Evidence-Based Medicine

101.12.18 腦神經外科

R2林奕呈

Clinical Scenario

- A 64 years old female with underlying disease of hypertension and type II diabetic mellitus under regular medication control.
- She had acute right side weakness and numbness 2 weeks ago. She admitted to 署屏hospital with the impression of acute ischemic infraction.
- She discharged and OPD follow up with MRI report of acute ischemic infraction of left corona radiata and A-com artery aneurysm.

Clinical Scenario

- She was then transferred to our hospital.
- She arrived ER with clear conscious and BP:150/93mmHg, PR:90/min, RR:14/min, BT: 37.7’C
- Muscle power were 4+ of right side limbs and 5 of left side.
- Brain MRI revealed 4mm A-com artery aneurysm.

Background Questions

1. The clinical manifestations of intracranial aneurysm.

2. Epidemiology of aneurysmal subarachnoid hemorrhage

3. Natural history of unruptured intracranial aneurysms, (the rupture risk)

Q1: Clinical manifestations of intracranial aneurysm

- Most intracranial aneurysms are asymptomatic unless they rupture.
  - The prevalence of intracranial saccular aneurysms by radiographic and autopsy series is **5** percent.
- Some unruptured aneurysms can become symptomatic.
  - Symptoms include **headache** (may be severe and comparable to the headache of SAH), **visual acuity loss**, **cranial neuropathies**, **pyramidal tract dysfunction**, and **facial pain**.

Q2: Epidemiology of aneurysmal subarachnoid hemorrhage

- Most SAHs are caused by ruptured saccular aneurysms. Other causes include trauma, AVM, intracranial arterial dissections, and illicit drug use (especially cocaine and amphetamines).

- Aneurysmal SAH occurs at an estimated rate of 3 to 25 per 100,000 population. The mean age at onset is **55** years.

- Approximately 10% of patients with aneurysmal SAH die prior to reaching the hospital, 25 percent die within 24 hours of SAH onset, and about 45 percent die within 30 days.

Q3: Natural history of unruptured intracranial aneurysms

Table 1: Key findings related to the natural history data.

Risk factor	Key findings	References
Size	(i) Larger UIAs have greater RR (ii) Aneurysm size is a significant independent predictor of RR (iii) Defining a critical size threshold for aneurysm rupture remains difficult	ISUIA investigators 1998 [7] Wiebers et al. 2003 [8] Ishibashi et al. 2009 [9]
Enlargement	(i) In most cases, IAs are larger at time of rupture than at initial diagnosis (ii) Larger UIAs are more likely to grow (iii) Larger UIAs → greater growth risk → increased RR	Yasui et al. 1996 [10] Burns et al. 2009 [1] Matsubara et al. 2004 [11]
Previous SAH	(i) Prior history of aneurysmal SAH increases future RR (ii) Aneurysms <7 mm have an increased RR with prior history of SAH	ISUIA investigators 1998 [7] Wiebers et al. 2003 [8]
Location	(i) Posterior circulation aneurysms are widely considered to be more hazardous (ii) Include basilar artery, posterior cerebral artery, and vertebrobasilar distribution (iii) Intracavernous IAs are more benign	Weir et al. 2002 [12] Wermer et al. 2007 [13] Kupersmith et al. 1992 [14]
Morphology	(i) Multiple lobulations or loculations increases RR (ii) High dome : neck ratio increases RR (iii) Aneurysm angle, undulation index, and nonsphericity index are all predictors of aneurysm rupture	Hademenos et al. 1998 [15] Beck et al. 2003 [16] Dhar et al. 2008 [17] Raghavan et al. 2005 [18]
Patient characteristics	(i) Age, sex and comorbidities will influence aneurysmal RR (ii) Female sex and cigarette smoking are independent predictors of both UIA formation and growth (iii) These factors are especially important when making decision on whether to treat	Nahed et al. 2005 [19] Juvela et al. 2001 [20]

From: International Journal of Vascular Medicine Volume 2012, Article ID 898052

Foreground Question

➢ Should patient diagnosed unruptured intracranial aneurysm undergo surgical treatment?

- P: Patient with unruptured intracranial aneurysm
- I: Surgical intervention (clipping)
- C: Conservative observation
- O: Prognosis (mortality, morbidity)

