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Multidisciplinary Consensus on Assessment of Unruptured Intracranial Aneurysms

Proposal of an International Research Group

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Background and Purpose—To address the increasing need to counsel patients about treatment indications for unruptured intracranial aneurysms (UIA), we endeavored to develop a consensus on assessment of UIAs among a group of specialists from diverse fields involved in research and treatment of UIAs.

Methods—After composition of the research group, a Delphi consensus was initiated to identify and rate all features, which may be relevant to assess UIAs and their treatment by using ranking scales and analysis of inter-rater agreement (IRA) for each factor. IRA was categorized as very high, high, moderate, or low.

Results—Ultimately, 39 specialists from 4 specialties agreed (high or very high IRAs) on the following key factors for or against UIA treatment decisions: (1) patient age, life expectancy, and comorbid diseases; (2) previous subarachnoid hemorrhage from a different aneurysm, family history for UIA or subarachnoid hemorrhage, nicotine use; (3) UIA size, location, and lobulation; (4) UIA growth or de novo formation on serial imaging; (5) clinical symptoms (cranial nerve

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deficit, mass effect, and thromboembolic events from UIAs); and (6) risk factors for UIA treatment (patient age and life expectancy, UIA size, and estimated risk of treatment). However, IRAs for features rated with low relevance were also generally low, which underlined the existing controversy about the natural history of UIAs.

Conclusions—Our results highlight that neurovascular specialists currently consider many features as important when evaluating UIAs but also highlight that the appreciation of natural history of UIAs remains uncertain, even within a group of highly informed individuals. **(*Stroke*. 2014;45:1523-1530.)**

Key Words: cerebral aneurysm ■ consensus ■ Delphi technique ■ incidental aneurysm ■ natural history ■ therapeutics

Unruptured intracranial aneurysms (UIAs) have a prevalence of 2% to 3% in the general population.[1,2] UIAs often remain clinically asymptomatic for a long time or rupture, causing subarachnoid hemorrhage (SAH). Patients having SAH from a ruptured aneurysm have a poor prognosis with case-fatality rates up to 50%, which suggests that it could be beneficial to repair UIAs before they rupture.[3] On the contrary, observational natural history studies of UIAs suggest that only a fraction of UIAs rupture, although these data are partially biased by selection of specific subgroups of UIAs.[4,5] Nevertheless results from long-term follow-up studies of UIAs with less selection of patients by aneurysm treatment are, in part, consistent with these observations.[6] Aneurysm size is considered the major risk factor for UIA rupture and in many respects is what drives treatment decisions. However, it has been difficult to reconcile the low risk of rupture of small UIAs and the high proportion of small ruptured aneurysms in patients with SAH.[5,7] The resulting uncertainty about the natural history of UIAs and their appropriate treatment has become important as more people undergo brain imaging for nonspecific symptoms and are found to have incidental UIAs, which are usually small, that is, <7 mm in diameter.[5,8,9] Overall, the rupture rate of aneurysms is on average 9/100 000 people per year.[10] A limitation to making treatment decisions about UIAs is lack of consensus on factors that are associated with rupture of UIAs and that would allow for prediction of rupture. This limitation is compounded by generation of data that are not comparable between studies, and there is little clarity on what questions to ask in future studies. The goal of this work was to address these problems by convening a panel of specialists from diverse fields involved in research and treatment of UIAs. We used the Delphi consensus method to identify and rate all features thought necessary to assess and manage UIAs.

Methods

The goal of this project was to determine what highly informed individuals who study and treat UIAs considered to be relevant factors influencing their decisions about UIA management and to analyze the certainty within the group. The purpose of this process therefore was to establish consensus and was not to quantify the probable risk of rupture of UIAs or the treatment risk because there are already data on these questions that have been subjected to meta-analyses.[4,5,11–15] To achieve our objective we used a Web-based survey (www.surveymonkey.com) and a 5-step Delphi consensus approach.[16,17] Factors considered relevant to evaluate and treat UIAs based on knowledge derived from a multidisciplinary and international panel of neurovascular specialists were identified and rated. In the first phase of this project, a panel of specialists (see below) was assembled. Two authors who did not participate in the Delphi process then designed different survey rounds and analyzed the data in the second phase (N. Etminan and K. Beseoglu). In the first 4 rounds, panelists were blinded to their previous or their colleagues' ratings to reduce the risk of bias within the research group.

