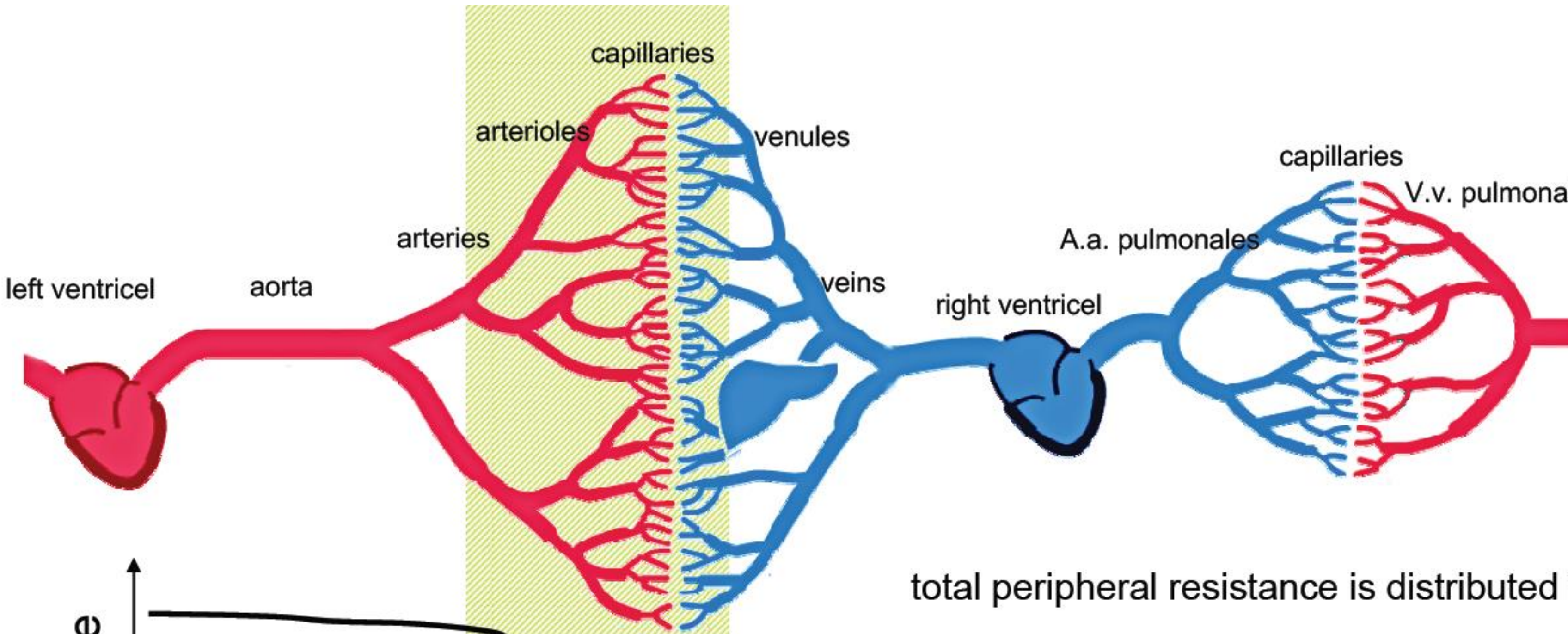
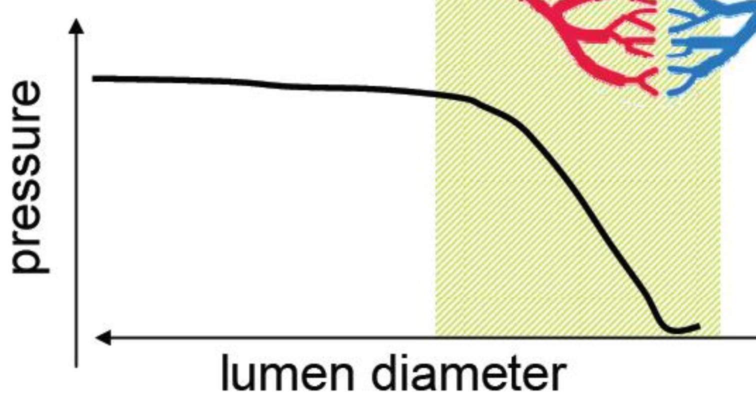
Vascular disease.
Structural evaluation of vascular disease

Goo-Yeong Cho, MD, PhD
Seoul National University Bundang Hospital

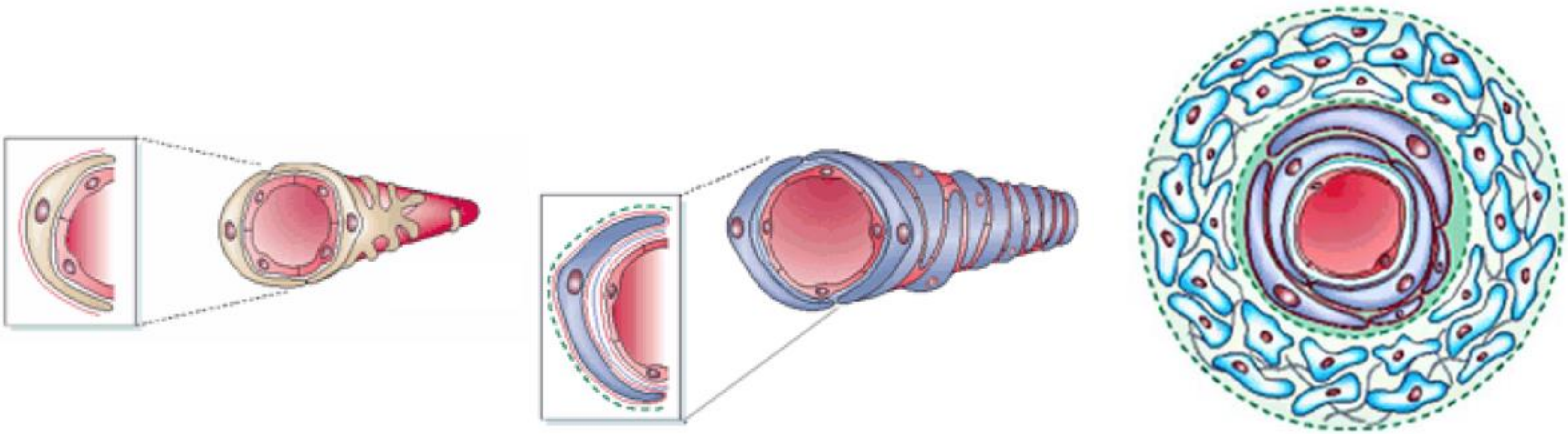




total peripheral resistance is distributed in

terminal arteries and arterioles:	45-50%
capillaries:	23-30%
venules:	3-4%
veins:	3%

resistance vessels
: arteries <300 μm in diameter
: capillaries <100 μm in diameter



Capillary	***Arteriole***	***Artery***	
Endothelial cell tube	Endothelial cell tube	Endothelial cell tube	-> intima
	Internal elastica lamina	Internal elastica lamina	
Pericytes	Smooth muscle cells	Smooth muscle cells	-> media
Basal lamina	Basal lamina	Basal lamina	
	External elastic lamina	Fibroblasts	->adventita
		Extracellular matrix	
		External elastica lamina	

Jain et al, *Nature Medicine* **9**, 685 -693 (2003)

Arteries

- Large arteries are elastic (conducting) arteries – pressure reservoirs
- Medium arteries are muscular (distributing) arteries – more smooth muscle
- Contraction or relaxation of muscle changes the size of the lumen, and so controls the blood pressure in the vessel.

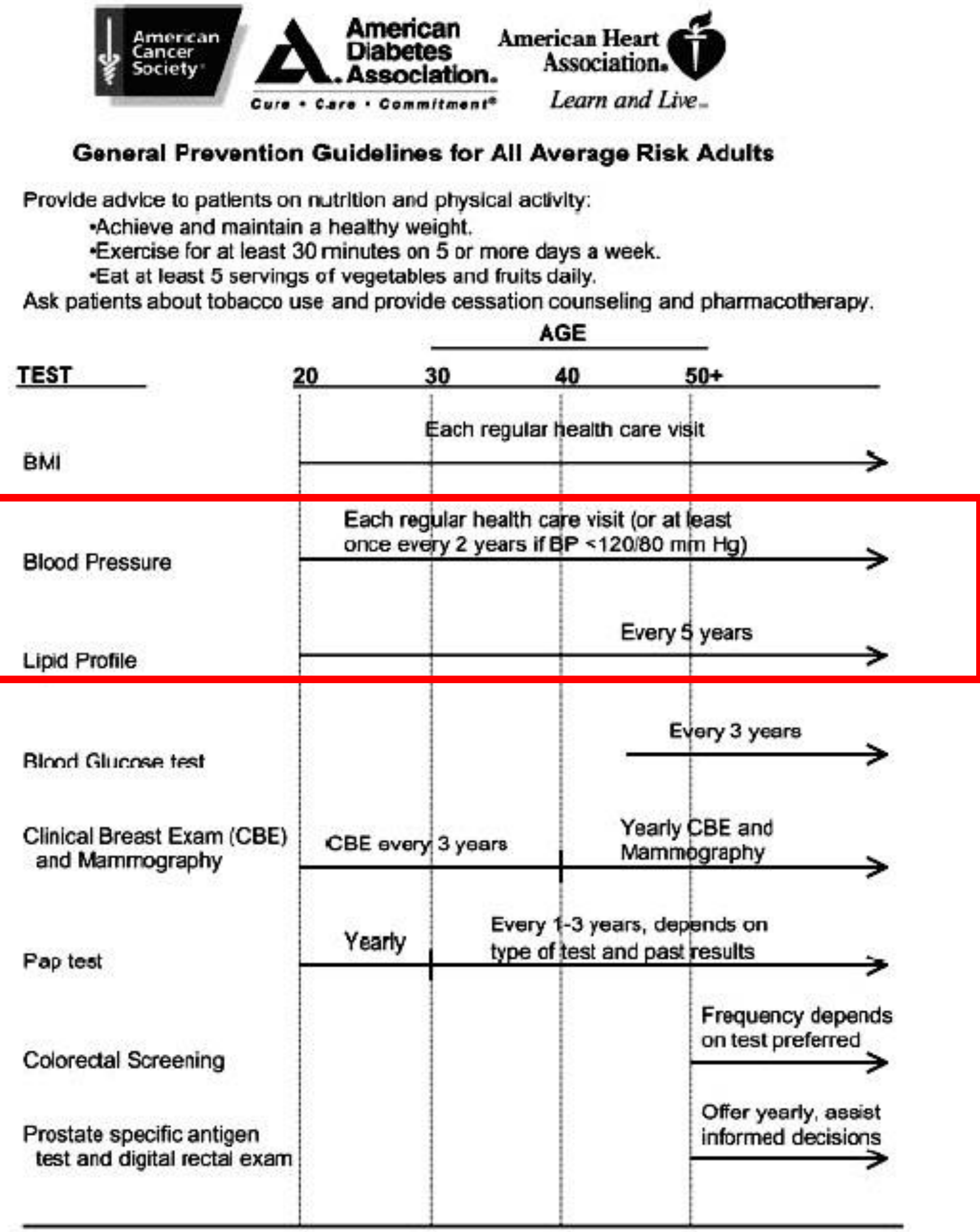
- Progressive over years
  - Starts with some injury to endothelium
    - Smoking, hypertension, hyperlipidemia, diabetes, autoimmune disease, and infection
  - Inflammation, release of enzymes by macrophages causes oxidation of LDL, which is then consumed by macrophages – foam cells – accumulate to form fatty streaks
  - Fatty streaks of lipid material appear first as yellow streaks and spots
  - Smooth muscle cells proliferate, and migrate over the streak forming a fibrous plaque

- Fibrous plaque results in necrosis of underlying tissue and narrowing of lumen
- Inflammation can result in ulceration and rupture of the plaque, resulting in platelet adherence to the lesion = **complicated lesion**
- Can result in rapid thrombus formation with complete vessel occlusion → tissue ischemia and infarction

Compliance

- The increase in volume a vessel can accommodate for a given increase in pressure.
  - Depends on the ratio of elastic fibers to muscle fibers in the vessel wall.
    - Elastic arteries more compliant than muscular arteries
    - Veins more compliant than either artery (blood reservoirs)
- Decreased compliance suggests an increased stiffness of vessel wall.
- Determines the vessel's response to changes in pressure.

