EDITORIAL

Leaving Tiny, Unruptured Intracranial Aneurysms Untreated
Why Is It So Hard?

S. Claiborne Johnston, MD, PhD

One of the frustrations that drove me back to focusing more on delivery of care and less on research was the difficulty in changing practice with the results of research. Nearly 20 years ago, my research group started to study the question of which intracranial aneurysms should be treated. The results were startling: the vast majority of small, unruptured aneurysms should be left untreated, even if the published evidence was off target by a large margin.[1] However, these results had little effect. In spite of 2 decades of largely confirmatory evidence for very small aneurysms (arbitrarily set at ≤3 mm in diameter) showing that coil embolization is not as safe as some believe and that rupture and growth rates are extremely low, many continue to recommend treatment for most of these aneurysms.

Related article

The updated analysis produced by Malhotra and colleagues[2] in this issue of *JAMA Neurology* paints the picture very clearly. The best approach for patients with aneurysms measuring 3 mm or less in diameter is to ignore the aneurysms: there is no need for follow-up imaging and certainly no need to try to treat them. Treating very small aneurysms is projected to reduce a person's healthy lifespan by nearly 2 years. That's right—you try to treat that little aneurysm and you are likely to knock a couple of years off someone's life. Could the estimates used in the model change the recommendation? The data would have to be unbelievably wrong to change the recommendation. For example, the annual rupture rate of an untreated aneurysm would need to be more than 1.7% to change the recommendation, and no study has shown a rate close to this, with a best estimate being 0.23%. Furthermore, one can always argue that the underlying studies could be better, but what happened to that oath we all took, "First do no harm…"? With the best estimate suggesting we shorten a patient's lifespan by 2 years when we treat a very small aneurysm, we should stop treating now rather than waiting for better data to change course.

Perhaps even more remarkable in this analysis is the conclusion that we do more harm than good from monitoring patients with magnetic resonance angiography regardless of whether the duration between scans is 1, 2, or 5 years, and this is without any consideration of cost. It would seem counterintuitive that more monitoring could be harmful when the monitoring itself is completely safe. However, we have seen from prostate-specific antigen testing for prostate cancer that the result of a screening test may worsen health outcomes.[3] Monitoring can push us to intervene and these interventions can have negative effects. It is an old story.

I suspect that these results, as with all those before them, will be ignored by some practitioners. I would like to examine several arguments I have heard through the years to justify treating such small aneurysms.

One frequent argument for proceeding with treatment even when the evidence recommends avoiding it is that the potential for the aneurysm to rupture produces anxiety that will affect a patient's quality of life, making treatment the right decision. However, when it is clear that the risk of rupturing the aneurysm or causing a stroke is greater by treating the aneurysm than leaving it alone, this concern should be reduced. We all know how suggestible patients can be, which makes it even more critical that we carefully educate them, perhaps even scripting the way we introduce the choices. Proper education and counseling are much safer and more appropriate interventions for this anxiety.

Another argument is that the procedural risks used in these models are inflated and do not reflect those at one's own institution. In fact, the estimates in the models are based on the published literature. Several studies have shown that there is a tendency to underreport adverse outcomes in case series such as these,[4] in part related to discomfort in accurately reporting adverse outcomes, so published estimates are probably underestimates. Furthermore, studies have shown that practitioners routinely underestimate their complication rates. The solution here is for physicians to distrust their own intuitions about local institutional complication rates and outcomes. The literature is almost certainly more accurate and should not be ignored. Your results are probably poorer than those published by your colleagues.

Some believe that the fact that many ruptured aneurysms are small means that the only way to prevent rupture is to treat small aneurysms. Although this idea is logical on the surface, it presumes that a static, small aneurysm existed for some number of months or years before rupturing, but the literature does not support that supposition. When we find and follow up small unruptured aneurysms, they almost never grow and almost never rupture. It is possible that the small aneurysms that rupture emerged days or even hours before rupture and that the ones we find incidentally are disproportionately stable. This possibility certainly fits the data.

A final argument I have heard to justify treatment of very small aneurysms is that a particular aneurysm is at high risk for rupture because of its configuration or location, the patient's family history, history of rupture of a different aneurysm, or some other consideration. Undoubtedly, there are higher-risk tiny aneurysms, and the literature suggests a

few such risk factors. However, the overall rates of rupture for tiny aneurysms are extremely low even when these subgroups are included, so these factors are of questionable importance in a given case.

Underlying these arguments are biases working behind the scenes, perhaps even subconsciously. Although we would love to deny it, we physicians are human and humans are by nature subject to an array of biases.

