Vascular Ultrasound for the Cardiologist

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Allam et al. (2011) JACC: Cardiovascular Imaging; 4(4): 315–327

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An Expensive Disease

- Epidemiology of cardiovascular disease
  - Leading cause of death in US, 17% of health expenditures
  - By 2030, 40.5% of the US population is projected to have some form of CVD.
- Economic Cost:
  - Between 2010 and 2030, total direct costs of CVD are projected to triple, from $273 billion to $818 billion.

Paul A. Heidenreich et al. Circulation. 2011;123:933-944

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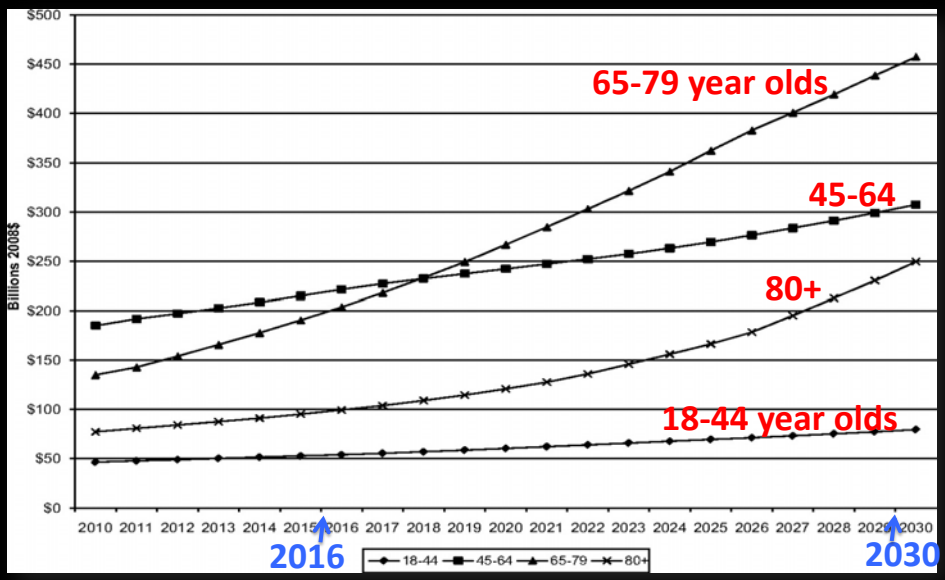

Paul A. Heidenreich et al. Circulation. 2011;123:933-944

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A silent disease

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A Challenging Diagnosis

- History & Physical
- Clinical Standard: Angiogram
  - Cost, availability, few but serious side effects
  - It's a lumenogram and may not correlated to events
- In between armamentarium of risk stratification tools available:
  - stress testing, Nuclear, Cardiac CT, Risk scores, biomarker
  - To predict morbidity and mortality
  - To identify suitability for angiography

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Limitations of Current Approaches

- Substantial cost, radiation, issues with portability and access
- Limited Applicability of scoring systems
  - may only identify 1/3 of those who have events during follow up (Framingham Risk Score)
- Socioeconomic disparities- Hispanics and blacks- higher prevalence but get less testing and care (*AHA Policy Statement, Heidenreich et al, Circulation 2011).*

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The ‘Barometer’ in the Storm

Carotid Plaque Assessment for Predicting Cardiovascular Disease

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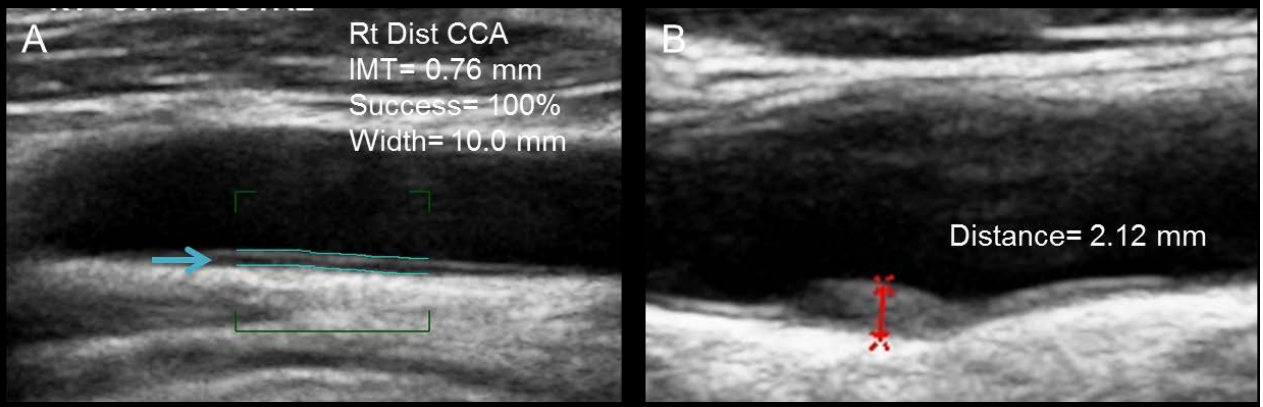
CIMT AND PLAQUE ASSESSMENT

- Early Imaging Biomarker
- Radiation free, less expensive, portable
- ‘Barometer’ or surrogate



Hetu, and Nambi; Curr Cardiovasc Risk Rep 2014

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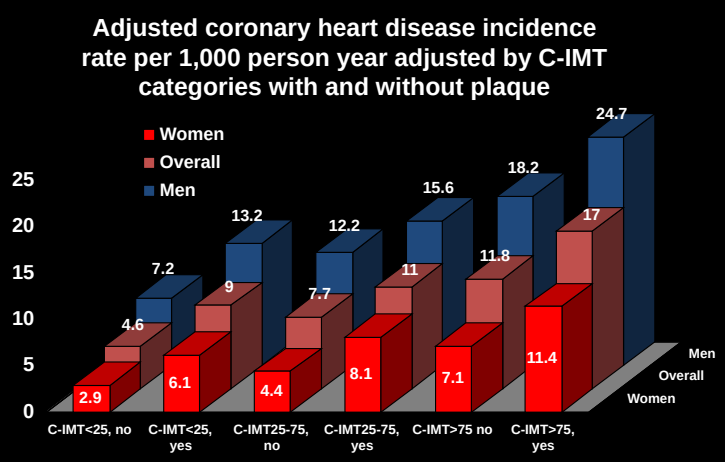
ARIC Study: Atherosclerosis Risk in Communities

CIMT study of 16K patients followed 15 y for CVD outcomes

CIMT incremental to traditional risk factors for prediction of events.

Plaque (yes/no)



Nambi et al. (2010) JACC 55(15):1600-7

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Plaque is 'Better' than CIMT

- ARIC: Presence of Plaque may be more strongly associated with risk than a diffuse increase in CIMT
- Meta-analysis by Inaba et al., 2012
  - Carotid plaque, compared with CIMT, had a significantly higher diagnostic accuracy for the prediction of future MI events and for the detection of CAD
  - Plaque more accurately predicts 10 year risk of CAD

Inaba et al. 2012 Atherosclerosis 220: 128-133

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	CIMT		Plaque	
Accuracy for assessing atherosclerosis	X	Reflects changes in the media (ie. media largest proportion of CIMT) rather than intima	✓	Generally reflective of atherosclerotic process
Reproducibility	X	Difficult to reproduce at follow up due to segment location	✓	Easy to relocate plaque of interest at follow-up: Good inter-observer variability demonstrated
	✓	Good inter- observer variability demonstrated		
Serial measures	✓	Serial changes measurable	✓	Serial measures quantifiable reliably
	X	Changes in CIMT difficult to quantify in short time frame (less than one year)		
Segments measured	X	Difficult to measure in the bulb	✓	Plaque can be measured in any segment, including bulb
Ease of use	✓	Automated software, widely available, rapidly measured	X	Requires specialized software, expertise, and more time consuming
Standardized approach	X ✓	Lacking, but some ASE recommendations available	X	Lacking; has a general definition but no recommendations

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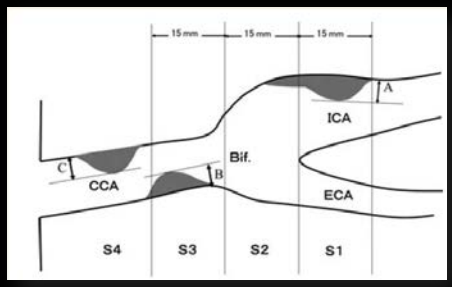
Plaque Is Important- If Only We Could Quantify?

