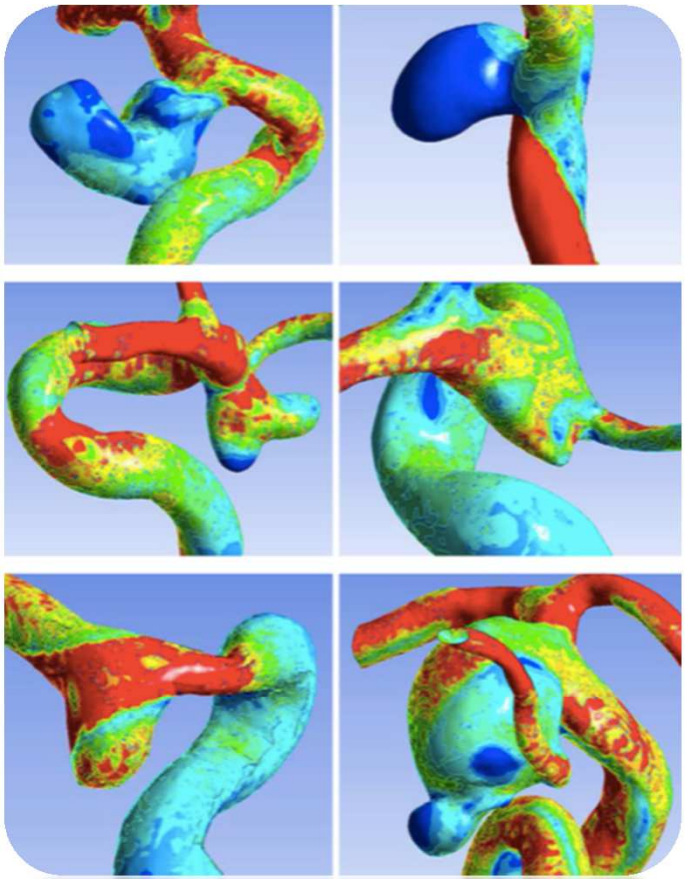

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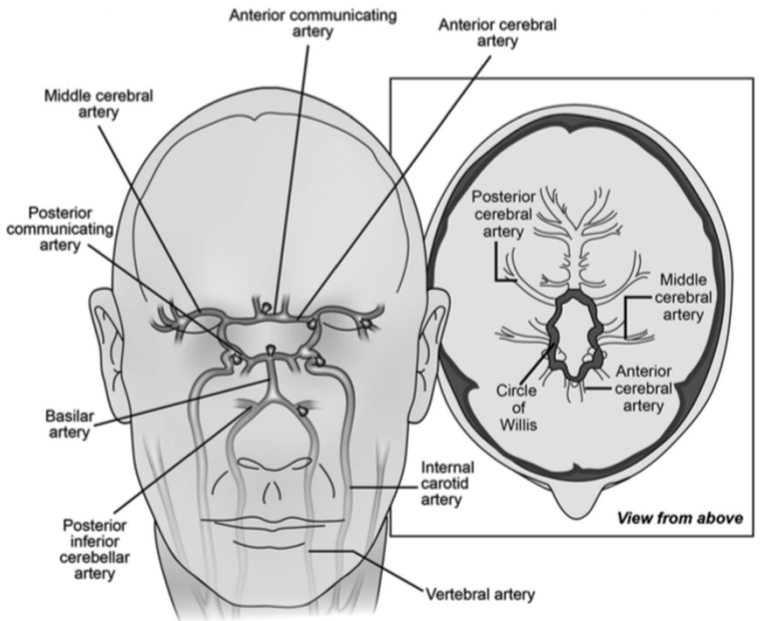
Aneurisma Cerebrale:
diagnosi e trattamento

Ferrara, 15 dicembre 2018

Epidemiologia degli aneurismi cerebrali

Definition

- A cerebral aneurysm is a **focal abnormal dilation of the wall of an artery** in the brain, that are **prone to rupture**.
- Most commonly located at **branching points** of the major arteries at the base of the brain, which course through the subarachnoid space.



Natural history, epidemiology and screening of unruptured intracranial aneurysms

Histoire naturelle, épidémiologie et dépistage des anévrismes intracrâniens non rompus

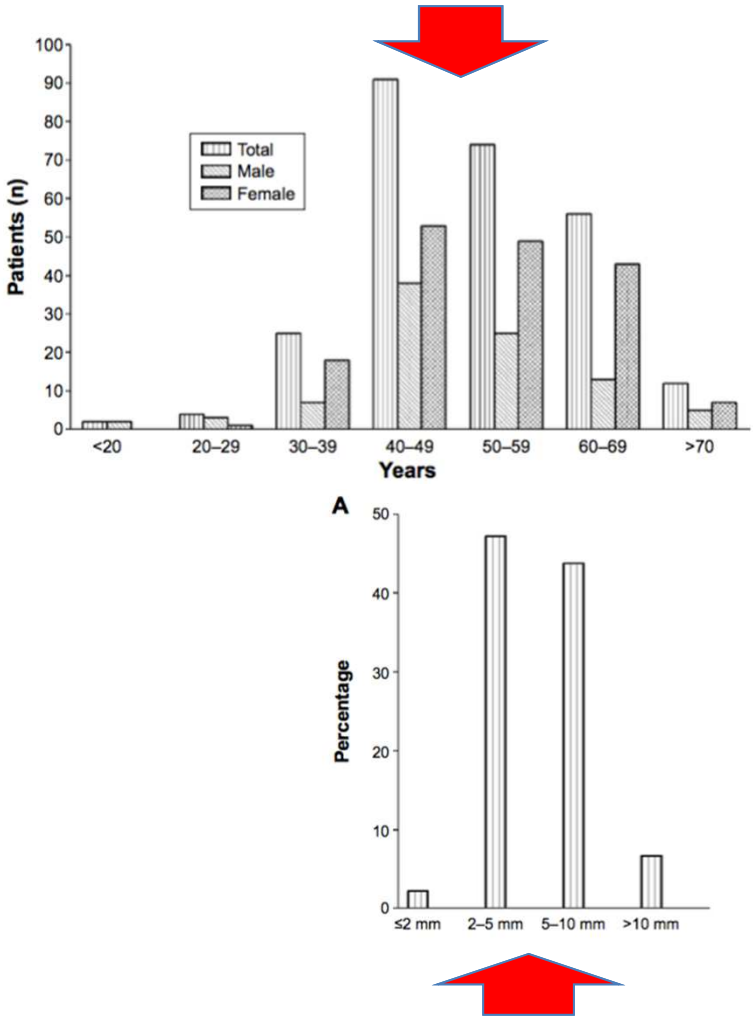
G.J.E. Rinkel

2008,35:99

- For adult without specific risk factors for unrupted aneurysms (UA) **the prevalence is 3.2%** (Juvela, 2011), autopsy series → **0.2-7.9%** → 3 to 12 million Americans; 1.6 million in Germany
- **Incidence** of intracranial aneurysm= **1 per 10,000 persons/year** in the USA
- **20–30%** of patients harboring **more than one** aneurysm
- There has been increased detection of UA due to the frequent use of **CT and MRI**
- The prevalence is higher in **women** (3 : 1 ratio), increase with **increasing age**
- It can occur at any age but are more common in **adults** than children (2%)
- Annual risk of rupture around **1%** (ISUIA, 1998; Wermer et al, 2007).
- It account for about **80–85% of nontraumatic subarachnoid hemorrhages** (SAH)

Chinese population

- the **female** predominance is **weaker** in the younger age group
- a tendency for males to have a slightly larger aneurysm size than females
- **ruptured aneurysms** are mostly in the size range of **2–5 mm**
- the prevalence of **multiple aneurysms** was **only 2.7%** in this cohort
- **high** proportion of ruptured aneurysms from the **PcoA and AcoA**
- higher incidence of AcoA aneurysm rupture on the left side and PcoA aneurysm rupture on the right side



Liu H et al. Neuropsychiatric Disease and Treatment 2015:11

Natural history, epidemiology and screening of unruptured intracranial aneurysms

Histoire naturelle, épidémiologie et dépistage des anévrismes intracrâniens non rompus

G.J.E. Rinkel 2008,35:99

- **50% to 80%** of all aneurysms **do not rupture** during the person's lifetime
- **65% to 85%** of UA are small, **<5 to 7 mm** in diameter
- **Risk factors for UA**: smoking (risk persists after smoking cessation), hypertension, alcohol, injury or trauma to blood vessels, blood infections, autosomic dominant polycystic kidney disease (5% to 40% and 10% to 30% multiple aneurysms), Marfan's syndrome, Ehlers-Danlos syndrome type IV, fibromuscular dysplasia, moyamoya disease, sickle cell disease, arteriovenous malformations of the brain, glicogenosys, Fabry,….
- Previous episode of SAH
- **7% to 20%** of pts with aneurysmal SAH have a **1st or 2nd-degree relative** with intracranial aneurysm→screening with AGF-MRI for people with 2 immediate relatives with IA and for all patients with autosomal dominant polycystic kidney disease

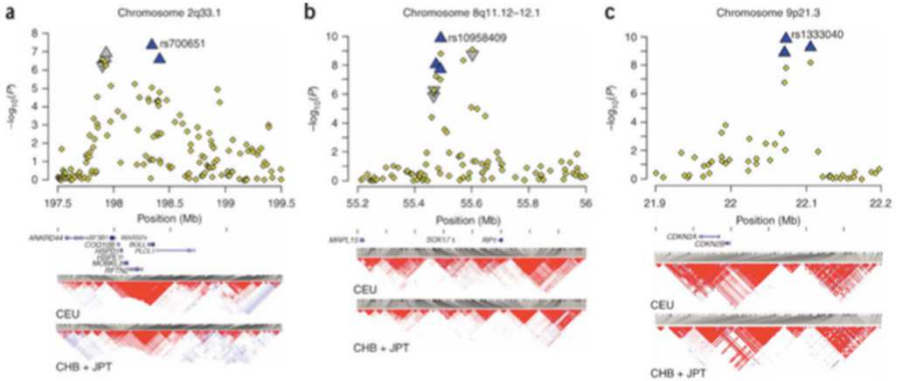
Juvela et al Stroke 2013; Can A et al. Neurology 2017;89:1408–1415

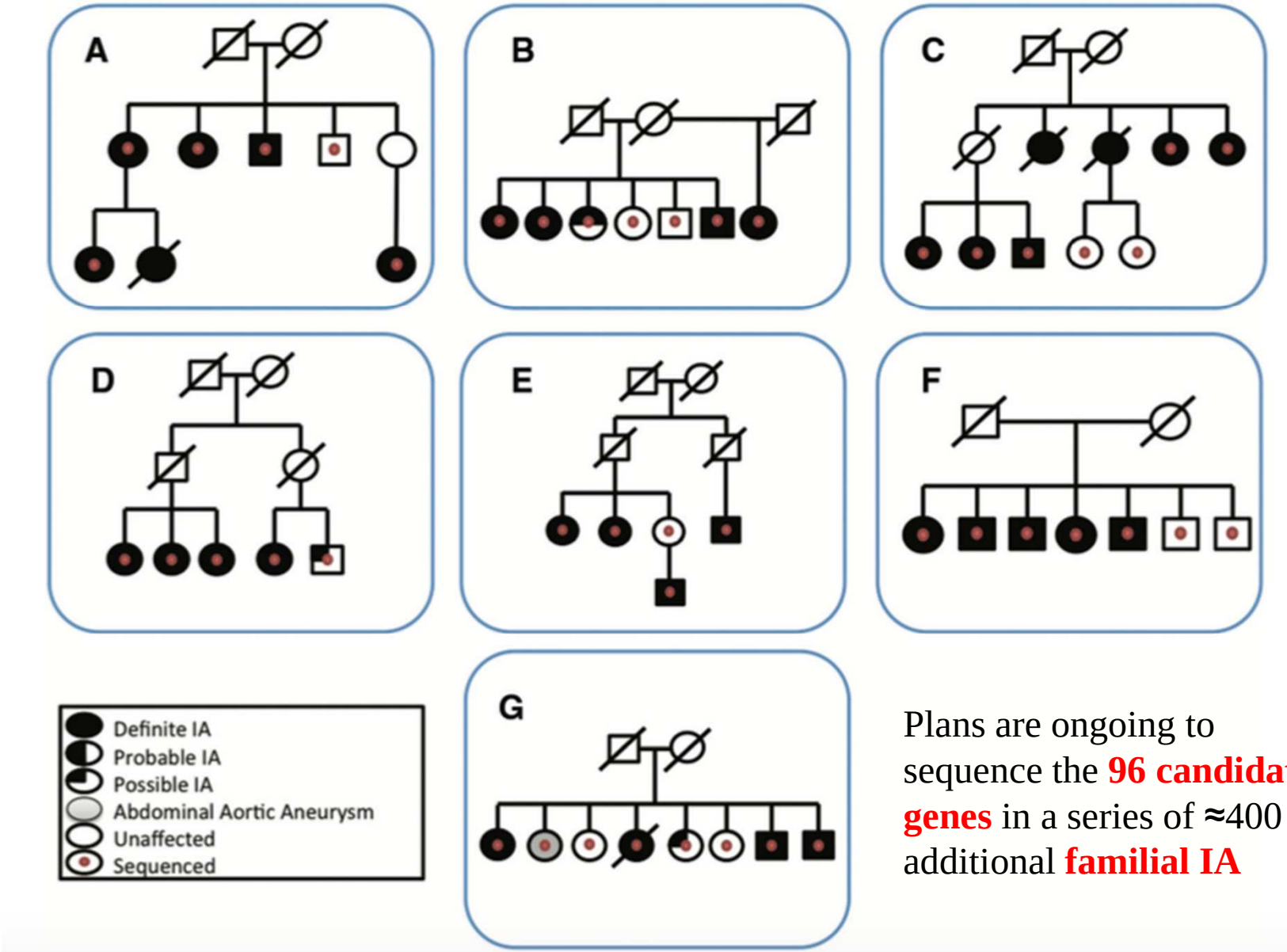
VIEWS & REVIEWS

Genetic risk factors for intracranial aneurysms

A meta-analysis in more than 116,000 individuals (Varinder S et al. Neurology 2013)

