# Evidence report for watchful waiting vs. surgical or endovascular treatment for patients with incidental intracranial aneurysm

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# Evidence report for watchful waiting vs. surgical or endovascular treatment for patients with incidental intracranial aneurysm

## Scoping

Prepared by EBSCO Information Services

October 2, 2019

Amended November 18, 2019

Prepared by EBSCO Health Innovations and EBM Development Department:

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# Abbreviations

## General abbreviations that may appear in this report

CI – confidence interval
CrI – credible interval
HR – hazard ratio
MA – meta-analysis
MD – mean difference
NA, N/A – not applicable
NR – not reported
OR – odds ratio
RCT – randomized, controlled trial
RR – risk ratio, relative risk
RtR – rate ratio
SMD – standardized mean difference
SR – systematic review
SRMA – systematic review and meta-analysis

## Abbreviations specific to this report

CT – computed tomography
CTA – computed tomographic angiography
IIA – incidental intracranial aneurysm
MR – magnetic resonance
MRA – magnetic resonance angiography
MRI – magnetic resonance imaging
UIA – unruptured intracranial aneurysm

# Methods

Using an established, structured template that delineates key elements for scoping (i.e., the population, interventions, and key outcomes to consider), we collaboratively agreed with UKSH on the scope of the present evidence report. Scoping was completed on October 2, 2019. Scoping was amended on November 18, 2019 to add descriptive summary FAQs pertaining to quality of life and the possible need for retreatment.

# Results – Criteria Selection for Critical Appraisal

## Population:

### *Inclusion criteria*

Patients aged ≤65 years with incidental intracranial aneurysm <20 mm

### *Exclusion criteria*

Patients for whom the clinical context suggests watchful waiting is inappropriate (e.g., presenting with signs/symptoms consistent with a sentinel leak or who have a second aneurysm).

Note about population: We do not include a lower limit for aneurysm size, but unless there are additional compelling factors present that suggest the rupture risk may be higher, treatment with surgical or endovascular intervention is generally only recommended for aneurysms >5-7 mm (due to aneurysms of this size generally having a low rupture risk).

## Options:

### *Watchful waiting*

The intervention is receiving watchful waiting, which amounts to regular follow-up visits and serial neuroimaging studies to monitor the incidental intracranial aneurysm.

### *Neurosurgical or endovascular treatment*

The intervention is neurosurgical clipping or endovascular treatment of the incidental intracranial aneurysm.

Note: Several terms are used throughout the literature for the endovascular treatment of aneurysms (e.g., interventional therapy/neuroradiological therapy/catheter-based therapy). For the sake of simplicity, the term endovascular treatment is used throughout the evidence report. It covers various procedures, including standard coiling and newer endovascular methods such as stent-assisted or balloon-assisted coiling, flow-diverting stents, and WovenEndoBridge (WEB) aneurysm Embolization devices. For descriptions of specific procedures (e.g., coiling) the corresponding term is used.

### *Note about options and approach to evidence report:*

Whether one considers randomized, controlled trials or observational studies, comparative data are lacking for watchful waiting versus neurosurgical or endovascular treatment of incidental intracranial aneurysms. Therefore, the best possible approach to this question will adopt a prognostic approach, describing chances/risks in each group, but not necessarily permitting direct comparisons.

Given aneurysm rupture risk may vary based on clinical parameters (e.g., size and location being key considerations[1-3]), the ideal answers for this evidence report would be provided by a validated clinical prediction rule that provides rupture risk and/or other patient-relevant outcomes based on a patient's clinical parameters. However, data on long-term rupture risk after neurosurgical or endovascular intervention are lacking,[1] and evidence on long-term aneurysm recurrence after neurosurgical or endovascular intervention (though ultimately a surrogate outcome) is dominated by data concerning treatment of ruptured aneurysms.[4] However, there are data on complications from receiving neurosurgical or endovascular intervention for an incidental intracranial aneurysm, including intraoperative rupture.[5]

We will approach this evidence report in a hierarchical fashion as follows:

1) We will seek to answer FAQs based on sufficiently-valid prediction rules that permit more individualized estimates of risk.
    a. In the ideal scenario, we will find one or more prediction rules with rigorous derivation and external validation. If there is more than one prediction rule, we will appraise the prediction rules to select the best fit-for-use prediction rule.
    b. If we find one or more prediction rules without external validation, we may consider prediction rules with sufficiently-valid internal validation to be the best evidence-based answer. However, this appraisal will depend on:
        i. the specifics of the reason for internal validation versus external validation,
        ii. the methods used for internal validation, and

iii. considering the context, namely the potential alternative of providing less individualized risk estimates that may be importantly higher or lower for any given individual

c. If we find a sufficiently-valid prediction rule, for purposes of the decision aid, we will still present "static" values for select groupings of risk factors based on what the available evidence for the prediction rule provides. For instance, we may provide a range of estimates based on size, location, age, and/or presence of comorbid hypertension as the evidence permits. Given the limitations of a paper-based decision aid (e.g., the impracticality of listing every possible pattern), we may select for presentation certain "exemplar" patterns based on the most common aneurysmal patterns seen in the available evidence while still noting that any person's specific risk may depend on other factors. We will also include a qualitative discussion of risk factors for rupture and will also include a direct reference to the sufficiently-valid prediction rule as appropriate.

2) If sufficiently-valid prediction rules do not exist, we will seek to provide stratified risk estimates based on the size and location of the aneurysm, with size and location acting not just as individual risk factors, but as interacting risk factors. If there are clear data to permit such stratification for both options listed above, we will present answers to the FAQs with this stratification. However, if data do not permit such stratification for one or both options, we may provide best overall estimates without any stratification and qualitatively identify risk factors associated with an increased or decreased risk of the outcome in consideration.

## Outcomes:

For some of the FAQs below, we will refer to the above protocol to provide answers; otherwise, where we say: "We will include a description of", we will answer the FAQ with descriptive responses, which do not involve systematic evidence searches, critical appraisal, or evidence synthesis.

### *FAQ 1: What does the treatment involve?*

We will include a description of the intervention, including the periodicity of follow-up for the watchful waiting option and length of hospital stay for the option of neurosurgical or endovascular intervention.

### *FAQ 2: What is my risk of the aneurysm rupturing in the next 5 years?*

This FAQ is only relevant for the watchful waiting option due to above-noted reasons (no reliable data for this outcome following treatment of incidental intracranial aneurysms).

We will seek to provide 5-year risk estimates for aneurysmal rupture in accordance with the above-noted approach. We will not consider annualized or 1-year rupture risk as sufficiently valid to estimate 5-year rupture risk, as aneurysmal behavior cannot be assumed to be linear/constant.[6-9] We also consider 1-year rupture risk as a standalone outcome to be considerably less relevant for patients than a 5-year risk.

As noted above, data on rupture risk after neurosurgical or endovascular intervention are lacking. However, we will include a description of this gap in the evidence and how it precludes an evidence-based answer to this question for neurosurgical or endovascular intervention.

### *FAQ 3: What are the risks of the procedure?*

This FAQ is only relevant for the option of neurosurgical or endovascular intervention.

We will seek to provide estimates of procedural complications in line with the above-noted approach, with the specific outcomes possibly being dictated by those outcomes provided by the clinical predication rule (if relevant). If there is not a sufficiently-valid prediction rule, risks to consider will include periprocedural (during or within 30 days of the procedure) mortality and complications. For periprocedural complications, we will consider the outcomes of intracranial ischemic complications (transient ischemic attack or ischemic stroke), intracranial hemorrhagic complications (intraoperative aneurysmal rupture, intracerebral hemorrhage, or epi- or subdural hematoma), and overall complications causing permanent or non-permanent morbidity or mortality.

