Unruptured Cerebral Aneurysms

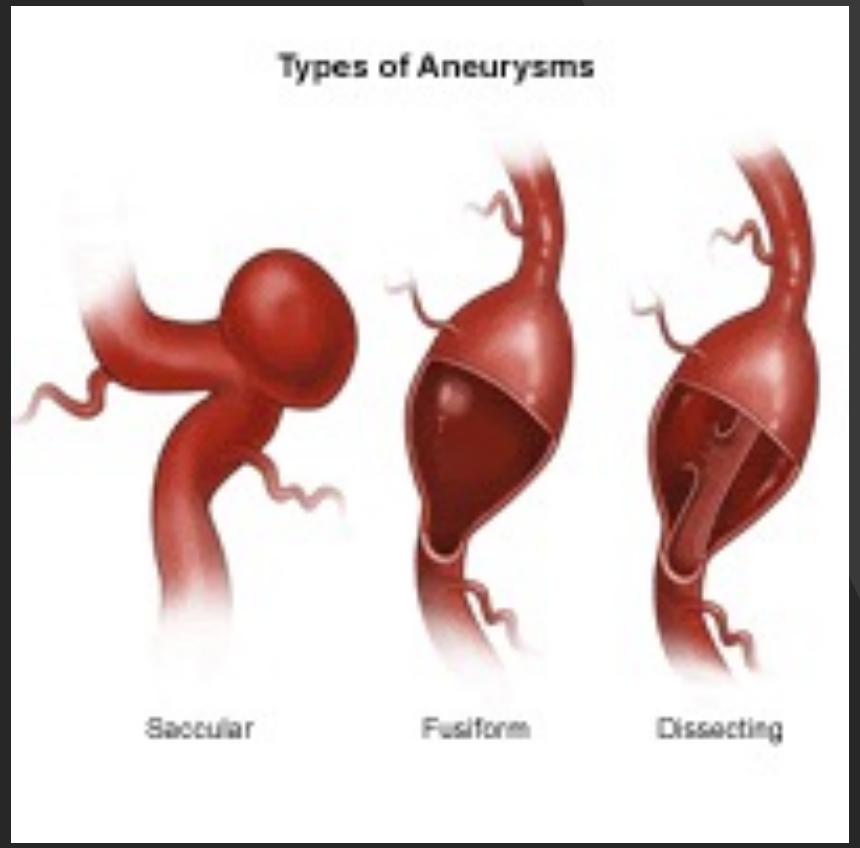
Objectives

- Epidemiology
- Pathophysiology
- Clinical manifestations
- Diagnosis
- Management

3 types of aneurysms

- **Saccular** (Berry): most aSAH
  - Thin/absent media, absent/fragmented internal elastic lamina
- Fusiform
  - dilation of entire arterial circumference
  - associated w/ atherosclerosis
- Mycotic
  - saccular or fusiform
  - distal branches of anterior circulation

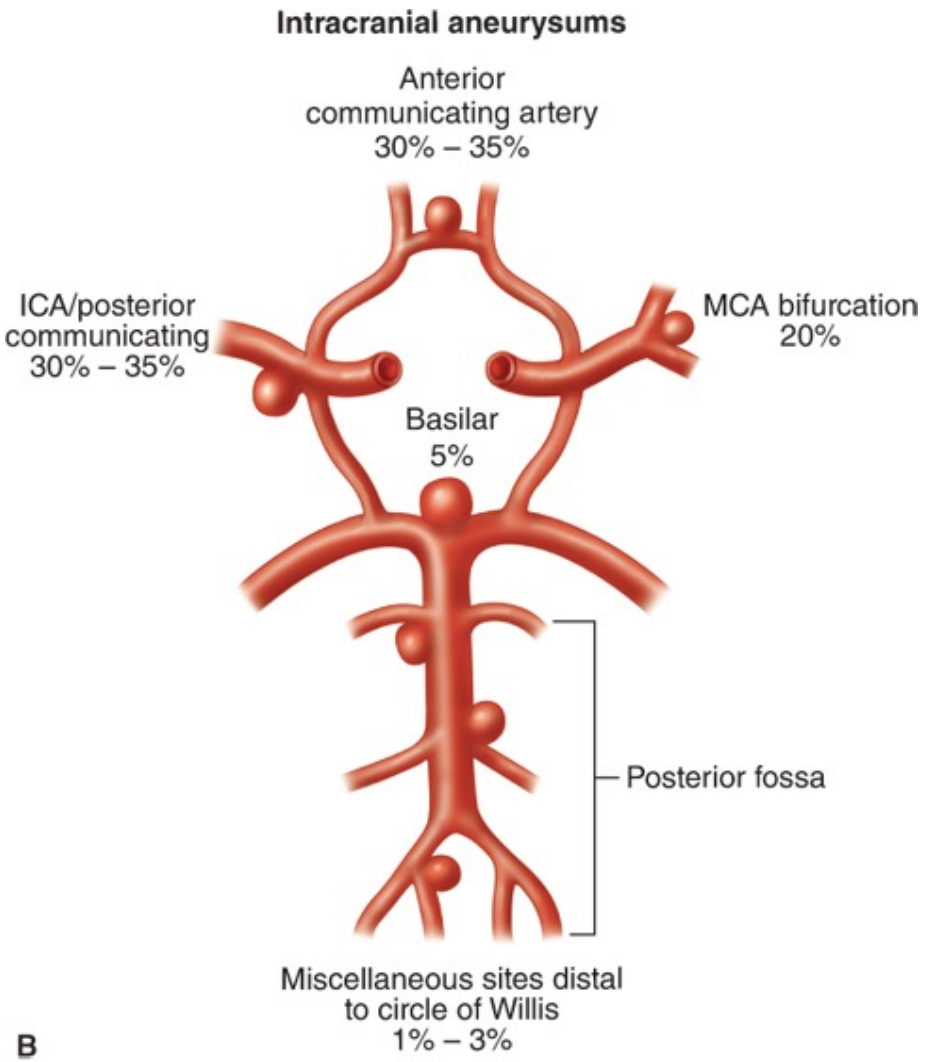
- * Pseudoaneurysm, Dissecting Aneurysm



Distribution

- Solitary: 70-75%
  - multiple: 20-30%

- Location
  - anterior circulation (85%)
  - arterial junctions / bifurcations of COW



Nat Rev Neurol. 2016;12(12):699.

