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Growth of unruptured aneurysms: A meta-analysis of natural history and endovascular studies

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ABSTRACT

The growth of unruptured intracranial aneurysms (UIAs) is a strong predictor of rupture. Clinical observations suggest that some UIAs might grow faster after endovascular treatment than untreated UIAs. There are no head-to-head comparisons of incidence rates of UIAs thus far.

Methods: We searched PubMed, Embase and Google Scholar for relevant articles from the inception of the databases to March 2020. We pooled and compared the incidence rates for the growth of aneurysms from natural history studies and endovascular treatment studies. Generalized linear models were used for confounder adjustment for the prespecified confounders age, size and location.

Results: Twenty-five studies (10 describing growth in natural history and 15 reporting growth after endovascular therapy) considering 6325 aneurysms were included in the *meta*-analysis. The median size of aneurysms was 3.7 mm in the natural history studies and 6.4 mm in endovascular treatment studies ($p = 0.001$). The pooled incidence rate (IR) of growth was significantly higher in endovascular treatment studies (IR 52 per 1000 person-years, with a 95% confidence interval (CI) 36–79) compared to natural history studies (IR 28 per 1000 person-years, 95% CI 17 – 46, p-value < 0.01) after adjustment for confounders.

Conclusion: Our results suggest that the incidence rate of cerebral aneurysm growth might be higher after endovascular therapy than the incidence rates reported in natural history studies. These results should be viewed in light of the risk of bias of the individual studies and the risk of ecological bias.

1. Introduction

The growth of unruptured intracranial aneurysms (UIAs) is a predictor for aneurysm rupture. The growth of an aneurysm may often play an important role in the decision to treat UIAs. Furthermore, the predictors of growth are the same as the predictors of rupture.[1,6] At this moment, despite advances in neuroimaging, there are no studies that allow in-depth characterization of this process. Our ability to accurately indicate growing aneurysms that are most likely to rupture at a later stage is limited.[14,21]

Treatment of UIAs to prevent eventual rupture relies on endovascular techniques, such as coiling, open surgical techniques, and microsurgical clip reconstruction of the parent vessel. Both techniques have particular risk profiles, and treatment is usually tailored to patient and aneurysm characteristics. Endovascular treatment is associated with a higher risk of recurrence than surgery.[16] Clinical observations in the authors' European and U.S. neurovascular centers suggested that certain aneurysms grow faster after endovascular treatment (coiling). The aim of this study was to assess the incidence rates of growth of untreated UIAs and compare them to those of endovascularly treated UIAs.

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Our hypothesis was that the incidence rate of growth after endovascular treatment is higher than the incidence rate of growth in untreated UIAs.

2. Materials and methods

2.1. Search strategy and selection criteria

We performed this systematic review and *meta*-analysis in accordance with the PRISMA guidelines[15] and best methodological practice for summary data on observational studies in general and pooling prevalence and incidence rates in particular.[18] We searched PubMed, Embase, Web of Science, the Cochrane Library and Google Scholar for relevant articles in English, German or French (*Supplementary Appendix, Search Strategy*). We included all studies meeting the inclusion criteria published before March 2020. We additionally screened citations of the selected studies to identify additional studies.

The inclusion criteria were as follows: an original article published or accepted in a peer-reviewed journal; participants with unruptured aneurysms only, both adult and pediatric patients without an age limit; and either followed in a natural history study or after endovascular therapy (coiling, stent-assisted coiling, flow diverters or web devices). We excluded case reports or case series and studies reporting ruptured aneurysms or a mix of ruptured and unruptured aneurysms when the results were not reported separately.

We first screened the titles and abstracts of articles retrieved from the search. The full text version was reviewed for articles considered relevant or for articles where a decision based on the title and abstract could not be made. Two investigators (VV and RD) independently screened the titles, abstracts and full texts of the relevant studies. Disagreements were solved by discussion and consensus. If multiple datasets existed for the same cohort, we included the largest and preferably most recent number of participants and excluded the others.

This study is registered with PROSPERO, number CRD42020150036.

