Management of Extra-Renal Complications

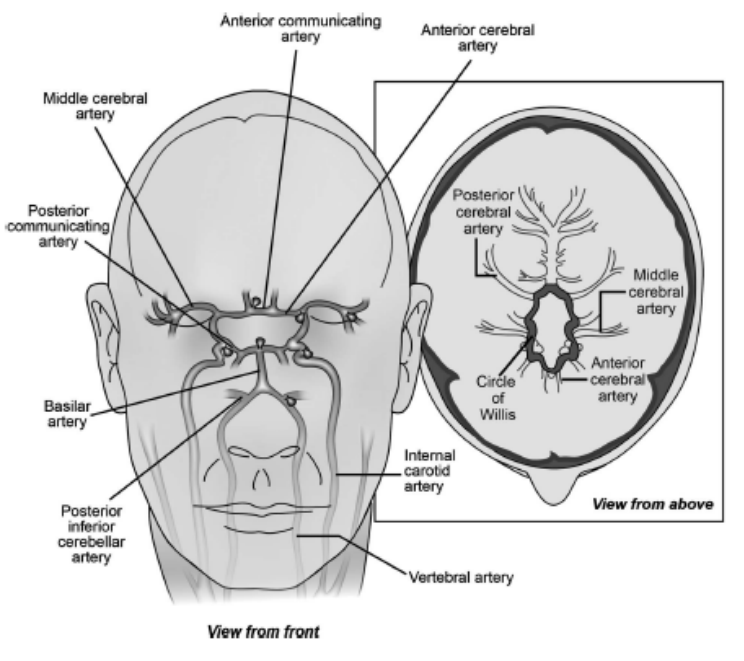
Prioritized:

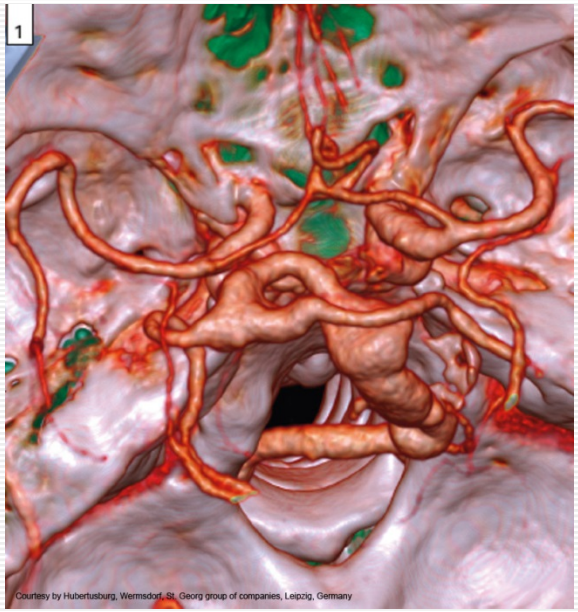
1. Is widespread screening for intracranial aneurysm of all patients with ADPKD justified? If not, in which patients should screening be recommended? If screening is negative, should patients be rescreened? At which time interval?

2. When an UIA is detected, what are the indications to intervene? If an UIA is recommended for conservative management, what are the recommendations for follow-up and to reduce the risk of rupture?

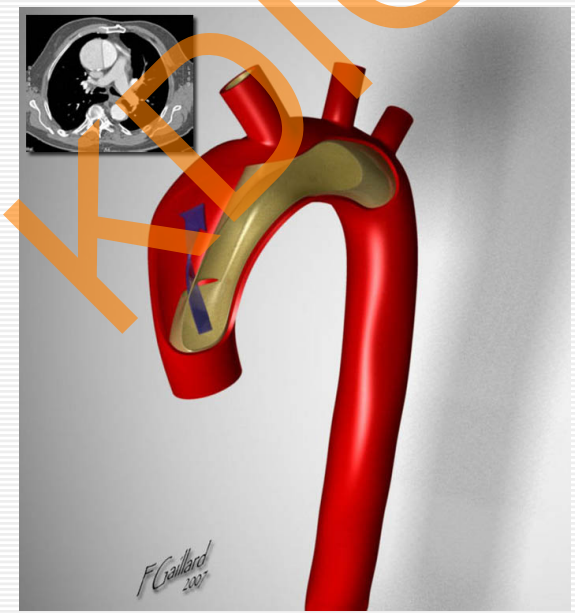
KDIGO Controversies Conference on ADPKD
Breakout Session Questions

The vasculopathy of ADPKD

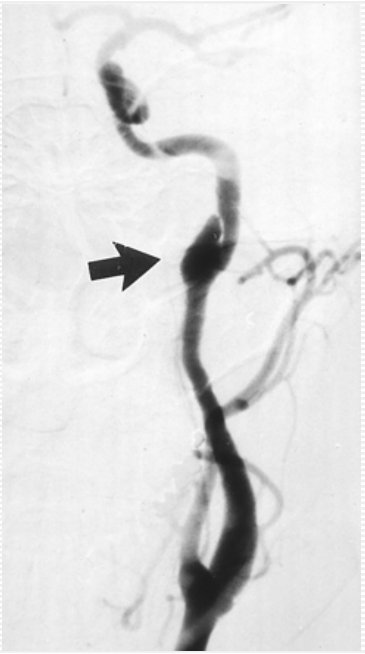




Dolichoectasia



Thoracic aortic dissection



Cervico-cephalic artery dissection

Vascular Expression of Polycystin

MATTHEW D. GRIFFIN,* VICENTE E. TORRES,* JOSEPH P. GRANDE,† and RAJIV KUMAR*

(J Am Soc Nephrol 8: 616–626, 1997)

Vascular Expression of Polycystin-2

VICENTE E. TORRES,*† YIQUIANG CAI,‡ XI CHEN,* GUANQUING Q. WU,‡ LIN GENG,‡ KATHLEEN A. CLEGHORN,† CHRISTOPHER M. JOHNSON,§ and STEFAN SOMLO‖

J Am Soc Nephrol 12: 1–9, 2001

Polycystin 1 is required for the structural integrity of blood vessels

Keetae Kim†, Iain Drummond†, Oxana Ibraghimov-Beskrovnaya‡, Katherine Klinger†, and M. Amin Arnaout†§

PNAS | February 15, 2000 | vol. 97 | no. 4 | 1731–1736

Cardiac defects and renal failure in mice with targeted mutations in *Pkd2*

Guanqing Wu[1,6], Glen S. Markowitz[7], Li Li[1], Vivette D. D'Agati[7], Stephen M. Factor[2], Lin Geng[9], Sonia Tibara[1], Jay Tuchman[1], Yiqiang Cai[1,6], Jong Hoon Park[1], Janet van Adelsberg[8], Harry Hou Jr[3], Raju Kucherlapati[4], Winfried Edelmann[5] & Stefan Somlo[1,4,6]

nature genetics • volume 24 • january 2000

Pathogenic Sequence for Dissecting Aneurysm Formation in a Hypomorphic Polycystic Kidney Disease 1 Mouse Model

Sabrine Hassane, Nanna Claij, Irma S. Lantinga-van Leeuwen, J. Conny Van Munsteren, Natascha Van Lent, Roeland Hanemaaijer, Martijn H. Breuning, Dorien J.M. Peters and Marco C. DeRuiter