Why do we screen for asymptomatic cancers but ignore asymptomatic CVD?



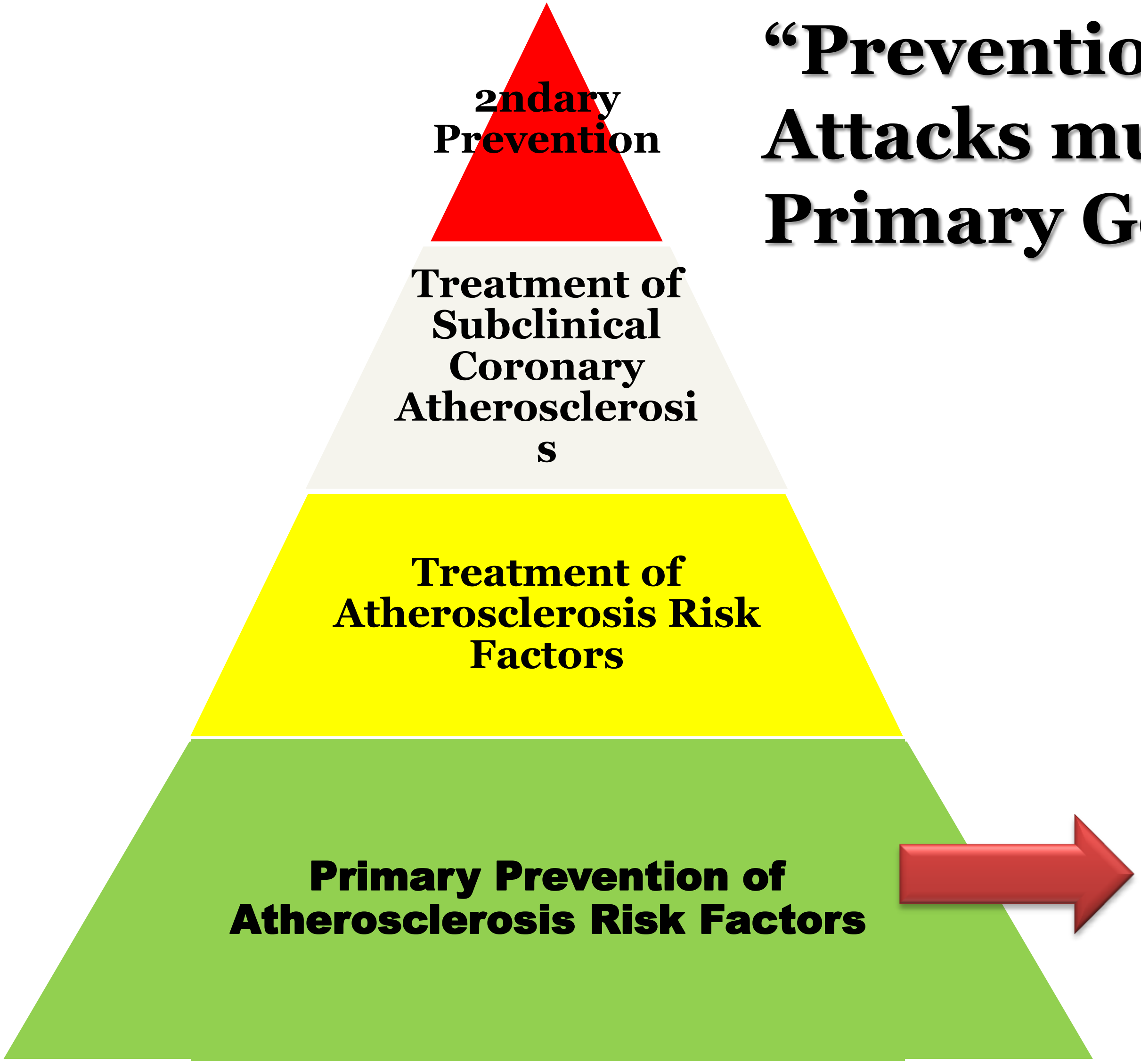
General prevention guidelines for all average-risk adults.

CVD Risk factors (ESH-ESC)

Sublinical organ damage

1. LVH on ECG
2. LVH on echocardiogram (LVMI > 125 (♂), > 110 (♀))
3. **Carotid IMT > 0.9 mm or plaque**
4. **PWV (carotid to femoral) > 12 m/sec**
5. Creatinine ♂ = 1.3-1.5 mg/dl, ♀ = 1.2-1.4
6. GFR < 60 ml/min
7. ABI < 0.9
8. Microalbuminuria 30-300 mg/day or
   albumin-creatinine ratio ♂≥ 22, ♀31 ≥ mg/g Cr

- Vascular disease screening and prevention
  - Who?
    - Age > 60 years with following risk (≥ 1)
    - DM, HTN, hyperlipidemia, smoking, CAD, stroke, PAD, FHx of vascular disease
  - What?
    - Screening: non-painful, no discomfort, no side effect
    - carotid duplex, abdominal USG, ABI
    - Disease specific test
      - TMT for claudication, PPG with thermal measurement, ABI, ...
      - Angiography, CT scan, MRI, ...

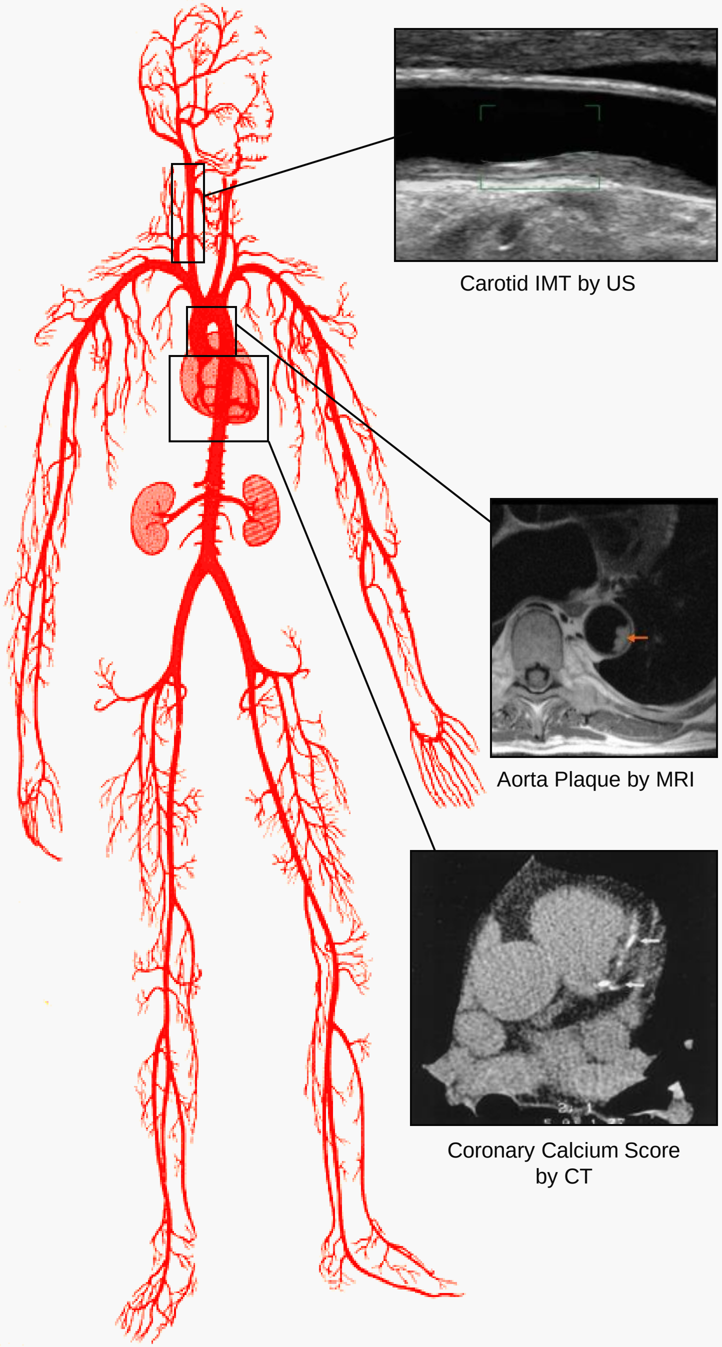


"Prevention of Heart Attacks must be the Primary Goal."

E Brauwald

FRS guided

Imaging guided


Carotid IMT by US

Aorta Plaque by MRI

Coronary Calcium Score by CT

Image–Guided Prevention

- Evidence supporting the use of non-invasive imaging tests to screen for CAD is gradually accumulating.

"Future image-guided interventions will enable …to detect critical illnesses at their most curable stage …before any symptoms or signs are noticeable.
The practice of medicine will shift … to one of prediction and prevention in asymptomatic, at-risk populations."

NIH Fact Sheet 'Image Guided Interventions'

Coronary Calcium as a Predictor of Coronary Events in Four Racial or Ethnic Groups

Robert Detrano, M.D., Ph.D. … M.D., J. Jeffrey Carr, M.D., M.S.C.E.,
… M.D., Ph.D., Aaron R. Folsom, M.D.,
… Moyses Szklo, M.D., Dr.P.H.,
… 'Leary, M.D., Russell Tracy, Ph.D.,
… Ph.D., and Richard A. Kronmal, Ph.D.

BACKGROUND

In white populations, computed tomographic measurements of coronary-artery calcium predict coronary heart disease independently of traditional coronary risk factors. However, it is not known whether coronary-artery calcium predicts coronary heart disease in other racial or ethnic groups.

METHODS

We collected data on risk factors and performed scanning for coronary calcium in a population-based sample of 6722 men and women, of whom 38.6% were white, 27.6% were black, 21.9% were Hispanic, and 11.9% were Chinese. The study subjects had no clinical cardiovascular disease at entry and were followed for a median of 3.8 years.

RESULTS

There were 162 coronary events, of which 89 were major events (myocardial infarction or death from coronary heart disease). In comparison with participants with no coronary calcium, the adjusted risk of a coronary event was increased by a factor of 7.73 among participants with coronary calcium scores between 101 and 300 and by a factor of 9.67 among participants with scores above 300 ($P<0.001$ for both comparisons). Among the four racial and ethnic groups, a doubling of the calcium score increased the risk of a major coronary event by 15 to 35% and the risk of any coronary event by 18 to 39%. The areas under the receiver-operating-characteristic curves for the prediction of both major coronary events and any coronary event were higher when the calcium score was added to the standard risk factors.

CONCLUSIONS

The coronary calcium score is a strong predictor of incident coronary heart disease and provides predictive information beyond that provided by standard risk factors in four major racial and ethnic groups in the United States. No major differences among racial and ethnic groups in the predictive value of calcium scores were detected.

N Engl J Med 2008;358:1336-45.