- 61 studies including 32.887 IA cases and 83.683 ctrls
- 19 single nucleotide polymorphisms associated with IA
  - **chromosome 9** within the CDKN2B antisense inhibitor gene, cyclin-dependent kinase inhibitor 2B antisense inhibitor gene
  - **chromosome 8** near the SOX17 transcription regulator gene
  - **chromosome 4** near the endothelin receptor A gene. Near the EDNRA gene
  - 10q24.32 (*CNNM2*), 12q22, 13q13.1 (*KL/STARD13*), 18q11.2 (*RBBP8*), and 20p12.1
- **Multiple pathophysiologic pathways**, mainly involved in vascular endothelial maintenance and extracellular matrix integrity, are likely to contribute to IA development and rupture





Plans are ongoing to sequence the **96 candidate genes** in a series of ≈400 additional **familial IA**

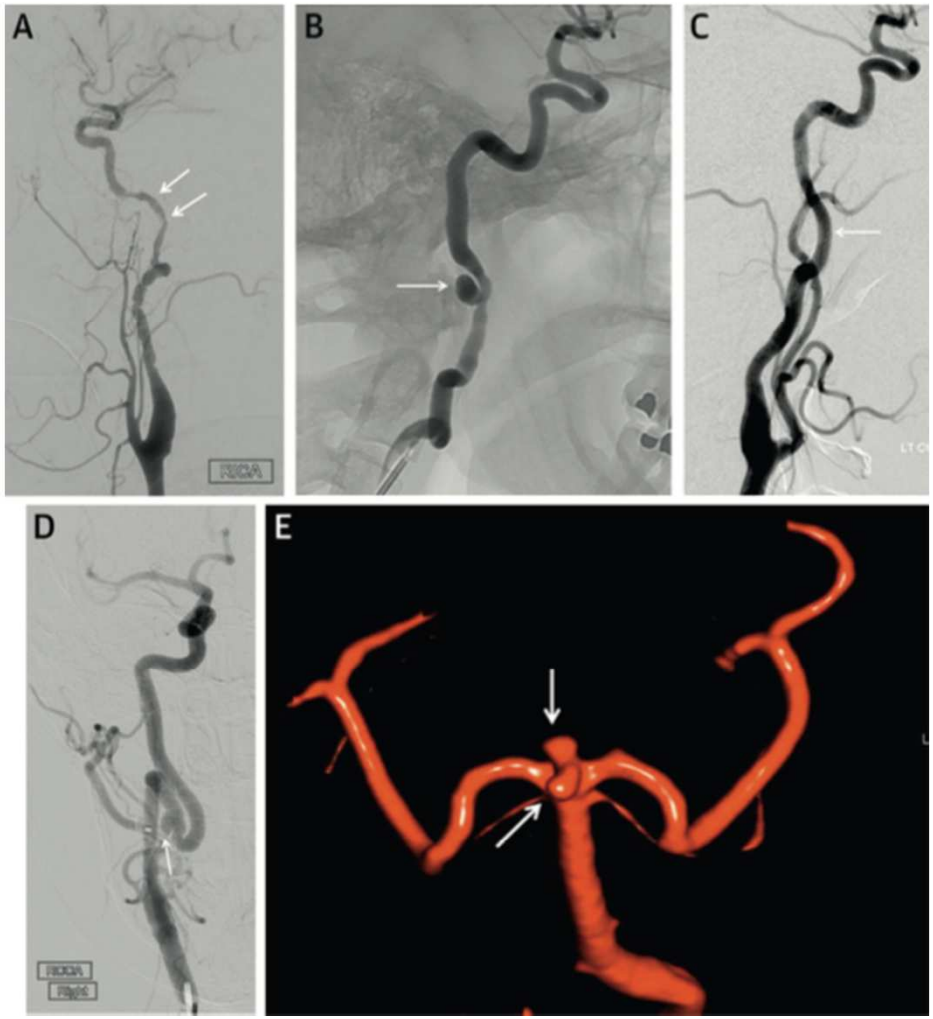
Whole Exome Sequencing of Intracranial Aneurysm. Foroud T et al, Stroke 2013

Dissection and Aneurysm in Patients With Fibromuscular Dysplasia

Findings From the U.S. Registry for FMD

Daniella Kadian-Dodov, MD,[a] Heather L. Gornik, MD, MHS,[b] Xiaokui Gu, MA,[c] James Froehlich, MD, MPH,[c] J. Michael Bacharach, MD, MPH,[d] Yung-Wei Chi, DO,[e] Bruce H. Gray, DO,[f] Michael R. Jaff, DO,[g] Esther S.H. Kim, MD, MPH,[b] Pamela Mace, RN,[h] Aditya Sharma, MBBS,[i] Eva Kline-Rogers, MS, RN, NP,[b] Christopher White, MD,[j] Jeffrey W. Olin, DO[a]

- FMD is a rare (4% popluation) noninflammatory arterial disease, (97.5% women)
- Arterial beading, stenosis, aneurysm, dissection, or tortuosity
- Dissection (25.7%)
- Aneurysm (21.7%),
  - extracranial carotid, 31%
  - renal 34%
  - intra- cranial arteries 21.5%
  - Aorta 10%



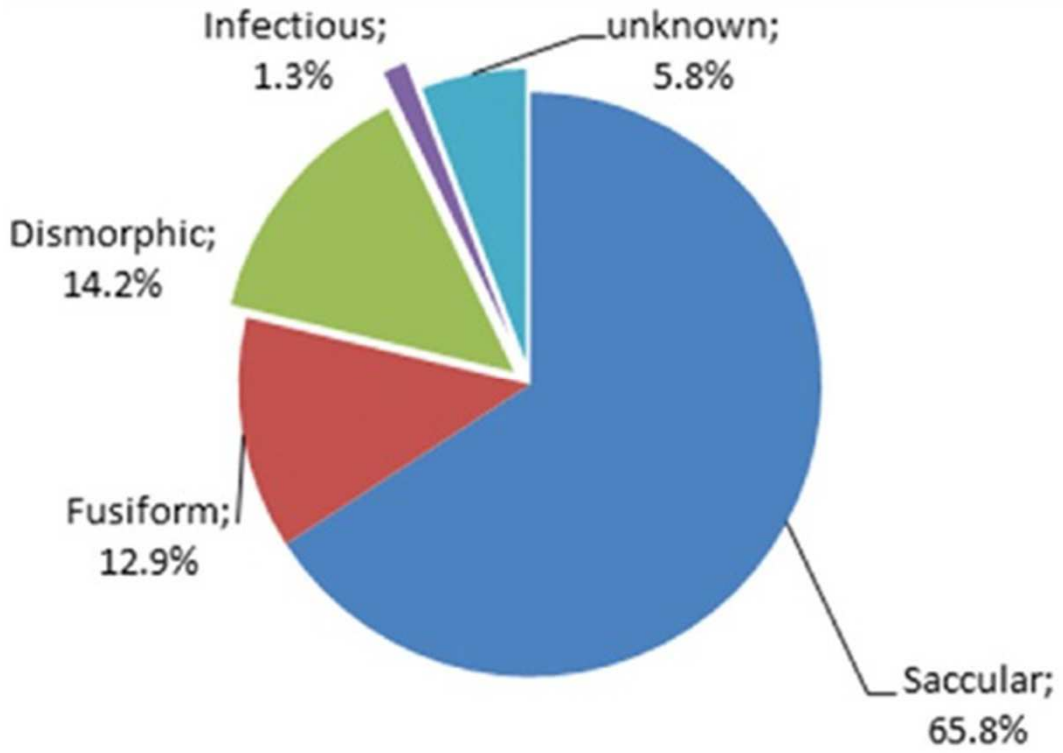
Journal of Stroke 2016;18(3):321-327.
Published online: August 4, 2016
DOI: https://doi.org/10.5853/jos.2016.00164

Prevalence and Characteristics of Unruptured Cerebral Aneurysms in Ischemic Stroke Patients

Ji Hwa Kim[a], Sang Hyun Suh[b], Joonho Chung[c], Yeo-Jin Oh[a], Sung Jun Ahn[b], Kyung-Yul Lee[a]

- The prevalence of UCAs was significantly higher in the **AIS group (7.7%)** than in the health check-up **(3.7%)**
- The mean aneurysm diameter was larger in the AIS group than in the health check-up group (3.75 mm vs. 3.02 mm, P=0.009).
- UCAs were primarily located in the internal carotid artery in both groups, and aneurysms in the middle cerebral artery were particularly common in the AIS group.
- **Hypertension was an independent risk factor of UCA in AIS**

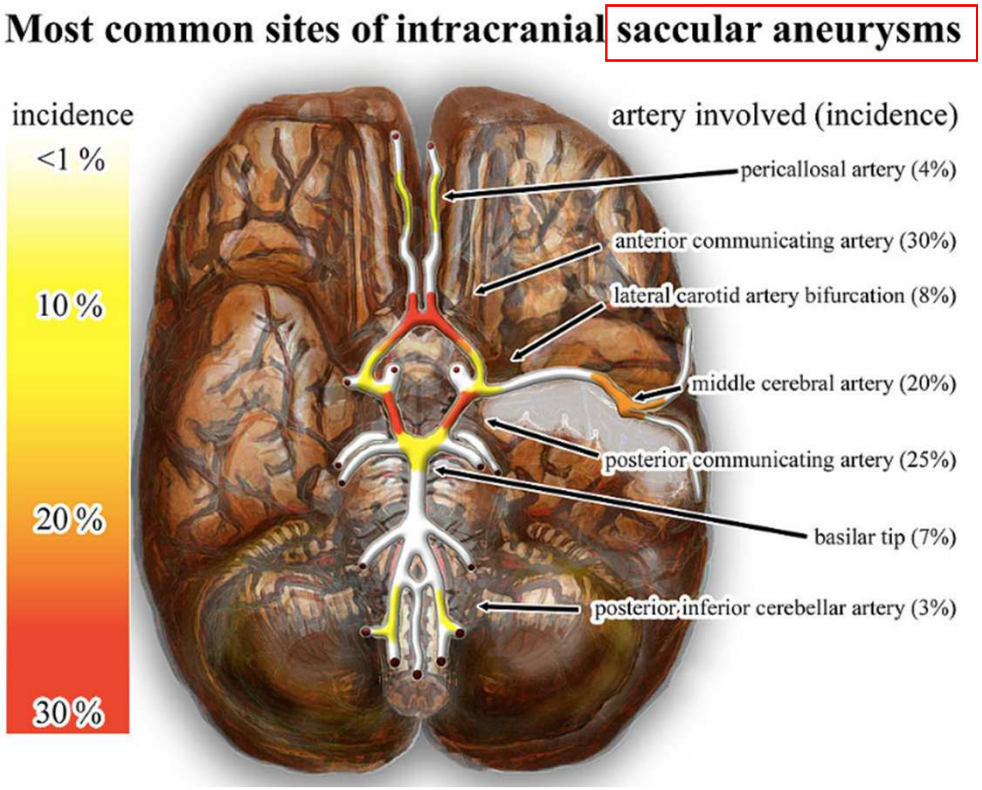
Frequency percentage of type of aneurysm in the studied patients