An example of such a bias is optimism. Even the proceduralists with the best skills have cases with complications. Going to work every day requires that they minimize the emotional effect of these complications on themselves. It would be too great a burden to acutely feel a complete sense of responsibility for every avoidable death or disabling complication, particularly in the highly risky and complex area of cerebrovascular disease. Proceduralists must be built to bounce back and move on; however, taken too far, this attitude can create a bias toward underestimating the rate and outcome of these same complications. This bias toward optimism about one's own outcomes is not universal, of course, and we have all seen both "cowboys" and "turtles," with the latter representing those we refer to when caution is preferred.

Career advancement is a bias to which we are all subject. For some, the longer the list of treated patients, the more impressive the published case series, and the greater the bragging rights and consequent referral base. Financial incentives also play into treatment decisions more than any of us would like to admit. Whether a physician benefits directly from treating more cases, as in private practice or with similar incentive plans, or benefits indirectly by achieving relative-value units that justify a high salary or bonus, the incentive to do more in our health care system is a very strong one. Physicians, department chairs, and hospitals are all complicit. One way to reduce this bias is to make sure the physicians making the decision about when treatment is necessary are not financially incentivized to do so.

Finally, the bias to do things as they have always been done is powerful in medicine. My generation of stroke physicians was taught that unruptured aneurysms were time bombs that should be identified and defused as soon as possible. It is extremely difficult to unteach that belief, with years of experience and all our trusted colleagues and mentors pushing in the opposite direction. The best solution here is probably to allow for greater coordination of care in multidisciplinary teams, where members keep each other up to date and ensure alignment with the latest and most reliable evidence. Greater devotion to tracking and achieving better outcomes could also help change the calculus to constant evolution toward the best treatment approach.

I hope this updated analysis will change the standard for how we approach tiny unruptured aneurysms. More important, I hope it is also a call to arms for creating a more responsive and responsible system of care that reduces the outcome of our biases and more closely adheres to the interests of the patient. Such a system would reward good outcomes rather than more care, and would include direct, ongoing feedback of outcomes to encourage integration of the best data elsewhere and generate new data in the delivery of care. Given my own frustration with the effect and pace of research, I am moving on to developing that system. Wish me luck. I will need it.

ARTICLE INFORMATION

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JAMA Neurology | Original Investigation

Management of Tiny Unruptured Intracranial Aneurysms
A Comparative Effectiveness Analysis

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IMPORTANCE Unruptured intracranial aneurysms (UIAs) are relatively common in the general population and are being increasingly diagnosed; a significant proportion are tiny (≤3 mm) aneurysms. There is significant heterogeneity in practice and lack of clear guidelines on the management of incidental, tiny UIAs. It is important to quantify the implications of different management strategies in terms of health benefits to patients.

OBJECTIVE To evaluate the effectiveness of routine treatment (aneurysm coiling) vs 3 strategies for imaging surveillance compared with no preventive treatment or routine follow-up of tiny UIAs.

DESIGN, SETTING, AND PARTICIPANTS A decision-analytic model-based comparative effectiveness analysis was conducted from May 1 to June 30, 2017, using inputs from the medical literature. PubMed searches were performed to identify relevant literature for all key model inputs, each of which was derived from the clinical study with the most robust data and greatest applicability. Analysis included 10 000 iterations simulating adult patients with incidental detections of UIAs 3 mm or smaller and no history of subarachnoid hemorrhage.

INTERVENTIONS The following 5 management strategies for tiny UIAs were evaluated: annual magnetic resonance angiography (MRA) screening, biennial MRA screening, MRA screening every 5 years, aneurysm coiling and follow-up, and no treatment or preventive follow-up.

MAIN OUTCOMES AND MEASURES A Markov decision model for lifetime rupture was constructed from a societal perspective per 10 000 patients with incidental, tiny UIAs. Outcomes were assessed in terms of quality-adjusted life-years. Probabilistic, 1-way, and 2-way sensitivity analyses were performed.

RESULTS In this analysis of 10 000 iterations simulating adult patients with a mean age of 50 years, the base-case calculation shows that the management strategy of no treatment or preventive follow-up has the highest health benefit (mean [SD] quality-adjusted life-years, 19.40 [0.31]). Among the management strategies that incorporate follow-up imaging, MRA every 5 years is the best strategy with the next highest effectiveness (mean [SD] quality-adjusted life-years, 18.05 [0.62]). The conclusion remains robust in probabilistic and 1-way sensitivity analyses. No routine follow-up remains the optimal strategy when the annual growth rate and risk of rupture of growing aneurysms are varied. When the annual risk of rupture of nongrowing UIAs is less than 1.7% (0.23% in base case scenario), no follow-up is the optimal strategy. If annual risk of rupture is more than 1.7%, coiling should be performed directly.