Coronary calcium score

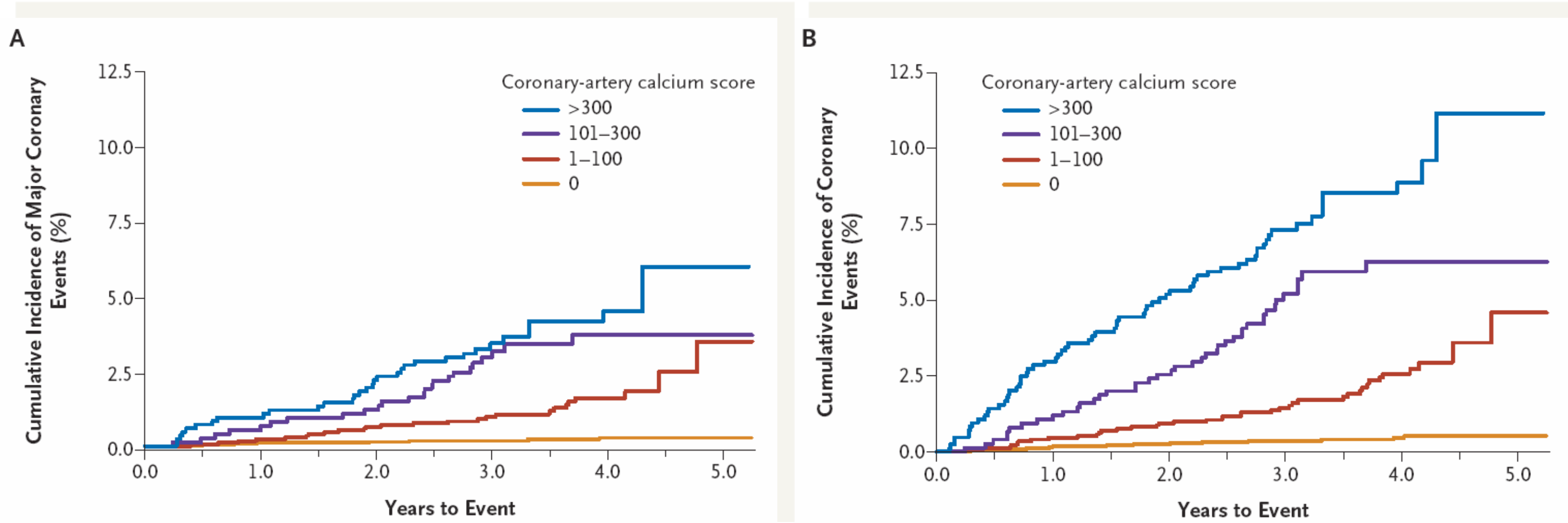


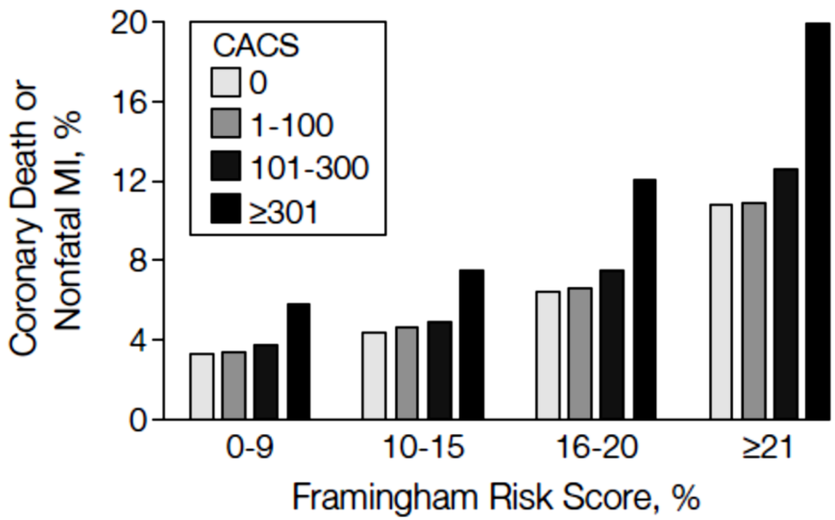
Table 4. **Risk of Coronary Heart Disease Associated with Coronary-Artery Calcium Score in Four Racial or Ethnic Groups.***

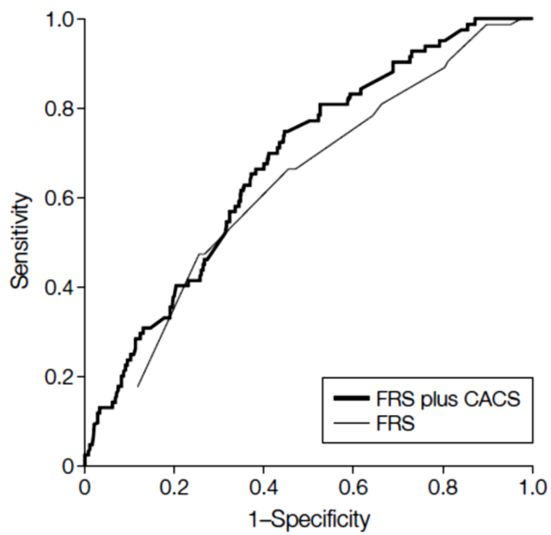
Racial or Ethnic Group	Major Coronary Event†			Any Coronary Event		
	No.	Hazard Ratio (95% CI)‡	P Value	No.	Hazard Ratio (95% CI)‡	P Value
White	41	1.17 (1.06–1.30)	<0.005	74	1.22 (1.13–1.32)	<0.001
Chinese	6	1.25 (0.95–1.63)	0.11	14	1.36 (1.12–1.66)	<0.005
Black	18	1.35 (1.16–1.57)	<0.001	38	1.39 (1.25–1.56)	<0.001
Hispanic	24	1.15 (1.02–1.29)	<0.025	36	1.18 (1.07–1.30)	<0.001

For future risk stratification

- Calcium score in real clinical practice?
  - Additional value over FRS

JAMA. 2004;291:210-215





High CACS can modify predicted risk obtained from FRS alone, especially among patients in the intermediate risk category in whom clinical decision making is most uncertain

Carotid IMT or plaque?

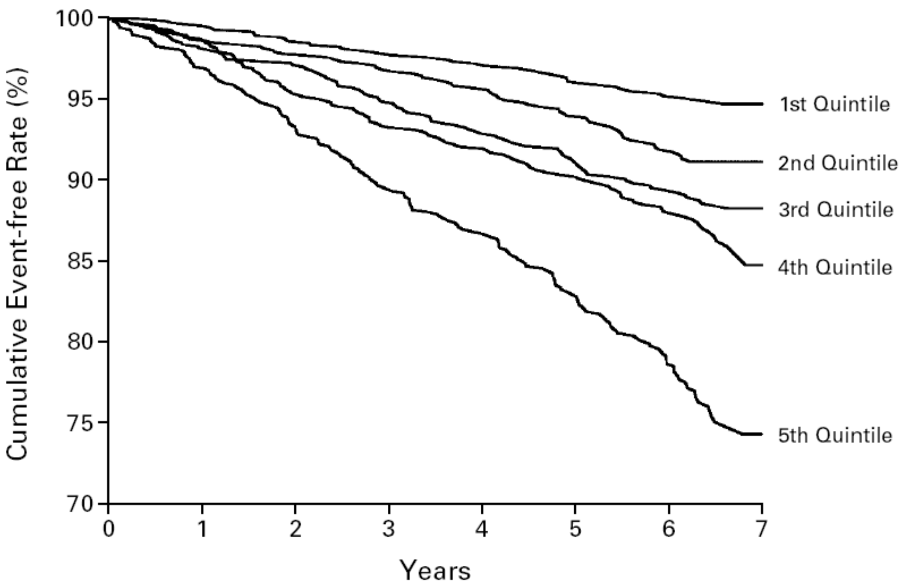
Carotid USG:

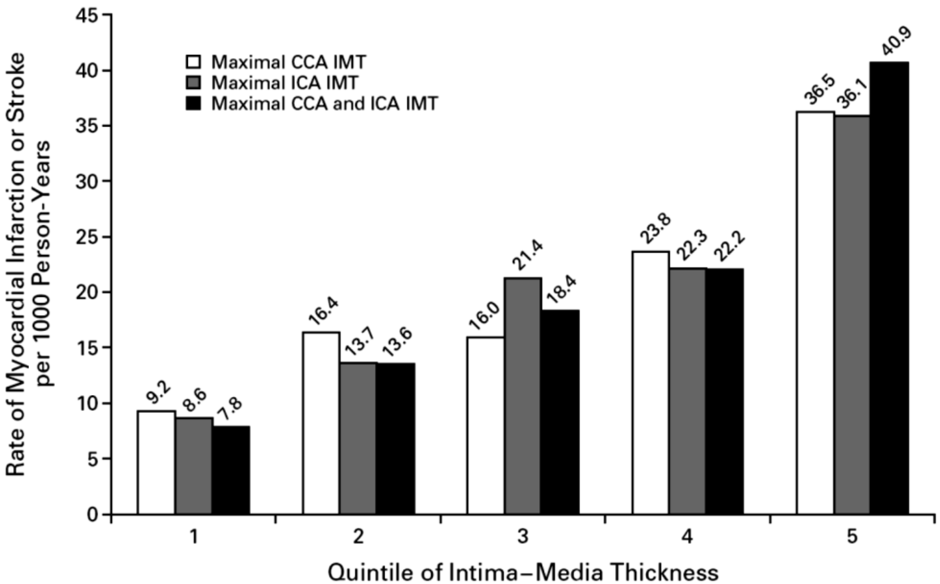
1st step in the diagnostic strategy

- Highly accurate and reliable test
- Advantage
  - Direct visualization of the extracranial arteries
  - Accurate determination of degree of stenosis
  - Assess presence of morphology of plaque
  - Useful tool to evaluate revascularization procedures
  - Identify non-atherosclerotic abnormalites
    - Carotid dissection
    - Firbomuscular disease
    - Trauma

Carotid-Artery IMT as a Risk Factor for MI and Stroke in Older Adults

- 4,476 patients > 65 years with no clinical CV disease
- Primary end-points
  - New MI / Stroke
- Median follow-up 6.2 years

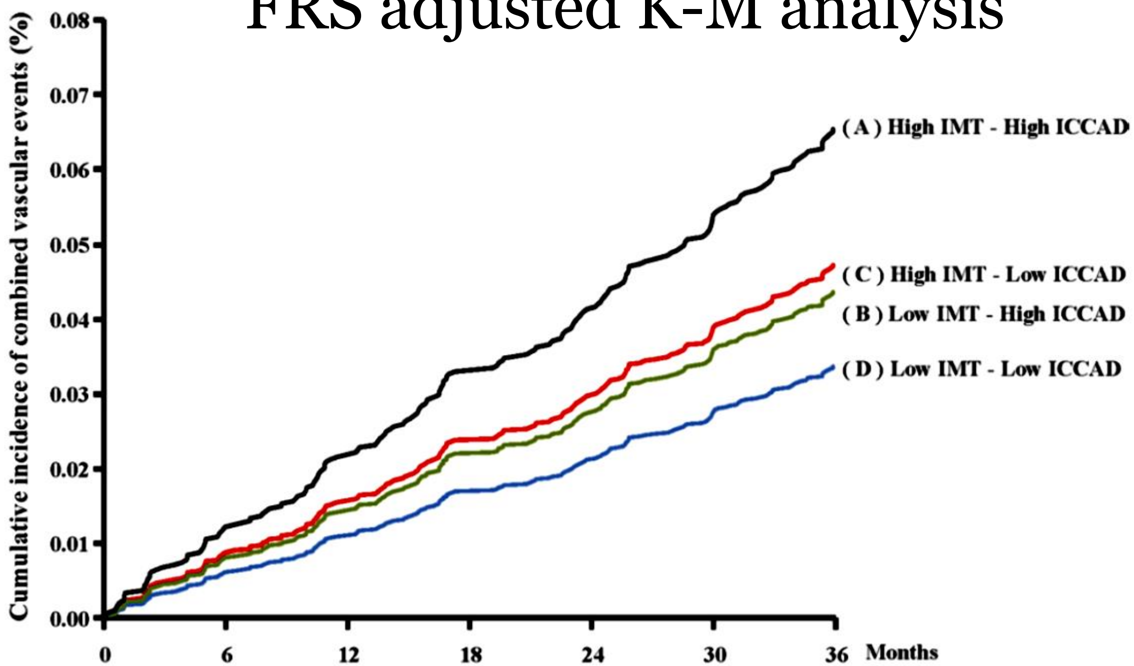




IMPROVE

- 3,703 subjects with 36.2 months f/u
- ≥ 3 vascular risk factors without documented atherothrombosis

FRS adjusted K-M analysis



No. at Risk

	0	6	12	18	24	30	36
(A)	1235	1190	1173	1117	1098	1061	785
(B)	616	585	582	564	559	546	415
(C)	618	593	588	575	571	558	427
(D)	1234	1195	1190	1157	1152	1134	913

J Am Coll Cardiol 2012;60:1489–99

Hypertension
JOURNAL OF THE AMERICAN HEART ASSOCIATION

American Heart Association

Common Carotid Intima-Media Thickness Measurements Do Not Improve Cardiovascular Risk Prediction in Individuals With Elevated Blood Pressure: The USE-IMT Collaboration