- Plaque Score (PS)
- Maximum Plaque height (mm)
- Total Plaque Area (mm^2)



But plaque is an irregular 3D phenomenon and so out of plane using 2D US

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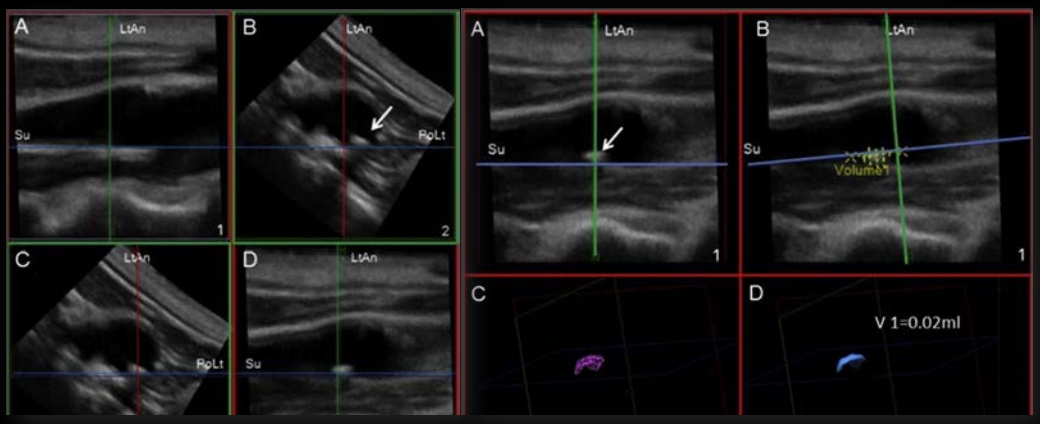
Can Carotid Bulb Plaque Assessment Rule Out Significant Coronary Artery Disease? A Comparison of Plaque Quantification by Two- and Three-Dimensional Ultrasound



JASE, 2013, 26:1, 86-95

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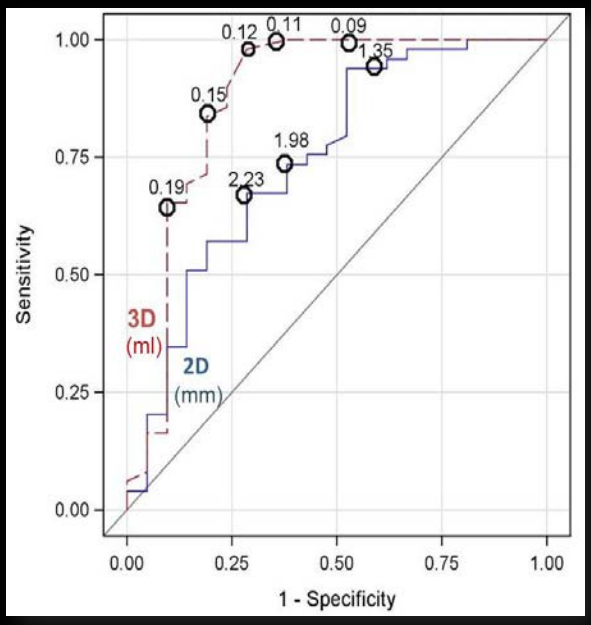

Carotid Plaque Volume Predicts Angiographic CAD

- A threshold value of 0.09 ml (by 3D) had significantly greater **sensitivity for CAD compared with 2D methods**

Johri AM et al., JASE, 2013, 26:1, 86-95

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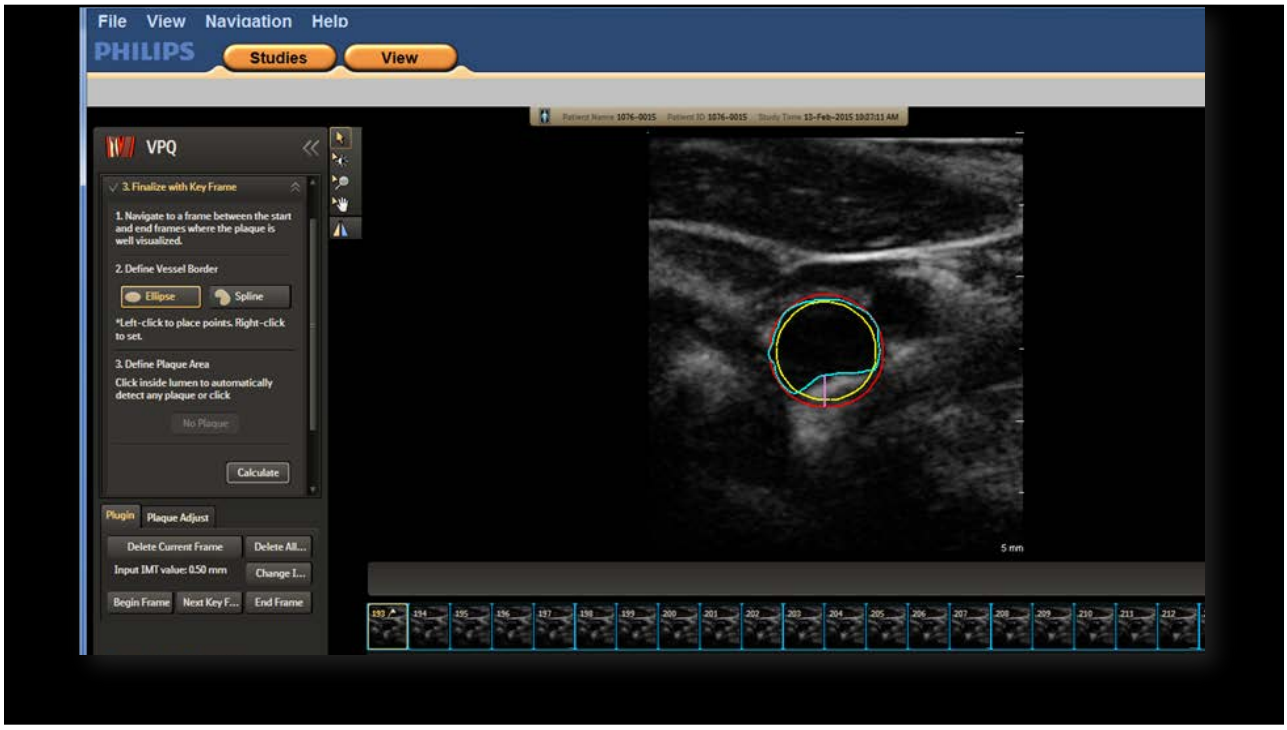

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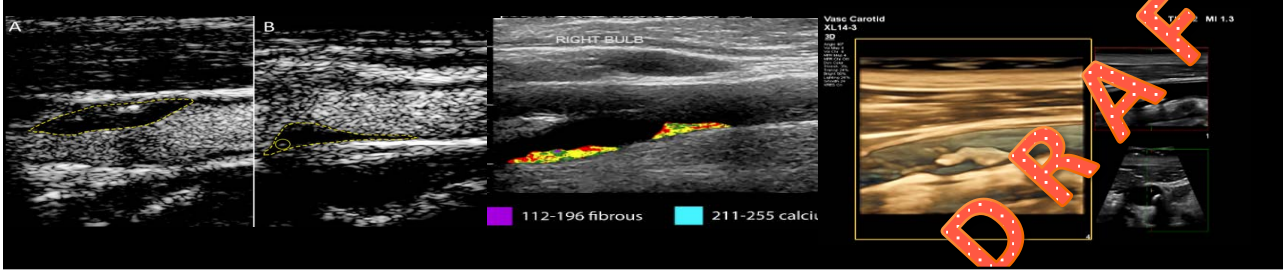
NEW ASE Guideline- Completed & Under Review by Guidelines Committee

The Assessment of Carotid Arterial Plaque by Ultrasound for the Characterization of Atherosclerosis and Evaluation of <u>Cardiovascular Risk</u>

A.M. Johri, V. Nambi, T. Naqvi, S. Feinstein, M. Park, E. Kim, H. Becher, H. Sillesen, *under review*



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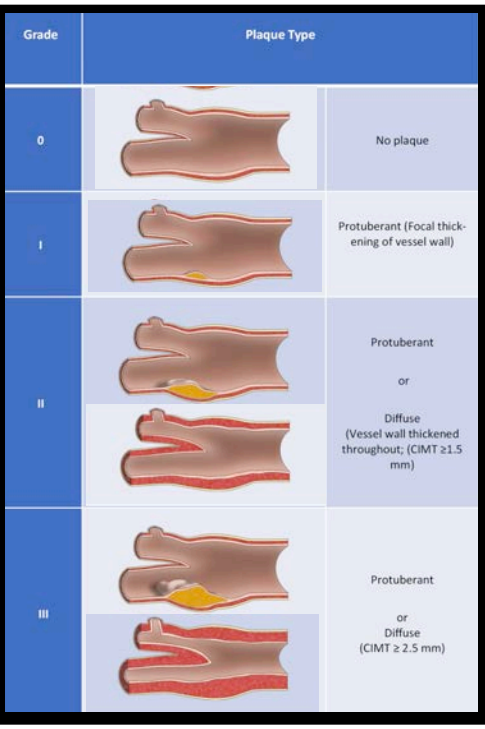

