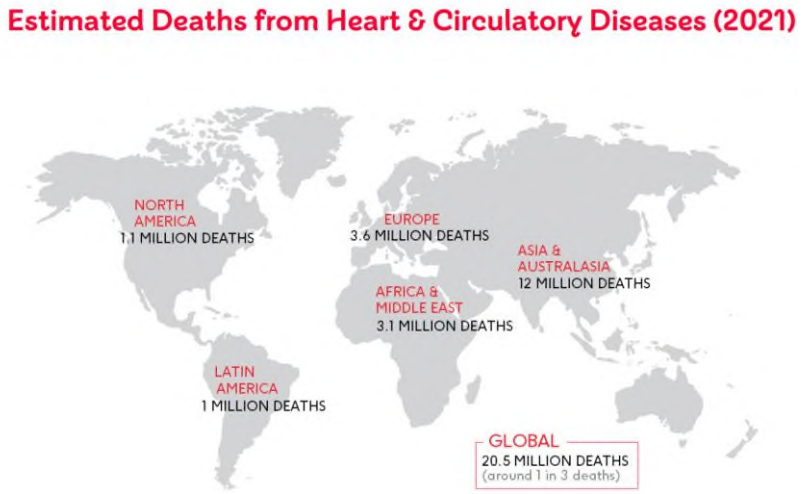
ΕΛΛΗΝΙΚΗ ΔΗΜΟΚΡΑΤΙΑ
Εθνικόν και Καποδιστριακόν Πανεπιστήμιον Αθηνών
ΙΔΡΥΘΕΝ ΤΟ 1837

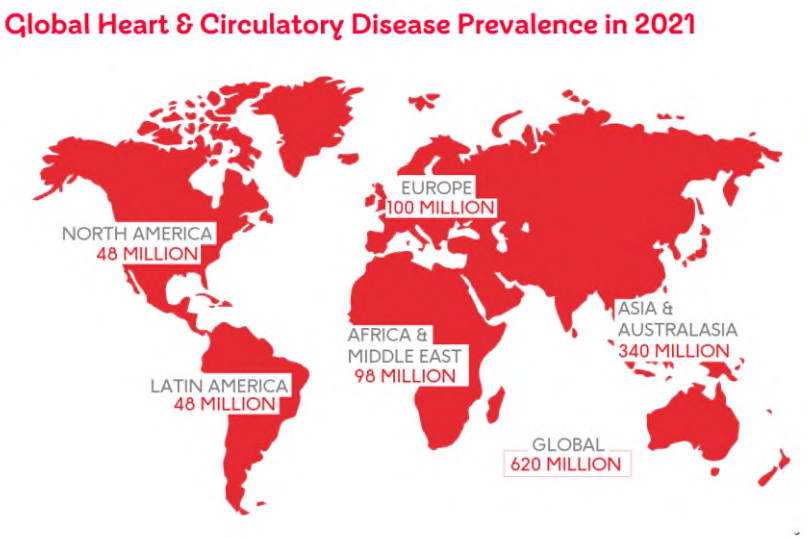
Καρδιομεταβολική Ιατρική, Πρόγραμμα Μεταπτυχιακών Σπουδών
Εθνικό και Καποδιστριακό Πανεπιστήμιο Αθηνών

Ο ρόλος της στεφανιαίας ενδοθηλιακής δυσλειτουργίας και διατμητικής τάσης στην εξέλιξη της στεφανιαίας νόσου.

Dr Marina Zaromytidou, MSc, PhD
Cardiologist, Inherited Cardiac Diseases,
St Bartholomew's Hospital,
BARTS Trust, London

The Heart and Circulatory Diseases Burden on Public Health





Lindstrom et al (2022) Global Burden of Cardiovascular Diseases and Risks Collaboration, 1990-2021, JACC
World Health Organization (2020) Global Health Estimates for 2019
British Heart Foundation

The Heart and Circulatory Diseases Burden on Public Health

- Coronary heart disease is the most diagnosed heart disease worldwide
- Coronary heart disease kills an estimated nine million people each year – in 2019 it was the world's single biggest killer.

Biggest Killers Worldwide (GBD 2019 Estimates)

	MEN		WOMEN		TOTAL	
1	Coronary heart disease	5.0 million	Coronary heart disease	4.2 million	Coronary heart disease	9.1 million
2	Stroke	3.3 million	Stroke	3.2 million	Stroke	6.6 million
3	COPD	1.9 million	COPD	1.4 million	COPD	3.3 million
4	Lung cancer	1.4 million	Lower respiratory infections	1.2 million	Lower respiratory infections	2.5 million
5	Lower respiratory infections	1.3 million	Alzheimer's/dementia	1.0 million	Lung cancer	2.0 million

Lindstrom et al (2022) Global Burden of Cardiovascular Diseases and Risks Collaboration, 1990-2021, JACC
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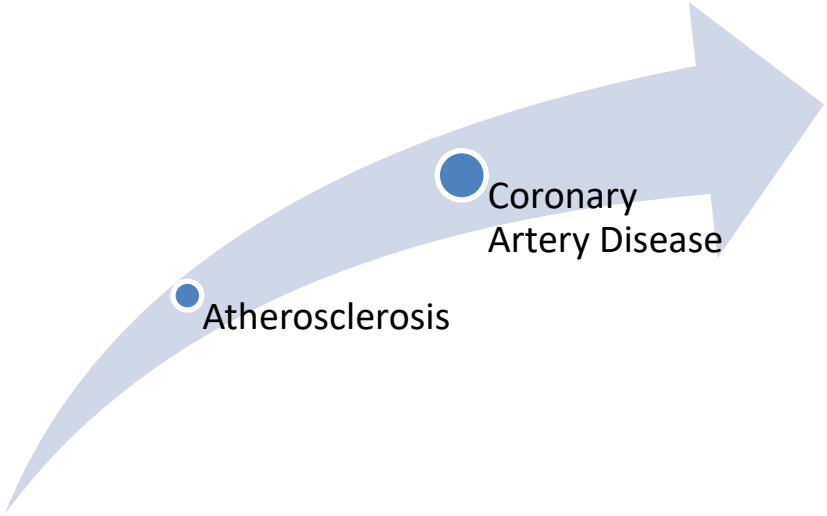
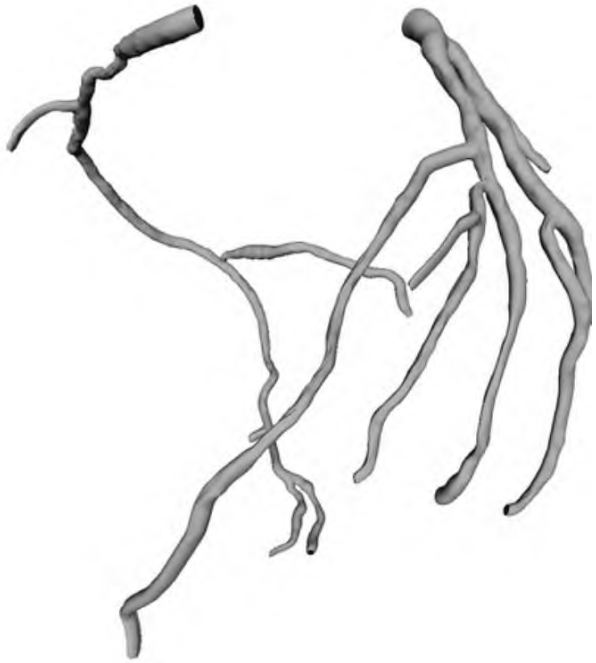
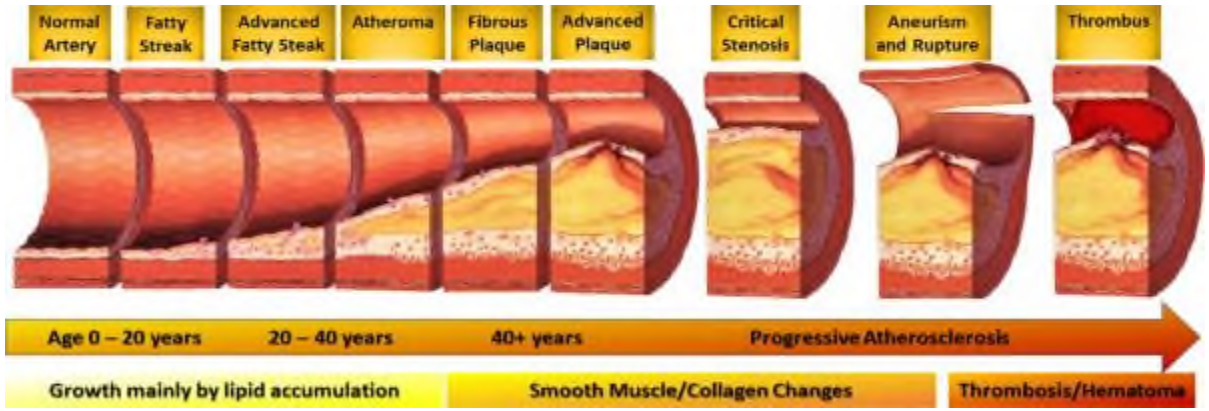
What causes Coronary artery Disease