Epidemiology

- Acquired
- Prevalence ~3%
  - 4070 healthy Japanese adults: 4.3%
- Mean age ~50 years
  - Most develop 4^{th}-6^{th} decades
- Prevalence ↑ F
  - <50 y: F=M
  - >50 y: ↑ F predominance 2:1
    - Estrogen deficiency
      - ↓ collagen content
- Genetic factors
  - CTD (Ehlers-Danlos), AD-PCKD (7x ↑ risk), Moyamoya
  - Family history in absence of (genetic) syndrome
  - SNPs: loci near elastin, endothelin receptor, HDAC9 genes

Table 1 | **Risk factors for aneurysm formation**

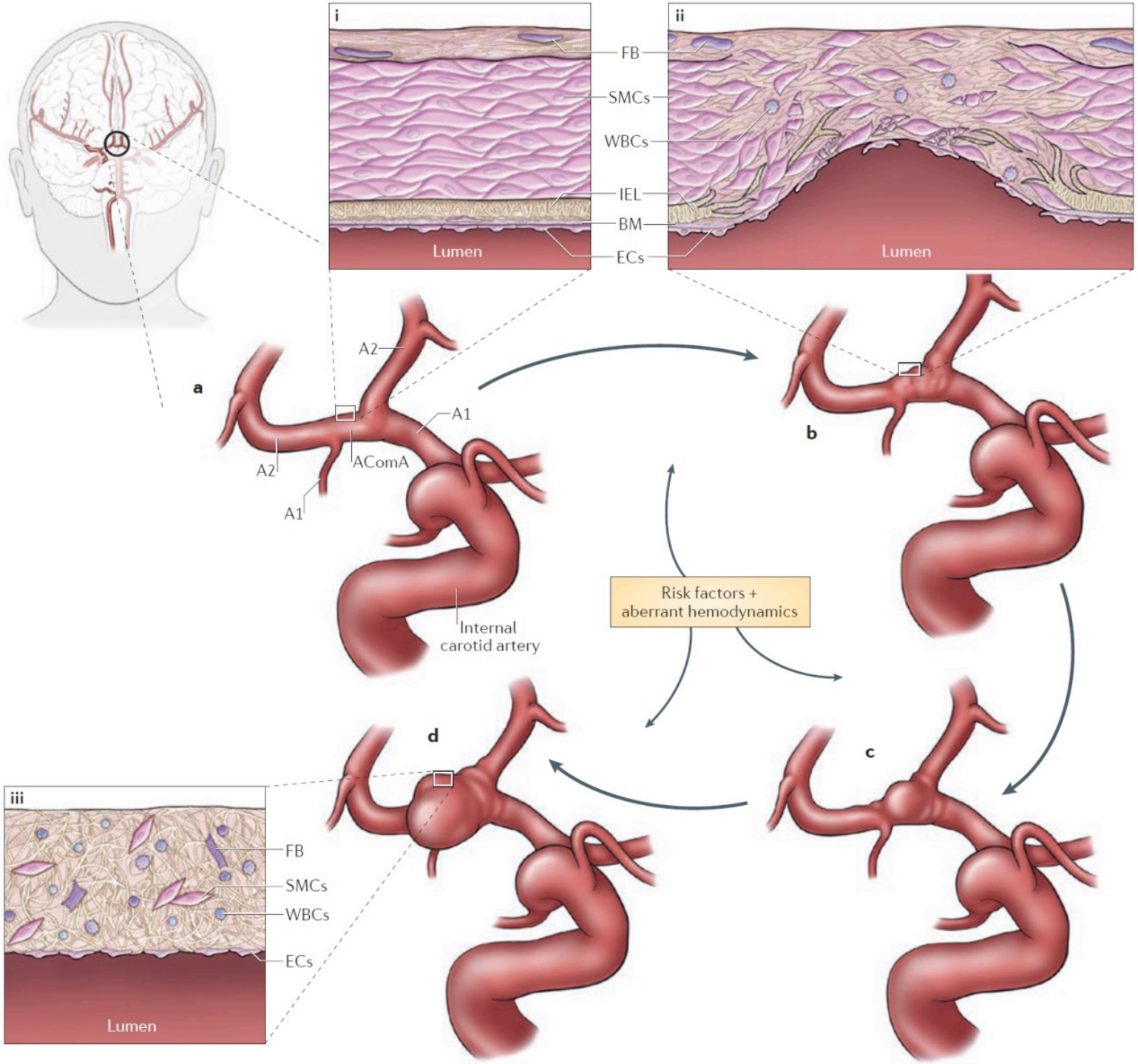
Risk factor	Increase in risk (95% CI in brackets)
Smoking	OR 4.07 (1.09–15.15)*‡
	OR 3.0 (2.0–4.5)§
	HR 3.8 (1.5–9.4)
	HR 5.61 (2.86–11.1)*
Hypertension	HR 2.3 (1.1–4.9)§
	OR 2.9 (1.9–4.6)*
Concomitant smoking and hypertension	OR 8.3 (4.5–15.2)
Family history for stroke other than SAH	OR 1.6 (1.0–2.5)*
Positive familial history for aneurysm	HR 2.7 (1.0–7.4)
Multiple aneurysms	HR 3.2 (1.2–8.6)§
Female sex	OR 4.73 (1.16–19.38)*‡

*Multivariate analysis. ‡Age-adjusted. §Aneurysm formation

Lancet Neurol. 2011;10(7):626.
Nat Rev Neurol. 2016;12(12):699.
J Neurosurg. 2018 Apr 6;130(2):573-578.

Pathophysiology

- Multifactorial
  - Hemodynamic stress
    - Hyperdynamic + turbulent flow → structural/degenerative vessel wall alterations
  - Endothelial dysfunction → Inflammation → ECM degradation
- Pathology
  - Discontinuous endothelium
  - Lack of internal elastic lamina
  - T cell + macrophage infiltration
  - Collagen (tensile strength)