2D Plaque Thickness

0

<1.5 mm

1.5 – 2.4 mm

>2.5 mm

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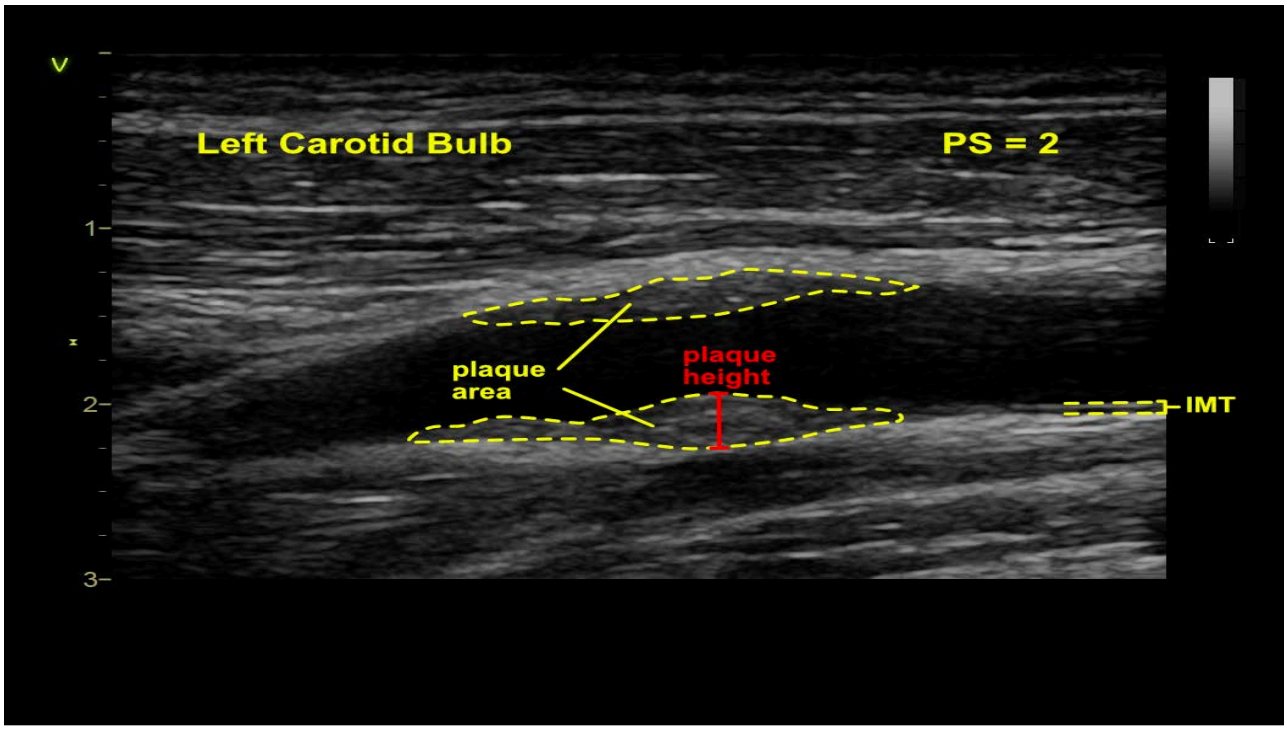

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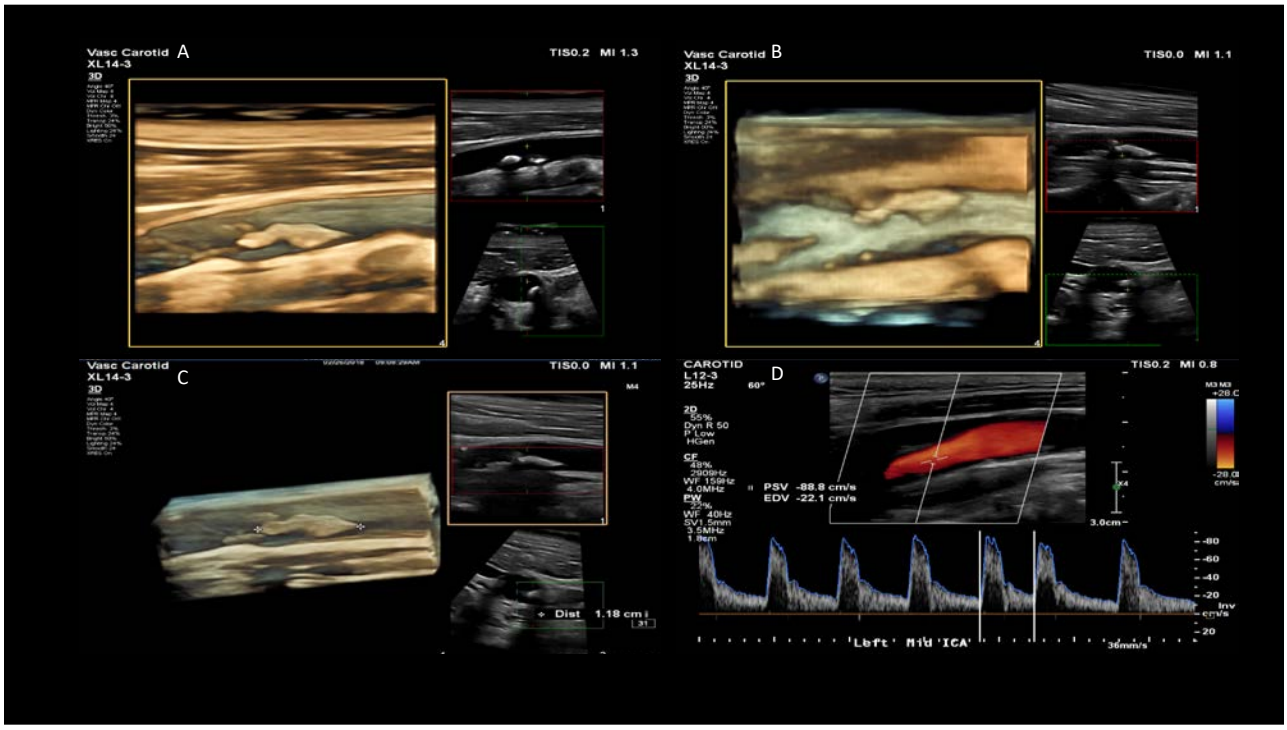

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Risk Score (Asymptomatic At-Risk Population) (Greenland et al., 2010)

- *Low Risk: <6% FRS*
- *Intermediate Risk: Grey Area (6-10% to ≤20% FRS)*
- *High Risk: ≥20% FRS*

Intermediate Risk Patients

Carotid Ultrasound

European Guidelines on CVD Prevention in Clinical Practice (Class IIb, Level B) (Piepoli et al., 2016)

Plaque Present

No Plaque

3D Available?

CIMT Measurement

Yes

No

≥1.5mm

<1.5mm

Plaque Volume

Plaque Height

Diffuse Plaque

Serial Measurements not recommended

Threshold TBD ≥0.05mL

≥1.5mm

Risk Factor Modification, Consider Further Testing, Consider Rx

Concept In Development

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Beyond Quantification: Could the Detection of Vulnerable Plaque defined by Composition

Identify the Vulnerable Patient?

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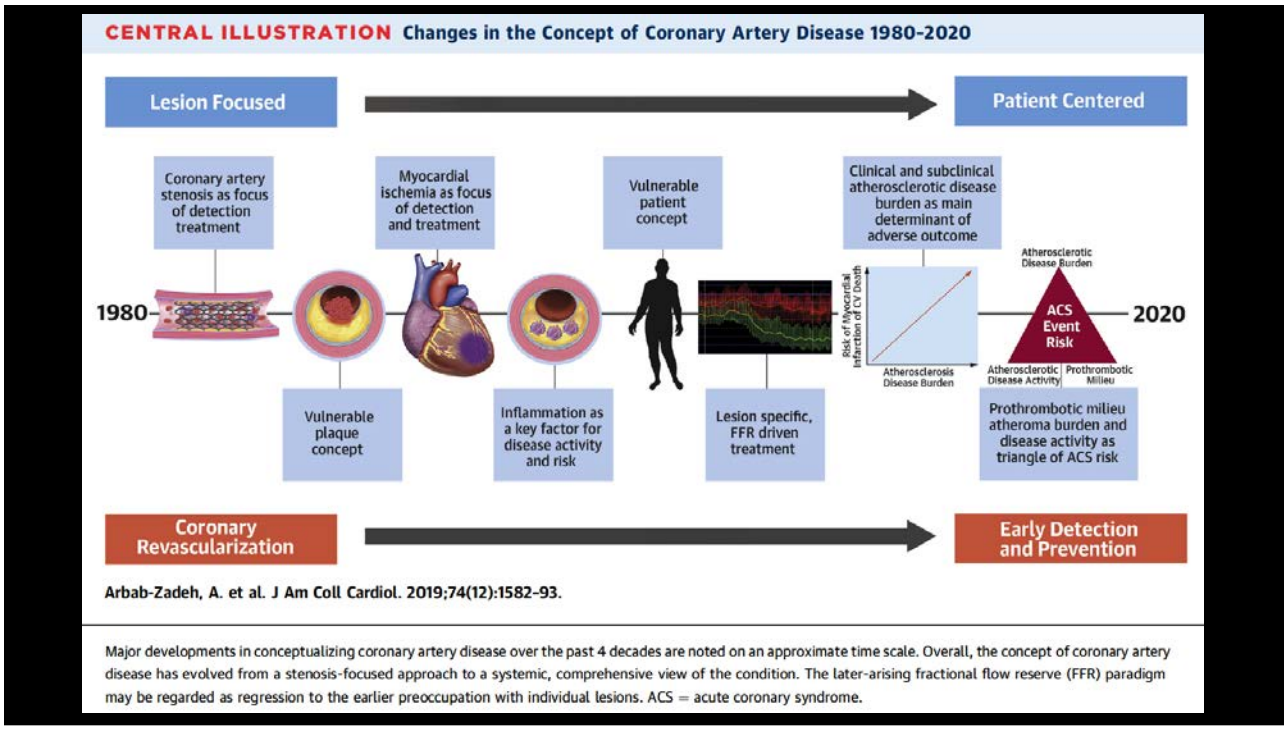

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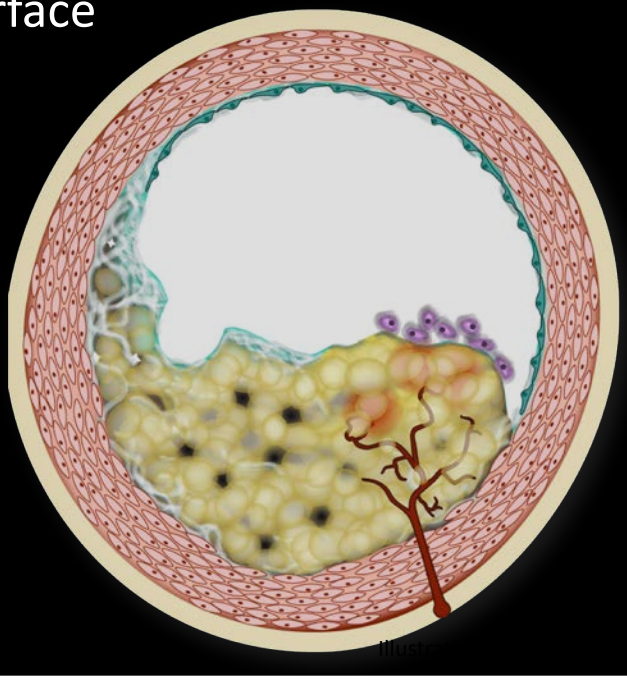
Below the Surface