### *FAQ 4: How will it affect my quality of life?*

The outcome of interest is quality of life. We will provide descriptive summaries informed by the 2015 American Heart Association and American Stroke Association guideline on the management of unruptured intracranial aneurysms.

## *FAQ 5: Will I need additional treatment?*

The outcome of interest is the need for additional treatment. We will provide descriptive summaries informed by the 2015 American Heart Association and American Stroke Association guideline on the management of unruptured intracranial aneurysms.

## *FAQ 6: How long does it take to recover?*

This FAQ is only relevant for the option of neurosurgical or endovascular intervention.

We will include a description of time to return to usual activity, including work and driving.

_____

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9. Juvela S, Poussa K, Lehto H, Porras M. Natural history of unruptured intracranial aneurysms: a long-term follow-up study. Stroke. 2013 Sep;44(9):2414-21. doi: 10.1161/STROKEAHA.113.001838. Epub 2013 Jul 18. Note: Although the authors of this study discuss a constancy in the rupture risk, they also include contradictory statements in their own data (e.g., “the risk of aneurysm rupture decreased markedly after our last follow-up [study]”).

# Evidence report for watchful waiting vs. surgical or endovascular treatment for patients with incidental intracranial aneurysm

## Evidence Synthesis

Prepared by EBSCO Information Services

October 8, 2019

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# Results – Summary of Findings

## FAQ 1: What does the treatment involve?

Decisions about management should always involve a discussion of benefits and risks in the context of patient values and preferences. As noted by the 2015 American Heart Association and American Stroke Association guidelines: "Several factors should be considered in selection of the optimal management of [incidental intracranial aneurysms], including the size, location, and other morphological characteristics of the aneurysm; documented growth on serial imaging; the age of the patient; a history of prior aSAH; family history of cerebral aneurysm; the presence of multiple aneurysms; or the presence of concurrent pathology such as an arteriovenous malformation or other cerebrovascular or inherited pathology that may predispose to a higher risk of hemorrhage". Additionally, in general, aneurysms smaller than 5 to 7 mm are often managed with watchful waiting due to their low rupture risk (Greving 2014, Malhotra 2017).

*Watchful waiting*

Watchful waiting means having CT scans or MRIs to keep track of the shape and size of the aneurysm. Some people may prefer this option to avoid having a procedure. However, there is a risk the aneurysm will rupture while being tracked. You and the surgeon will decide how often you should have a CT or MRI. This will depend on things like the size and location of the aneurysm, whether the aneurysm grows, and what other conditions you might have. If the aneurysm changes, the surgeon may recommend a procedure to treat the aneurysm. You can also change your mind later if you decide you want to have a procedure to treat the aneurysm.

*Neurosurgical or endovascular treatment*

There are two main ways to treat a brain aneurysm: neurosurgical treatment (often called "clipping") or endovascular treatment (most often something called "coiling"). Some people may prefer one of these options because they are worried about the aneurysm rupturing. However, each option is a major procedure that also has risks. If a patient wants neurosurgical or endovascular treatment, one might be better than the other. This may depend on things like the size, shape, and location of the aneurysm and the age and health of the patient.

In "clipping", the surgeon:

- makes an opening in the skull
- finds the blood vessel with the aneurysm, and
- puts a metal clip at the bottom of the aneurysm

In "coiling", the surgeon:

- puts a long, flexible tube into a blood vessel in the upper leg
- moves the tube through the blood vessels to reach the aneurysm, an
- puts a metal coil inside the aneurysm

The treatment blocks the aneurysm from the normal blood vessels. You may stay in the hospital for 4 to 6 days after neurosurgical treatment or 1 to 2 days after endovascular treatment. The surgeon may want to get imaging studies after either procedure.

(References consulted for this descriptive summary include: American Association of Neurological Surgeons nd, American Heart Association and American Stroke Association 2015, Greving 2014, Hackenberg 2018, Healthwise 2018, Johns Hopkins nd, Liebeskind 2018, Mayfield Clinic 2018, Mayo Clinic 2019, NIH/NLM 2018, Toth 2018)

## FAQ 2: What is my risk of the aneurysm rupturing in the next 5 years?

*Watchful waiting*

Overall, out of 100 people with aneurysms, about 3 to 4 (3% to 4%) may have their aneurysm rupture over the next 5 years. However, your personal risk of rupture depends a lot on the size and location of your aneurysm, your blood pressure, and whether you have had had bleeding in your brain before. Your risk may be 0 out of 100 (0%) to more than 15 out of 100 (greater than 15%). Your clinician can tell you what your risk is. There is not enough information to know what your risk of rupture is over the rest of your lifetime. (Low certainty evidence from 1 systematic review and meta-analysis [Greving 2014]) If the aneurysm ruptures, this causes bleeding in the brain. When this happens, 27 to 44 out of 100 (27% to 44%) may die within a month. Of those who live, 45 out of 100 (45%) may need help to do some of the things they used to do. (Certainty not assessed for these descriptive statistics from Nieuwkamp 2009 and Macdonald 2017) The risk of dying while in the hospital may be lower if a person is treated at a hospital that is more used to treating people who have bleeding in the brain. (Certainty not assessed for this finding from Rush 2017)

*Neurosurgical or endovascular treatment*

After getting neurosurgical or endovascular treatment, your long-term risk of rupture is probably low. However, there is not enough research to use numbers when talking about this risk. If you already have a low risk of rupture without neurosurgical or endovascular treatment, getting neurosurgical or endovascular treatment may not be able to reduce your risk any further.

## FAQ 3: What are the risks of the procedure?

*Watchful waiting*

This FAQ does not apply. The risk of watchful waiting is the risk of the aneurysm rupturing while under surveillance. This is addressed in FAQ 2.

*Neurosurgical or endovascular treatment*

Overall, out of 100 people who are treated with neurosurgical clipping, about 7 (7%) may have a problem after the procedure. This may cause only minor disability or severe disability. It may get better or last the rest of your life. Some people may die, but this may only occur in fewer than 1 out of 100 people (less than 1%). (Very low certainty evidence from 1 systematic review and meta-analysis [Algra

2019]) Major problems include things like death, coma, stroke, heart attack, blood clot, serious infection, or needing a machine to breathe. Your personal risk of a major problem depends on things like the specifics of your aneurysm, your age, and your health, including other conditions you have. Your risk of a major problem may be 6 out of 100 (6%) to 31 out of 100 (31%). Your clinician can tell you what your risk is. (Low certainty evidence from 1 risk prediction study [Dasenbrock 2019])

Overall, out of 100 people who are treated with endovascular treatment, about 4 (4%) may have a problem after the procedure. This may cause only minor disability or severe disability. It may get better or last the rest of your life. Some people may die, but this may only occur in fewer than 1 out of 100 people (less than 1%). (Very low certainty evidence from 1 systematic review and meta-analysis [Algra 2019]) Your personal risk of a problem depends on things like the specifics of your aneurysm and your health, including other conditions you have. Your risk may be 2 out of 100 (2%) to 33 out of 100 (33%). Your clinician can tell you what your risk is. (Low certainty evidence from 1 risk prediction study [Ji 2016])

## FAQ 4: How will it affect my quality of life?

*Watchful waiting vs. neurosurgical or endovascular treatment*

Some people who choose to have neurosurgical or endovascular treatment have a decrease in their quality of life after the procedure. If this happens, they may feel normal again within 1 to 3 years. Some people who choose to keep track of the shape and size of the aneurysm may have anxiety about the possibility of the aneurysm rupturing. The best person to decide whether to keep track of the aneurysm or have it treated with neurosurgical or endovascular procedures is the patient.

(References consulted for this descriptive summary include: American Heart Association and American Stroke Association 2015)

## FAQ 5: Will I need additional treatment?

*Watchful waiting*

Some people who first decide to keep track of the aneurysm change their minds later and have neurosurgical or endovascular treatment. If the aneurysm changes over time, your clinician may recommend neurosurgical or endovascular treatment.