2.2. Data extraction

Data extraction was performed by two separate investigators (VV and ISV) and compared, with disagreements solved by discussion and consensus. We used a predefined standardized data extraction set to collect information from eligible studies. From each eligible study, we extracted the year of publication, country where the study was performed, number of patients, number of aneurysms, length of follow-up, aneurysm location (percentages of aneurysms in the anterior circulation anterior communicating artery (ACom), internal carotid bifurcation and paraclinoidal internal carotid (ICA), middle cerebral artery (MCA), posterior communicating artery (PCom), and basilar artery), baseline aneurysm size (median and range), baseline dome-to-neck ratio (median and range), percentage of aneurysms fully occluded, and number of growing aneurysms or neck remnants during follow-up (as defined by the researchers).

2.3. Data analysis

We used the Mann-Whitney *U* test for nonnormally distributed variables to compare the characteristics of the included studies.

Analyses were run in R version 3.6.1 using the 'meta' packages 4.9–9.[3] Incidence rates and confidence intervals were calculated using the Jackson method[13] for each individual study and graphically presented using forest plots. The pooled estimates of natural history studies and endovascular therapy studies were then compared using a random effects model and the DerSimonian-Laird estimator.

Heterogeneity between studies was assessed using Cochran's Q, I2, and H statistics, with an I2 of more than 75% indicating substantial heterogeneity.[11] We used the metafor and metareg packages to calculate the adjusted incidence rate (aIR) for both natural history and endovascular studies. An influence analysis was also performed to identify outliers based on the Viechtbauer method.[30]

Risk of bias was assessed using the Agency of Healthcare Research and Quality Methodological Evaluation of Observational Research (MORE) checklist for observational studies of incidence or prevalence of chronic diseases for natural history studies and the Risk of Bias in Nonrandomized Studies of Interventions (ROBINS-I) Cochrane tool for the intervention studies. Risk of bias was assessed independently by two researchers (VV and ISV), and differences were solved by discussion and consensus.

We performed sensitivity analyses including only the most recent studies (after 2010) to compare the most recent results of endovascular interventions with the natural history and sensitivity analyses in which outliers were excluded (such as studies including only one aneurysm location).

We calculated the aIR per study and pooled the aIR values using generalized linear models, aiming to adjust for known covariates associated with growth (present in the ELAPSS score). Based on the data available, we attempted to adjust for median age, median size, ACom, PCom, MCA and ICA locations. If enough data were not available, we adjusted for the locations present in the maximum number of studies in both natural history and endovascular groups and performed sensitivity analyses by including all locations (and adjusting for fewer studies). The residual heterogeneity, calculated by the I^2 estimate, was used to draw conclusions regarding the adjusted IR.

Publication bias was assessed using funnel plots according to the method of Begg and Eggar.[4,9]

3. Results

Our search yielded 3439 articles and conference abstracts identified through the search strategy and an additional 75 articles identified through manual screening of citations. After screening, 25 studies (10 describing growth in natural history and 15 reporting growth after endovascular intervention, *Supplementary Fig. 1*) with 6325 aneurysms were included in the final *meta*-analysis (*Supplementary Fig. 2*).

Most natural history studies (5) were carried out in East Asia (Japan, South Korea), 3 were carried out in the United States of America and 2 in Europe. Likewise, most intervention studies were carried out in Southeast Asia.

Each natural history study included between 72 and 1325 patients. Each endovascular therapy study included between 30 and 732 patients. The median follow-up was 42 months in the natural history studies and 30 months in the endovascular therapy studies. Patients in the natural history group were older (median 62 years) than those in the endovascular therapy group (median 56 years) (Table 1).

The most represented aneurysms were those from the anterior circulation, with median frequencies of 88% in the natural history studies and 90% in the endovascular therapy studies.

The main significantly different characteristic of the included studies was the median size, which was 3.3 mm in the natural history studies and 6.4 mm in the endovascular therapy studies ($p = 0.001$). Growth was measured using varying techniques and very often using a combination of techniques within the same study (Table 2). Digital subtraction angiography (DSA) was never

Table 1
Characteristics of included patients in the studies (FU = follow-up, Acom = anterior communcationg artery, Pcom = posterior communicating artery, MCA = Middle Cerebral Artery, ICA = Internal Carotid Artery).