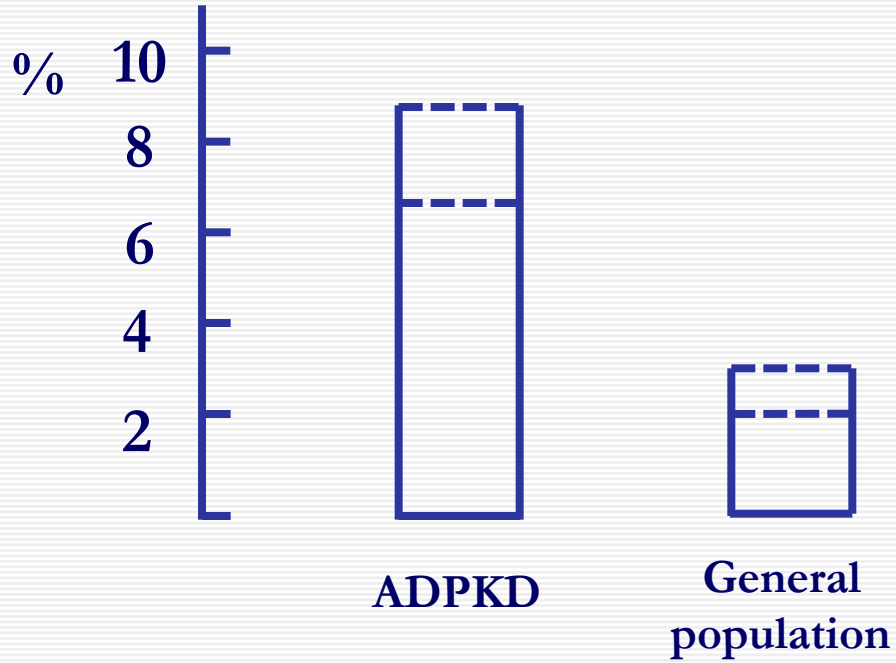
Arterioscler Thromb Vasc Biol. 2007;27:2177-2183

Cardiovascular Polycystins: Insights From Autosomal Dominant Polycystic Kidney Disease and Transgenic Animal Models

Delphine Bichet, Dorien Peters, Amanda Jane Patel, Patrick Delmas, and Eric Honoré*

(Trends Cardiovasc Med 2006;16:292–298)

The prevalence of unruptured intracranial aneurysms (UIAs) is 2 to 3 times higher in patients with ADPKD than in the general population



(Pirson, JASN 2002; 13 : 269
Neumann HP, Cerebrovas Dis Extra 2012; 2: 71
Vlak M, Lancet Neurol 2011; 10: 626)

Prevalence of IA in ADPKD : Source data

Table 22.1 Prevalence of asymptomatic saccular intracranial aneurysms in autosomal dominant polycystic kidney disease

	Chapman *et al.* (1992)	Huston *et al.* (1993)	Ruggieri *et al.* (1994)	Total
Method	Angio or CT	MRA	MRA	
Subjects (*n*)	88	85	93	266
Mean age (yrs)	36	45	48	43
Subjects with ICA (*n*)	4 (4.5%)	9 (10.6%)	8 (8.6%)	21 (7.9%)
ICA (*n*)	8	9	11	28
6–10 mm	0	2	2	4
3–5	7	2	5	14
< 3	1	5	4	10

Angio, conventional angiography; CT, thin-section high-resolution contrast-enhanced computerized tomography; MRA, magnetic resonance angiography.

(Intracranial aneurysms in autosomal dominant Polycystic kidney disease. In: Oxford Clinical Nephrology Series)

Prevalence of IA in ADPKD may be higher in some populations

Screening for Intracranial Aneurysm in 355 Patients With Autosomal-Dominant Polycystic Kidney Disease

H.W. Xu, MD, PhD; Sheng Qiang Yu, MD, PhD; Chang Lin Mei, PhD; Ming Hua Li, MD, PhD

Background and Purpose—The association of autosomal-dominant polycystic kidney disease (ADPKD) with intracranial aneurysm (ICAN) is well known but little is known about the characteristics of ICAN in ADPKD. The purpose of this study was to investigate the prevalence and characteristics of ICAN in ADPKD.

Methods—We screened 355 patients with ADPKD (mean age, 46.5±13.2 years; range, 7 to 87 years) with 3-dimensional time-of-flight MR angiography. Size, location, and morphology of aneurysms were assessed. The prevalence and characteristics of ICAN in patients with ADPKD were evaluated. Patients with ICAN found by MR angiography and moderate renal function subsequently were recommended to undergo digital subtraction angiography for comparison.

Results—The prevalence of ICAN in ADPKD was 12.4% (95% CI, 8.95% to 15.82%) with an equal gender distribution. The prevalence increased as age increased, reaching a peak value of 23.3% (95% CI, 16.85 to 29.75%) in the 60- to 69-year age group. The prevalence of ICAN in patients with ADPKD with a positive family history of hemorrhagic stroke or ICAN was higher than patients with ADPKD lacking such family history (relative risk, 1.968; 95% CI, 1.57 to 2.67). The mean diameter of ICAN was 3.85±3.25 mm. The most frequent site of ICAN was the internal carotid artery. The result of digital subtraction angiography of 15 patients with 18 ICANs and moderate renal function corresponded to the detection of MR angiography.

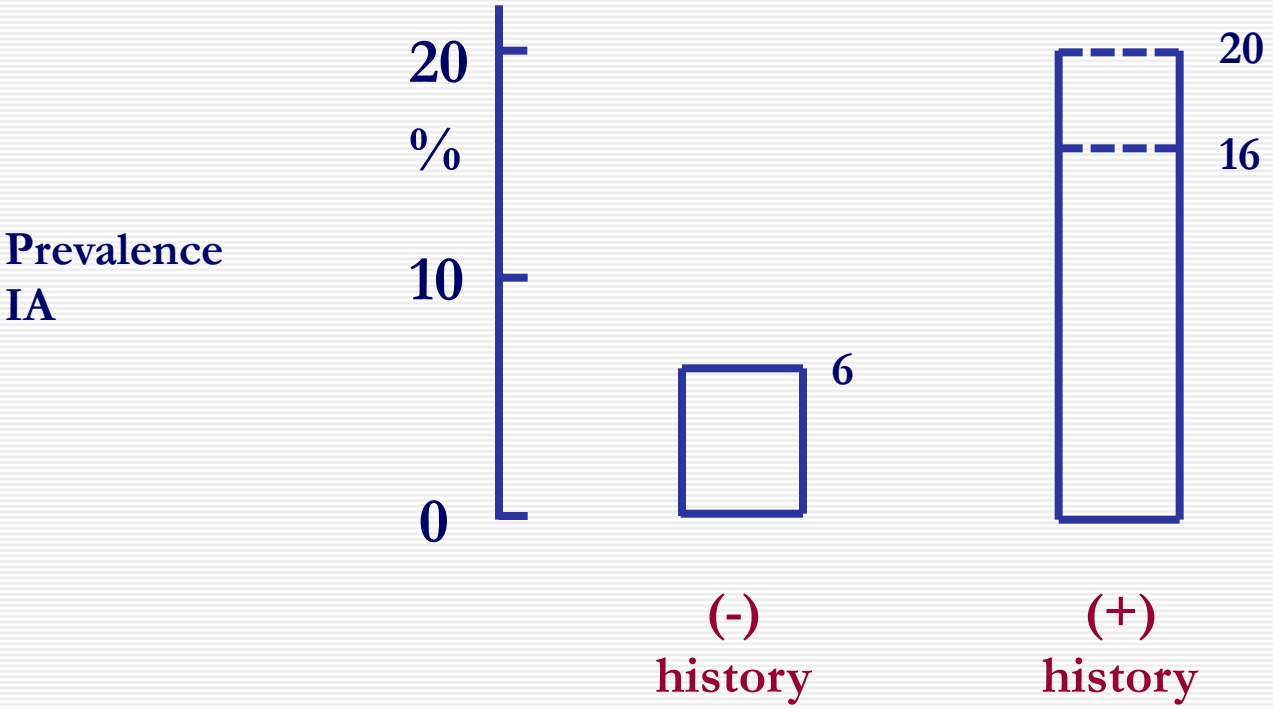
Conclusion—The characteristics of ICAN in patients with ADPKD were different from some previous reports. Systematic screening of ICAN with 3-dimensional time-of-flight MR angiography is recommended for patients with ADPKD, particularly for adult patients (≧30 years) or patients with a positive family history of hemorrhagic stroke or ICAN. (***Stroke*.** **2011;42:204-206.**)

