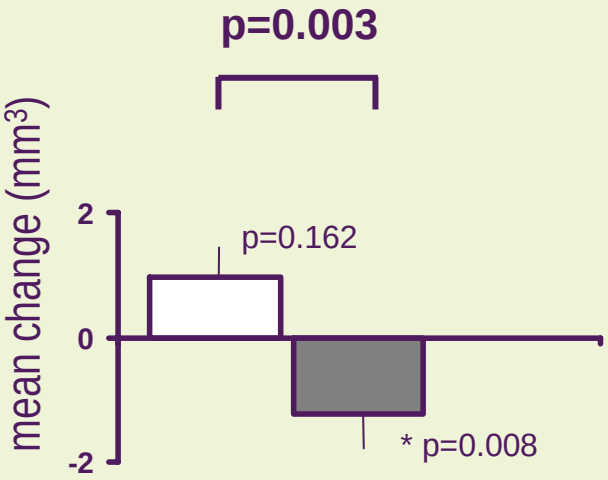
change from baseline in necrotic core volume

entire region of interest [mean 48 mm]

key secondary endpoint



the worst 10 mm subsegment

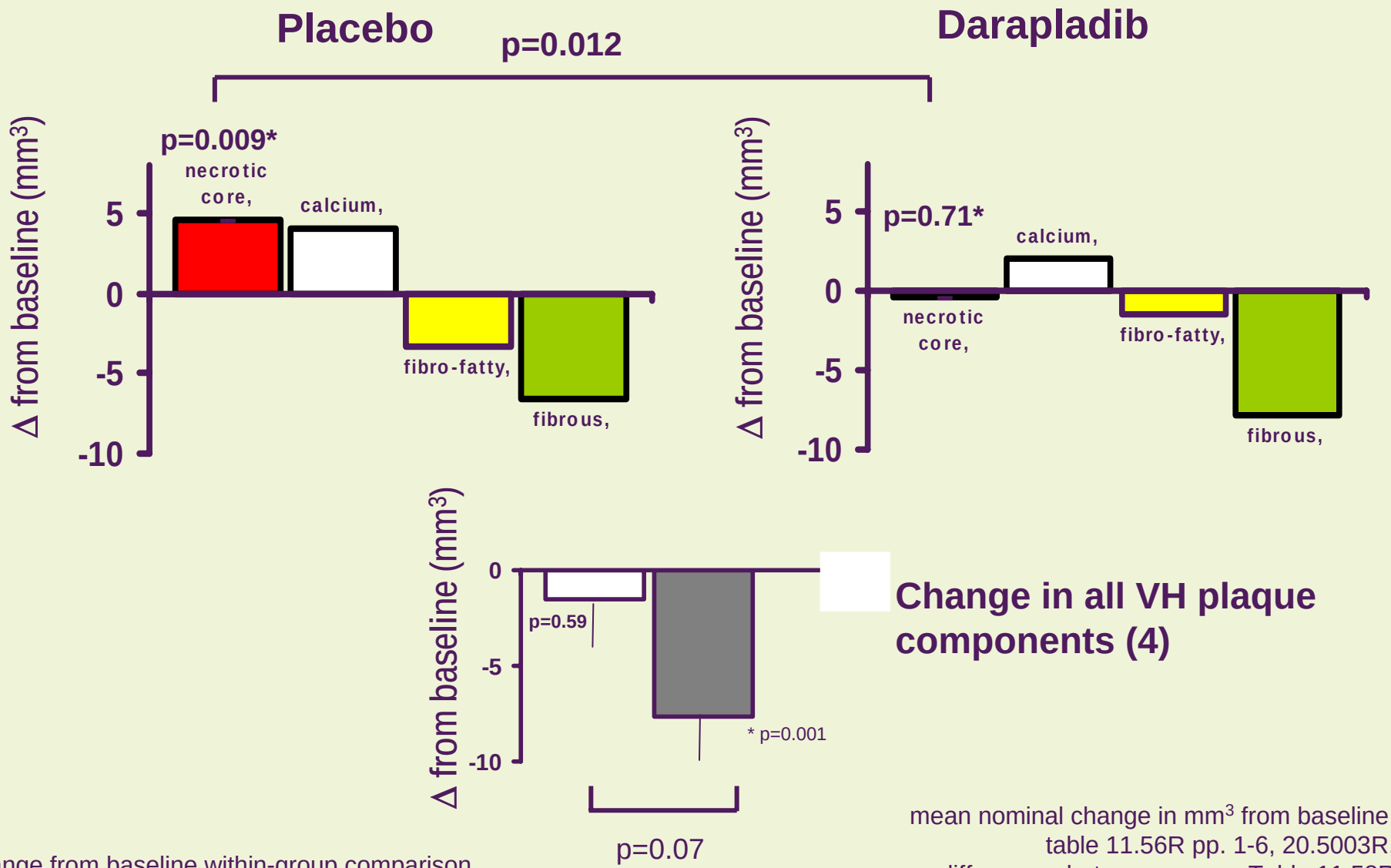


placebo (plus standard of care) n=110

darapladib 160 mg (plus standard of care) n=129

Between groups comparison: ANCOVA adjusted for ACS, pooled country, baseline value and segment length; within groups comparison: paired t test

IBIS-2: changes in overall plaque composition: differential effects of darapladib



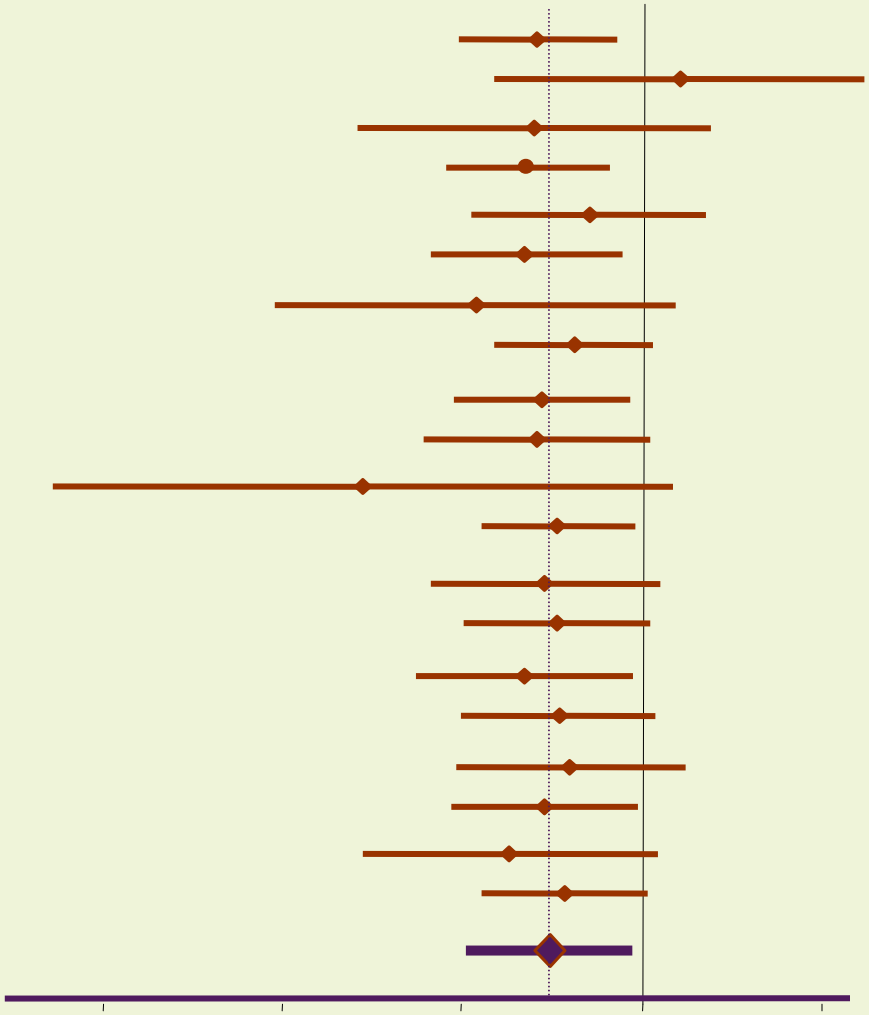
* change from baseline within-group comparison
Table 11.57R, 20.5002R

mean nominal change in mm^3 from baseline
table 11.56R pp. 1-6, 20.5003R,
differences between groups Table 11.58R

IBIS-2

Plaque Composition

Subgroup analysis



<65 yrs (n=172)
≥65 yrs (n=67)

Female (n=38)
Male (n=201)

Smoker (n=90)
Non-smoker (n=149)

DM (n=33)
non-DM (n=206)

BP <140/90 mmHg (n=174)
BP ≥140/90 mmHg (n=65)

eGFR <60 ml/min/1.73 m^2 (n=19)
eGFR ≥60 ml/min/1.73 m^2 (n=217)

Prior statins (n=70)
No prior statins (n=160)

ACS (n=118)
non-ACS (n=121)

on-treatment LDL <70 mg/dL (n=67)
on-treatment LDL ≥70 mg/dL (n=169)

on-treatment HDL <40 mg/dL (n=45)
on-treatment HDL ≥40 mg/dL (n=194)

Overall (n=239)

Biomarkers

Lp-PLA_2, LDL-c, hs-CRP

Significant reduction in Lp-PLA_2 activity in the darapladib-treated group:

- placebo: 153 μM/min/L (95% CI, 147 to 159) vs darapladib: 62 μM/min/L (95% CI, 58 to 65); -59% reduction, p<0.001

Comparable on-treatment LDL-c values:

- placebo: 88 ± 34 mg/dL vs darapladib: 84 ± 31 mg/dL, p=0.37

hs-CRP at 12 months

co-primary endpoint*

Placebo: 1.11 mg/L (95% CI, 0.9 to 1.4)

Darapladib: 0.86 mg/L (95% CI, 0.7 to 1.0)

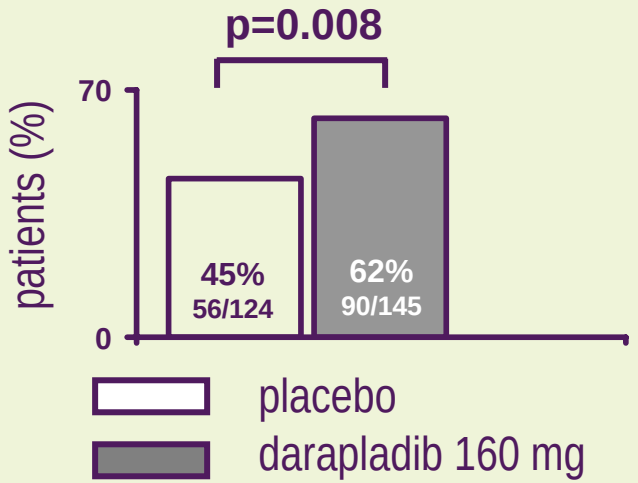
-22%, p=0.08 observed values analysis

-15%, p=0.22 repeated measures analysis

-12%, p=0.35 LOCF analysis (≥ 3mo.)*

achieved hs-CRP <1 mg/L at 12 months

(post-hoc)



Between groups comparison: ANCOVA adjusted for ACS, pooled country, and treatment as covariates.