	Natural history		Endovascular treatment		p-value (Mann-Whitney *U* test)
	Median	Range (min–max of medians)	Median	Range (min – max of medians)	
FU (months)	42	(10.1–144)	31	(8.4 – 117.6)	0.07
Age	62	(55–65)	56	(48 – 61.2)	**0.002**
% Female	77	(63–84)	73	(48 – 84)	0.8
% Anterior Circulation	88.5	(64–93)	89.5	(0–100)	0.9
%ACom	11.6	(0 – 19.7)	8.6	(0 – 24.3)	0.3
%PCom	6	(0–7.5)	1.1	(0 – 17.2)	0.7
%Basilar	6.8	(0–9)	6.8	(0–100)	0.7
%MCA	31.4	(19.8–43)	16	(0–100)	**0.04**
%ICA	44.2	(25.1 – 52.5)	37	(0 – 73.8)	0.5
Median size	3.7	(2 – 7.1)	6.4	(3.5 – 10.5)	**0.01**
Median dome/neck ratio	NA	NA	1.4	(1.1–2)	NA
Percentage aneurysms above greater than 15 mm (large, very large, giant)	1.5	(0–3)	NA	NA	NA

used in natural history studies but was often used in endovascular studies.

The pooled prevalence of growth of unruptured aneurysms for natural history studies was 10% [95% CI 6%- 15%] and for endovascular therapy was 12% [95% CI 9% – 16%], a nonsignificant difference using a random effects model. The pooled incidence rate for natural history studies was 28 per 1000 aneurysm-years [95% CI 17 to 46] and 52 per 1000 aneurysm-years [95% CI 36 to 75] for endovascular studies, a statistically significant difference (p-value < 0.01) (Fig. 1). The I^2 was between 80 and 90% for every analysis, which prompted us to use random effect models for all analyses.

The influence analysis revealed three papers, all including only aneurysms of one location as outliers. However, similar results were found in the prespecified sensitivity analyses excluding four studies carried out before 2010 (*Supplementary Figure 3*) and excluding the three outliers revealed by the influence analysis (*Supplementary Figure 4*).

We calculated the adjusted IR (aIR), adjusting for median age, median size and location. We included 6 natural history papers and 11 endovascular therapy papers in which this information was available. The aIR for endovascular therapy was 48 per 1000 person-years [95% CI 37 to 62] and 30 per 1000 person-years for natural history [95% CI 30 to 40], a 47% higher aIR for endovascular therapy studies. The residual heterogeneity was 0% for both natural history and endovascular studies (Table 3, Fig. 2).

All articles were judged as being either at serious or critical risk of bias, mainly due to the selection bias confounded by the indication and reporting biases (*Supplementary Appendix, Risk of Bias Table*). Of these, 12/15 endovascular therapy studies were judged as being at critical risk of bias, and 3/15 were judged as being at serious risk of bias. Of the natural history studies, 8/10 were judged as being at serious risk of bias according to the MORE scale.

No publication bias was present when applying visual inspection to the funnel plots.

4. Discussion

4.1. Summary of results

In this *meta*-analysis, a significantly higher incidence rate of aneurysm growth was found after endovascular therapy (aIR 48 per 1000 person-years) than in natural history studies (aIR 30 per 1000 person-years). This difference remained statistically significant after adjustment for confounders, and the sensitivity analyses showed similar results.

4.2. A potential theory: Inflammation and growth

Aneurysm growth seems to be linked to ongoing inflammation in the diseased wall.[28] Given that endovascular techniques also induce inflammation, this might underpin the effect we measured in our *meta*-analysis.

Endovascular techniques induce inflammation of the aneurysm wall to promote thrombosis and thus induce aneurysm healing and exclusion from circulation. Inflammation-inducing coils are thought to promote faster thrombosis.[27,29] Recently published studies have shown promising results when hydrogel coils were used.[5,26] However, the use of these bioactive coils has been a topic of great debate thus far, as the long-term effects of the inflammation they induce are still unknown.[7] It is also unknown whether inflammation, which leads to growth and rupture, is influenced in any way by the inflammation induced by endovascular treatment of aneurysms.