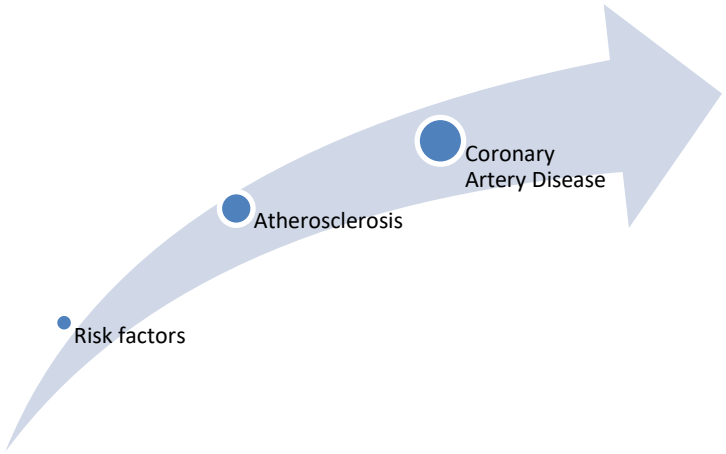


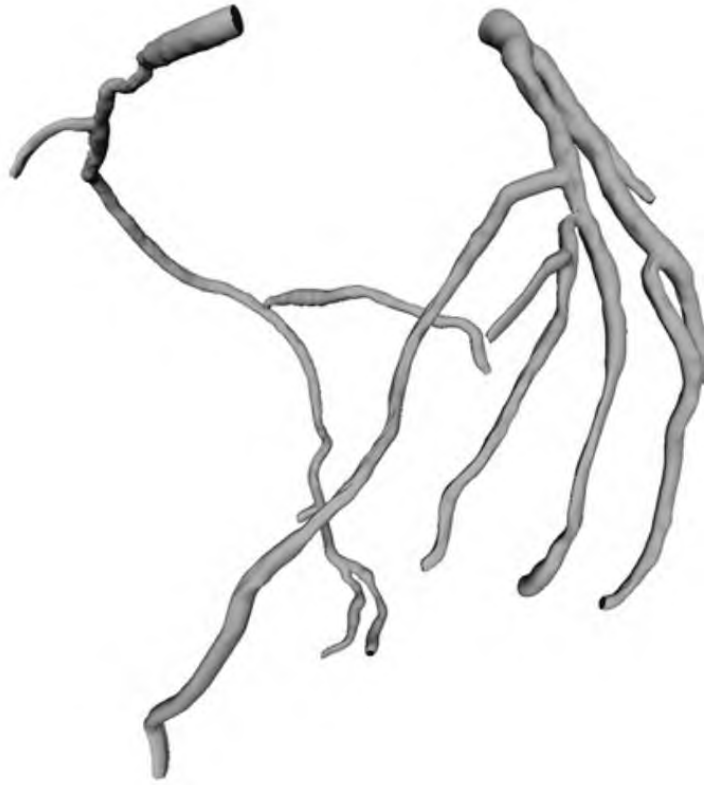


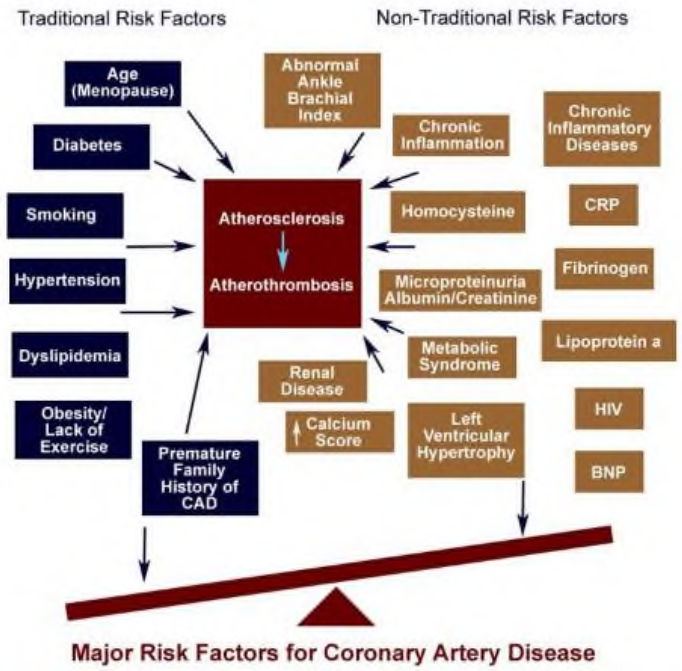


Atherosclerosis Chaya Gopalan Ph.D., FAPS, Erik Kirk Ph.D., in Biology of Cardiovascular and Metabolic Diseases, 2022

