

# Vessel wall imaging of atherosclerotic disease: changes to come

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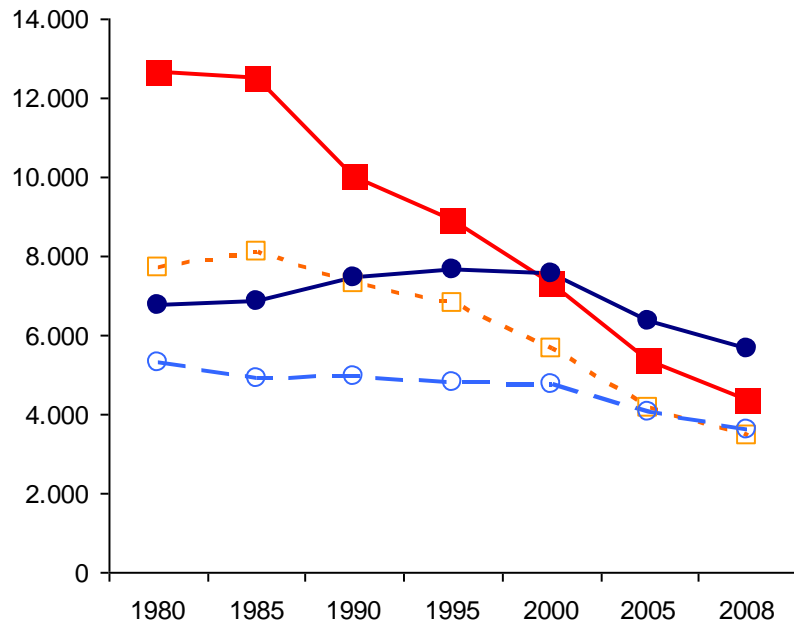


Maastricht University *Leading in Learning!*

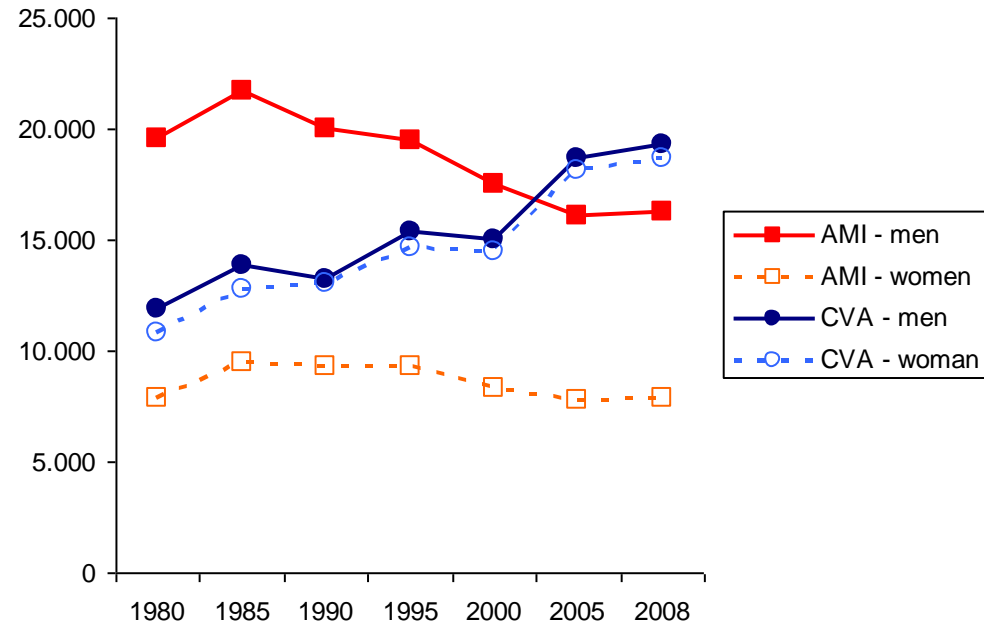


## CVA (ischemic stroke): only minor decrease in # of deaths while hospitalization increases

### # of cardiovascular deaths in the Netherlands



### # of hospitalizations in the Netherlands



Source: report Dutch Heart Foundation

# Patients with carotid plaque are at risk for stroke

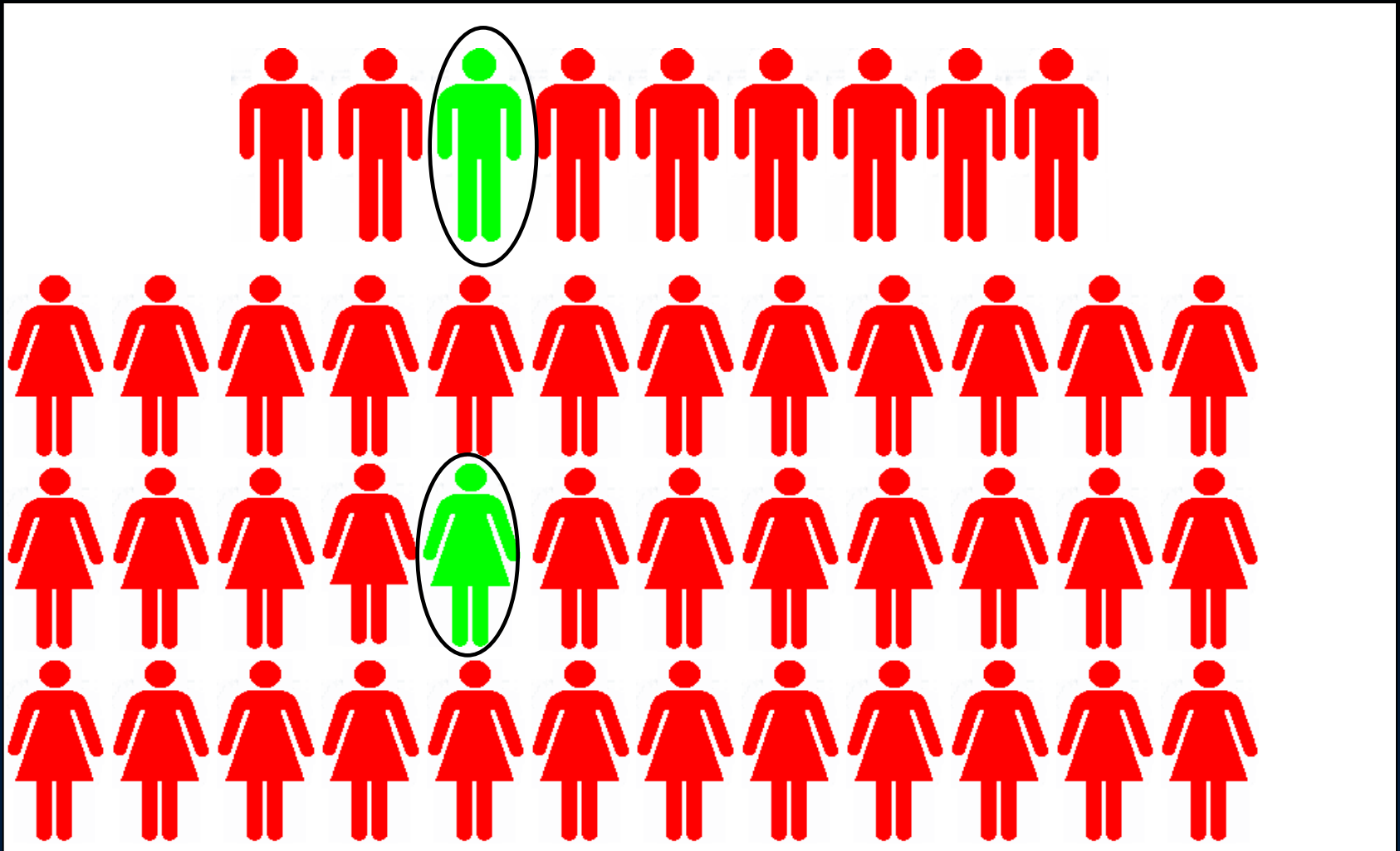
Patient management is currently based on degree of stenosis



