University of Glasgow

Forum Of Claims and Underwriting (Scotland)
14th June 2018
Edinburgh

Atherosclerosis
The world's worst serial killer

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Pasquale.Maffia@glasgow.ac.uk

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Institute of Infection, Immunity and Inflammation

University of Glasgow

Institute of Cardiovascular & Medical Sciences (ICAMS)

CoRE GLASGOW

4

Gifted by Prof. J. Walton, Dept. of Mathematics, Texas A&M University

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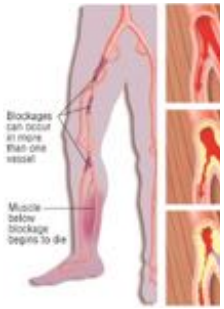
Clinical Manifestations

Transient Ischemic Attack / Stroke

Angina (pain) / Myocardial Infarction

Peripheral Arterial Disease



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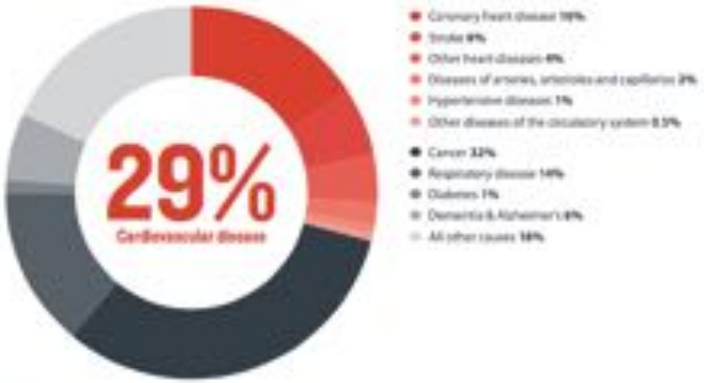
Death by CVD in men, United Kingdom 2012



www.heartstats.org

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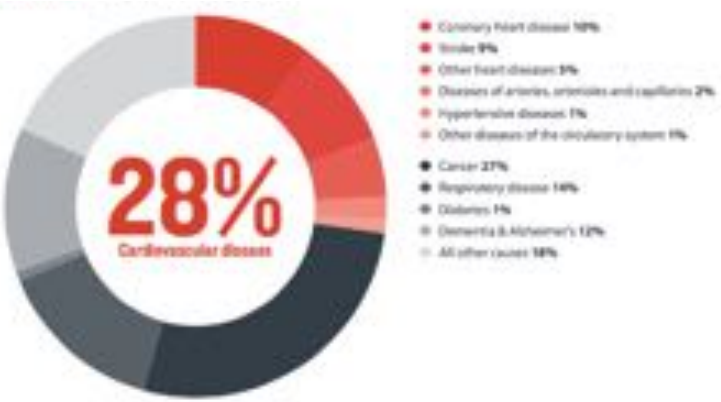
Death by CVD in women, United Kingdom 2012



www.heartstats.org

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Around 41,000 deaths were from stroke – 6% of male and 9% of female deaths

CHD by itself is the biggest single cause of death in the UK

www.heartstats.org

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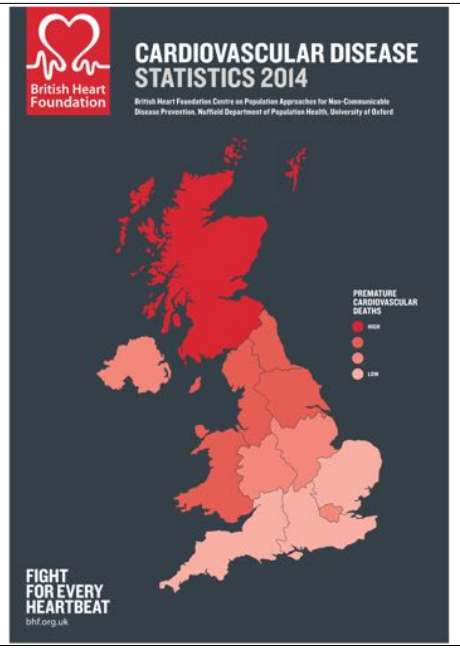

Age-standardised premature death rates for CVD, CHD and stroke are highest in Scotland and the North West of England

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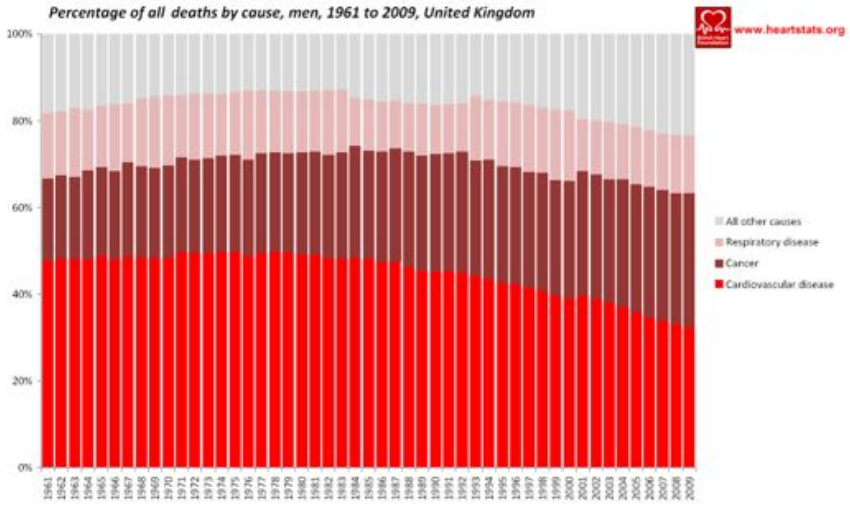