What causes Coronary artery Disease

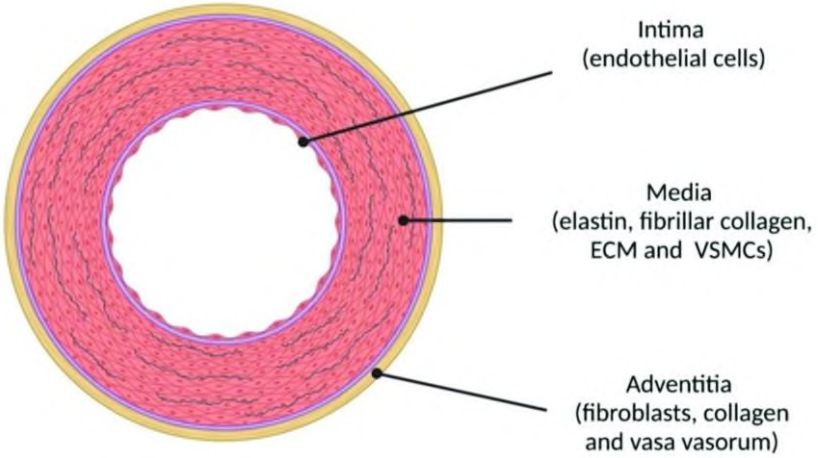


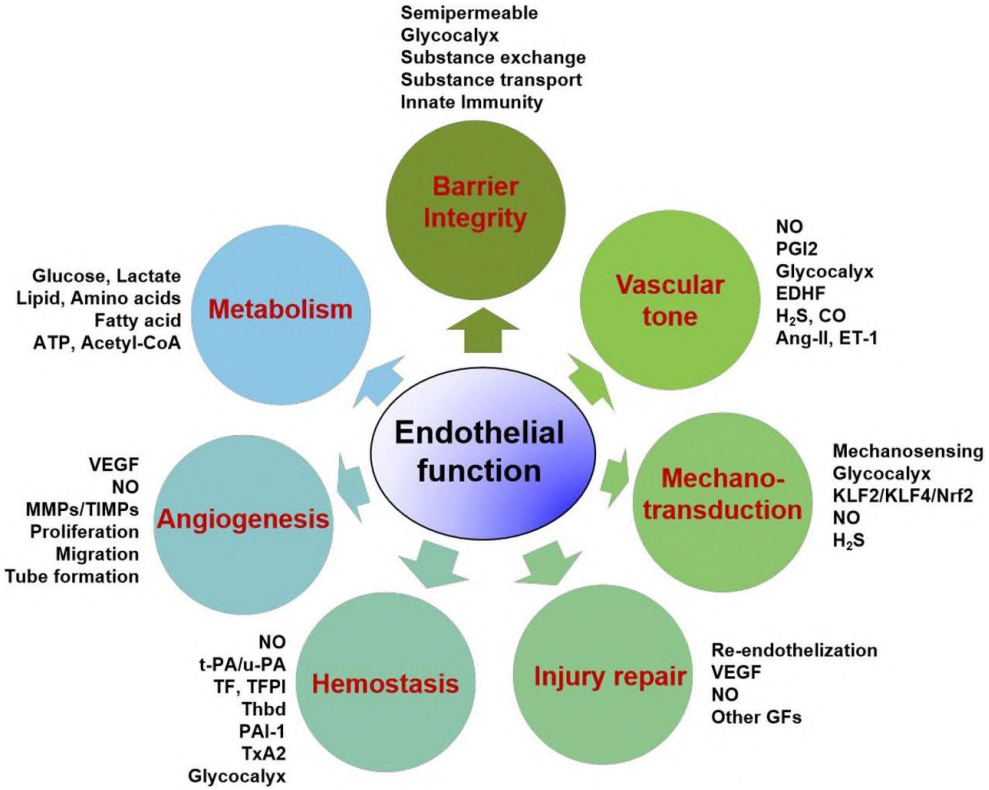




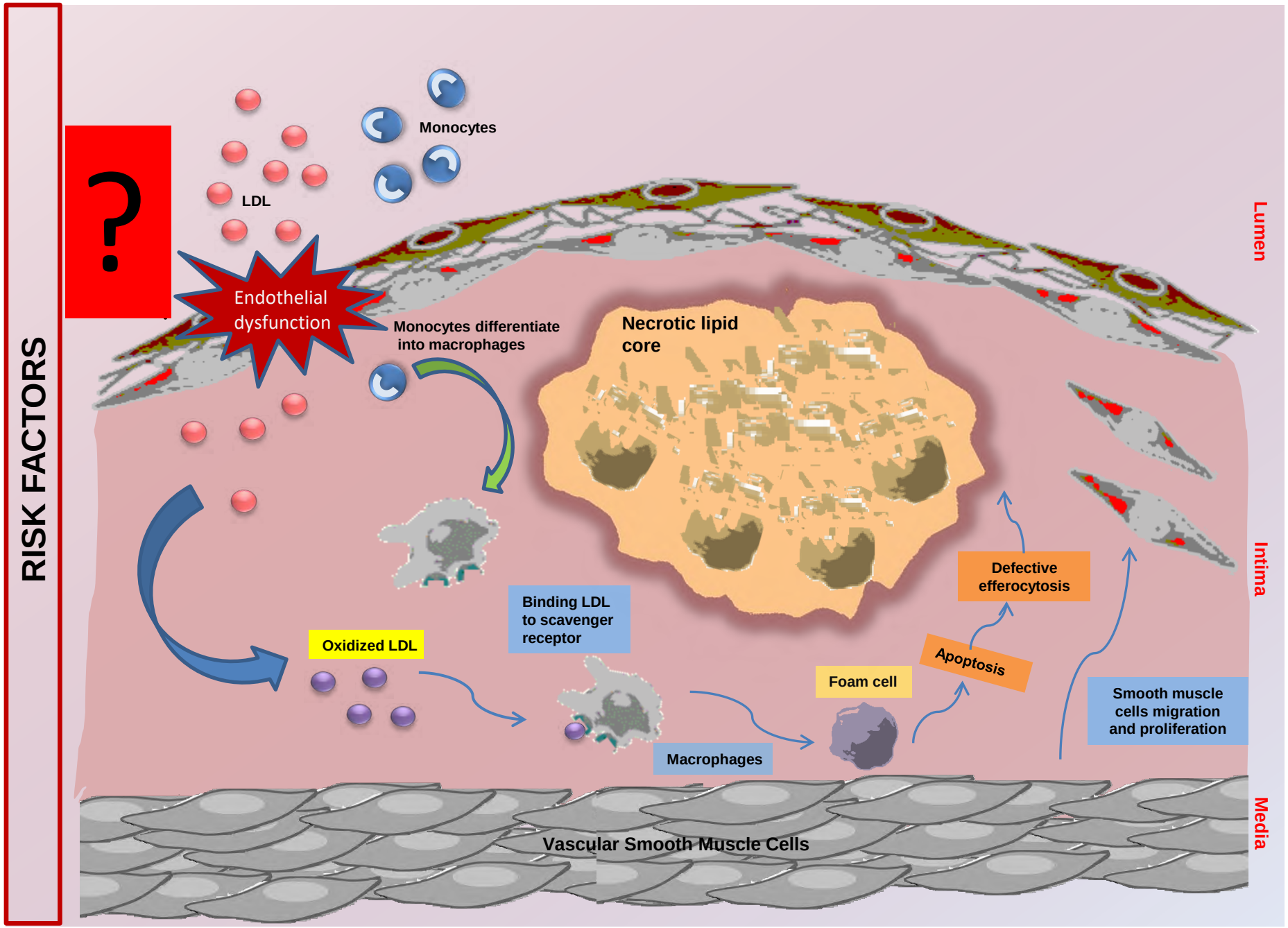
Medscape, theheart.org

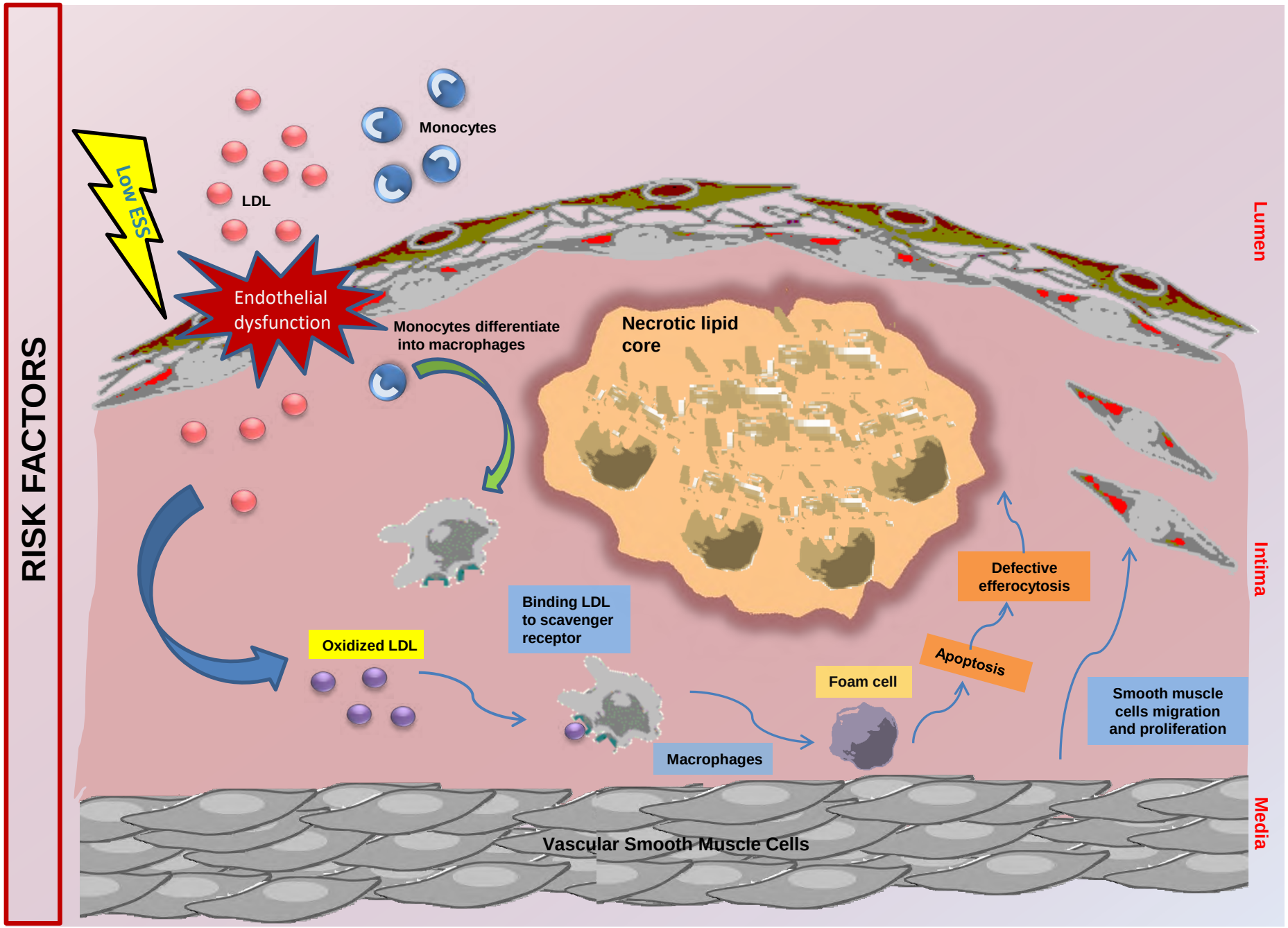
Meet the endothelium





Gonzalez-Clemente et al. (2021). Journal of Clinical Medicine. 10. 3616.10.3390/jcm10163616.


RISK FACTORS
?
LDL
Monocytes
Endothelial dysfunction
Monocytes differentiate into macrophages
Necrotic lipid core
Lumen
Intima
Media
Oxidized LDL
Binding LDL to scavenger receptor
Macrophages
Foam cell
Apoptosis
Defective efferocytosis
Smooth muscle cells migration and proliferation
Vascular Smooth Muscle Cells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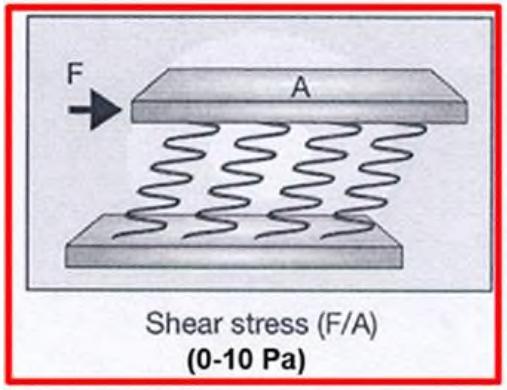
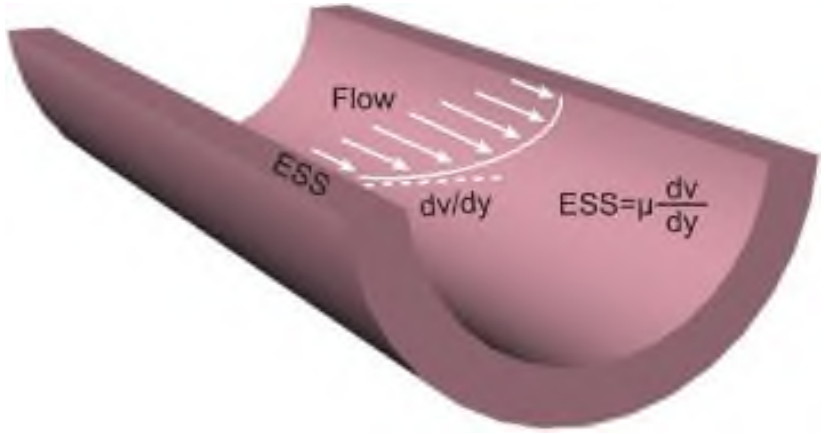
Meet Endothelial shear stress

Endothelial shear stress is the tangential stress derived from the friction of the flowing blood on the endothelial surface of the arterial wall and is expressed in units of force / unit area (N/m2or Pascal [Pa] or dyne/cm2; 1 N/m2= 1 Pa = 10 dyne/cm2) (26, 27) (Table 1).

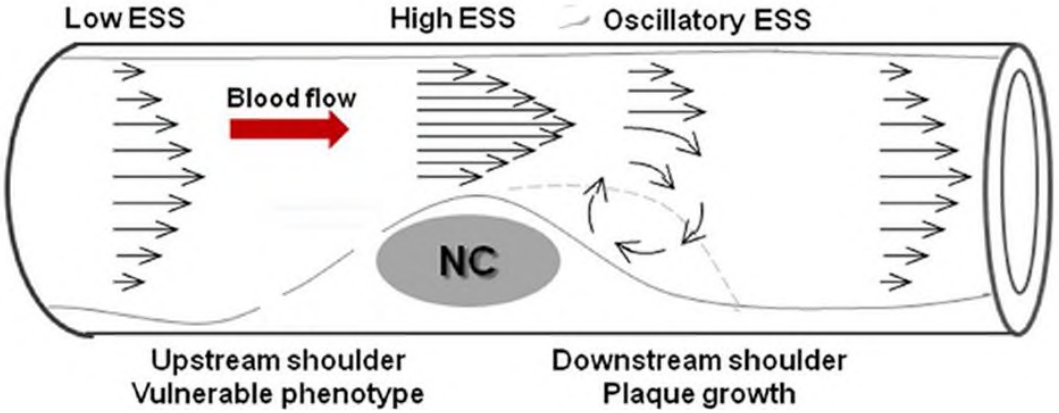


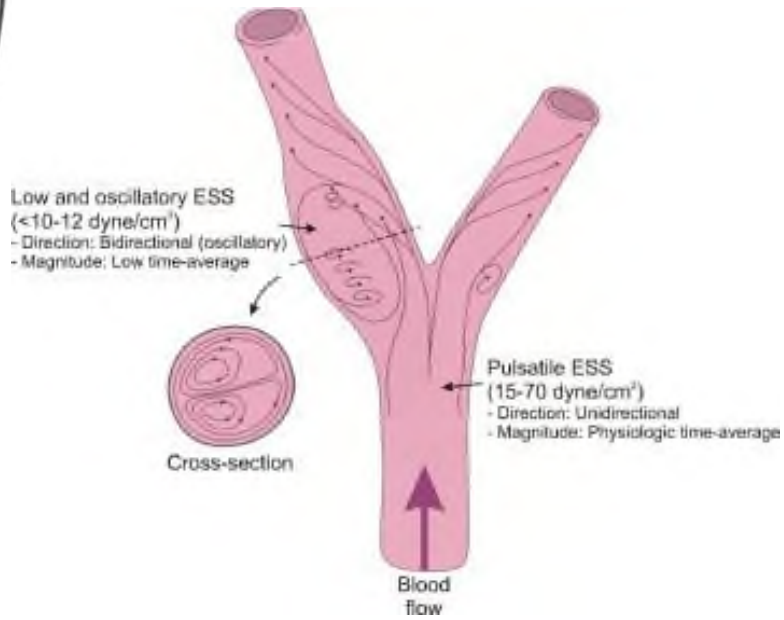


Endothelial shear stress is proportional to the product of the blood viscosity (μ) and the spatial gradient of blood velocity at the wall

Endothelial shear stress and blood flow

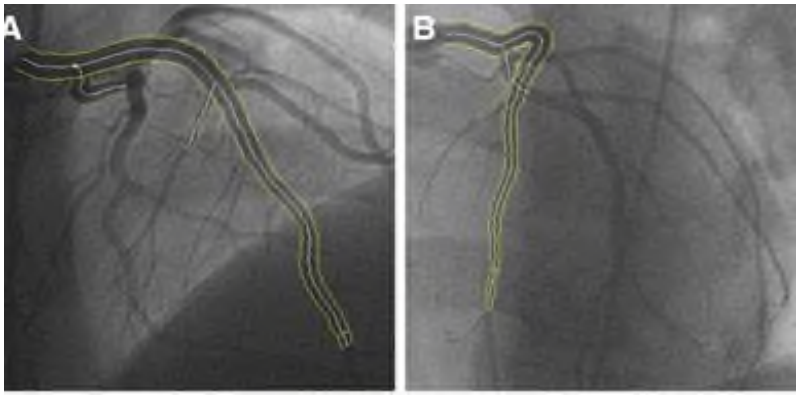
Branch points, curvatures or bifurcations exhibit disturbed flow and low ESS in contrary to laminar, undisturbed flow.