Hypertension. 2014;63:00-00.
Online Data Supplement

Name	Acronym or Abbreviation	Location	Number of Individuals With Elevated Blood Pressure (% of total, n=17 254)	Total Number of Participants	90th Percentile of IMT	Number of Events	References
Atherosclerosis Risk in Communities	ARIC	United States	2351 (14)	14 322	0.83	1192	28
Carotid Atherosclerosis Progression Study	CAPS	Germany	916 (5)	3885	0.90	128	22
Cardiovascular Health Study	CHS	United States	1090 (6)	3121	1.03	712	29
Malmö Diet and Cancer Study	Malmö	Sweden	2825 (16)	4767	0.94	315	30
Tromsø Study	Tromsø	Norway	2200 (13)	4242	0.97	558	31
Multi-Ethnic Study of Atherosclerosis	MESA	United States	1313 (8)	5894	0.95	167	32
Kuopio Ischemic Heart Disease Risk Factor Study	KIHD	Finland	406 (2)	879	0.95	152	33
Edinburgh Artery Study	EAS	United Kingdom	346 (2)	622	1.00	21	34
The Firefighters and Their Endothelium Study	FATE	Canada	438 (3)	1441	0.95	33	35
Charlottesville Study	Charlottesville Study	United States	312 (2)	610	1.03	712	36
Northern Manhattan Study	NOMAS Study	United States	589 (3)	1093	0.83	57	37
The Hoorn Study	Hoorn Study	The Netherlands	118 (1)	248	1.04	11	38
Osaka Follow-Up Study for Carotid Atherosclerosis 2	OSACA2 Study	Japan	182 (1)	403	1.15	19	39
Whitehall II	Whitehall II	United Kingdom	2440 (14)	9748	0.98	257	40
Rotterdam Study	Rotterdam	The Netherlands	1433 (8)	3718	0.92	642	41
Non-Invasive measurements of Atherosclerosis in the Nijmegen Biomedical Study	NIMA-NBS	The Netherlands	295 (2)	1200	0.97	17	42,43

Net reclassification tables in HTN

Distribution of 17,254 hypertensives without and with events across risk categories

Non-events		FRS+CIMT <5%	FRS+CIMT 5-10%	FRS+CIMT 10-20%	FRS+CIMT >20%
FRS	**<5%**	3,959	312	0	0
FRS	**5-10%**	412	4,455	398	1
FRS	**10-20%**	0	445	3577	178
FRS	**>20%**	0	0	186	1,317

n	Classification
n=13,308	No change (87.3%)
n=889	Up classification (5.8%)
n=1,043	Down classification (6.8%)

FRS+CIMT

Events		FRS+CIMT <5%	FRS+CIMT 5-10%	FRS+CIMT 10-20%	FRS+CIMT >20%
FRS	**<5%**	105	20	0	0
FRS	**5-10%**	22	371	50	0
FRS	**10-20%**	0	60	692	56
FRS	**>20%**	0	0	49	589

n	Classification
n=1,757	No change (87.2%)
n=126	Up classification (6.3%)
n=131	Down classification (6.5%)

- There is no added value of measurement of CIMT in HTN for improving CV risk prediction.
- For those at intermediate risk, the addition of CIMT to an existing CV risk score is small, but statistically significant.

Common Carotid Intima-Media Thickness Measurements in Cardiovascular Risk Prediction

A Meta-analysis

14 population-based cohorts contributing data for 45,828 individuals.

A Distribution of 45 828 individuals without and with events in USE-IMT across risk categories

Without events

Framingham Risk	Framingham Risk With CIMT <5%	5%-20%	>20%
<5%	20 271 →	867	–
5-20%	1115	← 17 280 →	362
>20%		315	← 1611

Total without events, No. (%)	
39 162 (93.6)	No change
1229 (2.9%)	Up classification
1430 (3.4%)	Down classification

With events

Framingham Risk	Framingham Risk With CIMT <5%	5%-20%	>20%
<5%	537 →	67	–
5-20%	69	← 2410 →	102
>20%		85	← 737

Total with events, No. (%)	
3684 (91.9%)	No change
169 (4.2%)	Up classification
154 (3.8%)	Down classification

The addition of common CIMT measurements to the FRS was a/w small improvement in 10-year risk prediction of MI or stroke, but this improvement is unlikely to be of clinical importance

JAMA. 2012;308(8):796-803

ORIGINAL ARTICLE

Carotid-Wall Intima–Media Thickness and Cardiovascular Events

Joseph F. Polak, M.D., M.P.H., Michael J. Pencina, Ph.D., Karol M. Pencina, Ph.D., Christopher J. O'Donnell, M.D., M.P.H., Philip A. Wolf, M.D., and Ralph B. D'Agostino, Sr., Ph.D.

Framingham Offspring Study cohort, composed of non-Hispanic whites, who were undergoing the sixth examination cycle, from February 1995 through September 1998.

N Engl J Med 2011;365:213-21.

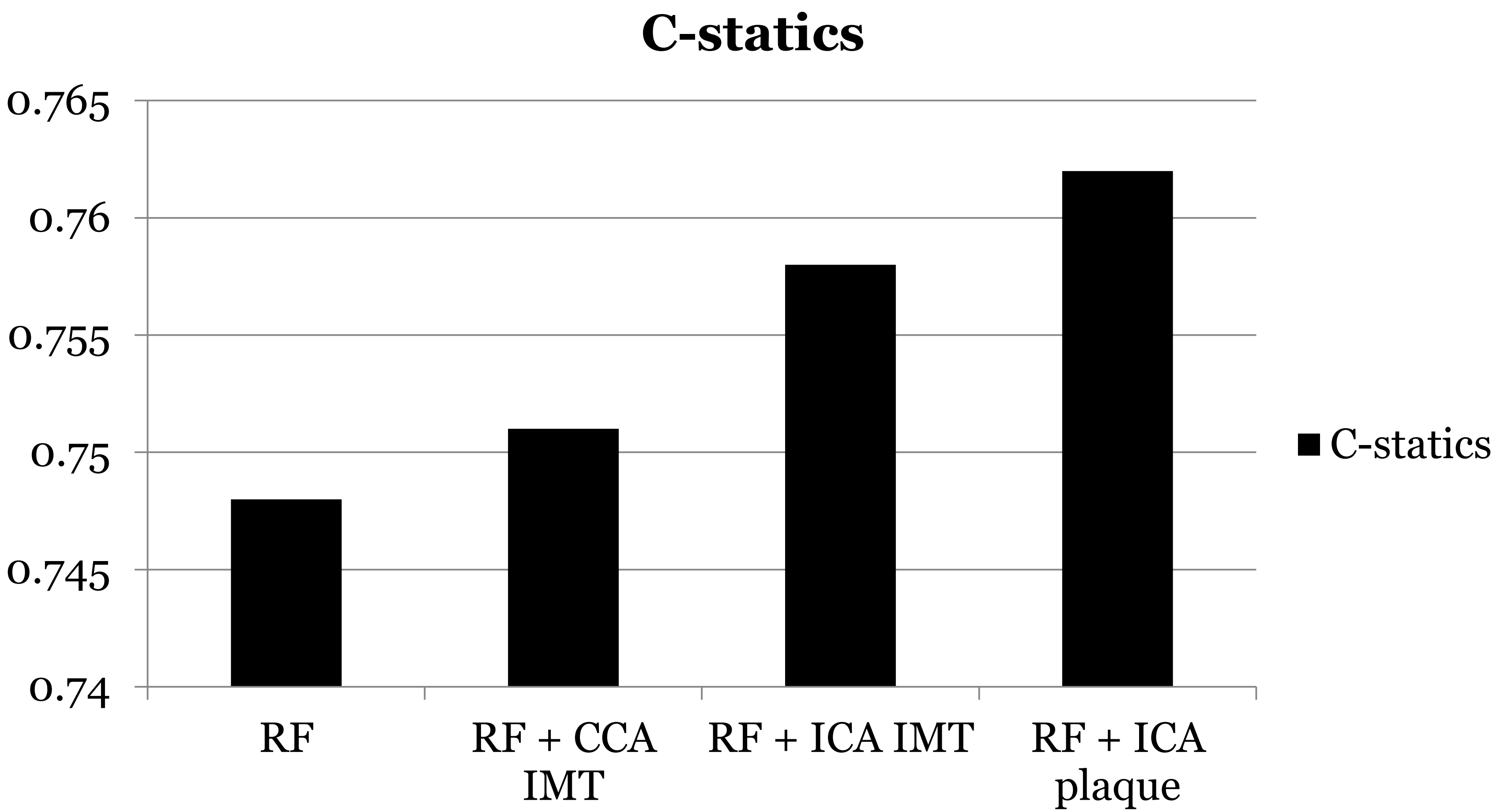
Table 2. Hazard Ratios for Cardiovascular Disease, According to Models with and without Common Carotid Artery (CCA) Intima–Media Thickness.*

Risk Factor
Sex, female v
Age, per incr
Systolic pres
Treatment fo
Cholesterol,
Total
HDL
Diabetes, ye
Cigarette sm
CCA intima–
Per incre
Per incre
C statistic

Table 3. Hazard Ratios for Cardiovascular Disease, According to Models with and without Internal Carotid Artery (ICA) Intima–Media Thicknesses.*

Risk Factor	Model with Risk Factors Only		Model with Risk Factors and ICA Intima–Media Thickness		Model with Risk Factors and ICA Intima–Media Thickness >1.5 mm	
	Hazard Ratio or C Statistic (95% CI)	P Value	Hazard Ratio or C Statistic (95% CI)	P Value	Hazard Ratio or C Statistic (95% CI)	P Value
Sex, female vs. male	0.74 (0.57–0.95)	0.02	0.78 (0.61–1.01)	0.06	0.79 (0.61–1.02)	0.07
Age, per increase of 1 yr	1.05 (1.04–1.07)	<0.001	1.05 (1.03–1.06)	<0.001	1.04 (1.03–1.06)	<0.001
Systolic pressure, per increase of 1 mm Hg	1.01 (1.01–1.02)	<0.001	1.01 (1.01–1.02)	<0.001	1.01 (1.00–1.02)	0.002
Treatment for high blood pressure, yes vs. no	1.55 (1.21–2.00)	<0.001	1.51 (1.18–1.95)	0.001	1.47 (1.14–1.89)	0.003
Cholesterol, per increase of 1 mg/dl						
Total	1.00 (1.00–1.01)	0.02	1.00 (1.00–1.01)	0.03	1.00 (1.00–1.01)	0.03
HDL	0.98 (0.97–0.99)	<0.001	0.98 (0.97–0.99)	<0.001	0.98 (0.97–0.99)	<0.001
Diabetes, yes vs. no	1.44 (1.06–1.97)	0.02	1.41 (1.03–1.92)	0.03	1.38 (1.01–1.88)	0.04
Cigarette smoking, yes vs. no	2.23 (1.67–2.98)	<0.001	2.10 (1.57–2.81)	<0.001	1.97 (1.47–2.64)	<0.001
ICA intima–media thickness						
Per increase of 1 mm			1.26 (1.16–1.36)	<0.001		
Per increase of 1 SD			1.21 (1.13–1.29)	<0.001		
Thickness ≥1.5 mm, representing plaque					1.92 (1.49–2.47)	<0.001
C statistic	0.748 (0.719–0.776)		0.758 (0.730–0.785)		0.762 (0.734–0.789)	

HR for CV disease



- The maximum internal and mean CCA IMT both predict CV outcomes
- But only the maximum IMT of (and presence of plaque in) the ICA significantly (albeit modestly) improves the classification of risk of CV disease in the Framingham Offspring Study cohort

Follow up IMT: surrogate marker?