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Prescriptions

307 million

In 2013, more than 307 million prescriptions were dispensed for CVD in England, more than six times as many as issued in 1981

Interventions

92,000+

Over 92,000 percutaneous coronary interventions (PCI) were carried out in the UK in 2012, more than twice as many as a decade ago

Economic costs

£6.8bn

More than £6.8 billion was spent on treating CVD within the NHS in England in 2012/13. 63% of these costs came within secondary care and 27% within primary care.

www.heartstats.org

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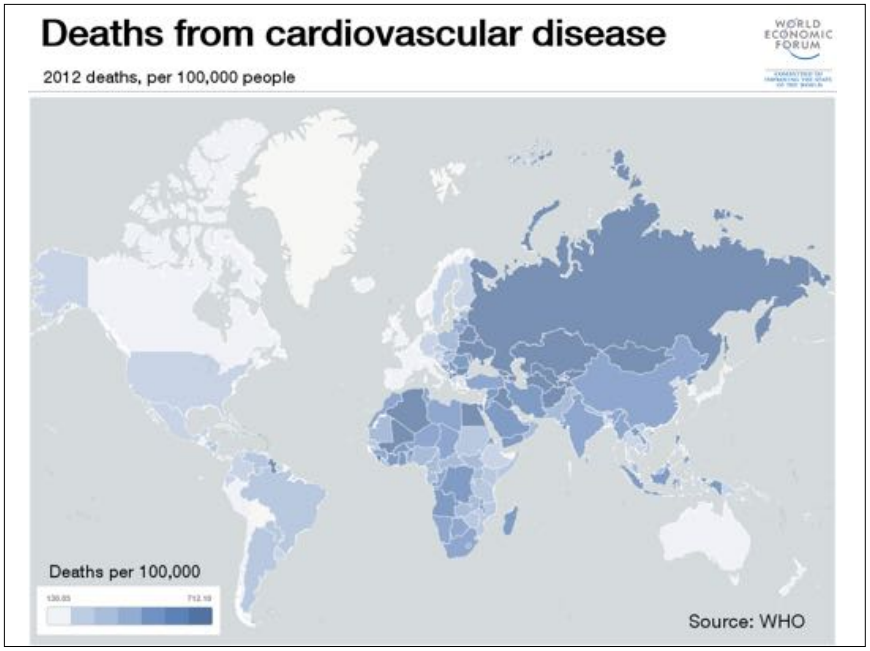

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Risk Factors

Permanent factors:
Increasing age
Gender
Family history of early coronary heart disease (e.g. in men <55 years and women <65 years)
Race, e.g. many South Asian races at higher risk.

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Risk Factors

Lifestyle, social and environmental factors:
Cigarette smoking
Lack of regular physical exercise
Diet: High-fat increase CVD risk
High alcohol intake
Psychosocial factors (e.g. stress, depression, deprivation).

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Risk Factors

Coexisting conditions:
Hypertension (35%-45% in Africa)
Diabetes
Hyperlipidaemia
Obesity
Systemic inflammation, eg in systemic lupus erythematosus, rheumatoid arthritis, periodontitis, etc.
Infection?

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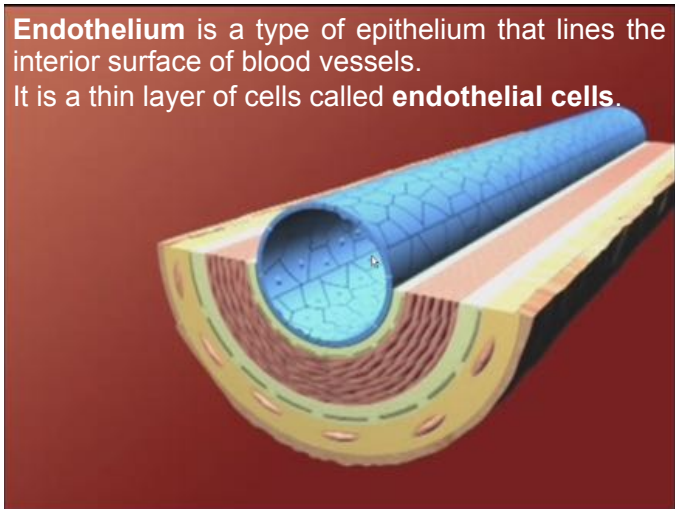
Coronary Heart Disease (CHD)

The heart gets its own supply of blood from a network of blood vessels on the heart's surface called **coronary arteries**.
Coronary heart disease is the term that describes what happens when your heart's blood supply is blocked or interrupted by a build-up of fatty substances in the coronary arteries.