The characteristics of UIAs are similar in ADPKD and the general population

	ADPKD	General population
Location in the anterior circulation	80 – 100%	80 – 90%
Multiple	18 – 30%	35%
<6 mm	80 – 90%	70 – 80%

(Pirson, JASN 2002; 13 : 269
Irazabal, Clin J Am Soc Nephrol 2011; 6 : 1274
Vlak M, Lancet Neurol 2011; 10: 626
Rozenfeld AJNR, Am J Neuroradiol 2013; in press)

In the ADPKD population, the only clinical characteristic associated with the presence of an UIA is a family history of IA



(Pirson, JASN 2002; 13 : 269
Irazabal, Clin J Am Soc Nephrol 2011; 6 : 1274)

Prevalence of IA in ADPKD according to family history : source data

Table 22.2 Prevalence of asymptomatic ICA* among 263 ADPKD patients according to the existence of a definite family history of ICA or subarachnoid haemorrhage

Study	Positive family history		Negative family history
Chapman *et al.* (1992)	2/29		2/59
Huston *et al.* (1993)	6/27		3/56
Ruggieri *et al.* (1994)	4/21		6/71
Total	12/77 (15.6%)	$P < 0.05$	11/186 (5.9%)

*21 were saccular, 2 were fusiform.

(Intracranial aneurysms in autosomal dominant Polycystic kidney disease. In: Oxford Clinical Nephrology Series)

Screening for Intracranial Aneurysm in 355 Patients With Autosomal-Dominant Polycystic Kidney Disease

H.W. Xu, MD, PhD; Sheng Qiang Yu, MD, PhD; Chang Lin Mei, PhD; Ming Hua Li, MD, PhD

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Conclusion—The characteristics of ICAN in patients with ADPKD were different from some previous reports. Systematic screening of ICAN with 3-dimensional time-of-flight MR angiography is recommended for patients with ADPKD, particularly for adult patients (≧30 years) or patients with a positive family history of hemorrhagic stroke or ICAN. (***Stroke*.** **2011;42:204-206.**)

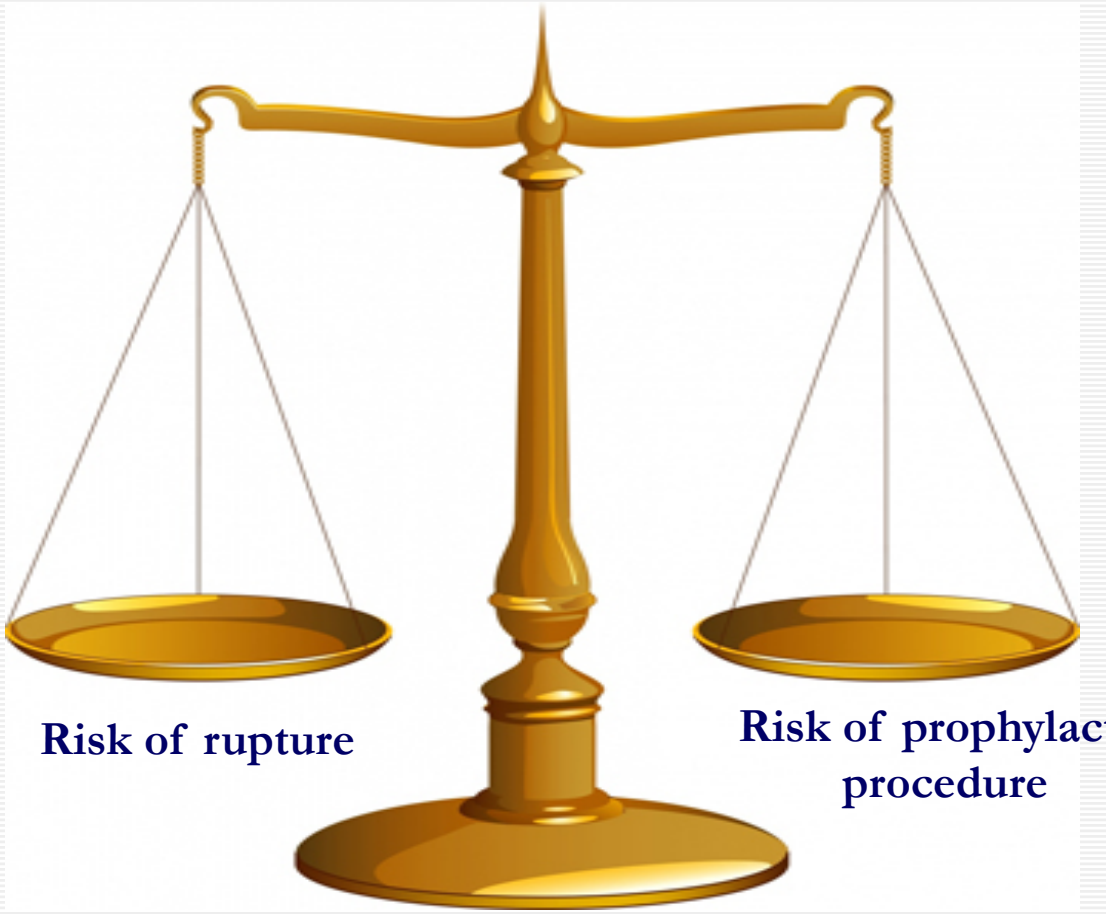
The risk of rupture of an UIA is low, but rupture is devastating

- The vast majority of UIA remain asymptomatic both in the general population and in ADPKD patients.

- But rupture entails a mortality rate of 50% and treatment of a ruptured IA also carries
  - a mortality rate of 10% and
  - a morbidity rate of 20%

Should Patients with Autosomal Dominant Polycystic Kidney Disease Be Screened for Cerebral Aneurysms?

M.N. Rozenfeld, S.A. Ansari, A. Shaibani, E.J. Russell, P. Mohan, and M.C. Hurley



Risk of rupture of UIA in the general population

Risk of rupture of UIA in the ADPKD population

Risk of prophylactic repair of an UIA

Decision – analysis

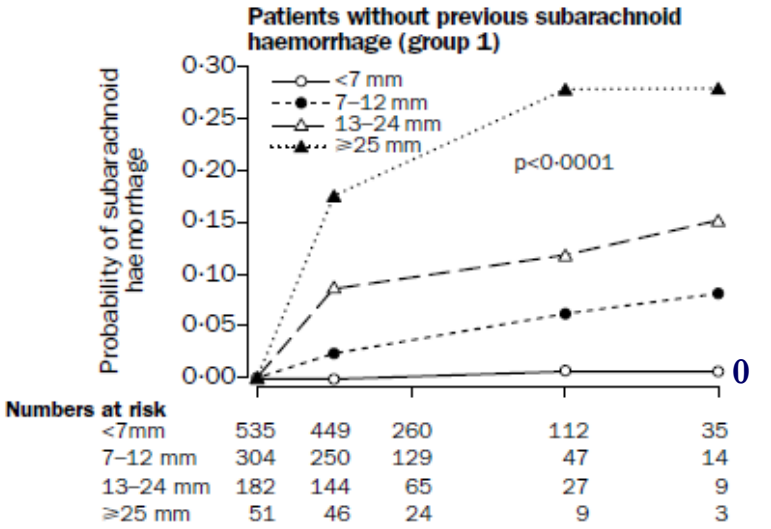
Practical attitude in ADPKD

Unruptured intracranial aneurysms: natural history, clinical outcome, and risks of surgical and endovascular treatment