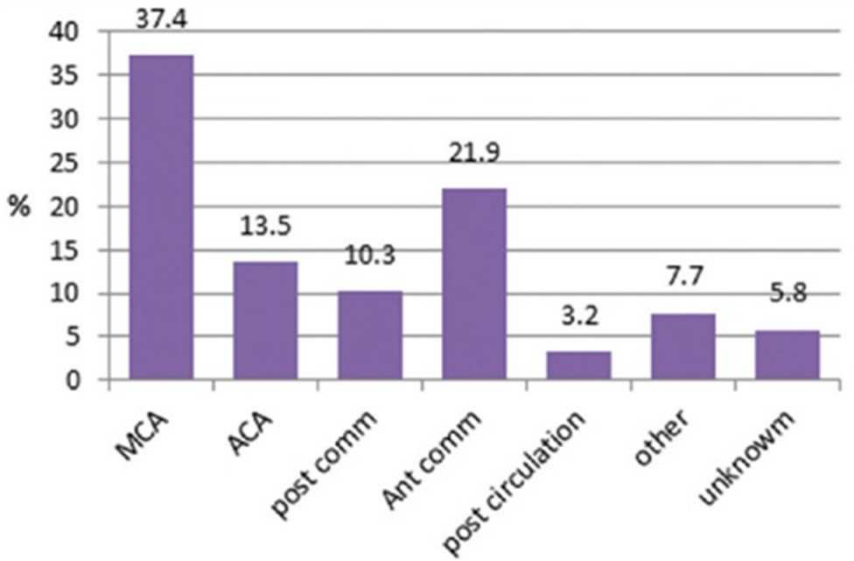


Classified by pathogenesis

- **Saccular, berry, or congenital aneurysms = 90%** located at the major branch points of large arteries (anterior circulation in 85-95% of cases)
- **Dolichoectatic, fusiform, or arteriosclerotic aneurysms** are elongated outpouchings of proximal arteries = **7%**
- **Giant saccular** aneurysms= greater than 25 mm (**3-5%** of all)
- **Microaneurysms** of small perforating vessels may result from hypertension
- **Multiple saccular** aneurysms are noted in **20-30%** of pts with cerebral aneurysms
- **Mirror aneurysms** (occurring at the same locations bilaterally) are found in about **9%**
- **Infectious or mycotic aneurysms** are situated **peripherally= 0.5%**
- **Other distal**: neoplastic aneurysms, rare sequelae of embolized tumor fragments, and traumatic aneurysms
- **Traumatic injury** also may result in dissecting aneurysms in proximal vessels

Frequency percentage of anatomical position of aneurysm incidence

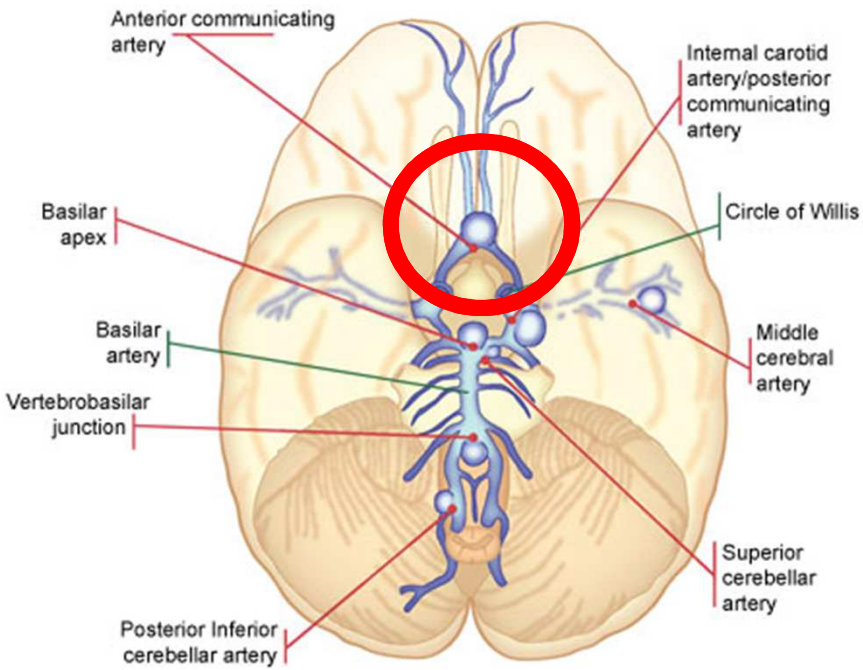




- Anterior circulation in 85-95% of cases
- Posterior circulation are less frequent (10–20%) with a higher risk of rupture
- Dolichoectatic aneurysms affect predominantly the vertebrobasilar system.

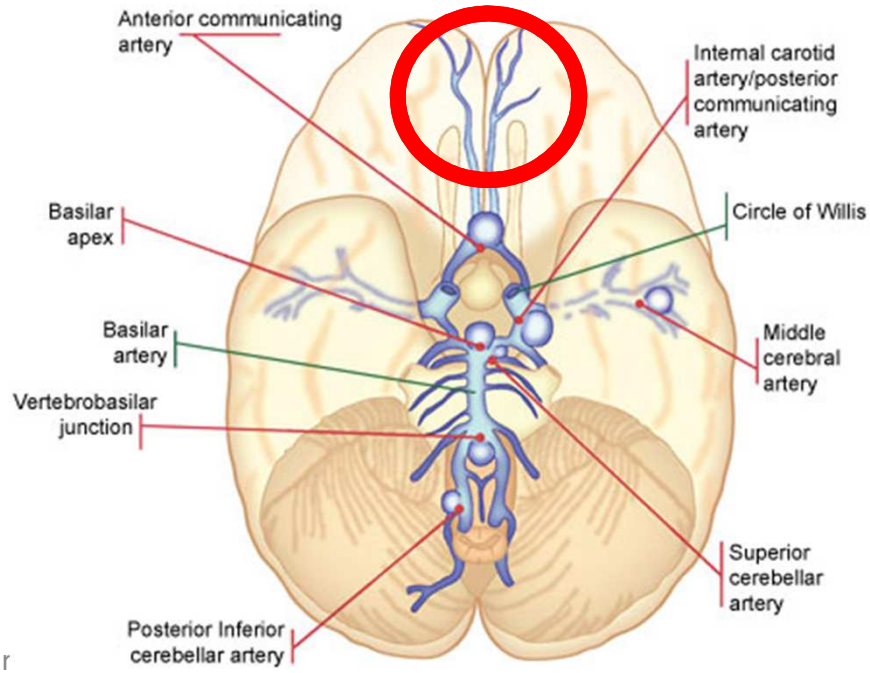
Anterior communicating artery

- The most common site of **aneurysmal SAH** (**34%**)
- It accounts for about **21.9%**
- Usually, ACoA aneurysms are **silent until they rupture**.
- Suprachiasmatic pressure may cause **altitudinal visual field deficits, abulia or akinetic mutism, amnestic syndromes, or hypothalamic dysfunction.**
- Neurological deficits in aneurysmal rupture may reflect intraventricular hemorrhage (79%), intraparenchymal hemorrhage (63%), acute hydrocephalus (25%), or frontal lobe strokes (20%).



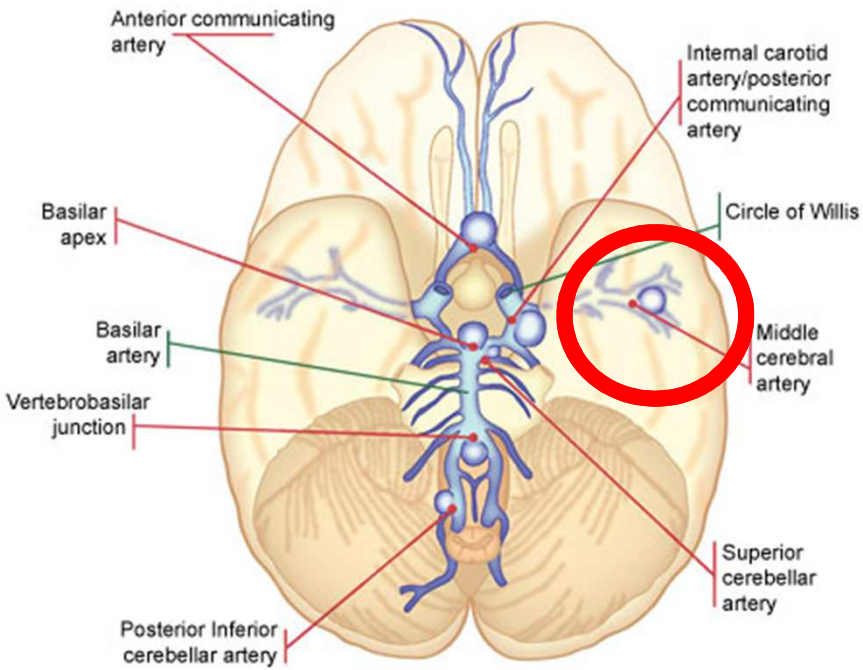
Anterior cerebral artery

- Aneurysms of this vessel, excluding ACoA, account for about **5%** of all cerebral aneurysms
- Most are **asymptomatic** until they rupture
- **Frontal lobe** syndromes, anosmia, or motor deficits



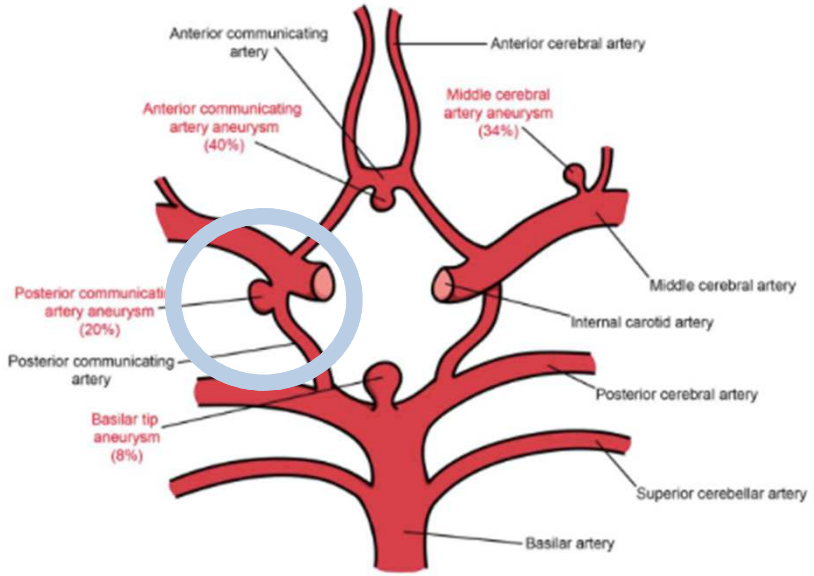
Middle cerebral artery

- It accounts for about **20%** of aneurysms, typically at first or second division in the sylvian fissure
- Aphasia, hemiparesis, hemisensory loss, anosognosia, or visual field defects or seizure



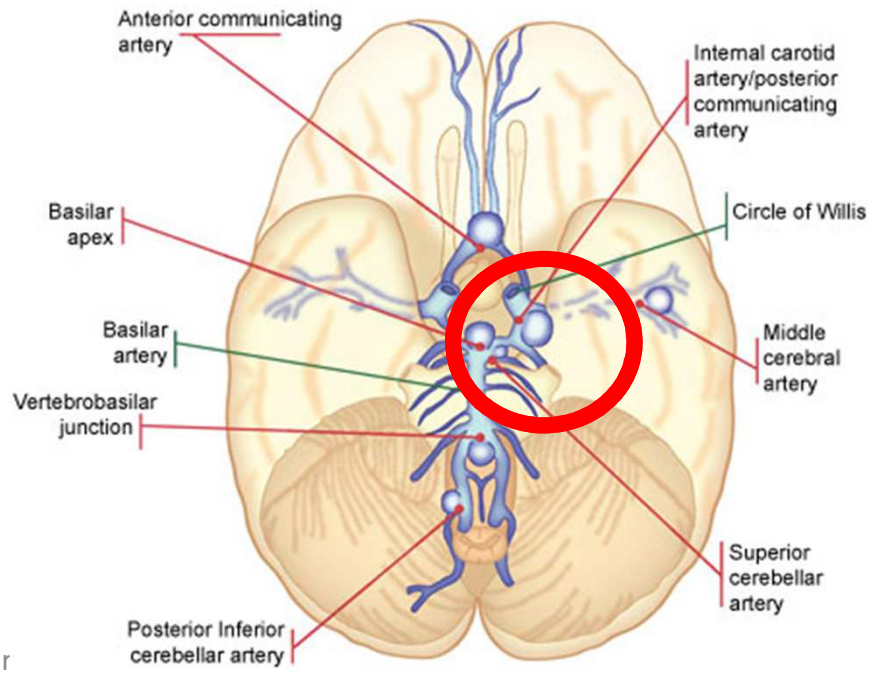
Posterior communicating artery

- Aneurysms present at the junction of the termination of the ICA and PCoA account for **23%** of cerebral aneurysms; they are directed laterally, posteriorly, and inferiorly.
- **III CN**, Pupillary dilatation, ophthalmoplegia, ptosis, and hemiparesis may result



