

# Presymptomatic Screening for Intracranial Aneurysms in Patients with Autosomal Dominant Polycystic Kidney Disease

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## Abstract

**Background and objectives** Intracranial aneurysm rupture is the most devastating complication of autosomal dominant polycystic kidney disease. Whether selective or widespread intracranial aneurysm screening is indicated remains controversial.

**Design, setting, participants & measurements** Records of 3010 patients with autosomal dominant polycystic kidney disease evaluated at the Mayo Clinic between 1989 and 2017 were reviewed. Those who had presymptomatic magnetic resonance angiography screening were included.

**Results** Ninety-four intracranial aneurysms were diagnosed in 75 of 812 (9%) patients who underwent magnetic resonance angiography screening. Sex, age, race, and genotype were similar in the groups with and without aneurysms; hypertension and history of smoking were more frequent in the aneurysm group. Twenty-nine percent of patients with aneurysms compared with 11% of those without aneurysms had a family history of subarachnoid hemorrhage ( $P < 0.001$ ). Most aneurysms were small (median diameter = 4 mm; range, 2–12 mm); 85% were in the anterior circulation. During a total imaging follow-up of 469 patient-years, *de novo* intracranial aneurysms were detected in five patients; eight intracranial aneurysms grew (median = 2 mm; range, 1–3 mm). During a total clinical follow-up of 668 patient-years, seven patients had preemptive clipping or coil embolization; no intracranial aneurysms ruptured. During a total clinical follow-up of 4783 patient-years in 737 patients with no intracranial aneurysm detected on the first magnetic resonance angiography screening, two patients had an intracranial aneurysm rupture (0.04 per 100 person-years; 95% confidence interval, 0 to 0.10). The rate of intracranial aneurysm rupture in large clinical trials of autosomal dominant polycystic kidney disease was 0.04 per 100 patient-years (95% confidence interval, 0.01 to 0.06).

**Conclusions** Intracranial aneurysms were detected by presymptomatic screening in 9% of patients with autosomal dominant polycystic kidney disease, more frequently in those with familial history of subarachnoid hemorrhage, hypertension, or smoking. None of the patients with and two of the patients without aneurysm detection on screening suffered aneurysmal ruptures. The overall rupture rate in our autosomal dominant polycystic kidney disease cohort was approximately five times higher than that in the general population.

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## Introduction

Autosomal dominant polycystic kidney disease (ADPKD) is characterized by progressive development of bilateral kidney cysts and extrarenal abnormalities, including intracranial aneurysms. The high mortality and morbidity associated with intracranial aneurysm rupture have prompted debate regarding the benefits of presymptomatic screening. We have reported that most unruptured intracranial aneurysms detected by presymptomatic screening in patients with ADPKD using magnetic resonance angiography (MRA) during 1989–2009 were small and in the anterior circulation and that their growth and rupture risks did not seem to be higher than those of unruptured intracranial aneurysms in the general

population (1). Whether selective or widespread screening for unruptured intracranial aneurysms is indicated remains controversial (2). This report includes new patients diagnosed between 2009 and 2017, substantially extends the follow-up in the previous report, and reviews the incidence of intracranial aneurysm rupture in recent longitudinal studies and clinical trials of ADPKD.

## Materials and Methods

### Study Participants

The medical records from 3010 patients with ADPKD evaluated between 1989 and 2017 at Mayo Clinic in Rochester, Minnesota were reviewed. Patients who

underwent presymptomatic screening with MRA were included. Main indications included family history of intracranial aneurysm or subarachnoid hemorrhage, before major elective surgery or kidney transplantation, and high-risk occupations. Exclusion criteria were (1) previous intracranial aneurysm diagnosis at another center, (2) previous history of intracranial hemorrhage or aneurysm treatment, (3) neurologic symptoms other than typical migraine or common headache before the first MRA, and (4) diagnosis of intracranial tumor (Figure 1). Data were collected through June 2018.

### Imaging Screening for Intracranial Aneurysms

The MRA screening technique has been previously described (1). Only those measuring  $\geq 2$  mm were considered to be definite aneurysms. All MRA images were reviewed by the same radiologist (J.H.). Decisions regarding treatment were made in consultation with a neurovascular neurologist or surgeon. When observation was advised, follow-up MRAs were recommended every 6 months during the first year, annually for 3 years, and less frequently thereafter. Aneurysm growth was defined as a  $\geq 1$ -mm diameter increase compared with a previous MRA. When no aneurysm was found, imaging follow-up after 5–10 years was recommended to patients at an increased risk on the basis of our experience and existing literature (3).

### Clinical Considerations and Follow-Up

Hypertension was defined as persistent BP  $>130/80$  mm Hg or needing pharmacologic antihypertensive treatment. Hyperlipidemia was defined by serum total cholesterol  $>240$  mg/dl, serum triglycerides  $>200$  mg/dl, serum LDL  $>160$  mg/dl, or receiving medication for hyperlipidemia. Positive family history required a diagnosis of intracranial aneurysm or subarachnoid hemorrhage in a first

degree relative. Clinical follow-up was the period from MRA detection to last patient contact. All patients diagnosed by presymptomatic screening were contacted when possible. Follow-up of patients without aneurysms on the presymptomatic screening was obtained from the medical records and death certificates.