IBIS-2

Chromosome 9p21 locus and CAD– X-Sectional Studies

A Common Variant on Chromosome 9p21 Affects the Risk of Myocardial Infarction

Anna Helgadottir,[1*] Gudmar Thorleifsson,[1*] Andrei Manolescu,[1*] Solveig Gretarsdottir,[1]

Genome-wide association study of 14,000 cases of seven common diseases and 3,000 shared controls

The Wellcome Trust Case Control Consortium*

A Common Allele on Chromosome 9 Associated with Coronary Heart Disease

Ruth McPherson,[1*†] Alexander Pertsemlidis,[2*] Nihan Kavaslar,[1] Alexandre Stewart,[1]

Repeated Replication and a Prospective Meta-Analysis of the Association Between Chromosome 9p21.3 and Coronary Artery Disease

Heribert Schunkert, MD; Anika Götz, MSc; Peter Braund, MSc; Ralph McGinnis, PhD;

Chromosome 9p21.3 Coronary Heart Disease Locus Genotype and Prospective Risk of CHD in Healthy Middle-Aged Men

Philippa J. Talmud,[1] Jackie A. Cooper,[1] Jutta Palmen,[1] Ruth Lovering,[2] Fotios Drenos,[1] Aroon D. Hingorani,[3] and Steve E. Humphries[1*]

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 AUGUST 2, 2007 VOL. 357 NO. 5

Genomewide Association Analysis of Coronary Artery Disease

Nilesh J. Samani, F.Med.Sci., Jeanette Erdmann, Ph.D., Alistair S. Hall, F.R.C.P., Christian Hengstenberg, M.D.,

Four SNPs on Chromosome 9p21 in a South Korean Population Implicate a Genetic Locus That Confers High Cross-Race Risk for Development of Coronary Artery Disease

Gong-Qing Shen, Lin Li, Shaoqi Rao, Kalil G. Abdullah, Ji Min Ban,

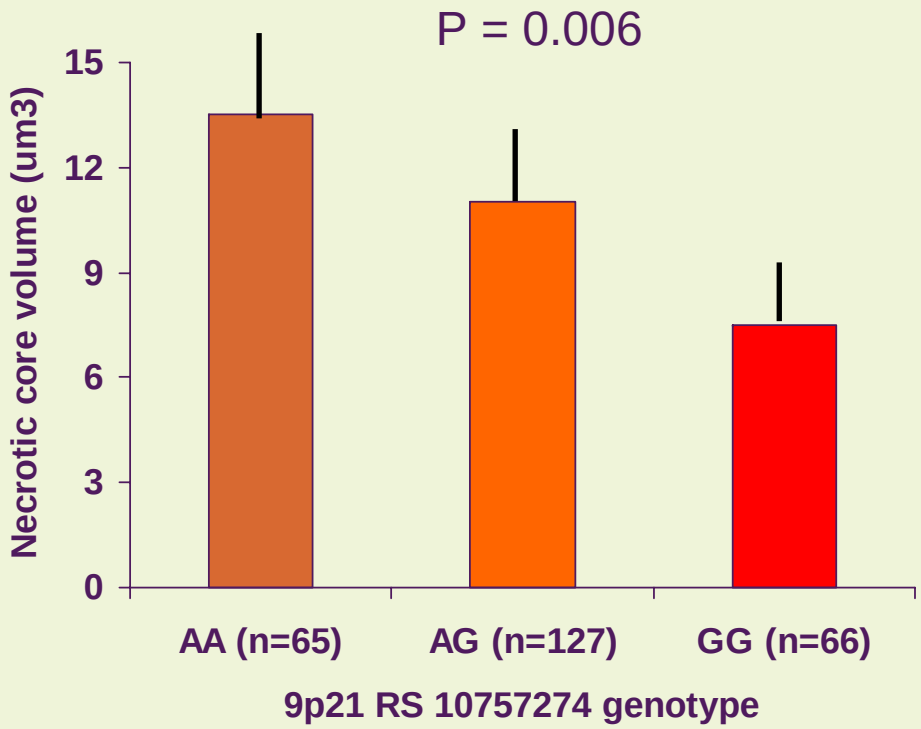
Whole Genome Analyses Suggest Ischemic Stroke and Heart Disease Share an Association With Polymorphisms on Chromosome 9p21

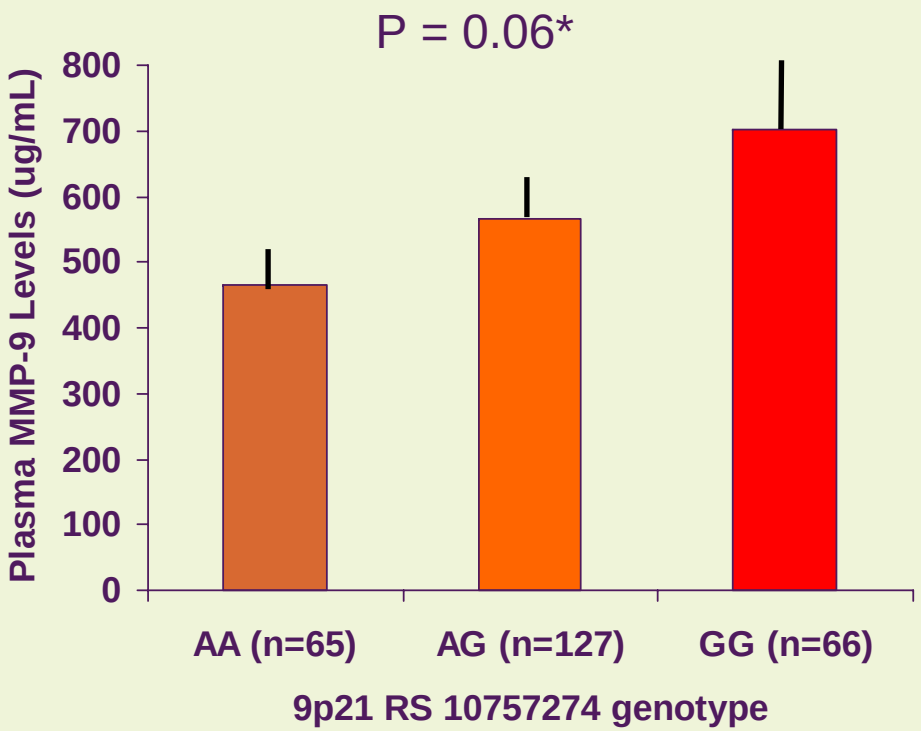
Mar Matarin, PhD; W. Mark Brown, MA; Andrew Singleton, PhD; John A. Hardy, PhD; James F. Meschia, MD; for the ISGS investigators

Overall risk (r)/non-Risk (nr) allele frequency : ~ 50/50%
Overall genotype frequency : 25% nr/nr, 50% r/nr, 25% r/r
Overall risk for CAD : ~35% increase per risk allele
Increased risk for AAA, Stroke, cerebral aneuvrysm
No Association with known CVRFs. Mechanism unknown

IBIS-2

Effect of 9p21 Locus on Necrotic Core and Plasma MMP9 Levels at Baseline





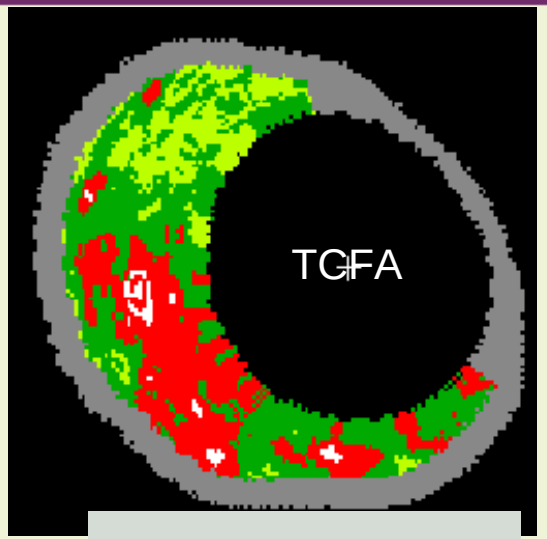
Note : G = risk allele for CAD
Mean +/- SEM

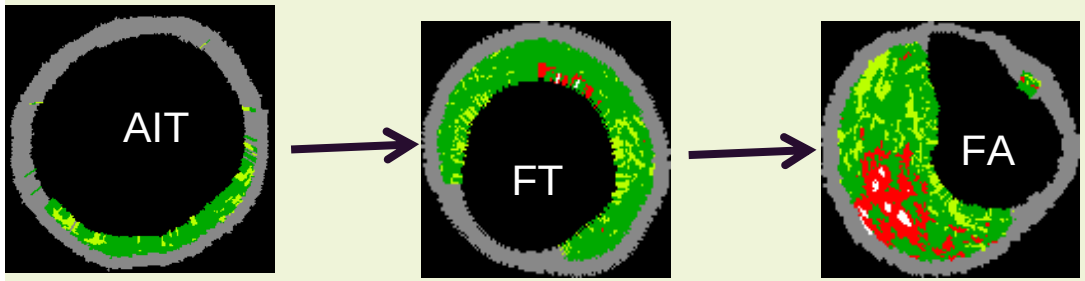
*p = 0.002 using mixed model over study period

One interpretation

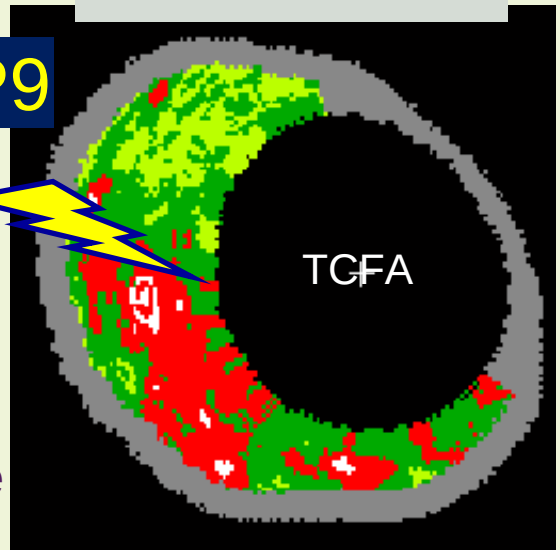
The inverse relationship between necrotic core and risk allele for 9p21 might be explained by positive relationship with metalloproteinase; Plaque rupture occurs prematurely in those with 9p21 risk allele through disruptive effect of MMP-9 without giving time for build-up of large necrotic core like in patients with 9p21 non-risk allele.