DSA

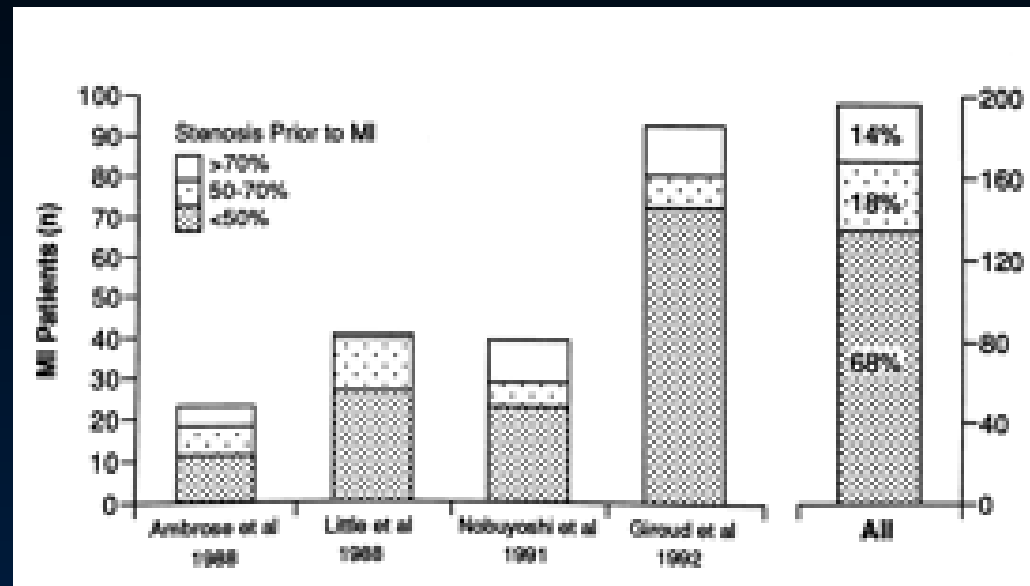
Rothwell et al., Lancet 2003

# Symptomatic patients with 50-99% carotid stenosis: number needed to treat (CEA) to prevent one stroke in 5 years



## Coronary artery disease

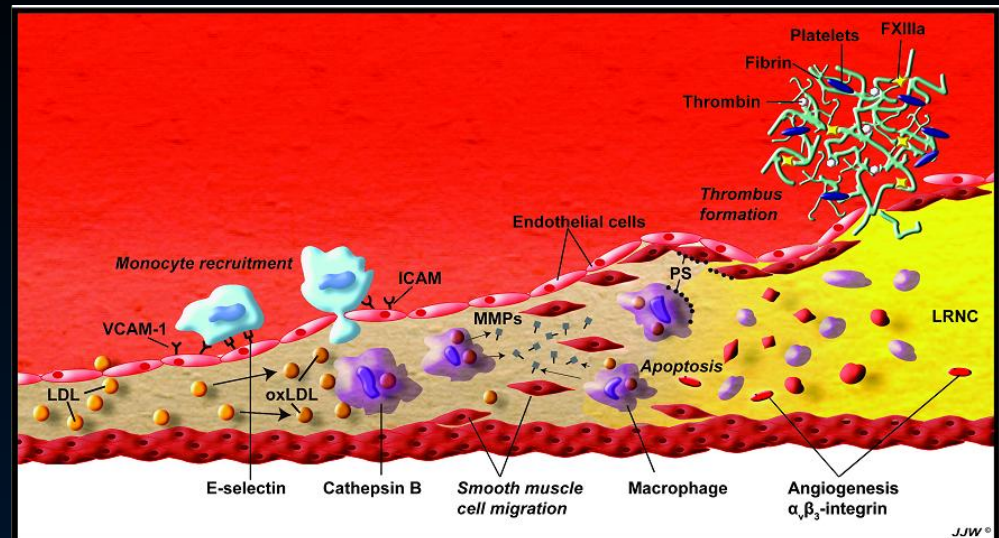
68 % of the myocardial infarctions evolves from plaques that are only mildly to moderately obstructive months to years before infarction.



Falk et al, Circulation 1995

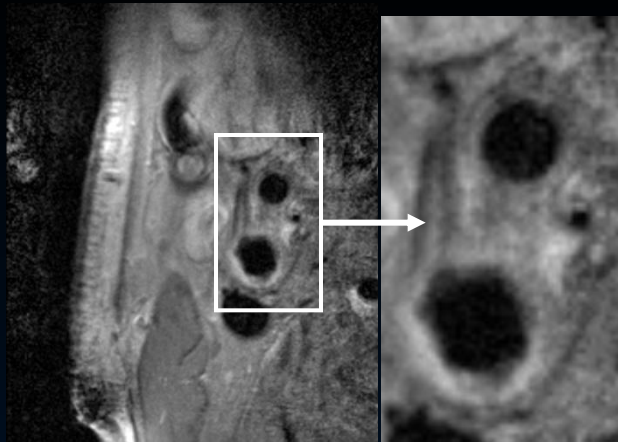
## Hallmarks of vulnerable plaque

- Inflammation
- Angiogenesis
- Intraplaque hemorrhage
- Thin or ruptured fibrous cap
- Large lipid-rich necrotic core
- Thrombus