### Mutation Analyses

All *PKD1* and *PKD2* exons were amplified from genomic DNA or *PKD1*-specific fragments for the duplicated region of *PKD1* and analyzed using direct Sanger sequencing (4) or a capture panel and next generation sequencing (5). Missense changes were evaluated as described previously (4) (ADPKD Mutation Database 2018; <http://pkdb.mayo.edu>).

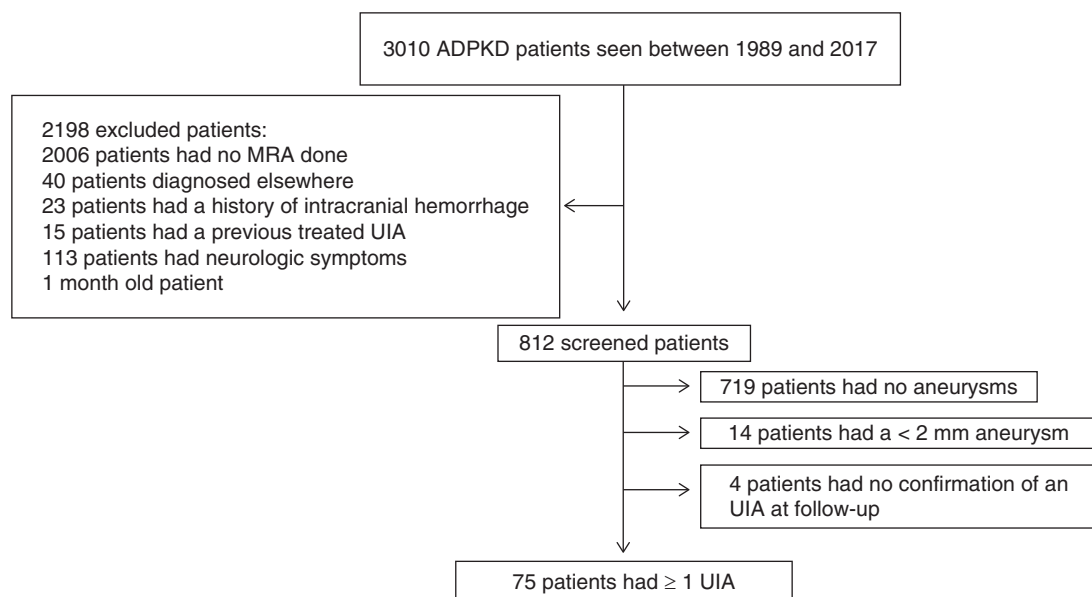
### Statistical Analyses

Baseline data are presented as means and SD or range; *t* tests or chi-squared tests were used for comparisons between groups. Univariate analysis was done to assess risk factors for aneurysm growth. The 95% confidence intervals (95% CIs) for event rates were calculated using  $\lambda \pm 1.96 \times \sqrt{\lambda/n}$ , where  $\lambda$  is the mean rupture rate and *n* is the total patient-years, assuming that the number of events follows a Poisson distribution.

## Results

### Baseline Clinical Parameters and Genetic Analyses

Eight hundred twelve patients with ADPKD underwent presymptomatic MRA screening between 1989 and 2017 (Figure 1). Ninety-four unruptured aneurysms  $\geq 2$  mm were diagnosed in 75 (9%) patients. Sex distribution, age, race, and genotype of the two groups were not different (Table 1). Hypertension and history of smoking, but not dyslipidemia, were more frequent in the patients with



**Figure 1. | Study flow chart for the inclusion of patients in the study.** ADPKD, autosomal dominant polycystic kidney disease; MRA, magnetic resonance angiography; UIA, unruptured intracranial aneurysm.

aneurysms. Patients with aneurysms had more advanced CKD. The demographic and clinical characteristics of the patients who did and did not undergo presymptomatic MRA screening were similar (Supplemental Table 1).

Twenty-eight (37%) of the patients with aneurysms compared with 132 (18%) of patients without aneurysms had familial history of intracranial aneurysm or subarachnoid hemorrhage ( $P<0.001$ ) (Table 1). This difference was accounted for by the disparity in the frequency of familial history of subarachnoid hemorrhage (29% versus 11%) rather than the frequency of unruptured intracranial aneurysms only (8% versus 7%). Aneurysms were detected by presymptomatic screening in 47 of 652 (7%) patients without familial history of intracranial aneurysm, six of 59 (10%) patients with familial history of unruptured intracranial aneurysms only, and 22 of 101 (22%) patients with familial history of subarachnoid hemorrhage ( $P<0.001$ ). Ten patients with a positive family history had two or more family members with a history of intracranial aneurysm or subarachnoid hemorrhage.