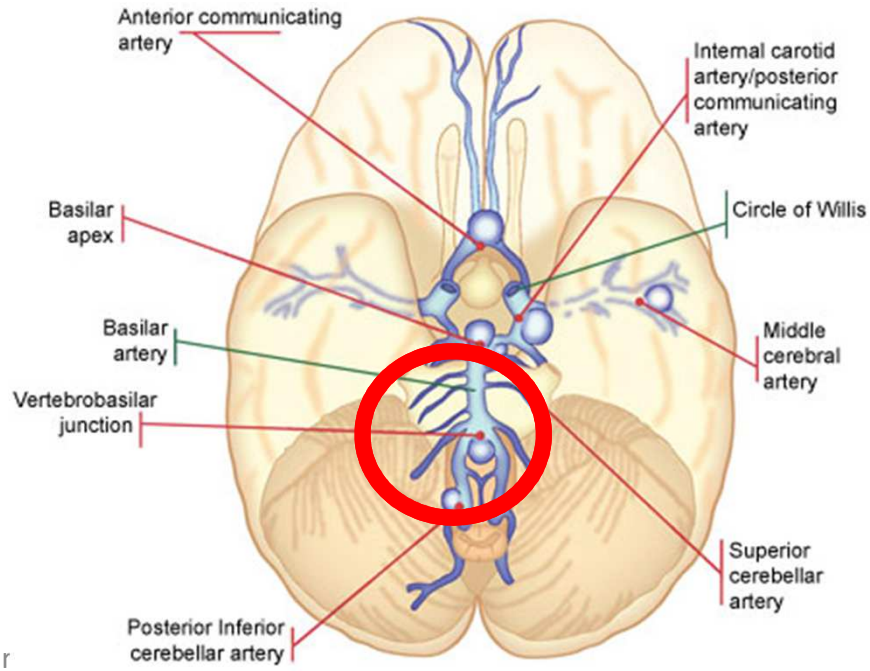
Internal carotid artery

- It accounts for about **4%** of all cerebral aneurysms
- Supraclinoid aneurysms may cause **III paresis** or variable **visual defects** and **optic atrophy** due to compression of the optic nerve
- Chiasmal compression may produce **bilateral temporal hemianopsia**, Hypopituitarism or anosmia may with giant aneurysms.
- **Cavernous-carotid** aneurysms ophthalmoplegia and trigeminal sensory loss.
- Rupture produces a carotid-cavernous fistula, SAH, or epistaxis.



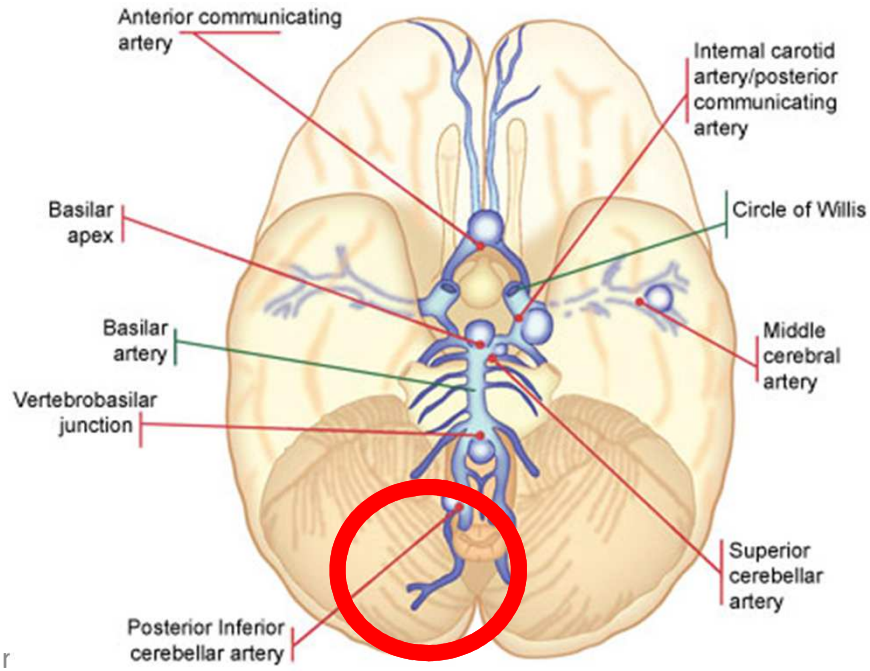
Basilar artery

- Basilar tip aneurysms the most common in the posterior circulation, accounting for **5%** of all aneurysms.
- Clinical associated with SAH, although bitemporal hemianopsia or an oculomotor palsy may occur.
- Dolichoectatic aneurysms may cause bulbar dysfunction, respiratory difficulties,
  or neurogenic pulmonary edema.



Vertebral artery or posterior inferior cerebellar artery

- Typically result in **ataxia**, **bulbar** dysfunction, or **spinal involvement.**



Clinical presentation

- Unruptured intracranial aneurysms may be **incidental findings**
- **Compressions**
  - middle cerebral artery aneurysms causing hemiparesis, visual field defect, or seizure
  - anterior communicating artery usually silent. Suprachiasmatic pressure may cause altitudinal visual field deficits, abulia or akinetic mutism, amnestic syndromes, or hypothalamic dysfunction.
  - posterior communicating artery or basilar artery aneurysms causing third cranial nerve palsy,
  - cavernous sinus aneurysms causing a cavernous sinus syndrome
  - basilar distribution aneurysms causing compression of the brainstem
- **Transient ischemic attack** or **cerebral infarction** due to distal embolisation
- **SAH**

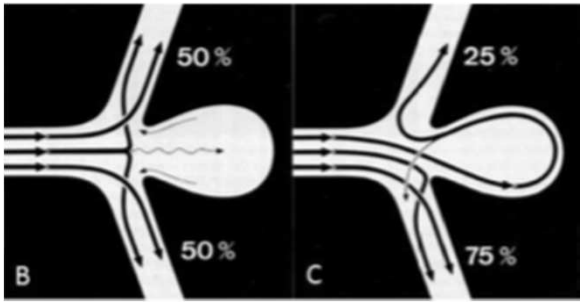
Unruptured Intracranial Aneurysms

Contemporary Data and Management

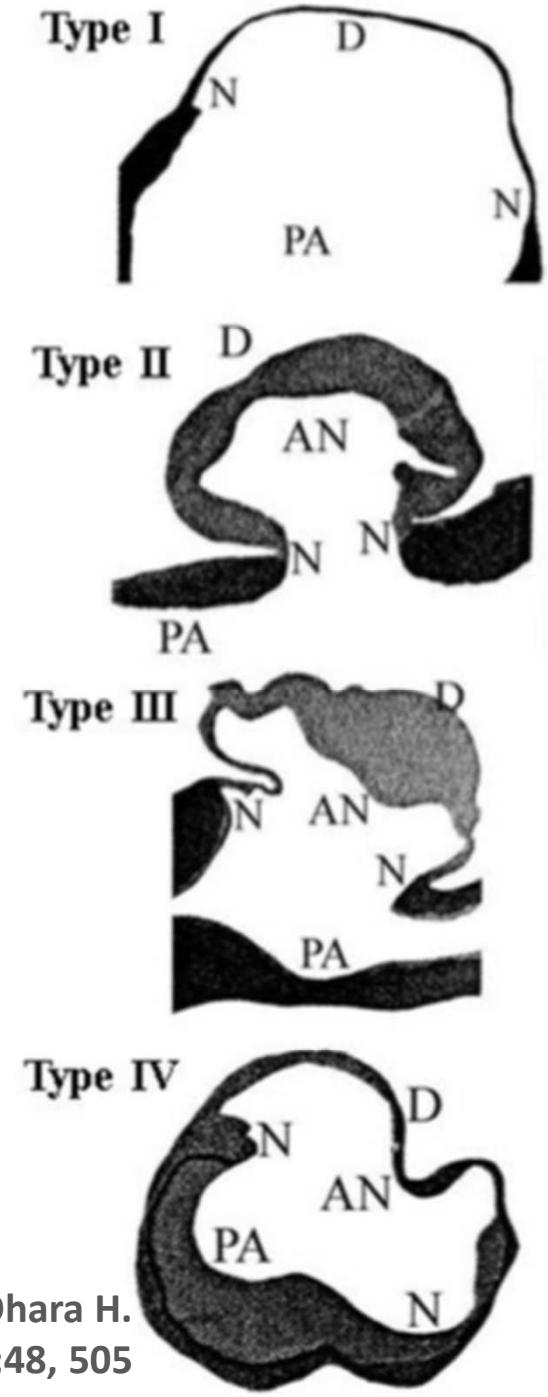
Katharina A.M. Hackenberg, Daniel Hänggi, and Nima Etminan

Originally published 9 Aug 2018 | Stroke. 2018;49:2268–2275

- **Muscular defects of the tunica media** and minimal support of adjacent brain parenchyma augment the pathologic potential of **chronic hemodynamic stress on the arterial wall.**
- **Focal turbulence** and **discontinuity of the normal architecture at vessel bifurcations** may account for the propensity of saccular aneurysm formation at these locations
- Distal aneurysms may be smaller, the risk of rupture may be dissimilar due to the relatively thinner wall thickness