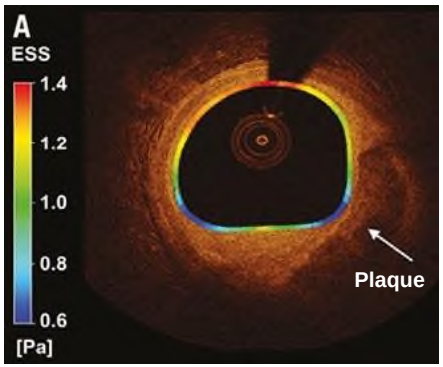


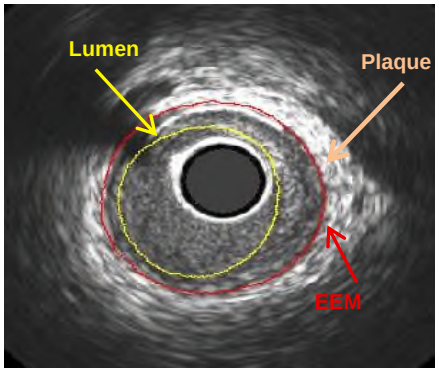
How to calculate Endothelial shear tress

A. Two angiographic planes

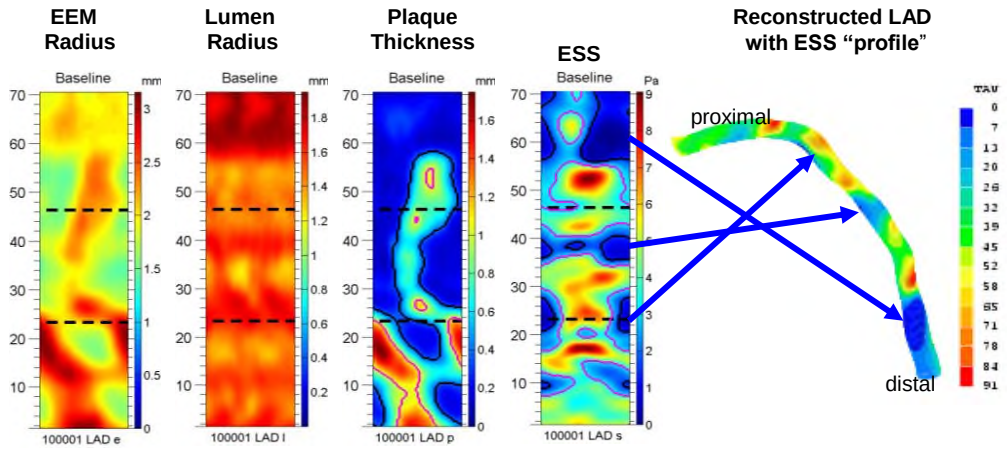


B. OCT/ IVUS segmentation



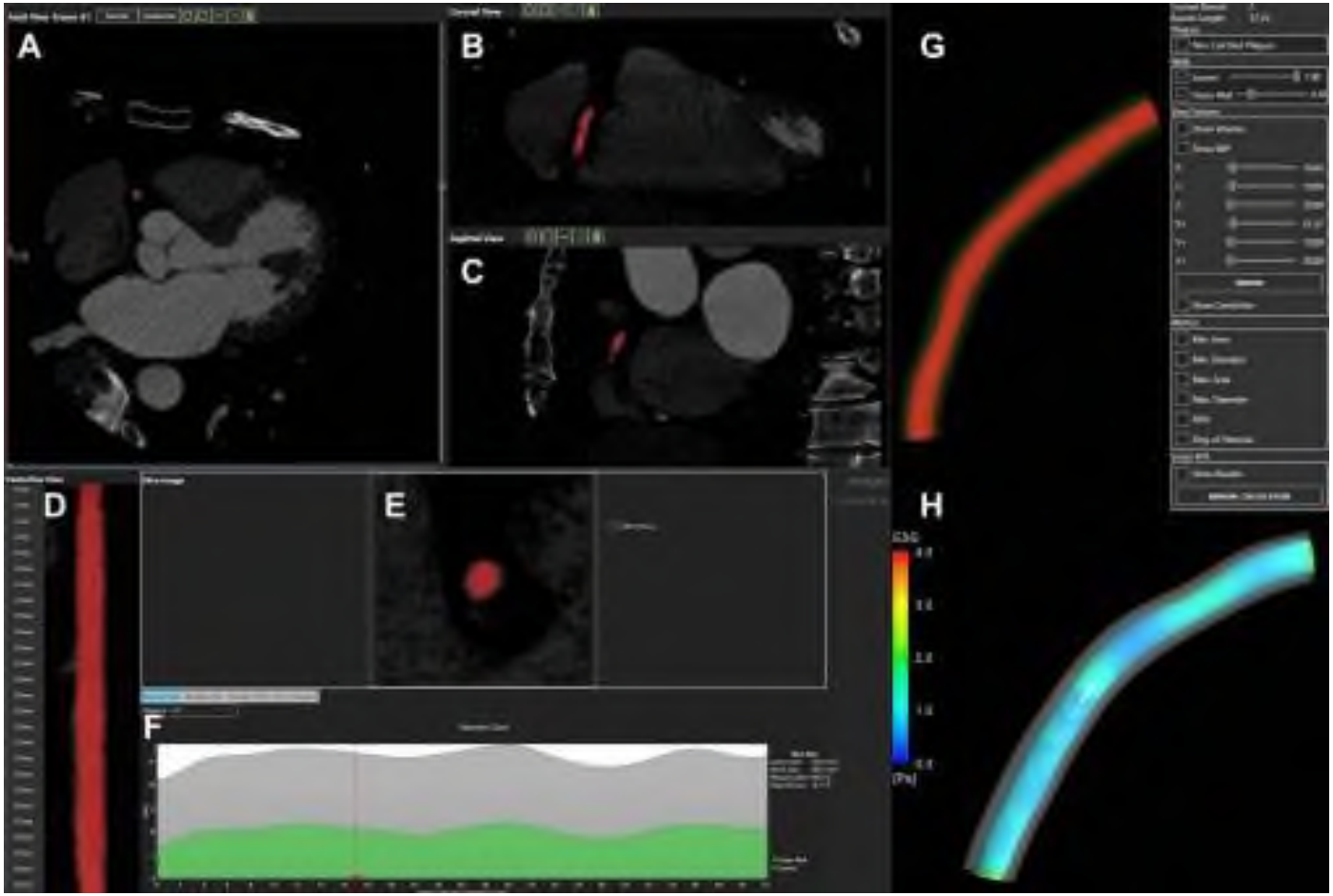


C. Computational fluid dynamics (CFD) and 3D reconstruction and ESS maps



Endothelial shear stress calculation with Computed tomography coronary angiography

Pros	Cons
Non-invasive	Resolution (Artifacts, including calcium)
Assessment of entire coronary tree	Pending validation



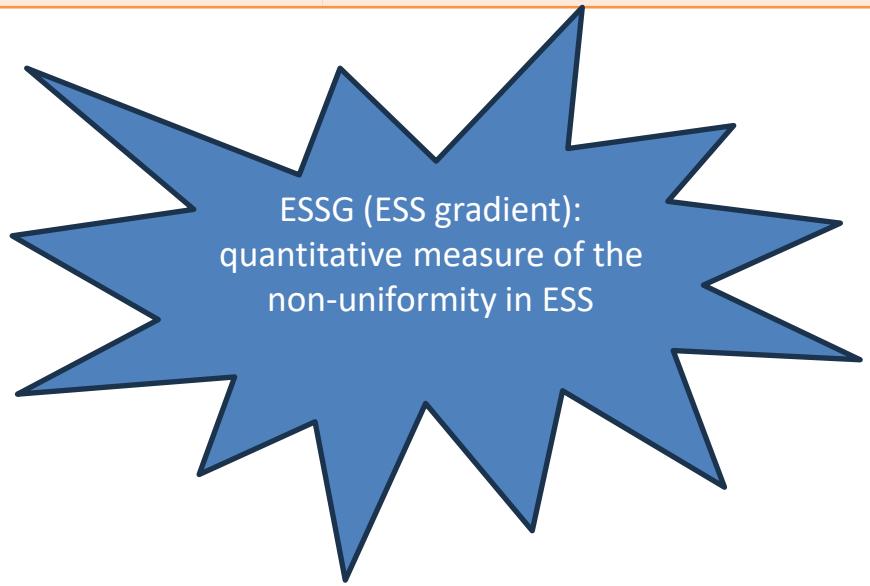
Schultz et al, International Journal of Cardiovascular Imaging 2023

Endothelial shear stress: what to look for

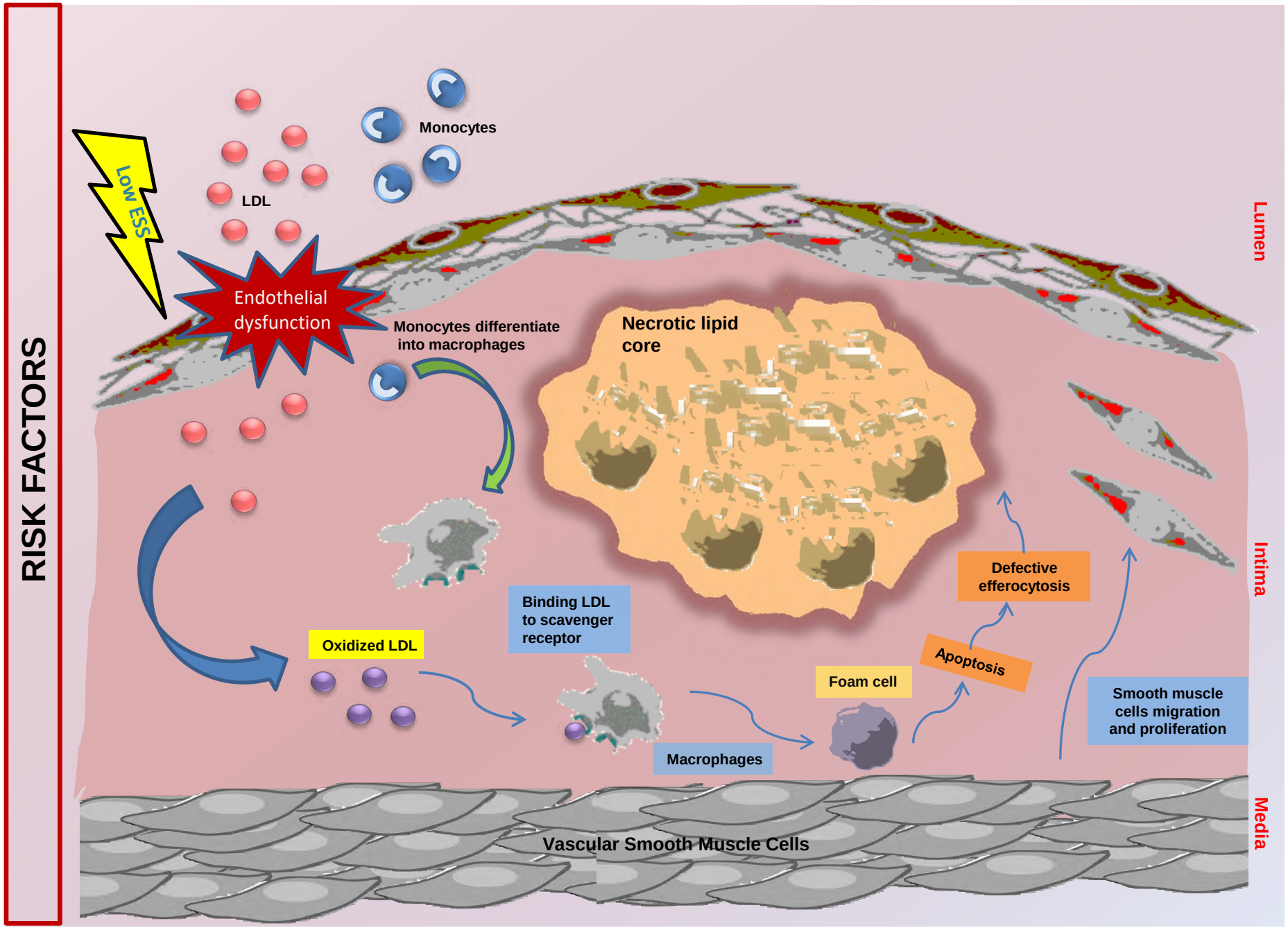
Levels of shear stress and its effects on atherosclerosis

