Slide 1

New frontiers in Interventional Cardiology- the Identification and Molecular Targeting of Vulnerable Atherosclerotic Plaque

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wellcome trust

British Heart Foundation

Imperial College London

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The emerging role of Academic Interventional Cardiology in the UK

Hammersmith Hospital- Primary Angioplasty Centre for NW London

NHLI- Imperial Centre for Translational and experimental Medicine

Imperial College Healthcare NHS Trust

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Aims and Objectives

- Outline the process of atherosclerosis
- Discuss the concept of vulnerable atherosclerotic plaque and its pathological significance.
- Outline the main interventional imaging technologies available to identify vulnerable plaque
- Present novel work undertaken by our group aimed to target vulnerable plaque
- Discuss the role of novel biomarkers in identifying vulnerable patients..

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Concept of plaque stabilisation

- emerged about 20 years ago in an attempt to explain the discrepancy between the reduction of cardiovascular events in patients receiving lipid lowering therapy without concomitant regression of coronary atherosclerosis in angiography.

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The hypothesis of Plaque stabilisation

- A plaque can be stabilised by increasing the thickness of fibrous cap, reducing inflammation in the fibrous ap and reducing the size of atheromatous care.
- A plaque may be stabilised against thrombosis independent of changes in plaque size and luminal obstruction.

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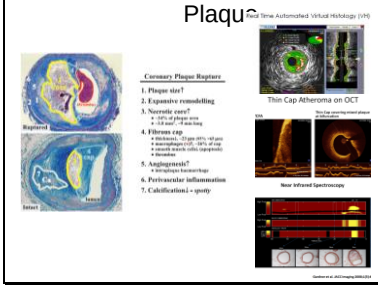
Characteristics of Vulnerable Plaqu



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Thin Cap fibro-atheroma Fibroatheroma
TCFA

- IVUS VH definition: a large (>10% of plaque area) necrotic core component that is in extensive contact (>30° arc) with the lumen. Invisible cap.
- OCT derfinition : lipid-rich plaque with fibrotic cap thickness <65 µm.

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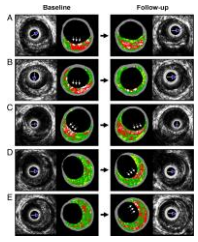
Representative Images of Serial Intravascular Ultrasound at Baseline and Follow-Up



Kubo, T. et al. J Am Coll Cardiol 2010;55:1590-1597

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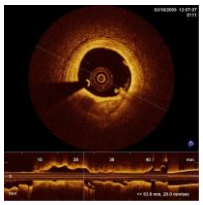
Burst Cap and Thrombus



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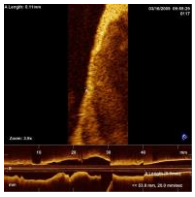
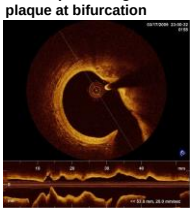
Thin Cap Atheroma on OCT

TCFA



Thin Cap covering mixed plaque at bifurcation



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The PROSPECT Trial

Providing Regional Observations to Study Predictors of Events in the Coronary Tree

A Natural History Study of Atherosclerosis Using Multimodality Intracoronary Imaging to Prospectively Identify Vulnerable Plaque

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PROSPECT – Study Design

- A prospective, multicenter natural history study using 3 vessel multimodality intracoronary imaging to quantify the clinical event rate due to atherosclerotic progression and to identify those lesions which place pts at risk for unexpected adverse cardiovascular events

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PROSPECT - Design

700 pts with ACS

UA (with ECGΔ) or NSTEMI or STEMI >24º undergoing PCI of 1 or 2 major coronary arteries at up to 40 sites in the U.S. and Europe

Metabolic S.
- Waist circum
- Fast lipids
- Fast glu
- HgbA1C
- Fast insulin
- Creatinine