9p21 non-risk allele

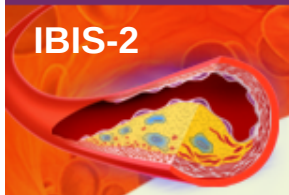




MMP9



9p21 risk allele



Conclusions

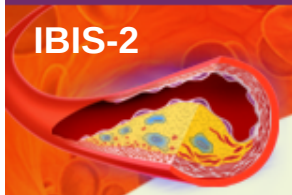
- Darapladib, a potent and selective Lp-PLA_2 inhibitor, did not significantly affect plaque deformability or hs-CRP levels
- Darapladib halted expansion of necrotic core when compared to standard of care alone. This effect was consistent across several clinical subgroups and was observed after only 12 months of treatment
- The results confirm a pro-atherogenic role of Lp-PLA_2 and its impact on the composition of atherosclerotic plaques in humans
- Chronic Lp-PLA_2 inhibition may represent a novel approach for plaque stabilization, if clinical benefit of this therapy is confirmed in future event-driven trials

Publication of complete results of IBIS-2 in Circulation

Vascular Medicine

Effects of the Direct Lipoprotein-Associated Phospholipase A_2 Inhibitor Darapladib on Human Coronary Atherosclerotic Plaque

Patrick W. Serruys, MD, PhD; Héctor M. García-García, MD, MSc; Pawel Buszman, MD, PhD; Paul Erne, MD, PhD; Stefan Verheye, MD, PhD; Michael Aschermann, MD; Henrikus Duckers, MD, PhD; Oyvind Bleie, MD; Dariusz Dudek, MD; Hans Erik Bøtker, MD; Clemens von Birgelen, MD, PhD; Don D'Amico, MA; Tammy Hutchinson, MSc; Andrew Zambanini, MD; Frits Mastik; Gerrit-Anne van Es, PhD; Antonius F.W. van der Steen, PhD; D. Geoffrey Vince, PhD; Peter Ganz, MD; Christian W. Hamm, MD; William Wijns, MD; Andrew Zalewski, MD, PhD; for the Integrated Biomarker and Imaging Study-2 Investigators



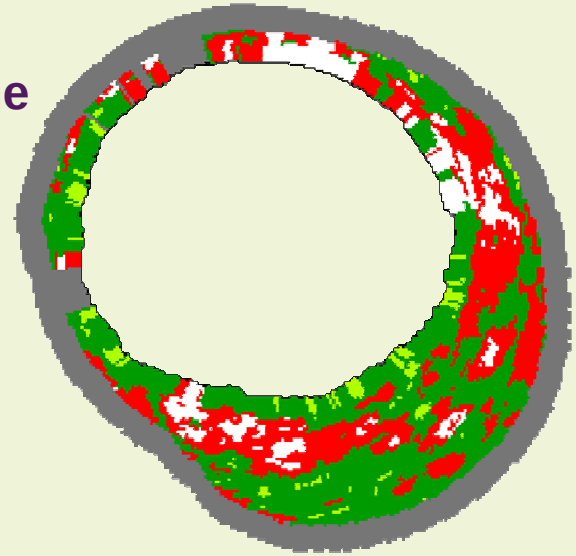
Methods : Analysis of 9p21 Locus in IBIS-2

- Baseline subjects with genotypes n=258
  - Follow-up IVUS n=226
  - Follow-up biomarker n=250
- Genotypes :
  - 3 SNPs for 9p21 locus
- Analysis : additive model, nominal and empirical p-value (10.000 permutations)

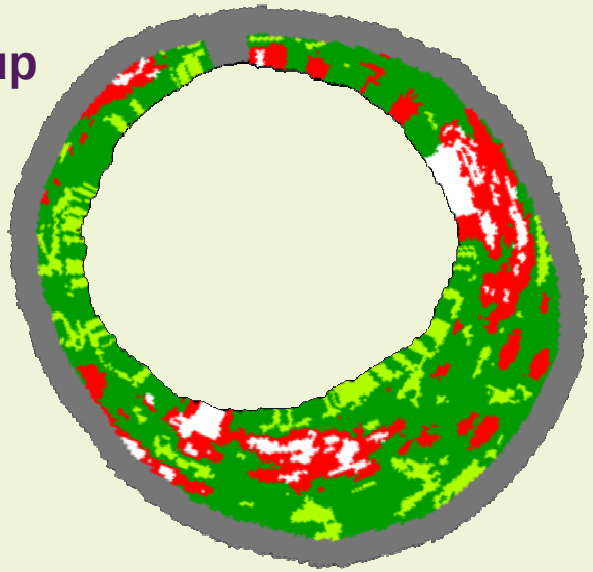
IBIS-2

Darapladib-treated

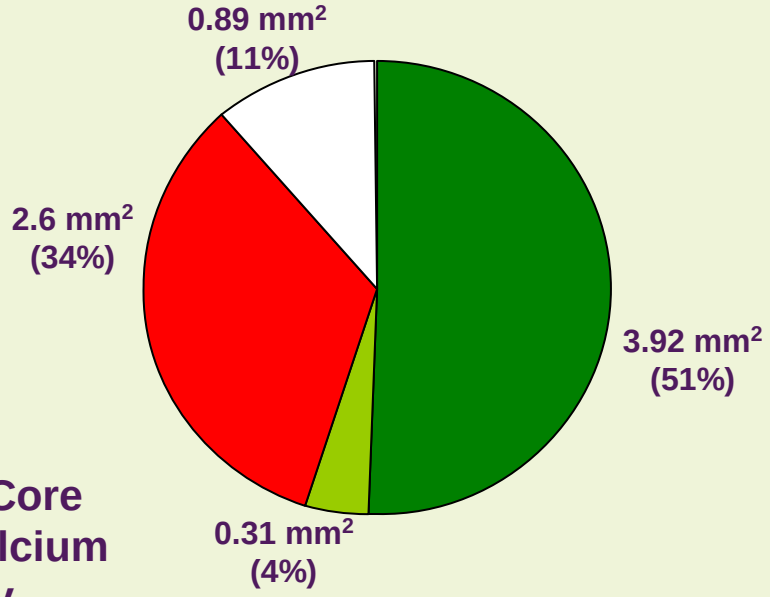
Baseline

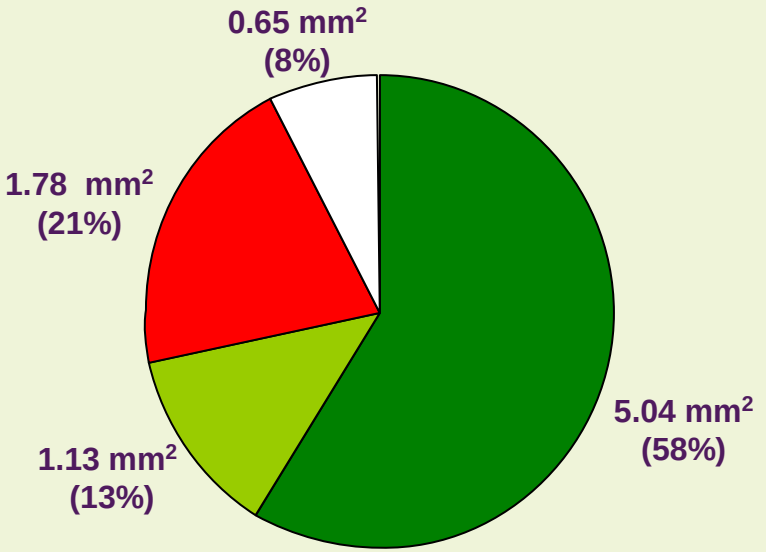


Follow-up



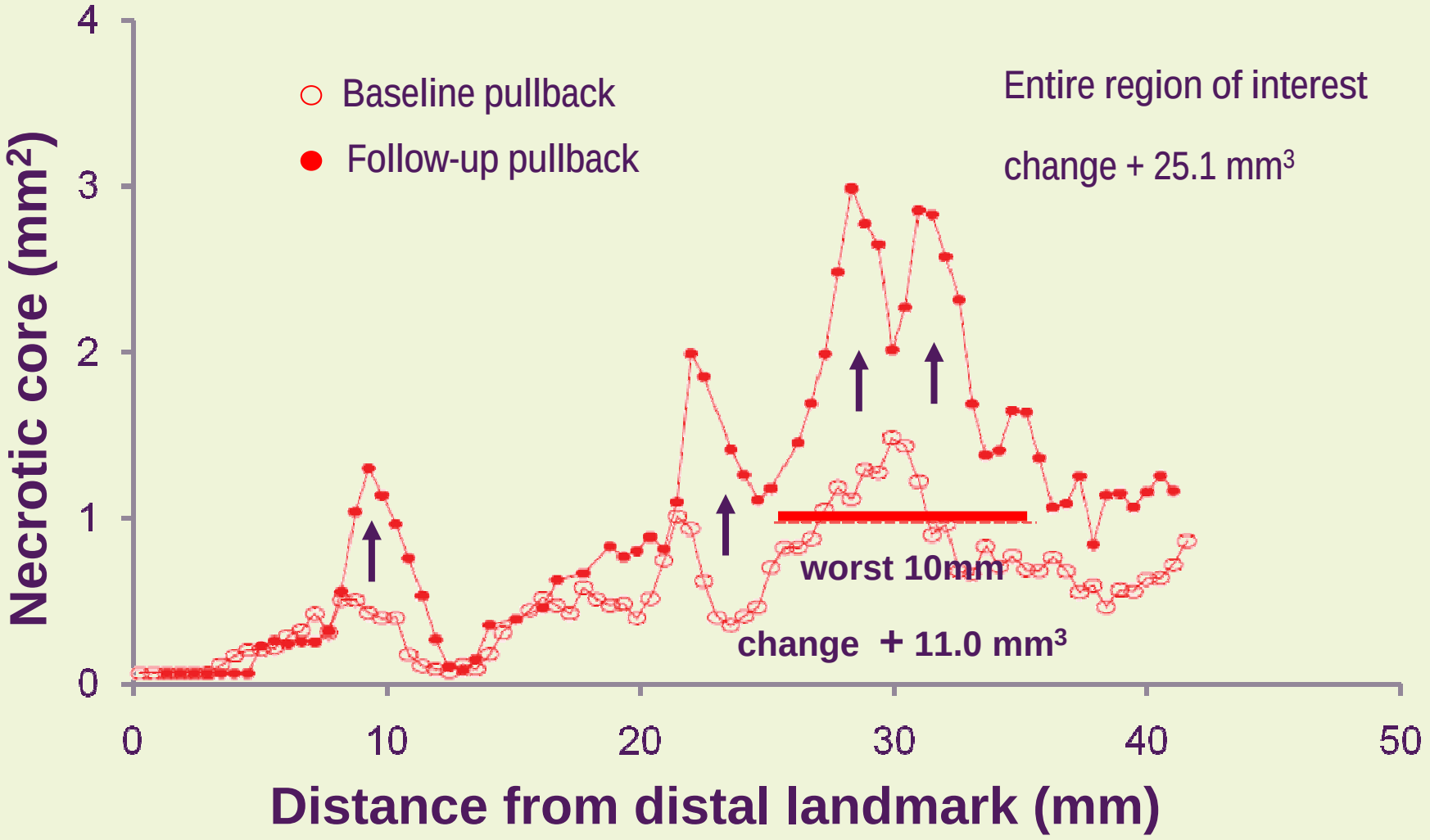
Necrotic Core
Dense Calcium
Fibro-fatty
Fibrous