- The Making of a **Vulnerable Plaque**

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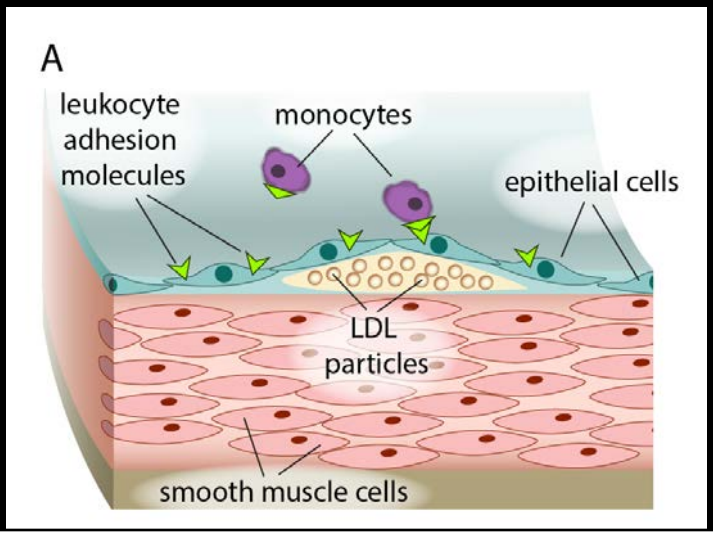
LDL particles infiltrate the intima, oxidation promotes epithelial cells to express leukocyte adhesion molecules for the recruitment of monocytes.



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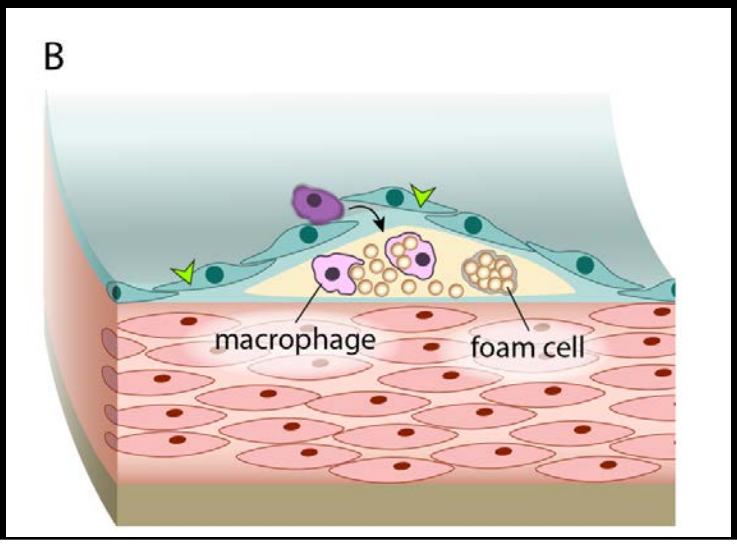
Monocytes migrate into the intima, differentiate into macrophages, take up oxidized LDL particles and become foam cells.



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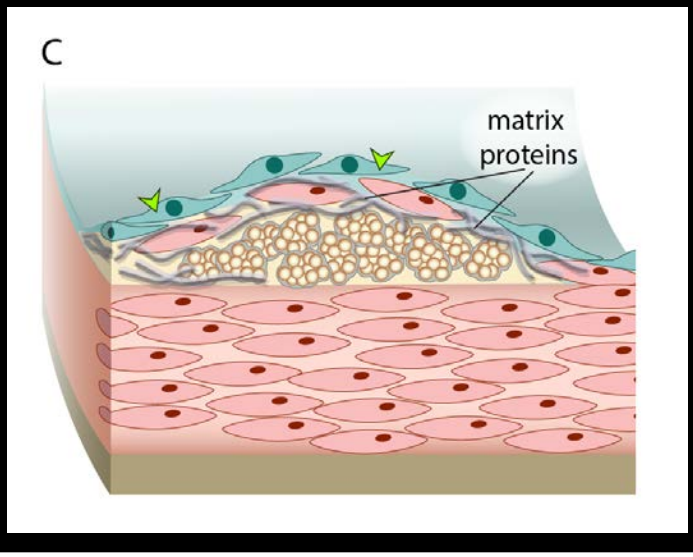
SMCs migrate to the intima, produce matrix proteins, contribute to the fibrous cap.



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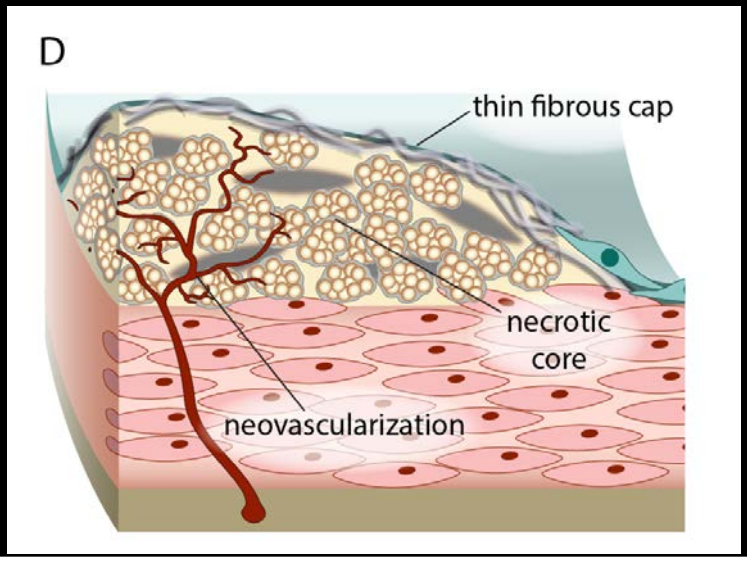
SMCs, epithelial cells, and macrophages undergo apoptosis or necrosis, resulting in a necrotic core, fibrous cap becomes thin and rupture-prone.

Neovascularization from adventitial vasa vasorum in advanced lesions.



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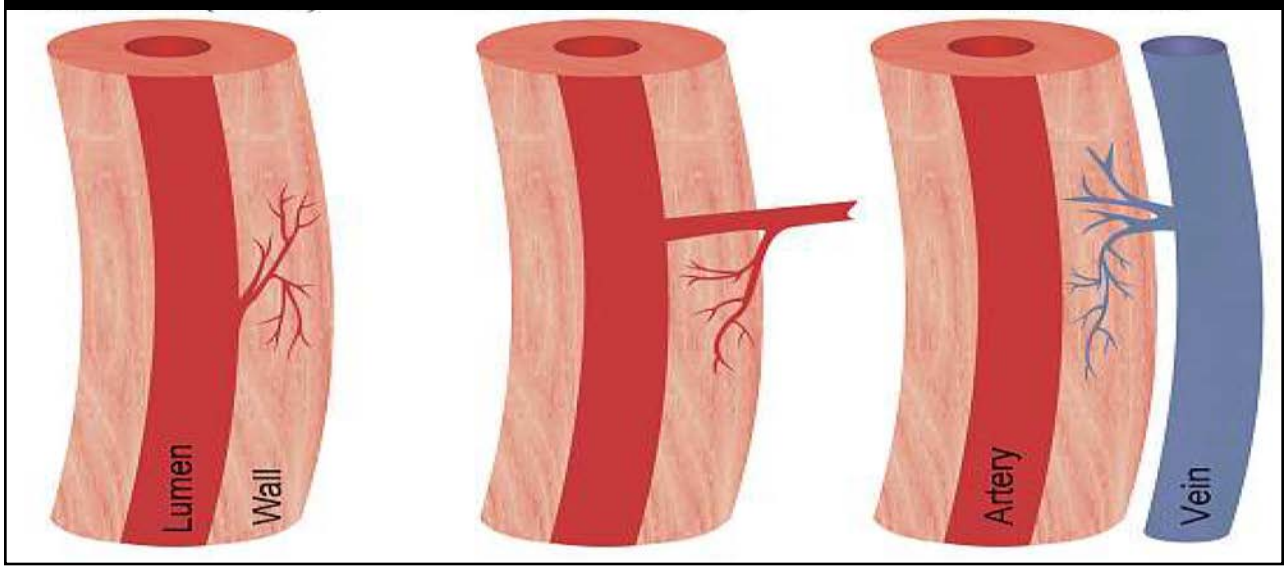
Vasa Vasorum ***Interna*** | **Vasa Vasorum** ***Externa*** | ***Venous*** **Vasa Vasorum**