Specialist Panel

Specialists who were known from previous collaborations or based on their scientific publication record to have expertise in the treatment of cerebral UIAs and SAH were contacted about participation in the study.[18] We also performed a literature search using the terms cerebral aneurysm, subarachnoid hemorrhage, or unruptured intracranial aneurysms and identified and then contacted the senior authors of the top 40 articles, based on citations in the Web of Science. The panel was purposely designed to select prominent physicians from a variety of specialties (neurosurgery, neurology, neuroradiology, and epidemiology) and to represent different continents. Every specialist who agreed to participate was included. The key purpose of this panel was to reach and formulate a consensus based on the current clinical evidence and practice in UIA management.[19]

Delphi Process

The Delphi process is a scientific method typically used to systematically reach a consensus on a controversial or complex subject among a group of professionally and geographically dispersed specialists.[20] We used a modified Delphi approach, consisting of 5 rounds to identify and rate the most relevant features used to assess and manage UIAs[16,17] (Figure):

- Pre-Delphi phase (recruitment of expert panel): In September 2012, 40 specialists were contacted via e-mail and asked to participate in the project. The recruitment phase was finished a week after the initial contact.
- Delphi Round 1a (identification of relevant items): By definition, the first round of the Delphi process consists of open-ended questions to identify all factors relevant to the subject. Open-ended questions and a Web-based survey were used to ask panel members to submit all clinical, radiological, and therapeutic factors/variables they each considered relevant to the risk of rupture and for treatment of UIAs, based on current evidence and practice. Participants also were asked to list any missing factors or items in the open questions for each category. Every reply from Round 1 was used to generate a list of features/cofactors considered necessary to assess UIAs.
- Delphi Round 1b (definition of items): We identified that definitions varied for some items (eg, hypertension or familial aneurysms). The panel members were asked to pick one from different definitions for the most common items (see under Definitions).
- Delphi Round 2 (rating and prioritization of items): The suggested items and additional items listed by panel members in round 1 were compiled and included for subsequent rating by every member. Panel members were asked to rate each feature listed in round 1 of the survey using a 0 to 10 scoring system, with 0 reflecting nonrelevance and 10 reflecting absolute importance. To avoid bias, the results of round 2 were not presented to the panel until completion of round 3.
- Delphi Round 3 (rerating of all items from Round 2): To achieve a more robust consensus and to exclude significant deviations over time, panel members repeated the round 2 survey 4 weeks later.