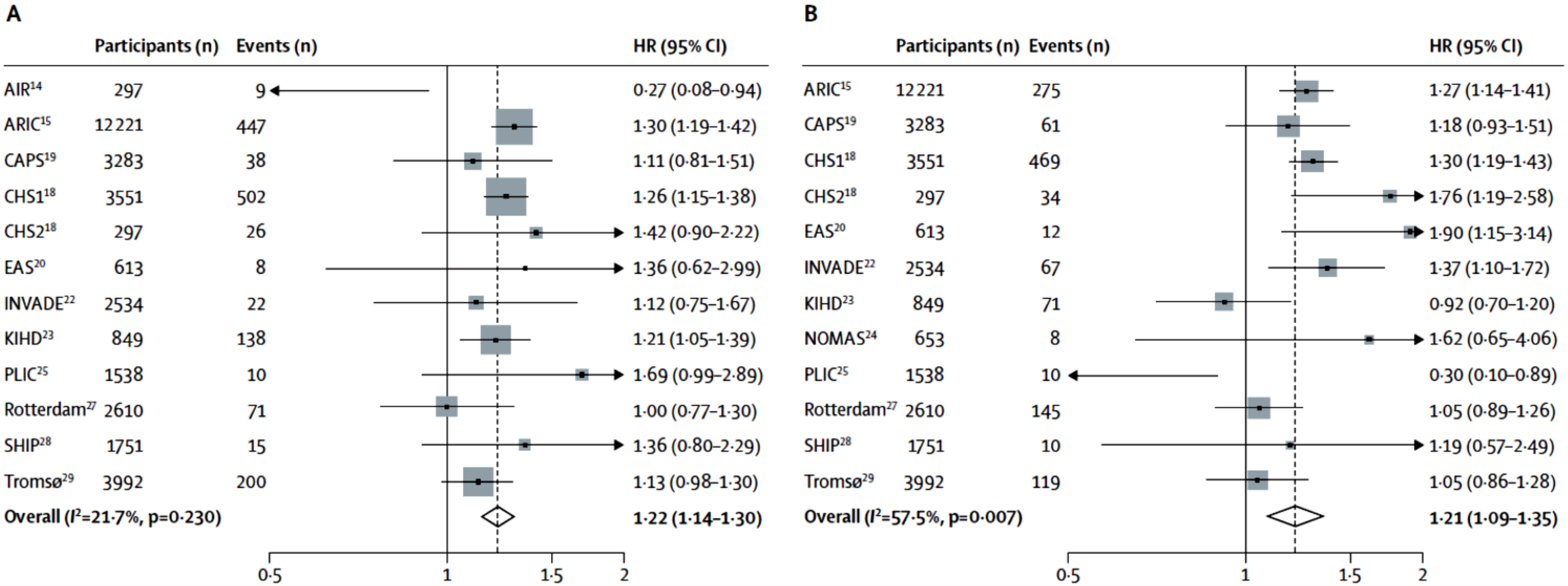
Carotid intima-media thickness progression to predict cardiovascular events in the general population (the PROG-IMT collaborative project): a meta-analysis of individual participant data

Matthias W Lorenz, Joseph F Polak, Maryam Kavousi, Ellisiv B Mathiesen, Henry Völzke, Tomi-Pekka Tuomainen, Dirk Sander, Matthieu Plichart, Alberico L Catapano, Christine M Robertson, Stefan Kiechl, Tatjana Rundek, Moïse Desvarieux, Lars Lind, Caroline Schmid, Pronabesh DasMahapatra, Lu Gao, Kathrin Ziegelbauer, Michiel L Bots, Simon G Thompson, on behalf of the PROG-IMT Study Group

- Of 22 eligible studies, 16 with 36,984 participants
- two ultrasound visits 2–7 years (median 4 years) apart

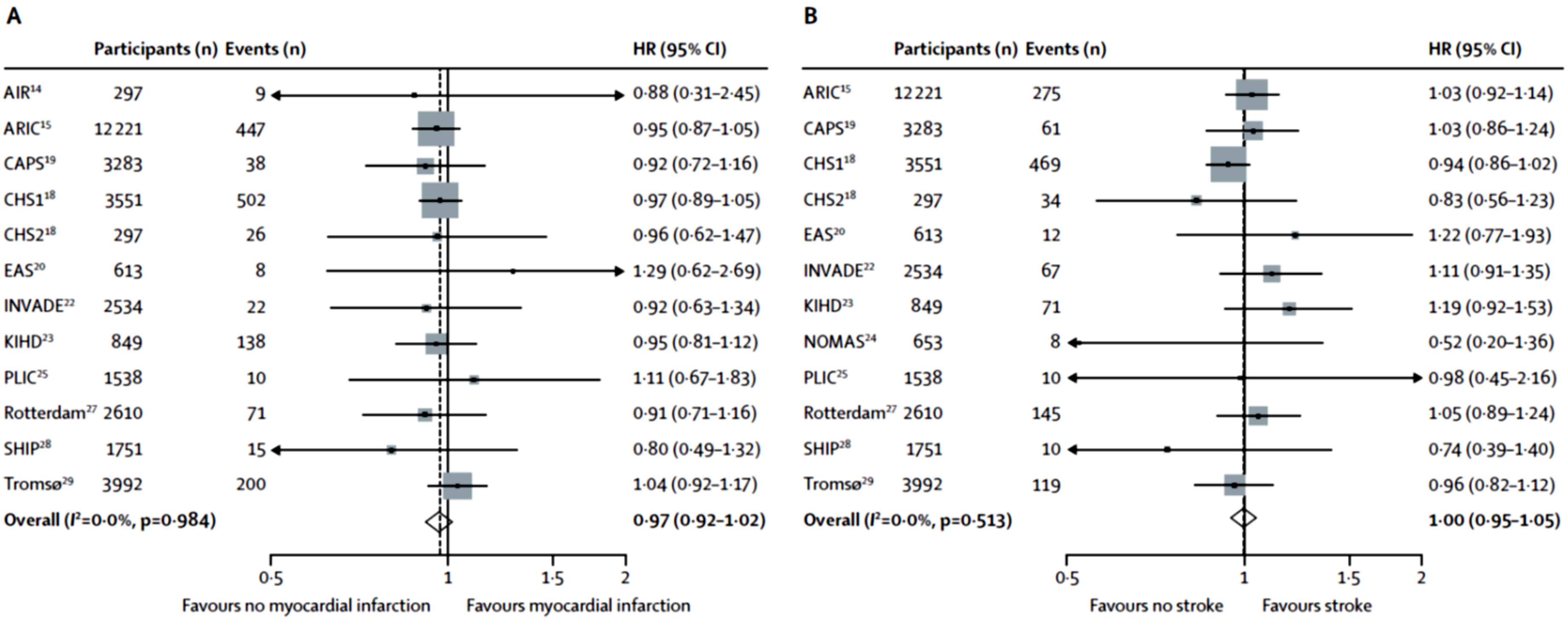
***Lancet* 2012; 379: 2053–62**

Mean CCA IMT

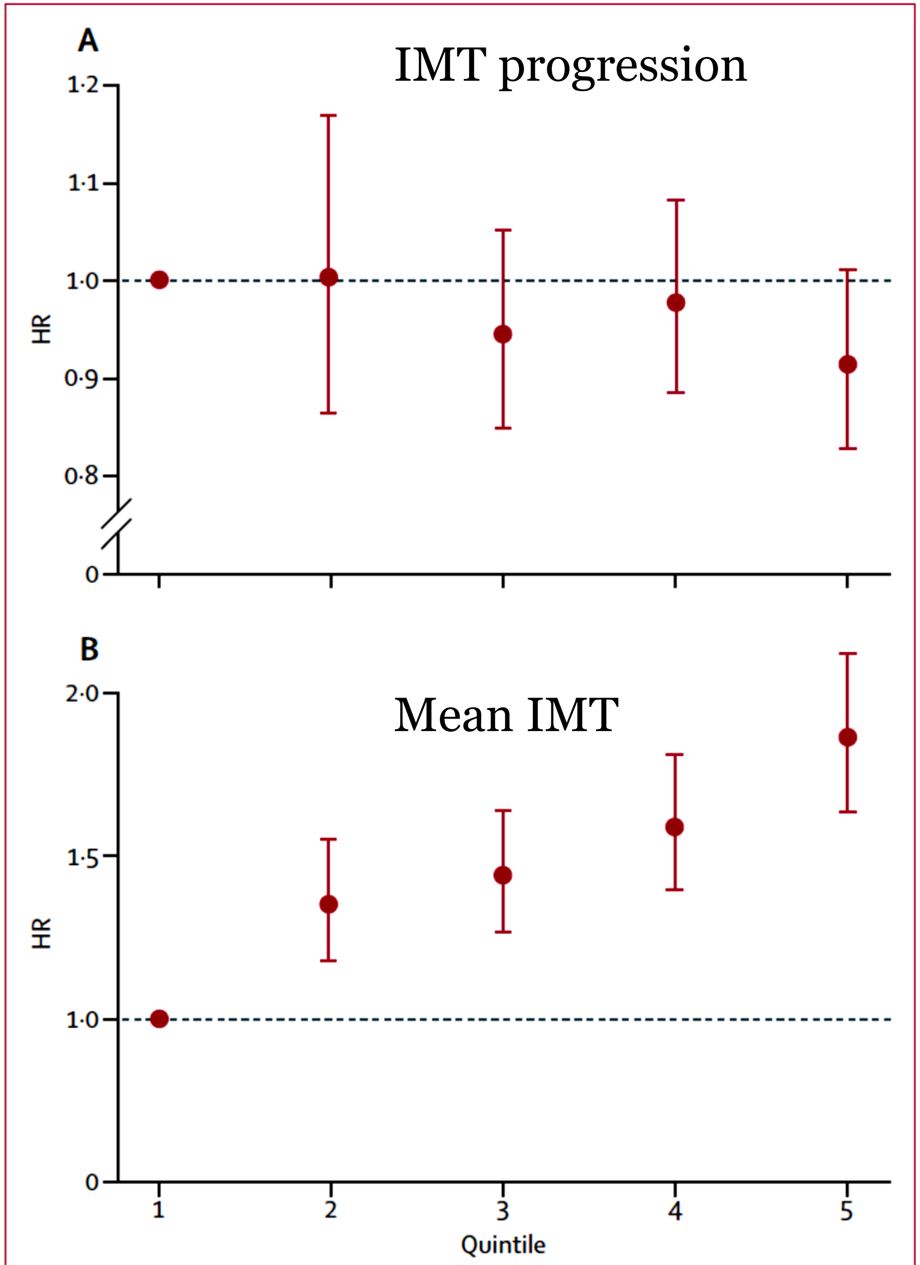


- The association of cIMT (mean of baseline and follow-up) with the endpoints was significant and positive.
- These associations were attenuated after adjustment for vascular risk factors, as expected.

IMT progression?

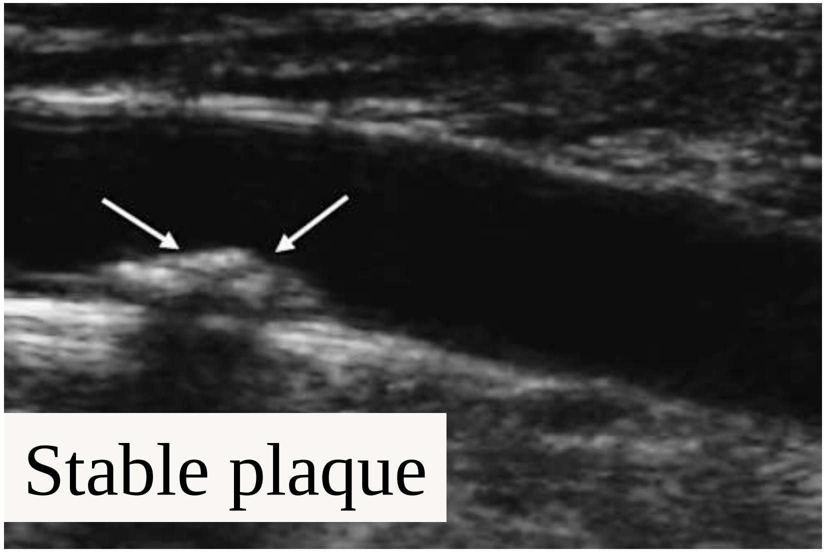


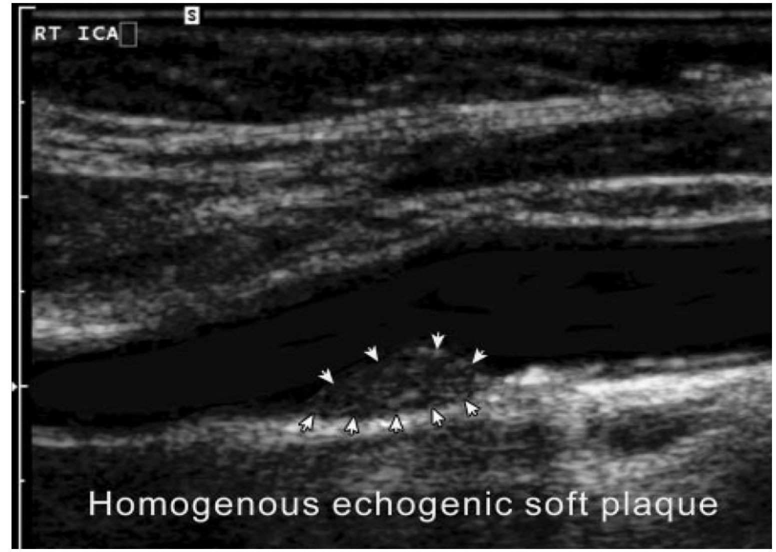
- The association between cIMT progression assessed from two ultrasound scans and CV risk in the general population remains unproven.
- No conclusion can be derived for the use of cIMT progression as a surrogate in clinical trials



- mean CCA IMT: good predictor

How about plaque?