CONCLUSIONS AND RELEVANCE Given the current literature, no preventive treatment or imaging follow-up is the most effective strategy in patients with aneurysms that are 3 mm or smaller, resulting in better health outcomes. More aggressive imaging surveillance for aneurysm growth or preventive treatment should be reserved for patients with a high risk of rupture. Given these findings, it is important to critically evaluate the appropriateness of current clinical practices, and potentially determine specific guidelines to reflect the most effective management strategy for patients with incidental, tiny UIAs.

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Editorial
Supplemental content

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Unruptured intracranial aneurysms (UIAs) are relatively common in the general population and are being increasingly diagnosed owing to more frequent use of less invasive imaging techniques and higher resolution of images.[1] A large number (≤87.6%) of these incidental UIAs are small, measuring less than 3 to 4 mm.[2] Small aneurysms (≤7 mm) uncommonly cause aneurysmal symptoms and are labeled as incidental.[3,4] The natural history of UIAs remains poorly understood, and only 0.25% of UIAs eventually rupture, contributing to uncertainty regarding their optimal management.[5-7]

The American Heart Association and American Stroke Association guidelines for management of patients with UIAs were updated in 2015.[3] However, these guidelines do not specify separate recommendations for small (3-7 mm) and tiny (≤3 mm) aneurysms, although their natural history, risk of rupture, and success of treatment might be different from those of aneurysms measuring more than 7 mm.[8,9] A recent meta-analysis found that the reported rupture rate for tiny aneurysms was 0% in 5 of 7 studies and less than 0.4% in the remaining 2 studies.[10] These small aneurysms are frequently treated because aneurysmal subarachnoid hemorrhage (SAH) is reportedly the result of rupture of aneurysms with diameters 5 mm or less.[11-13] A recent meta-analysis of endovascular coiling of tiny intracranial aneurysms concluded that coiling can be performed safely and effectively, with favorable long-term angiographic and neurologic outcomes.[14] However, coil embolization of aneurysms that are 3 mm or less is particularly challenging, and the meta-analysis found a 7% intraprocedural rupture rate and a 4% incidence of thromboembolic complications.[14] These findings also must be interpreted in the context of a very low reported risk of rupture of small aneurysms.[8,11,15-17] Patients with no history of SAH who are harboring aneurysms measuring 7 mm or less are often followed up conservatively using magnetic resonance angiography (MRA) to assess changes in size and/or morphologic characteristics.[17] However, the utility, duration, and frequency of follow-up imaging are also not clearly established.

In a 2015 international survey of 203 neurosurgeons, most endorsed treatment of all asymptomatic aneurysms regardless of size.[18] A more recent study showed that 11% of treating physicians always or usually recommend treatment of anterior circulation aneurysms measuring less than 5 mm without a family or personal history of SAH.[19] Another 30% of physicians treated these small aneurysms 40% to 60% of the time. Follow-up imaging schedules were reported to be highly variable.

We performed a comparative effectiveness analysis from a societal perspective to assess the following 5 strategies in managing tiny UIAs measuring 3 mm or less: annual surveillance using MRA, biennial surveillance using MRA, surveillance using MRA every 5 years, coiling and MRA follow-up, and no treatment or preventive follow-up.

Key Points

Question What is the optimal management of tiny (≤3 mm) unruptured intracranial aneurysms?

Findings In this comparative effectiveness analysis, calculations show that routine preventive treatment (coiling) or aggressive imaging follow-up have lower health benefits from a societal perspective than no preventive treatment or imaging follow-up.

Meaning Routine treatment or frequent imaging follow-up is not effective in the general population with tiny unruptured intracranial aneurysms, but may be more appropriate in selected patients at high risk of rupture.

Methods

We define tiny aneurysms as those measuring 3 mm or less and small aneurysms as those measuring 3 to 7 mm. A decision tree with Markov modeling was constructed from a societal perspective with TreeAge Pro Suite 2014 (TreeAge Software Inc). By using computational simulation, decision analytic modeling can be considered as a complement to performing a large-cohort randomized clinical trial. The advantages include being able to compare several strategies and estimating the optimal strategy based on the most favorable outcomes for patients. The model covered the life span of a patient with the above-mentioned 5 strategies as potential options. With probabilistic sampling, the model simulated parallel cohorts of patients with tiny UIAs treated by different strategies and computed the respective outcomes for comparison. Outcomes were assessed in terms of quality-adjusted life-years (QALYs), which is a comprehensive utility metric accounting for both life expectancy and quality of life for patients in a specified health state. Institutional review board approval was not sought because no patient data are included in the study.

Model Structure

The model starts with a 50-year-old patient, representing the base case scenario as a patient of mean age harboring an intracranial aneurysm measuring 3 mm or smaller. A simplified flowchart of the model is presented in eFigure 1 in the Supplement. In all 5 strategies, the risk of death from other causes is considered on a yearly basis, constant across strategies but different across years. The presence of multiple aneurysms would put patients at a higher risk of SAH and the risk was compounded.