PCI of culprit lesion(s)
Successful and uncomplicated

Formally enrolled

Biomarkers
- Hs CRP
- IL-6
- sCD40L
- MPO
- TNFα
- MMP9
- Lp-PLA2
- others

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3-vessel imaging post PCI

Culprit artery, followed by non-culprit arteries

Angiography (QCA of entire coronary tree)

IVUS
Virtual histology
Palpography (n=~350)

Proximal 6-8 cm of each coronary artery

Meds rec
Aspirin
Plavix 1yr
Statin
Repeat biomarkers @ 30 days, 6 months

F/U: 1 mo, 6 mo, 1 yr, 2 yr, ±3-5 yrs

MSCT Substudy N=50-100
Repeat imaging in pts with events

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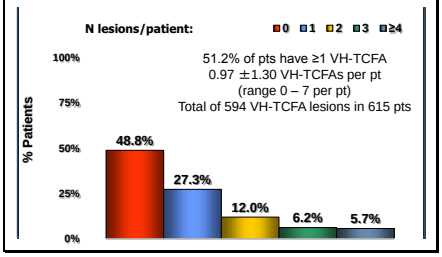
PROSPECT: Imaging Summary

Per patient incidence of VH-TCFAs



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PROSPECT: MACE

3-year follow-up, non hierarchical

	All	Culprit lesion related	Non culprit lesion related	Indeter-minate
Cardiac death	1.9% (12)	0.2% (1)	0% (0)	1.8% (11)
Cardiac arrest	0.5% (3)	0.3% (2)	0% (0)	0.2% (1)
MI (STEMI or NSTEMI)	3.3% (21)	2.0% (13)	1.0% (6)	0.3% (2)
Unstable angina	8.0% (51)	4.5% (29)	3.3% (21)	0.5% (3)
Increasing angina	14.5% (93)	9.2% (59)	8.5% (54)	0.3% (2)
Composite MACE	20.4% (132)	12.9% (83)	11.6% (74)	2.7% (17)
Cardiac death, arrest or MI	4.9% (31)	2.2% (14)	1.0% (6)	1.9% (12)

Rates are 3-yr Kaplan-Meier estimates (n of events)

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PROSPECT: Multivariable Correlates of Non Culprit Lesion Related Events

Independent predictors of lesion level events by logistic regression analysis

Variable	OR [95% CI]	P value
PB_{MLA} ≥70%	4.99 [2.54, 9.79]	<0.0001
VH-TCFA	3.00 [1.68, 5.37]	0.0002
MLA ≤4.0 mm²	2.77 [1.32, 5.81]	0.007
Lesion length ≥11.6 mm	1.97 [0.94, 4.16]	0.07

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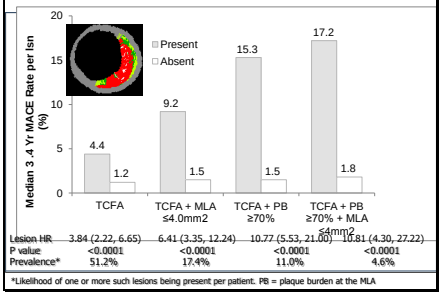
PROSPECT: VH-TCFA and Non Culprit Lesion Related Events



*Likelihood of one or more such lesions being present per patient. PB = plaque burden at the MLA

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PROSPECT - Conclusions

- Approximately 20% of pts with ACS successfully treated with stents and contemporary medical Rx develop MACE within 3 years, with adverse events equally attributable to recurrence at originally treated culprit lesions (treatment failure) and to previously untreated non culprit coronary segments
- Approximately 12% of pts develop MACE from non culprit lesions during 3 years of follow-up
- Patients treated with contemporary medical therapy who develop non culprit lesion events present most commonly with progressive or unstable angina, and rarely with cardiac death, cardiac arrest or MI