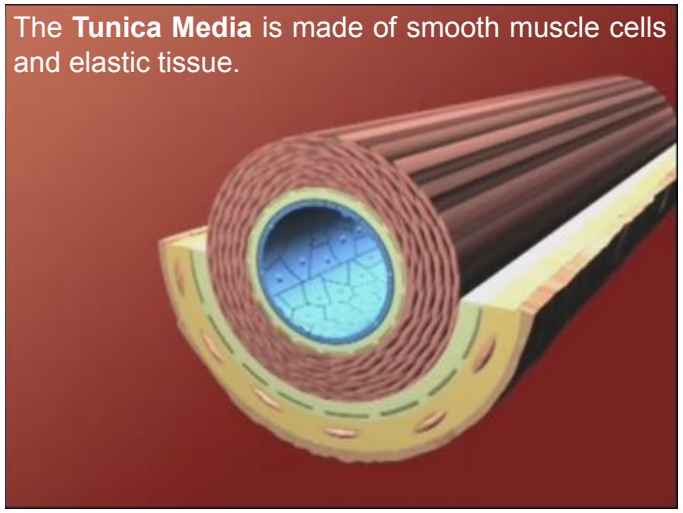
http://mediabyran.kib.ki.se/video/educational/coronary/index_se.html

Arterial Structure



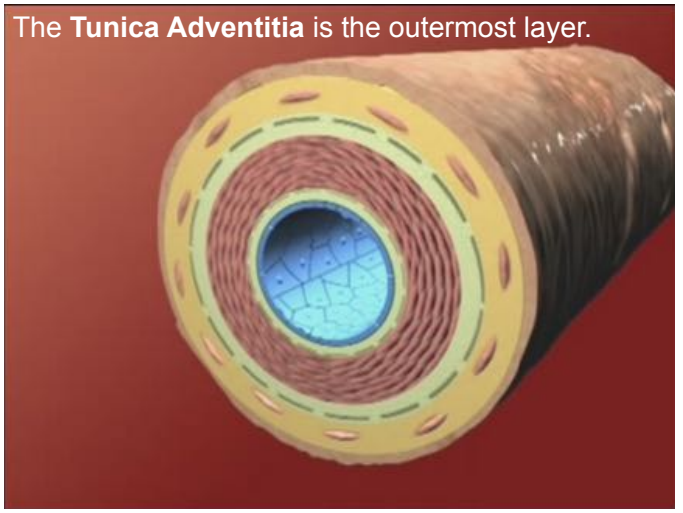
http://mediabyran.kib.ki.se/video/educational/coronary/index_se.html

Arterial Structure



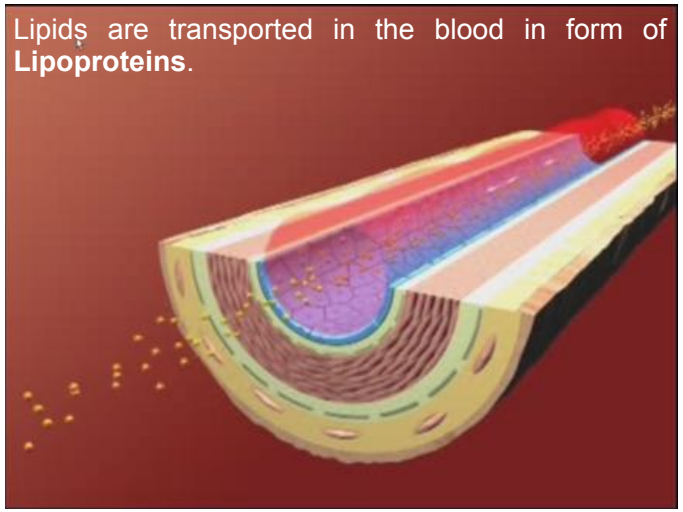
http://mediabyran.kib.ki.se/video/educational/coronary/index_se.html

Arterial Structure



http://mediabyran.kib.ki.se/video/educational/coronary/index_se.html

Lipids are transported in the blood in form of **Lipoproteins**.



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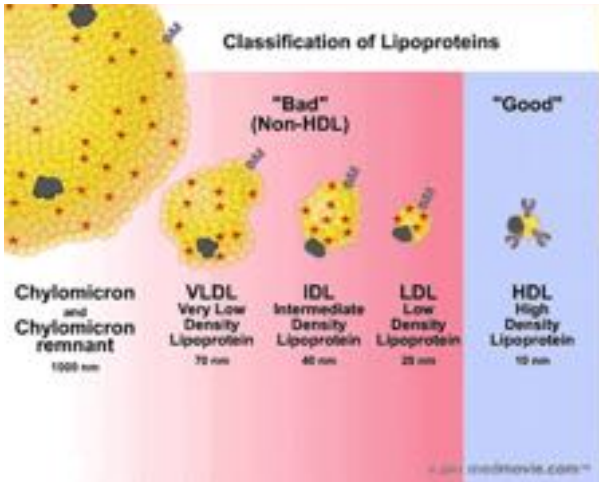

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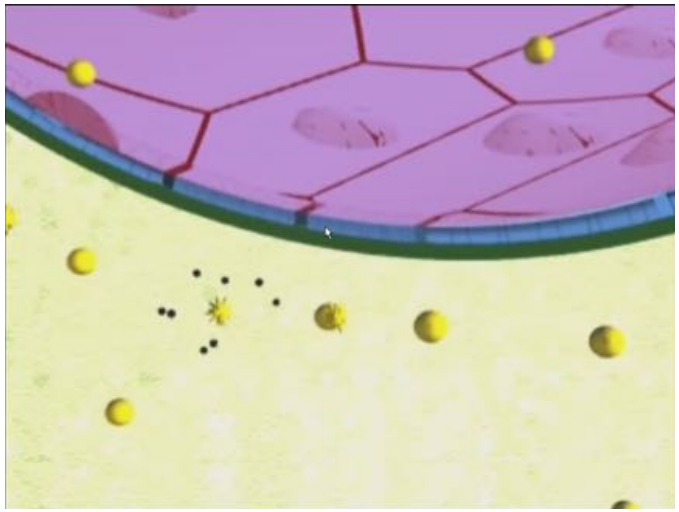
Accumulation of LDL in the Sub-endothelial Layer