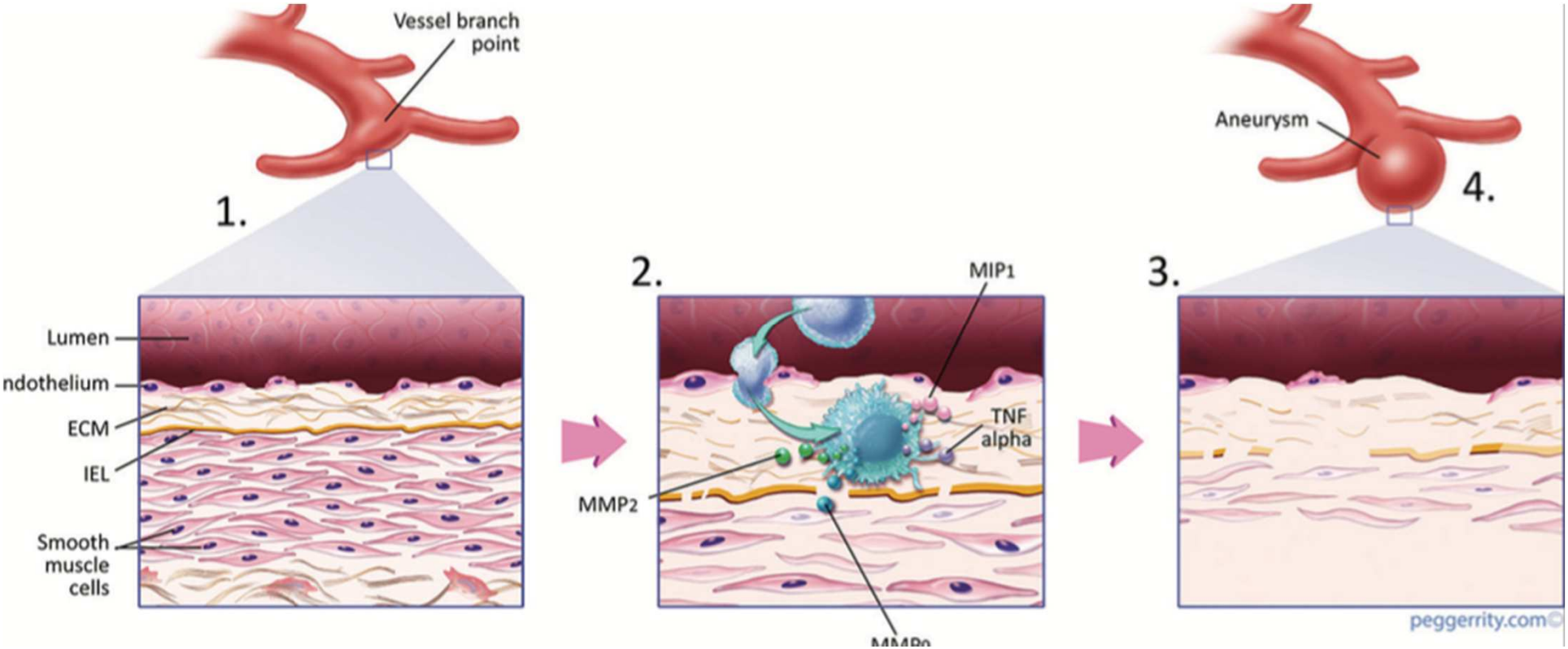


Steiger
1987



Suzuki J and Ohara H.
J. Neurosurg, 1978;48, 505

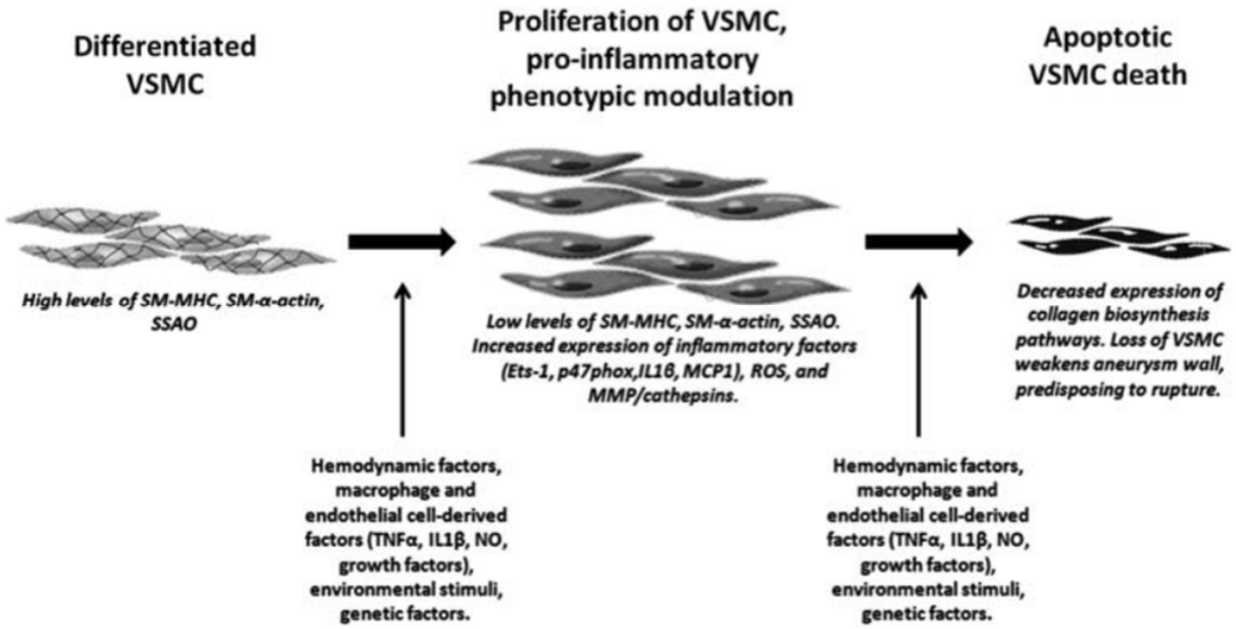
- **Several mechanosensors**→ ion channels, integrins, cell adhesion molecules, G-protein-coupled receptors, have been identified at the apical and basal surfaces of the endothelium --> to **identify variations** in **wall shear stress and adapt lumen diameter**
- activation of **inflammatory mediators**, such as the master regulator of inflammation, nuclear factor-kappaB (NF-κB)
- **Mechanical stressors** can **denude the endothelium**, triggering the expression of chemoattractants, pro-inflammatory cytokines



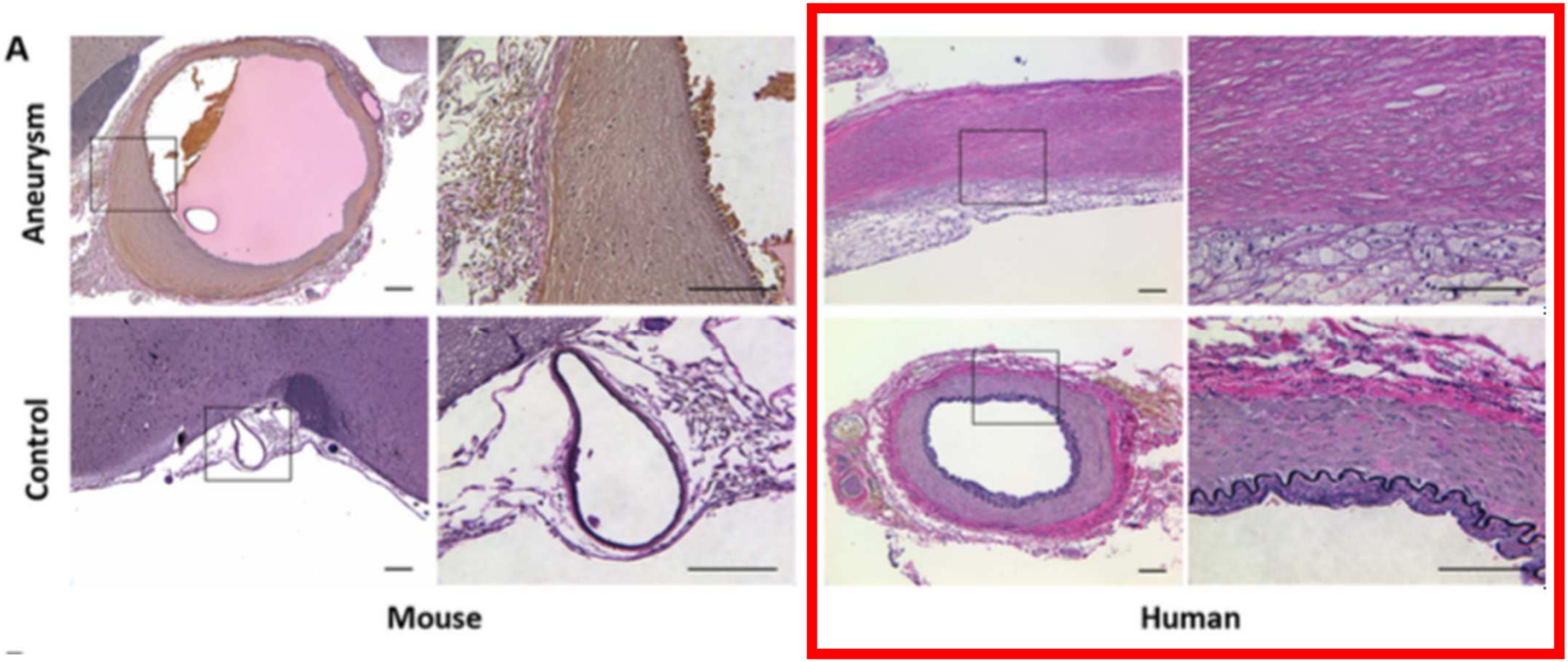
Biology of intracranial aneurysms: role of inflammation

Nohra Chalouhi[1], Muhammad S Ali[1], Pascal M Jabbour[1], Stavropoula I Tjoumakaris[1], L Fernando Gonzalez[1], Robert H Rosenwasser[1], Walter J Koch[2] and Aaron S Dumont[1]

- It has been hypothesized that IA begins with a **hemodynamically induced endothelial dysfunction** followed by the development of an **inflammatory reaction** and **Vascular smooth muscle** cells **phenotypic modulation** in the arterial wall that ultimately leads to proteolysis and **extracellular matrix degradation** via matrix **metalloproteinases** (MMPs) and **apoptosis** playing major roles, with concomitant vessel wall inflammation



Journal of Cerebral Blood Flow & Metabolism (2012) 32, 1659



- Light microscopic images of murine and human intracranial aneurysm and control artery with elastic Van Gieson staining→ **destruction of elastic lamina in both murine and human aneurysms (**dark blue to black)

Hosaka K, et al. J NeuroIntervent Surg 2014;6:474

Plasma Soluble Human Elastin Fragments as an Intra-Aneurysmal Localized Biomarker for Ruptured Intracranial Aneurysm

Daichi Nakagawa, MD, PhD; Mario Zanaty, MD; Joseph Hudson, BA; Nahom Teferi, MD; Daizo Ishii, MD; Lauren Allan, DO; Pascal Jabbour, MD; Santiago Ortega-Gutierrez, MD, MS; Edgar A. Samaniego, MD; David M. Hasan, MD

Elastin Fragment Level in Human Cerebral Aneurysms *Nakagawa et al*

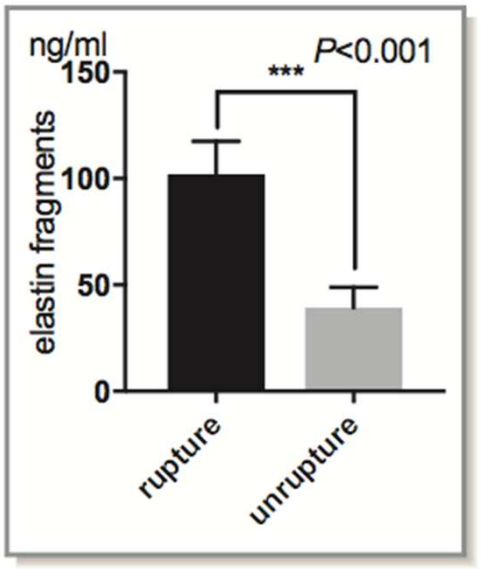
Clinical Perspective

What Is New?

- A significantly higher concentration of soluble elastin fragment was observed in the lumen of ruptured intracranial aneurysms when compared with nonruptured ones.

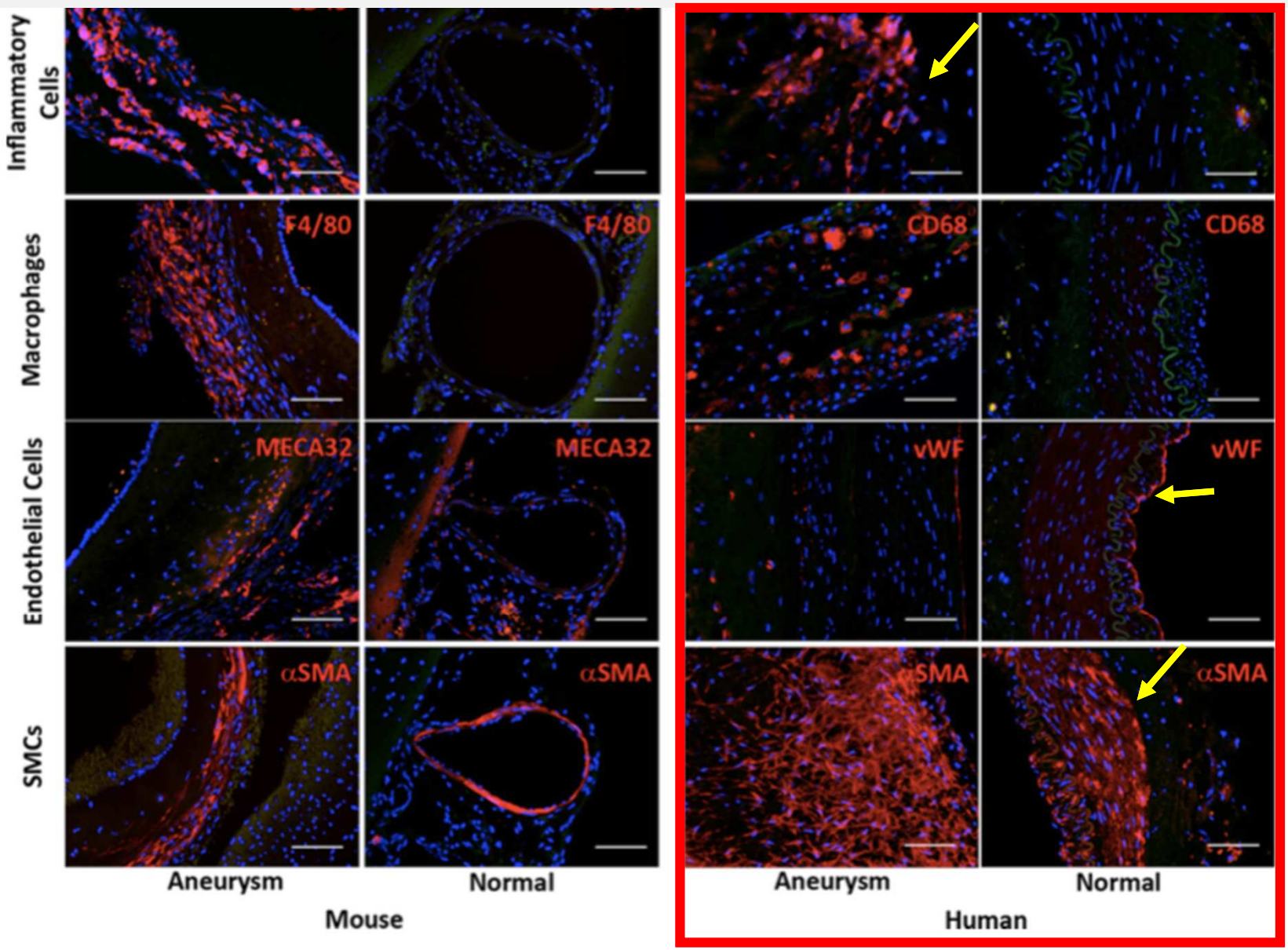
What Are the Clinical Implications?

- The results of our study suggest a pathophysiological scenario where a gradual increase in elastin degradation renders the aneurysm unstable, thus precipitating rupture.