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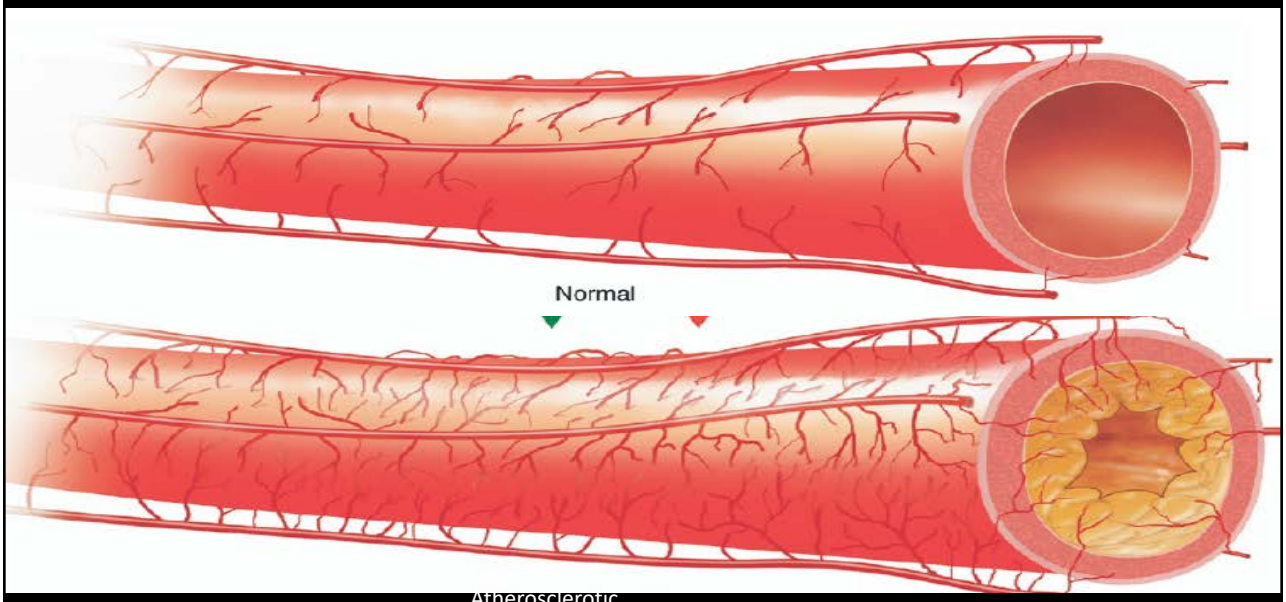
Neovascularization in Disease



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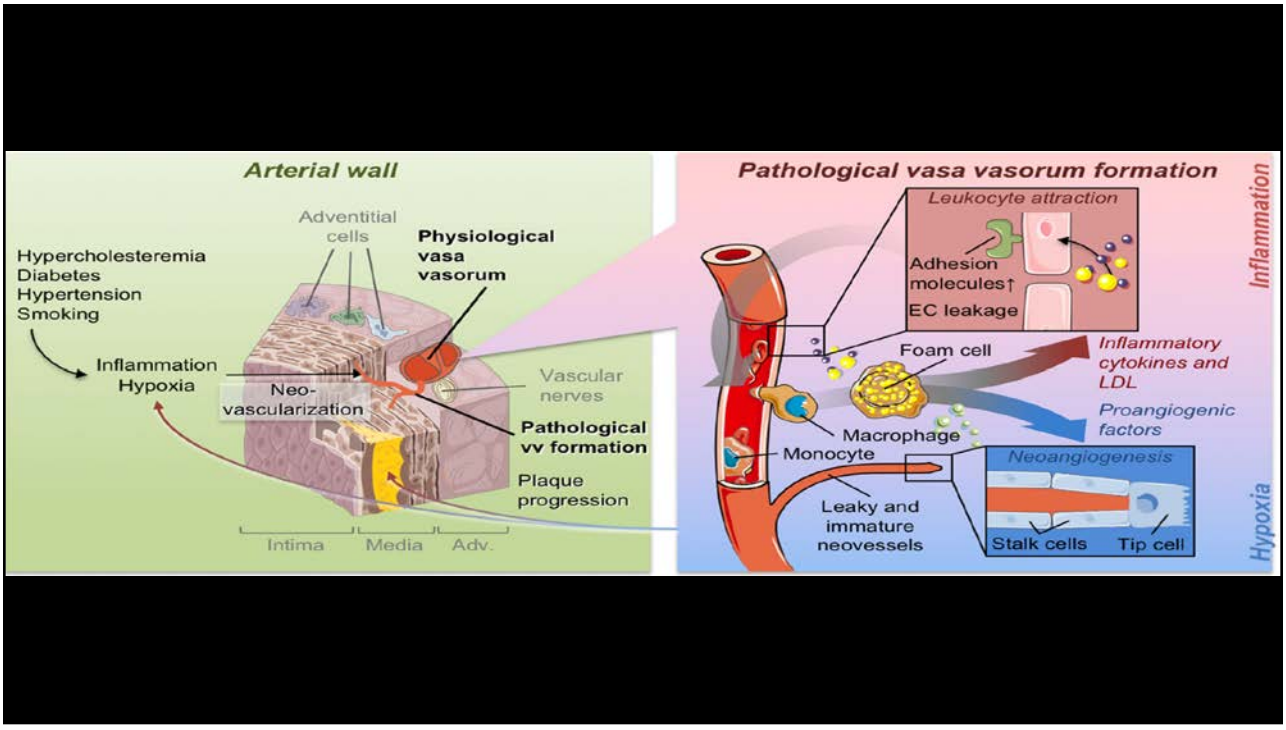

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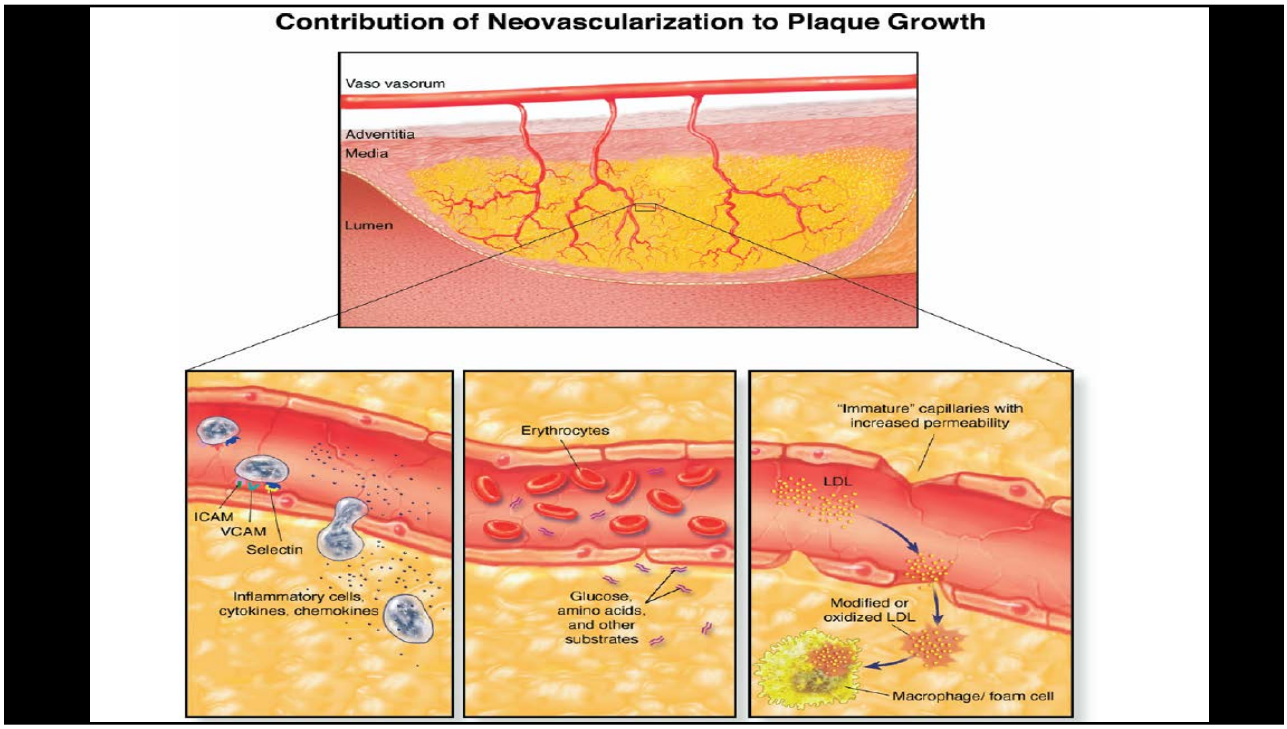
Contribution of Neovascularization to Plaque Growth
Vaso vasorum
Adventitia
Media
Lumen
ICAM
VCAM
Selectin
Inflammatory cells, cytokines, chemokines
Erythrocytes
Glucose, amino acids, and other substrates
"Immature" capillaries with increased permeability
LDL
Modified or oxidized LDL
Macrophage/ foam cell