Search Database

- Key word: unruptured intracranial aneurysm, treatment

UpToDate

DynaMed

ACP PIER

BMJ Clinical Evidence

ACP journal club

Evidencebasedmedicine.com

Cochrane Library

BMJ Evidence Updates

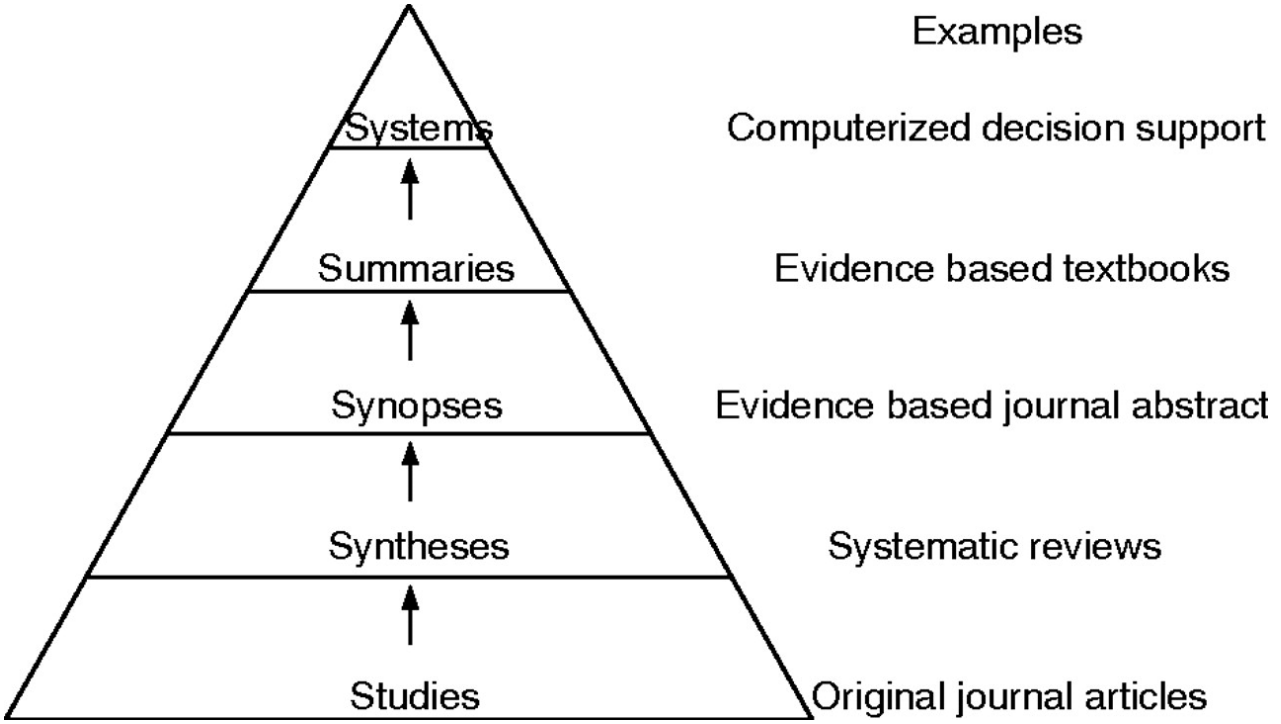
Other Systemic reviews eg. PubMed systemic reivew