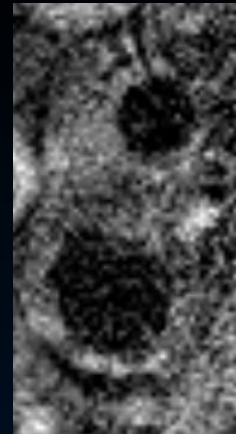


Miserus RJJHM, et al (2006); *Drug Discovery Today: Technologies*, Volume 3, Issue 2,, Pages 195-204

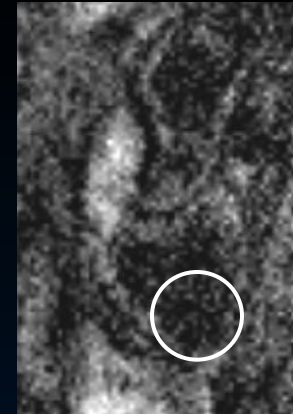
# Accumulation of USPIOs (ferumoxtran-10) in macrophages gives focal signal loss in MR images



PDw TSE



T2\*w FFE;  
pre

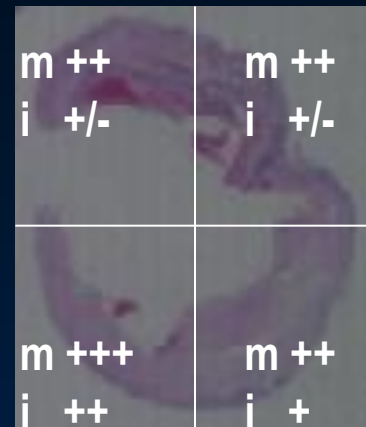


T2\*w FFE;  
24h

Kooi et al.,  
Circulation  
2003

- Kooi et al., Circulation 2003
- Trivedi et al., Stroke 2004
- Trivedi et al., ATVB 2006
- Tang et al, Stroke 2006

**USPIOs could lead to foam cell apoptosis ->**  
**Filip Segers, 10:35, DAS II**



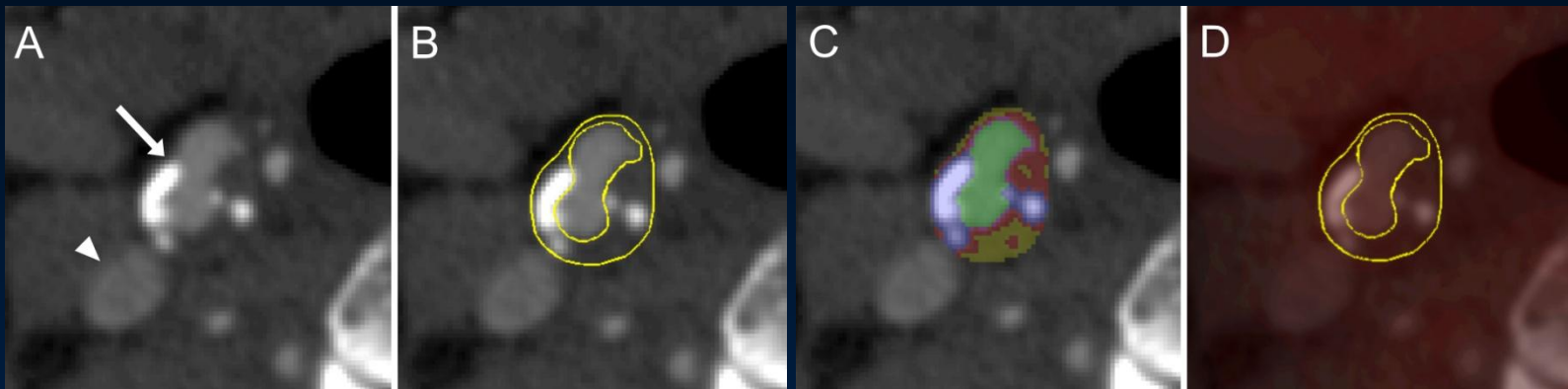
HE staining

m: CD68  
(macrophages)

i: PERL's  
(USPIO)

## $^{18}\text{F}$ -FDG PET: higher SUVs at the symptomatic side only in patients who were scanned within 38 days

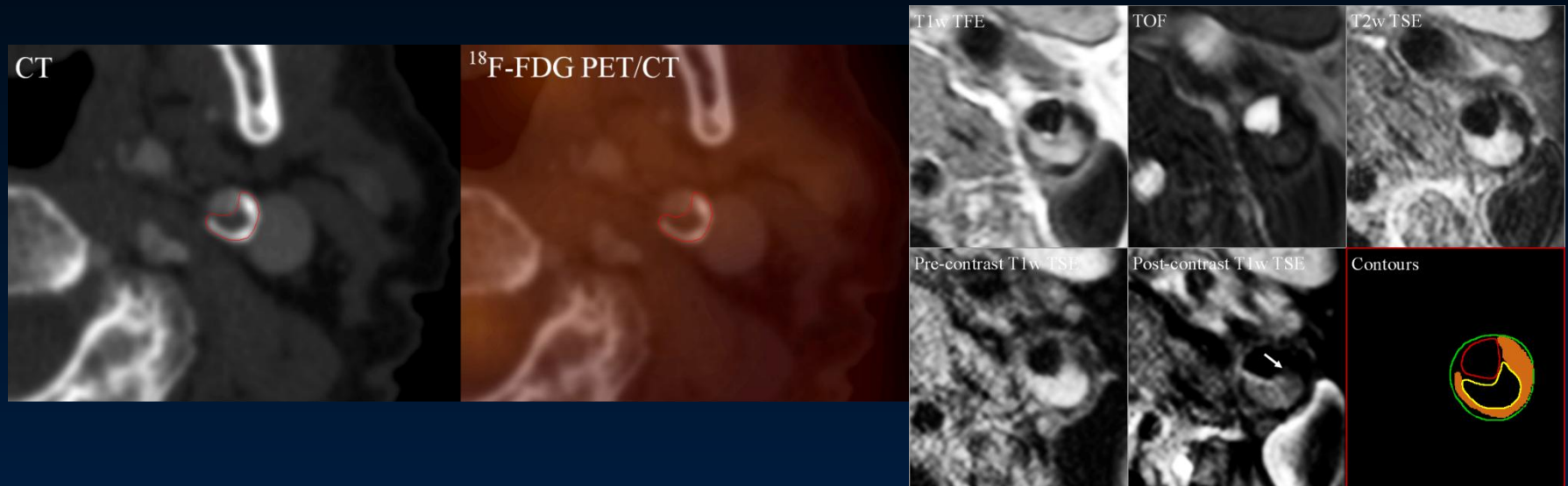
50 TIA/stroke patients with 30-69% ipsilateral carotid stenosis	Symptomatic side mean value SE	Asymptomatic side mean value SE	<i>P</i> value
Max $^{18}\text{F}$ -FDG SUV			
All patients	1.46 ± 0.05	1.44 ± 0.06	0.160
Only patients within 38 days (n=38)	1.53 ± 0.06	1.42 ± 0.06	<b><u>0.015</u></b>