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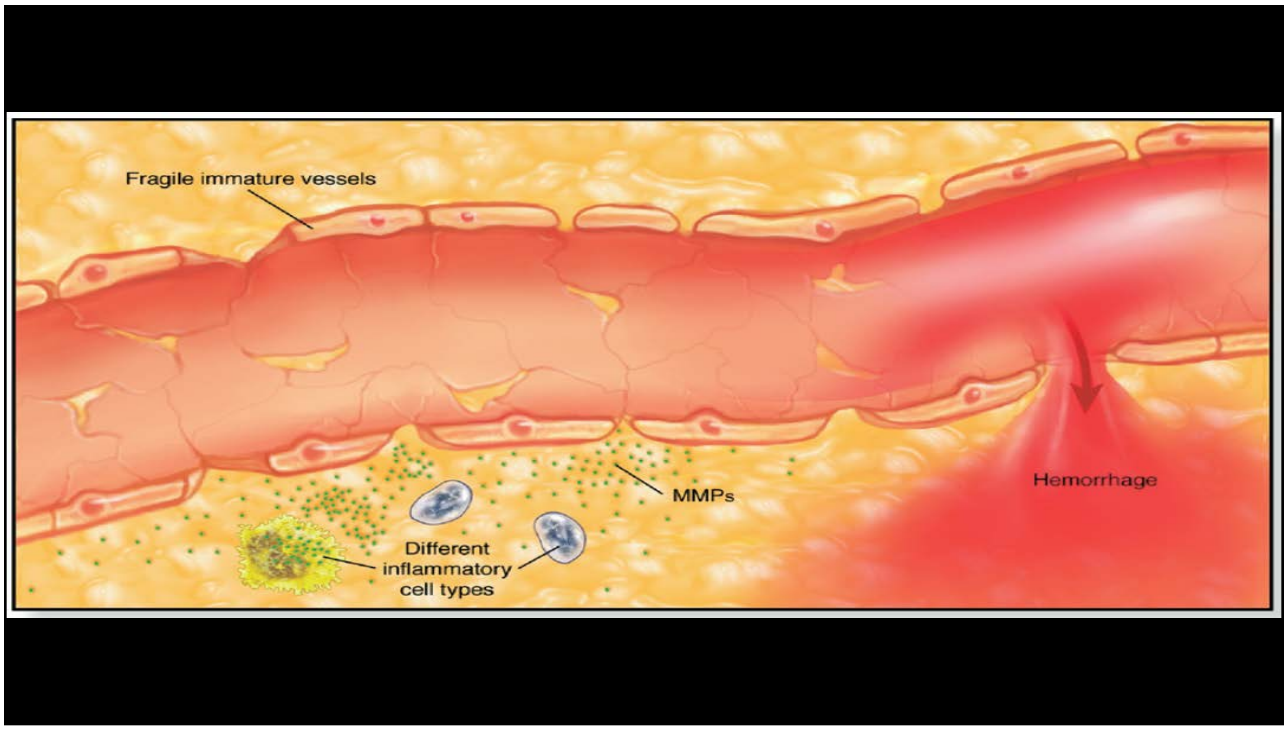
Fragile immature vessels
MMPs
Hemorrhage
Different inflammatory cell types

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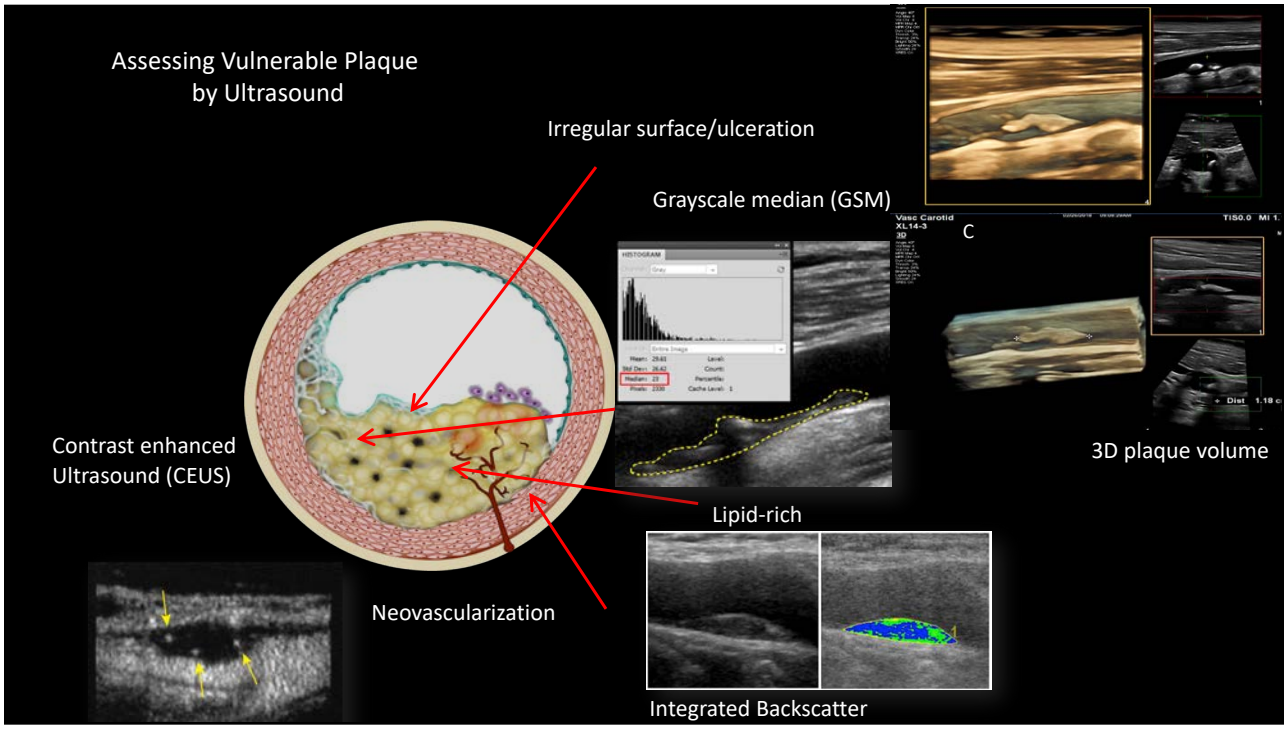

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ESC European Society of Cardiology

European Heart Journal - Cardiovascular Imaging (2019) **0**, 1–9
doi:10.1093/ehjci/jez070

Carotid intraplaque neovascularization predicts coronary artery disease and cardiovascular events

Laura E. Mantella[1], Kayla N. Colledanchise[1], Marie-France Hétu[2], Steven B. Feinstein[3], Joseph Abunassar[2], and Amer M. Johri[1,2,*]

[1]Department of Biomedical and Molecular Sciences, Queen's University, 18 Stuart Street, Kingston, Ontario K7L 3N6, Canada; [2]Department of Medicine, Cardiovascular Imaging Network at Queen's (CINQ), Queen's University, Kingston Health Sciences Centre, 76 Stuart Street, Kingston, Ontario K7L 2V7, Canada; and [3]Department of Medicine, Rush University Medical Center, 1653 W Congress Pkwy, Chicago, IL, USA

Received 4 January 2019; editorial decision 22 March 2019; accepted 25 March 2019

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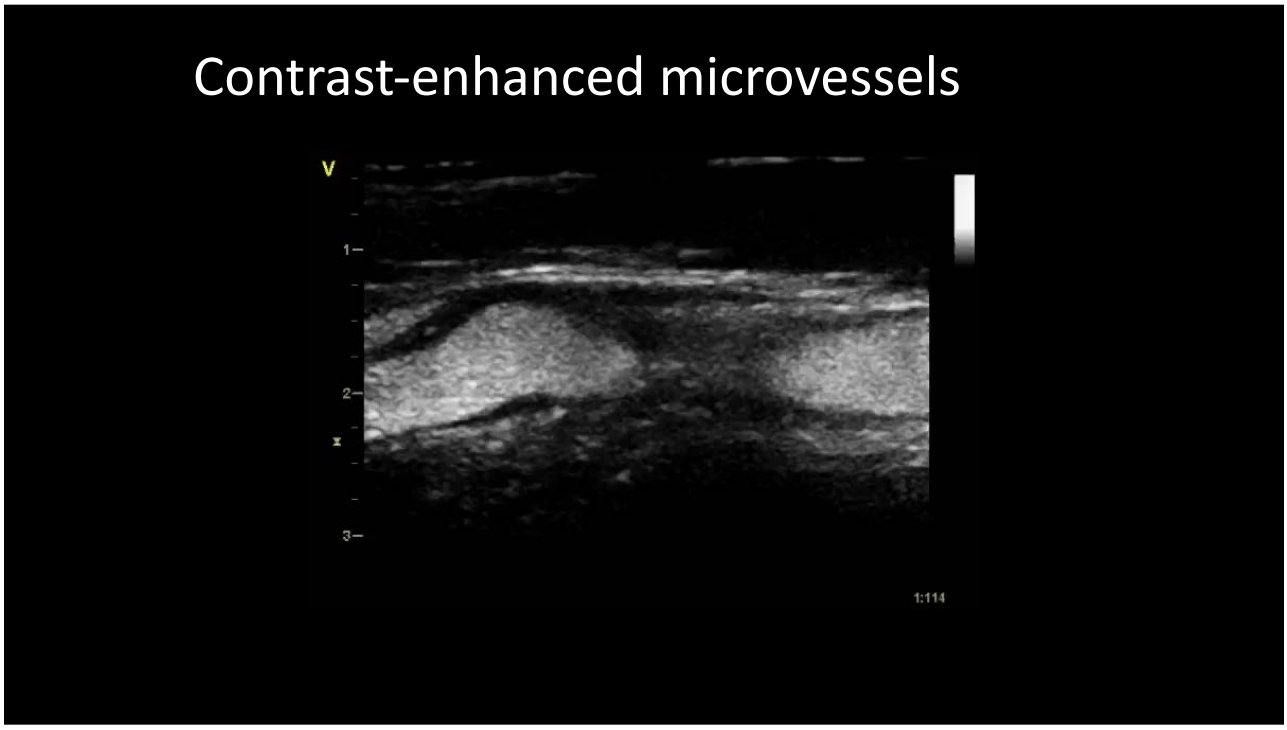