PubMed

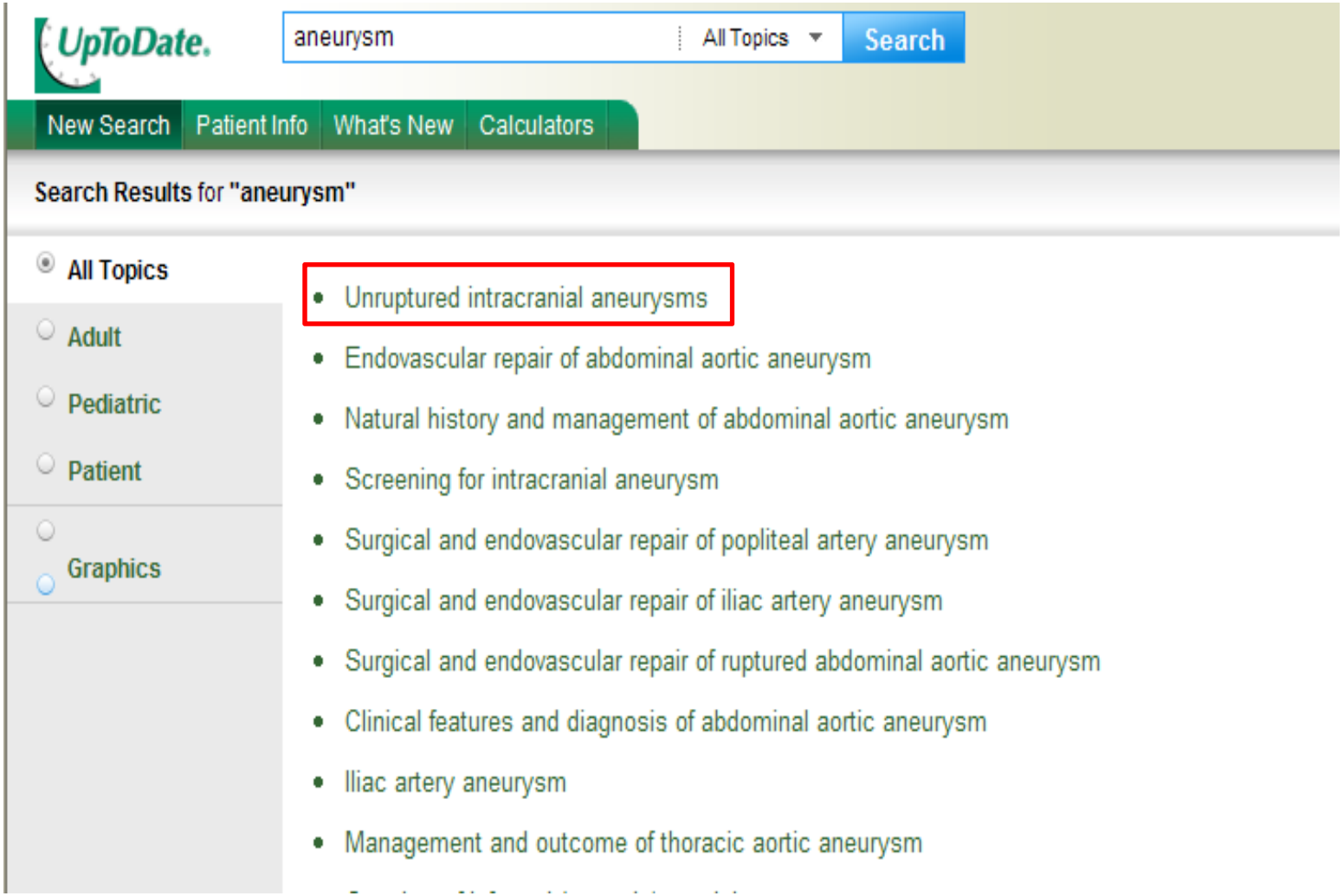
SUMsearch

TRIP

Google



Summaries: UpToDate



Unruptured intracranial aneurysms

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- Management: controversial. Weight the natural history of the aneurysm, the risks of intervention, and patient preferences.

- *Risk of intervention*: report from International Study of Unruptured Intracranial Aneurysms (ISUIA), a prospective observational study in 1917 patients under open surgical repair.
  - Age > 50
  - size > 12mm
  - posterior circulation

- *Benefit of intervention*: a cost-effect analysis used the 2003 ISUIA data report following observation result
  - For 50 years old patients, treatment was ineffective or not cost effective for aneurysms with following characteristics:
    - Small, <7mm, due to low risk of rupture
    - Located in the cavernous carotid artery
    - Large, >25mm and located in the posterior circulation, due to high risk of complications from treatment
  - For 40 years old patients, treatment was ineffective or not cost effective for aneurysms with following characteristics:
    - Small (<12mm) or large (>25mm) and located in the cavernous carotid artery
    - Small, <7mm and located in the anterior circulation

Whom to Treat

- Stroke council of the America Heart Association recommendations
  - Symptomatic intradural aneurysms of all sizes should be considered for treatment
  - Incidental, small (<7mm) aneurysms in patient without previous SAH, observation rather than intervention is general advocated
  - Asymptomatic aneurysms ≥7 to 10mm warrant strong consideration for treatment.

- Search

- No related topic

Aggregate analysis of the literature for unruptured intracranial aneurysm treatment (Structured abstract)

Centre for Reviews and Dissemination

Database of Abstracts of Reviews of Effects 2012 Issue 4

Original article: Lee T, Raytion M, Sciacca R, Mohr J P, Pile-Spellman J. Aggregate analysis of the literature for unruptured intracranial aneurysm treatment. *American Journal of Neuroradiology*.2005;26(8):1902-1908. Links

CRD summary

This review evaluated adverse outcomes after surgical clipping and endovascular coil embolization of unruptured intracranial aneurysms. The authors concluded that reporting bias may have led to an underestimate of morbidity and mortality after surgical clipping. **The limited search, incomplete reporting of review methods, and differences between the studies make it difficult to assess the reliability of the results.**

Search Studies: PubMed

- Key word: unruptured intracranial aneurysm, treatment
- Results: 3 articles
  1. Small Unruptured Intracranial Aneurysm Verification Study: SUAVe Study, Japan
  2. Management of incidentally discovered intracranial vascular abnormalities
  3. Rationale for Treating Unruptured Intracranial Aneurysms: Actuarial Analysis of Natural History Risk versus Treatment Risk for Coiling or Clipping Based on 14,050 Patients in the Nationwide Inpatient Sample Database

Article 1

Stroke
JOURNAL OF THE AMERICAN HEART ASSOCIATION

American Heart Association | American Stroke Association

Small Unruptured Intracranial Aneurysm Verification Study : SUAVe Study, Japan

Makoto Sonobe, Tomosato Yamazaki, Masahiro Yonekura and Haruhiko Kikuchi

Stroke. 2010;41:1969-1977; originally published online July 29, 2010;
doi: 10.1161/STROKEAHA.110.585059
Stroke is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231