## Comparison between $^{18}\text{F}$ FDG PET and MRI/CT

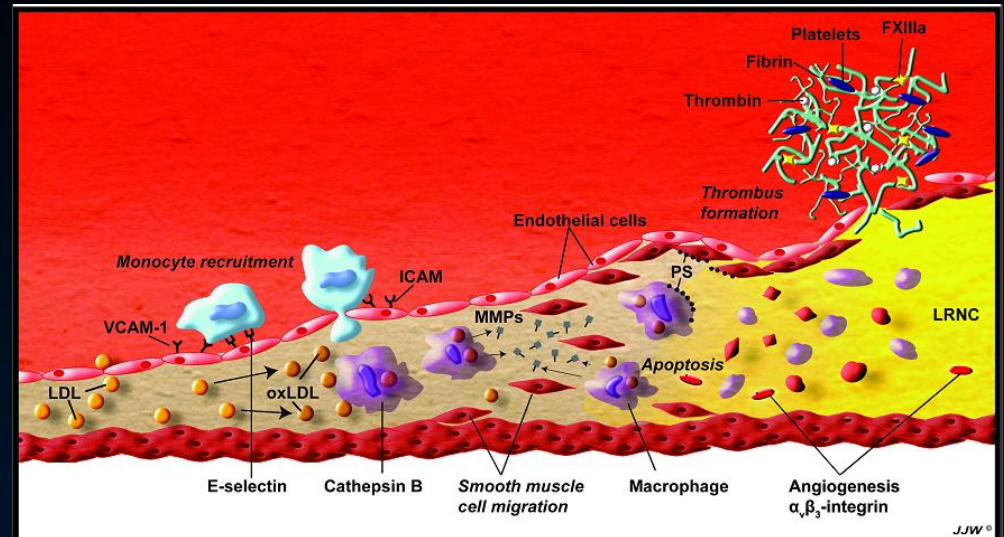
- Larger uptake of  $^{18}\text{F}$  FDG in plaques with IPH
- No strong correlation between  $^{18}\text{F}$  FDG PET and morphometric measures based on MRI/CT



Kwee et al, Stroke 40:3718-3724 (2009)

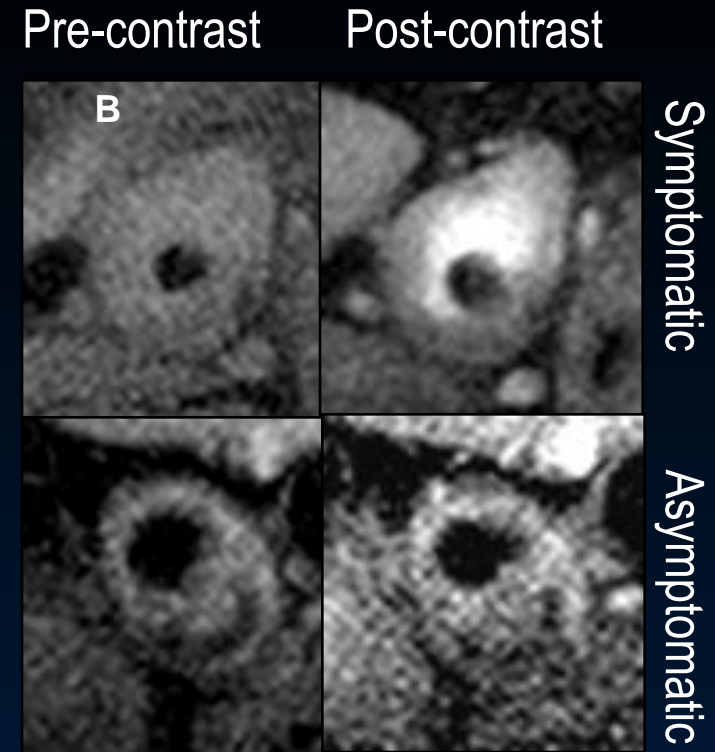
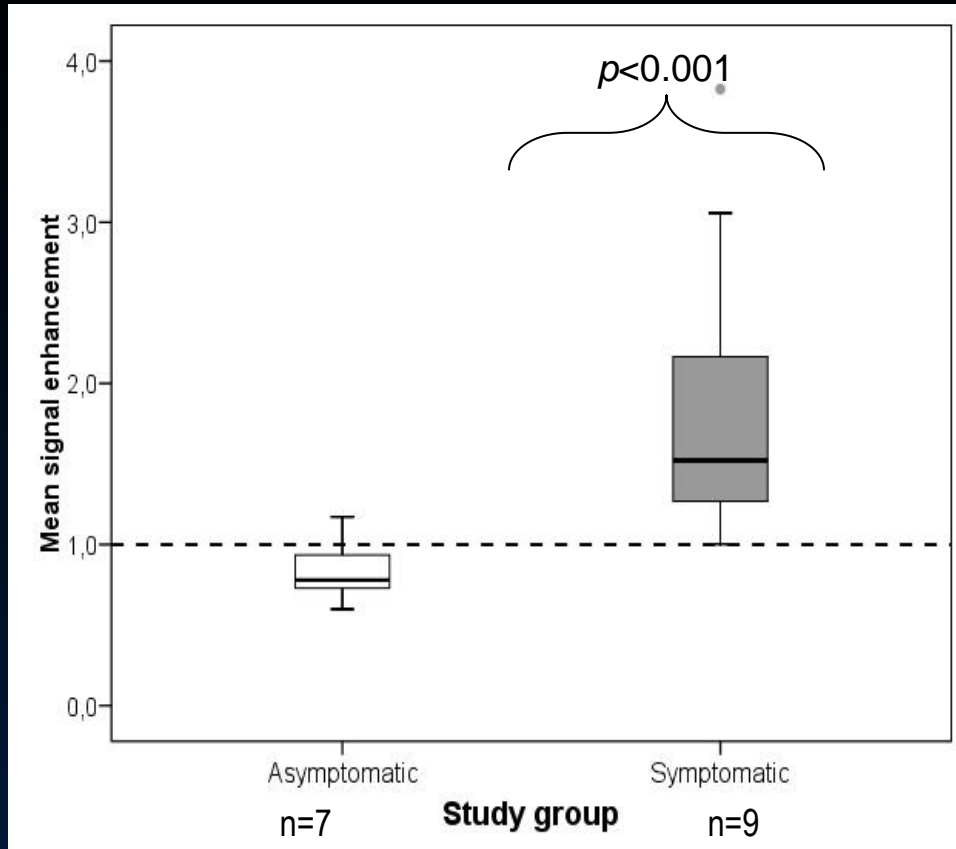
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Miserus RJJHM, et al (2006); *Drug Discovery Today: Technologies*, Volume 3, Issue 2,, Pages 195-204