Inflammatory processes intrinsically occurring inside the aneurysm wall as a reaction to hemodynamic shear stress and circumferential wall stress are postulated to lead to growth and eventual rupture of the aneurysm.[28] Recent reports suggest an association between white blood cell count and increasing aneurysm size.[8] Inflammation and thrombosis also play an essential role in aneurysm healing after endovascular treatment. Several reports suggest the possibility of perifocal edema and white matter changes around aneurysms after endovascular treatment. [22,23,27] Histological studies on growing aneurysm remnants show similar inflammation in the vicinity of the coil mass and in the aneurysm wall.[25] There is a high likelihood that the two inflammatory processes influence each other, but the dynamics of this relationship are unknown. The recent growing use of flow diverters might obviate the risks associated with the risk of growth after coiled aneurysms.

4.3. Differences between natural history studies and endovascular therapy studies

The most important difference observed between natural history studies and endovascular therapy studies is aneurysm size. There is an inevitable selection bias in patients who are included in natural history studies, both in terms of survivor bias due to confounding by indication.

Many studies have pointed out the fact that the size of an aneurysm is one of the strongest risk factors for aneurysm growth.[1,2,6] The PHASES score, developed to predict the 5-year rupture risk, aids clinicians in decision-making for UIAs.[10] This metric also relies heavily on the aneurysm size. Therefore, the

Table 2
Characteristics of included natural history and endovascular therapy studies, with summaries of variables.

Paper	N aneurysms	N growth	FU (months)	Age	Female (%)	Country	Anterior circulation (%)	Location (%)					Median size (mm) + range or mean + standard deviation (SD)	Dome/neck ratio	Imaging
								ACOM	PCOM	ICA	ACM	Basilar			
Natural History															
Matsumoto (2012)	129	11	144	65	63	Japan	86						2 (0–20)		MRA
Park (2014)	72	2	42	63	65	South-Korea	89	20	0	25	40	7	4 (1,5–13)		MRA
Sonobe (2010)	374	25	41	62	64	Japan	90	13		39	35	7	3,3 (1–5)		MRA/CTA
Choi (2018)	173	28	73	58	82	South-Korea	93	9	8	50	21	2	2,4 (1,1–6,9)		MRA/CTA
Inoue (2012)	1325	18	10	65	64	Japan									MRA
Leemans (2019)	333	38	55			the Netherlands									MRA
Villablanca (2013)	258	46	27	61	84	USA	64						5,7 (4,8–8,9)		CTA
Bor (2015)	363	57	25	55	77	USA + the Netherlands	88	0		50	43	0	3 (⟨2 −⟩15)		MRA/CTA
Giordan (2018)	385	64	48	62	80	USA	88	16	6	38	28		7,1 (SD 4,7)		MRA/CTA
Chien (2020)	520	87	33	62	83	USA	91			53	20	9	4,8 (SD 4)		CTA
Endovascular therapy															
Cognard (1999)	54	4	40			France	81	24	0	35	20	0	4,5 (2–8)	1,5 (⟨1 −⟩2)	DSA
Gentric (2013)	93	13	15	52	69	France	90	9	17	42	30	10	5,5 (2,5–20)	1,2 (NA)	DSA/MRA/CTA
Iijima (2005)	53	6	15	48	72	France	100	0	0	0	100	0	7 (3–13)	2 (NA)	MRA/CTA
Im (2008)	358	21	14	58	75	South-Korea	90	16	11	65	13	1	4,72 (2–7)		MRA
Maldonado (2013)	46	7	37	53	71	France	90	13	0	37	41	2	8,2 (SD 5,3)		DSA/MRA
Oishi (2012)	427	72	31	60	73	Japan	90	19	15	30	16	7	5,1 (2–9,5)	1,7 (0,71–4)	DSA/MRA
Soeda (2004)	79	12	8	58	78	Japan	66	0	1	65	0	34			DSA/MRA/CTA
Abecassis (2019)	30	2	29	61	76	USA	0	0	0	0	0	100	8,3 (SD 4,72)	1,4 (SD 0,42)	MRA/CTA
Gao (2018)	61	11	38	56	68	China	81	6	8	62	5	5	7,4 (1,37–21,7)	1,7 (NA)	DSA
van Eijck (2015)	40	1	118	52	68	the Netherlands	0	0	0	0	0	100	10,5 (1–30)		MRA
Feng (2017)	174	10	9	54	70	China	93	9	16	62	2		3,5 (SD 1,0)	1,09 (NA)	DSA
Jeong (2017)	732	75	31	58	68	South-Korea	94						4,3 (2,6–18,7)		MRA/CTA
Kim (2017)	85	11	34	54	85	South-Korea	100	0	0	0	0	0	5,8 (SD 4,1)	1,4 (NA)	DSA/MRA
Teramoto (2019)	84	9	24	59	75	Japan	64	9	13	38	4	18	7,8 (SD 3,1)	1,4 (SD 0,32)	DSA/MRA
Cho (2017)	76	30	36	56	48	South-Korea	49						7,7 (SD 5,6)		DSA/MRA