Stroke. 2013 Dec;44(12):3613-22.
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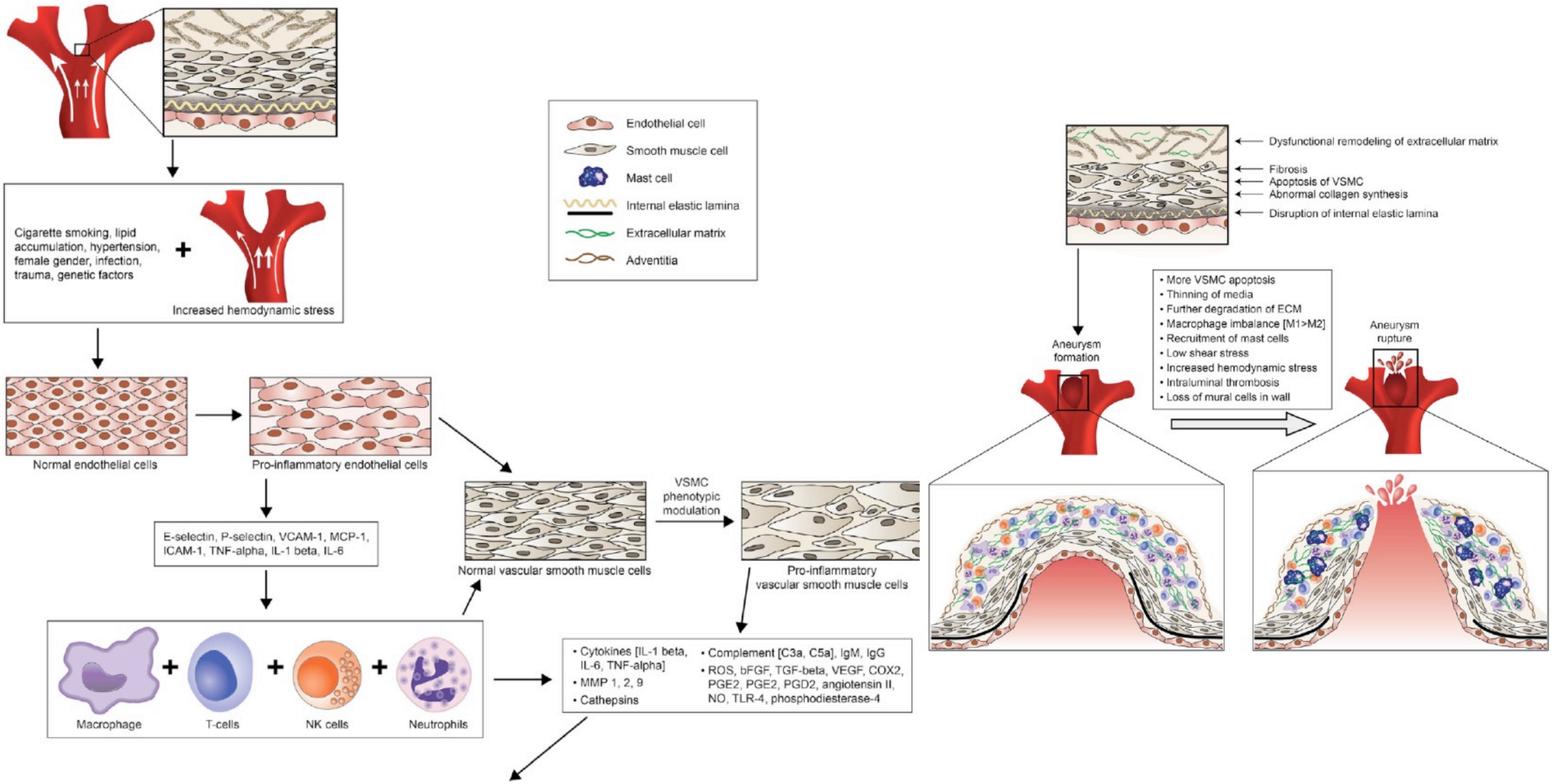


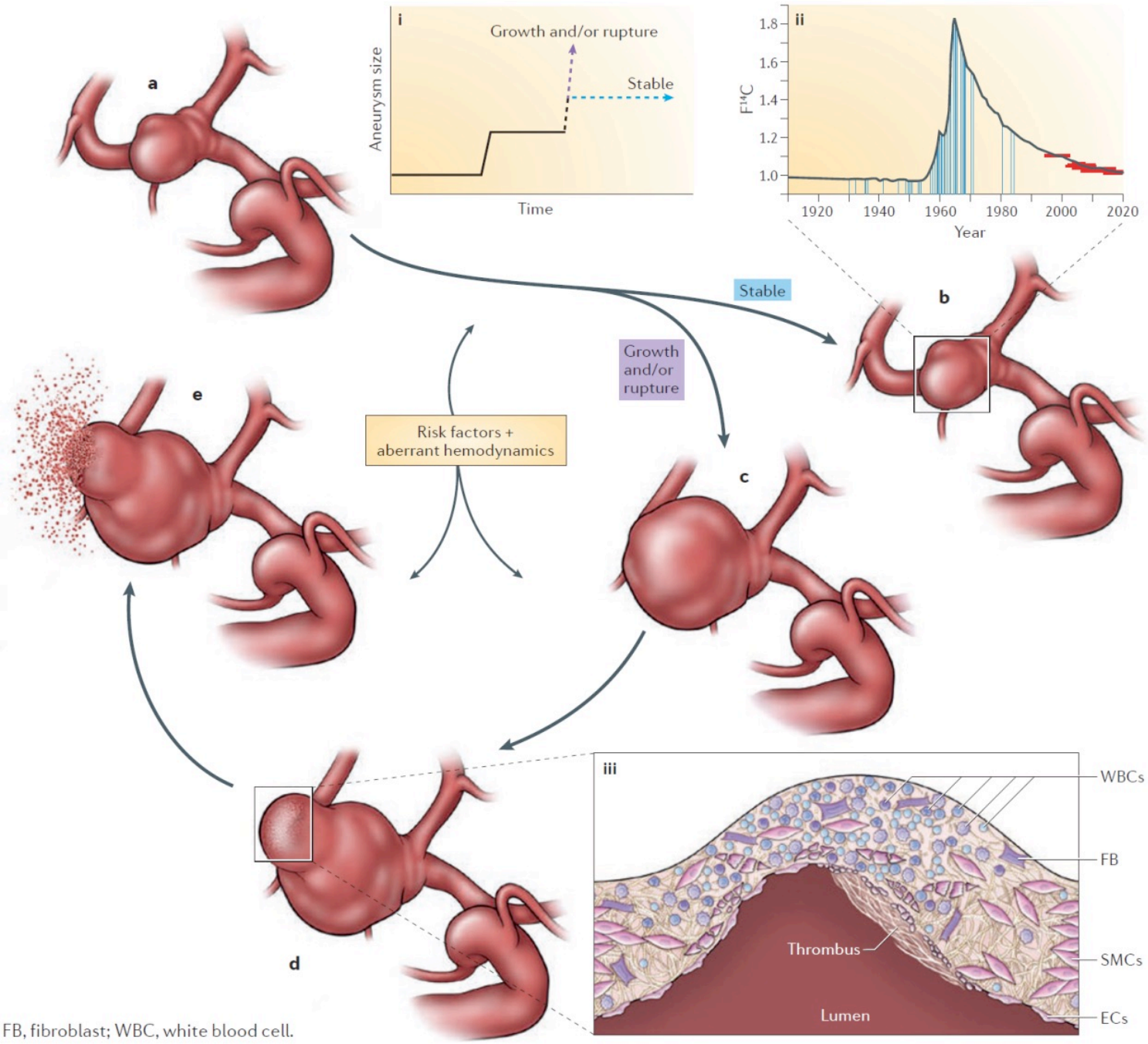
World Neurosurg. 2019;130:277–284.