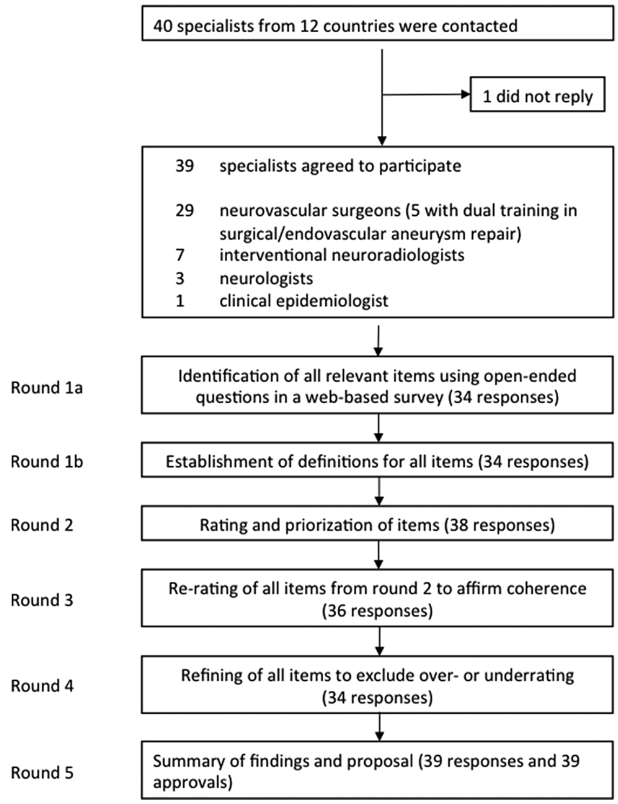

Figure. Illustration of the Delphi consensus approach to identify and rate all features considered relevant to assess and manage unruptured intracranial aneurysms.

- Delphi Round 4 (refining of items): Every item and the corresponding relevance ratings were then presented to the panel to evaluate whether they might have been underrated or overrated.
- Delphi Round 5 (summary of findings and proposal): In the final round, the panel was presented the proposal and asked to approve or disprove the final consensus version.

Definitions

All nonsaccular aneurysms, that is, rare aneurysms associated with specific diseases/entities (eg, collagen disorders, dwarfism, Moya-Moya syndrome), and aneurysms in patients <18 years were excluded because they are rare, may have a distinct natural history, and would increase the complexity of the proposal. A complex aneurysm was defined as an aneurysm of any size that also has any of the following features: wide neck, lobulations, calcifications, intra-aneurysm thrombus, proximal vessel tortuosity/stenosis, branch artery incorporated into the neck or aneurysm sac. Aneurysm size was defined as the greatest CA diameter, measured using 3-dimensional reconstruction of the catheter angiograms. Aneurysm lobulation was defined as irregular, daughter-sack–like protrusion of the aneurysm wall on the 3-dimensional angiographic reconstruction images. Aspect ratio was defined as the ratio of aneurysm neck and aneurysm dome diameter. Size ratio was the largest aneurysm diameter divided through parent vessel diameter. Hypertension, irrespective of whether it was treated or untreated, was defined as systolic blood pressures >140 mm Hg and diastolic blood pressure >90 mm Hg.[21] Current nicotine use was defined as a risk factor for adults who had smoked 100 cigarettes in their lifetime and smoked cigarettes every day (daily) or some days (nondaily) at the time of clinical presentation.[22] Familial aneurysms were defined to be present in families where ≥2 first degree relatives were diagnosed with a UIA or SAH previously.[23] Current drug use was defined as a risk factor in case of a recent cocaine or amphetamine exposure, that is, within 1 year of clinical presentation. Clinical or radiological signs of mass effect were defined as any symptoms or findings indicative of a space-occupying effect from an UIA, such as nausea, vomiting, focal neurological or radiological findings (midline shift and herniation, edema, cranial nerve compression). Cranial nerve deficits were defined as any deficits from compression of a cranial nerve, for example, visual disturbances, oculomotor dysfunction for anterior circulation, and lower cranial nerve deficits (IX, X, or XI) for posterior circulation aneurysms. Psychiatric disorders were defined as manifest clinical depression, bipolar affective disorder, schizoaffective psychosis, or obsessive-compulsive disorders with resulting impairment of the patient's ability to live alone. Neurocognitive disorders were defined as dementia, Alzheimer disease, frontotemporal neurocognitive disorder, and resulting impairment of the patient's ability to live alone because of the neurocognitive disorder. Concomitant chronic or malignant disease were defined as any cardiovascular-, pulmonary, -renal or gastrointestinal, musculoskeletal, and central nervous chronic or malignant disease that impaired the patient's life expectancy. Concomitant thrombophilic diseases were defined as Factor-V Leiden mutation, antiphospholipid antibody syndrome, antithrombin III deficiency, and protein C/S deficiency. Concomitant coagulopathies were defined as hemophilia and von Willebrand disease. Concomitant use of anticoagulants was defined as concomitant treatment with warfarin, dabigatran, rivaroxaban, or apixaban in the presence of an UIA. Concomitant use of platelet inhibitors was defined as concomitant treatment of patients with aspirin or clopidogel in the presence of a UIA. Treatment was defined as neurosurgical clipping or endovascular repair of a UIA. Conservative management was defined as observation or medical treatment (eg, for epilepsy).