If coiling is performed after detection of an aneurysm, the patient can experience complications, die from the procedure, or have an uneventful recovery. After coiling, we assume that the patient will be followed up with MRA at 6 months and 1 year, and undergo imaging annually in subsequent years.[3] After coiling, patients will also have the risks of regrowth or recanalization with retreatment, as well as the possibility of rebleeding.

No Preventive Option

If no follow-ups are performed, the patient would have an annual risk of rupture. If such an event does occur, the patient is assumed to be treated with coiling and may subsequently experience mild, moderate, or severe disability, or die from the SAH. After coiling, follow-up is similar to that in unruptured aneurysms.

Imaging Follow-up

If preventive screening is performed annually for an unruptured aneurysm, growth can be observed on each follow-up.

As patients with growing aneurysms would be expected to be at a higher risk of rupturing, patients are assumed to undergo coiling with changes in size or morphologic findings, with subsequent similar risks after coiling and imaging follow-up. Rupture can occur in nongrowing aneurysms, which would not be preventable by imaging surveillance.

When screening is performed every 2 or 5 years, the subtree structures (eFigure 1 in the Supplement) are the same as the annual screening strategy, but the effectiveness is discounted in 2- or 5-year intervals, and clinical parameters are compounded.

No complications owing to imaging were included in the model because of the noninvasive nature and lack of radiation exposure with MRA.

Clinical Parameters

An overall discount rate of 3% for effectiveness was used in the model, as per the standard practice of comparative effectiveness analysis in the United States.[20] Half cycle correction was performed for all strategies.

All clinical parameters were derived from recently published large cohort studies or meta-analyses specific to patients with small aneurysms. The annual growth rate (1.22%) and risk of rupture (0.23%) were extracted from a study by Sonobe et al[11] with a large cohort of patients harboring tiny aneurysms. The study by Sonobe et al[11] was the only one that included both rupture and growth rates for tiny aneurysms. The outcome of coiling, including mortality, morbidity, and retreatment rates, was derived from a recent systematic review and meta-analysis by Yamaki et al.[14] The incidence of de novo aneurysm formation was reported to be 0.97% per person-year by Zali et al,[21] with more than 7 years of follow-up. We assumed that the risks of rupture of de novo aneurysms were the same as for existing aneurysms, and that their risks of rupture were independent of one another. For the model, all growths were assumed to be detected and growth seen on results of imaging was assumed to be true positive, as angiography would be performed subsequently to confirm the findings. Most clinical parameters, when possible, were assigned β distributions, which are flexible and bounded by 0 and 1, making it useful for varying probability inputs in probabilistic sensitivity analysis.

We assigned differential annual mortality rates from nonaneurysmal causes, as the model was of a lifetime horizon. The differential mortality rates were computed from the 2010 United States Life Tables.[22] Patients with moderate to severe disability would have a 17% excess rate of mortality.[23]

Outcomes

The health state parameters were based on a previous cost-effectiveness analysis by Greving et al,[24] and included a disutility for patient awareness of having an unruptured aneurysm. We assigned a temporary 5% disutility for discomfort and anxiety from the coiling procedure. We assumed that if a patient experienced more than 1 episode of SAH, he or she would develop moderate to severe disability or die. A full list of parameters is presented in **Table 1**.[11,14,21,24-26]

Statistical Analysis

Base case calculation was carried out using the mean value for each parameter. Probabilistic sensitivity analysis simulation was performed with 10 000 iterations, modeling 10 000 patients. In addition, key variables, including annual growth rate, overall rupture rate, and utility of SAH, are varied across a wide range in 1-way, 2-way, and probabilistic sensitivity analyses.

Results

Base Case Calculation

In the base case calculation, all imaging strategies were dominated by the strategy of no scheduled follow-up: all imaging strategies showed lower effectiveness than no follow-up, which had an expected health benefit of a mean (SD) 19.40 (0.31) QALYs. Among the imaging strategies, imaging every 5 years is the best strategy with the next highest effectiveness (mean [SD] QALYs, 18.05 [0.62]). Coiling is the least favorable option because of high risks of complications and the least favorable outcome (mean [SD] QALYs, 17.53 [0.30]). The detailed results are presented in **Table 2**.

Probabilistic Sensitivity Analysis

We performed probabilistic sensitivity analyses to simulate a cohort of 10 000 patients as iterations. The 2 strategies for comparison were follow-up every 5 years vs no follow-up, since they were the 2 strategies with the highest QALYs from the base case calculations. In the simulation, follow-up every 5 years is better only 0.050% (95% CI, 0.037%-0.066%) of the time. No scheduled follow-up is the optimal strategy in the remaining iterations.

Sensitivity Analyses

The growth rate of tiny UIAs was varied across a wide range while keeping other variables fixed. The result shows that no follow-up is better throughout the entire range. If imaging is to be performed, the most effective imaging strategy is every 5 years, irrespective of the growth rate (**Figure 1**).