Aneurysm Growth

Table 2 | **Risk factors for aneurysm growth**[19,24,59,88]

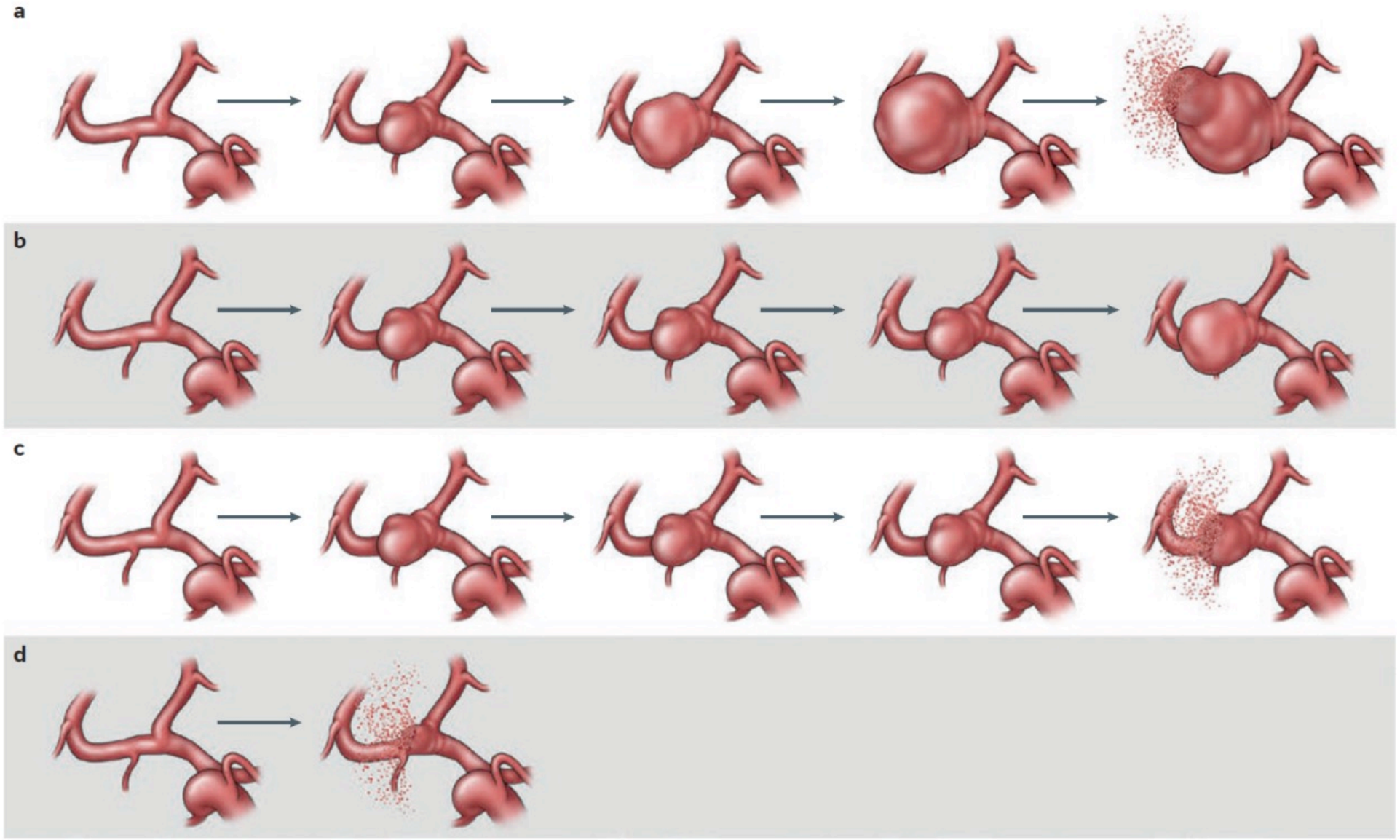
Risk factor	Risk ratio	95% CI
Smoking	2.2–3.9*	Not reported
Female sex	3.3	1.1–10
Hypertension	2.3	1.1–4.9
Initial aneurysm size	1.1‡	0.8–1.5
	2.56§	1.93–3.39
Multiple aneurysms	2.04	1.56–2.66
Multilobed aneurysm	2.9	1.0–8.5
Oblonged aneurysm	2.4	1.0–5.8
Posterior circulation	2.0	0.6–7.0

*Range over several studies. ‡Per mm increase in size.
§Compared with aneurysms </=4 mm.



FB, fibroblast; WBC, white blood cell.

Nat Rev Neurol. 2016;12(12):699.