### Baseline MRA Findings

Ninety-four saccular aneurysms were detected in 75 patients (64 in 49 women and 30 in 26 men). Fourteen (19%) patients had multiple aneurysms. Twelve (16%) patients had two aneurysms, one (1%) had three aneurysms, and one (1%) had six aneurysms. Eighty-three (88%) aneurysms were in the anterior circulation, and 11 (12%) aneurysms

were in the posterior circulation (Supplemental Table 2). Most were small, with a median diameter of 4 mm (range, 2–12 mm).

### Follow-Up of Patients with Intracranial Aneurysm Detected by Presymptomatic Screening at Baseline

**MRA Imaging Follow-Up.** Sixty-one of the 75 patients had one or more follow-up MRAs (mean  $=4\pm3$ ; median =3; interquartile range [IQR], 4; range, 1–17 studies) before any intervention. During a cumulative imaging follow-up of 469 patient-years (mean  $=8\pm7$  years; median =6; IQR, 8; range, 1–29 years), *de novo* aneurysms measuring  $\geq 2$  mm were detected in five patients (Table 2), including a left middle cerebral artery aneurysm that increased from 2 to 5 mm during follow-up. The rate of *de novo* intracranial aneurysm formation in these 75 patients was 1.07 (95% CI, 0.13 to 2.0) per 100 patient-years. Aneurysm growth was detected in eight (13%) patients (Table 3), including one patient with a *de novo* aneurysm also listed in Table 2. Average increase in diameter was  $2\pm1$  mm (median =2; IQR, 2; range, 1.0–3.0 mm) over a mean follow-up period of  $179\pm82$  months (median, 190; IQR, 159; range, 60–266). No growth or *de novo* aneurysm formation was detected in the remaining 49 patients who had at least two MRA studies (Figure 2).

There were no significant differences between patients with and without aneurysm growth (Supplemental Table 3). Fourteen of the 75 patients did not have imaging follow-up (four died from unrelated causes, two had been recently

**Table 1. Demographic, genetic, and clinical characteristics of the study population with or without an intracranial aneurysm at the initial screening**

Variable	Overall, n=812	With, n=75	Without, n=737
Sex (% men:women)	353:459 (43:57)	26:49 (35:65)	327:410 (44:56)
Mean age at the first MRA (SD), yr	51 (13)	51 (11)	51 (13)
<b>Age group, yr, n (%)</b>			
30–39	138 (17)	8 (11)	130 (18)
40–49	231 (28)	27 (36)	204 (28)
50–59	238 (29)	21 (28)	217 (29)
60–69	205 (25)	19 (25)	186 (25)
<b>Race, n (%)</b>			
White	730 (90)	66 (88)	664 (90)
Other	42 (5)	3 (4)	39 (5)
Not reported	40 (5)	6 (8)	34 (5)
<b>Genotype available, n (%)</b>			
<i>PKD1</i> truncating	360 (44)	41 (55)	319 (43)
<i>PKD1</i> nontruncating	173 (48)	20 (49)	153 (48)
<i>PKD2</i>	111 (31)	11 (27)	100 (31)
Other	38 (11)	7 (17)	31 (10)
NMD	7 (2)	0 (0)	7 (2)
Hypertension, n (%)	31 (9)	3 (7)	28 (9)
Dyslipidemia, n (%)	631 (78)	67 (90)	564 (77)
Smoking history, n (%)	393 (48)	33 (44)	360 (49)
CKD stage, n (%)	197 (24)	32 (43)	167 (23)
1–2	253 (31)	11 (15)	242 (33)
3–4	326 (41)	45 (63)	281 (38)
ESKD	226 (28)	16 (22)	210 (29)
<b>Family history of intracranial aneurysm (%)</b>			
Unruptured only	160 (20)	28 (37)	132 (18)
Ruptured/subarachnoid hemorrhage	59 (7)	6 (8)	53 (7)
None	101 (12)	22 (29)	79 (11)
	652 (80)	47 (63)	605 (82)

MRA, magnetic resonance angiography; NMD, no mutation detected.

**Table 2. Clinical characteristics of patients with *de novo* intracranial aneurysm formation during follow-up**

Characteristic	Patient No.				
	4	37	106	133	162
Age at first MRA, yr	51	67	29	48	45
Sex	W	W	M	W	W
IA location on first MRA	Bilateral MCA	R ACA	R MCA	R SCA	BA
Time to detection of <i>de novo</i> , mo	149	90	61	165	193
Location of the <i>de novo</i> IA	ACA	L MCA	L MCA	L ICA	L ACA
Size of previous IA, mm	3.0	3.5	3.0	2.0	3.0
Time from first positive to last MRA, mo	0	0	198	24	84
Size of the <i>de novo</i> IA, mm	2	3	2	2	3
Genotype	PKD1T	PKD1NT	PKD1T	PKD1NT	PKD1T
Family history of IA/SAH	Yes	Yes	Yes	Yes	Yes
Hypertension	Yes	Yes	Yes	Yes	Yes
Treatment with ACEI or ARB	Yes	Yes	Yes	Yes	Yes
Dyslipidemia	Yes	Yes	No	Yes	No
Statins	Yes	Yes	No	Yes	No
History of smoking	No	No	No	Yes	No
eGFR at first MRA, ml/min per 1.73 m <sup>2</sup>	14	13	49	44	57
eGFR at last follow-up, ml/min per 1.73 m <sup>2</sup>	TX	TX	TX	TX	TX
Death	No	No	No	No	No

MRA, magnetic resonance angiography; W, women; M, men; IA, intracranial aneurysm; MCA, middle cerebral artery; R, right; ACA, anterior cerebral artery; SCA, superior cerebellar artery; BA, basilar artery; L, left; SAH, subarachnoid hemorrhage; ACEI, angiotensin converting enzyme inhibitor; ARB, angiotensin receptor blocker; TX, kidney transplant.

diagnosed, three only had clinical follow-up, and five were lost to follow-up).