# Only symptomatic patients show enhancement of plaque using albumin-binding contrast agent (gadovosveset)

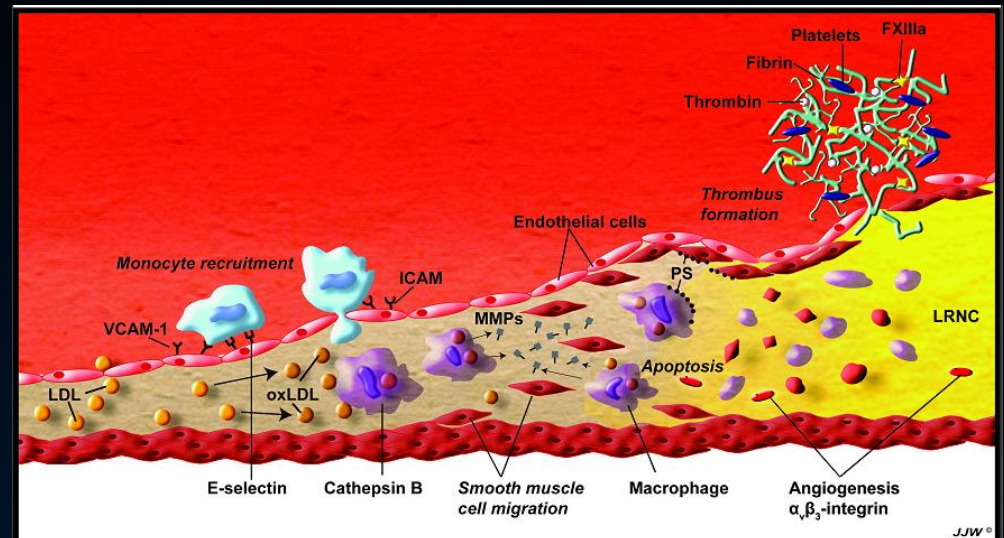


Dose 0.03 mmol/kg body weight; post-contrast imaging time 24 hours

Lobbes et al., Invest Radiol 45:275-281 (2010)

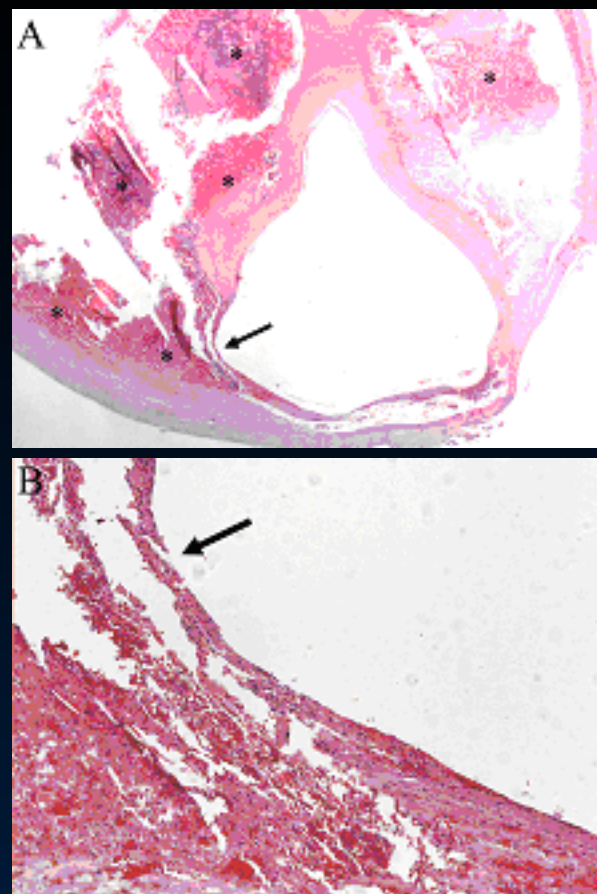
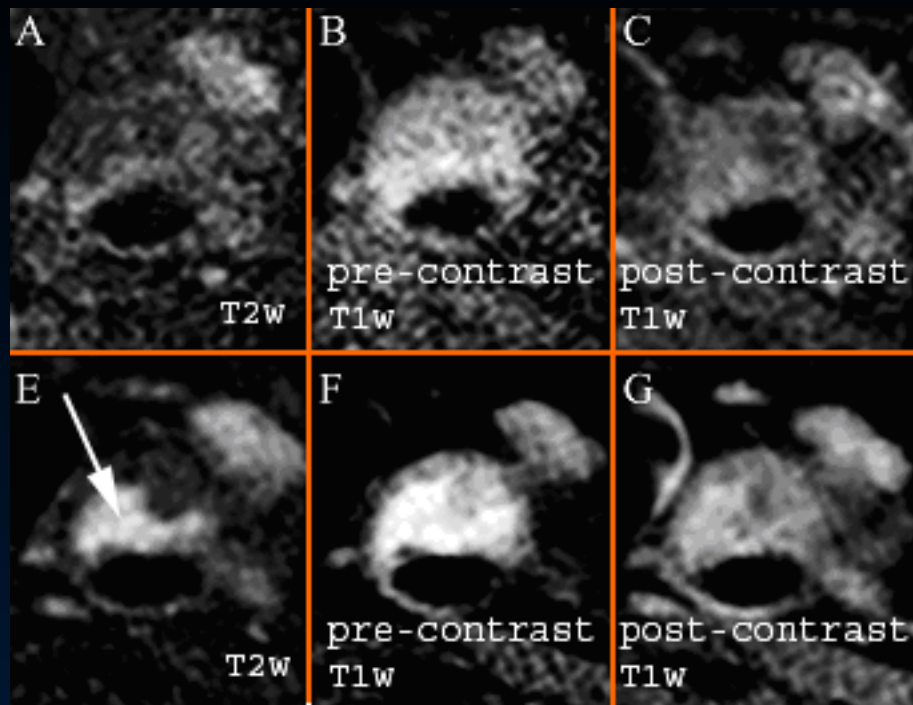
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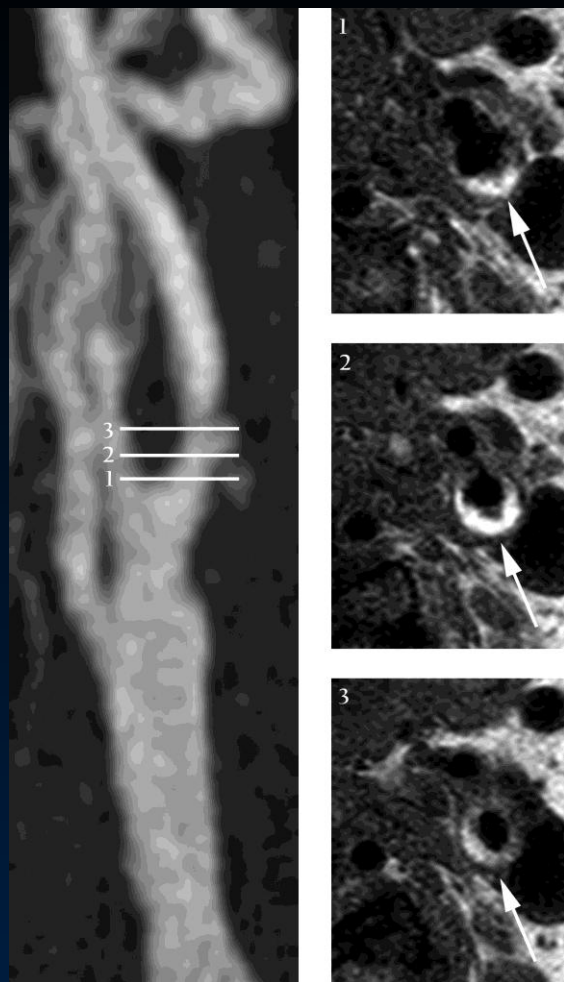
Miserus RJJHM, et al (2006); *Drug Discovery Today: Technologies*, Volume 3, Issue 2,, Pages 195-204