Unstable plaque

Rapid increase in size → symptomatic

Significance of plaque morphology:

Plaque morphology as risk of cerebral events
: natural course of carotid disease

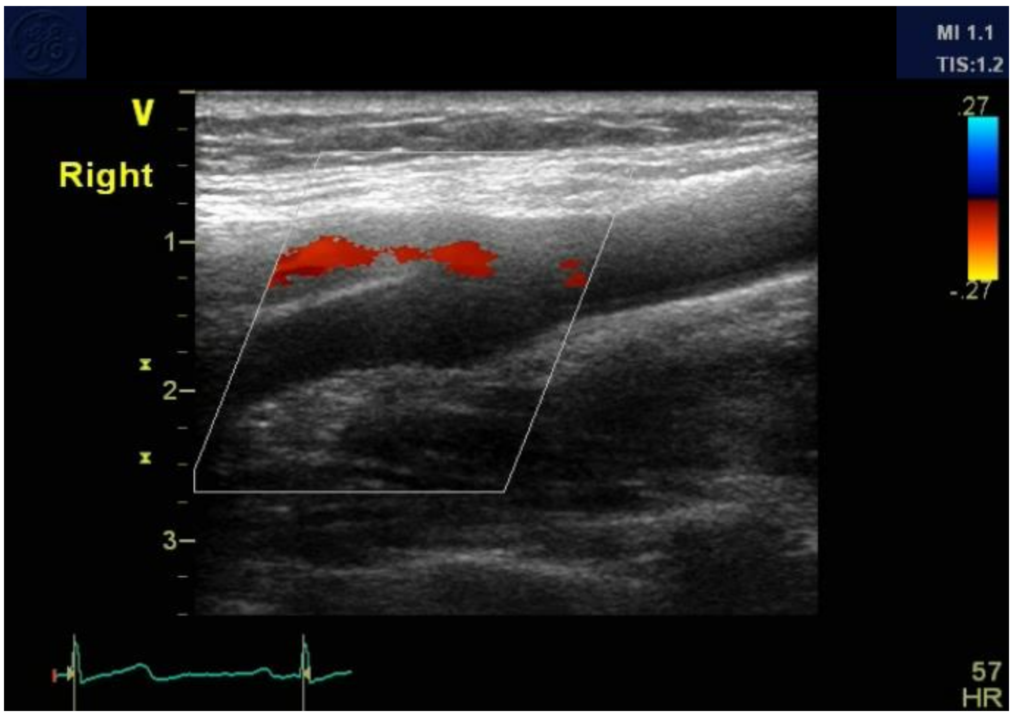
Echolucent plaques= lipid&macrophage rich = unstable

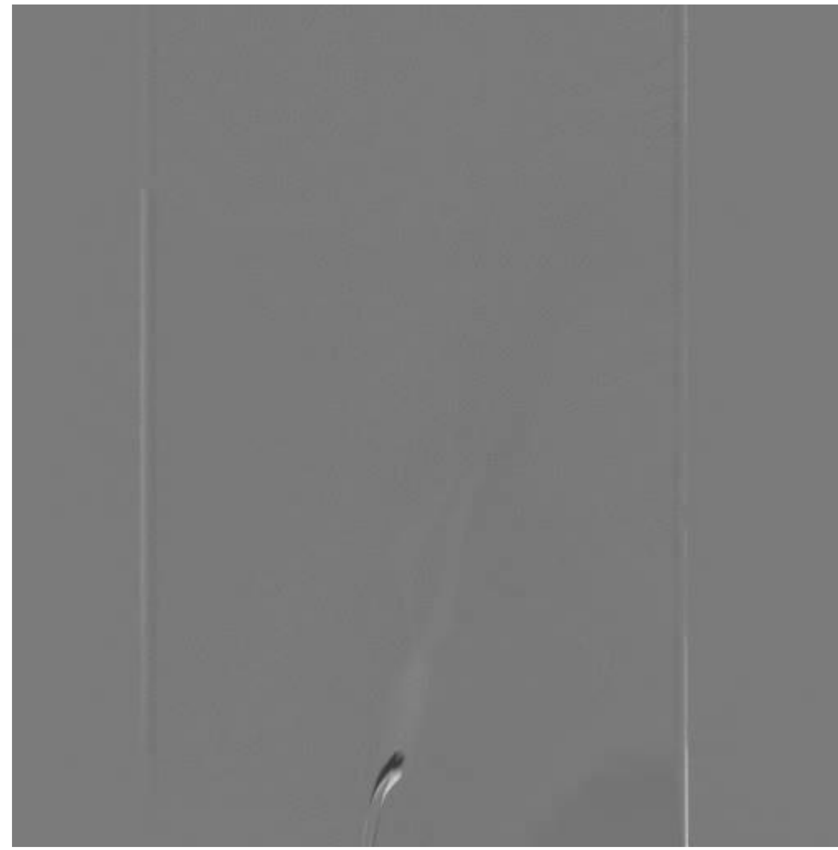
	risk of stroke
• Asymptomatic	2 -5% / year
• Ulceration	7.5% / year
• High grade + TIA	13% / year
• High grade + stroke	5-9% / year
• Echolucency vs density	increase 2-5 fold
• *Thin/ruptured fibrous cap*	*increase > 10 fold?*

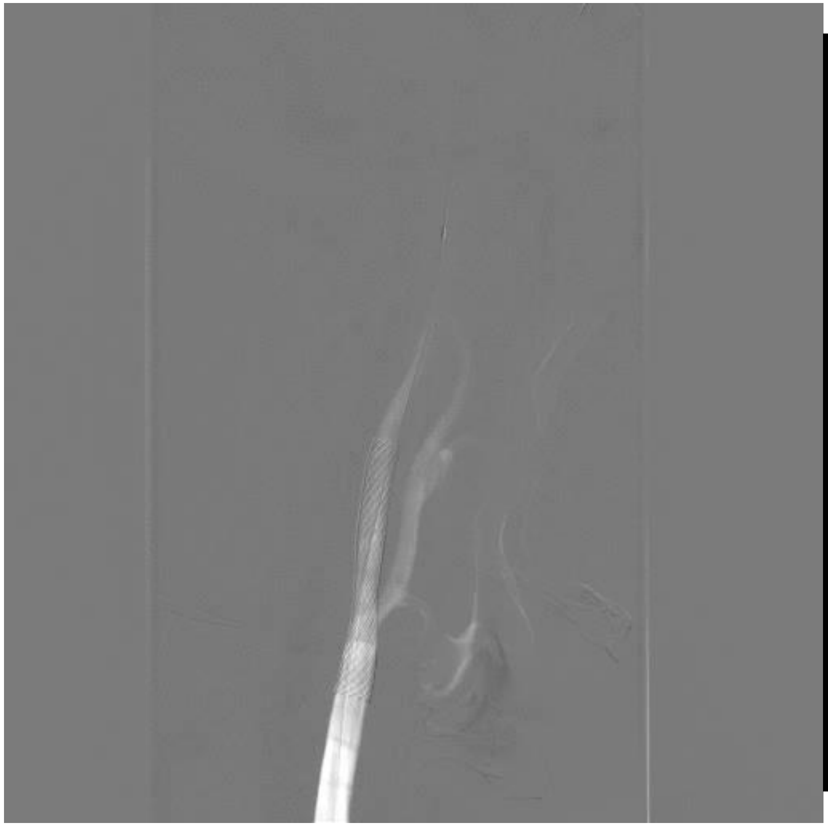
SNUH SEOUL NATIONAL UNIVERSITY BUNDANG HOSPITAL

Carotid stenosis

Tight ICA stenosis







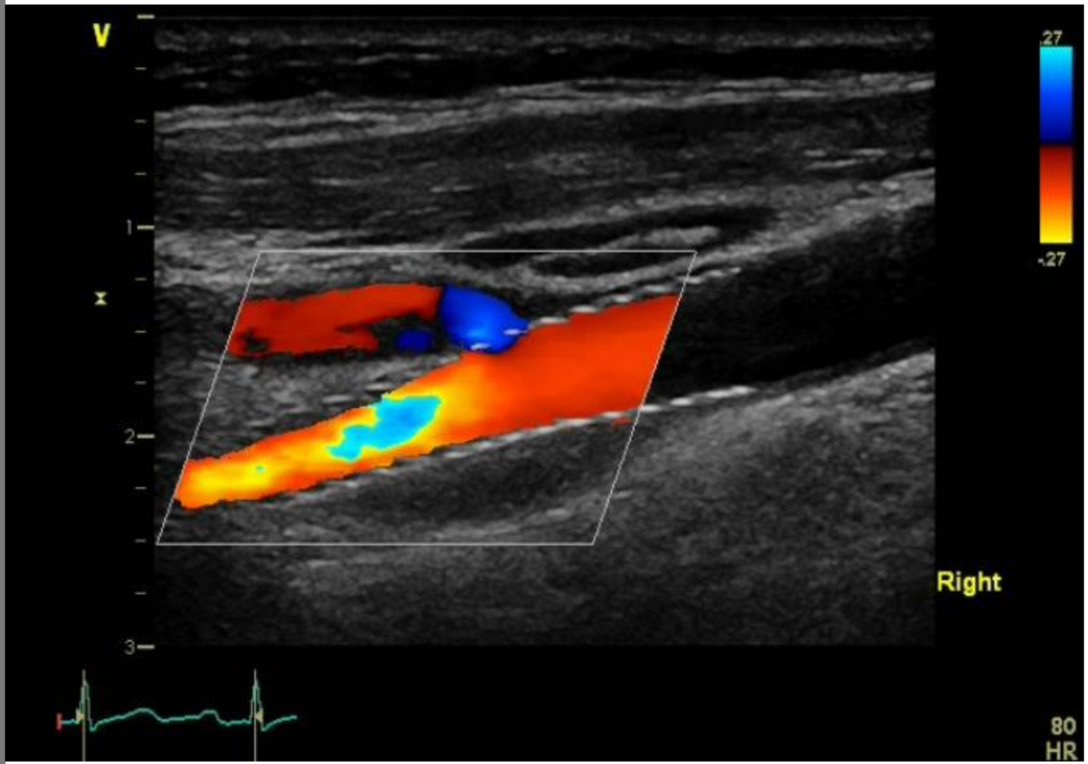
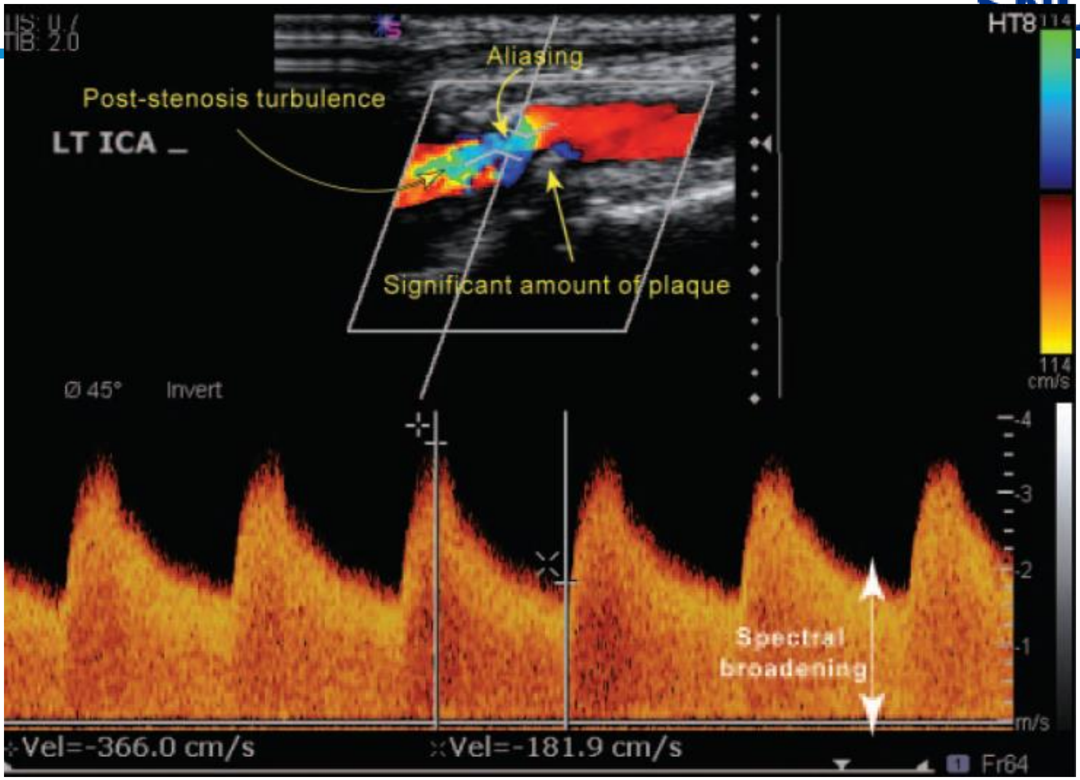