Statistical Analysis

Statistical analysis was performed using SPSS 15.0.1 (Ulead Technologies, Chicago, IL). Medians and interquartile ranges were determined for each item rated in rounds 2 and 3. Medians were chosen over means to account for the small sample size and to avoid distortion by outliers and skewed distributions. To classify the relevance of each item to evaluate a UIA based on the panel ratings, 3 groups were established: high relevance (median 7–10), moderate relevance (median 4–6), and low relevance (median 0–3). Medians of ratings and interquartile ratios are presented.

The exploratory analysis of this project focused on intrarater agreement, that is, variances in ratings between rounds 2 and 3 for each specialist and inter-rater agreement (IRA), that is, the homogeneity of ratings among the panel. Differences in individual ratings between rounds 2 and 3 were evaluated using the nonparametric Wilcoxon signed-rank tests for matched pairs. Significance was accepted at a level of $P<0.05$. The skew of the distribution of votes was determined as a measure of the direction of ratings in round 3. A negative skew (asymmetry in the distribution of votes) reflected the tendency for higher relevance, a positive skew for lower relevance. A skewness value that approached zero corresponded to a symmetrical distribution of votes.

The standardized quartile coefficients of dispersion (v_r^*) were calculated to determine the degree of inter-rater agreement for every item. In deciding the relevance of an item for the rating of each item according to $v_r^* = \frac{\frac{Q_3 - Q_1}{Q_2}}{\sqrt{n-1}}$ with $0 \le v_r^* \le 1$, thus v_r^* approaching zero corresponds to a high degree of inter-rater agreement. The degree of agreement was classified using the calculation of quartiles of v_r^* as such (1) the lower quartile was defined as low IRA, (2) the second quartile as moderate IRA, (3) the third quartile as high IRA, and (4) the upper quartile as very high IRA.

Results

Thirty-nine out of the 40 contacted specialists from 12 countries and 4 continents agreed to participate in September 2012. The subspecialties and panel composition are illustrated in the Figure. For all rounds, the predefined minimum participation rate of 85% was fulfilled (87% in round 1, 97% in round 2, 92% in round 3, 87% in round 4, and 100% in round 5; Figure). The panel proposed 60 features they considered necessary to assess and decide about management of a UIA in round 1. These were subsequently rated for their relevance in rounds 2 and 3. In round 4, the research group reached consensus for all ratings from rounds 2 and 3 because the panel votes in this round did not reveal significant overrating or underrating of factors in this round. For analytic and illustrative purposes, the items were classified as patient, aneurysm, or treatment related. In the final round, all 39 panel members approved the proposal. The v_r* ranges for the IRA classification were based on 1.000 to 0.160 for low (first quartile), 0.159 to 0.101 for moderate (second quartile), 0.100 to 0.070 for high (third quartile), 0.069 to 0.000 for very high IRA (fourth quartile).

Patient-Related UIA Items

Twenty-eight patient-related items were listed in round 1 (Table 1). The subsequent ratings in rounds 2 and 3 defined the following items that were considered highly relevant to support aneurysm treatment and that were generally independent of other factors: (1) patient age <30 years, (2) familial intracranial aneurysms, (3) previous SAH from a different aneurysm, and (4) current nicotine consumption.

However, despite patient age <30 years being rated as highly relevant, IRA for this agreement was moderate. For the other age categories rated with moderate or low relevance, the IRAs were very high. Additionally, the only items rated highly relevant with high or very high IRA in favor of treatment were familial intracranial aneurysms and current nicotine consumption.