We similarly varied the risks of rupture of growing and nongrowing aneurysms. The model shows that no follow-up is best regardless of the risk of rupture (**Figure 2**). If imaging has to be considered, the best imaging strategy is 5-year follow-up if the risk of rupture of growing aneurysms is lower than 10.8%. Annual follow-up should be performed if the risk is higher than 10.8% (eFigure 2 in the Supplement). On the other hand, when the risk of rupture of small, nongrowing aneurysms is smaller than 1.7% per year, no follow-up is the optimal strategy. When the risk is higher, coiling should be performed directly (**Figure 3**).

A 2-way sensitivity analysis was performed, varying both the risk of rupture of growing aneurysms (0%-40%) and the proportion of growing aneurysms (0%-40%) among all tiny aneurysms (eFigure 3 in the Supplement). The result shows that when either the proportion or risk of rupture of growing aneurysms is lower than 4%, no follow-up is the optimal strategy regardless of the value of the other variable. When the rupture risk is between 4% and 8%, follow-up

Table 1. All Parameters

Variable	Mean Value With Reference(s), %	Distribution	Source
Clinical Parameters			
Annual growth rate of UIA <3 mm	1.22	β (α = 11, β = 890), SD = 0.37%	Sonobe et al,[11] 2010
Annual rupture rate of growing UIA	0	Normal, SD = 9.25%, lower bound at 0%	Sonobe et al,[11] 2010
Annual rupture rate of nongrowing UIA	0.23	β (α = 2, β = 861), SD = 0.16%	Sonobe et al,[11] 2010
Annual incidence of de novo aneurysm formation	0.97	β (α = 9, β = 919), SD = 0.32%	Zali et al,[21] 2014
Proportion of patients with SAH with good long-term neurologic outcomes	52.5	β, SD = 5%	Yamaki et al,[14] 2016
Proportion of patients with SAH developing moderate to severe disability	17.5	Calculated by 1 − proportion of patients with SAH with good long-term neurologic outcome − SAH mortality	Sonobe et al,[11] 2010
SAH mortality	30	β, SD = 3%	Yamaki et al,[14] 2016
Proportion of good long-term neurologic outcome after coiling	89	β, SD = 5%	Yamaki et al,[14] 2016
Perioperative mortality associated with endovascular coiling	3	β, SD = 1%	Yamaki et al,[14] 2016
Risk of moderate disability from coiling	8	Calculated by 1 − proportion of good long-term neurologic outcome − mortality after coiling	Yamaki et al,[14] 2016
Rate of retreatment after coiling in unruptured aneurysms	7	β, SD = 1%	Yamaki et al,[14] 2016
Rate of retreatment after coiling in ruptured aneurysms	7	β, SD = 3%	Yamaki et al,[14] 2016
Rate of rebleeding after coiling	0.16	β (13, 8338)	Molyneux et al,[25] 2015
Effectiveness, QALYs			
Well	1	NA	NA
Awareness of the UIA (range)	0.92 (0.87-1.0)	Triangular	Greving et al,[24] 2009
Mild disability (range)	0.72 (0.65-0.80)	Triangular	Greving et al,[24] 2009
Moderate to severe disability (range)	0.41 (0.25-0.65)	Triangular	Greving et al,[24] 2009
Coiling	5% disutility	NA	NA
SAH (range)	0.64 (0.52-0.71)	Triangular	Bor et al,[26] 2010

Abbreviations: NA, not applicable; QALYs, quality-adjusted life-years; SAH, subarachnoid hemorrhage; UIA, unruptured intracranial aneurysm.

Table 2. Base Case Calculation Results

Management Strategy	Expected Health Benefit, Mean (SD), QALYs
No follow-up	19.40 (0.31)
Follow-up every 5 y	18.05 (0.62)
Annual follow-up	17.93 (0.56)
Biennial follow-up	17.65 (0.58)
Coiling	17.53 (0.30)

Abbreviation: QALYs, quality-adjusted life-years.

should be performed every 5 years if the annual growth rate of tiny aneurysms is high. When the rupture risk is greater than 8%, annual follow-up should be performed if growth rate is intermediate and coiling should be performed if the growth rate is high.