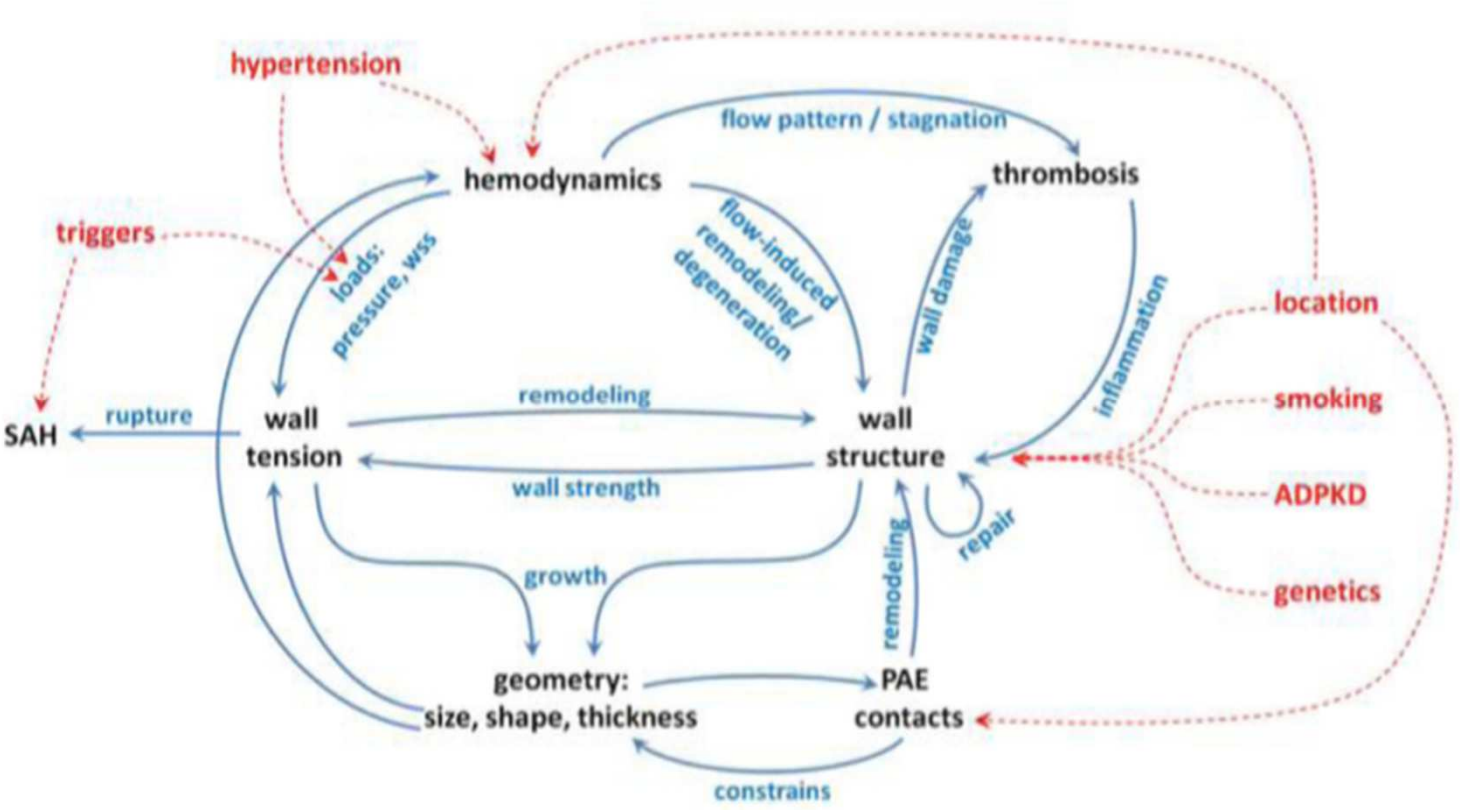


Journal of the American Heart Association 2018

Infiltration of inflammatory (CD45 (red) positive) cells and macrophages (F4/80 (red) positive cells) into the murine and human aneurysm, absence in ctrl
Destruction of intimal endothelial (MECA32 (red) positive) cells and thickening of the smooth muscle (αSMA (red) positive) cell layer in aneurysm wall.



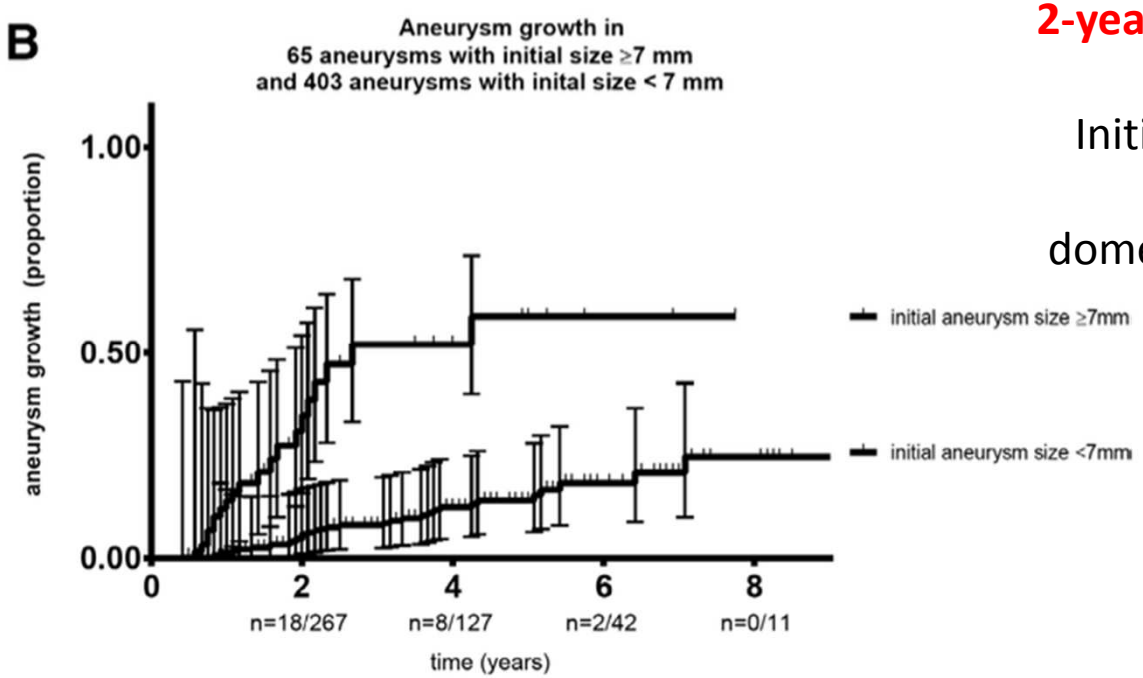
- There is a **cycle of wall degeneration and weakening** in response to changing hemodynamic loading and biomechanic stress
- This progressive **wall degradation** drives the **geometrical evolution** of the aneurysm **until it stabilizes or ruptures**
- **Risk factors** such as location, genetics, smoking, co-morbidities, and hypertension seem to **affect different components of this cycle**



Ann Biomed Eng. 2014

Aneurysm growth

- Risk of aneurysm growth over a **4-year period** (Burns JD et al Stroke 2009;40:406–411)
- UA < 8 mm→ 6.9%
- UA 8–12 mm→ 25%
- UA greater than 12 mm→ 83%
- middle cerebral artery location
- presence of more than one aneurysm



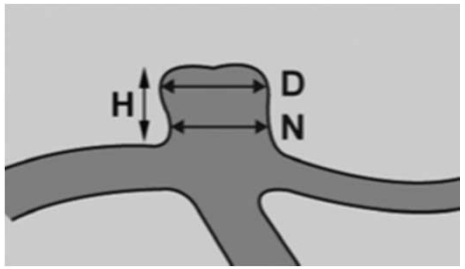
2-year period *Risk factors for growth in:*

1) All aneurysms

Initial aneurysm size, dome/ neck ratio

2) Small aneurysms

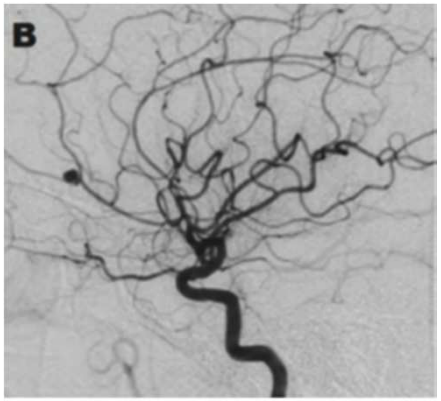
dome/neck ratio, multilobarity, smoking

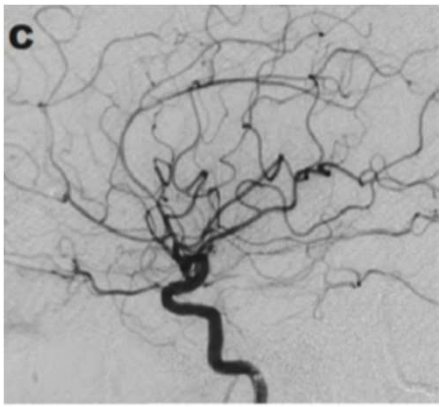


***Bor ASE. Stroke*. 2015;46:42**

Case Report

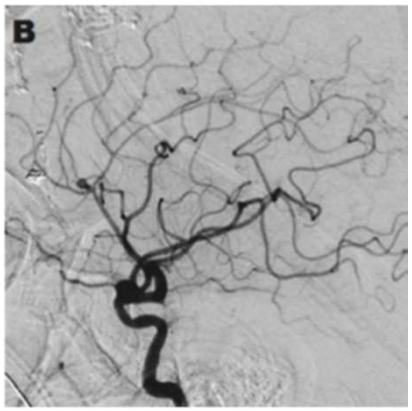
Impact of Methamphetamine Abuse: A Rare Case of Rapid Cerebral Aneurysm Growth with Review of Literature





A) Left distal AC artery aneurysm

B) After coiling



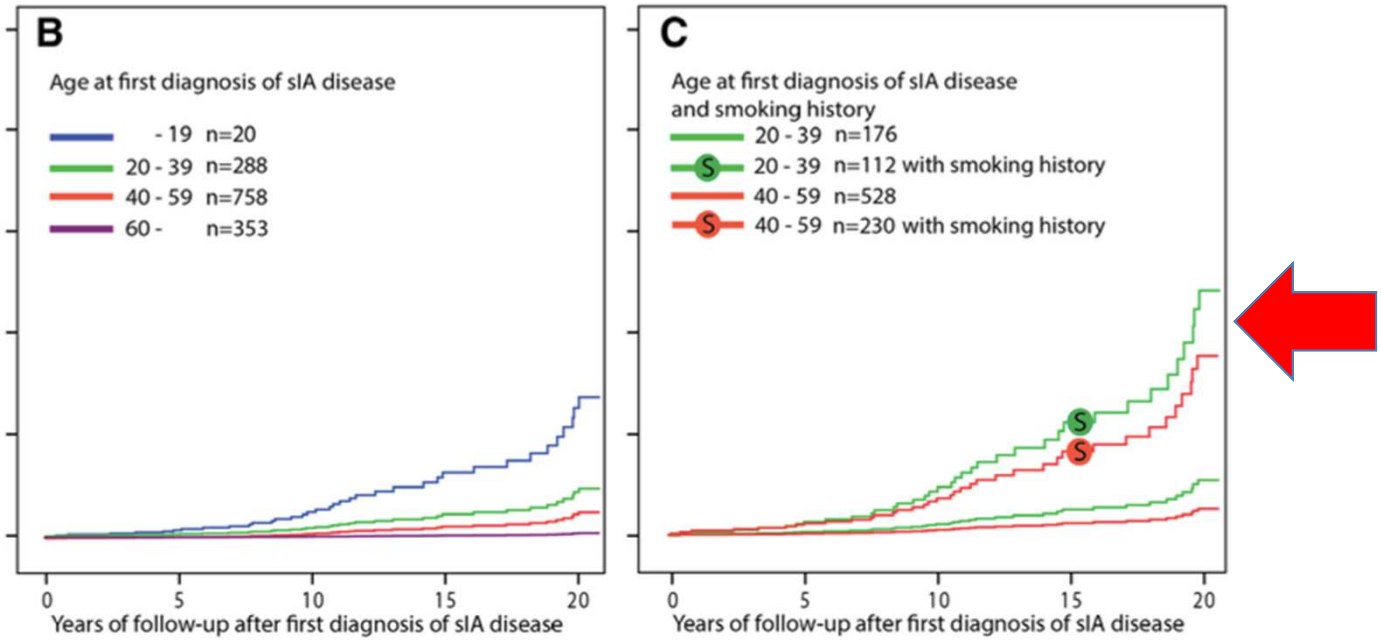
B) **Less than 3 wks** from previous saccular aneurysm at the **callosomarginal** and **pericallosal** bifurcation