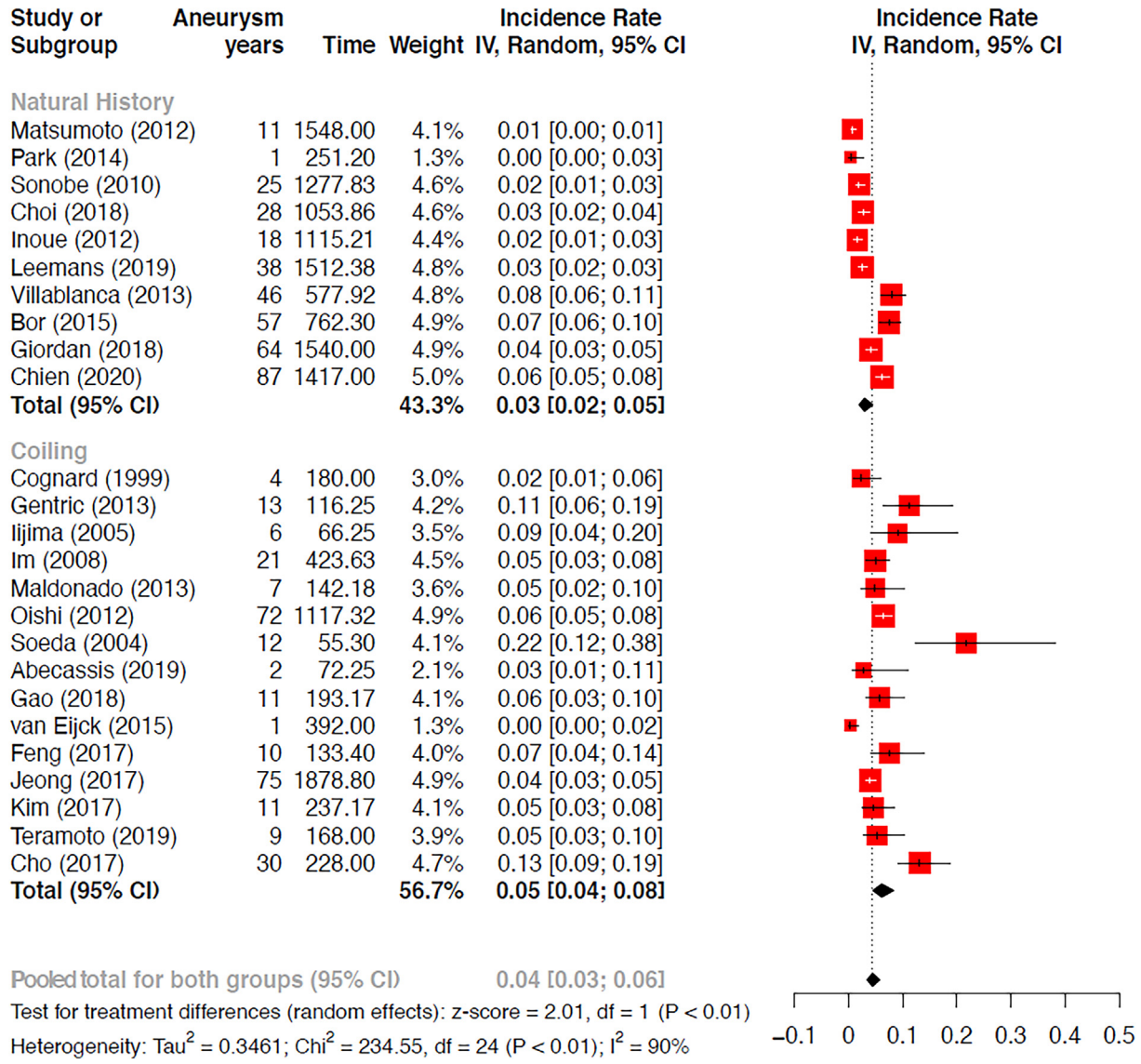

Fig. 1. Forest plot for the pooled incidence rates. In the forest plot above, the results of natural history studies were pooled. In the forest plot below, the results of endovascular therapy studies were pooled. At the bottom of the figure, the z-score of the random effects model was used to compare the unadjusted IRs. (IV = inverse variance).

Table 3
The results of *meta*-regression and the Incidence Rate (IR) and adjusted Incidence rate (aIR).

	Confounders	IR/aIR (per 1000 patient-years)	95% CI	Z-score	p-value	I^2
Natural History	Unadjusted	28	(17 – 46)	−2.00	0.045	95%
Coiling	Unadjusted	52	(36–79)			89%
Natural History	Age + Size	31	(23–41)	−2.20	0.028	81%
Coiling	Age + Size	57	(42–79)			77%
Natural History	Age + Size + Location	30	(30–40)	−2.04	0.041	0%
Coiling	Age + Size + Location	48	(37–62)			0%

two groups (natural history and endovascular treatment) are likely to have, at baseline, a different risk of growth. To make matters more complex, growth was measured on different imaging modalities, which might introduce a measurement bias. Most likely the very small aneurysms of the natural history group need to grow more than those