**Clinical Follow-Up.** During a cumulative clinical follow-up of 668 patient-years (mean =  $9 \pm 7$ ; median = 9; range, 0–28 years), none of the 94 intracranial aneurysms detected by presymptomatic screening ruptured. Seven aneurysms in seven patients were treated with surgical clipping or coil embolization (Supplemental Table 4). Surgical clipping was performed in two aneurysms measuring <7 mm in

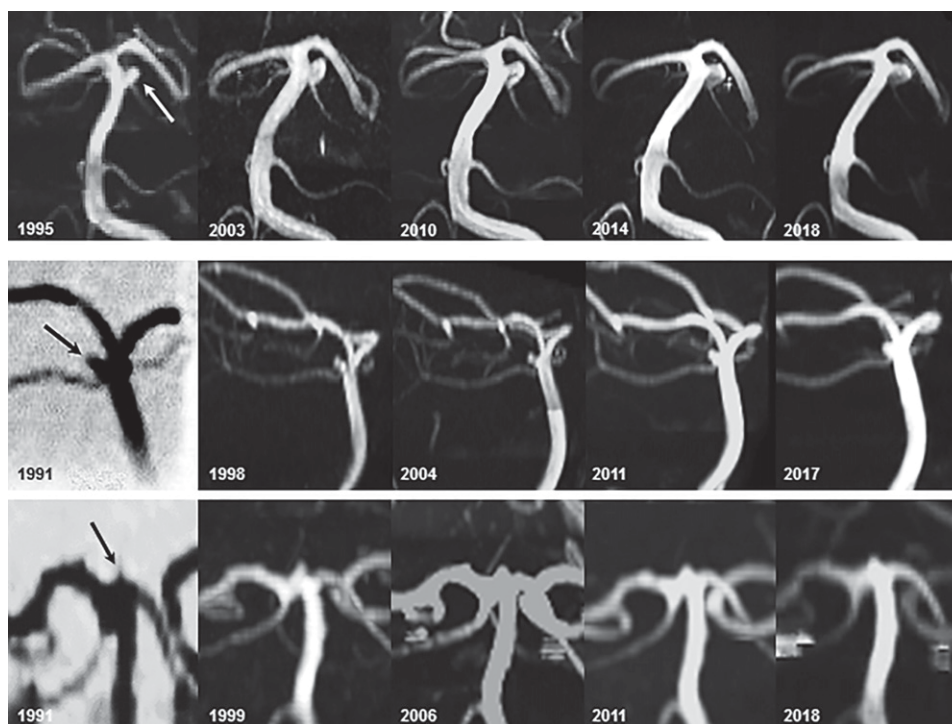
diameter: a 5-mm middle cerebral artery aneurysm and a 3-mm basilar artery aneurysm. Five aneurysms measuring  $\geq 7$  mm in diameter were clipped or coiled. One patient experienced a transient behavioral change associated with an acute left frontal infarct after the clipping of an anterior communicating artery aneurysm. A postoperative anterior temporal territory infarct without neurologic deficit was noted on a follow-up MRA in another patient. No other complications, aneurysmal growth, or new intracranial

**Table 3. Clinical characteristics of the patients with intracranial aneurysms that increased in size during follow-up**

Characteristic	Patient No.							
	40	106	106	155	162	165	242	582
Age at first MRA, yr	48	29	29	45	45	59	61	47
Sex	W	M	M	M	W	W	M	W
Location	R ICA	R MCA	L MCA	ACoA	BA	R ICA	R PA	R MCA
Size at first MRA, mm	2	3	2	5	5	4	4	2
Duration of follow-up, mo	107	259	259	98	266	207	60	173
Number of MRAs	6	9	9	3	17	5	4	7
Size at last MRA, mm	3	4	5	6	6	5	6	5
Increase in size, mm	1	1	3	1	1	1	3	3
Genotype	PKD1	PKD1	PKD1	NA	PKD1	NA	NA	NA
Family history of UIA/SAH	SAH	UIA	UIA	No	SAH	No	SAH	No
Hypertension	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Dyslipidemia	No	No	No	No	No	Yes	Yes	Yes
History of smoking	No	No	No	Yes	No	No	Yes	Yes
eGFR at first MRA, ml/min per 1.73 m <sup>2</sup>	48	60	60	34	57	44	59	35
eGFR at last follow-up, ml/min per 1.73 m <sup>2</sup>	TX	TX	TX	13	TX	15	57	TX
Death	No	No	No	No	No	No	Yes	No

MRA, magnetic resonance angiography; W, women; M, men; R, right; ICA, internal carotid artery; MCA, middle cerebral artery; L, left; ACoA, anterior communicating artery; BA, basilar artery; PA, pericallosal artery; NA, not available; UIA, unruptured intracranial aneurysm; SAH, subarachnoid hemorrhage; TX, kidney transplant.