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PROSPECT - Conclusions

- While plaques which are responsible for unanticipated future MACE are frequently angiographically mild, most untreated plaques which become symptomatic have a large plaque burden and a small lumen area (which are detectable by IVUS but not by angiography)
- The prospective identification of non culprit lesions prone to develop MACE within 3 years can be enhanced by characterization of underlying plaque morphology with virtual histology, with VH-TCFAs representing the highest risk lesion type
- The combination of large plaque burden (IVUS) and a large necrotic core without a visible cap (VH-TCFA) identifies lesions which are at especially high risk for future adverse cardiovascular events

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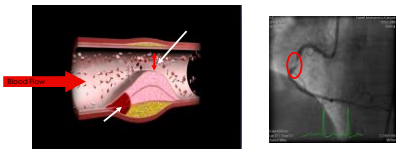
Culprit of the Culprit Concept



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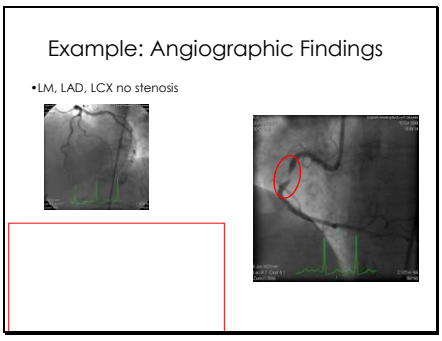

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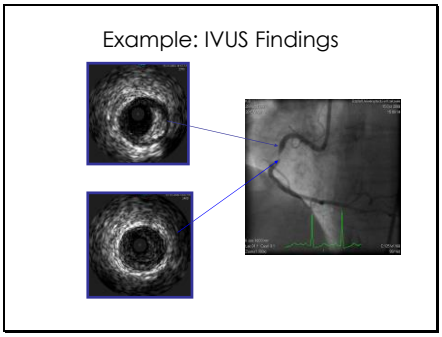

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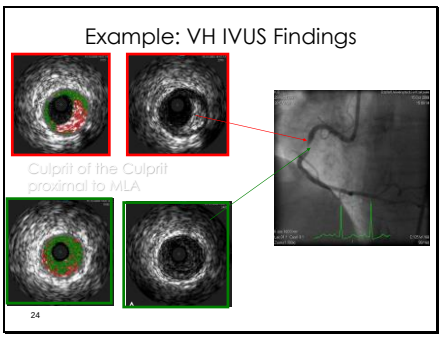

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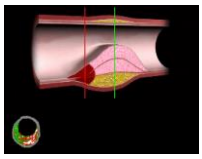
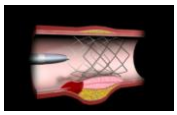
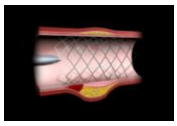


has ruptured



Angio guided



VH IVUS guided stent choice

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Molecular identification of vulnerable plaque- so what?

- A risk stratification tool beyond Framingham Risk Scoring, or morphological risk stratification techniques (CT/ IVUS/OCT/Lipiscan)
- Use in progression studies (eg when studying statins)
- Potential as a carrier for targeted drug delivery
- Use as an adjunctive tool for the interventional cardiologist- where to stent and what with?

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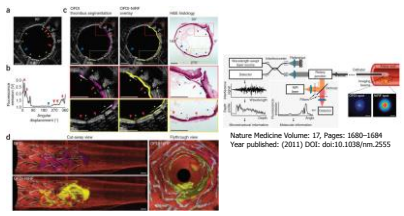
Dual-modality intra-arterial catheter for simultaneous microstructural and molecular imaging using OFDI and NIRF



Nature Medicine Volume: 17, Pages: 1680–1684 Year published: (2011) DOI: doi:10.1038/nm.2555

Nature Medicine Volume: 17, Pages: 1680–1684 Year published: (2011) DOI: doi:10.1038/nm.2555

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LO1 – an anti-oxidised LDL autoantibody

