Growth of Unruptured Aneurysms: A Meta-analysis of Natural History and Endovascular Studies

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Abstract

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

In this meta-analysis, we compared the incidence rates of growth of untreated UIAs and endovascularly treated UIAs.

Methods: We searched PubMed, Embase and Google Scholar for relevant articles and conference abstracts in English, German or French from the inception of the databases to March 2020. We performed a meta-analysis by pooling the incidence rates for growth of aneurysms from natural history studies and endovascular treatment studies. Generalized linear models were used for multivariable adjustment for the prespecified confounders age, size and location.

Results: 25 studies (10 describing growth in natural history and 15 reporting growth after endovascular therapy) with 6325 aneurysms were included in the meta-analysis. Median size of the aneurysm 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, 95% Confidence Interval (CI) 36–79) compared to natural history studies (IR 28 per 1000 person-years, 95% CI 17–46), also after adjustment.

Conclusion: The incidence rate of growth in endovascularly treated aneurysms was higher than in natural history studies. However, these results should be viewed in the light of high risk of bias of the individual studies and risk of ecological bias.

Introduction

The growth of unruptured intracranial aneurysms (UIAs) is a predictor for aneurysm rupture. 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 for rupture.[1,6] At this moment, despite advances in neuroimaging, there are no studies which allow in-depth characterization of this process. Our ability to accurately indicate growing aneurysms which are most likely to rupture at a later stage is limited.[14,21]

Treatment of UIAs in order to prevent eventual rupture relies either on endovascular techniques, such as coiling, or open surgical techniques, 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 compared to 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.

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

Materials And Methods

Search strategy and selection criteria

We performed this systematic review and meta-analysis in accordance with the PRISMA guidelines[15] and also 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: an original article published or accepted in a peer-reviewed journal; participants with unruptured aneurysms only, both adult and pediatric without age limit; 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, studies reporting ruptured aneurysms or a mix of ruptured and unruptured, when the results were not reported separately.

We first screened 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 and abstracts and full texts of the relevant studies. Disagreements were solved by discussion and consensus. If multiple datasets were of 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.

Data extraction

Data extraction was done 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 year of publication, country where study was performed, number of patients, number of aneurysms, length of follow-up, aneurysm location (percentage of aneurysms in the anterior circulation and percentage of aneurysms of the anterior communicating artery (ACom), internal carotid bifurcation and paraclinoidal internal carotid (ICA), middle cerebral artery (MCA), posterior communicating artery (PCom), basilar artery), baseline aneurysm size (median and range), baseline dome-to-neck ratio (median and range), percentage of aneurysms fully occluded, number of growing aneurysms or neck remnants during follow-up (as defined by the researchers).

Data analysis

We used the Mann-Whitney-U test for non-normally 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 were then compared between natural history studies and endovascular therapy studies using a random effects model and the DerSimonian-Laird estimator.

Heterogeneity between studies was assessed using the Cochran's Q, I^2, and H statistics, with an I^2 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 method of Viechtbauer.[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 Non-randomized 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), in order 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 adjusted IR per study and pooled the adjusted IR 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 was not available, we would adjust for the locations present in the maximum number of studies in both natural history and endovascular groups and perform sensitivity analyses by including all locations (and adjusting for less 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]

Results

Our search yielded 3439 articles and conference abstracts identified through the search strategy and a further 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 Figure 1*) with 6325 aneurysms were included in the final meta-analysis (*Supplementary Figure 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 South East Asia.

Natural history studies included between 72 and 1325 patients and endovascular therapy studies between 30 and 732. 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 in the endovascular therapy group (median 56 years) *(Table 1*).

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

The main statistically different characteristic of 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 used in the 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 12% [95% CI 9% – 16%], a non-significant 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 (*Figure 1*). The I^2 was between 80-90% 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]. The residual heterogeneity was 0% for both natural history and endovascular studies (*Table 3, Figure 2*).

All articles were judged as either at serious or critical risk of bias, mainly due to selection bias, confounding by indication and reporting bias (*Supplementary Appendix, Risk of Bias Table*).

Publication bias was not present when applying visual inspection to the funnel plots.