Highly relevant patient-related aspects that independently supported conservative management of a UIA were (1) chronic or malignant diseases associated with a life expectancy <5 or 5 to 10 years and (2) neurocognitive disorders. For both items inter-rater agreement on relevance was very high. The majority of all other features in this category were either rated to be moderately relevant or irrelevant, with moderate to low IRAs.

Additionally, 7 items were proposed to lower the risk of rupture of UIAs, that is, as protective measures (Table 1). The most relevant modifiable items were blood pressure control and nicotine cessation. However, only nicotine cessation was rated with very high IRA. The remaining items were rated as moderately relevant or irrelevant, the majority of which exhibited considerable ambiguity (low IRA).

Aneurysm-Related UIA Items

Twenty aneurysm-related items were listed in round 1 (Table 2). Ratings in round 2 and 3 identified the following features considered important (high relevance) in support of treatment: (1) UIA size >13 mm, (2) UIA sac lobulation, (3) UIA location (anterior or posterior communicating artery or basilar artery bifurcation), (4) UIA growth or de novo formation, and (5) symptoms, such as cranial nerve deficits, mass effect, and thromboembolic events from the UIA. IRA for rating of these items was consistently high or very high, although there was moderate or low IRA related to the relevance of UIA <7 mm in diameter.

Treatment-Related UIA Items

Sixteen treatment-related items were listed (Table 3). The most relevant feature considered to increase treatment risk was aneurysm diameter >20 mm. A feature considered most relevant to favor conservative management of a UIA was patient age >80 years or life expectancy <5 years. IRA among the panel members for these items was very high. The importance of individual patient factors to decide about treatment such as age, life expectancy, aneurysm size, and individual risk of treatment were generally rated with high or very high IRAs.

Discussion

The key findings of this study are that many factors are considered to be relevant to an appropriate assessment of UIAs rupture risk by a group of specialists presumably knowledgeable on the natural history UIAs, and that the relative importance of factors rated as irrelevant is yet uncertain, as evident by low IRAs. The most relevant factors identified for UIA treatment decisions were (1) patient age, life expectancy, and comorbid diseases, (2) modifiable and nonmodifiable risk factors for aneurysm formation and rupture (previous SAH from a different aneurysms, family history for intracranial aneurysms or SAH, nicotine consumption), (3) UIA size, location, and lobulation, (4) UIA growth and de novo formation on serial imaging, (5) clinical symptoms (cranial nerve deficit, mass effect, and thromboembolic events from the aneurysm), and (6) risk factors for UIA treatment (patient age and life expectancy, aneurysm size, and estimated individual risk of treatment).

The natural history of UIAs remains incompletely understood. The largest natural history studies include the International Study of Unruptured Intracranial Aneurysms (ISUIA) and the Study on the Natural Course of Unruptured Cerebral Aneurysms in a Japanese Cohort (UCAS Japan).[4,5] Both these studies reported low 5-year cumulative risks of rupture for anterior circulation aneurysms <7 mm in diameter. In UCAS Japan, greater rupture rates for UIAs of the anterior or posterior communicating artery and irregular shaped UIAs were reported compared with UIAs at different parent arteries or of regular shape. Despite some methodological concerns, such as selection bias, sample size, short observational periods, and ethnic/racial composition of the cohorts, these data show that only a fraction of UIAs rupture during a short observation period and that most of these are >7 mm in diameter. However, a high proportion of ruptured aneurysms are <7 mm in diameter.[7,24] To explain this discrepancy, it has been hypothesized that UIAs undergo episodes of instability and growth followed by periods of stabilization, with stochastic or discontinuous rather than linear growth.[25,26] Therefore, short observation intervals may not accurately account for this.[26,27] However, until more knowledge is available, clinicians must rely on many factors, as outlined in Tables 1–3 to decide on the risk of treatment or rupture. Our proposal provides more guidance on the relevance of these features needed to assess UIAs, based on a consensus among a large, international and multidisciplinary group of neurovascular specialists.