Natural history

1692 patients with UIAs ≥ 2 mm without (1077) or with (615) prior history of SAH

Overall annual rupture risk : 0,7 %

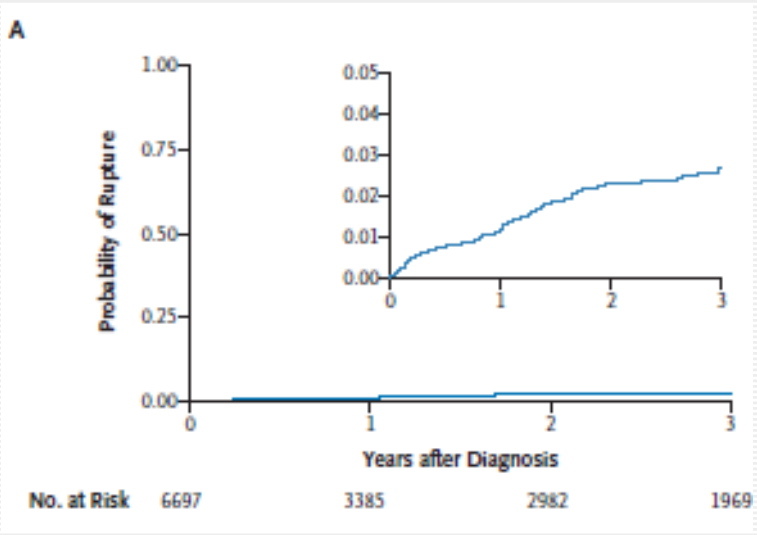


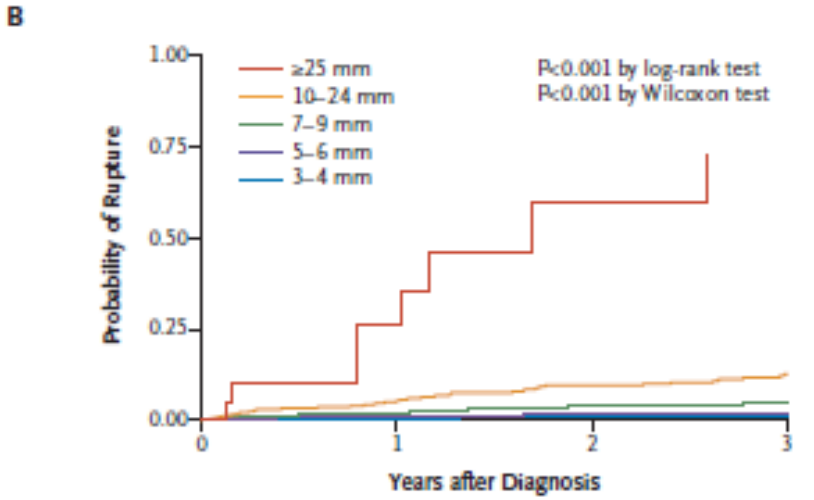
(ISUIA investigators, Lancet 2003; 362:103)

The Natural Course of Unruptured Cerebral Aneurysms in a Japanese Cohort

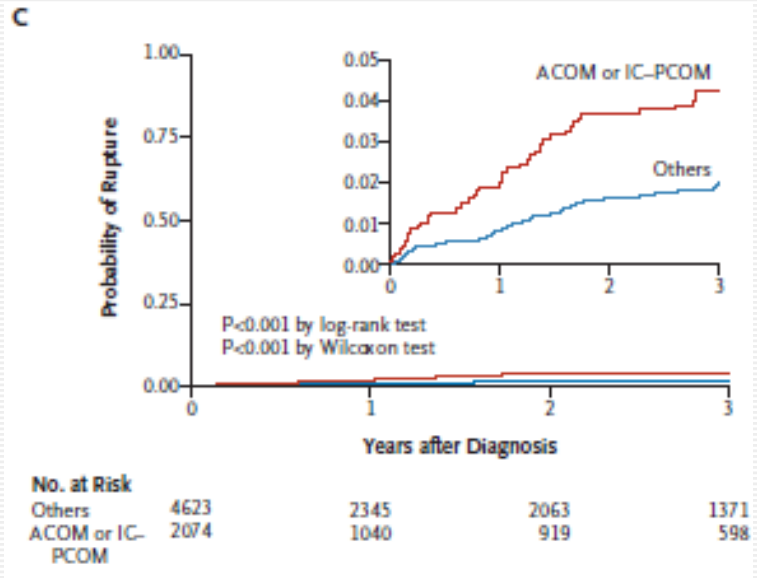
Natural history
5720 pts with UIAs ≥ 3 mm
91% incidentally

Overall annual rupture risk :
0,9 %





No. at Risk				
3–4 mm	3132	1882	1681	1102
5–6 mm	1854	809	712	471
7–9 mm	1016	418	363	240
10–24 mm	661	268	223	154
≥25 mm	34	8	3	2



(UCAS Japan investigators, N Engl J Med 2012; 366: 2474-82)

Other, epidemiological, risk factors for rupture of UIAs in the general population

Studies assessing the risk of SAH in patients known to have an UIA or that had investigated the characteristics of people who experienced a SAH without previously be know to have a UIA

	Odds ratio
- **HTA**	**2.5**
- **Smoking**	**3.1**
- **Alcohol > 150 g/w**	**1.5**

(Clarke M. Systematic review of reviews of risk factors for Intracranial aneurysms. Neuroradiology 2008; 50: 653)

Risk of rupture of UIA in the general population

Risk of rupture of UIA in the ADPKD population

Risk of prophylactic repair of an UIA

Decision – analysis

Practical attitude in ADPKD

Natural history of IA in ADPKD patients

	Total n	Mean F-U	n rupture	n growth	n new
Belz, 2003	n = 20	15 yrs			
	-11 SAH (+)		1	1	4
	- 9 SAH (-)		0	1	1
Gibbs, 2004	n = 21	7 yrs			
	- 7 FH (+)		0	0	1
	-14 FH (-)		0	1	0
Irazabal, 2012	n = 31	6 yrs			
	-17 FH (+)		0	1	1
	-14 FH (-)		0	1	0
Jiang 2013	n = 40	> 3 yrs	0	4	?
Total	n = 112	3-15 yrs	1	9	7/72

(Belz MM, Kidney Int 2003; 63:1824-30
Gibbs GF, Kidney Int 2004;65:1621-1627
Irazabal MV, Clin J Am Soc Nephrol 211;6:1274-85
Jiang T, Eur J Radiol 2013; in press)

Causes of Death in Autosomal Dominant Polycystic Kidney Disease[1,2]