V
.27
-.27
1
2
3
Right
80
HR

Table 1
Criteria for Diagnosis of ICA Stenosis with Gray-Scale and Doppler US

	Primary Parameters		Additional Parameters*	
Degree of Stenosis (%)	ICA PSV (cm/sec)	Degree of Plaque† (%)	ICA/CCA PSV Ratio	ICA EDV (cm/sec)
Normal	<125	None	<2.0	<40
<50	<125	<50	<2.0	<40
50–69	125–230	≥50	2.0–4.0	40–100
≥70 but less than near occlusion	>230	≥50	>4.0	>100
Near occlusion	High, low, or undetectable	Visible	Variable	Variable
Total occlusion	Undetectable	Visible, no detectable lumen	NA	NA

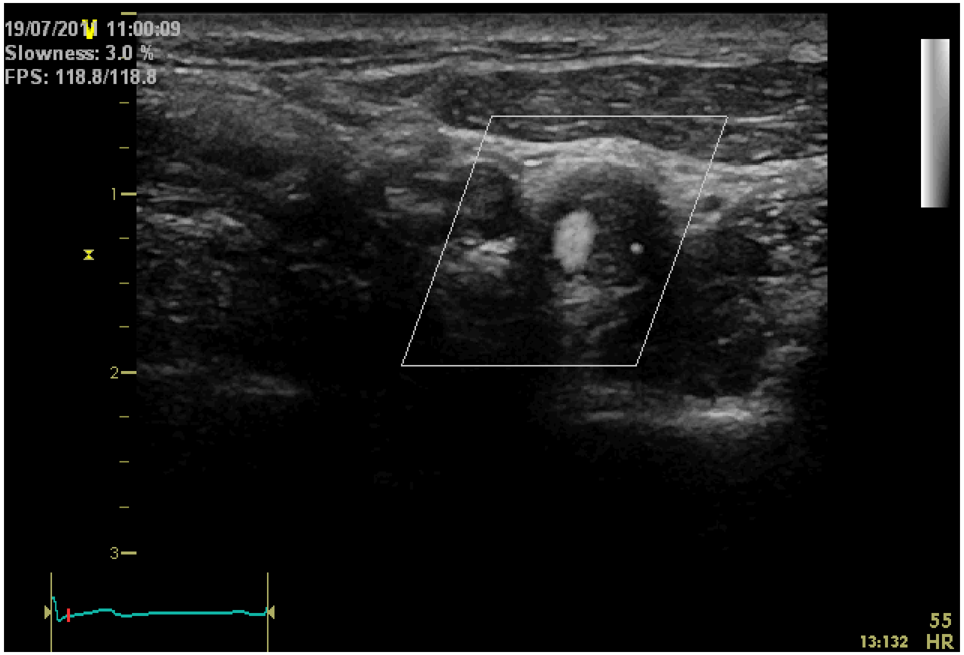
Source.—Reference 21.
*EDV = end-diastolic velocity, NA = not applicable.
†Estimated value based on the diameter reduction at gray-scale and color Doppler imaging.



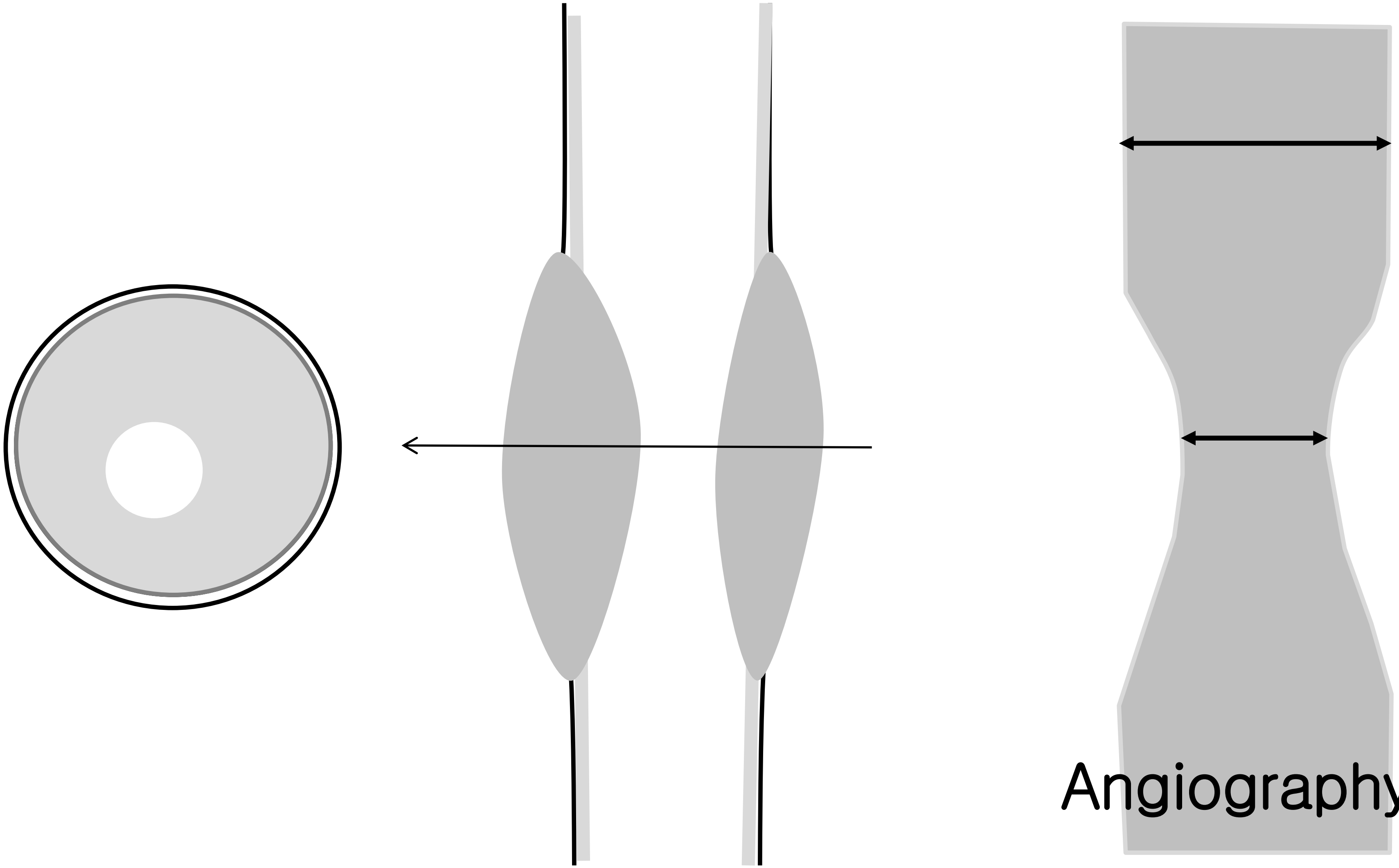
Sonographic features of severe ICA or CCA stenosis

- PSV > 230 cm/sec
- Plaque (≥ 50% DS)
- Color alaising despite a high velocity scale (≥ 100)
- ICA/CCA PSV ratio > 4.0
- High pitched sound at PW doppler imaging

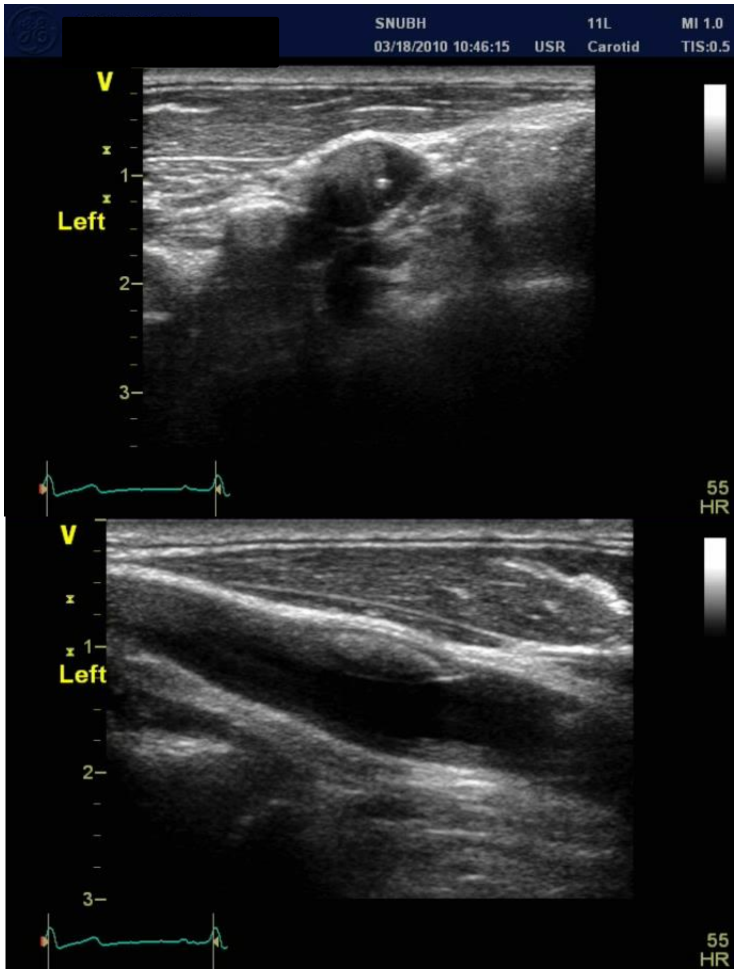
Tight stenosis?