- LO1 is an IgG3k monoclonal antibody generated by a hybridoma formed using splenocytes of a low density lipoprotein receptor knockout (LDLr $^{-/-}$) mouse
- LO1 reacts with oxidised LDL, but not with native LDL

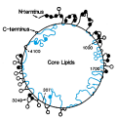

Figure adapted from figure 5 of Yang et al, , Arterioscler Thromb Vasc Biol. 1989

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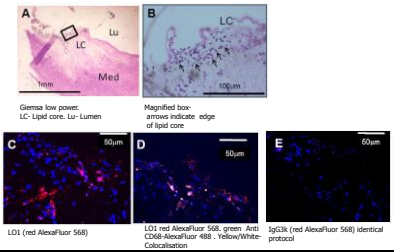
Immunocytochemical staining of human carotid atherosclerotic plaque with mAb LO1



Giemsa low power. LC- Lipid core. Lu- Lumen

Magnified box- arrows indicate edge of lipid core

LO1 (red AlexaFluor 568)

LO1 red AlexaFluor 568. green Anti CD68-AlexaFluor 488 . Yellow/White- Colocalisation

IgG3k (red AlexaFluor 568) identical protocol

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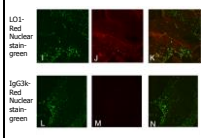
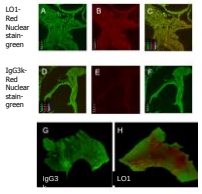
Immunocytochemical staining of LDLr$^{-/-}$ mouse aortic root and human carotid atherosclerotic plaque with directly labeled mAb LO1 (LO1-750)

LO1-750 vs IgG3k-750 on human culprit carotid plaque



LO1-750 vs IgG3k-750 on LDLr$^{-/-}$ aorta



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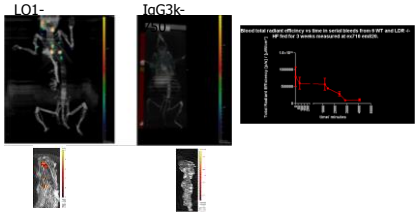
IVIS-Spectrum and High resolution CT Hybrid imaging on LO1-750 vs IgG3k in >6 month old LDLr $^{-/-}$ mouse and litter-mate control.



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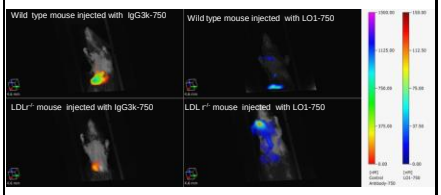
FMT study of LO1-750 in LDLr $^{-/-}$ vs IgG3k-750 and wild type controls.



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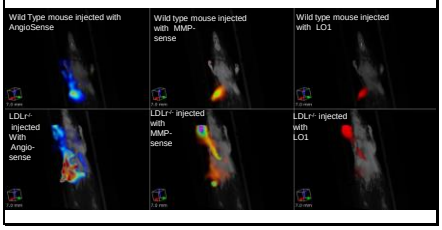
AngioSense, MMP Sense and LO1-750 in wild type (top panel) and LDLr$^{-/-}$ (bottom panel) animals



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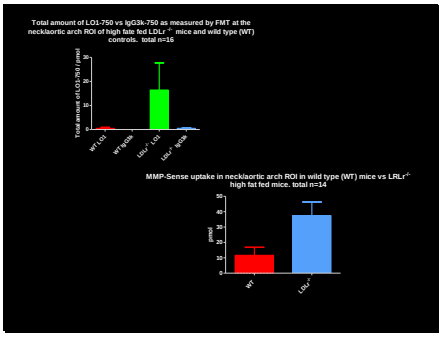