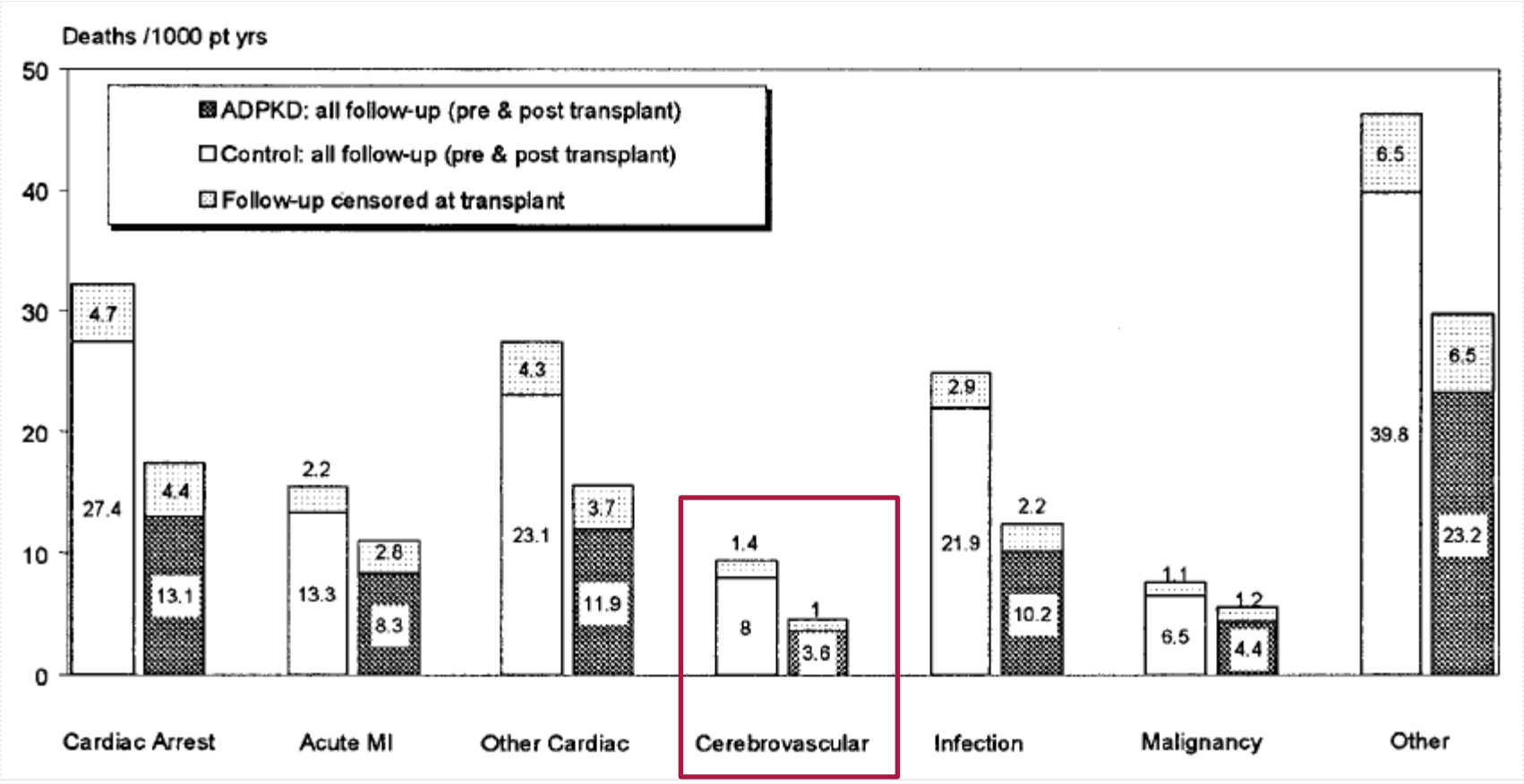
Godela M. Fick, Ann M. Johnson, William S. Hammond, and Patricia A. Gabow[3]

(J. Am. Soc. Nephrol. 1995; 5:2048–2056)

- **Medical records of 129 patients who died between 1956 and 1993 (58% had autopsy)**

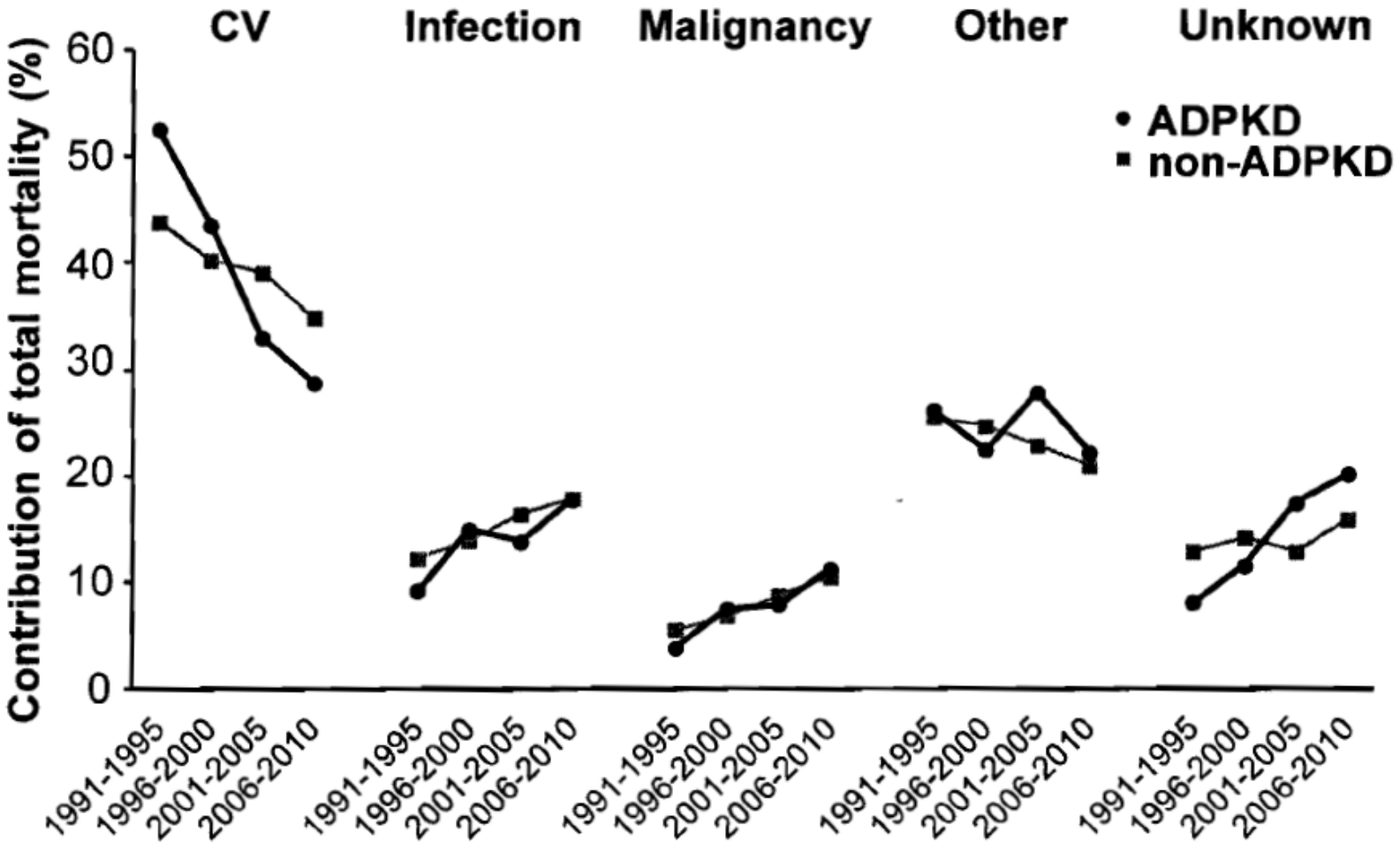
- **A ruptured IA was the cause of death in 8 (6%)**
  - **Mean age at death : 37 yr**
  - **7/8 before ESRD**

- **« Insufficiently treated hypertension in some ? »……**



American Journal of Kidney Diseases, Vol 38, No 4 (October), 2001: pp 777-784

Figure 6. Trends in causes of death in patients on renal replacement therapy for ADPKD and non-ADPKD. Adjusted for age and sex to the distribution of EU27 population in 2005. Abbrevation CV stands for cardiovascular.