http://mediabyran.kib.ki.se/video/educational/coronary/index_se.html

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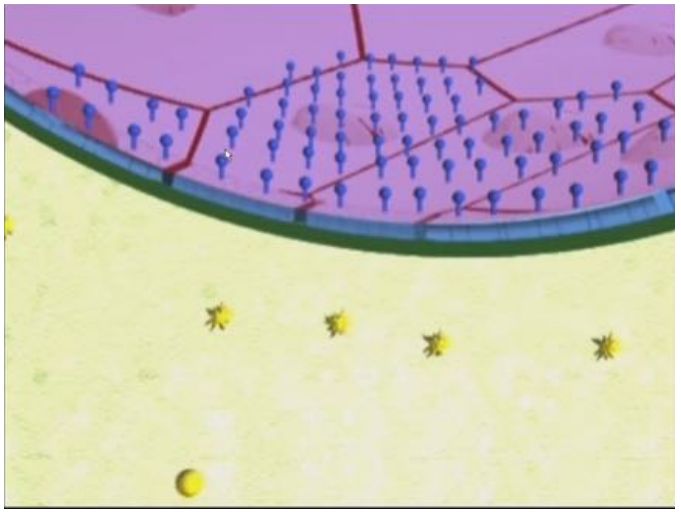
Oxidized-LDL Induce Endothelial Cell Activation



http://mediabyran.kib.ki.se/video/educational/coronary/index_se.html

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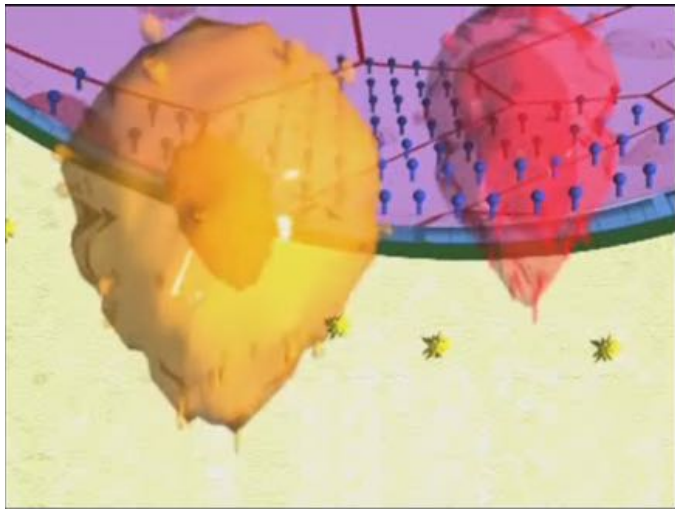
Endothelial Transmigration



http://mediabyran.kib.ki.se/video/educational/coronary/index_se.html

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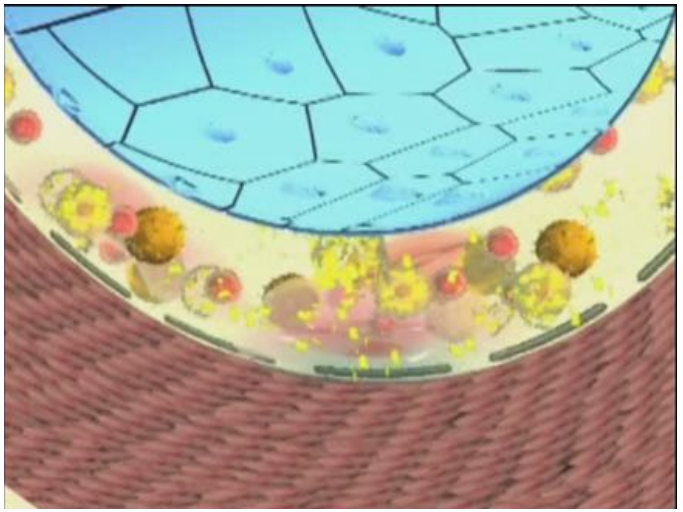
Atheroma Formation (Fatty Streak)



http://mediabyran.kib.ki.se/video/educational/coronary/index_se.html

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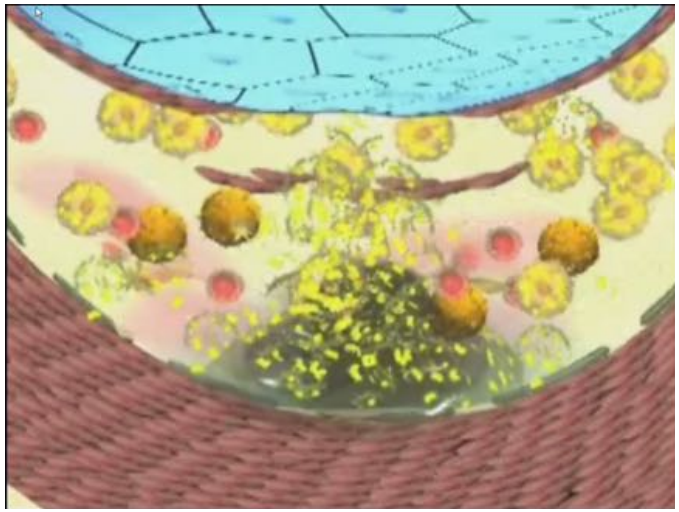
Fibrous Cap formation

Which comprises proliferation and migration of smooth muscle cells and net matrix deposition.