Fowler J et al.
Case Reports in Neurol Med 2018

De Novo Aneurysm Formation in Carriers of Saccular Intracranial Aneurysm Disease in Eastern Finland

Antti E. Lindgren, MD, PhD*; Sari Räisänen, BM*; Joel Björkman, BM; Hanna Tattari, BM; Jukka Huttunen, MD; Terhi Huttunen, MD, PhD; Mitja I. Kurki, PhD; Juhana Frösen, MD, PhD; Timo Koivisto, MD, PhD; Juha E. Jääskeläinen, MD, PhD†; Mikael von und zu Fraunberg, MD, PhD†

- The cumulative incidence of **de novo sIAs was 0.23%** per patient-year
- Significant: Smoking history and younger age at the first sIA diagnosis
- Pts <40 years at the first sIA should be scheduled for long-term AGF follow-up



***Stroke*. 2016;47:1213**

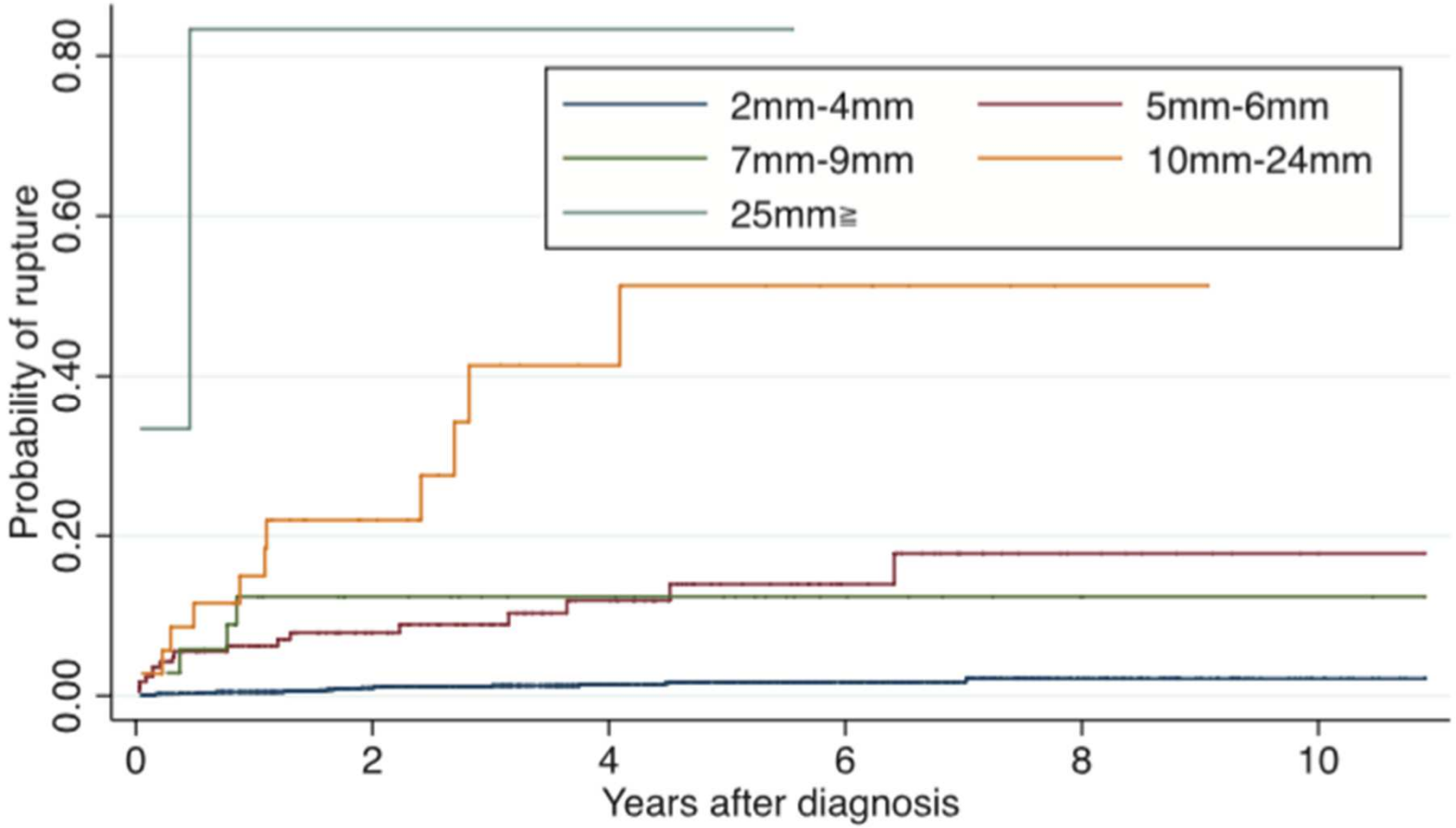
International Study of Unruptured Intracranial Aneurysms (ISUIA)

- Prospective cohort study that followed 1,692 patients with UA, **2mm or larger** 1,077 without prior history of SAH→ **5 yrs** cumulative risk of rupture
- **Annual aneurysmal rupture risk of 0.7-1%**
- **Two important factors** in predicting risk of rupture

1. **Size**→larger aneurysms (7mm or larger.)= greatest risk;
2. **Location**→location on the anterior or posterior communicating artery and presence of a daughter sac

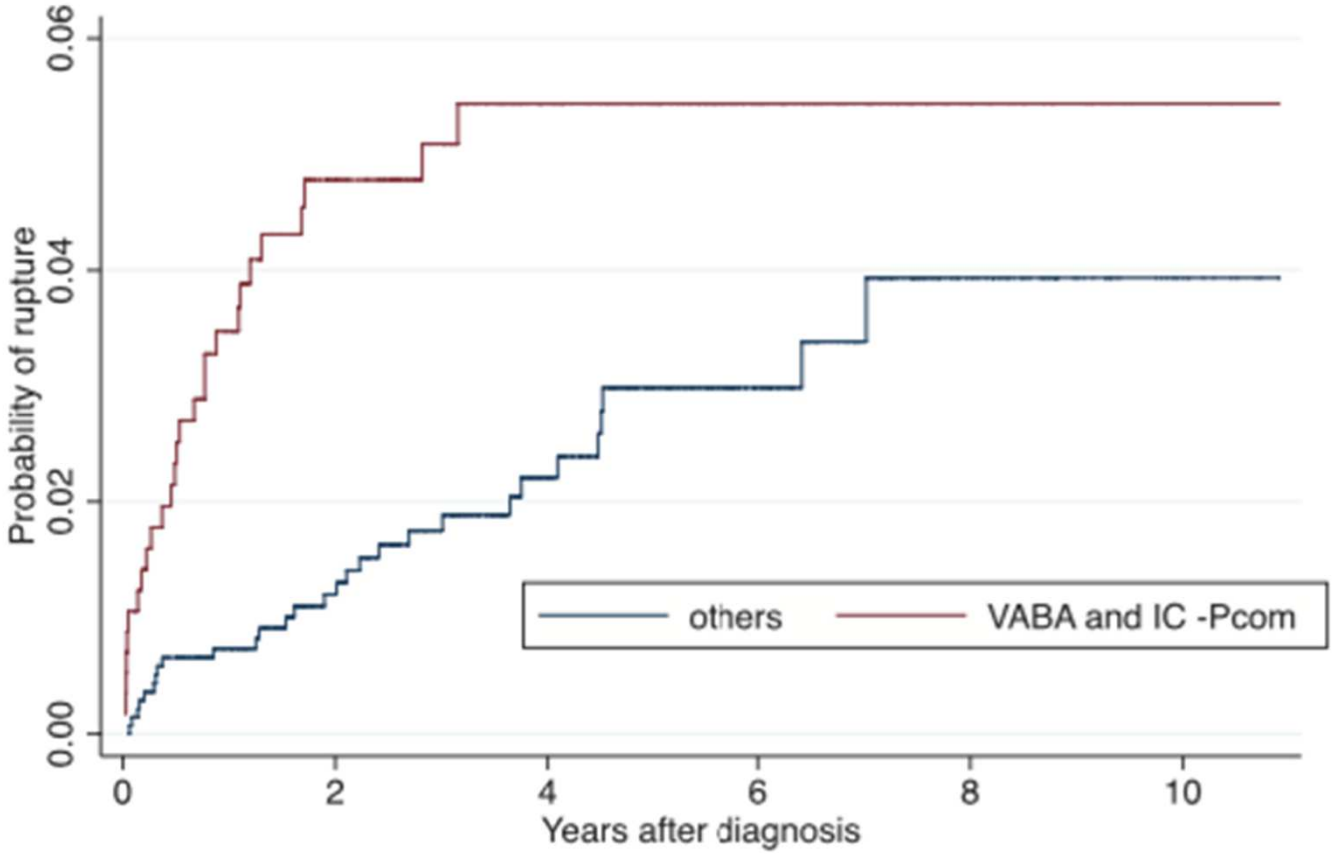
- **Irregular** multilobular, non-spherical shapes (oval, oblong and multilobulated) were found to be associated with rupture
- **Patient factors**: younger than 50 yrs, hypertension, multiple aneurysms
- Aneurysms presenting with subarachnoid hemorrhage tend to **bleed again** at a rate of **9% within the first 72 hours** after the initial episode
- **Aspirin**: the rate was higher among those not taking aspirin (40%) than among those taking aspirin (28%)

Size



Yuichi Murayama et al 2015

Site



C-pcom= internal carotid- posterior communicating artery
VABA= vertebral - basilar artery

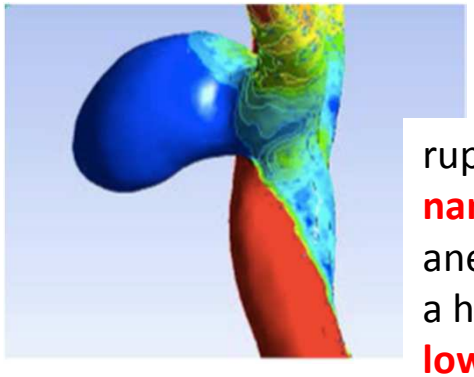
Yuichi Murayama et al 2015

Association between hemodynamics, morphology, and rupture risk of intracranial aneurysms: a computational fluid modeling study

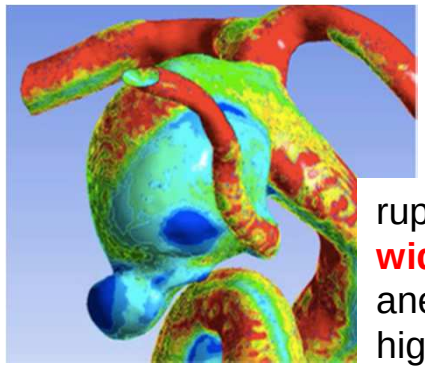
Tianlun Qiu[1] · Guoliang Jin[1] · Haiyan Xing[2] · Haitao Lu[3]

Neurol Sci (2017) 38:1009

- There are many contradictory results in the literature.
- **Low WSS** and high oscillatory shear index trigger an inflammatory cell-mediated pathway that could be associated with the growth and rupture of large, atherosclerotic aneurysms,
- **High WSS** combined with a positive WSS gradient triggers a mural cell-mediated pathway that could be associated with the growth and rupture of small or secondary bleb aneurysm



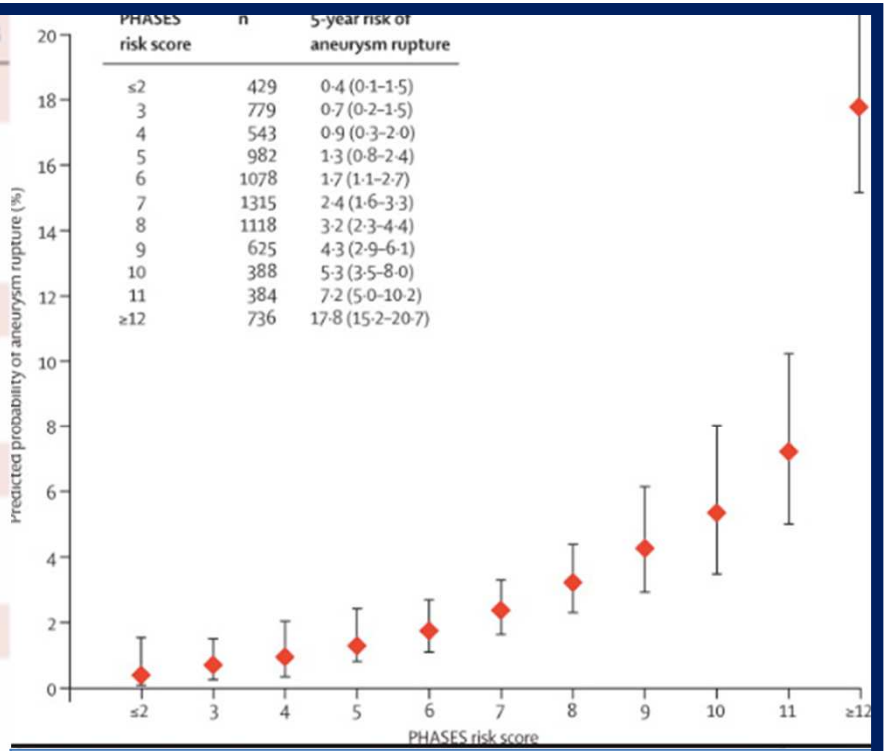
ruptured and **narrow-neck** aneurysm with a high ratio of **low WSS** area



ruptured and **wide-neck** aneurysm with a high ratio of **low or highest WSS** area