*Neurosurgical or endovascular treatment*

Most people do not need more treatment for their aneurysm after it has been treated with a neurosurgical or endovascular procedure.

(References consulted for this descriptive summary include: American Heart Association and American Stroke Association 2015)

## FAQ 6: How long does it take to recover?

How long it takes to recover depends on the treatment you get.

With neurosurgical treatment (clipping):

- It may take 2 to 8 weeks to recover
- You may feel tired for up to 12 weeks
- You may restart some activities in 1 to 3 weeks
- You may not be able to go back to work for at least 2 to 4 weeks
- You should avoid heavy lifting for up to 12 weeks (or until the surgeon says it is okay)

With endovascular treatment (coiling):

- It may take 2 to 7 days to recover
- You may feel tired for a few days
- You should avoid heavy lifting for 2 days (or until the surgeon says it is okay)
- You may restart your normal activities in 2 to 7 days

(References consulted for this descriptive summary include: American Association of Neurological Surgeons nd, American Heart Association and American Stroke Association 2015, Greving 2014, Hackenberg 2018, Healthwise 2018, Johns Hopkins nd, Liebeskind 2018, Mayfield Clinic 2018, Mayo Clinic 2019, NIH/NLM 2018, Toth 2018. For neurosurgical clipping, the lower bound of 2 weeks for recovery [from original of 3 weeks] and addition of 2 weeks as a lower bound for return to work [from original of 4 weeks] were added in response to clinician feedback in Germany as part of collaboration with UKSH.)

# Abbreviations

## General abbreviations that may appear in this report

CI – confidence interval
CrI – credible interval
HR – hazard ratio
MA – meta-analysis
MD – mean difference
NA, N/A – not applicable
NR – not reported
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## Abbreviations specific to this report that may appear in this report

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CTA – computed tomographic angiography
MR – magnetic resonance
MRA – magnetic resonance angiography
MRI – magnetic resonance imaging
UIA – unruptured intracranial aneurysm

# Methods

Where evidence is very limited, or the FAQ is scoped as a descriptive response, such that no evidence synthesis or processing is applied, the descriptive summary/-ies will be given.

For each FAQ for which evidence synthesis or processing is considered, the key concepts (results and factors affecting certainty of the results) from the included studies that are most relevant to evidence synthesis will be summarized in Evidence Review Tables. For each outcome, Evidence Synthesis Process tables will then articulate the method selected for evidence synthesis and justification of that method. We will do this for the effect estimate (i.e., answering the question "Is there a difference between the intervention and comparator?") and results will be presented with GRADE-based certainty of evidence ratings related to the certainty of effect estimates. For FAQs which require noncomparative/option-specific responses (i.e., the FAQ is "What will happen with this option?" rather than "How do things change with this option?") the Evidence Synthesis Process tables will be extended to include the method to produce noncomparative responses.

**For summary statements representing a plain language summary of evidence appraisal and synthesis**
We will include the following 2 items immediately after the summary statement as a parenthetical, regardless of whether they occur in the Summary of Findings section or the individual FAQs in the body of the Evidence Synthesis document:

- our certainty in the summary statement (categorized as High, Moderate, Low, or Very low), and
- the number and type of studies informing the statement, as well as a label for the studies in "[Author] [Year]" format.

If the study informing the summary statement is a systematic review and meta-analysis, then unless there are compelling reasons to proceed in a different manner, we will cite the systematic review and meta-analysis as the source. We will do this even if the result on which our summary statement is based comes from a subset of studies in that systematic review and meta-analysis (e.g., a meta-analysis of 5 out of 10 studies, because only 5 of the 10 reported on the outcome of interest). If EBSCO Information Services conducts its own meta-analysis of studies to inform a summary statement, we will list the individual studies.

**For summary statements representing a plain language summary of descriptive sources**
Certainty rating and provision of details about contributing studies do not apply. Accordingly, we will not include a parenthetical at the end of the summary statement. However, when descriptive summaries appear in the Summary of Findings section, we will include a general parenthetical citation of the references we consulted. We will place this at the end of the relevant FAQ in the Summary of Findings section. For summary statements occurring in the body of the Evidence Synthesis document, we will provide this general parenthetical citation as part of the longer descriptive summary component that precedes the simplified summary statement.

## Note about terminology used in this report

*This evidence report is intended to provide insight into the management of incidentally-discovered intracranial aneurysms. As noted by the 2015 guideline from the American Heart Association and American Stroke Association (hereafter 2015 AHA/ASA guideline), intracranial aneurysms are being discovered incidentally much more often now, likely as a result of an increase in neuroimaging studies being done for various other reasons. The 2015 AHA/ASA guideline also notes that most of these incidentally-discovered aneurysms will not cause problems, but how to manage them remains a difficult subject due to the potentially dire consequences of rupture (subarachnoid hemorrhage, which can cause*

*death or permanent disability). In the strictest delineation of the condition, unruptured intracranial aneurysms (UIAs) can be either symptomatic or asymptomatic, and only asymptomatic UIAs would qualify as incidental intracranial aneurysms (IIAs). In several cases, however, the evidence base does not clearly differentiate UIAs from IIAs. However, as alluded to above, UIAs could technically include some patients who have aneurysmal symptoms (e.g., cranial nerve palsy). As noted in the 2015 AHA/ASA guideline, symptomatic UIAs may be at higher surgical/procedural risk (if managed with surgical or endovascular techniques) and higher rupture risk (if managed with watchful waiting) compared with IIAs/asymptomatic UIAs. To maintain fidelity of the sources we consider below, we use the terminology the source used, but unless the source clearly indicated otherwise, we consider UIAs to be mostly comprised of IIAs/asymptomatic UIAs. Additionally, we preferentially use IIA throughout the report unless using UIA to maintain fidelity of the phrasing used by an original source.*

## Search Summary

**Number of articles screened and selected**

| | Screened | Selected* |
|---|---|---|
| **1st-round (DynaMed)** | Not applicable | |
| **2nd-round (Searches for prediction rule studies)** | 89 | 5 |
| **3rd-round (Searches for systematic reviews, guidelines, or other relevant sources not specific to prediction rules)** | Not applicable | |
| **4th-round (Study tracing)** | 4 | 1 |
| ***Total*** | *93* | *6* |

* Number shown is after deduplication

| | Articles selected for evaluation (Author Year) |
|---|---|
| **Systematic reviews** | 2 (Algra 2019, Greving 2014) |
| **Randomized, controlled trials** | 0 |
| **Other article types (e.g., observational studies, guidelines)** | 4 (Bijlenga 2017, Dasenbrock 2019, Ji 2016, Newman 2016) |

# Results – Synthesis Details

## FAQ 1: What does the treatment involve?

Decisions about management should always involve a discussion of benefits and risks in the context of patient values and preferences. As noted by the 2015 American Heart Association and American Stroke Association guidelines: "Several factors should be considered in selection of the optimal management of [incidental intracranial aneurysms], including the size, location, and other morphological characteristics of the aneurysm; documented growth on serial imaging; the age of the patient; a history of prior aSAH; family history of cerebral aneurysm; the presence of multiple aneurysms; or the presence of concurrent pathology such as an arteriovenous malformation or other cerebrovascular or inherited pathology that may predispose to a higher risk of hemorrhage". Additionally, in general, aneurysms smaller than 5 to 7 mm are often managed with watchful waiting due to their low rupture risk (Greving 2014, Malhotra 2017).

Regardless of the treatment method a person opts to pursue, lifestyle factors should be discussed and maximized. As noted by the 2015 guidelines from the American Heart Association and American Stroke Association: "The most important modifiable risk factors are cigarette smoking and hypertension, with excessive alcohol intake and oral contraceptive use being far less important. No studies have prospectively evaluated the impact of successful risk factor modification on either the development of UIA [unruptured intracranial aneurysm] or the rupture of a previously asymptomatic UIA."