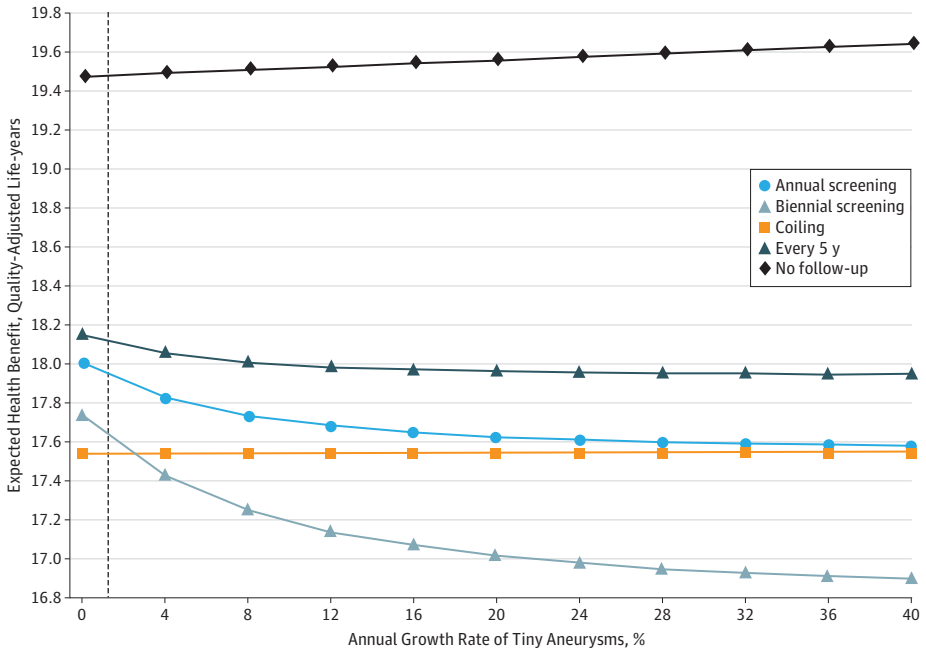
Results of sensitivity analysis further show that the conclusion does not change while varying the health states of patients with SAH after rupture of tiny aneurysms or the mortality from SAH caused by aneurysmal rupture (eFigures 4 and 5 in the Supplement).

Discussion

The natural history of UIAs remains poorly understood, which is especially true for small (3-7 mm) and tiny (≤3 mm) aneurysms.[27] The 2015 American Heart Association and American Stroke Association guidelines on the management of patients with UIAs recommend intermittent imaging studies at regular intervals to follow up UIAs that are managed conservatively (class I; level of evidence B).[3] This recommendation is based on the understanding that aneurysmal growth may increase the risk of rupture.[28] A first follow-up study at 6 to 12 months after initial discovery is recommended, followed by subsequent follow-up yearly or every other year (class IIb; level of evidence C).

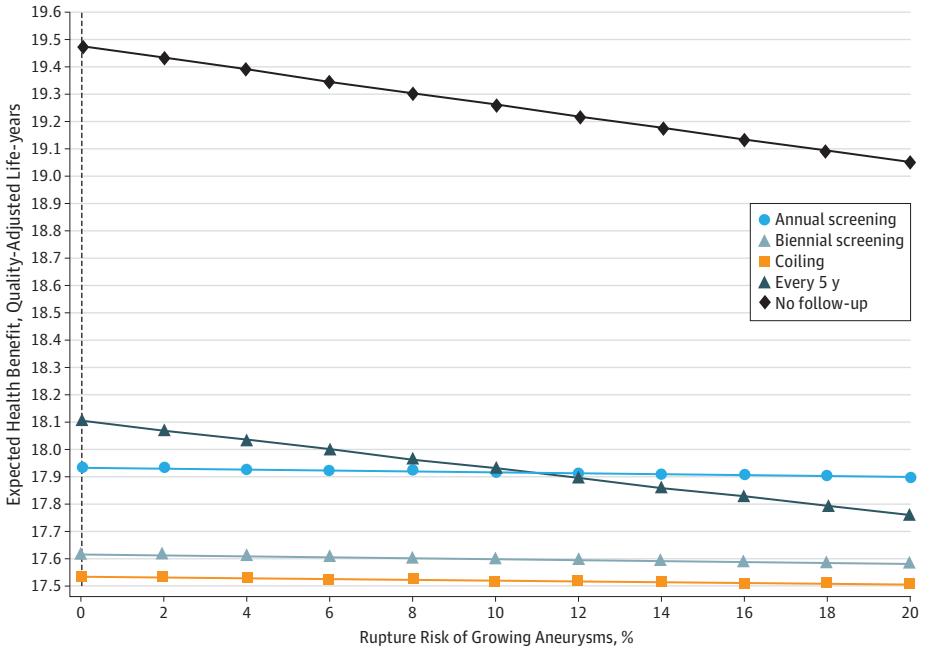
Patients with documented enlargement during follow-up should be offered treatment in the absence of prohibitive comorbidities (class I; level of evidence B). Long-term follow-up imaging may be considered after treatment, given the combined risk of aneurysm recurrence and formation of de novo aneurysm (class IIb; level of evidence B). The timing and duration of follow-up is, however, not defined for

Figure 1. One-Way Sensitivity Analysis Varying the Annual Growth Rate of Tiny Aneurysms



A higher health benefit is more favorable. No follow-up remains the optimal strategy throughout the range of 0% to 40% annual growth rate of unruptured intracranial aneurysms. The dotted vertical line indicates base case value.