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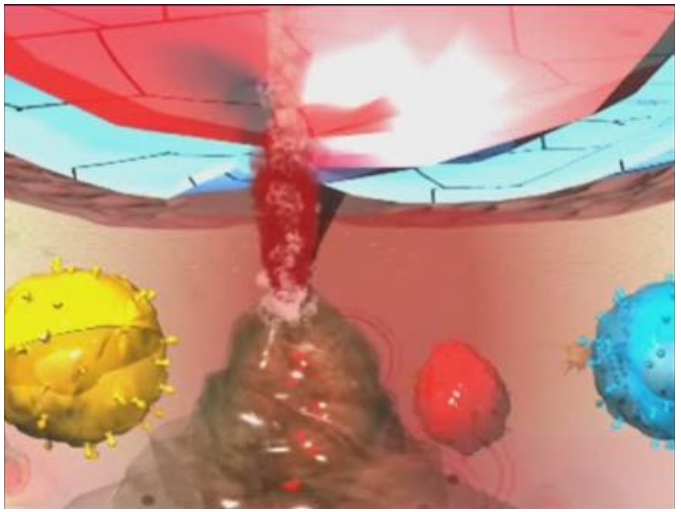
Inflammation Leads to Fibrous Cap Rupture



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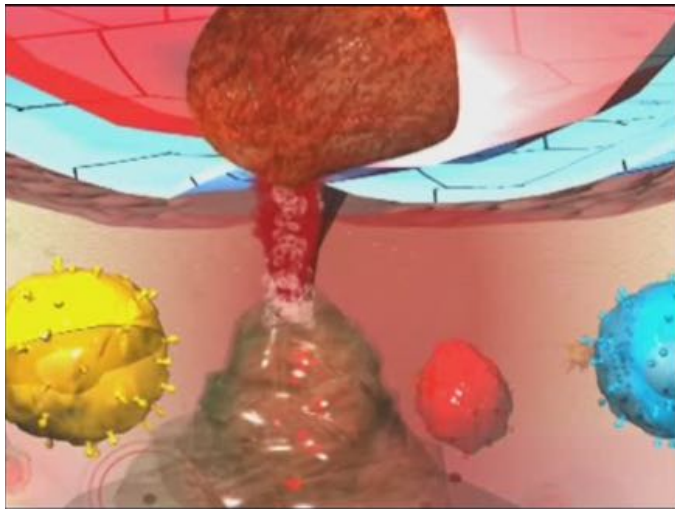
Blood Clot Formation



http://mediabyran.kib.ki.se/video/educational/coronary/index_se.html

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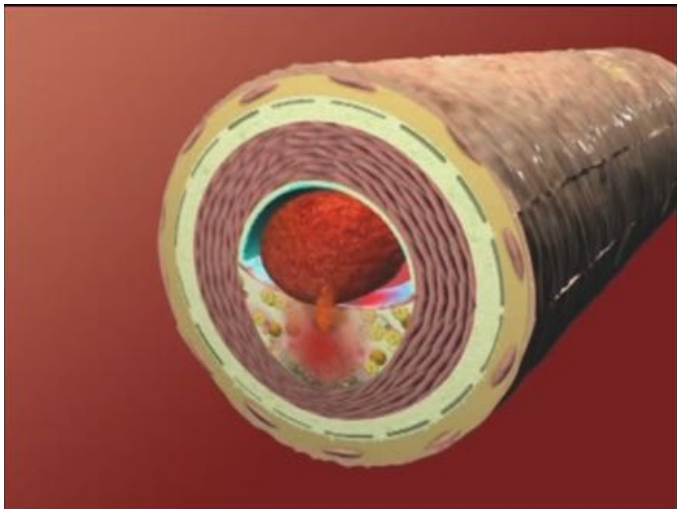
Ischemia Occurs When Blood Flow Is Stopped



http://mediabyran.kib.ki.se/video/educational/coronary/index_se.html

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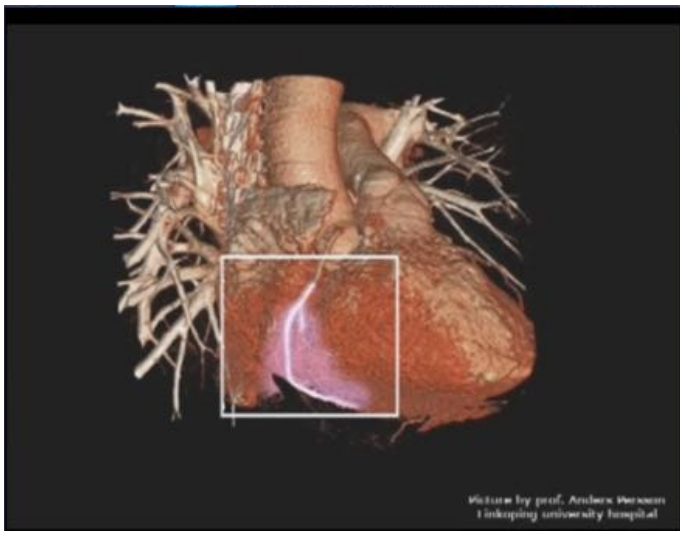
Myocardial Infarction



http://mediabyran.kib.ki.se/video/educational/coronary/index_se.html

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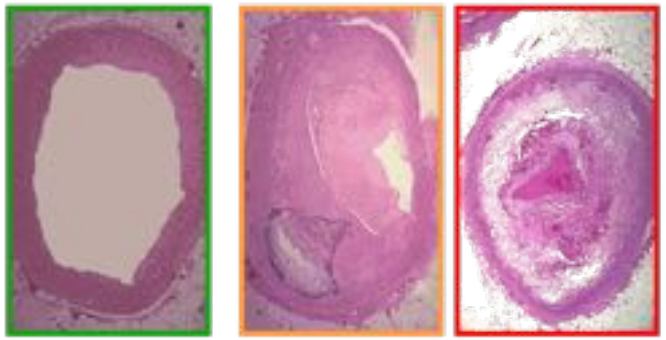
Morphology of Atheroma