# Intraplaque hemorrhage - a cause for stroke?



Kwee et al, Circulation 120:1637-1639 (2009)

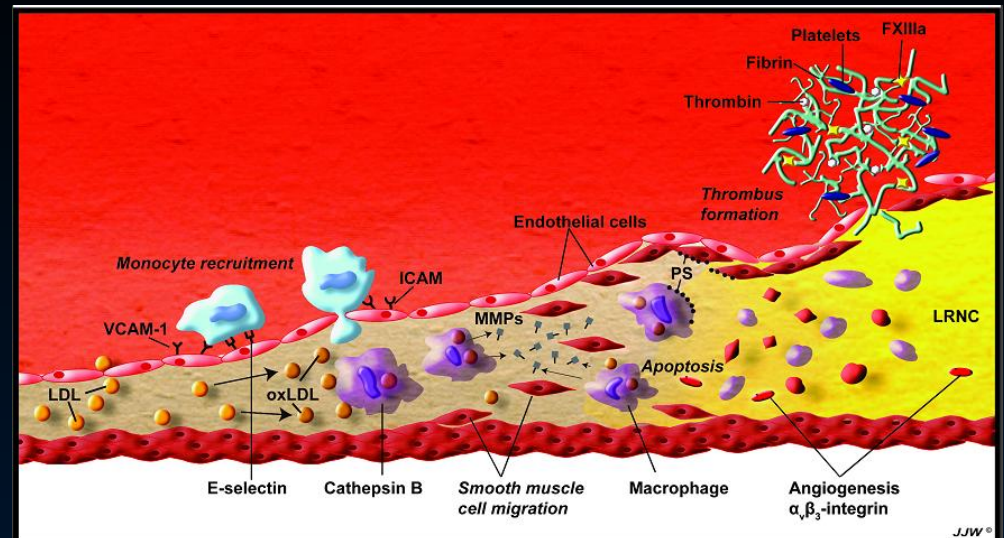
# Intraplaque hemorrhage can also be observed using a common neurovascular coil in patients with low grade stenosis



Van der Kolk et al, Cerebrovasc. Dis, 2010, 30:221-9

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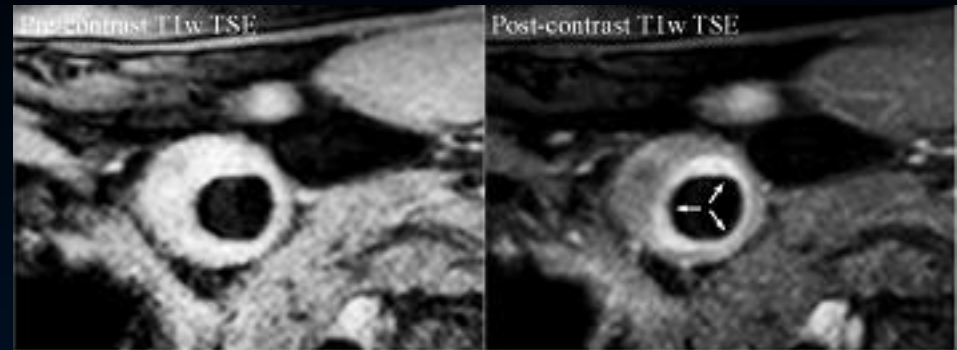


Miserus RJJHM, et al (2006); *Drug Discovery Today: Technologies*, Volume 3, Issue 2,, Pages 195-204

## FC status assessment with CE MRI:

good interobserver and very good intraobserver agreement.