### Watchful waiting

**Descriptive Summary (pre-synthesis and synthesis efforts not applicable for descriptive summaries)**

The surgeon will closely monitor the aneurysm with neuroimaging studies to see if it changes over time. Changes might impact the decision to pursue neurosurgical or endovascular treatment. After a incidental intracranial aneurysm (IIA) is first discovered, the next imaging study might be ordered 6 to 12 months later. After this first follow-up imaging study, the timing between subsequent imaging studies may range from 1 to 5 years depending on the patient's specifics, including the stability of the IIA (i.e., whether it changes/progresses). The exact interval should be individualized for each patient based on things like the size and location of the aneurysm and the person's medical conditions and medical history (e.g., hypertension, prior subarachnoid hemorrhage). Additionally, although not part of the PHASES model that predicts 5-year rupture risk (described below), morphology irrespective of size and growth may also impact rupture risk. For monitoring aneurysms, either computed tomographic or magnetic resonance angiography is considered acceptable. In the absence of a compelling indication for one or the other (e.g., a patient with an incompatible metallic device), time-of-flight magnetic resonance angiography may be preferable because it does not require intravenous contrast and does not expose the patient to radiation.

### Neurosurgical or endovascular treatment

**Descriptive Summary (pre-synthesis and synthesis efforts not applicable for descriptive summaries)**

The aneurysm will be treated with neurosurgery or endovascular therapy. Neurosurgery requires craniotomy and gentle manipulation of the brain tissue. Endovascular therapy occurs inside the cerebral blood vessels without craniotomy; thus, endovascular treatment is less invasive, though it still

requires a catheter to be placed in the femoral vasculature and advanced to the cerebral vasculature. Patients are asleep for neurosurgical or endovascular treatment. The neurosurgical method used is often called “clipping” and the endovascular method most used is often called “coiling”. However, there are other neurosurgical and endovascular methods as well, such as “bypass” (which can be done via neurosurgery or a combination of neurosurgery and endovascular methods) and “flow diversion” (which is done endovascularly). We describe these other methods briefly below, but we focus on clipping and coiling, especially for synthesis.

Neurosurgical treatment can include clipping or bypass (another method called “tubular retraction” may also be an option in some hospitals, but we do not consider it further here given its potentially limited availability). In clipping, a metal clip is placed at the base of the aneurysm (often called the “neck” of the aneurysm) to block blood from entering the aneurysm. In bypass, clips are placed to block off the section of the cerebral artery where the aneurysm is, and an artery from somewhere else in the patient’s body is used to reroute blood past this blocked section of the cerebral artery. Bypass may be done instead of clipping if the aneurysm is large or the cerebral artery itself is seriously damaged. As noted above, bypass can also be done with a combination of neurosurgical and endovascular methods (the main difference with the combination approach is the use of endovascular coiling instead of clips to block off the diseased section of the artery). The average hospital stay after neurosurgical clipping may be about 4 to 6 days.

Endovascular treatment uses fluoroscopic guidance and can include two major approaches to treatment: coiling or flow diversion. However, there are different subtypes to these approaches, and sometimes, a hybrid approach might be used. So, depending on the patient, the surgeon, and the facility, the actual endovascular procedure used may include “standard” coiling, stent-assisted coiling (a description of what a stent does occurs later in this paragraph), balloon-assisted coiling (where a balloon is inflated for a period of time at the neck of the aneurysm, which can help with getting the coil seated in place for certain kinds of aneurysms, such as those with an unfavorable neck:dome ratio), or flow diversion with devices like a stent. In coiling, a metal coil is placed inside the aneurysmal sac. This causes a reaction leading to blood clotting inside the aneurysm, which in turn acts like a “seal” to block blood from entering it. In flow diversion, a stent is placed inside the artery that encourages blood to flow along the normal arterial pathway rather than entering the aneurysm. Because the stent helps keep blood from entering the aneurysm, the aneurysm will eventually clot off and shrink. Flow diversion might be used if clipping or coiling will be difficult due to the specifics of the aneurysm and usually requires use of antiplatelet medication. The average hospital stay after endovascular treatment may be as short as 1 to 2 days.

In addition to the experience of the clinician and the capabilities of the facility, certain patient characteristics – such as age, the size and location of the aneurysm, and comorbidities – should be taken into account when deciding whether surgical or endovascular treatment is a better choice for any given patient.

With either neurosurgical or endovascular treatment, a neuroimaging study may be ordered prior to discharge and periodically after receiving the procedure. However, this is not always the case, and as noted in the 2015 guideline from the American Heart Association and American Stroke Association, “follow-up requirements for treated aneurysms remain uncertain.”

(American Association of Neurological Surgeons nd, American Heart Association and American Stroke Association 2015, Greving 2014, Hackenberg 2018, Healthwise 2018, Johns Hopkins nd, Liebeskind 2018, Mayfield Clinic 2018, Mayo Clinic 2019, NIH/NLM 2018, Toth 2018)

*Descriptive Summary Results for FAQ 1*

***Watchful waiting***

**Watchful waiting means having CT scans or MRIs to keep track of the shape and size of the aneurysm. Some people may prefer this option to avoid having a procedure. However, there is a risk the aneurysm will rupture while being tracked. You and the surgeon will decide how often you should have a CT or MRI. This will depend on things like the size and location of the aneurysm, whether the aneurysm grows, and other conditions you might have. If the aneurysm changes, the surgeon may recommend a procedure to treat the aneurysm. You can also change your mind later if you decide you want to have a procedure to treat the aneurysm.**

***Neurosurgical or endovascular treatment***

**There are two main ways to treat a brain aneurysm: neurosurgical treatment (often called "clipping") or endovascular treatment (most often something called "coiling"). Some people may prefer one of these options because they are worried about the aneurysm rupturing. However, each option is a major procedure that also has risks. If a patient wants neurosurgical or endovascular treatment, one might be better than the other. This may depend on things like the size, shape, and location of the aneurysm and the age and health of the patient.**

**In "clipping", the surgeon:**

- **makes an opening in the skull**
- **finds the blood vessel with the aneurysm, and**
- **puts a metal clip at the bottom of the aneurysm**

**In "coiling", the surgeon:**

- **puts a long, flexible tube into a blood vessel in the upper leg**
- **moves the tube through the blood vessels to reach the aneurysm, and**
- **puts a metal coil inside the aneurysm**

**The treatment blocks the aneurysm from the normal blood vessels. You may stay in the hospital for 4 to 6 days after neurosurgical treatment or 1 to 2 days after endovascular treatment. The surgeon may want to get imaging studies after either procedure.**

## FAQ 2: What is my risk of the aneurysm rupturing in the next 5 years?

### Watchful waiting

***Evidence Review Tables for FAQ 2***

Our evidence review identified the PHASES risk prediction method (hereafter "PHASES") as the most recognized and validated score for providing 5-year estimates for aneurysm rupture in patients with UIAs. PHASES charts for European patients aged < 70 years are included below (Greving 2014). They also reported an overall 5-year rupture risk of 3.4% (95% CI 2.9% to 4.0%). However, as seen in the tables below, a given individual's actual risk can vary considerably based on factors like aneurysm size and location and whether the person has hypertension or a prior subarachnoid hemorrhage.