Normal Plaque Thrombus

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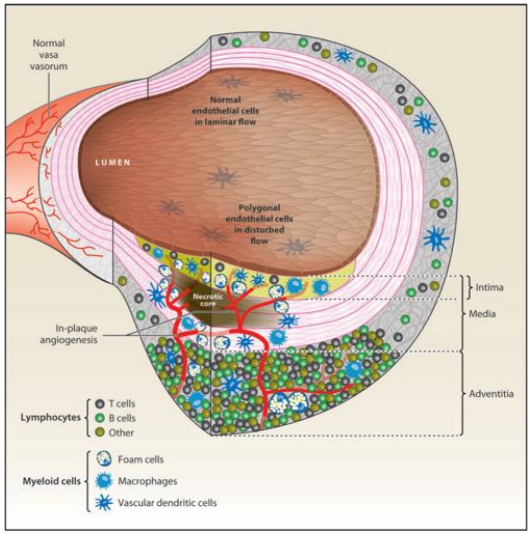
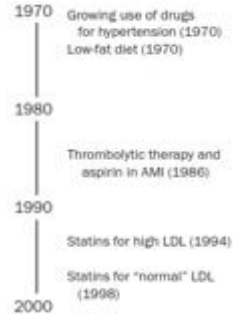
Immune response in atherosclerosis



Annu. Rev. Immunol. 2009. 27:165-97

Treatments in atherosclerosis



IL-1β blockade (Canakinumab) to reduce CVD death rates
End = April 2017

CANTOS
Canakinumab Anti-inflammatory Thrombosis Outcomes Study

Low-dose methotrexate to reduce MI rates, stroke & CVD death rates
Estimated end = December 2018

CIRT | CARDIOVASCULAR INFLAMMATION REDUCTION TRIAL

CV Risk Calculators

Health professionals commonly use risk calculators to assess the 10 year cardiovascular risk of patients

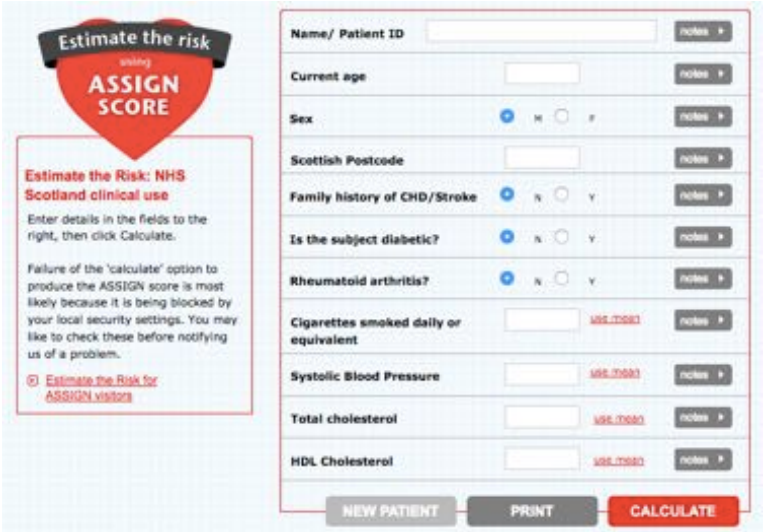
Framlingham - Until recently, NICE recomended this equation for calculating cardiovascular risk

Joint British Societies (JBS) - The official cardiovascular risk charts published in the British National Formulary (BNF) are based on those given in the JBS2 guidelines

JBS3 - The Joint British Societies' consensus recommendations for the prevention of cardiovascular disease (JBS3) are now available and refer to lifetime risk as well as 10 year risk. The calculator can be downloaded at the following link: www.jbs3risk.com

ASSIGN - Developed for use in Scottish populations ASSIGN includes risk factors, such as family history and social deprivation, not used by Framingham

QRISK®2 - This risk algorithm has been developed by doctors and academics working in the UK and is based on routinely collected data from many thousands of GPs across the country. A version using lifetime risk is available at www.qrisk.org



Inflammatory Biomakers
C-Reactive protein (CRP) (produced by liver)
Pentraxin 3 (PTX-3) (produced by vessel)
Interleukin (IL)-6

Plaque destabilisation markers
Myeloperoxidase (MPO) (metalloproteinase)
Pregnancy-associated plasma protein A (PAPPA)
Soluble cluster of differentiation 40 ligand (sCD40L)(platelets)
Tumor necrosis factor (TNF)-α

OMICS
Genomics, proteomics, metabolomics
Personalised (stratified) medicine

Acute myocardial infarction (AMI)
Acute ischemia (chest pain)
Changes in electrocardiogram (ECG)
Elevated markers (from blood or saliva)

Table I.

Biomarkers of myocardial infarction.