thick fibrous cap



$\kappa$  value

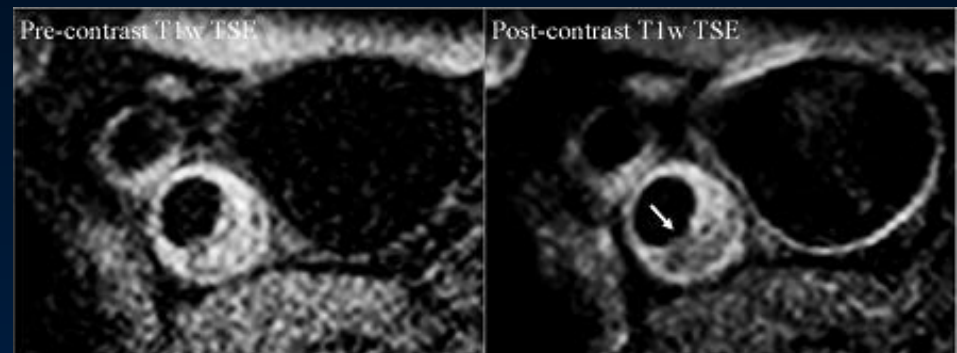
### Interobserver

observer 1 vs. observer 2 0.64

observer 1 vs. observer 3 0.71

observer 2 vs. observer 3 0.60

thin or ruptured fibrous cap



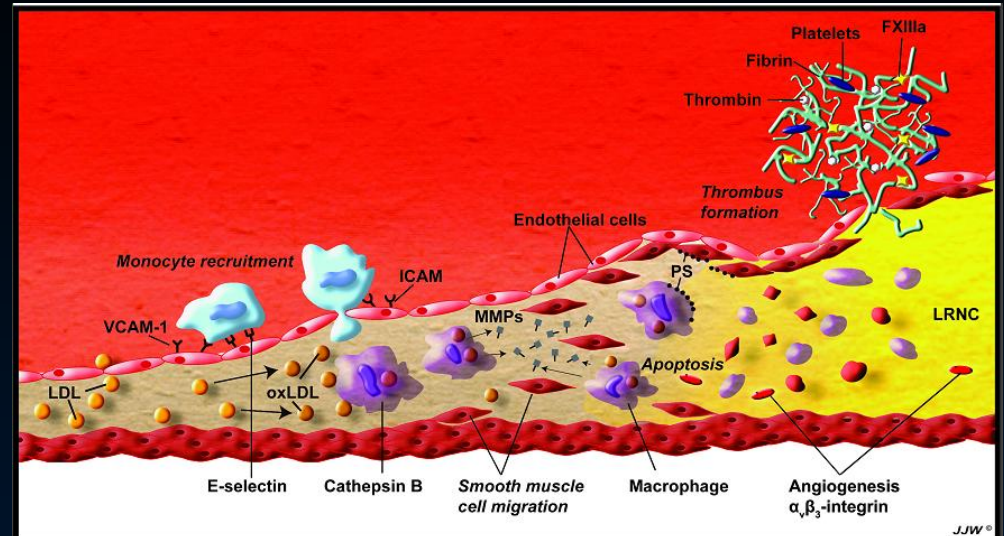
### Intraobserver

0.86



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Miserus RJJHM, et al (2006); *Drug Discovery Today: Technologies*, Volume 3, Issue 2,, Pages 195-204

## Complicated plaques are more frequently observed in plaques with moderate vs mild stenosis (n=100)

Carotid plaque features at MRI	All patients (n=100)		Patients with mild stenosis (n=61)		Patients with moderate stenosis (n=39)		P-value (mild vs. moderate stenosis)
	Mean or %	SE	Mean %	SE or %	Mean or %	SE	
Total plaque volume (mm <sup>3</sup> )	1027	33	1022	38	1035	59	0.844
<b>LRNC (%)</b>	9.0	1.3	<b>6.8</b>	<b>1.5</b>	<b>12.3</b>	<b>2.3</b>	<b><u>0.042</u></b>
Calcifications (%)	4.8	0.4	4.7	0.5	5.0	0.8	0.771
<b>Fibrous tissue (%)</b>	86.2	1.2	<b>88.4</b>	<b>1.4</b>	<b>82.7</b>	<b>2.2</b>	<b><u>0.024</u></b>
<b>Intraplaque hemorrhage</b>	31.0%		<b>19.7%</b>		<b>48.7%</b>		<b><u>0.002</u></b>
<b>Thin and/or ruptured fibrous cap</b>	46.0%		<b>36.1%</b>		<b>61.5%</b>		<b><u>0.013</u></b>

LRNC = lipid-rich necrotic core

## Plaque features vs age and statin use

- Increasing age was positively associated with IPH (OR [per year] 1.08;  $p = 0.011$ ).
- Statin use was negatively associated with complicated features (IPH: OR 0.30;  $p = 0.038$ ), thin and/or ruptured FC (OR 0.34;  $p=0.028$ ), % LRNC (B=7.91;  $p=0.007$ ).
- Statin use was positively associated with % fibrous tissue (B=7.77;  $p= 0.005$ ).

## Comparison between MRI and CT

### CT vs MRI:

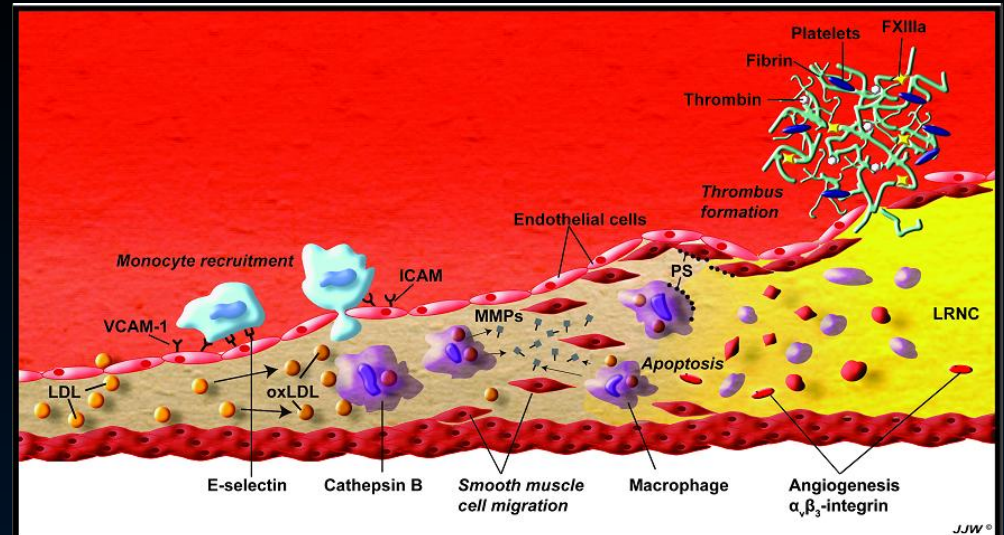
Correlations: CT vs MRI;  $\rho$ : 0.554-0.794;  $p < 0.001$

LRNC volume:

Stronger correlation in mildly calcified plaques ( $\leq 10\%$ ) ( $\rho = 0.730$ )  
vs severely ( $> 10\%$ ) calcified plaques ( $\rho = 0.475$ ).