IBIS-2

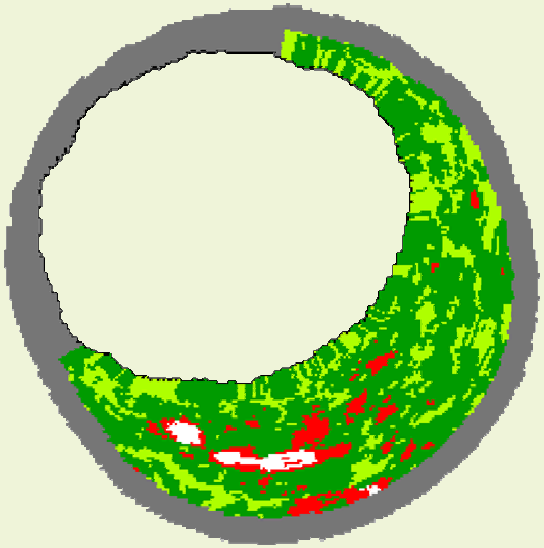
Placebo-treated (ID278)



IBIS-2

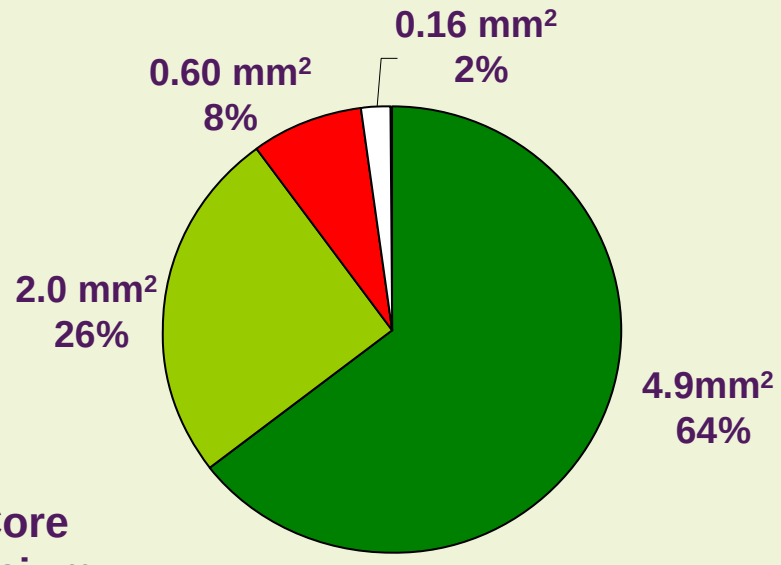
Placebo-treated

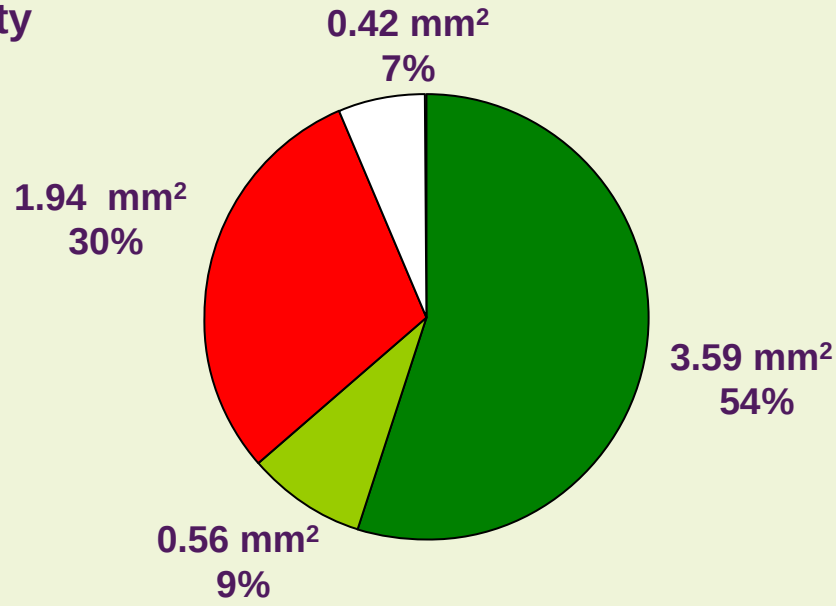
Baseline



Follow-up

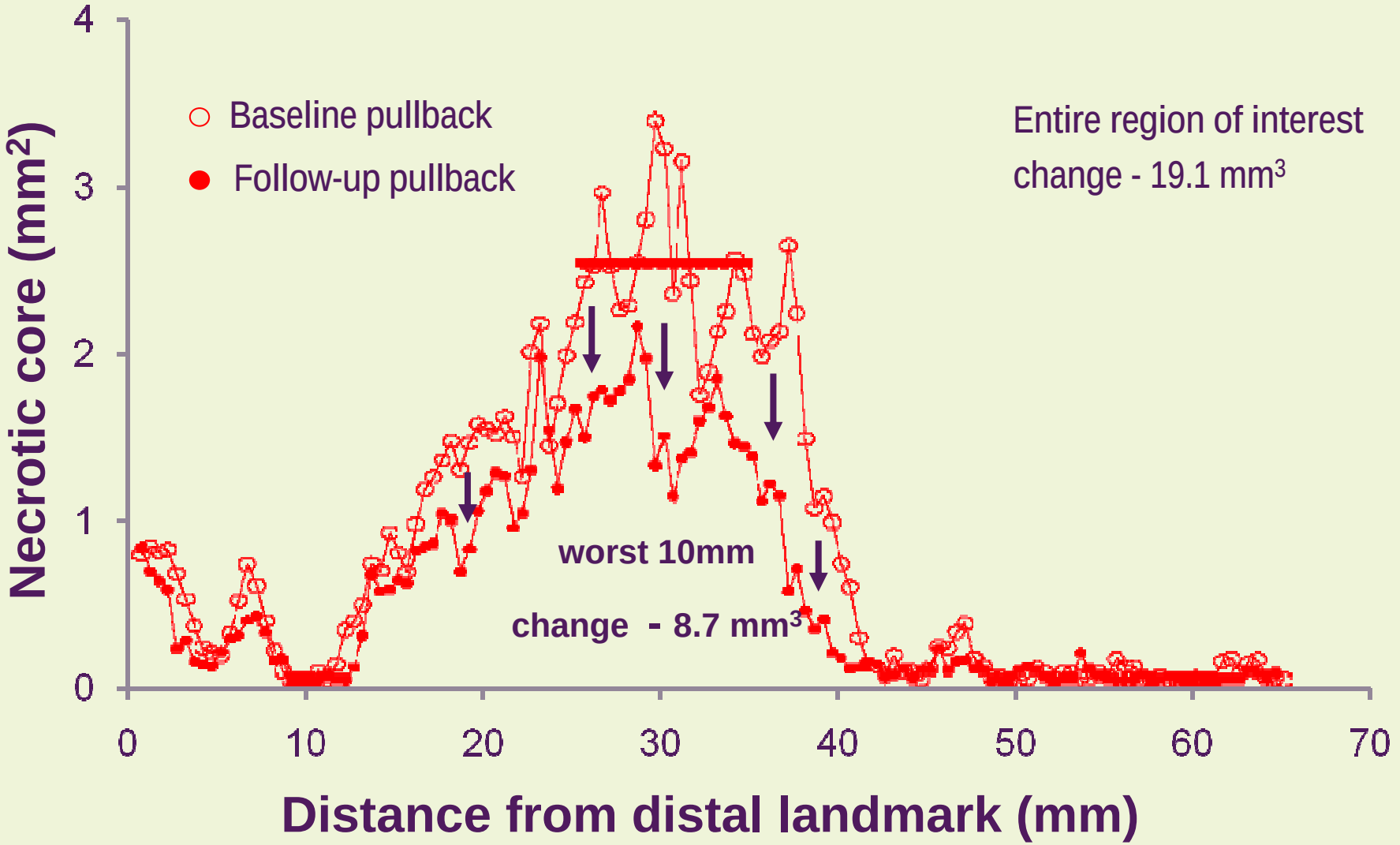
- Necrotic Core
- Dense Calcium
- Fibro-fatty
- Fibrous





IBIS-2

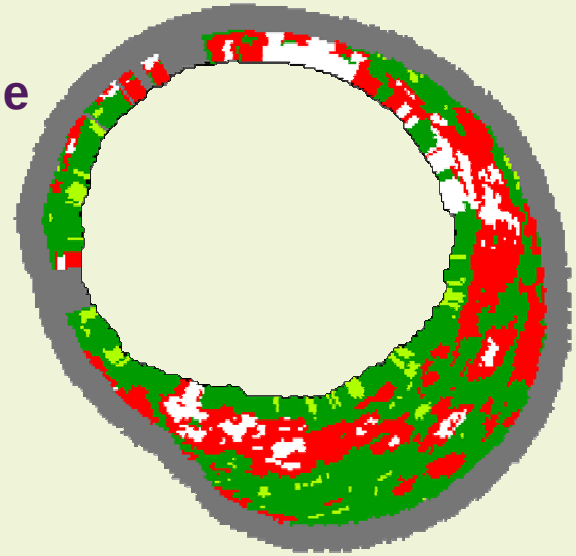
Darapladib-treated (ID465)