Print ISSN: 0039-2499. Online ISSN: 1524-4628

- Purpose: a prospective study was conducted to determine the optimal management for incidentally found small unruptured aneurysms
- Method: from Sep. 2000 to Jan. 2004. 540 aneurysms were registered. 448 aneurysms (<5mm in size) have been follow up for a mean of 41 months.
- Evidence level: 2b

Result

Table 1. Baseline Characteristics Obtained in Patients at the Beginning of Follow-Up

Characteristics	
No. of patients	374
Women	238 (63.6%)
No. of aneurysms	448
No. of multiple aneurysm cases	124 (33.2%)
Age, years	
Mean±SD	61.9±10.3
Median	62
Range	23–89
Concomitant diseases	
Hypertension	93 (24.9%)
Stroke	59 (15.8%)
Ischemic heart disease	26 (7.0%)
Diabetes mellitus	23 (6.1%)
Hhistory of SAH	36 (9.6%)
Family history of SAH	31 (8.3%)
Aneurysm detection	
Medical checkup (brain dock)	199 (53.2%)
Associated with investigation for brain tumor or stroke	116 (31.0%)
Associated with ruptured aneurysm	36 (9.6%)

Table 2. The Locations and the Sizes of Unruptured Aneurysms Enrolled in This Study

	Total	1.0–1.9 mm	2.0–2.9 mm	3.0–3.9 mm	4.0–5.0 mm
ICA	173 (38.6%)	7 (36.8%)	37 (35.2%)	77 (39.9%)	52 (39.7%)
MCA	158 (35.3%)	5 (26.3%)	36 (34.3%)	70 (36.3%)	47 (35.9%)
Acom	60 (13.4%)	4 (21.1%)	19 (18.1%)	19 (9.8%)	18 (13.7%)
Distal ACA	12 (2.7%)	3 (15.8%)		5 (2.6%)	4 (3.1%)
BA	33 (7.4%)		10 (9.5%)	16 (8.3%)	7 (5.3%)
VA	4 (0.9%)			2 (1.0%)	2 (1.5%)
Others	8 (1.8%)		3 (2.9%)	4 (2.1%)	1 (0.8%)
Total	448	19	105	193	131

ICA indicates internal carotid artery aneurysm; MCA, middle cerebral artery aneurysm; Acom, anterior communicating artery aneurysm; ACA, anterior cerebral artery aneurysm; BA, basilar artery aneurysm; VA, vertebral artery aneurysm.

Univariate patient-related and aneurysm-related risk factors associated with rupture of small unruptured aneurysms

Characteristic	All Patients	Rupture, %	Nonrupture, %	HR	95% CI	*P*
No. of patients	374	7 (1.9)	367 (98.1)			
Women	238	6 (2.5)	232 (97.5)	1.40	0.40–4.82	0.60
Men	136	1 (0.7)	135 (99.3)	1		
Age, years						
Average†	61.9±10.3	58.7±15.1	62±10.2			0.40
Median	62	64	62			
<50	38	2 (5.3)	36 (94.7)	3.51	0.74–16.63	0.11
≥50	336	5 (1.5)	331 (98.5)	1		
Aneurysm diameter, mm						
Mean±SD†	3.3±0.9	3.9±0.6	3.3±0.9			0.055
≥4.0	116	5 (4.3)	111 (95.7)	5.51	1.60–19.04	0.0069*
<4.0	258	2 (0.8)	256 (99.2)	1		
Multiple aneurysms	124	4 (3.2)	120 (96.8)	2.62	1.20–5.74	0.016*
Single aneurysm	250	3 (1.2)	247 (98.8)	1		
Site of aneurysm						0.26
ICA	173 of 448 (38.6)	1 (0.6)	172 (99.4)			
MCA	158 of 448 (35.3)	3 (1.9)	155 (88.1)			
ACoA	60 of 448 (13.4)	2 (3.3)	58 (96.7)			
Distal ACA	12 of 448 (2.7)	1 (8.3)	11 (91.7)			
BA	33 of 448 (7.4)	0 (0)	33 (100)			
VA	4 of 448 (0.9)	0 (0)	4 (100)			
HT	163	6 (3.7)	157 (96.3)	7.32	2.04–26.29	0.0023*
Non-HT	211	1 (0.5)	210 (99.5)	1		
Current smoker	32	0 (0)	32 (100)	0.22	0.16–3.00	0.82
Not current smoker	342	7 (2.0)	335 (98.0)			
Previous SAH	36	1 (2.8)	35 (97.2)	1.44	0.45–11.57	0.87
No previous SAH	338	6 (1.8)	332 (98.2)	1		
Family history of SAH	31	0 (9.4)	31 (100)	0.98	0.69–1.39	0.90
No family history	343	7 (2.0)	336 (98.0)			

*$P<0.05$.

†Unpaired *t* test for comparisons of rupture and nonrupture groups according to patient age and aneurysm diameter.

ICA indicates internal carotid artery; MCA, middle cerebral artery; ACoA, anterior communicating artery; ACA, anterior cerebral artery; BA, basilar artery; VA, vertebral artery; HT, hypertension.