Our results suggest that in addition to the most commonly acknowledged factors such as patient age, aneurysm size, and location, several other patient-, aneurysm-, and

Table 1. Patient-Related Factors

	Median	IQR	Relevance	Skew	*P* Value	Change Between Rounds 2 and 3	v_r*	IRA
Importance of patient age in relation to UIA treatment								
Age <30 y	8	6.75	High	−0.236	0.075		0.127	Moderate
Age range 30–60 y	6	4	Moderate	−0.277	0.972		0.048	Very high
Age range 61–80 y	5	3	Moderate	0.160	0.075		0.042	Very high
Age >80 y	2	3	Low	0.950	<0.001	Increase	0.038	Very high
Importance of risk factors supporting UIA treatment								
Previous SAH from a different aneurysm	9	3.75	High	−0.883	0.158		0.085	High
Family history for UIAs or SAH†	7	3.75	High	−0.871	0.566		0.000	Very high
Autosomal-dominant polycystic kidney disease	6	4.25	Moderate	−0.351	0.433		0.141	Moderate
Japanese, Finnish, or Innuit ethnicity	5	4	Moderate	−0.404	0.902		0.101	Moderate
Female sex	3	4	Low	0.393	0.343		0.225	Low
Postmenopause phase	2	5	Low	0.984	0.233		0.296	Low
Nicotine consumption (current)	8	3	High	−0.969	0.380		0.056	Very high
Hypertension (current)†	6	3	Moderate	0.051	0.764		0.085	High
Drug abuse (current)†	5	5	Moderate	−0.167	0.961		0.169	Low
Alcohol abuse (current)†	4	3	Moderate	0.294	0.626		0.118	Moderate
Contralateral stenoocclusive vessel disease	3	3	Low	0.286	0.317		0.169	Low
Concomitant anticoagulants	2	3.75	Low	1.071	0.400		0.507	Low
Concomitant platelet inhibitors	2	3	Low	1.157	0.184		0.282	Low
Importance of comorbid diseases supporting conservative management								
Chronic/malignant disease with life expectancy <5 y†	10	1	High	−2.421	0.466		0.017	Very high
Chronic/malignant disease with life expectancy 5–10 y†	7	3	High	−0.989	0.668		0.072	High
Chronic/malignant disease with life expectancy >10 y†	4	4	Moderate	0.401	0.347		0.148	Moderate
Impaired QOL because of neurocognitive disorder†	8	3	High	−0.590	0.366		0.068	Very high
Psychiatric disorder†	5	4	Moderate	0.267	0.056		0.101	Moderate
Coagulopathies†	5	4	Moderate	0.269	0.381		0.135	Moderate
Thrombophilic diseases†	5	5	Moderate	0.382	0.189		0.101	Moderate
Diabetes mellitus	2	2	Low	0.669	0.947		0.169	Low
Risk factor modification/protective factors								
Blood pressure control	8	4	High	−0.674	0.686		0.106	Moderate
Nicotine cessation	8	4	High	−1.020	0.331		0.085	High
Alcohol cessation	3	3	Low	0.278	0.136		0.169	Low
Aspirin use	2	5	Low	0.858	0.934		0.423	Low
Statin use	2	3	Low	0.959	0.775		0.254	Low
Regular exercise	2	4	Low	0.699	0.326		0.338	Low
Avoid rigorous physical activity	1	3	Low	0.676	0.118		0.592	Low
Other								
Patients' reduced QOL because of fear from subsequent rupture of an UIA	5	4	Moderate	0.263	0.440		0.135	Moderate

Importance of all patient-related items in relation to treatment indications for unruptured intracranial aneurysms (UIAs) and corresponding inter-rater agreement (IRA). The *P* values indicate differences in ratings between rounds 2 and 3, that is, intrarater agreement. Skew indicates the directionality of ratings within round 3, with negative skew indicating the tendency for higher relevance and positive skew lower relevance corresponding to an asymmetry in the distribution of votes. IQR indicates interquartile ratio; QOL, quality of life; SAH, subarachnoid hemorrhage; and v_r*, standardized quartile coefficient of dispersion.