		Effects in:		
Label	Range (Pa)	Early atherosclerosis	Advanced atherosclerosis	Stented segments
Oscillatory Low	0±0.5 0-1	Athero-prone	Athero-prone	Neoathero-prone
Normal/ high	1-7	Atheroprotective	No consensus	Neoathero-protective
Elevated	>7	NA	Erosion/ Rupture	NA

Types of flow
Laminar
Oscillatory
Unidirectional
Bidirectional



Gijsen, F… Serruys, P., 2019.. European Heart Journal 40, 3421–3433.https://doi.org/10.1093/eurheartj/ehz551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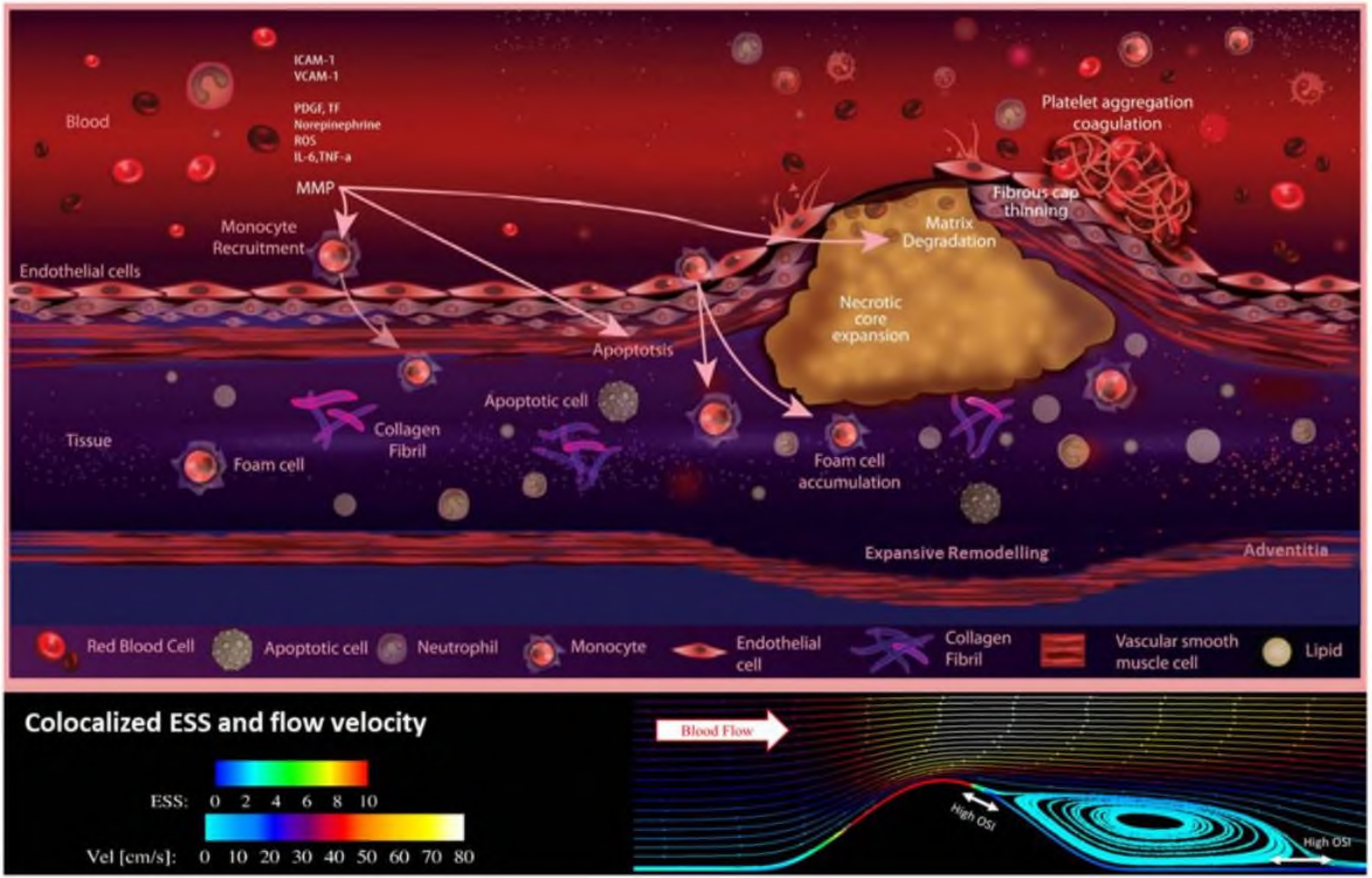
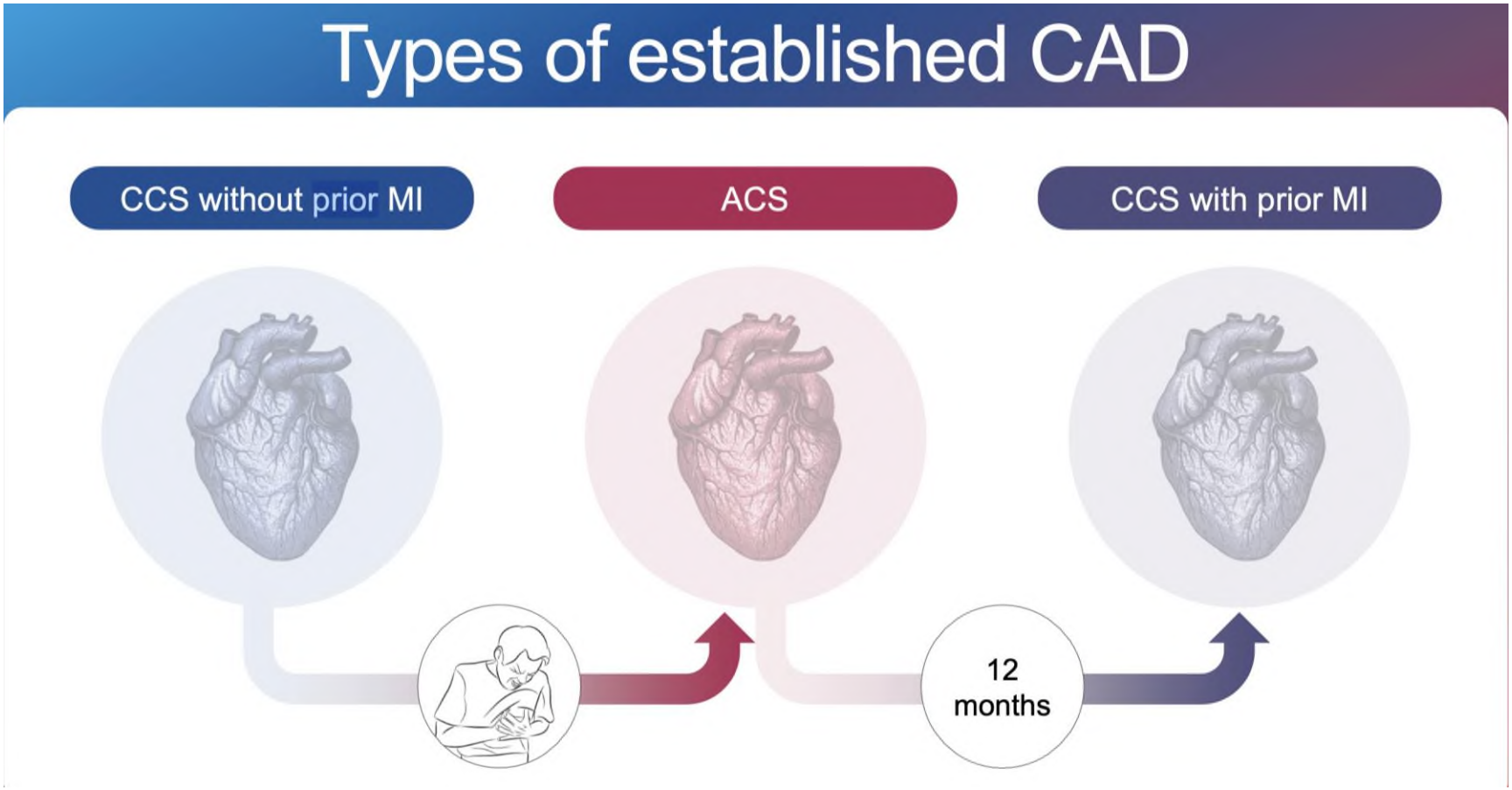
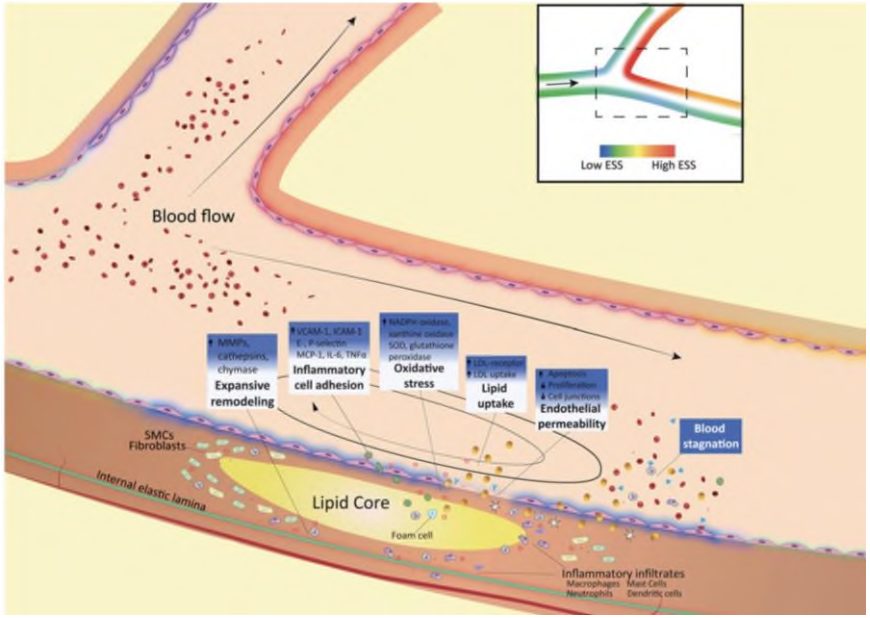