**Figure 2. | Stability of small intracranial aneurysms detected by presymptomatic screening.** (Top row) A 45-year-old woman with a family history of subarachnoid hemorrhage was found to have a 4.7-mm left superior cerebellar artery aneurysm in 1995; subsequent imaging demonstrated slight enlargement to a maximal size of 6.2 mm, which then remained stable through 2018. (Middle row) A 45-year-old woman was found to have a 2.0-mm right superior cerebellar aneurysm in 1991; subsequent imaging demonstrated stability of the aneurysm through 2017. (Bottom row) A 45-year-old woman with a family history of subarachnoid hemorrhage was found to have a 2.0-mm basilar tip aneurysm in 1991; subsequent imaging demonstrated stability of the aneurysm through 2017.

aneurysms were observed after follow-up periods of 10–93 months.

Three aneurysms measuring  $\geq 7$  mm in diameter in three patients were treated conservatively due to major comorbidities in two patients and because the aneurysm was considered to be at low risk for rupture in the third patient. A 59-year-old woman on maintenance hemodialysis with severe atherosclerosis had a 9.8-mm middle cerebral artery and a 4-mm internal carotid artery aneurysm on initial screening while being considered for kidney transplantation. She decided not to have endovascular coiling or surgery. There was no significant change on a follow-up MRA 31 months later. She declined additional imaging and died from an unrelated cause 117 months after the initial MRA. A 52-year-old woman on maintenance hemodialysis with a 7-mm left middle cerebral artery aneurysm and five additional smaller aneurysms died from an unrelated cause 2 months after the initial MRA. A 7-mm broad-based cavernous internal carotid artery aneurysm discovered in a 40-year-old man evaluated for kidney transplantation remained stable 85 months after the initial MRA.

Thirteen patients died during follow-up from causes unrelated to the intracranial aneurysms (Supplemental Table 5). Eight of these 13 patients had reached ESKD and were on dialysis or had received a kidney transplant.

#### Follow-Up of Patients with No Intracranial Aneurysm Detected by Presymptomatic Screening at Baseline

**MRA Follow-Up.** One hundred thirty-five of the 737 patients with no intracranial aneurysm detected on the

initial MRA screening had at least one additional MRA during a mean follow-up of  $7 \pm 4$  years. Three of these patients had *de novo* intracranial aneurysms measuring 2, 2, and 4 mm detected during an MRA follow-up of 933 patient-years. The rate of *de novo* aneurysm formation was 0.32 (95% CI, 0 to 0.68) per 100 patient-years.

**Clinical Follow-Up.** Intracranial aneurysm ruptures occurred in two of 737 patients with no aneurysm detected on the initial screening during a clinical follow-up of 4783 patient-years (0.04 per 100 patient-years; 95% CI, 0 to 0.10). The rupture rate for the whole cohort of 812 patients, including the 75 patients with an aneurysm detected on initial screening, was 0.04 (95% CI, 0 to 0.09) per 100 patient-years. The first patient was a 54-year-old woman with ADPKD, CKD stage 4, history of smoking, hypertension, and familial history of subarachnoid hemorrhage (mother and daughter) who experienced a sentinel headache 17 years after initial screening. A computerized tomography scan was negative, and an MRA showed a possible 2-mm right middle cerebral artery aneurysm. Five days later, the aneurysm ruptured, and a computerized tomography showed a subarachnoid hemorrhage. The aneurysm was coiled with full neurologic recovery without significant sequelae. The cerebral angiogram also revealed a 2-mm left middle cerebral artery aneurysm that was also coiled and a 1-mm anterior cerebral artery aneurysm. The second patient was a 29-year-old woman with severe ADPKD, bilateral nephrectomy, maintenance hemodialysis for 14 months, and familial history

of unruptured intracranial aneurysm (mother). She had a rupture of a 10-mm basilar artery aneurysm with a 3-mm daughter sac that led to her death 11 years after a negative head MRA. Eighty-three of 737 patients who had no aneurysm detected on the initial MRA screening have died. In one of them (described above), the cause of death was a ruptured intracranial aneurysm. No other deaths are known to be due to intracranial aneurysm rupture, but causes of death in 13 patients are not known.

## Discussion

The prevalence of intracranial aneurysms is four times higher in patients with ADPKD than in the general population (8%–12% versus 2%–3%, respectively) (6,7). Nonmodifiable and modifiable risk factors are associated with intracranial aneurysm development and rupture (8–10). Nonmodifiable factors include women, older age, history of prior aneurysm or subarachnoid hemorrhage, family history of intracranial aneurysm or subarachnoid hemorrhage, and Finnish or Japanese ethnicity. Modifiable factors include smoking, hypertension, and excess alcohol intake. The risk of subarachnoid hemorrhage is three to seven times higher in first degree relatives of patients with subarachnoid hemorrhage than in the general population but similar to the general population in second degree relatives (11).