†See under Definitions.

Table 2. Aneurysm-Related Factors

	Median	IQR	Relevance	Skew	*P* Value	Change Between Rounds 2 and 3	v_r*	IRA
Importance of aneurysm size supporting UIA treatment								
Aneurysm size >25 mm	10	0	High	−4.282	0.722		0.000	Very high
Aneurysm size 13–24 mm	8	2	High	−0.463	0.967		0.047	Very high
Aneurysm size 7–12 mm	6	2	Moderate	0.183	0.870		0.063	High
Aneurysm size 4–6 mm	3	2	Low	0.463	0.904		0.126	Moderate
Aneurysm size 1–3 mm	1	2	Low	0.209	0.439		0.378	Low
Importance of aneurysm morphology supporting UIA treatment								
Aneurysm lobulation	7	3	High	−0.172	0.380		0.072	High
Size ratio†	4	3	Moderate	0.313	0.542		0.148	Moderate
Aspect ratio†	4	3	Moderate	0.181	0.431		0.127	Moderate
Aneurysm sphericity	3	2	Low	0.269	0.527		0.113	Moderate
Aneurysm ellipticity	3	3	Low	0.502	0.749		0.169	Low
Importance of aneurysm location supporting UIA treatment								
AComA and PcomA	7	3	High	−0.380	0.589		0.085	High
Basilar artery bifurcation	7	3	High	−0.537	0.653		0.072	High
Vertebral artery	5	3	Moderate	0.203	0.221		0.113	Moderate
Importance of radiological findings supporting UIA treatment								
Aneurysm growth on serial imaging	9	2	High	−1.657	0.034		0.038	Very high
De novo aneurysm formation on serial imaging	8	3.75	High	−0.593	0.008		0.090	Very high
Aneurysm location (parent vessel, per se)	6	3	Moderate	0.007	<0.001	Decrease	0.085	Very high
Aneurysm multiplicity	4	3	Moderate	0.368	<0.001	Decrease	0.148	Moderate
Importance of clinical symptoms supporting UIA treatment								
Cranial nerve deficits†	9	2	High	−1.488	0.558		0.038	Very high
Clinical or radiological signs of mass effect because of aneurysm†	10	2	High	−1.243	0.129		0.038	Very high
Thromboembolic event from the aneurysm	7	3	High	−0.263	0.002	Decrease	0.099	Very high
Epilepsy	3	5	Low	0.424	0.391		0.310	Moderate
Chronic headaches	1	2	Low	0.675	0.594		0.338	Low

Importance of all aneurysm-related items in relation to treatment indications for unruptured intracranial aneurysms (UIAs) and corresponding inter-rater agreement (IRA). The *P* values indicate differences in ratings between rounds 2 and 3, that is, intrarater agreement. Skew indicates the directionality of ratings within round 3, with negative skew indicating the tendency for higher relevance and positive skew lower relevance corresponding to an asymmetry in the distribution of votes. AComA indicates anterior communicating artery; IQR, interquartile ratio; PComA, posterior communicating artery; and v_r*, standardized quartile coefficient of dispersion.

†See under Definitions.

treatment-related factors contribute to decision making in the daily management of UIAs. However, despite attaining a consensus from a panel of neurovascular specialists for these factors and their ratings, our data illustrate that there is heterogeneity or uncertainty related to importance of individual features that are considered to influence whether or not to treat a UIA. Interestingly, this ambiguity was generally low for factors, which were rated as highly relevant and, moreover, for ratings on the important factors associated with UIA treatment risk. Treatment of a UIA is a single and immediate event and thus more accurately estimable, which may explain high IRAs observed within the treatment category. Moreover, the existing knowledge on UIA treatment risks may be considered more representative and robust than those on the natural history of UIAs, especially for controversial UIA aspects, such as UIAs <7 mm or the importance of potential risk factors, such as alcohol use or concomitant use of anticoagulants or platelet inhibitors. Ultimately, our results underscore the need for a better understanding of the pathophysiology of aneurysm rupture, so that more appropriate radiological or other surrogates can be used to identify UIAs at increased risk of rupture.