Discussion

- Annual risk of rupture of small unruptured aneurysms:
  - The current study did not found a history of SAH to be associated with aneurysmal rupture
  - The data demonstrated the average annual risk of rupture of single unruptured aneurysms **<5mm** to be 0.34% /year. (10 patients were operated due to morphological change, this may caused bias)

Risk factors for rupture of small unruptured aneurysms

Table 4. Independent Predictive Variables for Aneurysmal Rupture

Characteristic	HR	95% CI	*P*
<50 years of age	5.23	1.03–26.52	0.046*
Aneurysm ≥4.0 mm	5.86	1.27–26.95	0.023*
Hypertension	7.93	1.33–47.42	0.023*
Multiple aneurysms	4.87	1.62–14.65	0.0048*

*$P<0.05$.

Surgical indications for incidentally found small unruptured aneurysms

- If patient is < 50 years old, is hypertensive , and harbors multiple aneurysms with diameters of ≥ 4mm, surgical or endovascular treatment can reasonably be considered for prevention of future aneurysm rupture.
- If aneurysm enlargement is documented during follow-up, the aneurysm should be treated with a surgical or an endovascular procedure.

Article 2

Neurosurg Focus 31 (6):E1, 2011

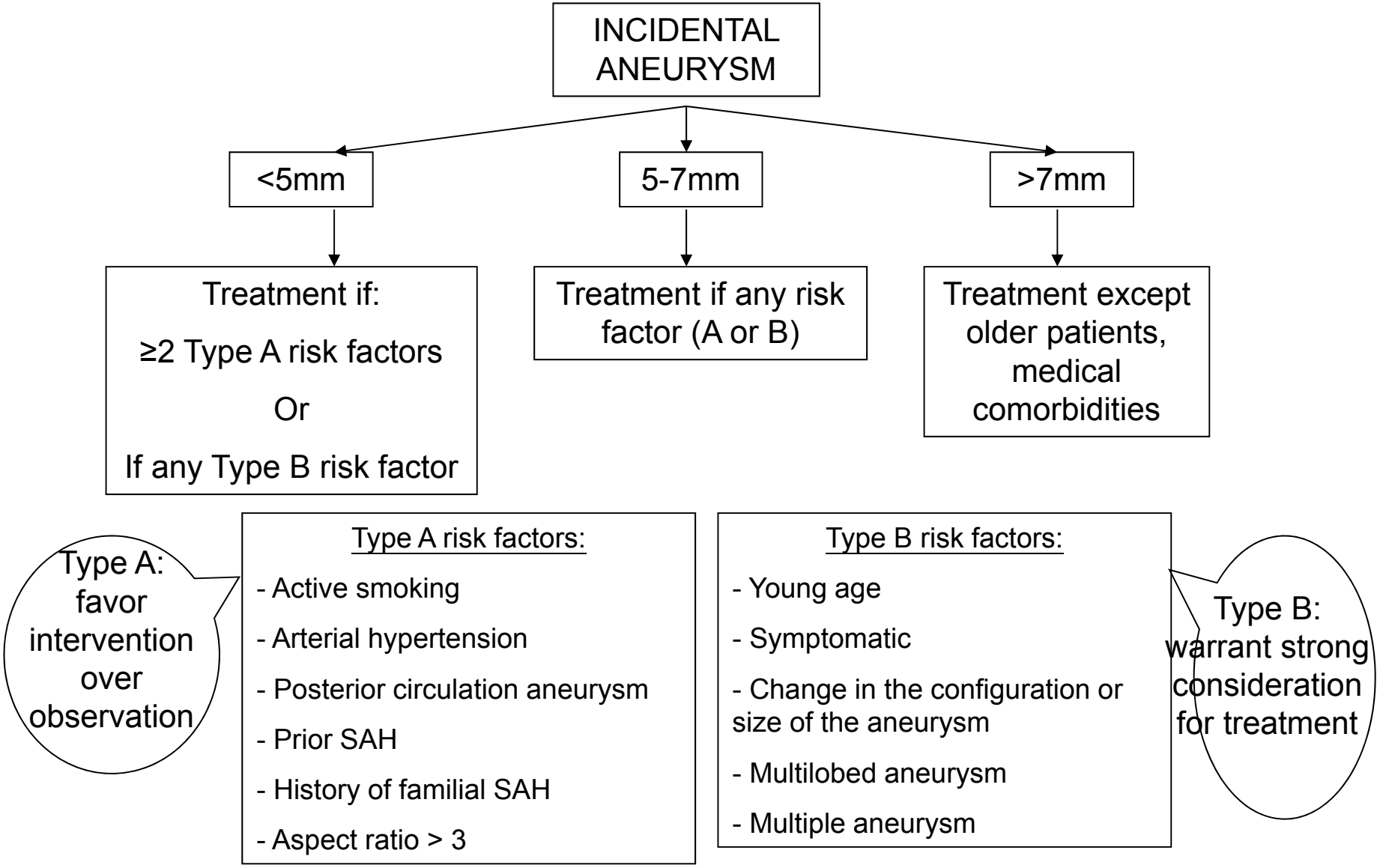
Management of incidentally discovered intracranial vascular abnormalities

Nohra Chalouhi, M.D., Aaron S. Dumont, M.D., Ciro Randazzo, M.D., Stavropoula Tjoumakaris, M.D., L. Fernando Gonzalez, M.D., Robert Rosenwasser, M.D., and Pascal Jabbour, M.D.