Discussion

Summary of results

In this meta-analysis a statistically significant higher incidence rate of growth after endovascular therapy was found when compared to natural history studies. This difference remained statistically significant after adjustment for confounders and the sensitivity analyses showed similar results.

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 in order 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 show promising results when hydrogel coils are used.[5,26] However, the use of these bioactive coils has been a topic of great debate so far, as the long-term effects of the inflammation they induce is still unknown.[7] It is also unknown whether the inflammation which leads to growth and rupture is influenced in any way by the inflammation induced by endovascular treatment of aneurysms.

The inflammatory processes intrinsically happening inside the aneurysm wall as a reaction to the 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 dynamic of this relationship is unknown. The recent growing use of flow diverters might obviate the risks associated with risk of growth after coiled aneurysms.

Differences between natural history studies and endovascular therapy studies

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

There are many studies pointing out the fact that size of the 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] It also relies heavily on aneurysm size. Therefore, the 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 over-represented population of basilar tip aneurysms. The aneurysms most often treated, AComs and PComs, are relatively under-represented. 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 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 in which 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] Also, 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, and so do scores based on them. The low rupture risk of small aneurysms is still a matter of debate.

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 in order to conduct the present meta-analysis. Due to this data not being available and thus no possibility to calculate the aneurysm-years-at-risk, we settled for aneurysm-years.[24] The data presented in our study is likely the result of pooling together patients with a relatively low risk of growth and patients with 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 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 3% of patients experiencing a subarachnoid haemorrhage from 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 reporting overall was poor in terms of aneurysm growth, which led to us not being able to use all included studies for the aIR. Reporting should be improved in future studies.

We also planned to extract the packing density of coils, the remnant neck size and to relate this to growth, but unfortunately this data was 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 would have given more reliable and precise effect size estimates.

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 which still need to be uncovered. More research is necessary in the field of inflammatory changes in the aneurysm wall in order 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 this effect.

Conclusion

In a meta-analysis of natural history studies and endovascular treatment studies, the pooled incidence rate of growth appeared significantly higher after endovascular treatment. These results need to be interpreted in the light of the risk of bias of the studies, potential ecological bias and the methodological limitations inherent in such an analysis. The relationship between inflammation and growth, as well as the influence of endovascular therapy on these processes demands further research.

Declarations

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Conflicts of interest/Competing interests None applicable

Availability of data and material Upon written reasonable request

Code availability Upon request

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Tables

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>15 mm (large, very large, giant)	1.5	(0 - 3)	NA	NA	NA

Table 2.

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

Cho (2017)	76	30	36	56	48	South-Korea	49	7,7 (SD 5,6)