Type	Marker
Obsolete	Aspartate aminotransferase
	Total CK
	Lactate dehydrogenase
Established	Troponin T
	Troponin I
	Myocardial fraction of CK
	Myoglobin
Emerging	Heart fatty acid-binding protein
	B-type natriuretic peptide
	Ischemia-modified albumin
	Pregnancy-associated plasma protein A
	Copeptin
	Growth differentiation factor-15

CK, creatine kinase.

Biomed Rep. 2015;3:743-748

Circulation

ORIGINAL RESEARCH ARTICLE

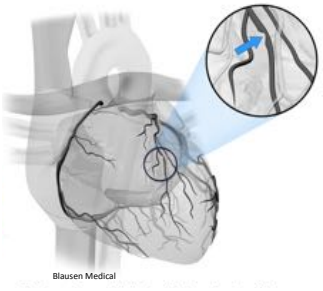
Direct Comparison of Cardiac Myosin-Binding Protein C with Cardiac Troponins for the Early Diagnosis of Acute Myocardial Infarction

Thomas E. Kaier, Raphael Twerenbold, Christian Puelacher, Jack Marjot, Nazia Imambaccus, Jasper Boeddinghaus, Thomas Nestelberger, Patrick Badertscher, Zaid Sabti, Maria Rubini Giménez, Karin Wildi, Petra Hillinger, Karin Grimm, Sarah Loeffel, Samyut Shrestha, Dayana Flores Widmer, Janosch Cupa, Nikola Kozhuharov, Òscar Miró, F. Javier Martín-Sánchez, Beata Morawiec, Katharina Rentsch, Jens Lohrmann, Wanda Kloos, Stefan Osswald, Tobias Reichlin, Ekkehard Weber, Michael Marber, Christian Mueller

Download PDF
DOI https://doi.org/10.1161/CIRCULATIONAHA.117.028084
Circulation. 2017;CIRCULATIONAHA.117.028084
Originally published September 26, 2017

Coronary Angiography / Angioplasty

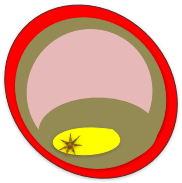
New Diagnostics Are Required for Atherosclerosis



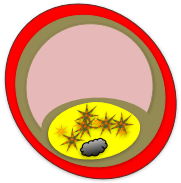
Current challenges in atherosclerosis:

- **Unmet need for earlier diagnosis**
- **Unable to assess plaque stability**

Stable Plaque

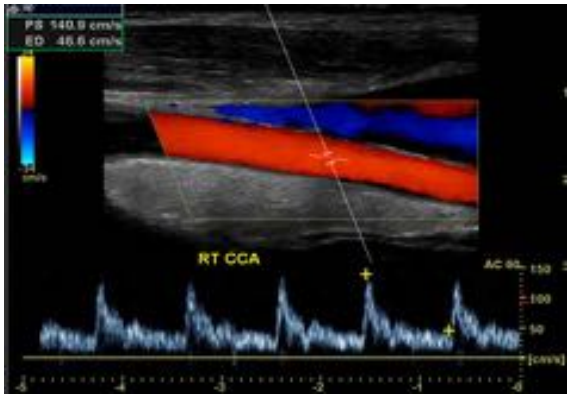


Unstable Plaque



Carotid Ultrasound

Carotid ultrasound is a painless imaging test that uses high-frequency sound waves to create pictures of the inside of your **carotid** arteries



RadiologyInfo.org

University of Glasgow

Functional imaging is a staple of todays medicine

EU annually requires*:

51 million CT scans

31 million MRI scans

~1 million PET scans

Anatomical and functional imaging

- Extensively used for anatomical imaging of **established** pathology
- Unable to distinguish pathophysiologic processes leading to clinically significant events

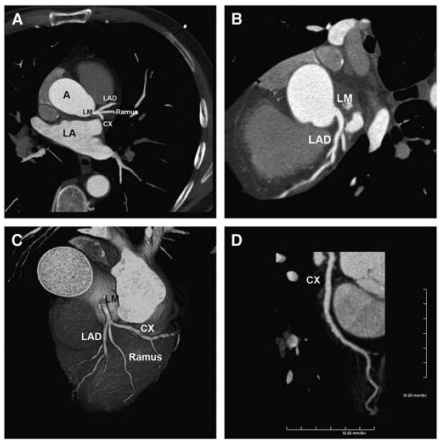
Molecular imaging

- The only currently used molecular imaging modality
- Fastest growing imaging modality with 21% annual increase**

*Eurostat data, 2016 ** EANM, 2011

Computerised Tomography (CT)

A **CT coronary** angiogram relies on a powerful X-ray machine to produce images of your heart and its blood vessels



JNMT Journal of NUCLEAR MEDICINE TECHNOLOGY

CT - Fat Attenuation Index (FAI)