Department of Neurosurgery, Thomas Jefferson University and Jefferson Hospital for Neuroscience, Philadelphia, Pennsylvania

Evidence Level 2b

(single observational cohort study)



✓ *Aspect ration*: height/neck width
✓ No defined cutoff age has been determined

Article 3

Rationale for Treating Unruptured Intracranial Aneurysms: Actuarial Analysis of Natural History Risk versus Treatment Risk for Coiling or Clipping Based on 14,050 Patients in the Nationwide Inpatient Sample Database

Matthew F. Lawson[1], Daniel W. Neal[2], J Mocco[1], Brian L. Hoh[1]

WORLD NEUROSURGERY, 2012

- Objective: to compare natural history rupture risk versus treatment risk for coiling and clipping small unruptured aneurysms using data in the Nationwide Inpatient Sample (NIS) database.
- Method:
  - Data was collected from NIS data base from 2002~2008. 14,050 hospitalizations for treatment of an UIA: 6611(47%) clipping.
  - Outcome: discharge disposition
    - favorable outcome: discharge home
    - poor outcome: skilled nursing facility, long-term care facility, hospice, in-hospital death.

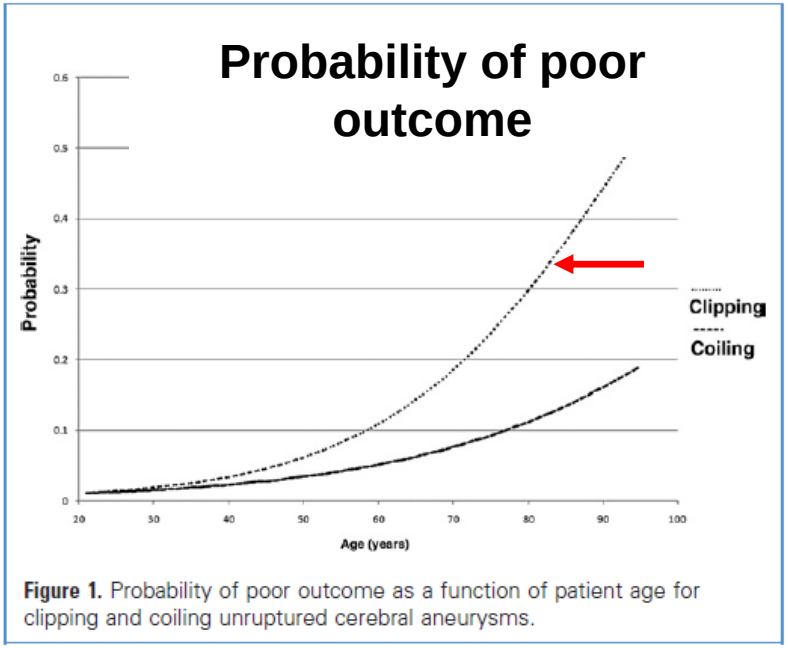
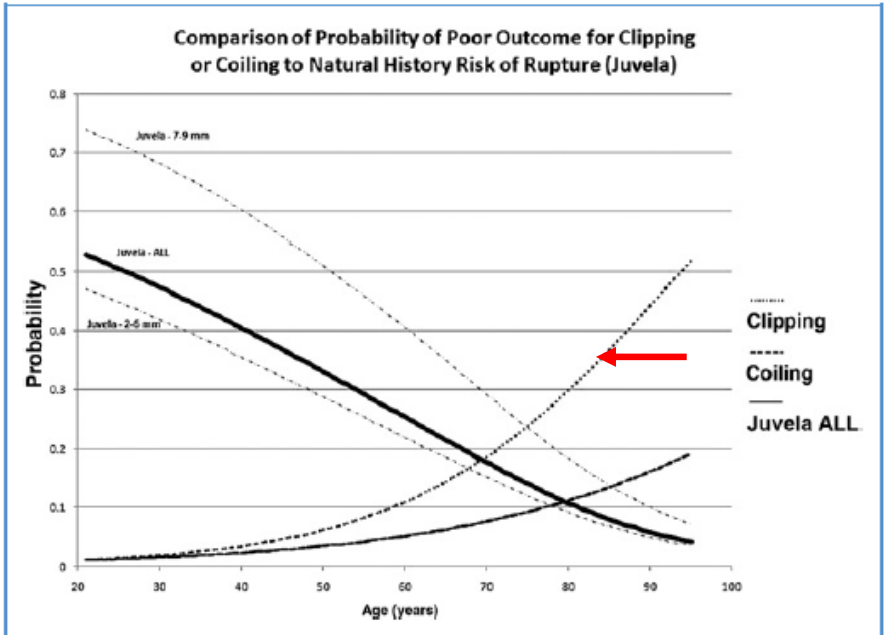
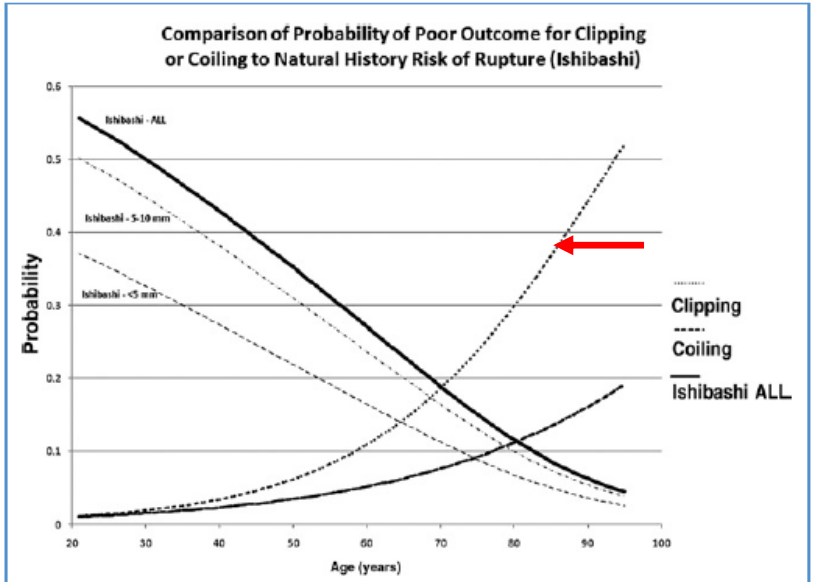