(Spithoven EM, Gansevoort RT et al. Renal replacement therapy for ADPKD in Europe : Analysis of data from the ERA-EDTA Registry Nephrol Dial Transpl, in press)

Risk of rupture of UIA in the general population

Risk of rupture of UIA in the ADPKD population

Risk of prophylactic repair of an UIA

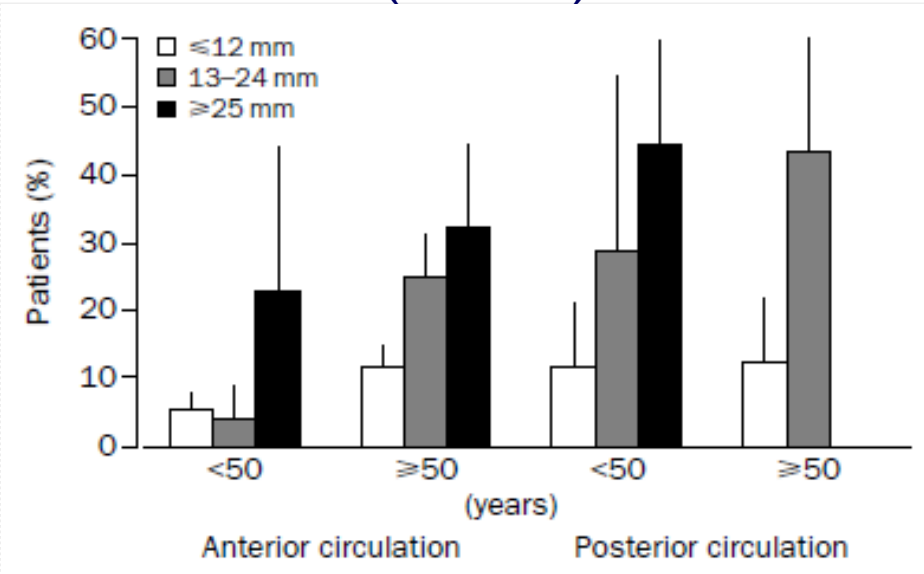
Decision – analysis

Practical attitude in ADPKD

Poor outcome (death or serious disability) at 1 year after repair of an UIA according to age, site and size

Surgical

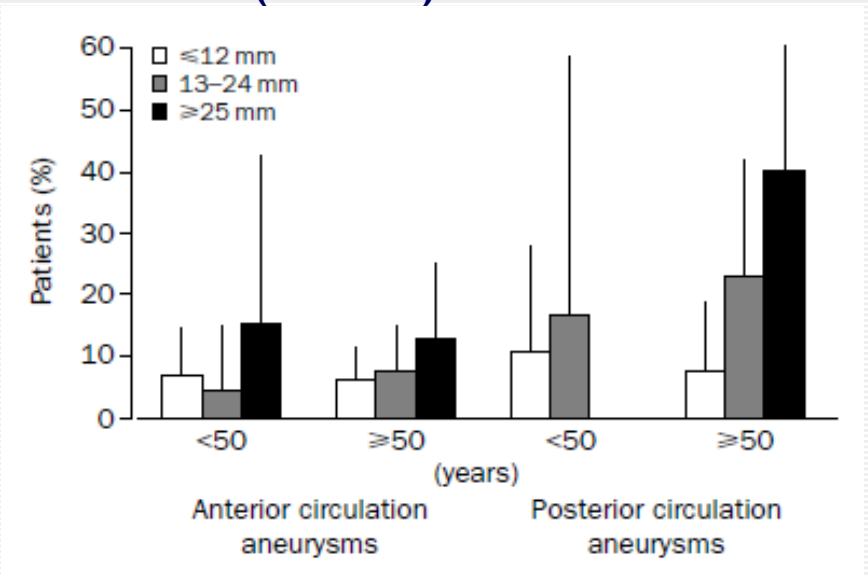
(n = 1917)



Overall mortality : 2.3 %
Overall morbidity : 9.8 %

Endovascular

(n = 451)



Overall mortality : 3.1 %
Overall morbidity : 6.4 %

(ISUIA investigators, Lancet 2003; 362:103)

Risk of rupture of UIA in the general population

Risk of UIA in the ADPKD population

Risk of prophylactic repair of an UIA

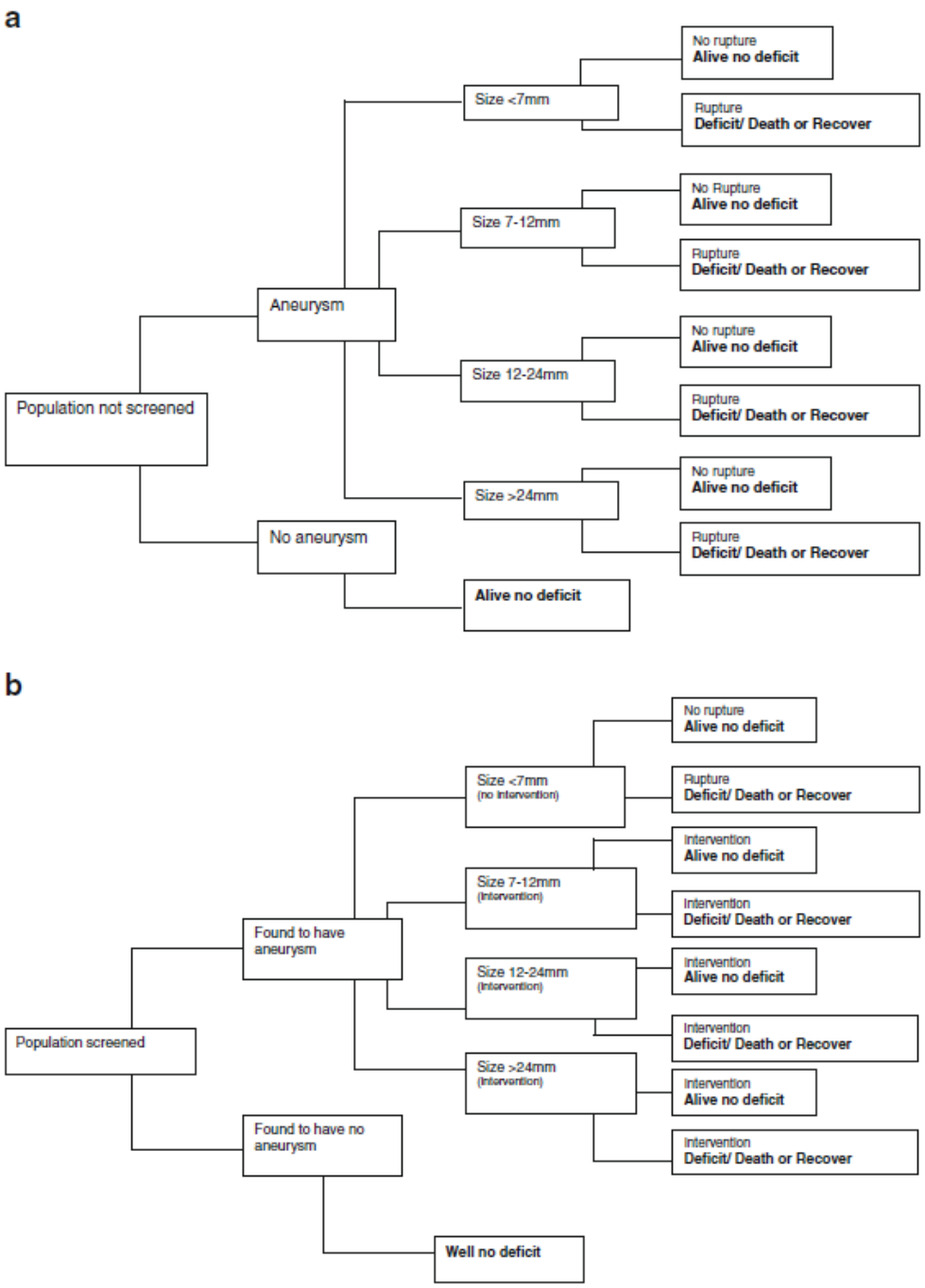
Decision – analysis

Practical attitude in ADPKD

A mathematical model of utility for single screening of asymptomatic unruptured intracranial aneurysms at the age of 50 years

Lucia M. Li · Diederik O. Bulters · Ramez W. Kirollos

Acta Neurochir (2012) 154:1145–1152



(Li LM, Acta Neurochir 2012; 154: 1145-1152)

Li decision analysis : main results

- The 5-yr risk of rupture at which screening results in a gain of QALY is 13% at a screening age of 50
  8% at a screening age of 30

- This threshold risk is not decreased by increasing the prevalence to 25%

- The risk of prophylactic intervention should be reduced to <25% of that reported in ISUIA to provide a clinical benefit in the general population

- The key determinant is the individual risk of rupture

Familial Clustering of Ruptured Intracranial Aneurysms in Autosomal Dominant Polycystic Kidney Disease