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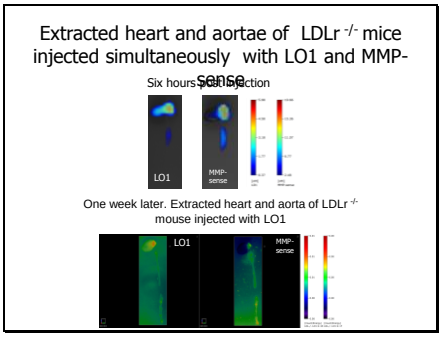

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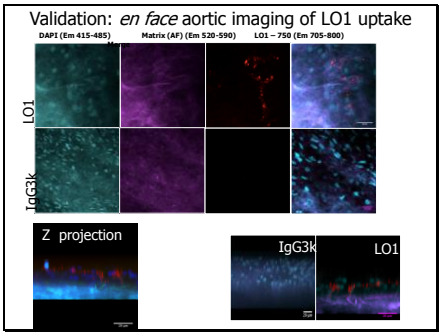

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From the vulnerable plaque to the vulnerable patient

Risk stratifcation beyond classical risk factors. Lipids and CRP

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ASCOT-ANTIOX.
The ASCOT Anti-Oxidised LDL Antibodies Substudy.

Khamis RY, Johns M et al
Heart 2011;97:e7 doi:10.1136/heartjnl-2011-300920b.9

IgG anti-malondialdehyde-LDL antibodies are independent predictors of protection from cardiovascular events in a substudy of the Anglo-Scandinavian Cardiac Outcomes Trial (ASCOT)

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Baseline Characteristics

Variable	All (n = 199)		Placebo (n = 99)		Atorvastatin (n = 100)	
Male sex, n (%)	184	(92%)	92	(92%)	92	(92%)
Age, years	63.4	(7.4)	63.4	(7.4)	63.5	(7.4)
Body mass index, kg/m^2	28.7	(4.1)	28.6	(4.1)	28.9	(4.1)
Systolic blood pressure, mmHg	159	(16)	159	(16)	159	(16)
Diastolic blood pressure, mmHg	93	(9)	93	(9)	93	(9)
Heart rate, bpm	70	(12)	71	(12)	69	(12)
Total cholesterol, mmol/l	5.6	(0.7)	5.5	(0.7)	5.6	(0.7)
Low density lipoprotein, mmol/l	3.5	(0.7)	3.5	(0.7)	3.4	(0.8)
High density lipoprotein, mmol/l	1.3	(0.4)	1.4	(0.4)	1.3	(0.3)
Triglycerides, mmol/l	1.6	(1.1, 1.9)	1.5	(1.0, 2.0)	1.6	(1.2, 1.9)
Creatinine, µmol/l	100	(15)	99	(15)	101	(15)
Fasting glucose, mmol/l	5.2	(0.6)	5.2	(0.6)	5.2	(0.6)
CRP, mg/l	2.98	(2.98, 4.99)	3.00	(0.77, 4.99)	2.56	(1.14, 4.74)
Current smokers, n (%)	44	(22)	21	(21)	23	(23)
IgM anti MDA-LDL abs at baseline, Standard-Corrected OD_{450}	0.70	(0.37)	0.71	(0.40)	0.70	(0.34)
IgM anti MDA-LDL abs at baseline, Standard-Corrected OD_{450}	0.70	(0.71)	0.83	(0.85)	0.69	(0.53)
IgG anti PC-BSA abs at baseline, Standard-Corrected OD_{450}	1.28	(0.48)	1.24	(0.48)	1.32	(0.47)
IgM anti PC-BSA abs at baseline, Standard- Corrected OD_{450}	0.87	(0.45)	0.89	(0.47)	0.85	(0.43)
Total IgG at baseline, Standard-Corrected OD_{450}	1.78	(0.27)	1.78	(0.28)	1.77	(0.26)
Total IgM at baseline, Standard-Corrected OD_{450}	1.14	(0.32)	1.10	(0.33)	1.14	(0.31)