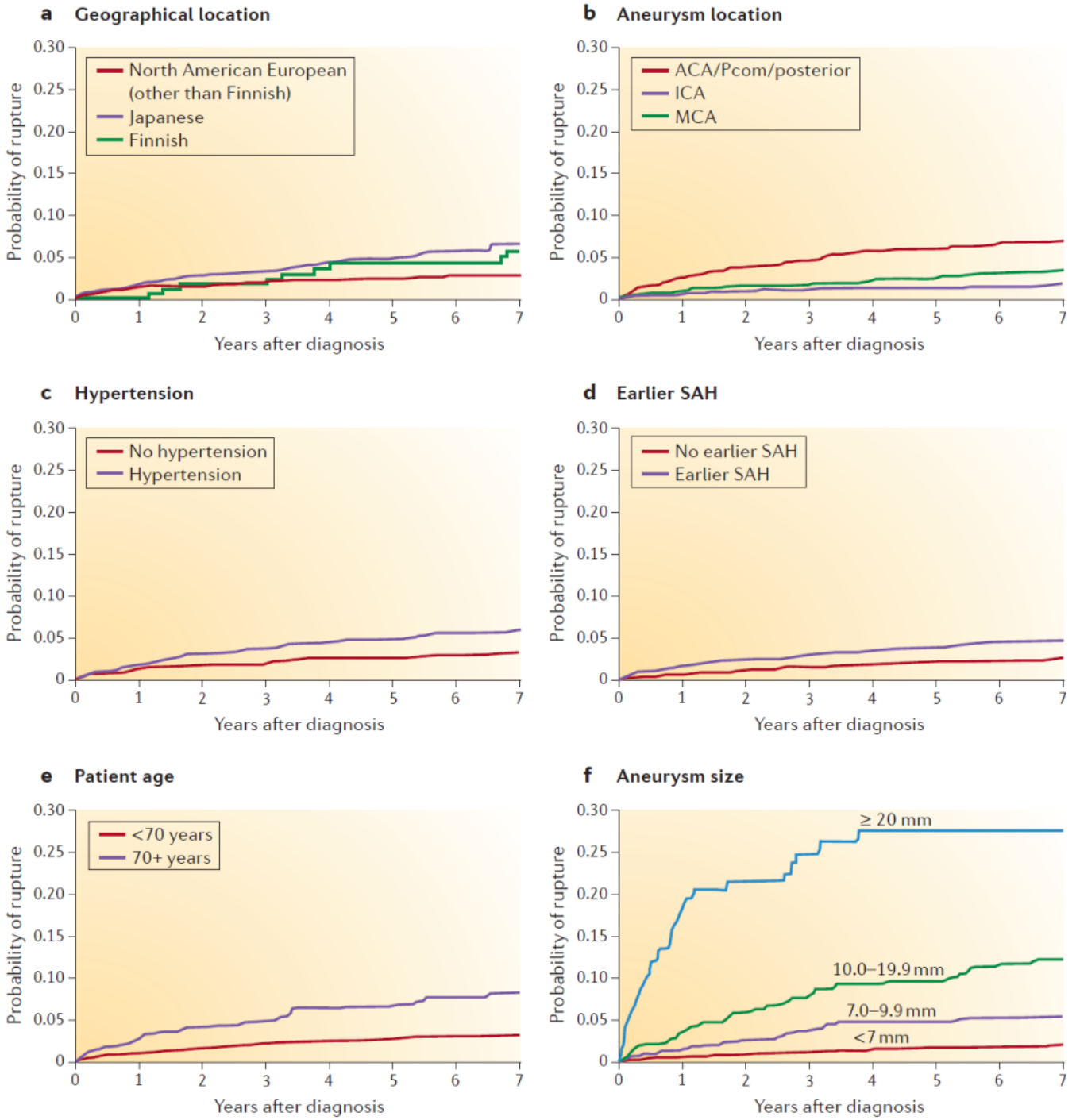


Nat Rev Neurol. 2016;12(12):699.

Aneurysm Rupture

- Cohort studies of asymptomatic, unruptured intracranial aneurysms
  - International Study of Unruptured Intracranial Aneurysms (ISUIA)
    - North America, Europe
  - Unruptured Cerebral Aneurysms Study (UCAS)
    - Japan
- Annual risk of rupture: 0.54-1.4%
  - ISUIA/UCAS: 0.95%
- Meta-analysis of 6 cohorts → PHASES score (rupture risk prediction model)

Nat Rev Neurol. 2016;12(12):699.



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

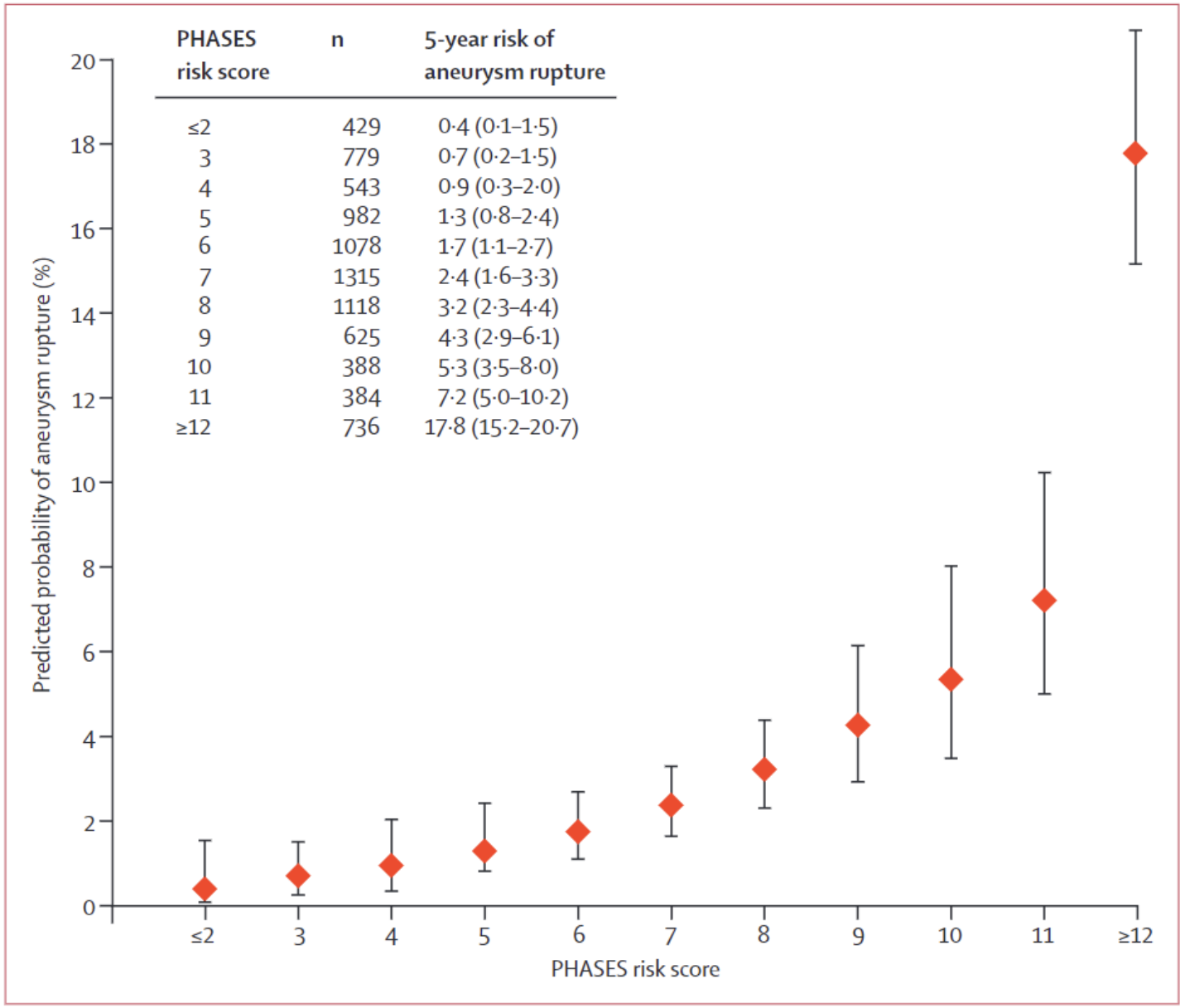


Figure 3: **Predicted 5-year risk of aneurysm rupture according to PHASES score**

Lancet Neurol. 2014;13(1):59.