**Risk prediction charts for aneurysm rupture within the next 5 years in patients aged < 70 years from North America and European countries (other than Finland)**

*For patients with no hypertension and no history of subarachnoid hemorrhage*

| | **aneurysm size** | | | |
|---|---|---|---|---|
| **aneurysm location** | ≥ 20 mm | 10 to 19.9 mm | 7 to 9.9 mm | < 7 mm |
| internal carotid artery | 5% | 1% | 1% | 0% |
| middle cerebral artery | 9% | 2% | 1% | 0% |
| anterior cerebral arteries*/posterior communicating artery/posterior circulation† | ≥15% | 4% to 5% | 2% | 1% |

* Includes the anterior cerebral artery, anterior communicating artery, and pericallosal artery
† Includes the vertebral artery, basilar artery, cerebellar arteries, and posterior cerebral artery

*For patients with hypertension but no history of subarachnoid hemorrhage*

| | **aneurysm size** | | | |
|---|---|---|---|---|
| **aneurysm location** | ≥ 20 mm | 10 to 19.9 mm | 7 to 9.9 mm | < 7 mm |
| internal carotid artery | 7% | 2% | 1% | 0% |
| middle cerebral artery | 12% | 3% | 1% | 1% |
| anterior cerebral arteries*/posterior communicating artery/posterior circulation† | > 15% | 6% to 7% | 2% to 3% | 1% |

* Includes the anterior cerebral artery, anterior communicating artery, and pericallosal artery
† Includes the vertebral artery, basilar artery, cerebellar arteries, and posterior cerebral artery

*For patients with both hypertension and history of subarachnoid hemorrhage*

| | **aneurysm size** | | | |
|---|---|---|---|---|
| **aneurysm location** | ≥ 20 mm | 10 to 19.9 mm | 7 to 9.9 mm | < 7 mm |
| internal carotid artery | 10% | 3% | 1% | 0% |
| middle cerebral artery | > 15% | 5% | 2% | 1% |
| anterior cerebral arteries*/posterior communicating artery/posterior circulation† | > 15% | 8% to 9% | 3% to 4% | 2% |

* Includes the anterior cerebral artery, anterior communicating artery, and pericallosal artery

† Includes the vertebral artery, basilar artery, cerebellar arteries, and posterior cerebral artery

### *Evidence Synthesis Process for FAQ 2*

| **Outcome** | **Approach taken and justification** | **Results** |
|---|---|---|
| risk of aneurysm rupture within the next 5 years | **Use of published prediction model.** PHASES is the only validated risk prediction method identified. Greving 2014 provides a systematic review of all relevant cohorts, derivation, and internal validation of PHASES (Low certainty). Bijlenga 2017 provides external validation of discrimination of PHASES (Moderate certainty). | **Use of risk predication tables.** (Moderate certainty for discrimination; Low certainty for precision of estimated risks/calibration) |

We also include below the overall risk of rupture from the PHASES study to give a basic overall example (from the perspective of a population average), but we feel it is important to emphasize this is likely a poor representation for any given patient (with the more appropriate method being an attempt to estimate individual risk as discussed herein). Although we realize the point estimate is 3.4%, we note the confidence interval bounds are 2.9% to 4.0%, so we use an estimate of 3% to 4% in the bolded synthesis statement below.

If an incidental intracranial aneurysm ruptures, it causes severe bleeding in the brain. This is called a subarachnoid hemorrhage. Death from subarachnoid hemorrhage is reported to vary widely, from about 8% to 67%; however, median case fatality rates ranged from 26.7% to 44.4%, and the median rate of death prior to hospital arrival may be 8.3% (from 39 studies, 35 reporting at 1 month, 2 reporting at 3 weeks, and 1 each reporting at 2 months and 3 months). Of those who survive, as many as 80% may be unable to resume their previous lifestyle at 3 to 6 months after the event, and as many as 45% may be unable to return to full independence (Nieuwkamp 2009, Etminan 2017, Macdonald 2017). Rush 2017 also notes in-hospital mortality may be better in high-volume hospitals, but these data do not permit inference into mortality outside the inpatient period.

### *Evidence Synthesis Results for FAQ 2*

**Overall, out of 100 people with aneurysms, about 3 to 4 (3% to 4%) may have their aneurysm rupture over the next 5 years. However, your personal risk of rupture depends a lot on the size and location of your aneurysm, your blood pressure, and whether you have had had bleeding in your brain before. Your risk may be 0 out of 100 (0%) to more than 15 out of 100 (greater than 15%). Your clinician can tell you what your risk is. There is not enough information to know what your risk of rupture is over the rest of your lifetime.** (Low certainty evidence from 1 systematic review and meta-analysis [Greving 2014]) **If the aneurysm ruptures, this causes bleeding in the brain. When this happens, 27 to 44 out of 100 (27% to 44%) may die within a month. Of those who live, 45 out of 100 (45%) may need help to do some of the things they used to do.** (Certainty not assessed for these descriptive statistics from Nieuwkamp 2009 and Macdonald 2017) **The risk of dying while in the hospital may be lower if a person is treated at a hospital that is more used to treating people who have bleeding in the brain.** (Certainty not assessed for this finding from Rush 2017)

## Neurosurgical or endovascular treatment

### *Descriptive Summary*

As stated in scoping, there are insufficient data on long-term rupture risk after neurosurgical or endovascular intervention of incidental intracranial aneurysms (American Heart Association and American Stroke Association 2015). Additionally, evidence on long-term recurrence after neurosurgical or endovascular intervention (though ultimately a surrogate outcome) is dominated by data concerning treatment of ruptured intracranial aneurysms (Hulsbergen 2019); these data thus come with very serious concerns for indirectness if trying to make inferences about patients with incidental intracranial aneurysms, because:

(1) recurrence is a surrogate outcome (recurrence alone is not a patient-relevant outcome), and

(2) it is not safe to assume that the long-term risk of post-intervention recurrence is the same for people who had treatment due to rupture and people who had preemptive treatment for an incidental intracranial aneurysm (those who had treatment due to rupture are by definition a higher risk group compared to those who had treatment for an unruptured aneurysm).

However, the available data from Hulsbergen 2019 also report on the rate of rebleeding after treatment with neurosurgical or endovascular intervention, finding rebleeding in 24/2,373 (1.1%) and 36/1,688 (2.1%) of clipped and coiled aneurysms, respectively, over a median follow-up of about 5.5 years (note the text says there were 25 and 35 events, respectively, but the forest plot contains 24 and 36 events, respectively; we use the data from the forest plot here, but using the results in the text would not result in substantive differences for the present purposes). Thus, even in this higher-risk population, rebleeding over about 5.5 years of follow-up was fairly low. This might thus be used to indirectly corroborate the notion that the risk of rupture in a lower-risk population (i.e., people with incidental intracranial aneurysms) is probably also low after either of these interventions. Crucially, however, comparative statements concerning the risk of rupture with intervention vs. the risk of rupture with no intervention are still fraught with methodologic problems, as there are no such data available. For people who have an incidental intracranial aneurysm and a relatively higher 5-year risk of rupture (e.g., a person of North American or European [other than Finnish] descent who is 55 years of age and has hypertension, no history of subarachnoid hemorrhage, and a 15 mm aneurysm in the posterior circulation), one might reasonably infer that clipping or coiling could possibly reduce the risk of rupture based on the predicted risk of 5-year rupture from the PHASES score (discussed above), the prior probability for these interventions helping to prevent rupture, and the data for rebleeding in Hulsbergen 2019. However, this is still very indirect from a methodologic perspective. Additionally, perhaps especially for people who have an incidental intracranial aneurysm and a relatively lower 5-year risk of rupture (e.g., a person of North American or European [other than Finnish] descent who is 55 years of age and has normal blood pressure, no history of subarachnoid hemorrhage, and an 8 mm aneurysm in the middle cerebral artery), it seems there would still be considerable uncertainty whether coiling or clipping could meaningfully reduce the risk of rupture compared to watchful waiting/active surveillance. Considering all of this, although the data do not permit quantitative inferences here, they can be used as part of informing qualitative responses.