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One year

Variable	Placebo (n = 99)	Atorvastatin (n = 100)	Difference (P-A)	95% CI	p
IgG anti MDA-LDL abs at baseline , Standard-Corrected OD450	0.74 (0.46)	0.76 (0.42)	-0.02	(-0.15, 0.11)	0.7
IgM anti MDA-LDL abs at baseline , Standard- Corrected OD450	0.85 (0.61)	0.87 (0.83)	-0.02	(-0.23, 0.20)	0.9
IgG anti PC-BSA abs at baseline , Standard-Corrected OD450	1.21 (0.59)	1.32 (0.66)	-0.1	(-0.29, 0.08)	0.3
IgM anti PC-BSA abs at baseline , Standard-Corrected OD450	0.93 (0.46)	0.92 (0.43)	0.18	(-0.11, 0.15)	0.8
Total cholesterol, mmol/l	5.5 (0.8)	4.0 (0.6)	1.5	(1.3, 1.7)	<0.001
Low density lipoprotein, mmol/l	3.4 (0.8)	2.1 (0.5)	1.3	(1.1, 1.5)	<0.001
High density lipoprotein, mmol/l	1.3 (0.4)	1.3 (0.4)	0	(-0.1, 0.1)	>0.9
log CRP, mg/l	0.69 (1.08)	0.29 (1.23)	0.39	(0.07, 0.72)	0.01

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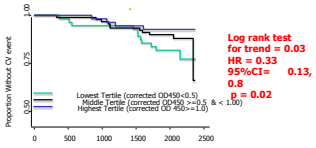
Kaplan-Meier survival estimates for population tertiles of IgG anti MDA-LDL Levels



Log rank test for trend = 0.03
HR = 0.33 95%CI= 0.13, 0.8
p = 0.02

Kaplan Meier survival curve reflecting the risk of major adverse cardiovascular events including cardiovascular death, heart attack, stroke, revascularisation in the study population. Being in the highest tertile significant protection against the composite end point of cardiovascular events including mortality with clear separation of the survival curves at 5 years

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Correlation matrices for baseline and one year

Table 3a. IgM	MDA-LDL at baseline	MDA-LDL at one year	PC-BSA at baseline
MDA-LDL at one year	0.56 (p<0.001)		
PC-BSA at baseline	0.47 (p<0.001)	0.27 (p<0.001)	
PC-BSA at one year	0.32 (p<0.001)	0.41 (p<0.001)	0.59 (p<0.001)

Table 3b. IgG	MDA-LDL at baseline	MDA-LDL at one year	PC-BSA at baseline
MDA-LDL at one year	0.53 (p<0.001)		
PC-BSA at baseline	0.19 (p=0.01)	0.15 (p=0.05)	
PC-BSA at one year	0.13 (p=0.1)	0.042 (p=0.6)	0.73 (p<0.001)

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Relationship between LDL and antibodies at baseline and one year

Table 3c	Baseline LDL		Year 1 LDL	
	r	p	r	p
Baseline anti MDA-LDL IgG	-0.13	0.10		
Year 1 anti MDA-LDL IgG			-0.04	0.65
Baseline anti MDA-LDL IgM	0.03	0.67		
Year 1 anti MDA-LDL IgM			-0.07	0.37
Baseline anti PC-BSA IgG	-0.07	0.38		
Year 1 anti PC-BSA IgG			-0.12	0.12
Baseline anti PC-BSA IgM	-0.04	0.60		
Year 1 anti PC-BSA IgM			-0.05	0.72
Baseline Total IgG	-0.08	0.31		
Baseline Total IgM	-0.03	0.84		

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Summary

- Identification of vulnerable plaque is so far elusive.
- Morphology based technologies (IVUS-VH and OCT are promising
- Antibody targeted imaging of highly oxidised LDL may add an important facet for the identification of ‘inflamed’ plaque
- Non invasive Identification of vulnerable patients needs to go hand in hand with interventional technologies