from the endovascular treatment series in order for growth to be noticed. However, aneurysms in natural history series were followed for a longer period of time, allowing ample time to measure and record growth.

Most of the included endovascular intervention studies, especially the most recent ones (after 2005), report results and growth of aneurysms requiring stent-assisted coiling or another endovascular neck remodeling technique. They also report an overrepresented population of basilar tip aneurysms. The aneurysms most often treated, AComs and PComs, are relatively underrepresented. It is safe to assume there is an amount of reporting bias involved in which studies focused on aneurysm growth after endovascular therapy automatically report a selected population with a higher

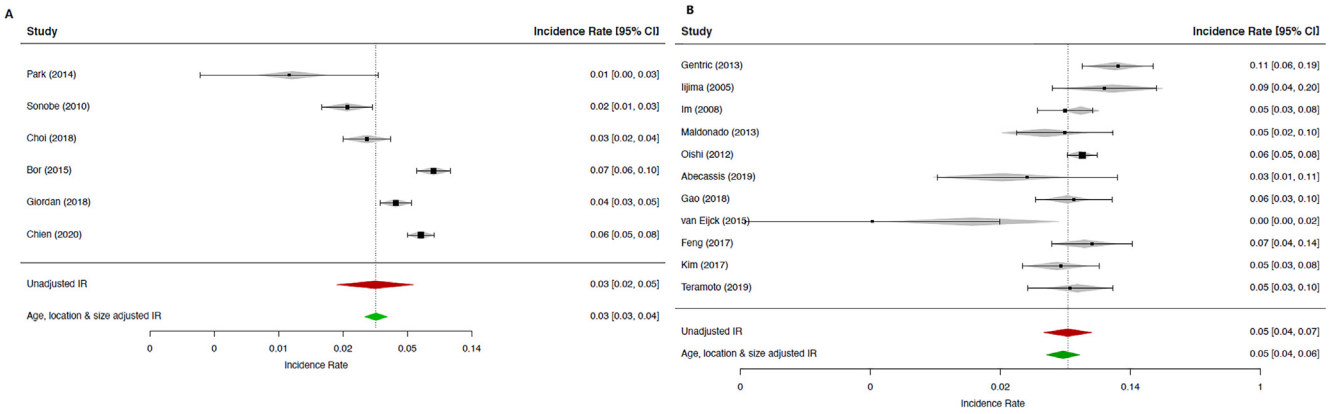

Fig. 2. Results obtained after generalized linear models were used to estimate the adjusted incidence rate (A = natural history studies; B = endovascular therapy studies).

baseline risk of growth. The aIR should be interpreted in light of the fact that the medians of covariates were used, which inevitably leads to information loss and potential ecological bias.