Figure 2. One-Way Sensitivity Analysis Varying the Rupture Risk of Growing Aneurysms



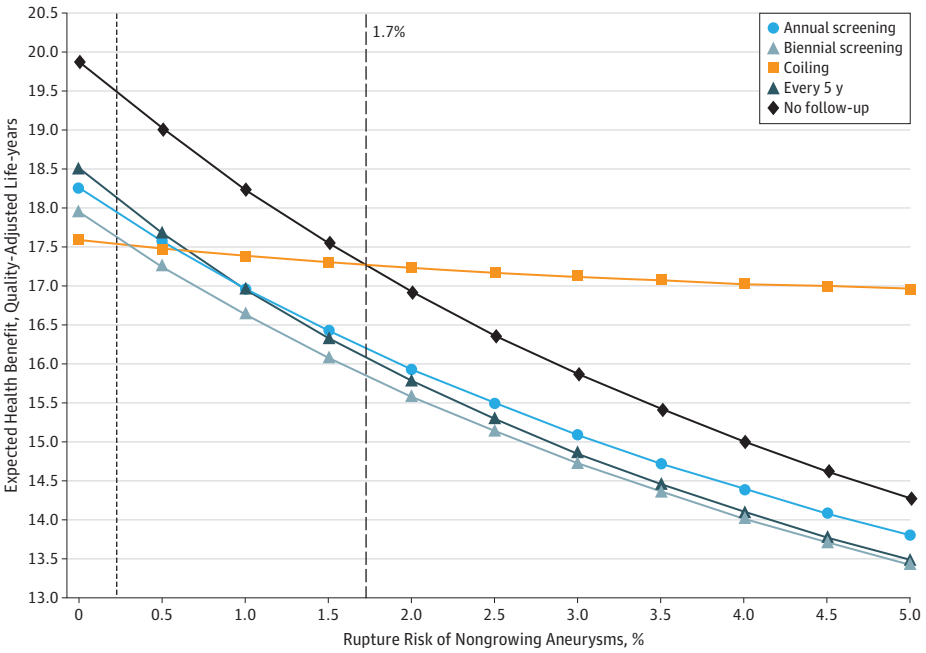
A higher health benefit is more favorable. No follow-up remains the optimal strategy throughout the range of 0% to 20% rupture risk of growing intracranial aneurysms. The dotted vertical line indicates base case value.

treated aneurysms as well as untreated aneurysms, and additional investigation has been deemed necessary.[3]

No specific guidelines exist regarding the management of tiny, incidentally detected UIAs measuring 3 mm or less. The incidence of rupture in tiny UIAs in the published literature is low.[10] The International Study of Unruptured Intracranial Aneurysms (ISUIA) had previously found the risk of rupture of anterior circulation aneurysms measuring 7 mm or less to be 0% in absence of a history of SAH.[8] Subsequent studies have shown a good percentage of small and tiny aneurysms among all ruptured aneurysms. Kassell and Torner[29] found that 13% of ruptured aneurysms out of 1092 cases were 5 mm or less in diameter, a significant discrepancy from the ISUIA data.

A positive correlation between aneurysm growth and rupture is critical to justify imaging surveillance to assess aneurysmal growth. The 3.1% rate of rupture for growing

Figure 3. One-Way Sensitivity Analysis Varying the Rupture Risk of Nongrowing Aneurysms



A higher health benefit is more favorable. No follow-up is the optimal strategy when the rupture risk of nongrowing intracranial aneurysms is less than 1.7%. When the risk is higher, coiling becomes the preferred strategy. The dotted vertical line indicates base case value.

aneurysms compared with the 0.1% rate for stable aneurysms has been reported for all aneurysms.[30] However, the growth and rate of rupture for aneurysms measuring 3 mm or smaller and their correlation may not be the same as for larger aneurysms. Although Villablanca et al[28] found a positive correlation between growth and rupture in aneurysms measuring 7 mm or less, a systematic review in 2010 found this association to be variable and unpredictable.[27]

Despite the low risk of rupture, these small aneurysms are being treated, increasingly by coiling.[14] The risks associated with surgical clipping have not been well categorized, and coiling is being performed more frequently.[31] Therefore, we focused on endovascular coiling for treatment of aneurysms in this study.

Our model parameters are based on the SUAVe study,[11] which is the only study, to our knowledge, that reported on growth as well as rates of rupture in tiny aneurysms. The study found an annual risk of rupture of 0.34% for single aneurysms measuring 5 mm or less. Seven cases (1.9% of all patients) experienced ruptures during follow-up. Only 2 of these 7 cases were aneurysms measuring less than 4 mm. None of the 7 ruptured aneurysms had change in size on follow-up.