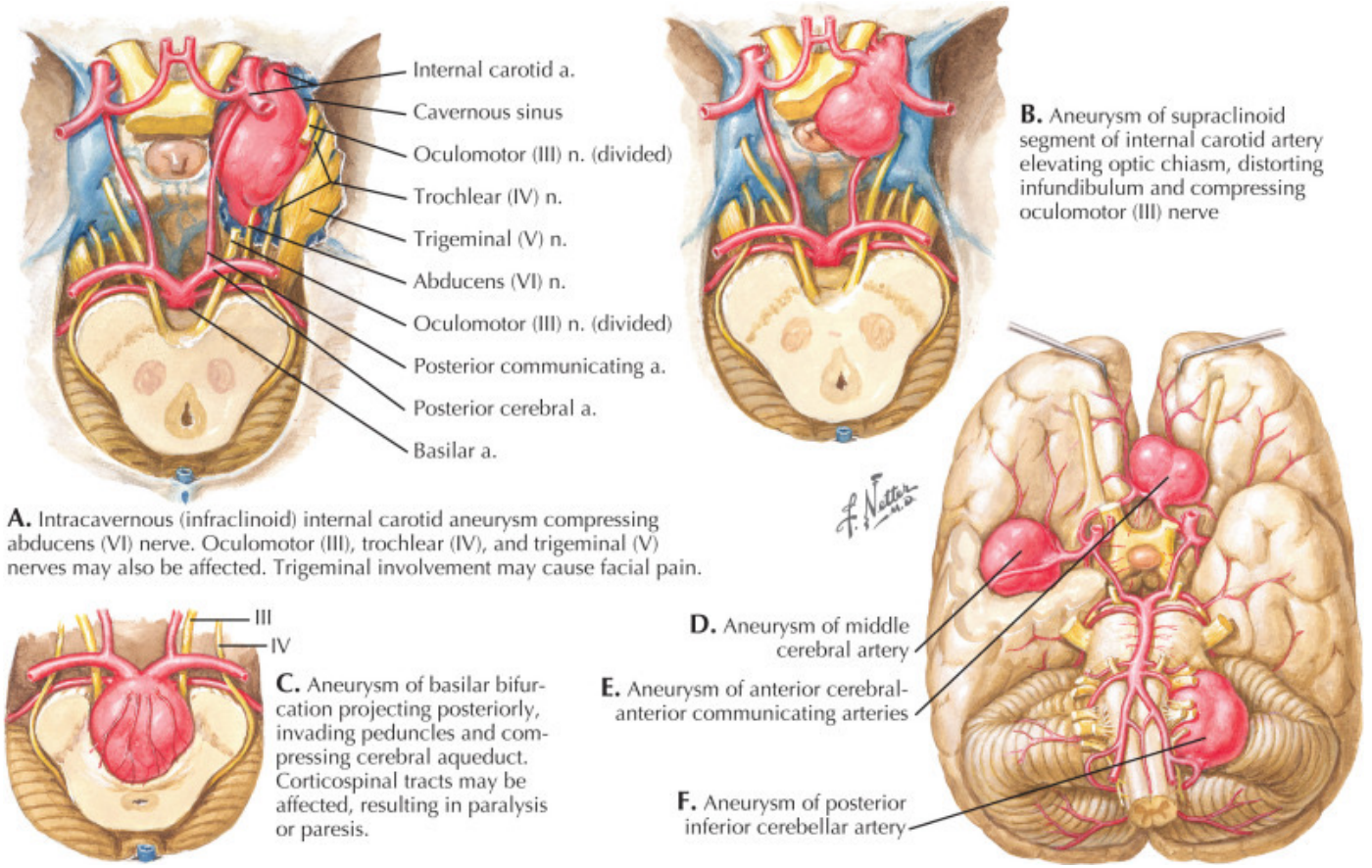
Table 3 | **Risk factors for intracranial aneurysm rupture**

Risk factor	Change in risk (95% CI in brackets)
Patient and aneurysm factors	
Hypertension[91,97]	HR 1.3 (1.0–1.7)*
	RR 2.5 (2.0–3.1)*
Heavy alcohol use (≥150 g per week)[97]	RR 2.1 (1.5–2.8)*
Smoking (current and former smokers combined)[97]	HR 2.4 (1.8–3.4)*
	HR 2.44 (1.02–5.88)*
Prior SAH from other aneurysm[91]	HR 1.4 (0.9–2.2)*
Familial SAH (two or more first-degree relatives)[98]	17-fold‡
Aneurysm growth on serial imaging[59]	12-fold§
Irregular aneurysm morphology/ presence of daughter sac[87,100]	HR 1.63 (1.08–2.48)
	OR 7.1 (6.0–8.3)
Multiple aneurysms[84]	HR 4.87 (1.62–14.65)*
Size of aneurysm (mm)[91]	
<5.0	Reference size
5.0–6.9	HR 1.1 (0.7–1.7)*
7.0–9.9	HR 2.3 (1.5–3.6)*
10.0–19.9	HR 5.5 (3.8–8.1)*
≥20.0	HR 20.8 (13.2–33.0)*
Aneurysm location[91]	
Middle cerebral artery	Reference location
Internal carotid artery	HR 0.5 (0.3–0.9)*
Anterior cerebral arteries (AcomA and ACA combined)	HR 1.7 (1.1–2.6)*
Posterior cerebral arteries (VA, BA and PCA combined)	HR 1.8 (1.2–2.8)*
Posterior communicating artery	HR 2.0 (1.4–3.0)*
Geographical region[91]	
Japanese population	HR 2. 7 (1.8–4.1)*
Finnish population	HR 3.6 (2.1–6.5)*

Nat Rev Neurol. 2016;12(12):699.

Symptoms/Signs

- Most asymptomatic
  - Incidental finding
  - aSAH
- Location + Growth → Mass effect, Ischemia
  - CN palsy (pupil-sparing 3rd)
  - Visual disturbance
  - Headache
  - Paresis



Netters Neurology, 3rd edition, 2020.