Size is merely a surrogate marker of a process that cannot be characterized differently at this point. There are no reliable markers to determine in which aneurysm and patients this process is ongoing or halted. The underlying assumption that aneurysms under 7 mm rarely bleed is partially based on the inherent survivor bias population included in the natural history studies. Recent papers show a preponderance of small aneurysms with a theoretical low rupture risk in subarachnoid hemorrhage series.[19] These aneurysms have low PHASES scores and still make up the majority of the patients seen with subarachnoid hemorrhage.[20,12] Additionally, a high prevalence of small aneurysms leading to fatal subarachnoid hemorrhage in an autopsy series has been published.[17] Natural history studies likely underestimate the risk of hemorrhage, as do scores based on them. The low rupture risk of small aneurysms is still a matter of debate.

4.4. The limitations of measuring and comparing the incidence of growth in unruptured aneurysms

A considerable amount of care in planning the study was given to the definition of the denominator of the incidence rate. We would have preferred to have the individual patient data of all studies available to conduct the present *meta*-analysis. Since these data were not available and it was not possible to calculate the aneurysm-years-at-risk, we settled for aneurysm-years.[24] The data presented in our study are likely the result of pooling together patients with a relatively low risk of growth and patients with a relatively high risk of growth. While larger aneurysms are postulated to have a much higher risk of growth, most of the aneurysms in both groups were small. Some endovascular studies have focused on smaller aneurysms.

Assuming there is a subset of patients in which aneurysm growth is triggered through endovascular treatment, these patients are now pooled together with low-risk patients. This subgroup is also impossible to identify using our data. These considerations force a cautious interpretation of our results. Nonetheless, we cannot exclude a significant influence of endovascular treatment on growth in certain aneurysms. Whether growing significant remnants after endovascular therapy can be equated with growing aneurysms and whether they have the same risk of bleeding is still a matter of debate. We only considered significant, growing recanalized aneurysms and growing remnants for comparison. All growing small neck remnants were excluded; otherwise, the numbers would have been much higher. The 18-year follow-up of a subgroup of the International Subarachnoid Aneurysm Trial showed that 3% of patients experienced a subarachnoid hemorrhage from the remnants of endovascularly treated aneurysms.[16]

We planned to perform sensitivity analyses including only studies reporting the outcomes of individual endovascular techniques (e.g., coiling, stent-assisted coiling, flow diverters) and compare them to the natural history. This was not possible, as the studies did not report the outcomes of the individual techniques. The overall reporting was poor in terms of aneurysm growth, which did not allow for use all included studies for aIR. Reporting should be improved in future studies.

We also planned to extract the packing density of coils and the remnant neck size and to relate this to growth, but unfortunately, these data were also not available. It is conceivable that a neck remnant might provide fertile ground for unopposed inflammatory changes, which might lead to further aneurysm expansion. An individual patient data *meta*-analysis would have solved many of the methodological issues we faced in this study and yielded more reliable and precise effect size estimates.

4.5. Future research focus

Aneurysm growth is used as a surrogate marker for aneurysm wall changes. However, the chain of events of aneurysm formation – growth – rupture has many unknown links that still need to be uncovered. More research is necessary in the field of inflammatory changes in the aneurysm wall to elucidate this process and identify patients at potential risk of inflammatory progression after endovascular treatment. Longitudinal vessel wall imaging, together with blood biomarkers of inflammation, could be used to assess this effect.

5. Conclusion

Our results suggest that the incidence rate of cerebral aneurysm growth might be higher after endovascular therapy than the incidence rates reported in natural history studies. These results need to be interpreted in light of the risk of bias of the studies, potential ecological bias and the methodological limitations inherent in such an analysis.

6. Declarations

Funding: No funding was received for this work.

Availability of data and material: Upon reasonable written request.

Code availability: Upon request.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jocn.2021.07.034.

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