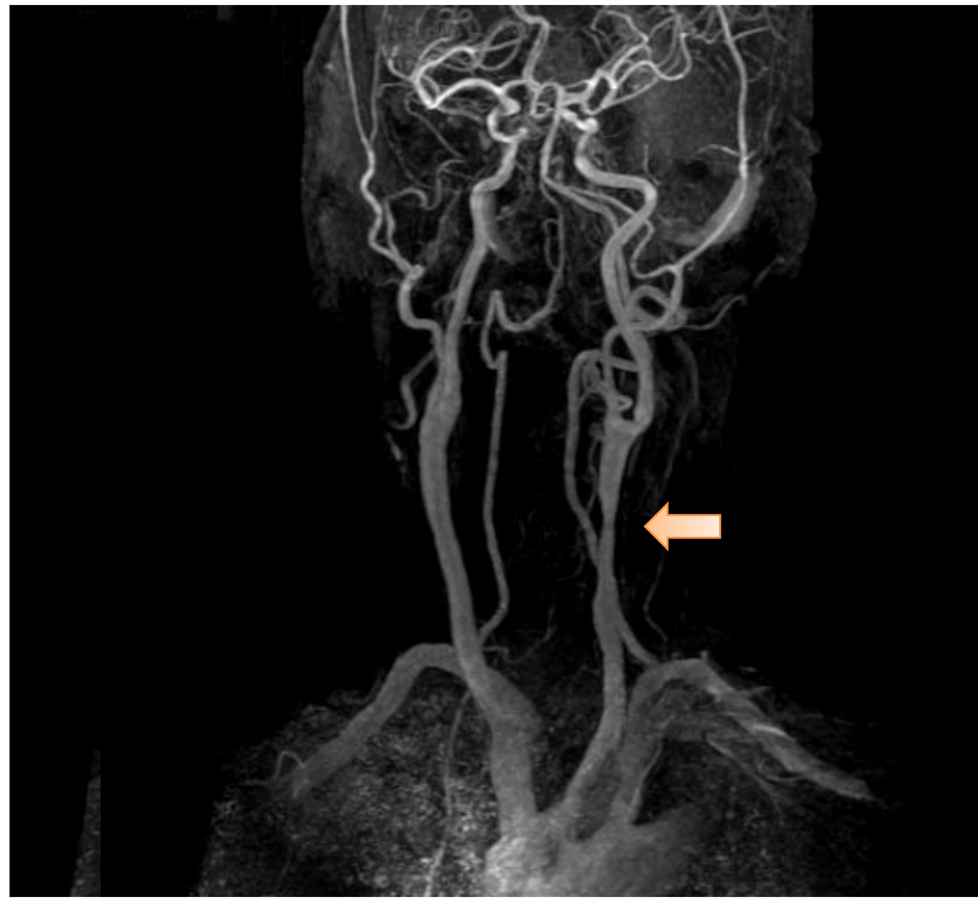


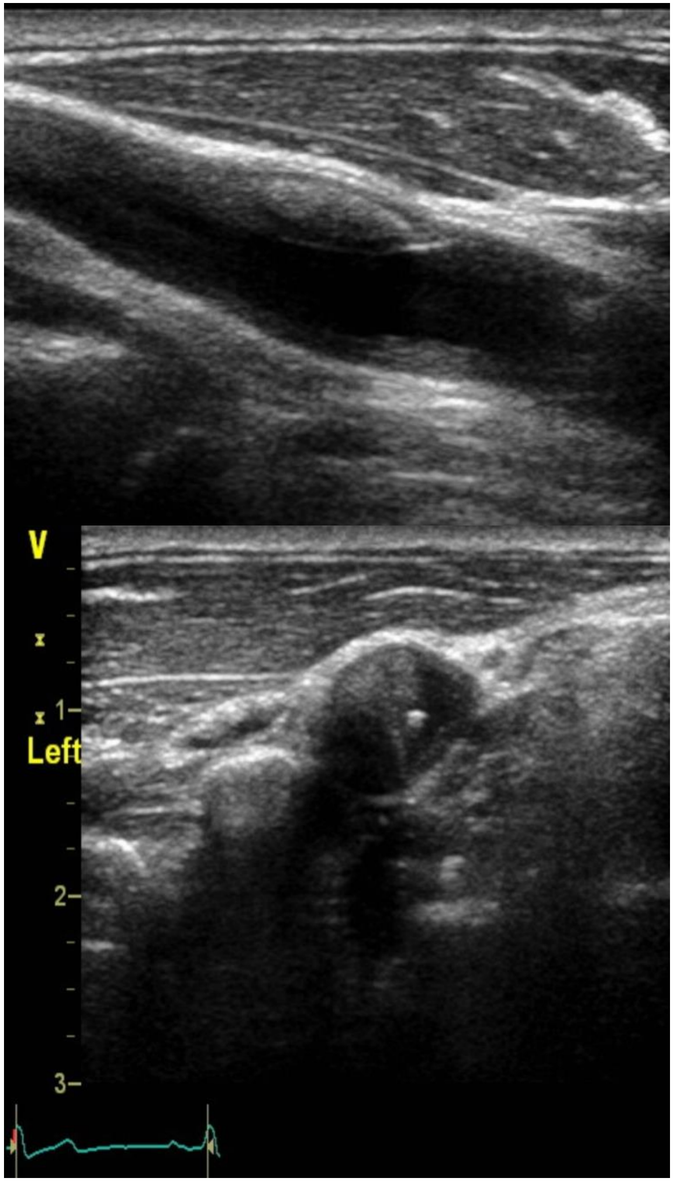
Positive remodeling



Significant stenosis by soft plaque



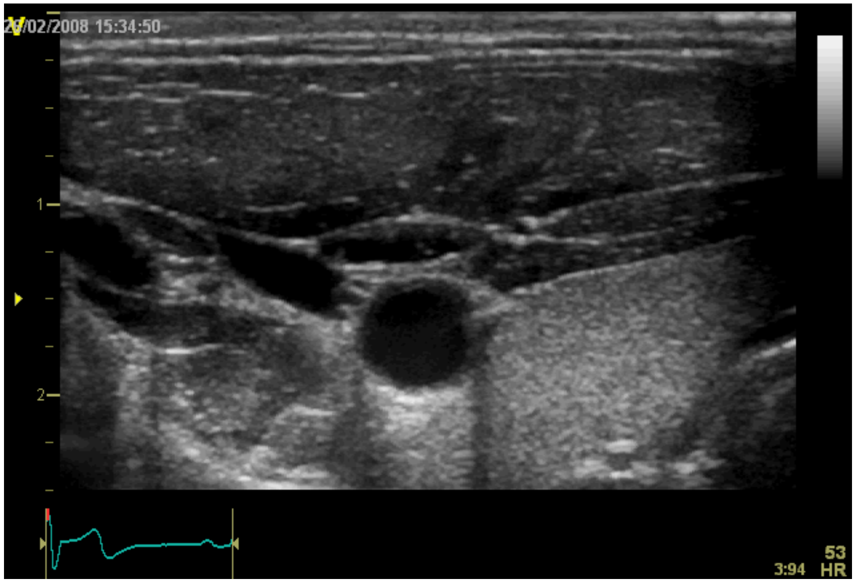


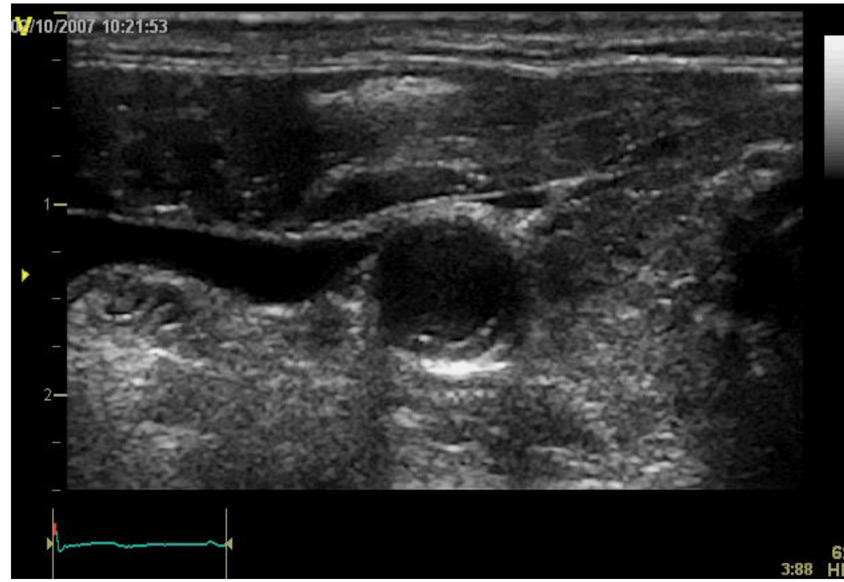

V
Left
1
2
3

Vascular stiffness

- Compliance, $\Delta D/\Delta P$ or $\Delta A/\Delta P$
  - – arterial stiffness at a site
- Augmentation index, Δaugmentation/PP
  - – systemic arterial stiffness
- Pulse wave velocity, $PWV = D / \Delta T$
  - – arterial stiffness at a segment

Compliance?





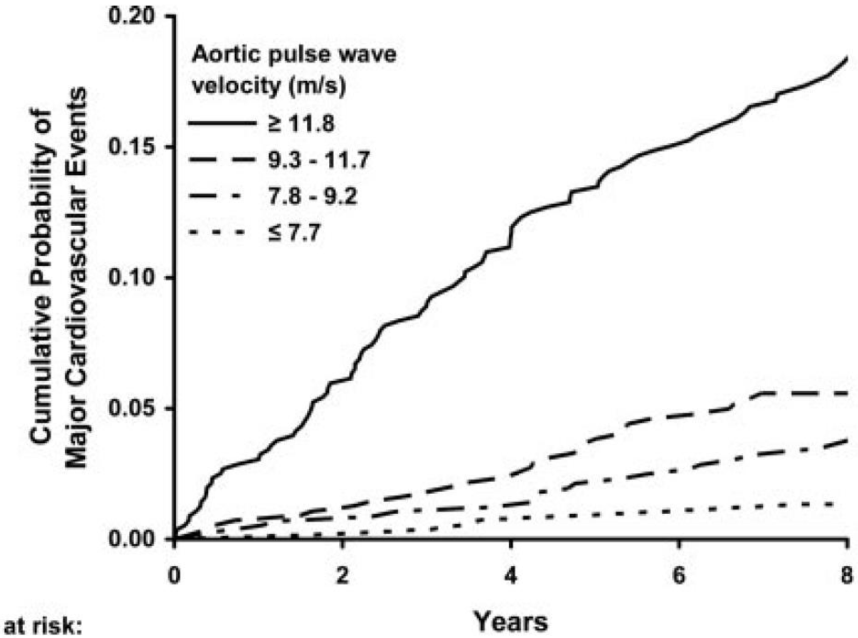
M/20
BP: 126/84 mmHg

M/75
BP: 146/68 mmHg

Arterial Stiffness and Cardiovascular Events : The Framingham Heart Study

- 2232 participiants
  - Median 7.8 years f/u

- Conclusion
  - Aortic PWV improves risk prediction when added to standard risk factors and may represent a valuable biomarker of CV disease risk in the community



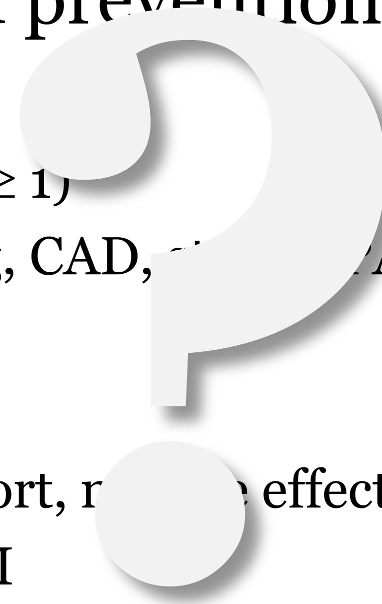
Number at risk:
Aortic pulse wave velocity (m/s)

≥ 11.8	560	513	462	424	161
9.3 - 11.7	555	542	529	502	246
7.8 - 9.2	573	561	551	537	278
≤ 7.7	544	541	535	531	275

Circulation. 2010;121:505-511

- The European guidelines for the management of hypertension and guidelines for CVD prevention in clinical practice *added* ***aortic PWV*** *as a recommended test for TOD*

Conclusion



- Vascular disease screening and prevention
  - Who?
    - Age > 60 years with following risk (≥ 1)
    - DM, HTN, hyperlipidemia, smoking, CAD, [illegible]AD, FHx of vascular disease
  - What?
    - Screening: non-painful, no discomfort, r[illegible]e effect
    - carotid duplex, abdominal USG, ABI
    - Disease specific test
      - TMT for claudication, PPG with thermal measurement, ABI, ...
      - Angiography, CT scan, MRI, ...