The effectiveness of presymptomatic screening and pre-emptive intervention to prevent aneurysmal rupture depends on the prevalence of intracranial aneurysms, yield of the screening procedure, risk of rupture with medical therapy only, morbidity and mortality associated with clipping or embolization of the aneurysm, technical success of these interventions, and risk of *de novo* aneurysm development and rupture (12–16). The information available on the natural history of unruptured intracranial aneurysms and their treatment derives mainly from studies in the general population.

The International Study of Unruptured Intracranial Aneurysms, a North American prospective study, followed 1692 patients with unruptured intracranial aneurysm and found that aneurysm size, aneurysm location (posterior circulation and posterior communicating artery), and previous subarachnoid hemorrhage are the strongest predictors of rupture (12,13). The Unruptured Cerebral Aneurysm Study from Japan followed 6697 patients and found that aneurysm size ( $>7$  mm), aneurysm location (anterior and posterior communicating arteries), and the presence of a daughter sac were associated with increased risk of rupture (15). Investigators from six prospective natural history studies pooled data on 8382 patients to develop a prognostication scoring system called PHASES on the basis of six risk factors: population, hypertension, age, aneurysm size and location, and previous subarachnoid hemorrhage from another aneurysm (16). In North America and European countries other than Finland, the 5-year rupture risks of an unruptured intracranial aneurysm  $<7$  mm in a patient  $<70$  years old with hypertension but without a history of a previous subarachnoid hemorrhage were 0% (internal carotid artery) and 1% (middle cerebral artery, anterior cerebral artery, posterior cerebral artery, and posterior circulation). For an unruptured

intracranial aneurysm measuring 7–9.9 mm, the risks were 1% (internal carotid artery and middle cerebral artery), 2% (anterior cerebral artery), and 3% (posterior cerebral artery and posterior circulation).

Much less is known on the natural history of intracranial aneurysms in ADPKD. Whether risks of growth and rupture are greater than in the general population is not known. In a study from Olmsted County, Minnesota, aneurysmal rupture rate for patients with ADPKD was approximately 0.05 per 100 patient-years compared with 0.01 per 100 patient-years in the general population (17,18). This difference was consistent with the different prevalence rate, suggesting a similar rupture risk.

We previously reported that most unruptured intracranial aneurysms detected by presymptomatic MRA screening in patients with ADPKD during 1989–2009 at our center were small and in the anterior circulation, with growth and rupture risks similar to those of unruptured intracranial aneurysms in the general population (1). This study substantially expands our previous observations. Between 1989 and 2017, unruptured intracranial aneurysms were detected in 75 (9%) of 812 patients, and they were more frequently detected in those with familial history of subarachnoid hemorrhage (22%) and those with hypertension or history of smoking. Most were small and in the anterior circulation. Seven patients had surgical clipping or coil embolization. During a cumulative clinical follow-up of 668 patient-years, no aneurysm detected by presymptomatic screening ruptured. During a total clinical follow-up of 4783 patient-years in the 737 patients with no intracranial aneurysms detected on the initial presymptomatic screening, two patients had an aneurysm rupture. The intracranial aneurysm rupture rate for the whole cohort of 812 patients was 0.04 per 100 patient-years (Table 4).

In a study from China, 54 unruptured intracranial aneurysms were detected by presymptomatic MRA screening in 44 (12%) of 355 patients with ADPKD (Table 4) (19). Sixteen percent had multiple aneurysms. Most were small (mean diameter  $=3.6 \pm 2.3$  mm), and all were in the anterior circulation. None ruptured or were treated during a cumulative follow-up of 144 patient-years (Table 4).

A more recent study from France (2) included 495 consecutive patients with ADPKD: 110 with and 385 without familial risk defined by familial history of intracranial aneurysm, intracranial aneurysm rupture, or subarachnoid hemorrhage or suspicion of intracranial aneurysm rupture (*i.e.*, sudden death or stroke of an unknown origin) in first or second degree family members (Table 4) (2). An intracranial aneurysm was detected in 19 (10%) of 185 patients who had MRA screening: 14 of 100 (14%) with familial risk and five of 85 (6%) without familial risk. Median follow-up for the entire group was 5.9 years. Six of the 19 patients with intracranial aneurysms underwent prophylactic treatment. Surgical repair in one patient was complicated by a postoperative ischemic stroke with minor neurologic sequelae. One of the 13 remaining patients suffered an aneurysmal rupture 5 months after MRA demonstration of a stable 3-mm anterior communicating artery. One of 166 patients with negative screening had a rupture of a right pericallosal artery aneurysm 5 years later. Three of 310 patients without screening also had an aneurysmal rupture after a median follow-up of 6 years.