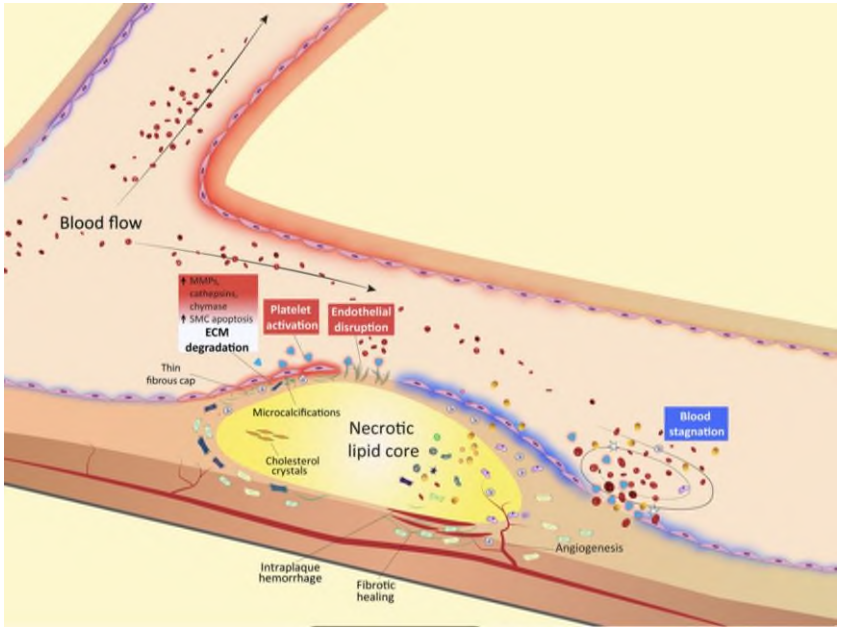
Gijsen, F… Serruys, P., 2019.. European Heart Journal 40, 3421–3433.https://doi.org/10.1093/eurheartj/ehz551

Endothelial shear stress and types of CAD: Clinical studies



Chronic Coronary Syndromes





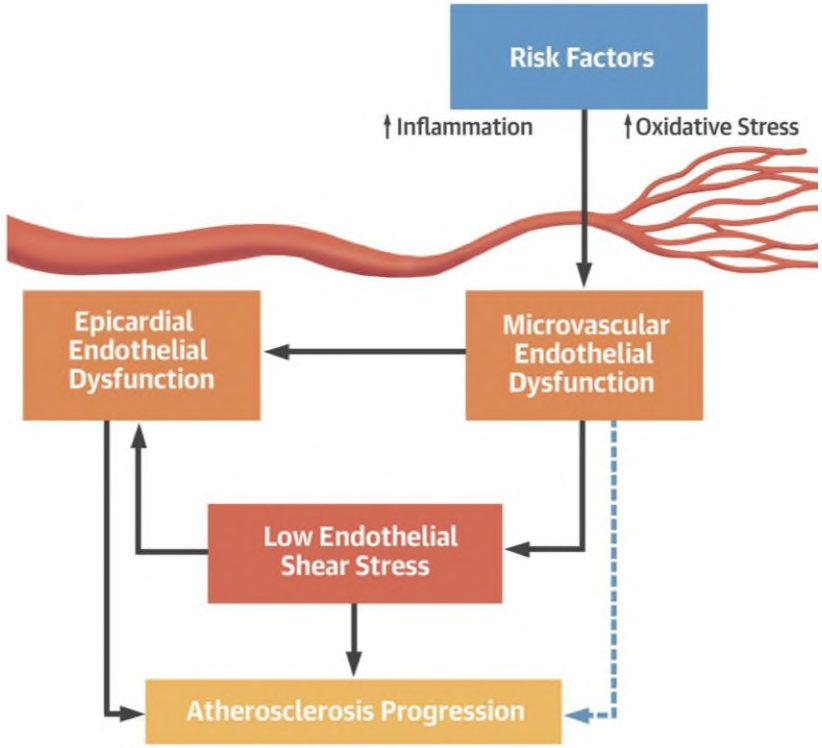
Low ESS linked to plaque progression and outward remodeling
Stone et al, Circulation 2003
Stone et al, EHJ 200
Samady et al, Circulation 2011
Stone et al, Circulation 2012
Vergallo et al, Circulation Cardiovasc Imaging 2014
Hung et al, JAHA 2016

Thondapu et al.Biomechanical stress in coronary atherosclerosis: emerging insights from computational modelling EHJ 2017

Local Low Shear Stress and Endothelial Dysfunction in Patients With Nonobstructive Coronary Atherosclerosis

Siasos G…Peter H. Stone, JACC 2018

- 65 patients with nonobstructive coronary atherosclerosis (luminal diameter stenosis <30%).
- Microvascular and epicardial coronary endothelial function was assessed by using intracoronary acetylcholine infusion.
- ESS was calculated with coronary angiogram/IVUS/CFD
- Microvascular endothelial dysfunction was associated with low ESS and more adverse epicardial plaque characteristics compared with patients with normal microvascular function.

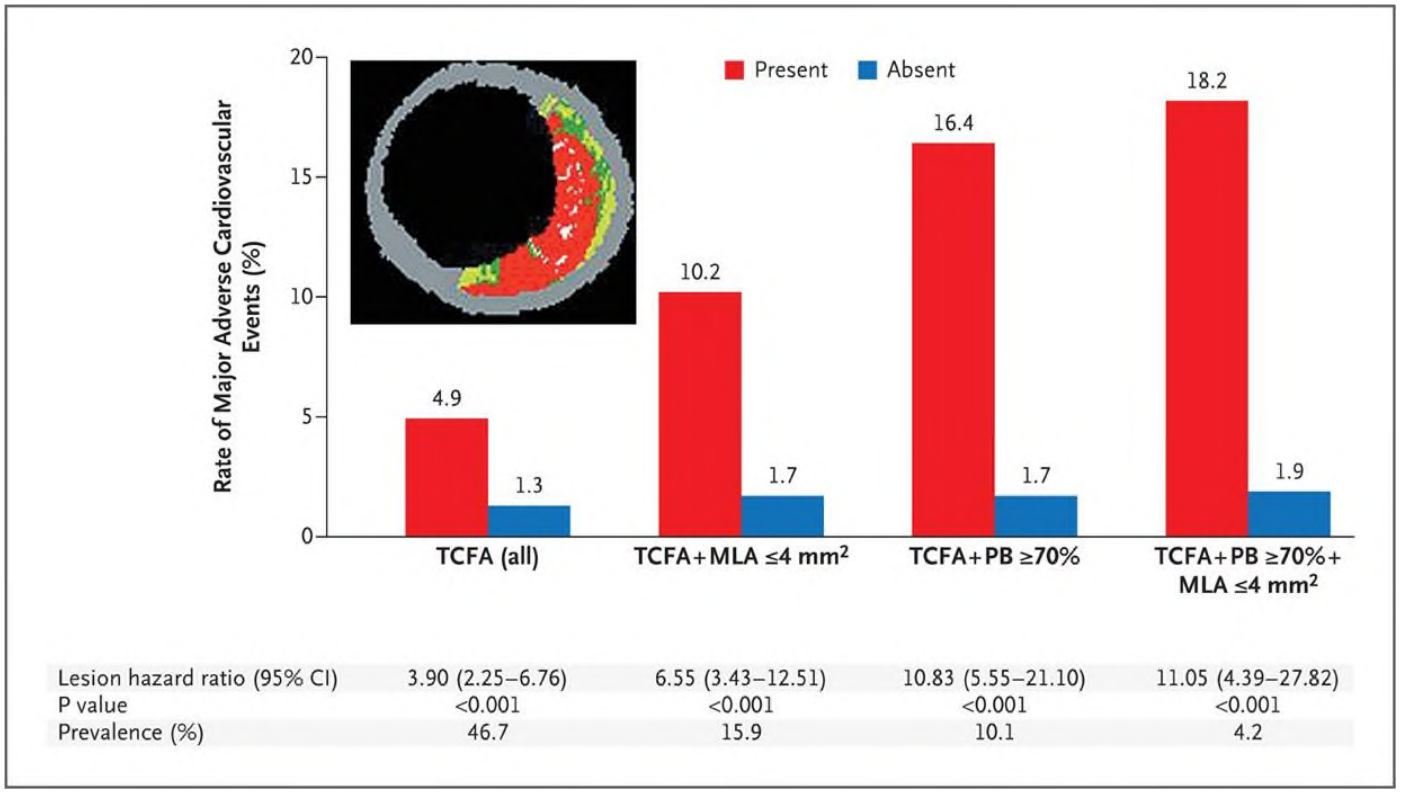


Acute coronary syndromes (ACS)

A Prospective Natural-History Study of Coronary Atherosclerosis

Gregg W. Stone et al, NEJM 2011

- Prospective study in 697 patients with PCI treated ACS
- 3.4 year follow up, 149 events (20%), mostly unstable/ progressive angina
- 50% of events attributed to non culprit lesions



Lesion hazard ratio (95% CI)	3.90 (2.25–6.76)	6.55 (3.43–12.51)	10.83 (5.55–21.10)	11.05 (4.39–27.82)
P value	<0.001	<0.001	<0.001	<0.001
Prevalence (%)	46.7	15.9	10.1	4.2

Prediction of Progression of Coronary Artery Disease and Clinical Outcomes Using Vascular Profiling of Endothelial Shear Stress and Arterial Plaque Characteristics The PREDICTION Study

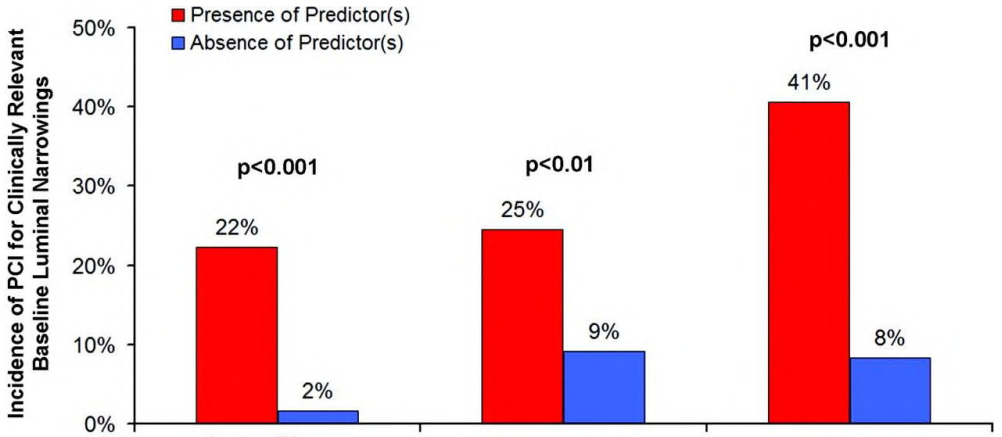
Peter H. Stone… Charles L. Feldman Circulation 2012

Outcome:

- Plaque burden is the most powerful predictor of plaque progression and luminal obstruction

- Low ESS provides substantial additive independent prognostication. 41% positive and 92% negative predictive value-Clinical significance limited by infrequent clinical events
  (20 events, 1 year follow up)

- 506 patients with PCI treated ACS
- 374 (74%) had repeat vascular profiling after 6-10months



Sensitivity	94%	42%	42%
Specificity	54%	82%	91%
Positive Predictive Value	22%	25%	41%
Negative Predictive Value	98%	91%	92%
Prevalence	22%	10%	6%

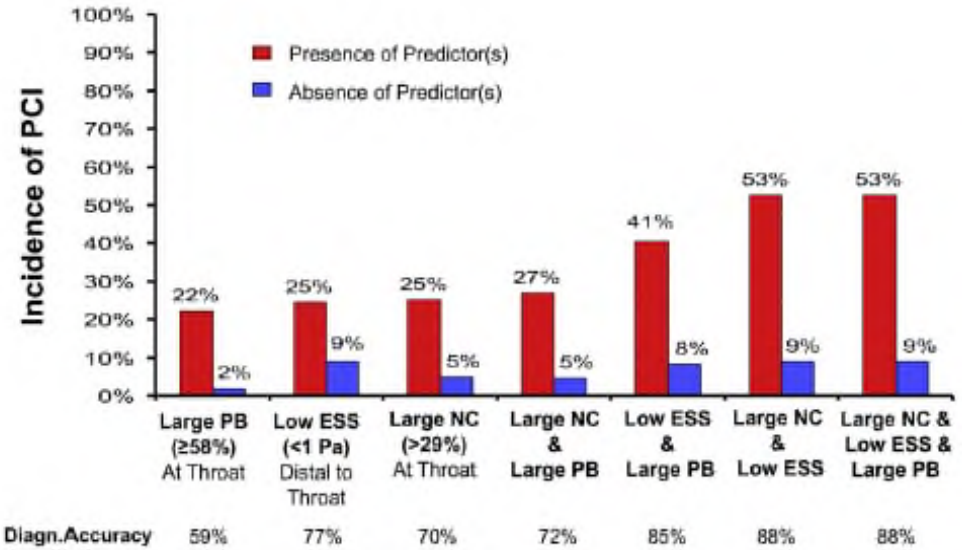
Role of Low Endothelial Shear Stress and Plaque Characteristics in the Prediction of Nonculprit Major Adverse Cardiac Events: The PROSPECT Study

Stone PH..Stone GW, Jacc Cardiovascular Imaging 2018

Outcome:

- Low local ESS (<1.3 Pa) was strongly associated with subsequent nc-MACE compared with physiological/high ESS
- No lesion without low ESS led to nc-MACE during follow-up, regardless of PB, MLA, or lesion phenotype at baseline.

- 145 lesions in 97 patients:
  23 nc-MACE lesions (13 TCFAs, 10 thick-cap fibroatheromas [ThCFAs])
  122 nc-non-MACE lesions (63 TCFAs, 59 ThCFAs)



Diagn.Accuracy	59%	77%	70%	72%	85%	88%	88%
Sensitivity	94%	42%	74%	74%	42%	32%	32%
Specificity	54%	82%	69%	72%	91%	96%	96%
Positive PV	22%	25%	25%	27%	41%	53%	53%
Negative PV	98%	91%	95%	95%	92%	91%	91%
Prevalence	22%	10%	16%	15%	8%	4%	4%

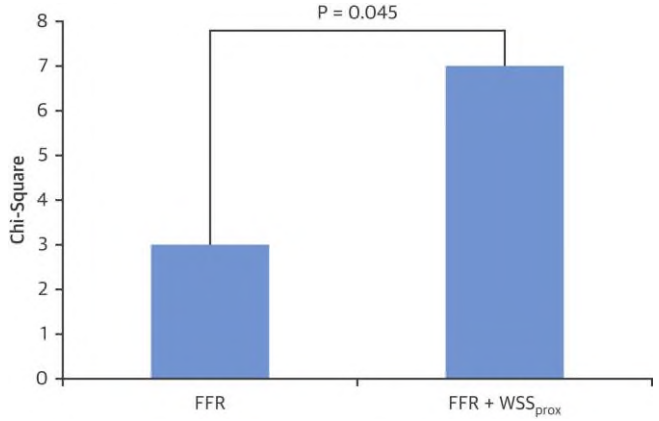
High Coronary Shear Stress in Patients With Coronary Artery Disease Predicts Myocardial Infarction

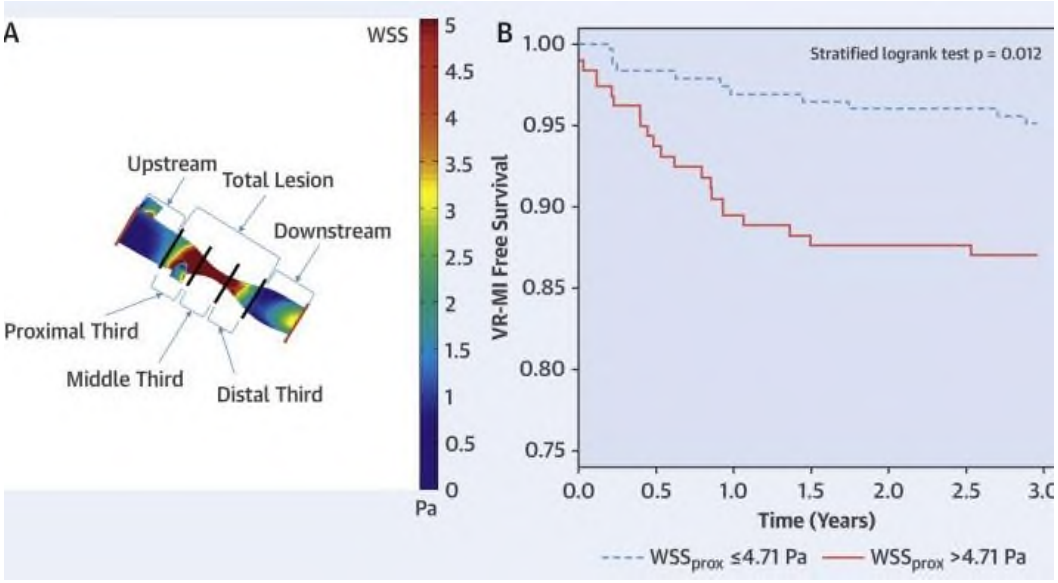
Kumar A…Samady H. JACC 2018

- FAME II population (stable angina and FFR ≤0.80, randomized PCI+OMT vs OMT)
- 29 culprit vessels with MI vs 29 vessels from non-MI control patients

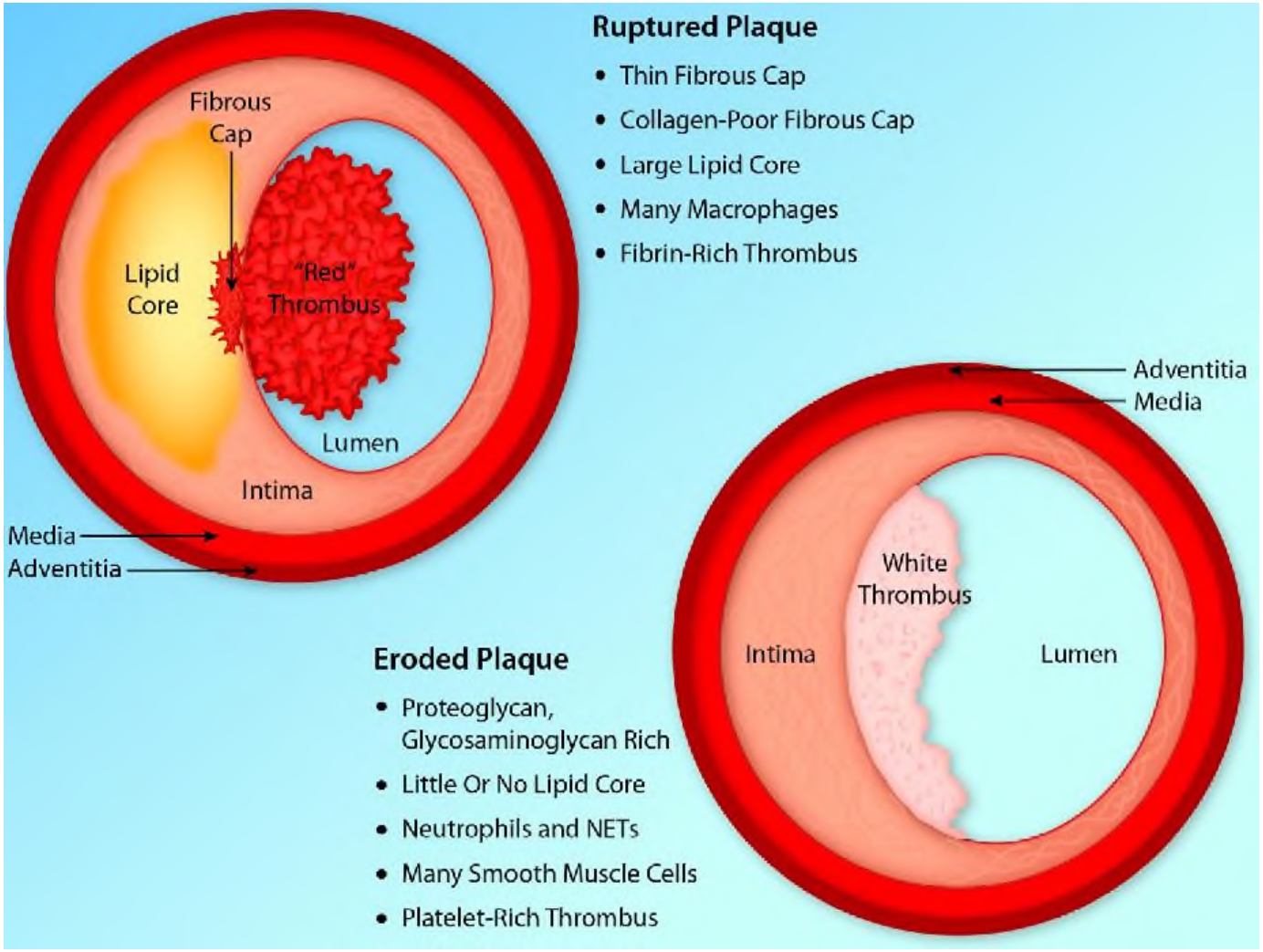
Outcome

- Higher ESS had the highest prognostic value to predict MI at 3 years.
- ESS had an incremental prognostic value over FFR in predicting MI.





Acute coronary syndromes: rupture vs erosion
Is ESS a factor?