SCIENCE TRANSLATIONAL MEDICINE | RESEARCH ARTICLE

ATHEROSCLEROSIS

Detecting human coronary inflammation by imaging perivascular fat

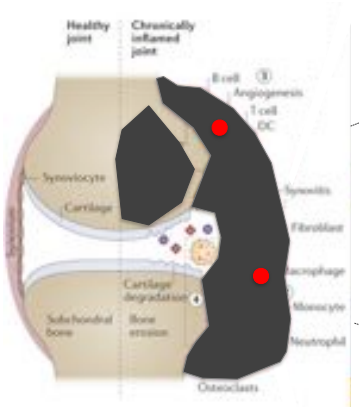
Alexios S. Antonopoulos,[1]* Fabio Sanna,[1]* Nikant Sabharwal,[2] Sheena Thomas,[1] Evangelos K. Oikonomou,[1] Laura Herdman,[1] Marios Margaritis,[1,3] Cheerag Shirodaria,[2] Anna-Maria Kampoli,[1] Ioannis Akoumianakis,[1] Mario Petrou,[4] Rana Sayeed,[4] George Krasopoulos,[4] Constantinos Psarros,[1] Patricia Ciccone,[1] Carl M. Brophy,[1] Janet Digby,[1] Andrew Kelion,[2] Raman Uberoi,[5] Suzan Anthony,[5] Nikolaos Alexopoulos,[6] Dimitris Tousoulis,[6] Stephan Achenbach,[7] Stefan Neubauer,[1,3,8] Keith M. Channon,[1,3,8] Charalambos Antoniades[1,3,8]†

Limitations of Anatomical Imaging

University of Glasgow

Distinct subtypes of synovial inflammation can be visualized in RA

PET tracers in development



Lymphoid

CD3, CD4, CD20, chemokine receptors

Stromal

ICAM-1, VCAM-1
Integrin $\alpha_V\beta_3$
RANK
P2X7 receptor

Myeloid

IL-6 receptor, TNFα
F4/80, Folate receptor
Mannose receptor, ST2
Chemokine receptors

S. Put, Arthritis Research & Therapy2014

University of Glasgow

Current clinical practice is severely limited to established disease

Cardiovascular disease

Clinical Scores:

- HEART score
- GRACE score

Peripheral blood biomarkers:

- Troponin I
- Troponin T

Imaging:

- ECG
- ECHO
- CCTA

Unable to:

- **Predict clinical onset**
- **Give accurate prognosis**
- **Stratify for treatment**
- **Predict clinical outcomes**

Consider:

- **Delays in scanning**
- **Delays in reporting**
- **Technical limitations**

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Molecular imaging biomarkers will be essential to drug development

Molecular imaging
in vivo monitoring of pathogenetic processes

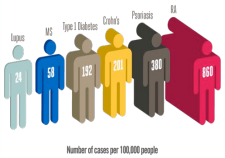
Development of biomarkers

"Biomarkers Market worth 53.34 Billion USD by 2021"
Markets & Markets report Feb 2017

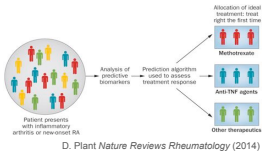
New drug discovery

to reach approximately 160 Billion USD by 2025.
Research & Markets report Feb 2017

Early correct diagnosis

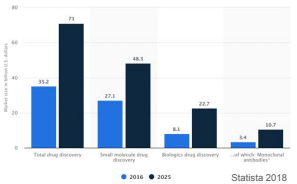


Treatment stratification



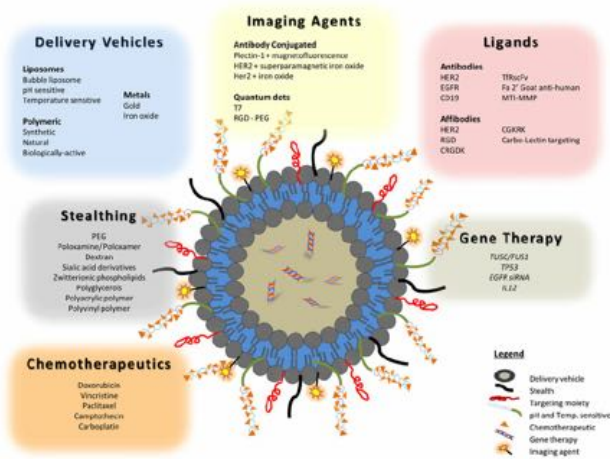
D. Plant *Nature Reviews Rheumatology* (2014)

New treatment modalities



Statista 2018

How Nanoparticles Could Help



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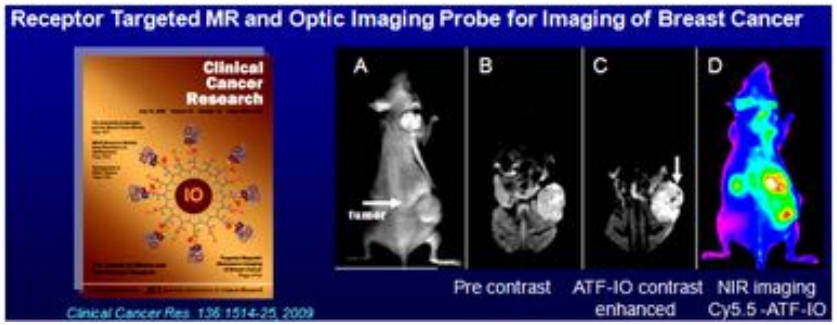
How Nanoparticles Could Help



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NanoMATe
NANOPARTICLES FOR MOLECULAR IMAGING OF ATHEROSCLEROSIS

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Reading List

General basic info are available on:

http://www.nhs.uk/conditions/Atherosclerosis/Pages/Introduction.aspx

https://www.nhs.uk/conditions/nhs-health-check/your-nhs-health-check-results-and-action-plan/#your-cholesterol-result

http://www.bhf.org.uk/heart-health/treatment/coronary-angioplasty-and-stent.aspx

http://www.bhf.org.uk/heart-health/treatment/coronary-bypass-surgery.aspx

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