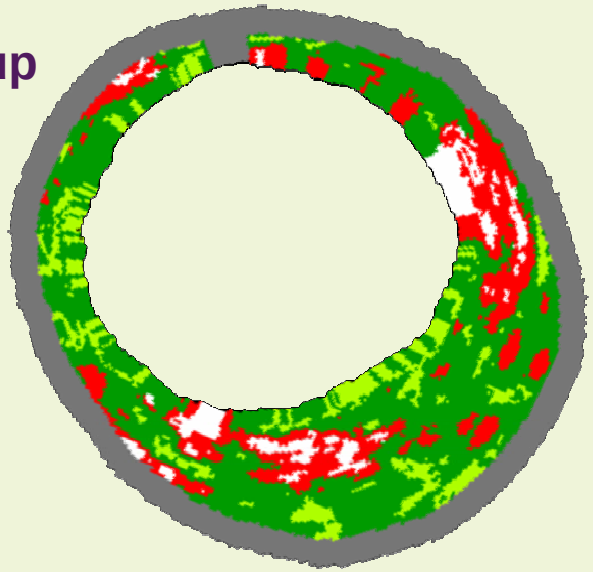
IBIS-2

Darapladib-treated

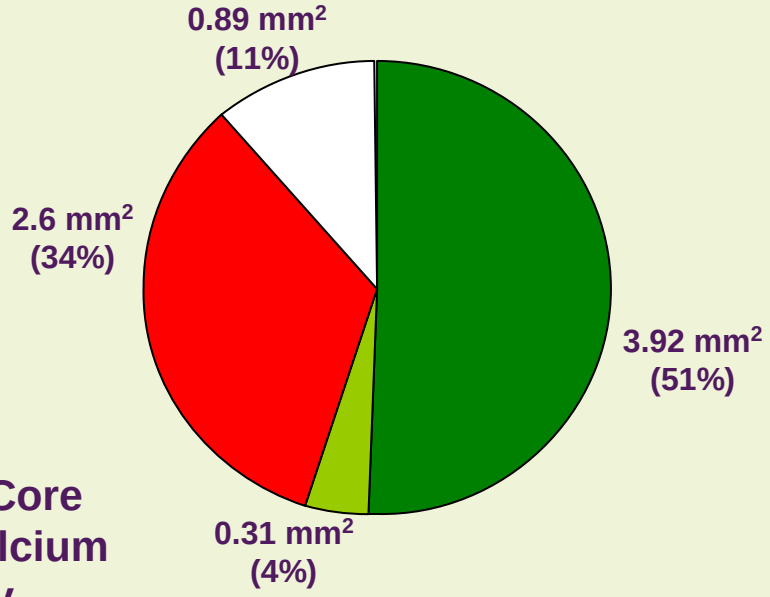
Baseline

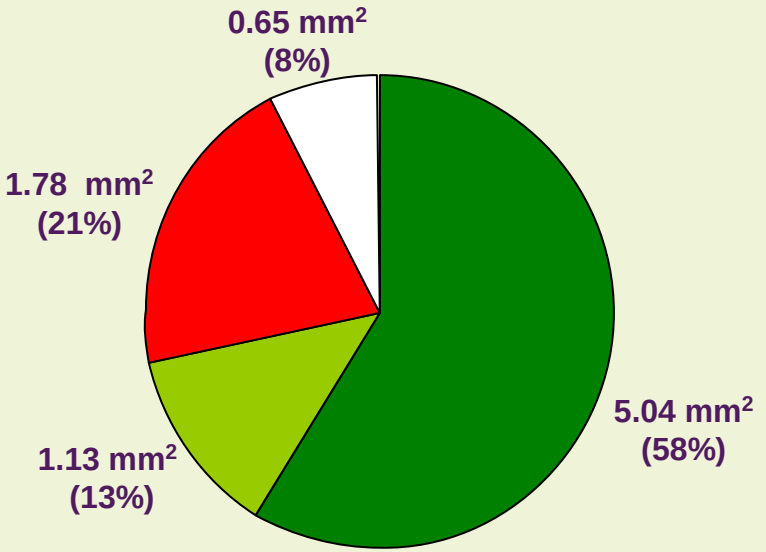


Follow-up



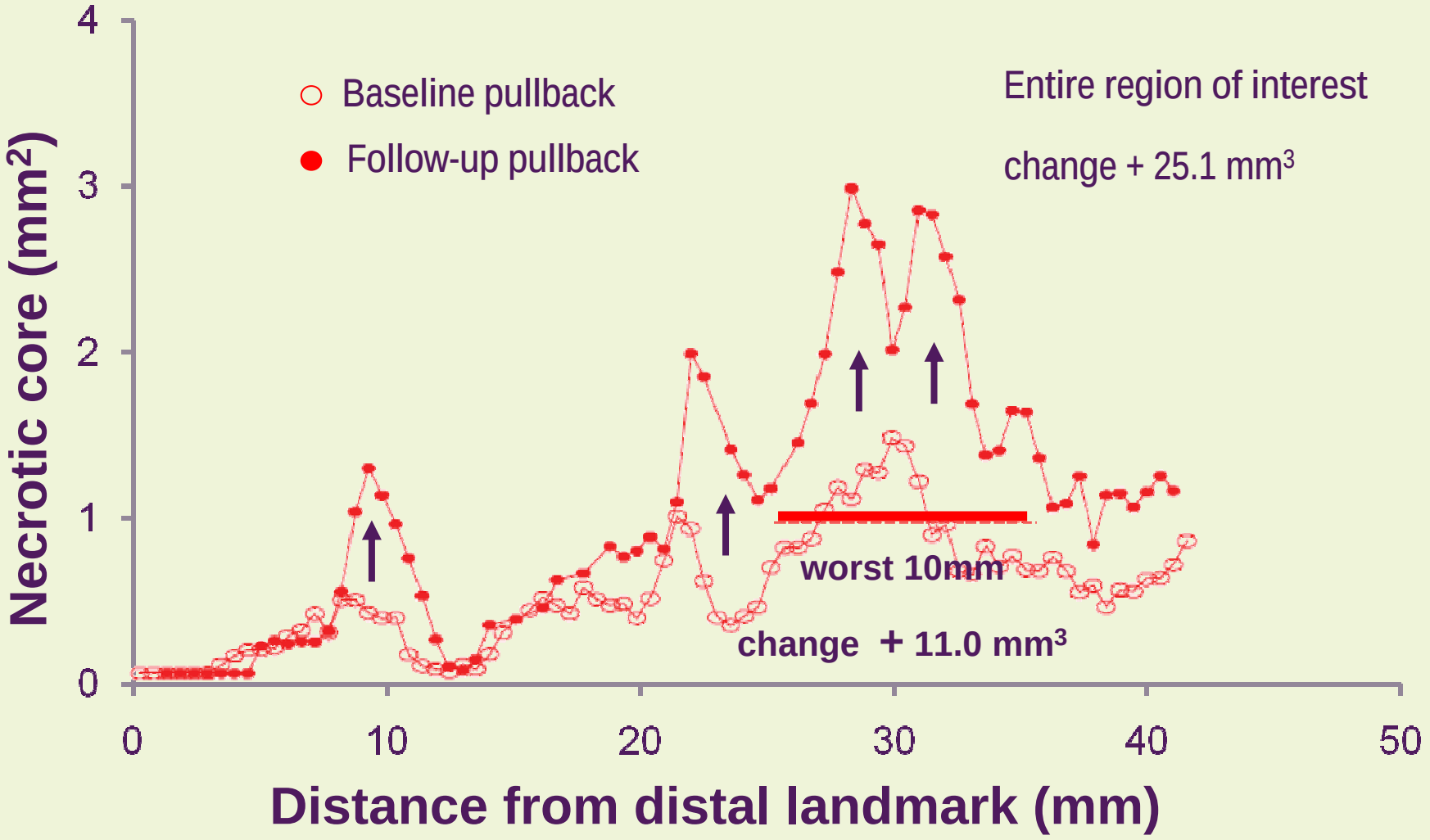
Necrotic Core
Dense Calcium
Fibro-fatty
Fibrous