### *Descriptive Summary Results for FAQ 2*

**After getting neurosurgical or endovascular treatment, your long-term risk of rupture is probably low. However, there is not enough research to use numbers when talking about this risk. If you already have a low risk of rupture without neurosurgical or endovascular treatment, getting neurosurgical or endovascular treatment may not be able to reduce your risk any further.**

## FAQ 3: What are the risks of the procedure?

### Watchful waiting

This FAQ does not apply. The risk of watchful waiting is the risk of the aneurysm rupturing while under surveillance. This is addressed in FAQ 2.

### Neurosurgical or endovascular treatment

Our evidence review has identified separate risk prediction scales for postoperative adverse events in UIA patients having neurosurgical clipping (Dasenbrock 2019) and endovascular treatment (Ji 2016). Additional evidence comes from a systematic review and meta-analysis of complications from neurosurgical clipping or endovascular treatment (Algra 2019).

***Evidence Review Tables for FAQ 3 – Neurosurgical clipping***

The risk prediction scale for neurosurgical clipping was developed and validated in a study that we judged to have Moderate certainty for discrimination and Low certainty for calibration (Dasenbrock 2019). A summary score is calculated based on totaling the number of points assigned for 8 individual component variables (ie, patient age, operative time, BMI, 3 comorbidity-related variables, and 2 lab value-related variables). A given summary score corresponds to a risk level category, which can be used to estimate risk of multiple different postoperative adverse events.

**Components of the risk score for neurosurgical clipping**

| Variable | Stratum | Number of points |
|---|---|---|
| patient age | 51 to 60 years of age | 2 |
| | 61 to 70 years of age | 4 |
| | > 70 years of age | 4 |
| anticipated operative time* | 240 to 330 minutes | 2 |
| | > 330 minutes | 3 |
| BMI | BMI > 35 kg/$m^2$ (WHO class II or III obesity) | 2 |
| Bleeding disorder† | bleeding disorder present | 1 |
| Cardiac disorder‡ | coronary artery disease or congestive heart failure present | 2 |
| Diabetes mellitus | diabetes mellitus present | 2 |
| Anemia (hematocrit < 36%) | anemia present | 2 |
| Leukocytosis (white blood cell count > 12,000/µl) | leukocytosis present | 3 |

* While the actual operative time is not known prior to surgery, surgeon may anticipate operative time based on aneurysm size, morphology, and planned surgical approach

† Combines several hypothrombotic conditions (vitamin K deficiencies, hemophilias, thrombocytopenia, and long-term anticoagulation), but does not include aspirin or other antiplatelet use

‡ Defined by NSQIP as congestive heart failure exacerbation or angina within 30 days, myocardial infarction within 90 days, or previous cardiac revascularization (percutaneous or surgical)

**Predicted risk of adverse outcomes based on risk score for neurosurgical clipping**

| Outcome | Very low risk (0-3) | Low risk (4-5) | Medium risk (6-7) | High risk (≥ 8) |
|---|---|---|---|---|
| Any adverse event | 7.0% | 15.7% | 19.7% | 38.1% |
| Major complication* | 6.1% | 12.0% | 18.2% | 31.0% |
| Coma or stroke | 3.0% | 3.7% | 9.1% | 19.1% |
| Mechanical ventilation | 0.6% | 2.8% | 3.0% | 9.5% |
| Medical complication† | 1.0% | 2.8% | 10.6% | 9.5% |
| Infectious complication | 2.0% | 2.8% | 6.1% | 11.9% |
| Extended hospitalization‡ | 5.1% | 17.0% | 28.8% | 45.2% |
| Nonroutine hospital discharge§ | 4.1% | 10.2% | 21.2% | 45.2% |

* includes death, stroke or coma, reoperation, airway complication (extubation failure or prolonged mechanical ventilation), cardiac complication (cardiac arrest or acute myocardial infarction), venous thromboembolism, sepsis, or surgical site infections

† includes cardiac complication (myocardial infarction or cardiac arrest), venous thromboembolism (pulmonary embolism or deep venous thrombosis), sepsis, urinary tract infection, or pneumonia

‡ defined as length of stay > 6 days (the upper quartile of length of stay in NSQIP study population)

§ defined as discharge from hospital as any disposition other than to home

**Pooled univariate risk estimates for neurosurgical clipping from high-quality studies as assessed by Algra 2019**

| Outcome | No. studies (no. events; no. patients) | Estimated risk | Certainty (reason for downgrade) |
|---|---|---|---|
| Clinical complication* | 11 (303; 4,059) | 6.89% (95% CI, 3.80% to 12.16%) | Very low[1,2] |
| Case fatality | 11 (5; 4,059) | 0.30% (95% CI, 0.00% to 0.94%) | Very low[1,2] |

*Defined as treatment complications that resulted in transient or permanent morbidity or mortality and that occurred ≤ 30 days after procedure.

1 Very serious concern for indirectness for clinical complication; serious concern for case fatality

2 Very serious concern for inconsistency for both outcomes

### *Evidence Synthesis Process for FAQ 3 – Neurosurgical clipping*

| Outcome | Approach taken and justification | Results |
|---|---|---|
| Major complications | **Use of published prediction model.** The risk score summarized is the only validated score identified. Dasenbrock 2019 provides a derivation, internal validation and external validation study (Moderate certainty for discrimination; Low certainty for precision of estimated risks/calibration). | **Report major complication risk quantitatively and specific risks qualitatively.** Simplicity for expression, and some reported outcomes include minor complications. |

We also include below the clinical complication risk and case fatality rate from the systematic review and meta-analysis by Algra 2019 to give a basic overall example (from the perspective of a population average), but we feel it is important to emphasize our concern that this may be a poor representation for any given patient (with the more appropriate method being an attempt to estimate individual risk as discussed herein).

### *Evidence Synthesis Results for FAQ 3 – Neurosurgical clipping*

**Overall, out of 100 people who are treated with neurosurgical clipping, about 7 (7%) may have a problem after the procedure. This may cause only minor disability or severe disability. It may get better or last the rest of your life. Some people may die, but this may only occur in fewer than 1 out of 100 people (less than 1%).** (Very low certainty evidence from 1 systematic review and meta-analysis [Algra 2019]) **Major problems include things like death, coma, stroke, heart attack, blood clot, serious infection, or needing a machine to breathe. Your personal risk of a major problem depends on things like the specifics of your aneurysm, your age, and your health, including other conditions you have. Your risk of a major problem may be 6 out of 100 (6%) to 31 out of 100 (31%). Your clinician can tell you what your risk is.** (Low certainty evidence from 1 risk prediction study [Dasenbrock 2019])

### *Evidence Review Tables for FAQ 3 – Endovascular treatment*

The risk prediction scale for endovascular treatment was from Ji 2016, which we judged to have Low certainty because of absence of external validation and because the outcome is a composite of transient and permanent neurological complications (whereas an outcome that instead limits to permanent complications may be more clinically relevant). The Ji 2016 risk model predicted a risk ranging from 2% to 33%. In the model developed by Ji 2016, a clinical score ranging from 0 to 3 is calculated as shown below. The clinical score can be used to estimate the risk of having postoperative neurological complications after endovascular treatment. The systematic review and meta-analysis by Algra 2019 also provides risk estimates (Very low certainty due to concern or very serious concern in the domains of indirectness and inconsistency). Both these sources considered standard coiling only as well as advanced methods, such as stent- or balloon-assisted coiling. Algra 2019 also considered flow diversion methods.