## Hallmarks of vulnerable plaque

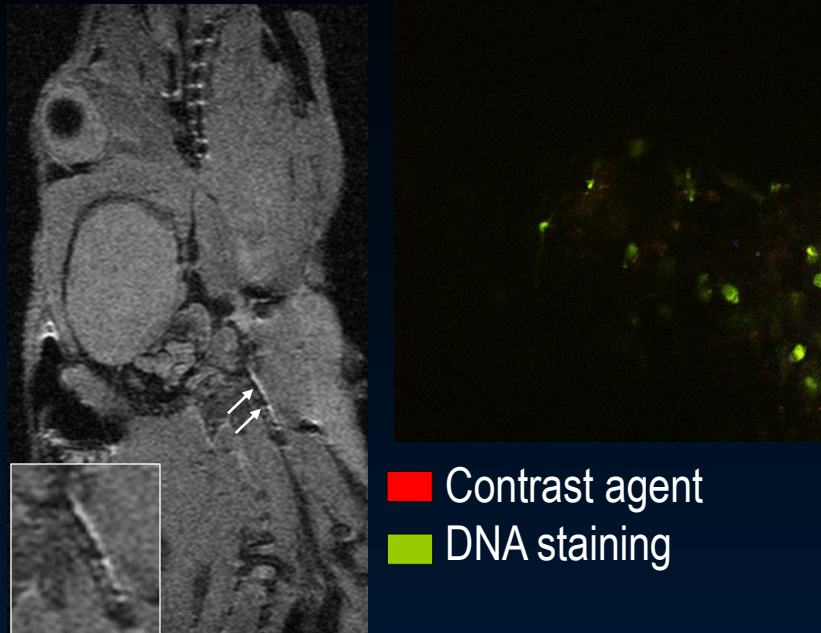
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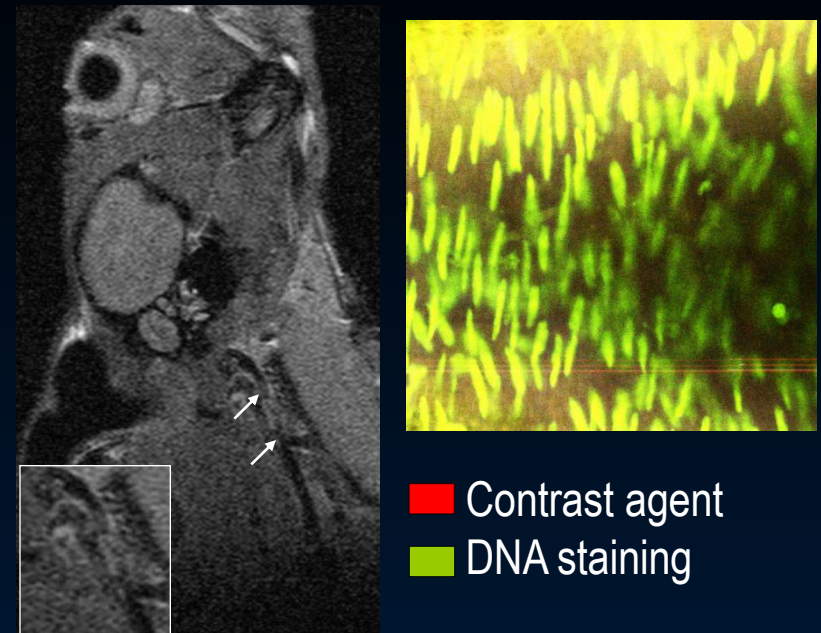
Miserus RJJHM, et al (2006); *Drug Discovery Today: Technologies*, Volume 3, Issue 2,, Pages 195-204

# In vivo imaging of thrombus

## Specific Contrast Agent



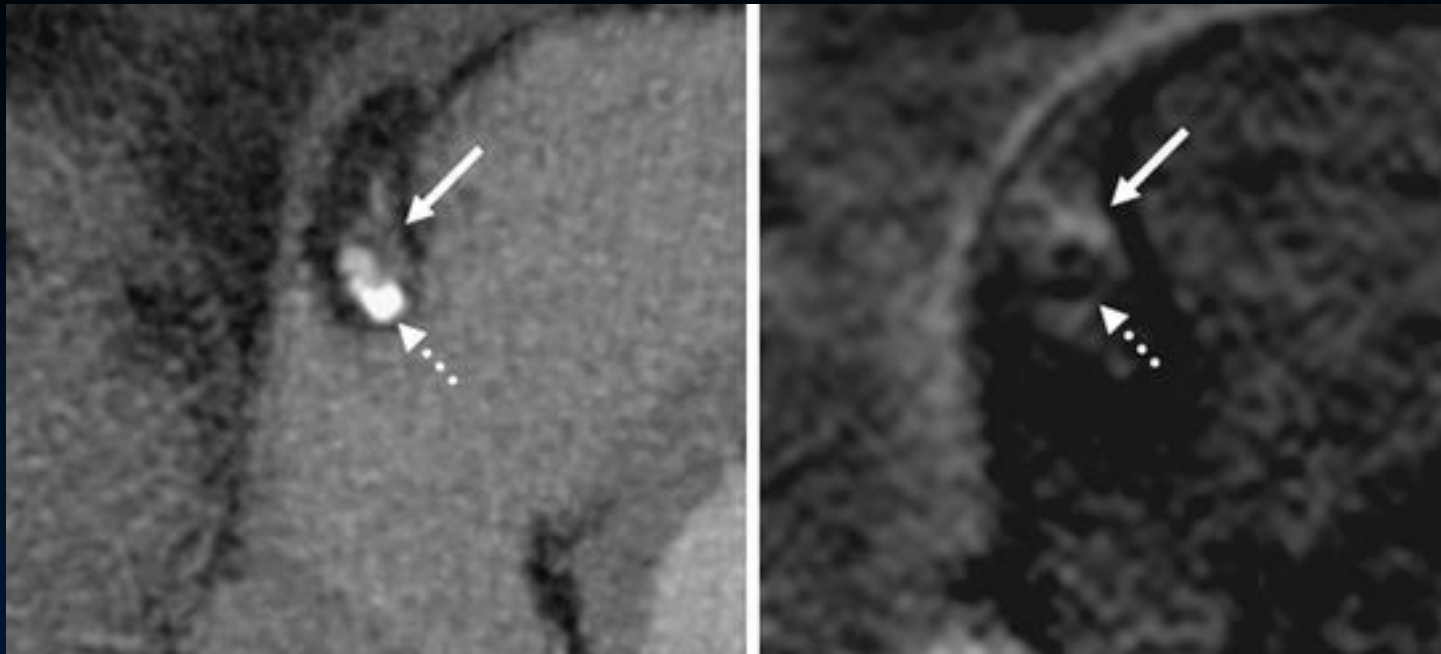
## Non-specific Contrast Agent



Thrombus formation was induced by 10%  $\text{FeCl}_3$  treatment of the carotid artery  
Dose:  $5.1 \mu\text{mol Gd /kg}$  body weight

Miserus et al, JACC Cardiovascular Imaging, 2, 987-96 (2009)

## Intraplaque hemorrhage can also be detected in coronary plaques



Oei et al, Eur. Radiol, 2010

## Conclusions

- Hallmarks of plaque vulnerability can be detected in carotid plaque
- Which Imaging feature is most important?
  - markers should be related to future CVAs in large multi-center studies
  - Intraplaque hemorrhage currently most promising
- Translation to coronary atherosclerotic plaques?



## Changes to come

### Personalized medicine

1. Risk assessment: cardiovascular risk markers, multi-serum marker approach
2. Selection of high-risk patient for non-invasive imaging
3. Individual assessment of risk for rupture → personalized therapy

Large international prospective clinical trials

## Maastricht University Medical Center

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Matthijs Lipperts  
Stefan Rozel+  
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Mat Daemen, MD, PhD

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