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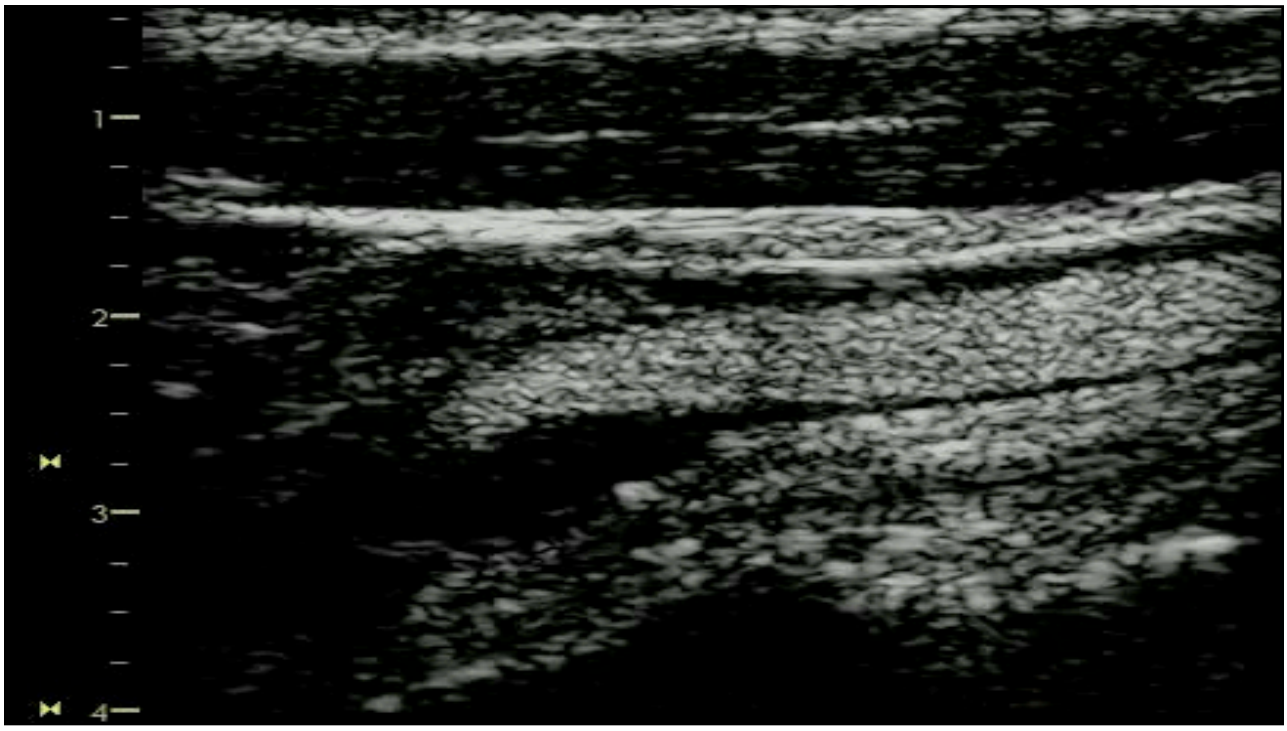

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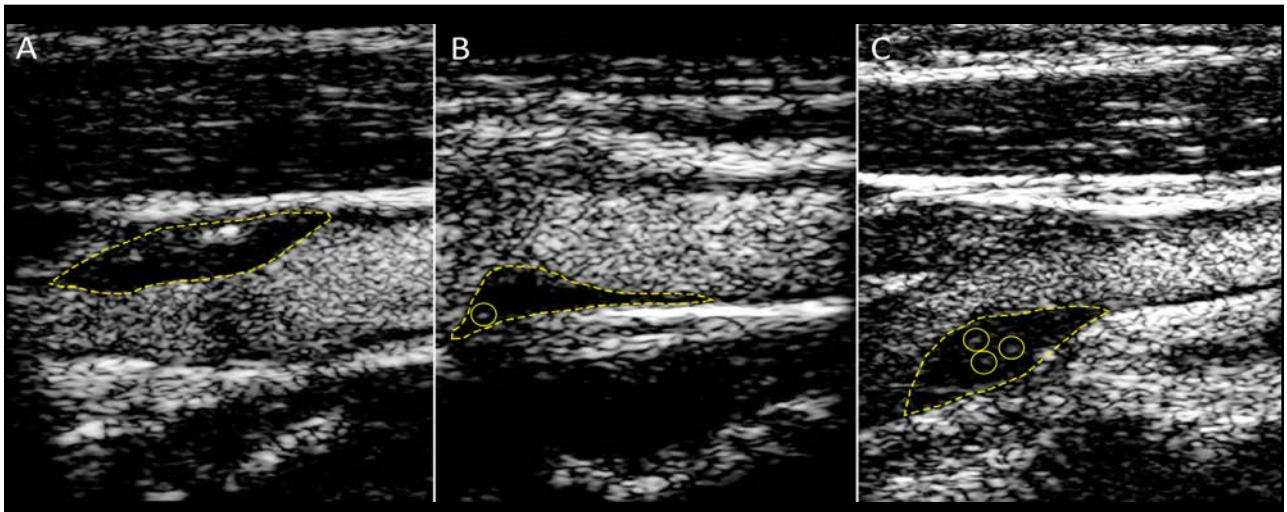

Laura Mantella *et al.* European Heart Journal CV Imaging 2019

Grade 0: No microbubbles within the plaque
Grade 1: Microbubbles < 0.5 mm from edge of the plaque
Grade 2: Microbubbles in the centre of the plaque

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Coronary Angiogram Grading

Coronary angiogram grading:

- 0 = no or minimal disease (0–19%)
- 1 = mild disease (20–49%)
- 2 = moderate disease (50–69%)
- 3 = severe (≥70% within any segment of the main branches of the coronary artery or ≥50% in the left main).

No significant CAD (<50% stenosis)

Significant CAD (≥50% stenosis)

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Carotid artery plaque characteristics in CAD

	Significant CAD, mean ± SD ($n = 284$)	Non-significant CAD, mean ± SD ($n = 175$)	*P*-value
CIMT	0.78 ± 0.2	0.72 ± 0.1	<0.0001
TPA	3.1 ± 1.3	2.43 ± 1	<0.0001
MPH	59.7 ± 45.9	38.9 ± 37.3	<0.0001
IPN	1.76 ± 0.4	0.45 ± 0.6	<0.0001

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Plaque characteristics for predicting CAD

	PPV (%)	NPV (%)	Sens (%)	Spec (%)
CIMT	75	46	46	75
TPA	72	51	65	59
MPH	72	58	76	53
IPN	93	87	92	89

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Significance

- CEUS of carotid artery plaque may be a valuable predictor of CAD and CV events
  - Value in lower risk population to be determined
- Further follow up and analysis of CV outcomes will elucidate the prognostic value of carotid artery CEUS as a risk stratification tool (in progress)
- Correlation with other imaging and biomarkers

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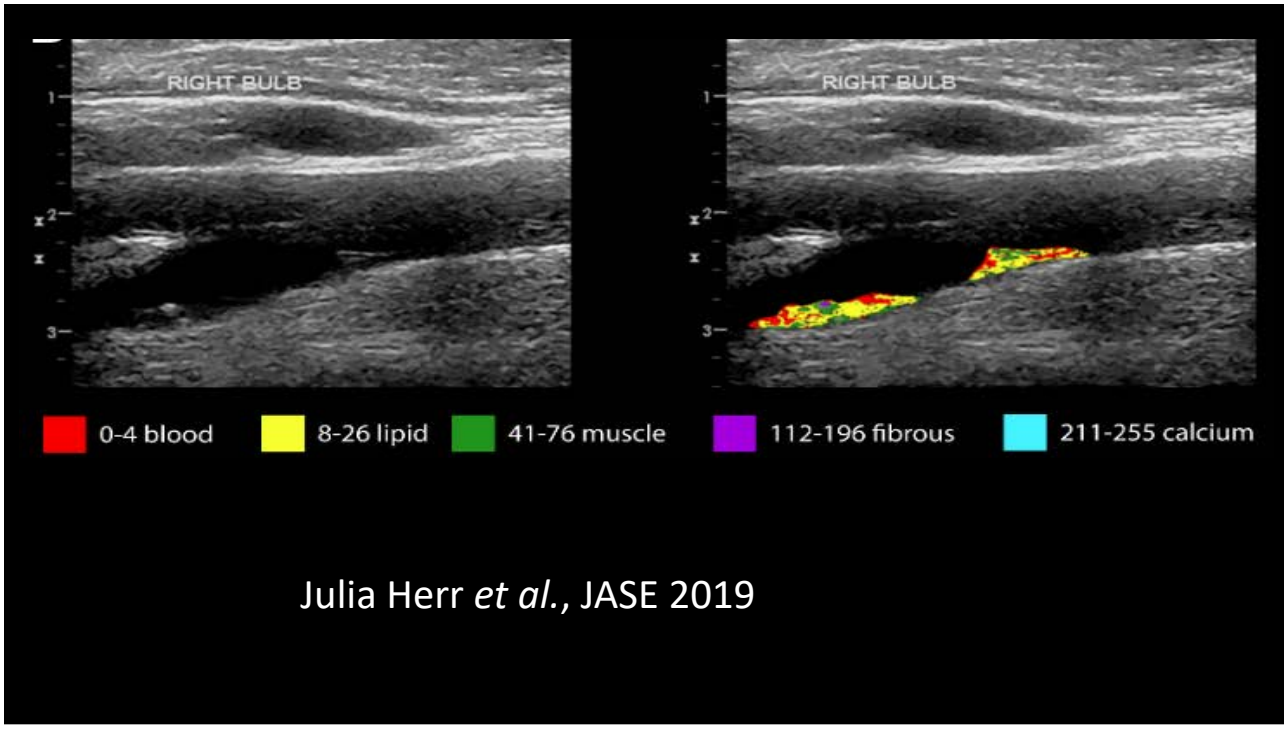

Julia Herr *et al.*, JASE 2019

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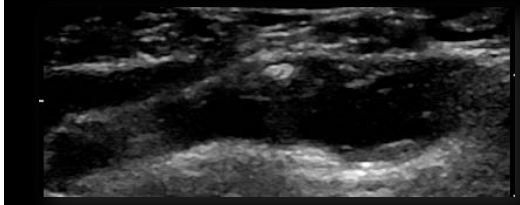
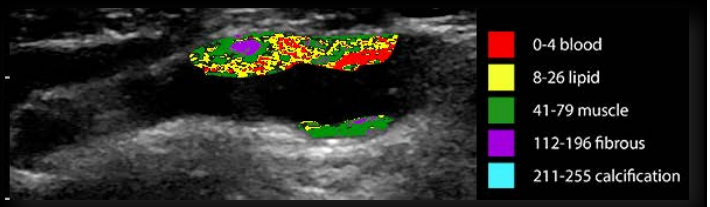
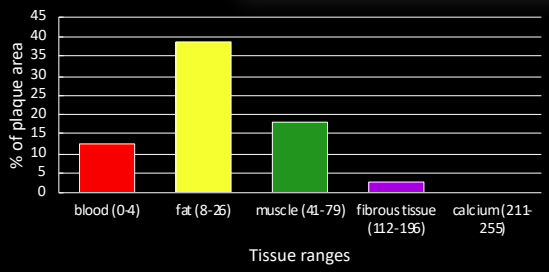


Angio Score 3,
History of MI= No

No History of MI:
% Fat higher in these patients.