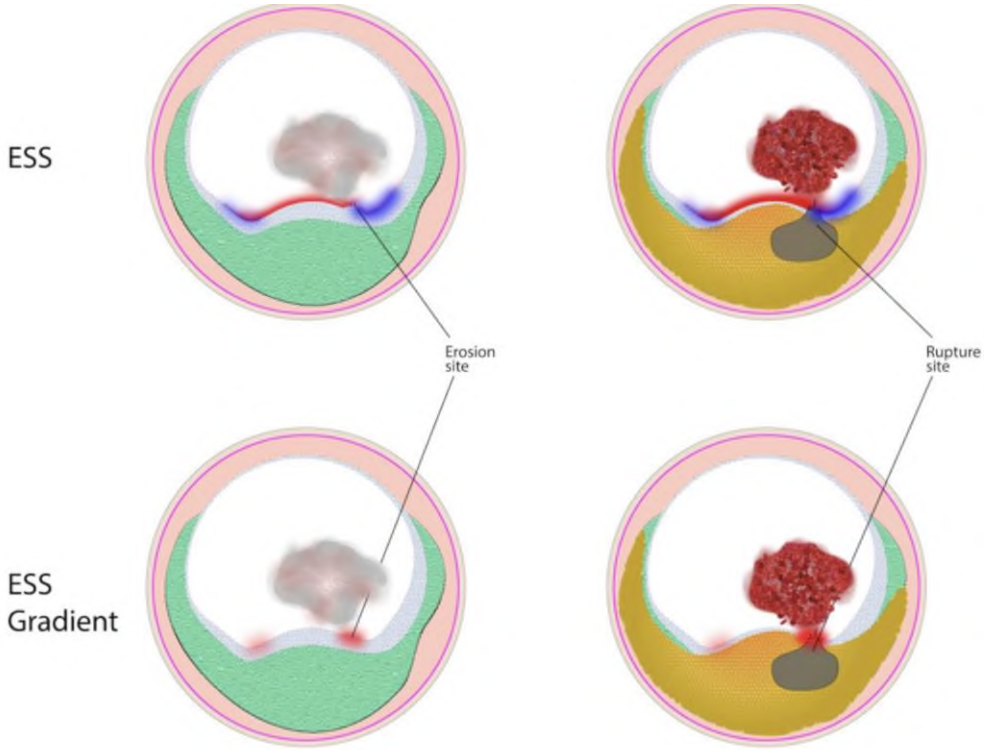


High spatial endothelial shear stress gradient independently predicts site of acute coronary plaque rupture and erosion

Thondapu et al, Cardiovascular Research 2021

Outcome:

- Rupture: high ESSG, layered plaque, and lipid
- Erosion: moderate/high ESSG, high oscillatory shear index (OSI)
- ESSG is higher at rupture sites
- ESS is similar between the two groups



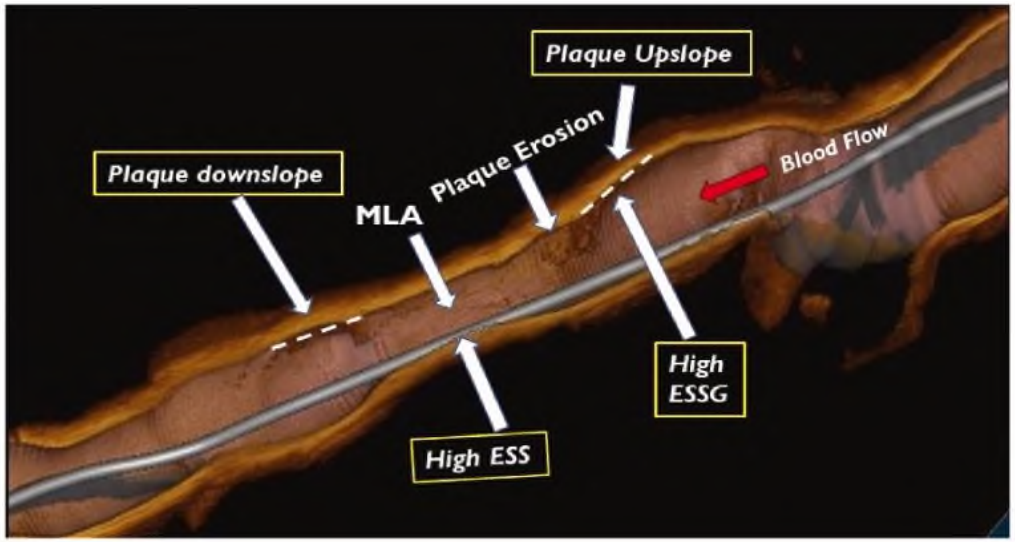
- 37 STEMI/NSTEMI patients who underwent vascular profiling with with OCT

The role of endothelial shear stress, shear stress gradient, and plaque topography in plaque erosion

Diaa Hakim…Peter H. Stone Atherosclerosis 2023

Outcome

- Erosion and thrombus formation were associated with high ESS and ESSG vs. similar plaques without destabilization.
- There was no difference in Min ESS between erosion and stable plaques.



- ESS and ESSG was compared between plaques with erosion and similar non-culprit control plaques that remained stable in 46 patients

Low vs high ESS in ACS

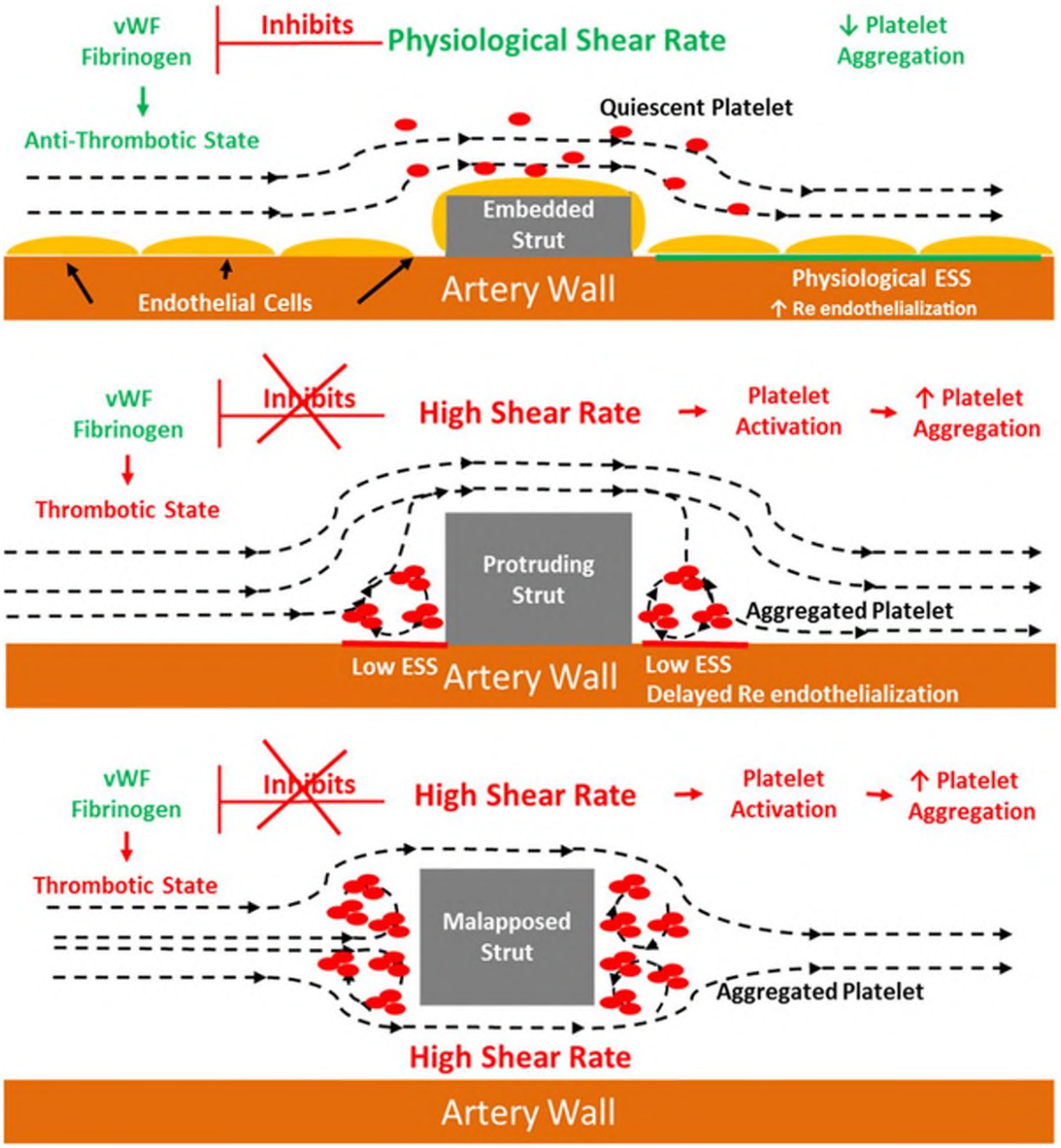
- Plaques exposed to either low or high ESS environments have been associated with plaque destabilization and new major acute cardiovascular events (MACE)
- Newer markers such as ESSG, seem to consistently be associated with MACE

	Low ESS	High ESS	High ESSG
Hakim et al, 2023		✓	✓
Thondapu et al, 2021		✓	✓
Bourantas et al, 2020		✓	✓
Kumar et al, 2018		✓	
Stone PH et al, 2018	✓		

Effects of endothelial shear stress after Stent Implantation

- Suboptimal stent implantation affects the local hemodynamic forces and can lead to unfavorable clinical outcomes.
- Regions of low ESS after PCI are colocated with neointima and neoatherosclerosis formation.
- High shear gradients and flow disturbances have been shown to increase the risk of thrombosis.

Wentzel et al	Circulation 2001
Gijsen et al	Am J Cardiol. 2003
Papafaklis et al	Int J Cardiol. 2009
Bourantas et al	Int J Cardiovasc Imaging. 2014
Bourantas et al	JACC Cardiovasc Interv. 2014
Bourantas et al	Int J Cardiol. 2015
Shishido et al	JAHA 2016
Torii et al	Int J Cardiol 2018
Tenekecioglu et al	Int J Cardiovasc Imaging 2019
Jin et al	Front Cardiovasc Med 2022
Beyene et al	Cardiovasc Revasc Med 2023



Local Hemodynamic Forces After Stenting Implications on Restenosis and Thrombosis, Jaryl Ng… Nicolas Foin ATVB 2017

Conclusions

- Endothelial dysfunction is a prerequisite in initiation of atherosclerotic process
- Hemodynamic parameters, such as ESS seem to trigger ED, in certain areas of the coronary tree with flow disturbance/separation (bifurcation, branches)
- Data from Coronary angiography (invasive and non-invasive), IVUS/OCT and CFD provide quantification of ESS
- Low ESS has been associated with atheromatic plaque progression
- Microvascular dysfunction may predispose to low ESS in epicardial arteries
- Changes in ESS (Low/High) have been associated with ACS
- High ESSG is an emerging marker associated with ACS
- Low ESS has been associated with neoatherosclerosis and ISR, high ESSG associated with thrombosis
- Advances in imaging modalities may allow less invasive and more accurate atheroma topography and ESS quantification, and implementation in clinical practice

Thank you for your attention