**Risk of neurological complications at ≤ 1 month in patients having endovascular treatment for UIAs**

*The clinical score is calculated as the sum of points assigned from 3 variables, with 1 point for each of the following:*

- *size > 10 mm*
- *core area (A1 segment of anterior cerebral artery, M1 segment of middle cerebral artery, P1 segment of posterior cerebral artery, internal carotid artery bifurcation, basilar artery, posterior inferior cerebellar artery, and anterior choroidal artery)*
- *cerebral ischemic comorbidities*

| | **Clinical score** | | | |
|---|---|---|---|---|
| | **0** | **1** | **2** | **3** |
| neurological complications (transient or permanent increase in modified Rankin Scale score) | 2% | 11% | 18% | 33% |

**Pooled univariate risk estimates for endovascular treatment from high-quality studies as assessed by Algra 2019**

| **Outcome** | **No. studies (no. events; no. patients)** | **Estimated risk** | **Certainty (reason for downgrade)** |
|---|---|---|---|
| Clinical complication* | 15 (445; 10,412) | 4.30% (95% CI, 2.59% to 7.07%) | Very low[1,2] |
| Case fatality | 14 (27; 9,352) | 0.12% (95% CI, 0.02% to 0.63%) | Very low[1,2] |

*Defined as treatment complications that resulted in transient or permanent morbidity or mortality and that occurred ≤ 30 days after procedure.

1 Very serious concern for indirectness for clinical complication; serious concern for case fatality

2 Very serious concern for inconsistency for both outcomes

### *Evidence Synthesis Process for FAQ 3 – Endovascular treatment*

Although the model developed by Ji 2016 lacks external validation, we noted in scoping that this may still constitute a better answer than providing one overall risk estimate that might be importantly higher or lower for a given individual. Therefore, we consider Ji 2016 to provide the best answer concerning risks from having endovascular treatment. We also include below the clinical complication risk and case fatality rate from the systematic review and meta-analysis by Algra 2019 to give a basic overall example (from the perspective of a population average), but we feel it is important to emphasize our concern that this may be a poor representation for any given patient (with the more appropriate method being an attempt to estimate individual risk as discussed herein).

For the simple, bolded synthesis statement, we give a range of all results and alert the user to the availability of more detailed risk estimation by virtue of the above mechanism.

### *Evidence Synthesis Results for FAQ 3 – Endovascular treatment*

**Overall, out of 100 people who are treated with endovascular treatment, about 4 (4%) may have a problem after the procedure. This may cause only minor disability or severe disability. It may get better or last the rest of your life. Some people may die, but this may only occur in fewer than 1 out of 100 people (less than 1%).** (Very low certainty evidence from 1 systematic review and meta-analysis [Algra 2019]) **Your personal risk of a problem depends on things like the specifics of your aneurysm and your health, including other conditions you have. Your risk may be 2 out of 100 (2%) to 33 out of 100 (33%). Your clinician can tell you what your risk is.** (Low certainty evidence from 1 risk prediction study [Ji 2016])

## FAQ 4: How will it affect my quality of life?

### Watchful waiting vs. neurosurgical or endovascular treatment

**Descriptive Summary (pre-synthesis and synthesis efforts not applicable for descriptive summaries)**

Although data appear to be limited, the 2015 guideline from the American Heart Association and American Stroke Association (AHA/ASA 2015) notes some people may experience a certain degree of decrease in quality of life after treatment of an incidental intracranial aneurysm (IIA). For the people in whom this happens, they may largely return to normal within 1 to 3 years of being treated. However, the 2015 AHA/ASA guideline also notes more generically that people may experience anxiety from knowing they have an untreated IIA. This makes obvious sense given the potentially dire consequences of the IIA rupturing, and people might still feel anxious about their intracranial aneurysm even if it is discovered incidentally, remains asymptomatic, has a low risk of rupture, and is being monitored with routine neuroimaging studies. For these people, the potential anxiolysis resulting from having surgical or endovascular treatment may result in an overall improved sense of quality of life or well-being, and this alone may be enough to outweigh any possible downsides of having endovascular or neurosurgical treatment. The best person to determine this balance is the patient who has the IIA.

(American Heart Association and American Stroke Association 2015)

**Descriptive Summary Results for FAQ 4**

**Some people who choose to have neurosurgical or endovascular treatment may have a decrease in their quality of life after the procedure. If this happens, they may feel normal again within 1 to 3 years. Some people who choose to keep track of the shape and size of the aneurysm may have anxiety about the possibility of the aneurysm rupturing. The best person to decide whether to keep track of the aneurysm or have it treated with neurosurgical or endovascular treatment is the patient.**

## FAQ 5: Will I need additional treatment?

### Watchful waiting

**Descriptive Summary (pre-synthesis and synthesis efforts not applicable for descriptive summaries)**
Sometimes people decide later that they want to have neurosurgical or endovascular treatment even though they first decided to pursue watchful waiting. Additionally, if the aneurysm changes over time (e.g., grows substantially), the clinician may recommend moving forward with treatment.

### Neurosurgical or endovascular treatment

**Descriptive Summary (pre-synthesis and synthesis efforts not applicable for descriptive summaries)**
Patients pursuing treatment with surgery or endovascular intervention may need to have additional treatment some time later. For instance, in one systematic review of endovascular treatment, 9.1% of people needed to be treated again.

(American Heart Association and American Stroke Association 2015)

**Descriptive Summary Results for FAQ 5**

***Watchful waiting***

**Some people who first decide to keep track of the aneurysm change their minds later and have neurosurgical or endovascular treatment. If the aneurysm changes over time, your clinician may recommend neurosurgical or endovascular treatment.**

***Neurosurgical or endovascular treatment***

**Most people do not need more treatment for their aneurysm after it has been treated with a neurosurgical or endovascular procedure.**

## FAQ 6: How long does it take to recover?

### Watchful waiting

This FAQ does not apply for the option of watchful waiting.

### Neurosurgical or endovascular treatment

**Descriptive Summary (pre-synthesis and synthesis efforts not applicable for descriptive summaries)**

As mentioned in FAQ 1, although there are procedures other than clipping and coiling for treatment, we focus on clipping and coiling here.

After neurosurgical clipping, it may take about 2 to 8 weeks to recover fully. Some people may feel tired for up to 12 weeks or more. Some people may feel dizzy, have headaches, or experience memory issues or feel confused. These symptoms may be worst in the first 1 to 2 weeks after the surgery and should get better with time. Patients may be advised to avoid strenuous activity for up to 3 months or until the surgeon gives clearance. Therefore, patients whose jobs involve heavy manual labor may have to be out from work during this time. Patients whose jobs do not involve heavy manual labor may still have to wait at least 2 to 4 weeks before they return to work. People may return to other normal activities within 1 to 3 weeks, but this should be individualized.

After endovascular coiling, patients may have bruising in the groin area where the catheter was inserted. There may also be some pain in this area, but it should not be severe. Patients may be advised to avoid strenuous activity for up to 2 days or until the surgeon gives clearance. Patients may feel tired for a few days after surgery, but they may be able to return normal activities in 2 to 7 days. The surgeon will give more individualized timelines.

(See FAQ 1 for references. For neurosurgical clipping, the lower bound of 2 weeks for recovery [from original of 3 weeks] and addition of 2 weeks as a lower bound for return to work [from original of 4 weeks] were added in response to clinician feedback in Germany as part of collaboration with UKSH.)