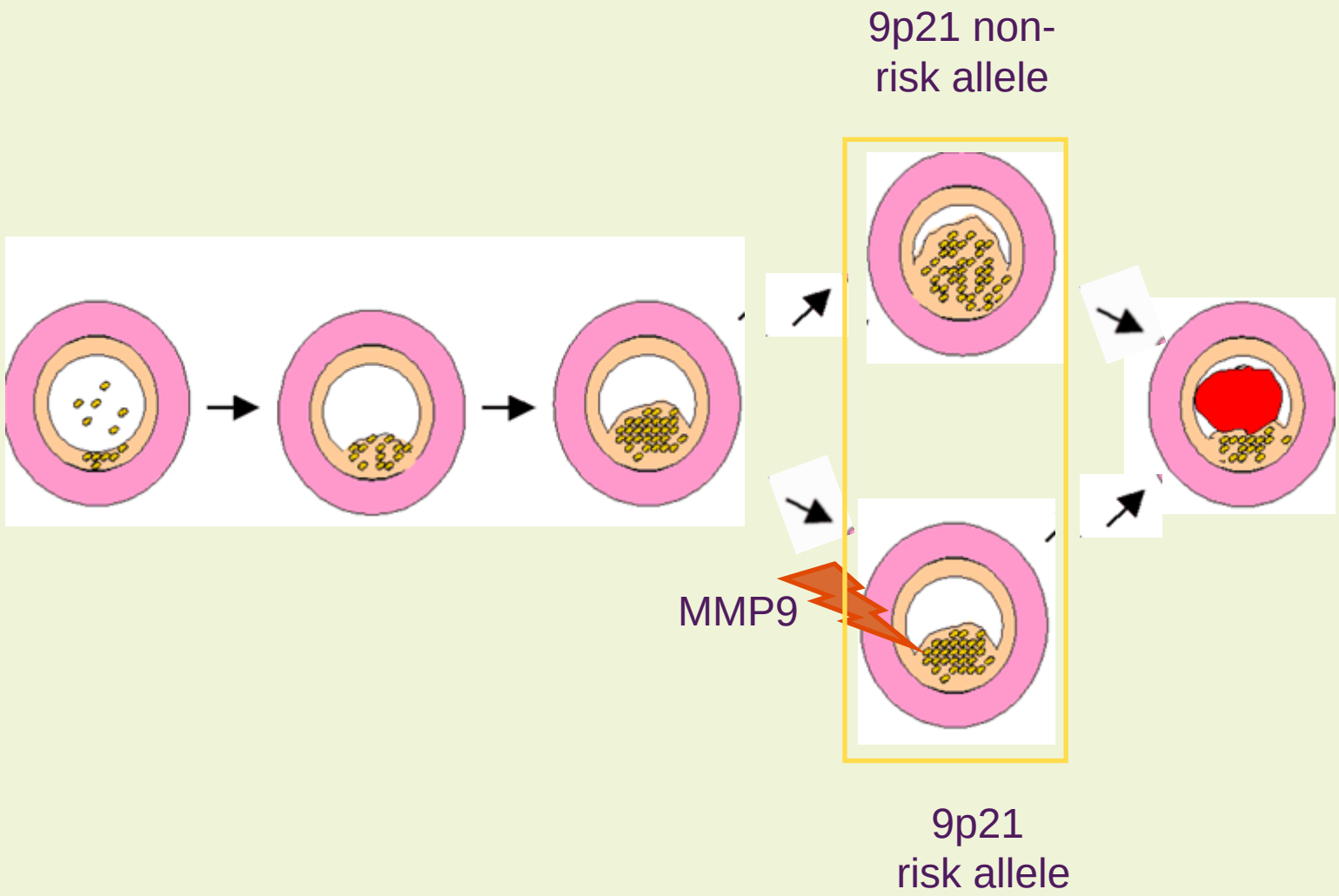


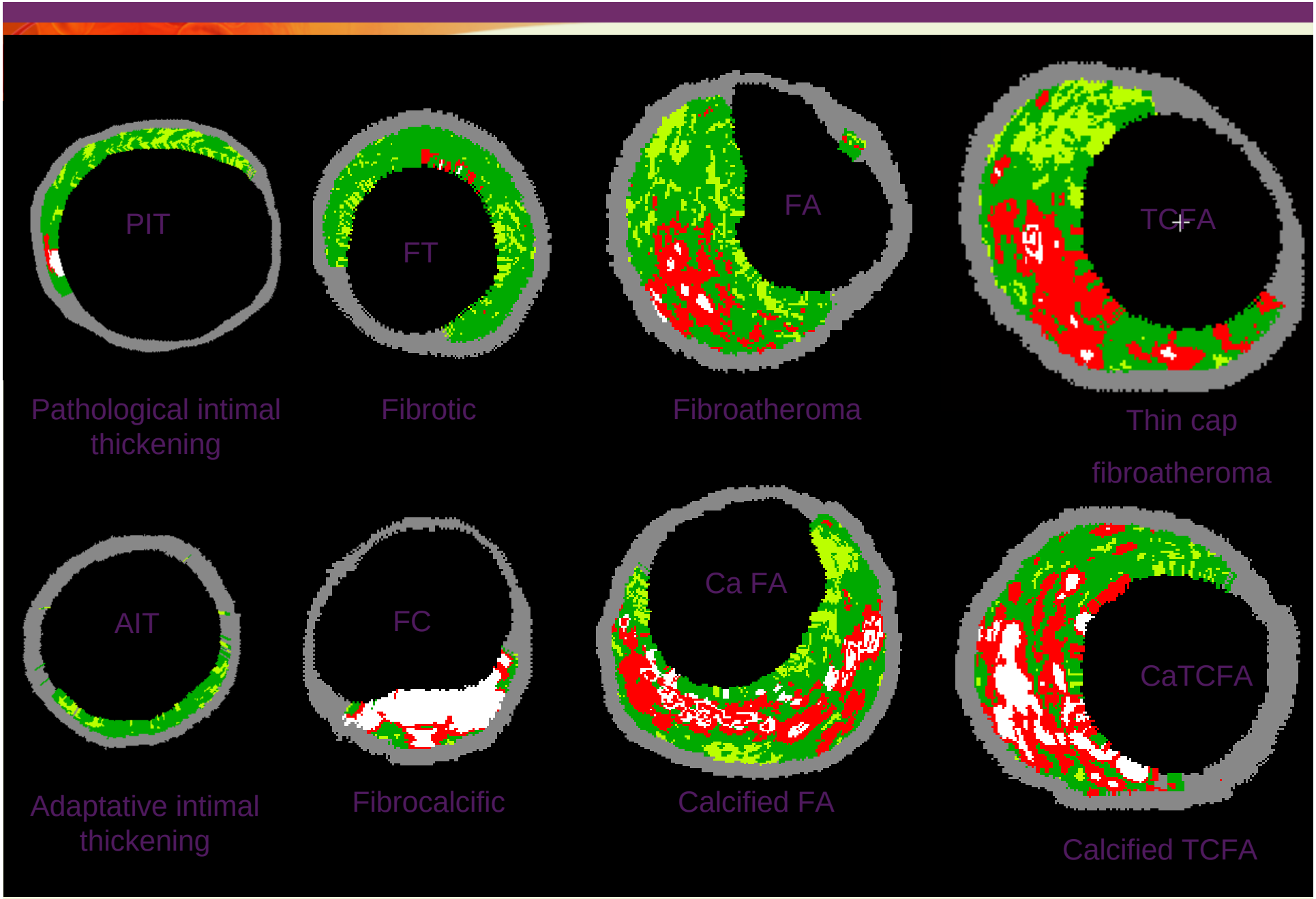
IBIS-2

Placebo-treated (ID278)



One interpretation





Atheroma heterogeneity

CAD Genetics and Darapladib

Cardiolysis Meeting
Rotterdam 02/24/09

Vincent Mooser MD
with the contribution by :
IBIS-2 Investigators !
Dawn Waterworth, Andrew Zalewski, Kijoung Song, Noha Lim, Xin Yuan, Mike Mosteller and Lon Cardon

Genetics

gsk GlaxoSmithKline

Chromosome 9p21 locus and CAD – X-Sectional Studies

A Common Variant on Chromosome 9p21 Affects the Risk of Myocardial Infarction

Anna Helgadottir,[1]* Gudmar Thorleifsson,[1]* Andrei Manolescu,[1]* Solveig Gretarsdottir,[1]

A Common Allele on Chromosome 9 Associated with Coronary Heart Disease

Ruth McPherson,[1]*† Alexander Pertsemlidis,[2]* Nihan Kavaslar,[1] Alexandre Stewart,[1]

Chromosome 9p21.3 Coronary Heart Disease Locus Genotype and Prospective Risk of CHD in Healthy Middle-Aged Men

Philippa J. Talmud,[1] Jackie A. Cooper,[1] Jutta Palmen,[1] Ruth Lovering,[2] Fotios Drenos,[1] Aroon D. Hingorani,[3] and Steve E. Humphries[1]*

Four SNPs on Chromosome 9p21 in a South Korean Population Implicate a Genetic Locus That Confers High Cross-Race Risk for Development of Coronary Artery Disease

Gong-Qing Shen, Lin Li, Shaoqi Rao, Kalil G. Abdullah, Ji Min Ban,

Genome-wide association study of 14,000 cases of seven common diseases and 3,000 shared controls

The Wellcome Trust Case Control Consortium*

Repeated Replication and a Prospective Meta-Analysis of the Association Between Chromosome 9p21.3 and Coronary Artery Disease

Heribert Schunkert, MD; Anika Götz, MSc; Peter Braund, MSc; Ralph McGinnis, PhD;

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 AUGUST 2, 2007 VOL. 357 NO. 5

Genomewide Association Analysis of Coronary Artery Disease

Nilesh J. Samani, F.Med.Sci., Jeanette Erdmann, Ph.D., Alistair S. Hall, F.R.C.P., Christian Hengstenberg, M.D.,

Whole Genome Analyses Suggest Ischemic Stroke and Heart Disease Share an Association With Polymorphisms on Chromosome 9p21

Mar Matarin, PhD; W. Mark Brown, MA; Andrew Singleton, PhD; John A. Hardy, PhD; James F. Meschia, MD; for the ISGS investigators

Overall risk (r)/non-Risk (nr) allele frequency : ~ 50/50%
Overall genotype frequency : 25% nr/nr, 50% r/nr, 25% r/r
Overall risk for CAD : ~35% increase per risk allele
Increased risk for AAA, Stroke, cerebral aneuvrysm
No Association with known CVRFs. Mechanism unknown

9p21 and CAD – Prospective Study

Clinical Chemistry 54:3
467–474 (2008)

Lipids, Lipoproteins, and Cardiovascular Risk Factors

Chromosome 9p21.3 Coronary Heart Disease Locus Genotype and Prospective Risk of CHD in Healthy Middle-Aged Men

Philippa J. Talmud,[1] Jackie A. Cooper,[1] Jutta Palmen,[1] Ruth Lovering,[2] Fotios Drenos,[1] Aroon D. Hingorani,[3] and Steve E. Humphries[1*]

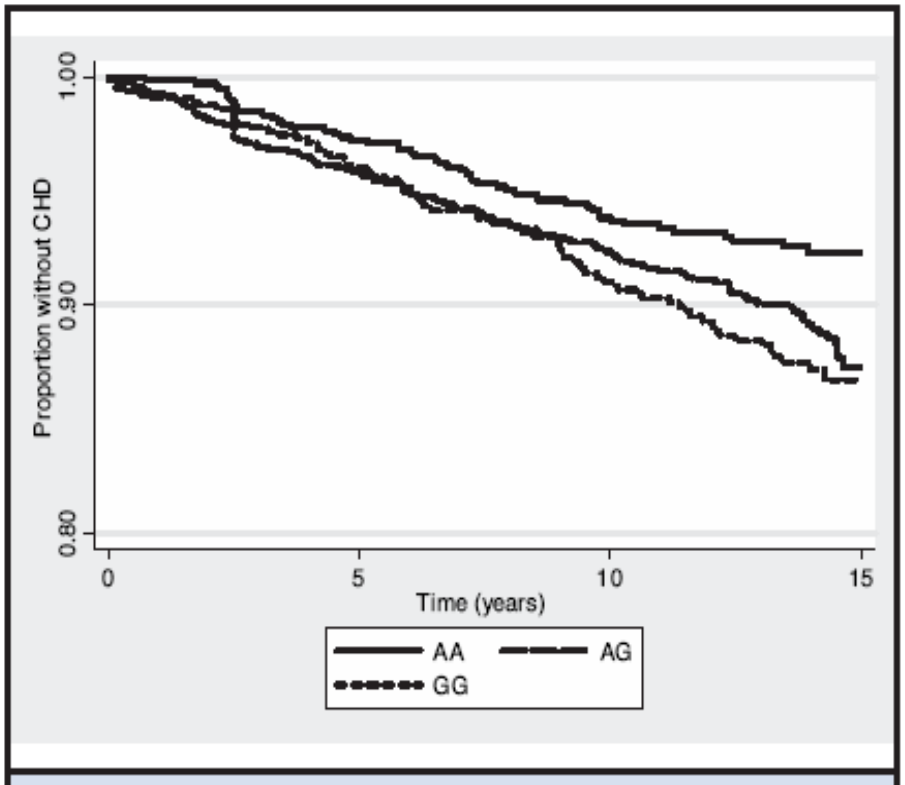


Fig. 1. Kaplan-Meier survival plot for rs10757274 A>G in NPHS-II men.

- Northwick Park Heart Study II
- 2742 healthy middle-aged men
  270 CAD events occurring
  15-year prospective study

Note : 9p21-associated risk of secondary event not reported

Genetics

9p21 and Darapladib : Questions

1. Does the 9p21 locus impact on the morphological and mechanical properties of coronary plaques ?

2. Does the 9p21 locus impact on the response to Darapladib-mediated inhibition of LpPLA2 ?

→ Potential relevance :

- → Better understanding of the biology of CAD
- → Enrichment with high-risk/high responders for future darapladib trials