There are several potential limitations of our study. First, the present data are derived from existing evidence and from personal opinions of specialists, that is, there may be bias. Additionally, the high proportion of surgical or radiological interventionists in our research group may or may not add to this bias because of a potentially higher tendency to treat UIAs, per se. Second, there was heterogeneity between ratings for some items, which emphasizes the existing uncertainty on

Table 3. Treatment-Related Factors

	Median	IQR	Relevance	Skew	*P* Value	Change Between Rounds 2 and 3	v_r*	IRA
Importance of aneurysm size in relation to treatment risk								
Aneurysm size >20 mm	10	2	High	−1.281	0.646		0.037	Very high
Aneurysm size 10–20 mm	6	2	Moderate	−0.084	0.858		0.091	High
Aneurysm size 3–9 mm	3	2	Low	1.257	1.000		0.122	Moderate
Aneurysm size <3 mm	2	3	Low	1.077	0.267		0.274	Low
Importance of patient age in relation to treatment risk								
Age >80 y, rate risk of treatment	8.5	3	High	−1.576	0.740		0.038	Very high
Age range 61–80 y, rate risk of treatment	6	2	Moderate	0.167	0.355		0.085	High
Age range 30–60 y, rate risk of treatment	4	1	Moderate	1.179	0.699		0.099	High
Age < 30 y	2	2	Low	2.759	0.160		0.148	Moderate
Importance of individual factors for treatment indication								
Patient age	9	2	High	−1.094	0.008	Decrease	0.053	Very high
Patients' life expectancy	9	2	High	−1.506	0.055		0.038	Very high
Aneurysm size	8	2	High	−0.729	0.447		0.085	High
Individual risk of treatment	8	2	High	−0.708	0.609		0.032	Very high
Aneurysm location	6	3	Moderate	−0.169	0.002	Decrease	0.135	Moderate
Aneurysm complexity (complex vs noncomplex)†	6.5	3	Moderate	−0.016	0.022	Decrease	0.099	High
Treatment modality (surgical vs endovascular aneurysm repair)	5	5	Moderate	0.237	0.047	Decrease	0.135	Moderate
Patient compliance for follow-up examinations	3	3	Low	0.956	0.203		0.296	Low

Importance of all treatment-related items in relation to treatment indications for unruptured intracranial aneurysms (UIAs) and corresponding interrater agreement (IRA). The *P* values indicate differences in ratings between round 2 and 3, that is, intrarater agreement. Skew indicates the directionality of ratings within round 3, with negative skew indicating the tendency for higher relevance and positive skew lower relevance corresponding to an asymmetry in the distribution of votes. IQR indicates interquartile ratio; and v_r*, the standardized quartile coefficient of dispersion.

†See under Definitions.

the natural history of UIAs. However, these data highlight areas of uncertainty and are contributing to identification of potentially interesting focus for further research. Third, the definition of some features, such as aneurysm complexity or categories for aneurysm size and patient age may be arbitrary. Although these definitions were applied consistently throughout the different Delphi rounds, reducing any potential bias, more precise and reproducible categorization is currently lacking. Fourth, we used different scales for aneurysm size and patient age to estimate the natural history of UIAs and their treatment because of the heterogeneous or limited prospective data on these subjects. Nevertheless, within our surveys, panel members were asked for the preferred categories for aneurysm size and patient age, and the majority of the panel (> 2/3) chose the ones used in this proposal.

Conclusions

Our results highlight that specialists in neurovascular disease consider many features to be important when evaluating UIAs. Importantly, our results also underline that the natural history of UIAs remains uncertain, which underlines the necessity for a more comprehensive understanding of UIA biology to address the increasing need to reliably counsel patients with UIAs.

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