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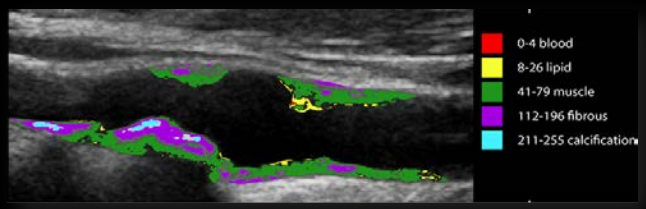
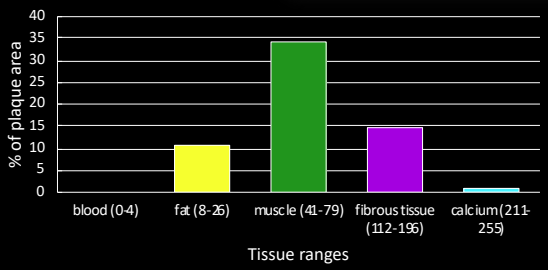
Angio Score 3
History of MI= Yes

History of MI:
% muscle and % fibrous tissue is significantly higher in patients with history of MI.





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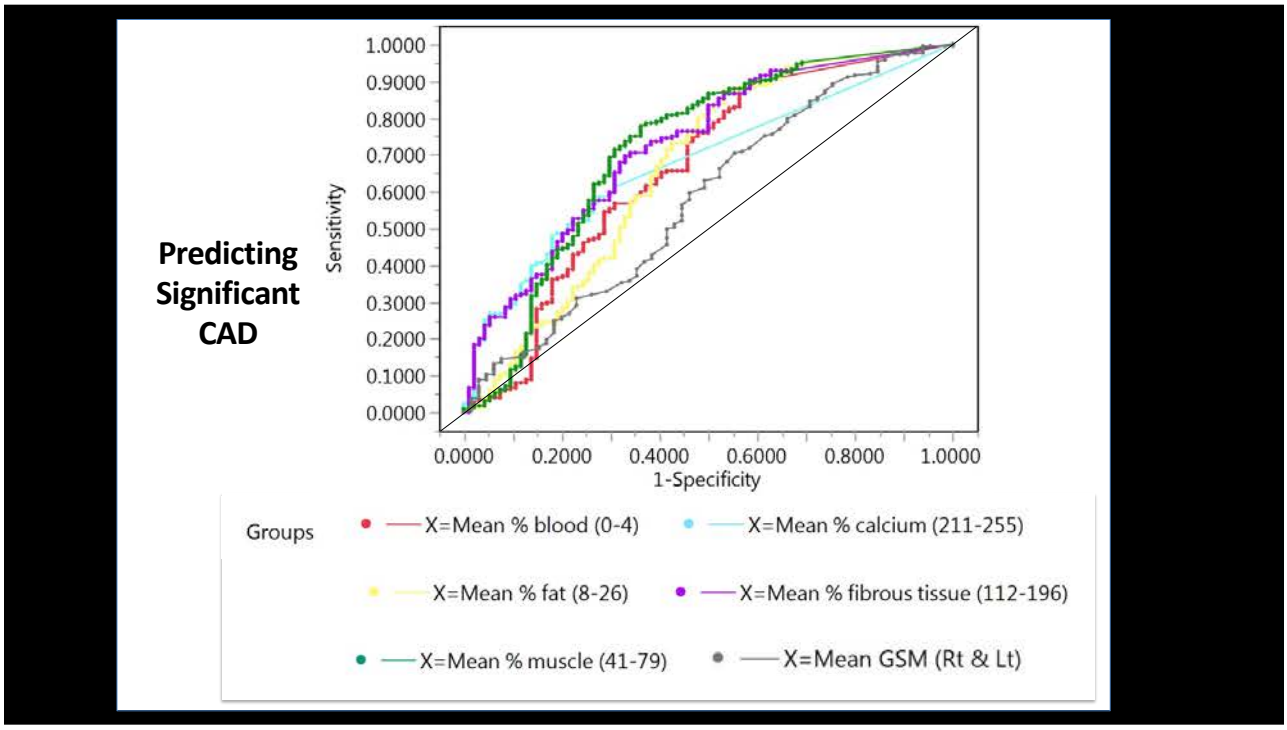
Predicting Significant CAD
Sensitivity
1.0000
0.9000
0.8000
0.7000
0.6000
0.5000
0.4000
0.3000
0.2000
0.1000
0.0000
0.0000
0.2000
0.4000
0.6000
0.8000
1.0000
1-Specificity
Groups
X=Mean % blood (0-4)
X=Mean % calcium (211-255)
X=Mean % fat (8-26)
X=Mean % fibrous tissue (112-196)
X=Mean % muscle (41-79)
X=Mean GSM (Rt & Lt)

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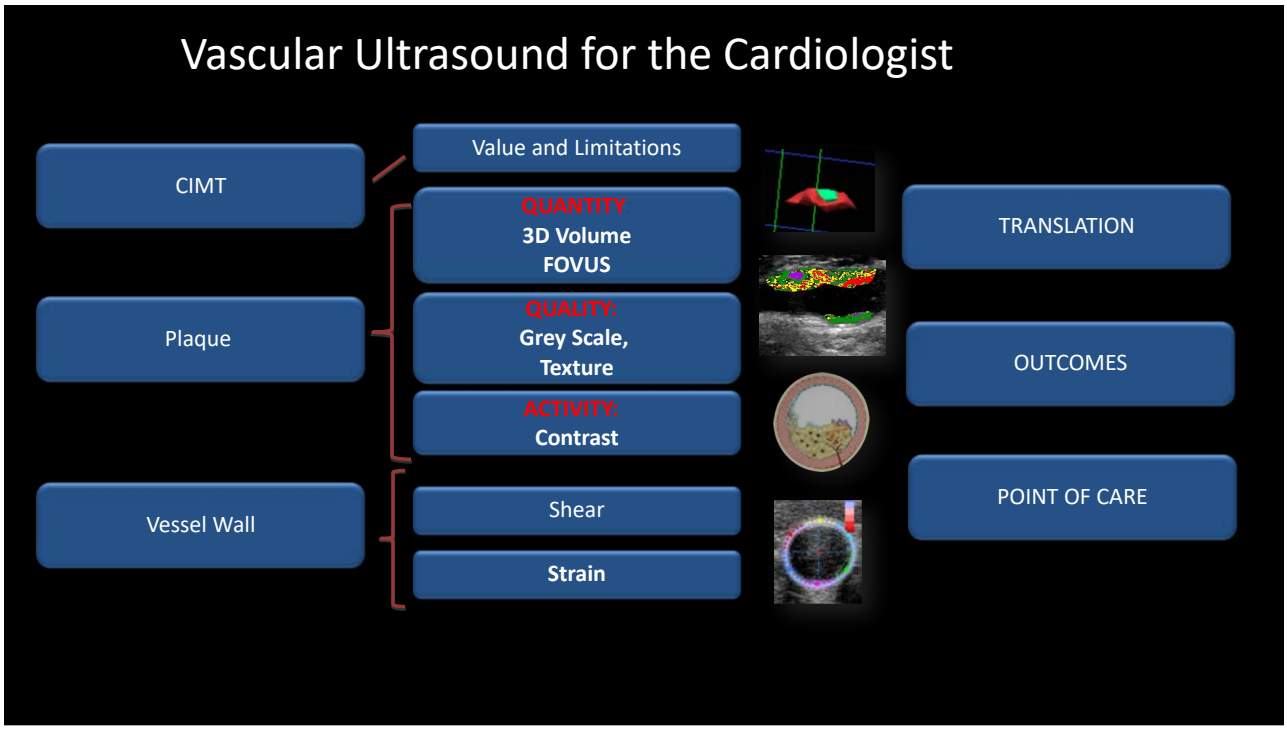
Vascular Ultrasound for the Cardiologist
CIMT
Plaque
Vessel Wall
Value and Limitations
QUANTITY
3D Volume
FOVUS
QUALITY:
Grey Scale,
Texture
ACTIVITY:
Contrast
Shear
Strain
TRANSLATION
OUTCOMES
POINT OF CARE

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The impact of Atherosclerosis is projected to be immense, we need better stratification tools

Carotid Ultrasound Plaque Quantification associated with Cardiovascular Outcomes may help to stratify patients

Standardized approaches to quantification using 2D and 3D methods are now available

Plaque Composition assessment using contrast and gray scale analysis may identify plaque vulnerability and hence the Vulnerable Patient

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