**Table 4. Rupture rates of intracranial aneurysms in patients with ADPKD**

Author/Study (Reference <sup>a</sup> )	Country	Patient No.	Sex, % Women	Age, <sup>b</sup> yr	UIAs	Follow-Up, Patient-yr	UIAs Treated	UIA Ruptures	Rupture Rate per 100 Patient-yr (95% CI)
<b>Patients with intracranial aneurysms detected by presymptomatic screening</b>									
Xu (19)	China	40	53	53	49	144 <sup>c</sup>	0	0	0
Flahault (2)	France	19	74	41	22	112 <sup>d</sup>	6	1 <sup>e</sup>	0.893 (0 to 2.6)
Sanchis	United States	75	64	51	94	668 <sup>c</sup>	7	0	0
All	—	134	63	—	165	924	13	1	0.108 (0 to 0.3)
<b>Patients with a negative presymptomatic screening</b>									
Schrier (3)	United States	136	—	—	—	1247 <sup>d</sup>	—	0	0
Flahault (2)	France	162	67	40	—	956 <sup>d</sup>	—	1 <sup>f</sup>	0.105 (0 to 0.31)
Sanchis	United States	737	56	51	—	4783 <sup>c</sup>	—	2 <sup>g</sup>	0.041 (0 to 0.10)
All	—	1035	54	—	—	6986	—	3	0.043 (0 to 0.09)
<b>Concurrent patients who had no presymptomatic screening</b>									
Flahault (2)	France	304	—	—	—	1794 <sup>d</sup>	—	3 <sup>h</sup>	0.167 (0 to 0.36)
<b>Patients participating in clinical trials</b>									
CRISP I-III (20)	United States	241	60	32	—	2747	—	0	0
REPRISE (21)	Global	1366	50	47	—	1605	—	3 <sup>i</sup>	0.187 (0 to 0.40)
TEMPO 3:4 (22)	Global	1444	48	39	—	3957	—	2 <sup>j</sup>	0.051 (0 to 0.12)
TEMPO 4:4 (23)	Global	1083	47	42	—	3529	—	1 (1) <sup>k</sup>	0.028 (0 to 0.08)
HALT PKD A (24)	United States	558	49	37	—	3125	—	0 <sup>l</sup>	0
HALT PKD B (25)	United States	486	52	49	—	2527	—	1 (1) <sup>m</sup>	0.040 (0 to 0.12)
EVEROLIMUS (26)	Germany	433	49	44	—	846	—	0	0
SUISSE (27)	Switzerland	100	39	32	—	158 <sup>d</sup>	—	0	0
ALADIN (28)	Italy	85	53	37	—	219 <sup>c</sup>	—	0 <sup>n</sup>	0
DIPAK (29)	Netherlands	305	53	48	—	702	—	0	0
All	—	6095	—	—	—	19,415	—	7	0.04 (0.01 to 0.06)
Total	—	7568	—	—	—	29,119	—	14	0.05 (0.02 to 0.07)

UIA, unruptured intracranial aneurysm; 95% CI, 95% confidence interval; CRISP I-II, Consortium for Radiologic Imaging Studies of Polycystic Kidney Disease; REPRISE, Replicating Evidence of Preserved Renal Function: an Investigation of Tolvaptan Safety and Efficacy in ADPKD; TEMPO, Tolvaptan efficacy and safety in management of autosomal dominant polycystic kidney disease and its outcomes; HALT PKD, Halt Polycystic Kidney Disease; EVEROLIMUS, ADPKD clinical trial; SUISSE, ADPKD clinical trial; ALADIN, Long-acting somatostatin on disease progression in nephropathy due to autosomal dominant polycystic kidney disease; DIPAK, Developing interventions to halt progression of ADPKD.

<sup>a</sup>Information was obtained from the referenced articles and/or principal investigators in large clinical trials for autosomal dominant polycystic kidney disease.

<sup>b</sup>Mean or median.

<sup>c</sup>Estimated from the number of patients and mean follow-up.

<sup>d</sup>Estimated from the number of patients and median follow-up.

<sup>e</sup>Anterior communicating artery.

<sup>f</sup>Pericallosal artery.

<sup>g</sup>Middle cerebral artery and basilar artery.

<sup>h</sup>Anterior communicating artery in all three.

<sup>i</sup>Two patients randomized to placebo and one patient randomized to tolvaptan. First patient: intracranial aneurysm at basilar artery and paraclinoid segment of internal carotid artery (site of a previous clipping procedure 9 years earlier). Second patient: basilar tip and anterior cerebral artery. Third patient: intracranial aneurysm location not available. One additional patient randomized to placebo had surgical clipping of a ruptured aneurysm 11 years before enrolment in the REPRISE; during the REPRISE, the patients had a fall and a traumatic subarachnoid hemorrhage that resolved without intervention.

<sup>j</sup>One patient randomized to placebo and one patient randomized to tolvaptan. First patient: middle cerebral artery. Second patient: location not available. One additional patient had an intracranial hemorrhage without evidence of aneurysm.

<sup>k</sup>Middle cerebral artery. One additional patient suffered an aneurysmal rupture 10 months after concluding his participation in the TEMPO 4:4 after starting hemodialysis and having a bilateral nephrectomy.