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%

Figures

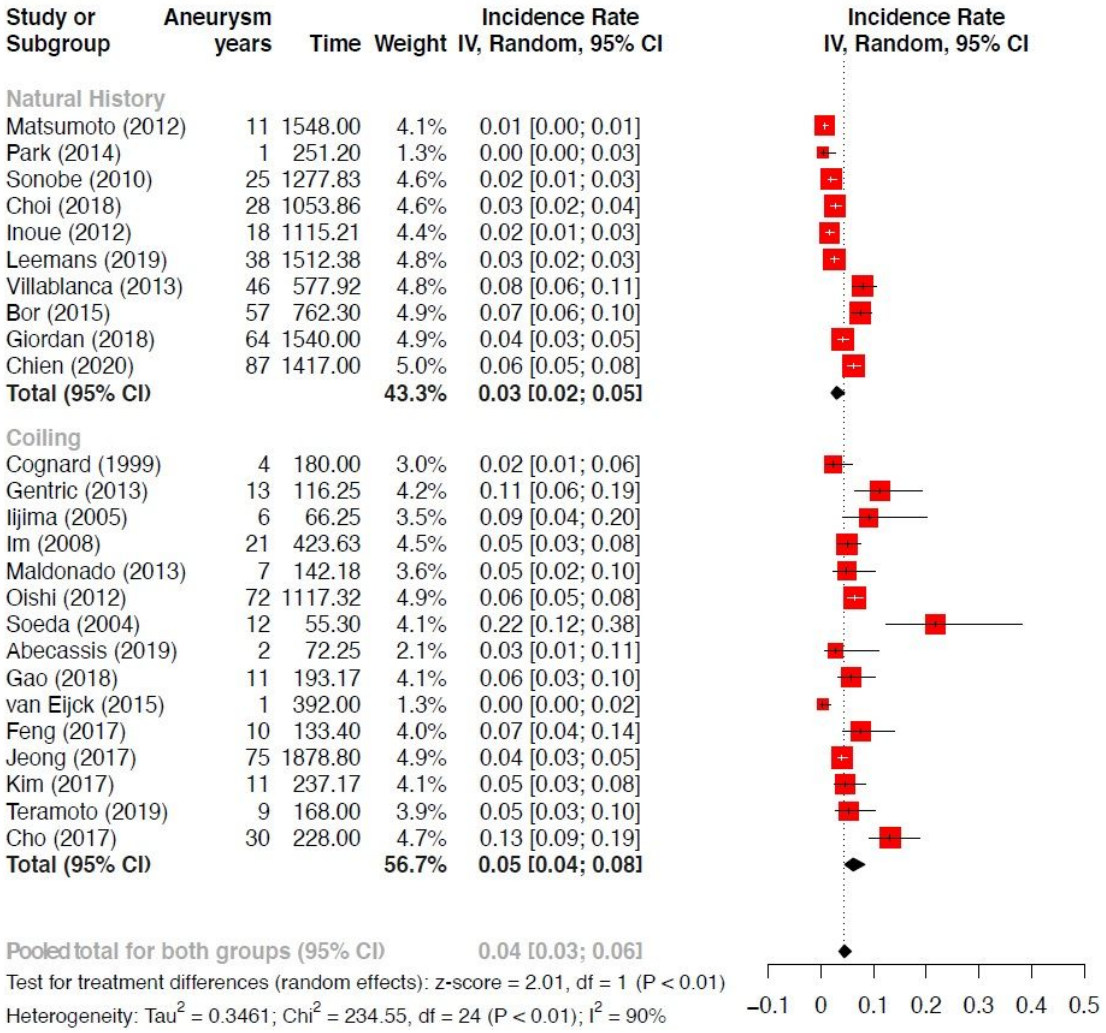

Figure 1

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

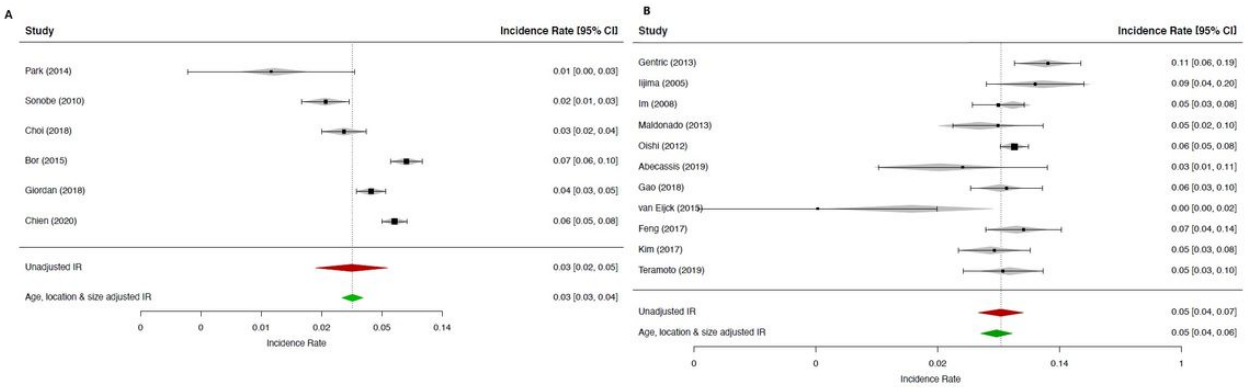

Figure 2

Results after generalized linear models to estimate the adjusted incidence rate (A= natural history studies; B= endovascular therapy studies)

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- PRISMAchecklistGrowth.doc
- SupplementaryAppendix.docx