PHASES aneurysm risk score	Points
(P) Population	
North American, European (other than Finnish)	0
Japanese	3
Finnish	5
(H) Hypertension	
No	0
Yes	1
(A) Age	
<70 years	0
≥70 years	1
(S) Size of aneurysm	
<7·0 mm	0
7·0–9·9 mm	3
10·0–19·9 mm	6
≥20 mm	10
(E) Earlier SAH from another aneurysm	
No	0
Yes	1
(S) Site of aneurysm	
ICA	0
MCA	2
ACA/Pcom/posterior	4

PHASES risk score	n	5-year risk of aneurysm rupture
≤2	429	0·4 (0·1–1·5)
3	779	0·7 (0·2–1·5)
4	543	0·9 (0·3–2·0)
5	982	1·3 (0·8–2·4)
6	1078	1·7 (1·1–2·7)
7	1315	2·4 (1·6–3·3)
8	1118	3·2 (2·3–4·4)
9	625	4·3 (2·9–6·1)
10	388	5·3 (3·5–8·0)
11	384	7·2 (5·0–10·2)
≥12	736	17·8 (15·2–20·7)



There is a progression of PHASES score between stable UIA, growing observed UIA, immediately treated UIA, and SAH groups. PHASES **score of ≤3** is associated with a **low but not negligible** likelihood of aneurysm rupture, and speciFIcity of the classiFIer is low

Bijlenga P. Et al, Stroke. 2017;48:2105

Risk of rupture of unruptured intracranial aneurysms

- The estimated incidence of aneurysmal SAH varies widely depending on **geographic location,** ranging from **3.9-19.4 per 100,000** individuals, with the highest reported rates in **Finland and Japan**, approximately **6-10/100,000 person-years** in USA

Table 1 - Five years cumulative rupture risk of unruptured intracranial aneurysms as reported by the ISUIA study group [7].
Tableau 1 Risque cumulatif de rupture à 5 ans des anévrysmes intracrâniens non rompus rapporté dans l'étude ISUIA [7].

Size	ACA/MCA/ICA (%)	Posterior communicating + posterior circulation (%)
< 7 mm no previous SAH	0 (confidence interval?)	2.5 (confidence interval?)
< 7 mm with previous SAH	1.5 (confidence interval?)	3.4 (confidence interval?)
7–12 mm	2.6 (confidence interval?)	14.5 (confidence interval?)
13–24 mm	14.5 (confidence interval?)	18.4 (confidence interval?)
> 24 mm	40 (confidence interval?)	50 (confidence interval?)

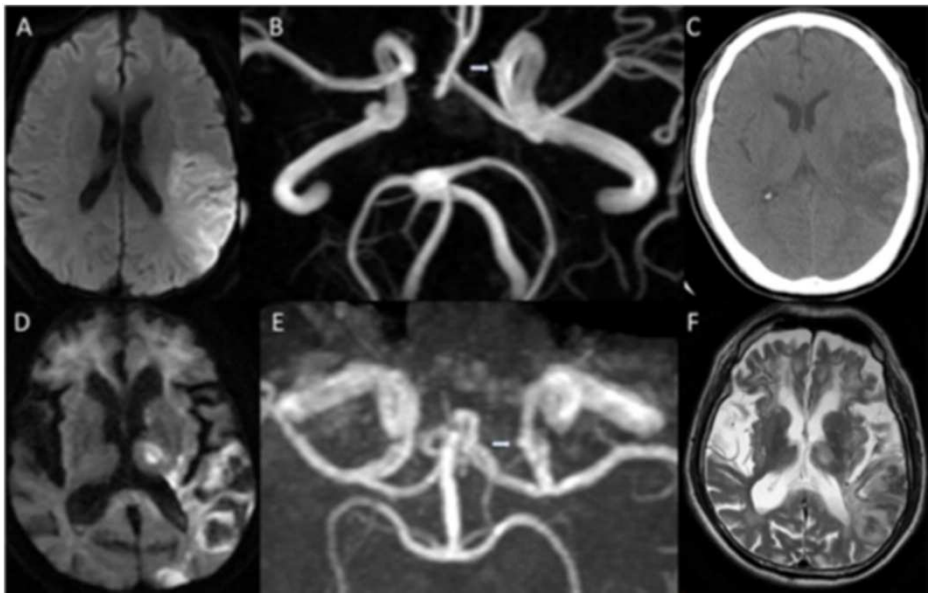
Wermer et al Stroke 2007; Juvela et al 2013

Author, year	Country	Sample size	Moon phase								p-value
			New moon	Waxing crescent	First quarter	Waxing gibbous	Full moon	Waning gibbous	Last quarter	Waning crescent	
		Number of patients (n)									
Present study	Lithuania	186	23	20	29	31	25	25	23	10	0.092
Ali et al., 2008	Lebanon	111	28*	7	16	11	18	7	15	9	**0.001**
Lahner et al., 2008	Austria	717	78	89	94	92	90	85	88	101	0.84
Kamp et al., 2013	Germany	655	87	87	83	76	79	87	78	78	0.971
Total, number		1669	216	203	222	210	212	204	204	198	0.955

The risk of intravenous thrombolysis-induced intracranial hemorrhage in Taiwanese patients with unruptured intracranial aneurysm

Wei Ting Chiu[1,2,3☯], Chien Tai Hong[1,2,3☯], Nai Fang Chi[1,2,3], Chaur Jong Hu[1,2,3], Han Hwa Hu[1,2,3], Lung Chan[1,2,3*]

- Administering **r-tPA** to patients with a **pre-existing aneurysm does not increase the bleeding risk**
- Asians are known to have a relatively higher bleeding risk, and little evidence is available regarding the risk of using r-tPA on Asian patients with intracranial aneurysms



2017

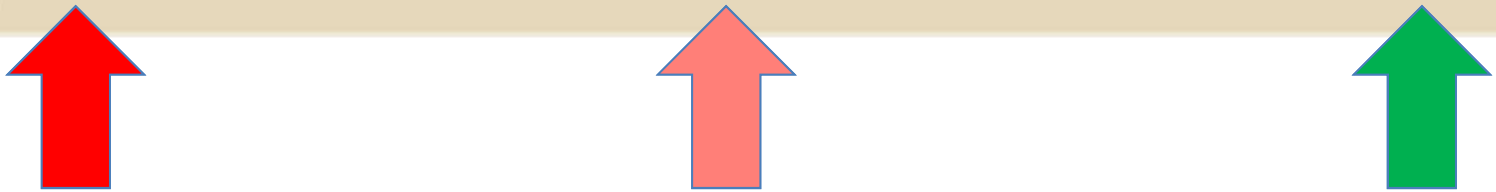
Size of Ruptured Intracranial Aneurysm — **Is Epidemiology Really Changing?**

- Novel epidemiologic trend in Finnish population suggesting a decrease in size of ruptured intracranial aneurysms over the past two decades (2660 patients from January 1989 to December 2008)
- Anterior circulation ruptured intracranial aneurysms accounted for 91% (MCA 33%, ACoA 32%, PCoA 14%, pericallosal A 5%)
- The **trend of increase in treatment rates** of UA is disproportionate to the rate of increase in population size (especially in developed countries). Larger UA are more likely to be symptomatic and more frequently treated.
- The **changes of treatment trends** could be an important factor determining average size of ruptured intracranial aneurysms presenting to hospitals.

Korja M et al Stroke 2018

RECOMMENDATION FOR SCREENING

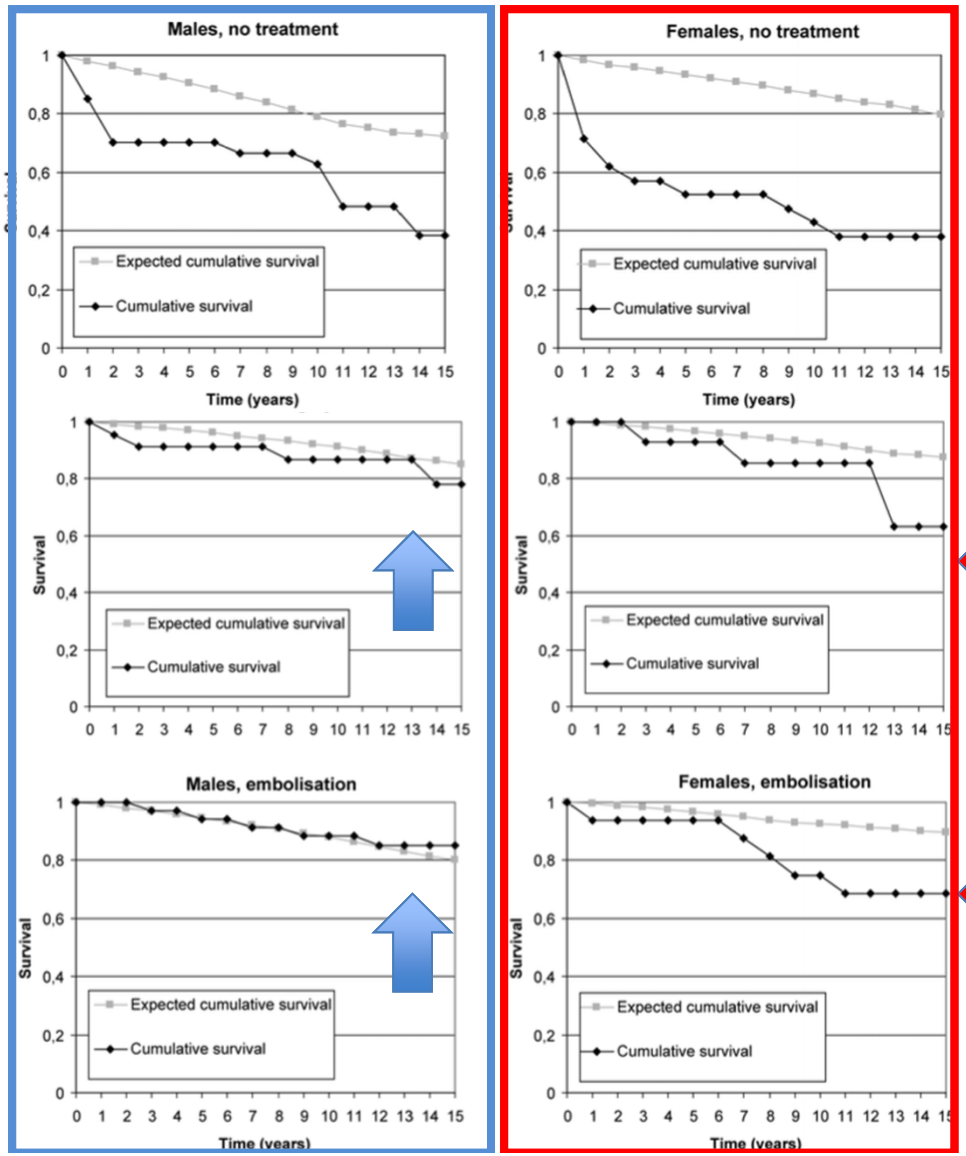
Recommendations for screening		
Strongly consider screening	**Possibly consider screening**	**Do not recommend screening**
• Patients with 2 or more family members with history of UIA or SAH **(8% risk)**	• Patients with ADPKD without family history of aneurysm	• General population
• ADPKD with family history of UIA or SAH	• Patients with one family **(4% risk)** member with UIA or SAH (per patient preference)	
• Patients with coarctation of the aorta		



L.N. Williams, R.D. Brown, Jr., Neurology: Clinical Practice 2013

Long-term excess mortality of patients with treated and untreated unruptured intracranial aneurysms

Liisa Pyysalo,[1] Tapio Luostarinen,[2] Leo Keski-Nisula,[3] Juha Öhman[1]



- Pts with UA have 50% excess long-term mortality compared with general population
- **Men with treated UA have a survival proportion comparable with matched general population**.
- **Women have 28% excess mortality after surgical treatment and 23% excess mortality after endovascular treatment**
- The reason for this is unclear., cardiovascular risk increases with age more sharply in women than in men