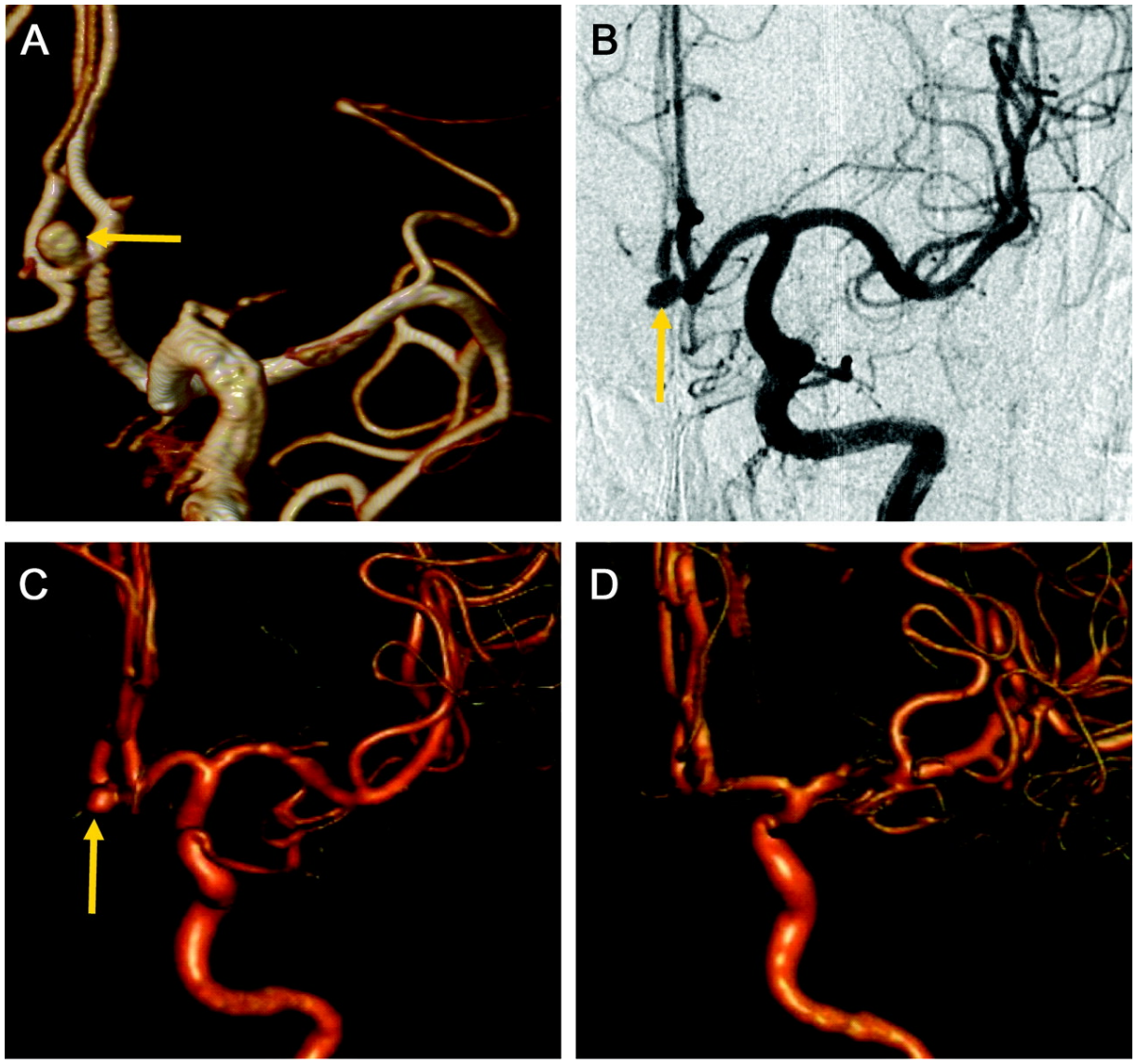
Diagnosis

- DSA: gold standard
- CTA/MRA sensitivity ↓ small aneurysms (<4-5mm)

- Multidetector CTA
  - Sensitivity: 97%
  - Specificity 98%
- 3D TOF-MRA (3 Tesla scanner)
  - Sensitivity: 99%
  - Specificity: 94%

- CTA or MRA; if neg but pretest probability high → DSA

Neurosurgery. 2003;53(3):597.
Ann Neurol. 2011;69(4):646.



M.-H. Li et al. Neurology 2011;77:667-676

Management

- No RCTs
- **HTN management, Tobacco Cessation, Limit ETOH**

- Monitoring
- Intervention: endovascular, clipping
  - Risk of rupture vs. risk of intervention
    - Shared decision-making
  - NSGY consultation

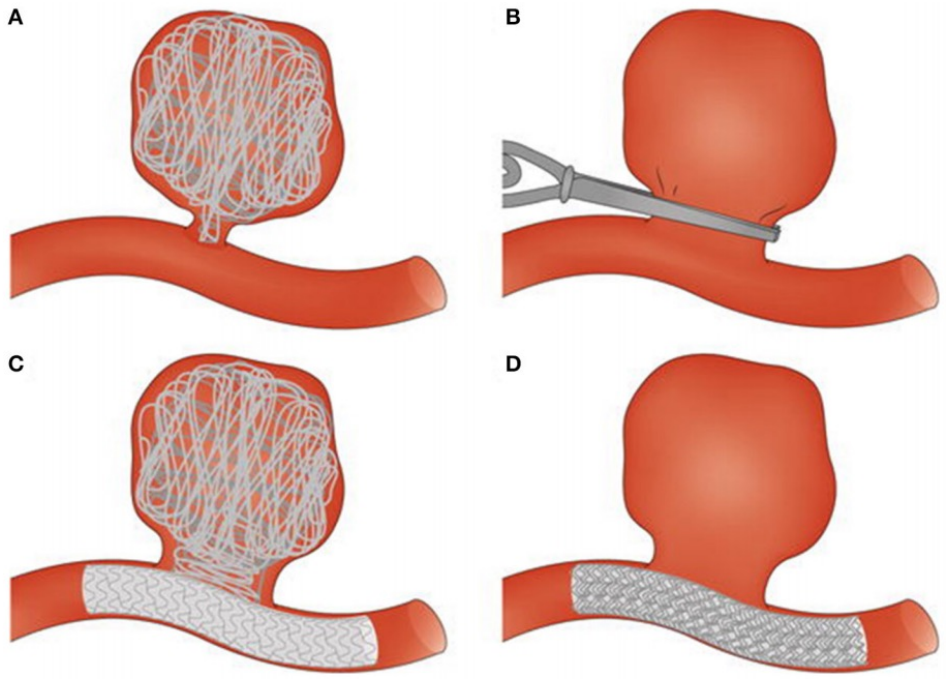


FIGURE 1 | Surgical and endovascular treatments for cerebral aneurysm thrombosis. **(A)** Endovascular coiling of the aneurysm sac. **(B)** Surgical clipping of the aneurysm neck. **(C)** Endovascular treatment combining use of coils and a stent. **(D)** Endovascular treatment with a flow diverter. Taken from Perrone et al. (2015).

Stroke. 2015 Aug;46(8):2368-400
Front Physiol. 2018 Apr 4;9:306.