The results of our study show that routine imaging follow-ups may not be effective in following up these tiny aneurysms, based on the current literature. If imaging must be performed, follow-up every 5 years is more effective than more frequent follow-up.

Furthermore, no preventive follow-up would be the optimal strategy, irrespective of the incidence of rupture in growing aneurysms. Among the imaging strategies, imaging every 5 years is the most effective strategy. The sensitivity analysis varying the risk of rupture in nongrowing aneurysms shows that coiling becomes optimal only when the risk of rupture in nongrowing aneurysms becomes greater than 1.7%. The risk of rupture reported in the literature is much smaller.[2] The Unruptured Cerebral Aneurysm study reported a rupture rate of 0.36% in UIAs measuring 3 to 4 mm.[15]

In a previous cost-effectiveness analysis, Greving et al[24] concluded that treatment was cost-effective for UIAs in 50-year-old patients with rates of rupture between 0.3% and 3.5% per year. However, the procedure-associated mortality and morbidity used in that analysis was much lower compared with the values for tiny aneurysms.[14] Furthermore, Greving et al[24] found that their results were highly sensitive to the utility of awareness of an untreated aneurysm, with only a slight decrease in quality of life from awareness of an aneurysm leading to substantial increase in incremental cost-effectiveness of treatment. However, the assigned utility of 0.92 is from a previous study on the outcome of finding a small aneurysm in patients who had previously undergone an operation for ruptured aneurysm.[32] That study clearly stated that the results could not be extrapolated to screening of patients without prior SAH. Our study results are similar to those of Johnston et al[33] from 1999, although our study is based on more recently available data, and their study did not assess the role of follow-up imaging.

More aggressive management strategies may be more appropriate in patients at higher risk of rupture. Hypertension, age less than 50 years, multiple aneurysms, posterior aneurysm location, and a larger size ratio have all been postulated to be high-risk features in UIAs.[2,13,15,17,34-38] Although these risk factors might tilt decision making toward aneurysm ablation, to our knowledge, there is no evidence in the literature that routinely following up these small aneurysms adds utility.

We assumed that all growths would be detected on MRA, and growth seen on results of imaging was assumed to be a true

positive. The criteria used to define growth are widely variable in the literature.[39] Sensitivity of MRA in detecting small changes in size or morphologic characteristics of tiny aneurysms could be questionable.[40,41] Also, false-positive MRAs may require digital subtraction angiography for confirmation, which would make imaging surveillance even less effective. Computed tomographic angiography would have much higher spatial resolution, but would not be ideal for imaging surveillance owing to radiation concerns.

Limitations

We did not study the effect of age, sex, or aneurysm location in our model on the effectiveness of the different strategies. These factors may need further study to stratify strategies based on risk.

An inherent limitation of most studies on the natural history of UIAs is possible selection bias, with patients at higher risk undergoing treatment and the rate of rupture being underestimated in patients who underwent conservative treatment. Our sensitivity analysis indicates that the decision of frequency of imaging surveillance would be altered only if risk of rupture is higher than 30%, which is not close to the low rates of rupture reported in patients with tiny aneurysms.

It has been postulated that the risk of rupture may be higher shortly after diagnosis of UIA and that the risk may decline with time.[42,43] This possibility might imply closer supervision of these aneurysms initially, with increased spacing of imaging over time. However, there is a lack of specific literature on dynamic growth patterns of small aneurysms. We did not factor this in our model but it might need consideration once more data are available.

The duration of follow-up imaging for unruptured aneurysms as well as aneurysms after coiling is not well understood. The frequency of follow-up in the first 5 years has been reported to be even more aggressive than that incorporated in this model, with many centers using multiple digital subtraction angiographies.[44] In the only long-term study of the natural history of UIAs, Juvela et al[45] found that the risk of bleeding from an unruptured aneurysm remained virtually constant during the first 25 years after diagnosis except for patients above 50 years of age.

Recent meta-analyses on UIAs show the wide variability in imaging modalities and parameters used to define growth of UIAs.[39] Except for the study by Juvela et al,[45] other studies assessing growth have a follow-up less than 5 years.[39] Our study emphasizes the need for better, more consistent, and longer-term studies reporting the growth and rate of rupture of UIAs to better define the optimal management of small UIAs. Clinical decisions are currently being made based on the limited evidence in the literature.

Conclusions

Management of tiny (≤3 mm) UIAs is often a dilemma. Given the current literature, our study reveals that no treatment or imaging follow-up is the most effective strategy, resulting in better health outcomes and lower health care spending. More aggressive management strategies might be appropriate in selected high-risk patients. Clinicians should discuss with patients all the potential variables involved in decision making, and policy makers may want to consider the study findings for future guidelines.

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