<sup>l</sup>One patient had a subdural hematoma.

<sup>m</sup>This patient had a ruptured anterior communicating artery aneurysm clipped 8 years before enrolment, and a recurrent aneurysm between the clips ruptured during the study. One additional patient had a subdural hematoma, and another had an intracranial hemorrhage due to an arteriovenous malformation.

<sup>n</sup>One unruptured intracranial aneurysm was detected by presymptomatic screening.

No patient died after aneurysm rupture, but three had moderate to severe neurologic sequelae. The overall rupture rate was 0.2% per 100 person-years, and it was the same regardless of familial risk.

These authors performed a cost-utility analysis to determine whether systematic screening strategy was superior to targeted screening strategy in patients with familial risk of intracranial aneurysm (2). The model suggested that systematic widespread screening provides a gain of 1.3 quality-adjusted life years compared with no screening and 0.7 quality-adjusted life years compared with targeted screening. The annual aneurysm rupture rates used in the model (0.2% or 0.4% in patients with ADPKD without or with familial risk of intracranial aneurysm and no screening and 0.9% in patients with monitored, untreated aneurysms), however, were substantially higher than those observed in this study and other studies (3,19–29): 0.04 per 100 patient-years in both groups (Table 4). This rate is approximately five times higher than the incidence of subarachnoid hemorrhage in the general population of 0.009 per 100 patient-years (30), which in 85% of the patients, is due to aneurysmal rupture (31).

Two patients with a negative presymptomatic intracranial aneurysm screening in our study later suffered an aneurysmal rupture. Both patients had significant risk factors for intracranial aneurysm development and rupture, pointing to the importance of correcting modifiable factors and follow-up screening of patients at a high risk. Rates of *de novo* intracranial aneurysm formation in our study were comparable with the rates observed in studies in the general population with unruptured aneurysms without a previous subarachnoid hemorrhage: 0.4 per 100 patient-years (95% CI, 0.2 to 0.8 per 100 patient-years) (30).

Our results and the review of the literature do not allow a firm conclusion on whether widespread or targeted screening for internal carotid arteries is beneficial in ADPKD. A large prospective study would be necessary to determine the clinical utility and cost-effectiveness of these strategies. At present, our preference continues to be targeted presymptomatic MRA (or computer tomographic angiography) screening of patients with familial history of documented aneurysmal rupture or unruptured intracranial aneurysm. We also recommend screening before major elective surgeries and in patients with high-risk occupations, in whom a loss of consciousness because of a ruptured intracranial aneurysm would place the life of others at risk. If the screening MRA is negative, we recommend rescreening of those with good life expectancy at 5-year intervals.

If an aneurysm is detected by presymptomatic screening, the PHASES score (on the basis of the population/ethnic group, age, aneurysm size and location of the intracranial aneurysm, and presence or absence of hypertension or previous subarachnoid hemorrhage from another intracranial aneurysm) can be used to estimate the risk of rupture (16). Decisions regarding the management of unruptured intracranial aneurysms are complex, and many factors need to be considered, including the age and general health of the patient; the location, size, and morphology of the intracranial aneurysm; and whether the aneurysm is coilable or clipable with an acceptable risk (31,32). A study from the National Inpatient Sample comparing the results of aneurysm clipping or coiling of unruptured

intracranial aneurysms in 189 patients with ADPKD and 3555 patients without ADPKD showed a significantly greater incidence of iatrogenic hemorrhage or infarction, embolic infarction, and carotid artery dissection in the patients with ADPKD compared with the control group (33). In general, conservative management of patients with small (particularly those measuring <7 mm) anterior circulation asymptomatic intracranial aneurysms detected by presymptomatic screening and without a personal or family history of subarachnoid hemorrhage is appropriate. After considering all aneurysm and patient characteristics, should intervention be indicated, the decision regarding endovascular or surgical management should be on the basis of a multidisciplinary review. For untreated small aneurysms, semiannual or annual repeat imaging studies are appropriate initially, but re-evaluation at less frequent intervals may be sufficient after the stability of the size of the aneurysm has been documented. Patients should be advised to eliminate tobacco and excessive alcohol use and aggressively treat hypertension and possibly, dyslipidemia (34) to minimize the risk for aneurysm growth and rupture. A reduction in incidence of subarachnoid hemorrhage by 0.6% per year between 1995 and 2003, possibly due to better control of modifiable risk factors, underlines the importance of preventive measures (35).

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## Supplemental Material

This article contains the following supplemental material online at <http://cjasn.asnjournals.org/lookup/suppl/doi:10.2215/CJN.14691218/-/DCSupplemental>.

Supplemental Table 1. Demographic and clinical characteristics of patients with ADPKD without and with presymptomatic screening for intracranial aneurysms.

Supplemental Table 2. Summary of IA locations.

Supplemental Table 3. Comparison between patients with enlarged and stable aneurysms.

Supplemental Table 4. Clinical characteristics of the patients with clipped or coiled intracranial aneurysms during follow-up.

Supplemental Table 5. Clinical characteristics of the patients who died during follow-up and causes of death.

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