General Indications for Intervention

- Symptomatic (aSAH, mass effect)
- ≥ 7-10 mm size
  - Age, comorbidities, location

* Basilar tip location, coexisting aneurysms with aSAH, growth, young age

- Intervention
  - Endovascular tx
    - ↓ morbidity/mortality
  - Surgical clipping
    - may ↓ aneurysm regrowth
- High-volume center

Stroke. 2015 Aug;46(8):2368-400
JAMA Neurol. 2019;76(3):282-293.

Figure 1. Overview of the Association Between Various Patient, Aneurysm, and Treatment Factors and Risk of Procedural Clinical Complications From Endovascular Treatment

Risk Factor	Risk Estimate (95% CI)
Female	1.06 (1.01-1.11)
History of subarachnoid hemorrhage	1.34 (0.46-3.91)
Coagulopathy	1.09 (1.03-1.16)
Cardiovascular comorbidity	
Smoking	1.45 (0.91-2.29)
Hypertension	1.27 (0.91-1.77)
Diabetes	1.81 (1.05-3.13)
Hyperlipidemia	1.76 (1.31-2.37)
Heart comorbidity	2.27 (1.53-3.37)
Wide aneurysm neck	1.71 (1.38-2.11)
Aneurysm location	
Posterior vs ICA	1.42 (1.15-1.74)
MCA vs ICA	1.25 (0.55-2.85)
ACA vs ICA	1.22 (0.63-2.38)
Aneurysm multiplicity	1.08 (0.65-1.81)
Advanced endovascular methods	
Stent vs no stent	3.43 (1.45-8.09)
SAC vs simple coil	1.82 (1.16-2.85)
SAC vs BAC	1.56 (0.86-2.82)
BAC vs simple coil	1.25 (0.71-2.20)

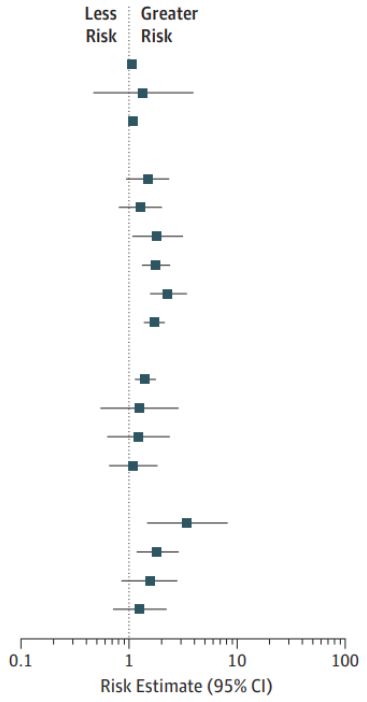
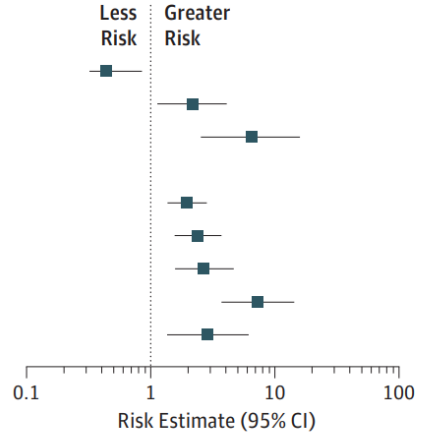


Figure 2. Overview of the Association Between Various Patient, Aneurysm, and Treatment Factors and Risk of Procedural Clinical Complications From Neurosurgical Treatment

Risk Factor	Risk Estimate (95% CI)
Female	0.43 (0.32-0.85)
Coagulopathy	2.14 (1.13-4.06)
Use of oral coagulation	6.36 (2.55-15.85)
Cardiovascular comorbidity	
Smoking	1.95 (1.36-2.79)
Diabetes	1.45 (1.03-2.03)
Heart comorbidity	2.71 (1.57-4.69)
Posterior vs ICA aneurysm location	7.25 (3.70-14.20)
Aneurysm calcification	2.89 (1.35-6.18)



Monitoring

Aneurysm Follow-Up (Patients Treated Without Surgery or Endovascular Coiling): Recommendations

1. **For patients with UIAs that are managed noninvasively without either surgical or endovascular intervention, radiographic follow-up with MRA or CTA at regular intervals is indicated. The optimal interval and duration of recommended follow-up are uncertain *(Class I; Level of Evidence B)*.**

2. **For patients with UIAs that are managed noninvasively without either surgical or endovascular intervention, a first follow-up study at 6 to 12 months after initial discovery, followed by subsequent yearly or every other year follow-up, may be reasonable *(Class IIb; Level of Evidence C)*.**

3. **For patients with UIAs that are managed noninvasively and in whom there are no contraindications to MRI, it may be reasonable to consider TOF MRA rather than CTAfor repeated long-term follow-up *(Class IIb; Level of Evidence C)*.**

- Repeat Imaging
  - MRA/CTA
  - 6 months after initial identification → annually → q2-3 years → longer reimaging interval
- Risk Factor Management

Stroke. 2015 Aug;46(8):2368-400

Key References

1. Etminan N, Rinkel GJ. Unruptured intracranial aneurysms: development, rupture and preventive management [published correction appears in Nat Rev Neurol. 2017 Feb 1;13(2):126]. *Nat Rev Neurol*. 2016;12(12):699–713.
2. Ruigrok YM. Management of Unruptured Cerebral Aneurysms and Arteriovenous Malformations. *Continuum (Minneap Minn)*. 2020;26(2):478–498.
3. Thompson BG, Brown RD Jr, Amin-Hanjani S, et al. Guidelines for the Management of Patients With Unruptured Intracranial Aneurysms: A Guideline for Healthcare Professionals From the American Heart Association/American Stroke Association. *Stroke*. 2015;46(8):2368–2400.

Questions?

Who should get screened if asymptomatic?

Screening: Recommendations

1. **Patients with ≥2 family members with IA or SAH should be offered aneurysmal screeningby CTA or MRA. Risk factors that predict a particularly high risk of aneurysm occurrence in such families include history of hypertension, smoking, and female sex *(Class I; Level of Evidence B)*.**

2. **Patients with a history of autosomal dominant polycystic kidney disease, particularly those with a family history of IA, should be offered screening by CTA or MRA *(Class I; Level of Evidence B)*, and it is reasonable to offer CTA or MRA to patients with coarctation of the aorta and patients with microcephalic osteodysplastic primordial dwarfism *(Class IIa; Level of Evidence B)*.**

Antithrombotic Use?

- Not contraindicated
  - ASA appears safe
  - AC may exacerbate degree of SAH and worsen outcome

→High risk aneurysm: risk/benefit analysis, shared-decision making

Stroke. 2015 Aug;46(8):2368-400