Figure 1. Probability of poor outcome as a function of patient age for clipping and coiling unruptured cerebral aneurysms.



Natural history risk



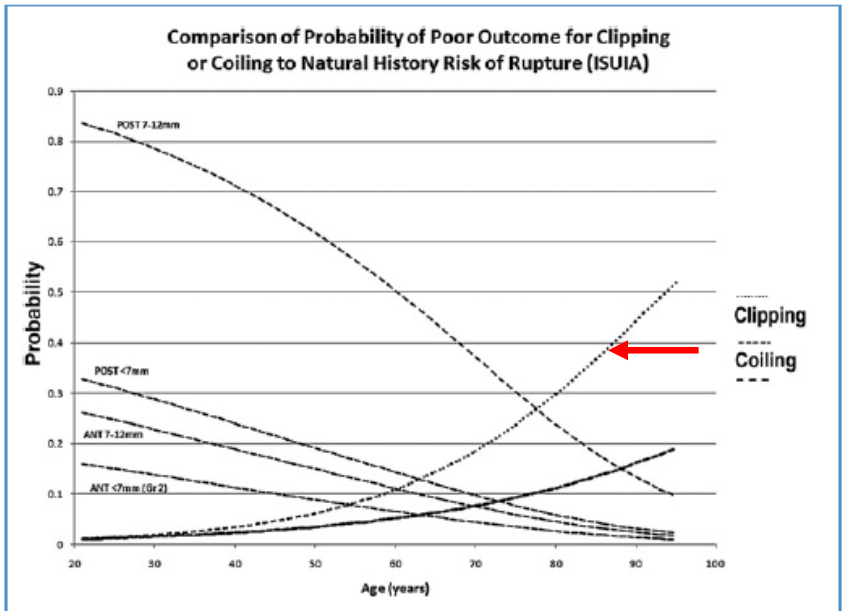


Table 3. Significant Predictors of Poor Outcome for Clipping Patients

Factor	Odds Ratio	Confidence Interval
Age	1.07	1.055–1.075
Alcohol abuse history	1.68	1.043–2.699
Congestive heart failure	1.85	1.140–2.987
Coagulopathy	3.01	1.755–5.159
Drug abuse history	3.41	1.930–6.037
Obesity	0.462	0.233–0.917

Table 4. The Natural History Rupture Risks From Several Prominent Studies and the Approximate Age Where the Natural History Rupture Risk Will Equal the Risk of Poor Outcome From Treatment