Mark M. Belz, MD, Richard L. Hughes, MD, William D. Kaehny, MD, Ann M. Johnson, MS, Godela M. Fick-Brosnahan, MD, Michael P. Earnest, MD, and Patricia A. Gabow, MD

American Journal of Kidney Diseases, Vol 38, No 4 (October), 2001: pp 770-776

• **Ruptured intracranial aneurysm (RICA) is a life-threatening complication of autosomal dominant polycystic kidney disease (ADPKD). A family history of RICA may be a risk factor for RICA. Six hundred eight adult members of 199 ADPKD families were interviewed, and family pedigrees were constructed. Individuals were classified as having definite, probable, or possible RICAs from evidence and history obtained in interviews. Central nervous system (CNS) events not consistent with RICA were classified as other CNS events. Seventy-seven CNS events occurred in 906 subjects with ADPKD (8.5%) versus 13 events in 823 subjects without ADPKD (1.6%; $P < 0.0001$). No event in subjects without ADPKD was consistent with an RICA. Twenty-seven other (non-RICA) CNS events occurred in subjects with ADPKD (3%) versus 13 events in subjects without ADPKD (1.6%; $P = 0.05$). The frequency of RICA was increased in subjects with ADPKD: 21 definite RICAs in subjects with ADPKD (2%) versus none in subjects without ADPKD ($P < 0.001$); 28 definite and probable RICAs in subjects with ADPKD (3%) versus none in subjects without ADPKD ($P < 0.001$); and 50 definite, probable, and possible RICAs in subjects with ADPKD (5.5%) versus none in subjects without ADPKD ($P < 0.001$). The null hypothesis that RICAs are randomly distributed among subjects with ADPKD was tested for definite RICAs (n = 21), definite and probable RICAs (n = 28), and definite, probable, and possible RICAs (n = 50). In the three categories, the null hypothesis was rejected at *P* less than 0.05, *P* less than 0.05, and *P* less than 0.005, respectively. Vascular CNS events occurred more frequently in ADPKD than non-ADPKD family members, and clustering of RICAs occurred in families with ADPKD.**

Risk of intracranial aneurysm bleeding in autosomal-dominant polycystic kidney disease

T Ring[1] and D Spiegelhalter[2]

Kidney International (2007) **72**, 1400–1402

Patients with autosomal-dominant polycystic kidney disease (ADPKD) carry an increased risk of developing intracranial aneurysms. Bleeding from these sites is a significant complication with the events reported to cluster in some families. In this study we determined if individualized risk of aneurysm rupture can be estimated based on family history using a Bayesian random effects model. Previously reported data were used to define distributions and to construct a model that fit these data. Our results confirm that intracerebral aneurysm bleeding in ADPKD patients tends to cluster in families and that basic family history can provide a simple estimate of family-specific risk.

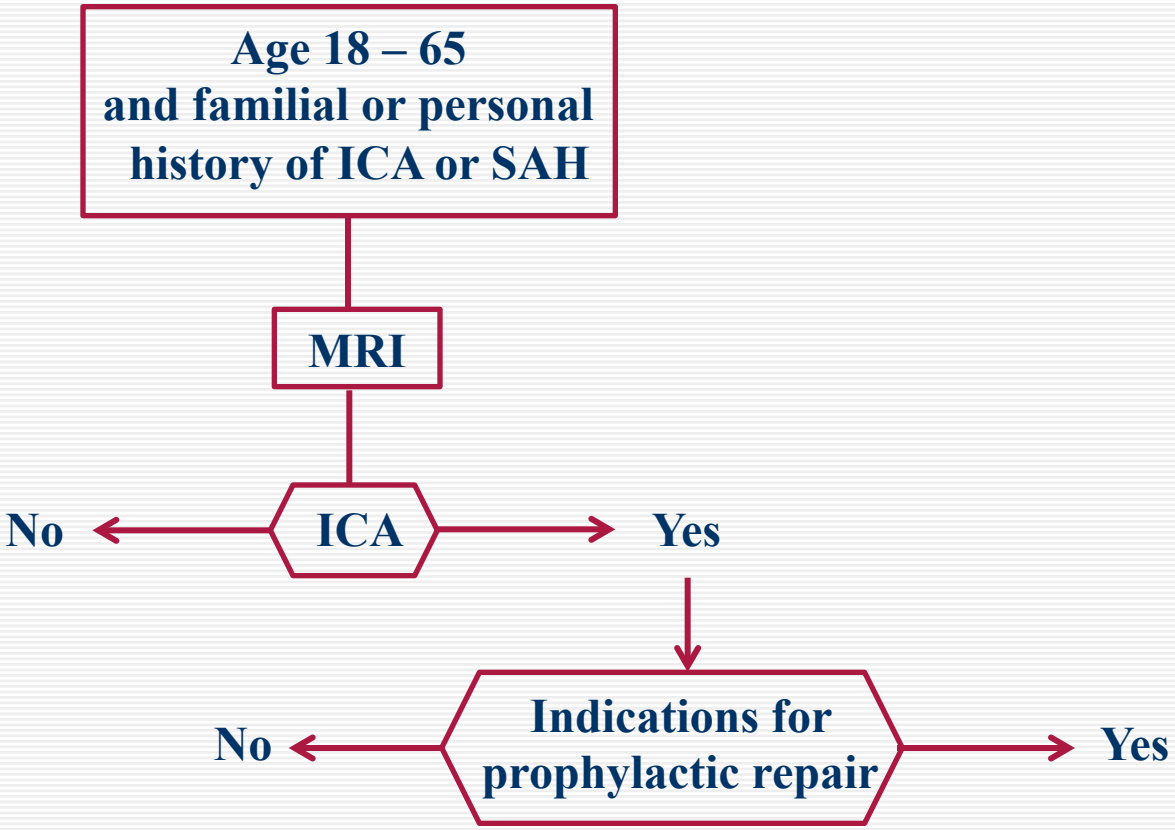
Risk of rupture of UIA in the general population

Risk of UIA in the ADPKD population

Risk of prophylactic repair of an UIA

Decision – analysis

Practical attitude in ADPKD


Age 18 – 65
and familial or personal
history of ICA or SAH
MRI
ICA
No
Yes
Indications for
prophylactic repair
No
Yes