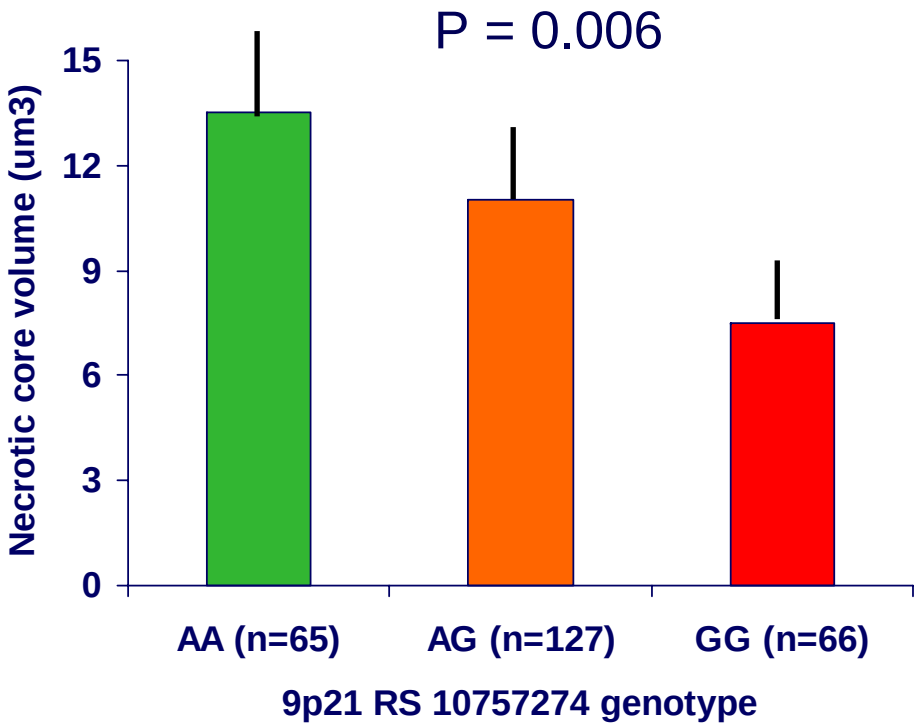
Genetics

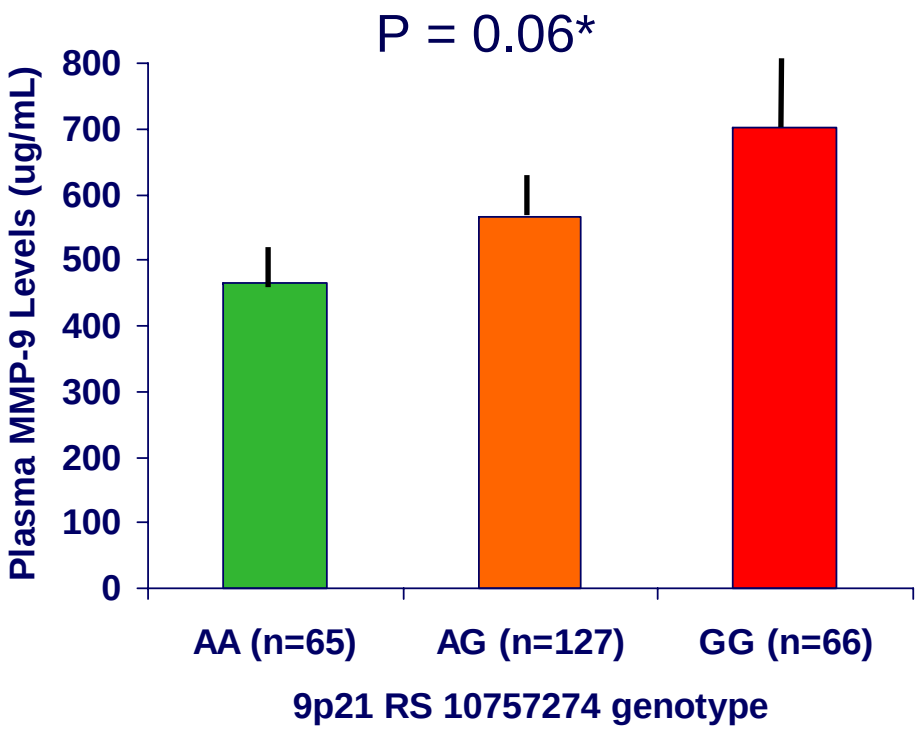
Methods : Analysis of 9p21 Locus in IBIS-2

- Baseline subjects with genotypes n=258
  - Follow-up IVUS n=226
  - Follow-up biomarker n=250
- Genotypes :
  - 3 SNPs for 9p21 locus
- Analysis : additive model, nominal and empirical p-value (10.000 permutations)

Genetics

Effect of 9p21 Locus on Necrotic Core and Plasma MMP9 Levels at Baseline





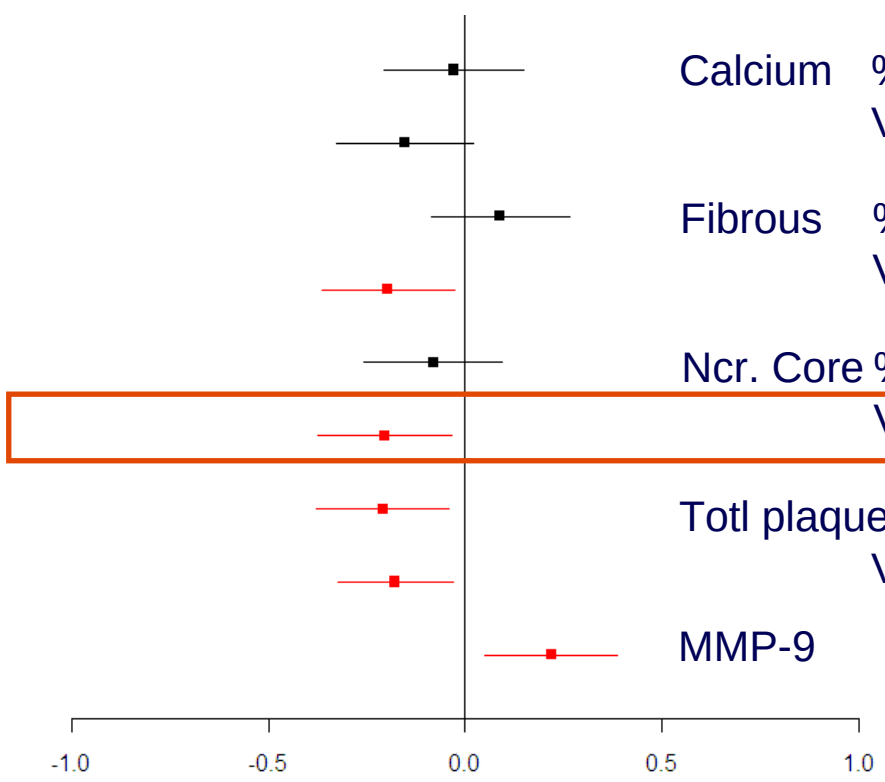
Note : G = risk allele for CAD
Mean +/- SEM

*p = 0.002 using mixed model over study period

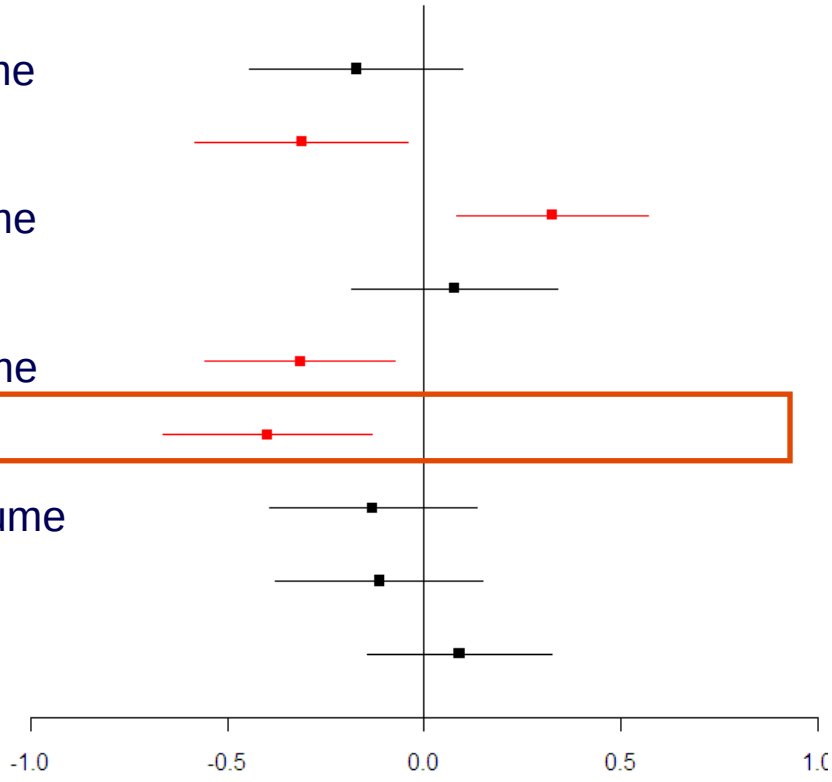
Genetics

9p21 vs Darapladib

Effect of lifetime exposure to 9p21 risk alleles



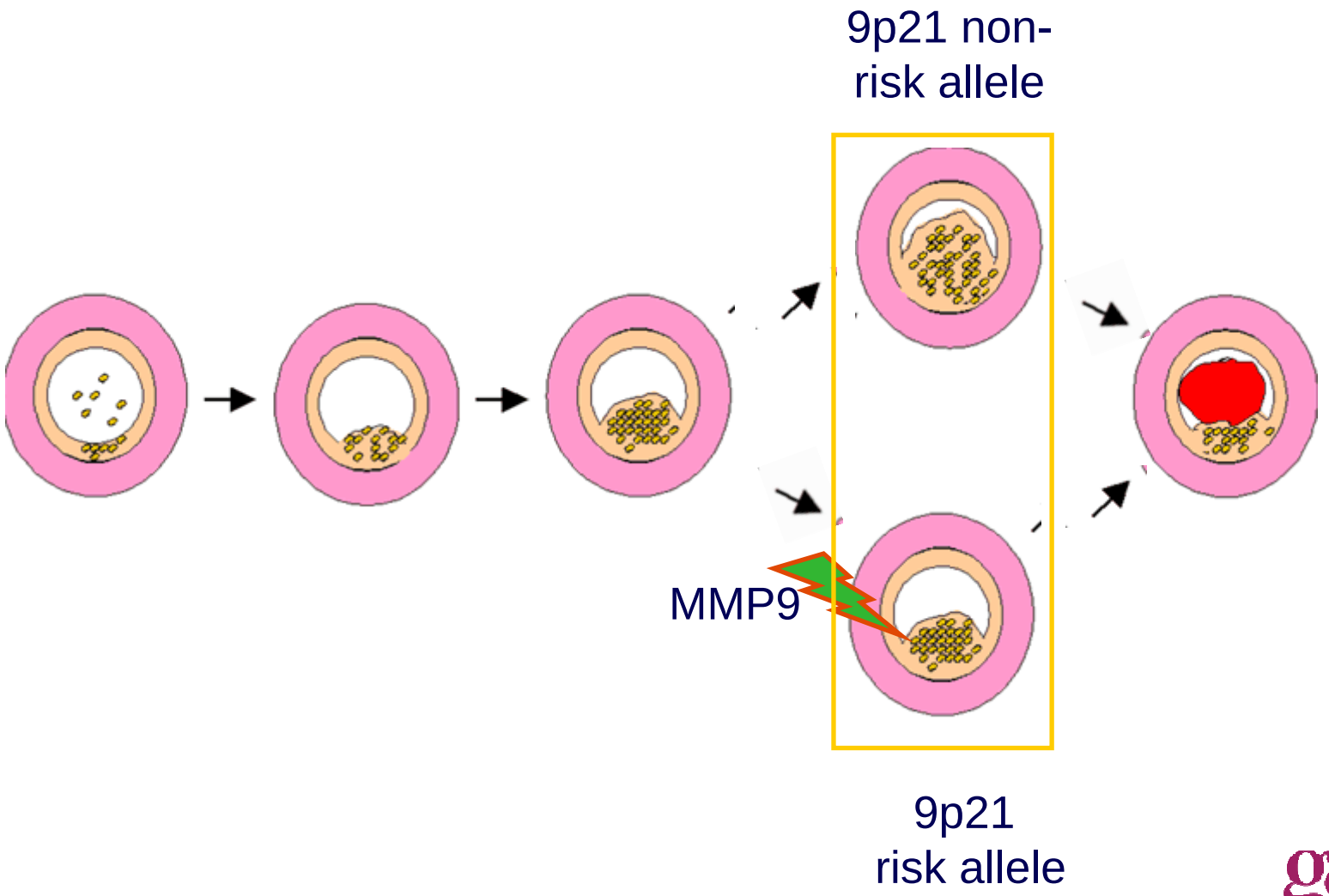
Effect of 1 yr Darapladib treatment



Betas and 95%CI shown.
Darapladib variables Z-score transformed
9p21 variables logged and Z-score transformed

Genetics

One interpretation



Genetics

Summary

- 9p21 risk allele for CAD/AAA associated with smaller plaques
- 9p21 associated with plaque size, not composition
  Darapladib associated with plaque composition, not size
- First direct evidence that 9p21 is a susceptibility locus for plaque rupture, possibly through increased MMP9 levels*
- No significant association between 9p21 and drug response or progression of the plaques (data not shown)

Notes : No effect of 9p21 on number of lesions, lumen size in LCAS Study (BMC Jan 27th, 2009, back-up slide) and in Salt Lake City Study (Am Heart J, Dec 2008, back-up slide).
**Consistent with increased compliance of abdominal aorta (J Int Med 2009, epub, back-up slide).*

Genetics

9p21 : Next Steps ?