	Number of Patients	Annual Rupture Risk (%)	Age Surgical Intercept	Age Coiling Intercept
Juvela et al., 2000 (10)				
All patients		1.3%	70	80
2–6 mm	116	1.1%	68	78
7–9 mm	16	2.3%	75	86
10–25 mm	10	2.8%	77	88
Ishibashi et al., 2009 (7)				
All patients		1.4%	71	81
<5 mm	392	0.8%	65	75
5–10 mm	108	1.2%	69	79
10–25 mm	24	7.1%	86	>95
>25 mm	5	43.1%	n/a	n/a
Tsutsumi et al., 2000 (13)				
All patients	62	2.5%	76	86
<10 mm	56	1.5%	71	81
>10 mm	6	7.9%	87	>95
ISUIA, 2003 (15)				
A <7mm (Group 2)		0.3%	55	64
A 7–12 mm		0.5%	61	70
A 13–24 mm		3.1%	78	89
A >24 mm		9.7%	89	>95
P <7 mm (Group 2)		0.7%	64	73
P 7–12 mm		3.1%	78	89
P 13–24 mm		4.0%	80	91
P >24 mm		13.0%	91	n/a

P, posterior; A, anterior; n/a, not available.

Conclusion

- Clipping of UIA are safe, with major morbidity about 4.75%
- Base on NIS reported outcomes and natural history studies, there is a rationale for performing clipping for patients less than 70 years old.
- For small aneurysms less than 10mm, there is rationale for clipping at less than age 67 years old.
- The ISUIA data for unruptured 7~12mm anterior circulation aneurysms demonstrate treatment benefit for patients < 61 years old for clipping.

Evidence level

Level	與[治療/預防/病因/危害]有關的文獻
1a	用多篇RCT所做成的綜合性分析(SR of RCTs)
1b	單篇RCT(有較窄的信賴區間)
1c	All or none
2a	用多篇世代研究所做成的綜合性分析
2b	單篇cohort及低品質的RCT
2c	Outcome research / ecological studies
3a	SR of case-control studies
3b	Individual case-control studies
4	Case-series(poor quality :cohort / case-control studies)
5	沒有經過完整評讀醫學文獻的專家意見

Appraisal: 嚴格評讀文獻

Are the results of the study valid?

- Was the assignment of patients to treatment randomized? No
- Were all patients who entered the trial properly accounted for and attributed at its conclusion? Yes
  - Was follow-up complete? Yes
  - Were patients analyzed in the groups to which they were randomized (intention to treat analysis)? No
- Were patients, their clinicians, and study personnel “blind” to treatment? No
- Were the groups similar at the start of the trial?
  - Baseline prognostic factors (demographics, co-morbidity, disease severity, other known confounders) balanced?
- Aside from the experimental intervention, were the groups treated equally? Yes

Will the result help me in caring for my patients ?

- Can the results be applied to my patient care? Yes
  - Patients similar for demographics, severity, co-morbidity and other prognostic factors? Yes
- Were all clinically important outcomes considered?
  - Yes
- Are the likely treatment benefits worth the potential harms and costs?
  - Yes

Apply

醫療現況	病人意願
跟病患解釋手術的風險、可能之後遺症及不接受手術的預後	病人願意接受動脈瘤切除手術
生活品質	**社會脈絡**
目前仍屬術後恢復期, E3-4VeM6	無

在「提出臨床問題」方面 的自我評估

- 我提出的問題是否具有臨床重要性？是
- 我是否明確的陳述了我的問題？
  - 我的foreground question 是否可以清楚的寫成PICOT？是
- 我是否清楚的知道自己問題的定位？（亦即可以定位自己的問題是屬於診斷上的、治療上的、預後上的或流行病學上的），並據以提出問題？是，屬於治療範圍
- 對於無法立刻回答的問題，我是否有任何方式將問題紀錄起來以備將來有空時再找答案？有

在「搜尋最佳證據」方面 的自我評估

- 我是否已盡全力搜尋？有
- 我是否知道我的問題的最佳證據來源？是
- 我是否從大量的資料庫來搜尋答案？是
- 我工作環境的軟硬體設備是否能支援我在遇到問題時進行立即的搜尋？是
- 我是否在搜尋上愈來愈熟練了？是
- 我會使用「斷字」、布林邏輯、同義詞、MeSH term，限制（limiters)等方法來搜尋？是
- 我的搜尋比起圖書館人員或其他對於提供病人最新最好醫療有熱情的同事如何？差不多

關於「應用到病人身上」的自我評估

- 我是否將搜尋到的最佳證據應用到我的臨床工作中？是
- 我是否能將搜尋到的結論如NNT, LR用病人聽得懂的方式解釋給病人聽？不能
- 當搜尋到的最佳證據與實際臨床作為不同時，我如何解釋？目前對於未破裂動脈瘤仍未有足夠的證據支持某種處理方式，實際上仍算是依主治醫師經驗給予治療。

改變「醫療行為」的自我評估

- 當最佳證據顯示目前臨床策略需改變時，我是否遭遇任何阻止改變的阻力？無
- 我是否因此搜尋結果而改變了原來的治療策略？做了那些改變？沒有

效率評估

- 這篇報告，我總共花了多少時間？
  - 十幾個小時
- 我是否覺得這個進行實證醫學的過程是值得的？
  - 是

Thanks for your attention !