Indications for prophylactic repair

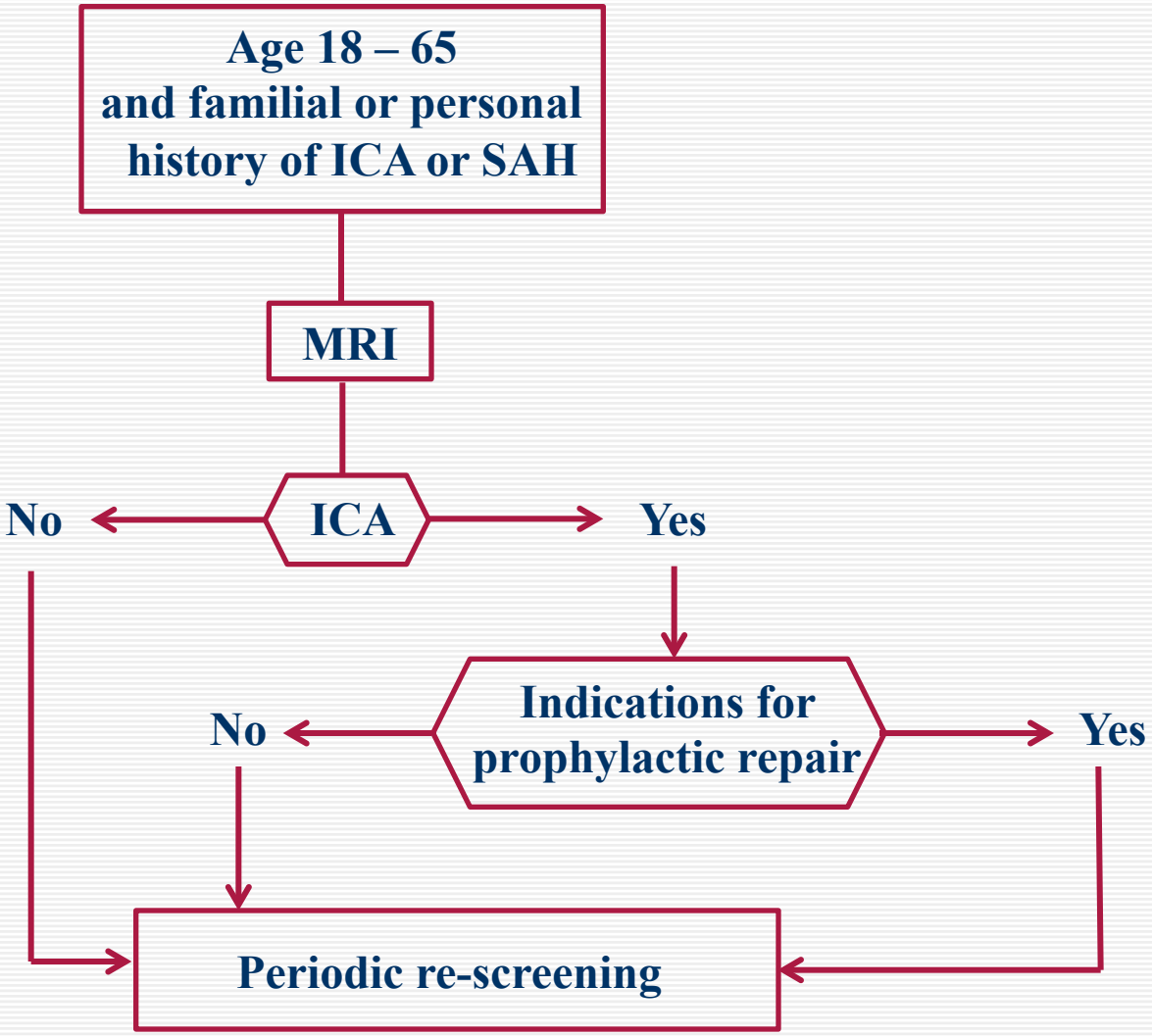
Rely on 3 main factors

- **IA characteristics :**
  size (> 6 – 7 mm), location, morphology
- **patient's age and general health**
- **doctor's (neuroradiologist/neurosurgeon) experience**

(Williams LN and Brown RD. Neurol Clin Pract 2013; 3: 99-108)

Conservative management for < 6 - 7 mm IA

- ~~Tobacco~~
- Aggressive treatment HTA
- Repeat imaging
  - At 6 months, and then annually for 3 years
  - if stable, every 2-3 yrs


Age 18 – 65
and familial or personal
history of ICA or SAH
MRI
ICA
No
Yes
Indications for
prophylactic repair
No
Yes
Periodic re-screening

But some recommend screening in all ADPKD patients whatever the family history

Screening for Intracranial Aneurysm in 355 Patients With Autosomal-Dominant Polycystic Kidney Disease

H.W. Xu, MD, PhD; Sheng Qiang Yu, MD, PhD; Chang Lin Mei, PhD; Ming Hua Li, MD, PhD

(*Stroke*. 2011;42:204-206.)

Characteristics of Intracranial Aneurysms in the Else Kröner-Fresenius Registry of Autosomal Dominant Polycystic Kidney Disease

Hartmut P.H. Neumann[a] Angelica Malinoc[a] Janina Bacher[a]
Zinaida Nabulsi[a] Vera Ivanovas[b] Nadine Ortiz Bruechle[g]
Irina Mader[g] Michael M. Hoffmann[c] Peter Riegler[j]
Annette Kraemer-Guth[f] Christian Burchardi[h] Elke Schaeffner[i]
Rodolfo S. Martin[k] Pablo J. Azurmendi[k] Klaus Zerres[g]
Cordula Jilg[d] Charis Eng[l] Sven Gläsker[e]

Cerebrovasc Dis Extra 2012;2:71–79

Should Patients with Autosomal Dominant Polycystic Kidney Disease Be Screened for Cerebral Aneurysms?

M.N. Rozenfeld, S.A. Ansari, A. Shaibani, E.J. Russell, P. Mohan, and M.C. Hurley

AJNR Am J Neuroradiol ●:● ● 2014

Let us recognize that a family history (FH) is found in only a minority of ADPKD patients presenting with a IA rupture

Intracranial aneurysms in autosomal dominant polycystic kidney disease.

Chauveau D, Pirson Y, Verellen-Dumoulin C, Macnicol A, Gonzalo A, Grünfeld JP.

Kidney Int. **1994** Apr;45(4):1140-6.

	FH (+)	FH (-)
n pedigrees	10 (18%)	45 (82%)
mean n ADPKD pts per families	5.2	4.1

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Zinaida Nabulsi[a] Vera Ivanovas[b] Nadine Ortiz Bruechle[g]
Irina Mader[g] Michael M. Hoffmann[c] Peter Riegler[j]
Annette Kraemer-Guth[f] Christian Burchardi[h] Elke Schaeffner[i]
Rodolfo S. Martin[k] Pablo J. Azurmendi[k] Klaus Zerres[g]
Cordula Jilg[d] Charis Eng[l] Sven Gläsker[e]

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FH (+) in only 5/27 (19%) families

The treshold size to intervene is also a matter a debate

Size distribution of 27 ruptures IA in patients with ADPKD

< 5 mm :	19 %
5 – 9 :	33 %
10 – 24 :	26 %
> 25	22 %

(Schievink J. Am Soc Nephrol 1992; 3: 88-95)

Table 2 Summary of recommendations

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	• Patients with ADPKD without family history of aneurysm	• General population
• ADPKD with family history of UIA or SAH	• Patients with one family member with UIA or SAH (per patient preference)	
• Patients with coarctation of the aorta		
Recommendations for treatment		
Strongly consider treatment with clipping or endovascular procedure	**Possibly consider treatment with clipping or endovascular procedure**	**Do not recommend treatment with clipping or endovascular procedure**
• UIA ≥12 mm in diameter	• 7 mm ≤ UIA < 12 mm in diameter + any of the following features:	• UIA < 7 mm in diameter in anterior circulation without any high-risk features such as family history of SAH or presence of daughter sac
• Symptomatic UIA	◦ UIA in younger patients	• Asymptomatic cavernous internal carotid aneurysms
• Enlarging UIA	◦ UIA in higher-risk locations such as posterior circulation or posterior communicating artery	
	◦ UIA with daughter sac	
	◦ Family history of SAH	
	• UIA <7 mm in diameter in younger patients + any of the following features:	
	◦ UIA in high-risk locations such as posterior circulation or posterior communicating artery	
	◦ UIA with daughter sac	
	◦ Family history of SAH	

Abbreviations: ADPKD = autosomal dominant polycystic kidney disease; SAH = subarachnoid hemorrhage; UIA = unruptured intracranial aneurysm.

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Table 1. Screening considerations for intracranial aneurysms

Who should be screened for ICAs?

(i) Any ADPKD patient with symptoms (severe or atypical headache, TIA, cranial nerve palsy)

(ii) Patient in a high-risk occupation (pilot)

(iii) Patient with a family history (initial screen should be prior to the time of the first event in the family)

(iv) Patients preparing for major surgery (such as renal transplant) or who will receive long-term anticoagulation (such as for a prosthetic heart valve)

(v) Patients with anxiety regarding an ICA

(vi) Patients with a prior history of ICA rupture.

Screening test: MR angiogram without gadolinium.

Intervention versus observation of an ICA: based on ICA characteristics (size and location), patient characteristics (age, functional status and occupation) and operator characteristics (risk of complications).

Rescreening: Every 5 years in high-risk patients. Consider rescreening once in low-risk patients after 10 years.

(Luciano RL. Nephrol Dial Transplant 2013, in press)