- Publication ? Additional material/analyses required ?
- Replication with Approach : ongoing
- Systematic analysis of the effect of 9p21 genotype on ‘omic’ biomarkers in AtheroRemo ?

  → Expected results :
  - Better understanding of the biology of 9p21in humans ?
  - Biomarkers for plaque instability (→ surrogate markers for interventions aimed at plaque stabilization ?)

- Need to collect DNA for all participants of Darapladib Trial

  → Expected results :
  - Post-hoc analysis of the effect of 9p21 on response to LpPLA2 inhibition

Genetics

Back-Up Slides

BMC Jan 27th, 09 : LCAS Study

BMC Cardiovascular Disorders

BioMed Central

Research article

Open Access

The 9p21 susceptibility locus for coronary artery disease and the severity of coronary atherosclerosis

Suet Nee Chen[1,2], Christie M Ballantyne[3], Antonio M Gotto Jr[4] and Ali J Marian*[1]

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Email: Suet Nee Chen - snchen@bcm.tmc.edu; Christie M Ballantyne - cmb@bcm.tmc.edu; Antonio M Gotto - Dean@med.cornell.edu; Ali J Marian* - Ali.J.Marian@uth.tmc.edu

* Corresponding author

Published: 27 January 2009

BMC Cardiovascular Disorders 2009, **9**:3 doi:10.1186/1471-2261-9-3

Received: 19 September 2008
Accepted: 27 January 2009

Genetics

BMC / LCAS

	Genotypes			
	GG	**GA**	**AA**	**P**
N = 288	77	162	49	
Number of coronary lesions (mean)	3.09 ± 1.43	2.93 ± 1.37	3.06 ± 1.30	0.639
≥ 1 coronary lesion (%)	77 (87.5)	161 (84.7)	49 (90.7)	0.495
Number of coronary occlusions(mean)	0.34 ± 0.59	0.27 ± 0.54	0.30 ± 0.50	0.636
≥ 1 coronary occlusion (%)	25 (28.4)	43 (22.6)	15 (27.8)	0.513
Baseline MLD (mm)	1.65 ± 0.39	1.69 ± 0.40	1.68 ± 0.40	0.819

Abbreviations: BMI: Body mass index; BP: Blood pressure; MI: Myocardial infarction; other abbreviations are as in Table 1
* indicates p value by non-parametric Kruskal-Wallis test

Genetics

Am Heart J, Dec 08

Genetics

(Am Heart J 2008;156:1155-1162.e2.)

Genetic variation at the 9p21 locus predicts angiographic coronary artery disease prevalence but not extent and has clinical utility

Jeffrey L. Anderson, MD, FACC,[a,b] Benjamin D. Horne, PhD, MPH,[a,c] Matthew J. Kolek, MD,[a] Joseph B. Muhlestein, MD, FACC,[a,b] Chrissa P. Mower, BS,[a] James J. Park, BS,[a] Heidi T. May, MSPH,[a,b] Nicola J. Camp, PhD,[c] and John F. Carlquist, PhD[a,b] *Murray and Salt Lake City, UT*

Table V. Extent of CAD by rs2383206 genotype

Severely diseased vessels	Low-risk homozygote (n [%] within genotype)	Heterozygote (n [%] within genotype)	High-risk homozygote (n [%] within genotype)
1	167 (47.7%)	438 (50.8%)	253 (46.3%)
2	100 (28.6%)	245 (28.5%)	150 (27.5%)
3	83 (23.7%)	180 (20.9%)	143 (26.2%)
			$P = .31$
CAD Index[26] Mean (SD)	44.7 (16.7)	43.8 (17.5)	45.4 (18.2)
			$P = .42$

Genetics

Original Article

Journal of INTERNAL MEDICINE

doi: 10.1111/j.1365-2796.2008.02020.x

Association of genetic variation on chromosome 9p21.3 and arterial stiffness

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From the [1]Division of Cardiovascular Medicine, Department of Medical and Health Sciences; [2]Division of Drug Research, Department of Medical and Health Sciences, Faculty of Health Sciences, Linköping University, Linköping; and [3]Atherosclerosis Research Unit, Center for Molecular Medicine, Department of Medicine, Karolinska Institute, Stockholm; Sweden

Genetics

Table 2 Characteristics according to rs10757274A/G

	Men			
	A/A	A/G and G/G	*P*	P_{Adj}
N	50	144		
Arterial wall properties				
Intima-media thickness (mm)	0.54 (0.13)	0.54 (0.14)	0.896	
Lumen diameter (mm)				
Diastolic	17.6 (2.5)	17.4 (3.9)	0.726	0.894[a]
Systolic	18.1 (2.5)	18.1 (3.4)	0.960	
ΔSysDia	0.48 (0.31)	0.64 (0.37)	0.013	
Compliance coefficient ($mm^2\ kPa^{-1}$)	1.68 (1.27)	2.08 (1.41)	0.048	0.025[b]
Distensibility coefficient ($10^{-3}\ kPa^{-1}$)	7.08 (5.47)	9.40 (7.06)	0.023	0.018[b]
Aortic stiffness (β)	35.77 (24.41)	25.96 (18.99)	0.008	0.011[c]
Wall stress ($dyne\ cm^{-2}$)	17.78 (5.17)	17.80 (5.63)	0.987	0.986[d]

Baseline characteristics (raw values) of imaging and biomarkers according to rs10757274 (9p21) in IBIS-2

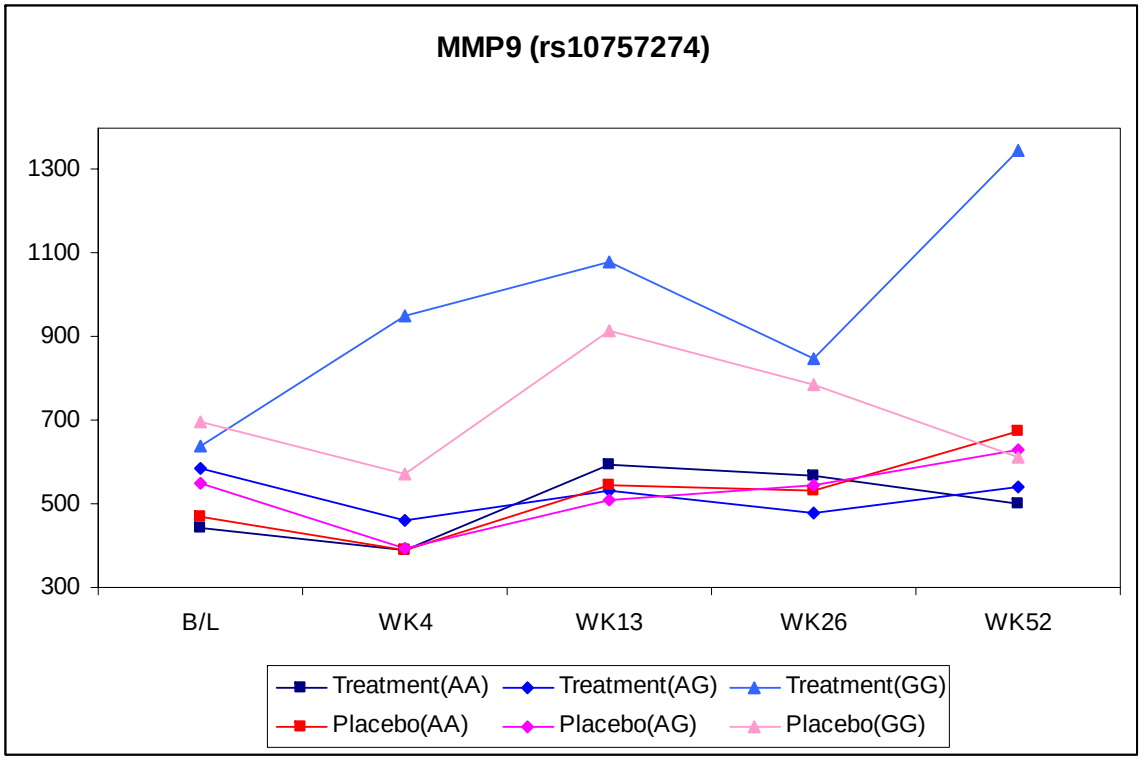
Parameters	AA	GA	GG	p-value
N	66	127	65	
ca_pct	7.34 ± 5.32	6.71 ± 5.22	7.28 ± 5.12	0.6169
ca_vol	14.58 ± 21.20	10.88 ± 11.36	10.22 ± 17.22	0.0911
fibrotissue_pct	58.78 ± 7.21	59.74 ± 7.78	60.28 ± 7.76	0.5736
fibrotissue_vol	99.80 ± 66.76	99.43 ± 76.52	71.34 ± 56.86	0.0121
nec_core_pct	14.68 ± 7.71	12.49 ± 6.73	12.97 ± 6.75	0.1474
nec_core_vol	27.38 ± 27.06	20.81 ± 18.45	16.46 ± 22.43	0.0182
tot_plaq_vol	172.58 ± 120.57	166.75 ± 125.20	122.28 ± 105.63	0.0105
LpPLA2	162.22 ± 43.18	168.39 ± 41.81	158.93 ± 46.82	0.4278
dens_34sp	0.57 ± 0.65	0.71 ± 0.62	0.73 ± 0.70	0.3585
hsCRP	8.04 ± 24.15	10.23 ± 21.63	10.31 ± 28.30	0.9183
CD40L	275.84 ± 410.88	275.99 ± 640.74	440.01 ± 1033.51	0.6668
IL6	4.95 ± 5.39	8.42 ± 17.11	7.24 ± 12.23	0.6621
MMP9	464.25 ± 472.68	567.54 ± 555.50	703.20 ± 834.94	0.0591
MPO	817.32 ± 661.96	1002.34 ± 899.51	964.05 ± 885.54	0.3675
oxPL_apoB	3190.88 ± 3652.02	4374.02 ± 5065.93	2763.73 ± 2868.92	0.1433
SICAM1	268.33 ± 80.73	254.60 ± 64.82	267.77 ± 70.51	0.3746
LDL	2.73 ± 0.95	2.85 ± 1.07	2.57 ± 1.04	0.1753
HDL	1.22 ± 0.28	1.20 ± 0.27	1.25 ± 0.36	0.8427
TG	1.90 ± 1.29	1.77 ± 1.13	1.94 ± 1.05	0.3951
CHOL	4.79 ± 1.11	4.83 ± 1.17	4.75 ± 1.26	0.7378
tot_plaq_vol_plus_media	350.85 ± 170.32	337.20 ± 173.19	274.87 ± 147.79	0.0092

* mean ± SD

Genetics

9p21 Other Findings in IBIS-2

- No significant effect on progression of plaques in placebo or treatment arms
- No significant interactions between genotype and size of the treatment effect
- Risk allele associated with increased plasma levels of MMP9 (p = 0.002 using mixed model)



Genetics