***Descriptive Summary Results for FAQ 4***

**How long it takes to recover depends on the treatment you get.**

**With neurosurgical treatment (clipping):**

- **It may take 2 to 8 weeks to recover**
- **You may feel tired for up to 12 weeks**
- **You may restart some activities in 1 to 3 weeks**
- **You may not be able to go back to work for at least 2 to 4 weeks**
- **You should avoid heavy lifting for up to 12 weeks (or until the surgeon says it is okay)**

**With endovascular treatment (coiling):**

- **It may take 2 to 7 days to recover**
- **You may feel tired for a few days**
- **You should avoid heavy lifting for 2 days (or until the surgeon says it is okay)**
- **You may restart your normal activities in 2 to 7 days**

# Evidence report for watchful waiting vs. surgical or endovascular treatment for patients with incidental intracranial aneurysm

## Search and Selection

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October 4, 2019

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# Abbreviations

## General abbreviations that may appear in this report

CI – confidence interval
CrI – credible interval
HR – hazard ratio
MA – meta-analysis
MD – mean difference
NA, N/A – not applicable
NR – not reported
OR – odds ratio
RCT – randomized, controlled trial
RR – risk ratio, relative risk
RtR – rate ratio
SMD – standardized mean difference
SR – systematic review
SRMA – systematic review and meta-analysis

## Abbreviations specific to this report that may appear in this report

CT – computed tomography
CTA – computed tomographic angiography
IIA – incidental intracranial aneurysm
MR – magnetic resonance
MRA – magnetic resonance angiography
MRI – magnetic resonance imaging
UIA – unruptured intracranial aneurysm

# Methods

**Note**: Because of the differences in this evidence report compared to most other evidence reports we produce, we have amended the methods for searching (specifically, second- through fourth-round searching) to better align with the scoping document for this report. This amendment is only intended for this evidence report.

First-round searching will consist of searching DynaMed Plus summaries pertinent to the topic. The search starts with DynaMed Plus because DynaMed Plus content is based on a thorough, systematic search and active literature surveillance system.

> Systematic literature surveillance (SLS) has been a cornerstone of creating DynaMed content since its inception. Currently, the SLS team works closely with members of McMaster University's Department of Health Research Methods, Evidence, and Impact to define and refine optimal search strategies, utilizing search terms for methodology and for clinical concepts (especially diagnosis and treatment) for each journal. These filters for PubMed searches are derived from PubMed Clinical Queries, McMaster University Hedges system, and DynaMed search filters and were found to capture >95% of relevant valid articles for use in DynaMed.[1]
> [1]Alper BS, Iorio A. Optimising search filters for active literature surveillance: a concordance study. Global Evidence Summit. Cape Town, South Africa; September 2017.
>
> The SLS team, in collaboration with McMaster University, continually evaluates and improves these filters to keep abreast of the ever-changing medical literature landscape. PubMed searches are performed daily. Each article is assessed by an external screener for clinical relevance, then reviewed by internal staff for both clinical relevance and validity. Any disagreements are settled by the Deputy Editor of the SLS team.
> In addition, the SLS team continually monitors the Journal source list against the list of journals catalogued in MEDLINE and existing DynaMed content to determine the set of journals that provide the highest yield for valid, clinically relevant content. As of November 2018, 507 Journals are systematically searched (see http://dynamed.com/home/content/content-sources). The journal selection threshold leads to routine adjustments to the number of journals selected.

Second-round searching for this evidence report will involve PubMed/MEDLINE® searches for prediction rules not identified in or more recent than those identified in first-round searching.

Third-round searching for this evidence report will involve searches for systematic reviews, guidelines or other relevant sources. This may be done to identify additional evidence sources if the results from the first two rounds of searching are insufficient.

Fourth-round searching will involve citation tracing from sources identified by earlier searches.

Additional selective searching, such as tracing citations from articles found or seeking related articles, may be done for additional concepts discovered.

Additional evidence updates may also be added continuously from feedback from any source.

## FAQ Summary

# Results

## First-round searching – DynaMed:

| DynaMed subsection | Number of article citations | Number of unique references included |
|---|---|---|
| DynaMed did not have relevant content for this evidence report. | | |

## Second-round searching – searches for prediction rules:

| Database | Search string | Number of search results | Number of references included |
|---|---|---|---|
| October 4, 2019 | (prediction rule[tiab] OR risk prediction[tiab] OR decision rule[tiab] OR discriminat*[tiab] OR validat*[tiab]) AND (rupture risk[tiab] OR risk of rupture[tiab] OR rupture rate[tiab] OR rate of rupture[tiab] OR rate of aneurysm rupture[tiab] OR risk of aneurysm rupture[tiab]) AND intracranial aneurysm*[tiab] | 54 | 2 (Bijlenga 2017, Greving 2014) |
| October 4, 2019 | (prediction rule[tiab] OR risk prediction[tiab] OR decision rule[tiab] OR discriminat*[tiab] OR validat*[tiab]) AND (complication[tiab] OR surgical outcome[tiab] OR outcome of surg*[tiab] OR outcome from surg*[tiab]) AND intracranial aneurysm*[tiab] | 35 | 3 (Algra 2019, Dasenbrock 2019, Ji 2016) |

**Third-round searching** – **searches for systematic reviews, guidelines, or other relevant sources not specific to prediction rules:**

| Source | Tracing | Number of search results | Number of references included |
|---|---|---|---|
| Not applicable | | | |

## Fourth-round searching – study tracing:

| Database | Search string | Number of search results | Number of references included |
|---|---|---|---|
| Dasenbrock 2019 | Tracing for possible additional prediction rules | 4 | 1 (Newman 2016) |

## Search summary:

**Number of articles screened and selected**

| | Screened | Selected* |
|---|---|---|
| **1st-round (DynaMed)** | Not applicable | |
| **2nd-round (Searches for prediction rules)** | 89 | 5 |
| **3rd-round (Searches for systematic reviews, guidelines, or other relevant sources not specific to prediction rules)** | Not applicable | |
| **4th-round (Study tracing)** | 4 | 1 |
| ***Total*** | *93* | *6* |

* Number shown is after deduplication

| | Articles selected for evaluation (Author Year) |
|---|---|
| **Systematic reviews** | 2 (Algra 2019, Greving 2014) |
| **Randomized, controlled trials** | 0 |
| **Other article types (e.g., observational studies, guidelines)** | 4 (Bijlenga 2017, Dasenbrock 2019, Ji 2016, Newman 2016) |

# Evidence report for watchful waiting vs. surgical or endovascular treatment for patients with incidental intracranial aneurysm

## Critical Appraisal of Evidence Reports

Prepared by EBSCO Information Services

October 4, 2019

Prepared by EBSCO Health Innovations and EBM Development Department:

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# Abbreviations

## General abbreviations that may appear in this report

CI – confidence interval
CrI – credible interval
HR – hazard ratio
MA – meta-analysis
MD – mean difference
NA, N/A – not applicable
NR – not reported
OR – odds ratio
RCT – randomized, controlled trial
RR – risk ratio, relative risk
RtR – rate ratio
SMD – standardized mean difference
SR – systematic review
SRMA – systematic review and meta-analysis

## Abbreviations specific to this report that may appear in this report

CT – computed tomography
CTA – computed tomographic angiography
IIA – incidental intracranial aneurysm
MR – magnetic resonance
MRA – magnetic resonance angiography
MRI – magnetic resonance imaging
UIA – unruptured intracranial aneurysm

## Methods

For each study selected for critical appraisal, we assessed for criteria needed for Level 1 [likely reliable] evidence ratings in DynaMed's Levels of Evidence criteria in which evidence quality is labeled in 1 of 3 levels:

- **(level 1 [likely reliable] evidence)** for studies with clinical outcomes and minimal risk of bias;
- **(level 2 [mid-level] evidence)** for studies with clinical outcomes and significant methodological or statistical limitations; and
- **(level 3 [lacking direct] evidence)** for reports that do not include scientific analysis of clinical outcomes or for study types that do not include comparisons between groups.
-

The specific concepts we critically assessed are fully mapped to cover all the criteria used in GRADE. We summarized key concerns identified that reduce the certainty of evidence in categories used for GRADE methods (i.e., risks of bias, indirectness, imprecision, inconsistency, and other considerations if relevant). In the study-level summaries inconsistency assessment was applied to consistency of within-study results – this applies to consistency across related outcomes for both original studies and for systematic reviews, and also applies to consistency across studies when applied to systematic reviews.

## FAQ Summary

*FAQ 1: What does the treatment involve?*

*FAQ 2: What is my risk of the aneurysm rupturing in the next 5 years?*

*FAQ 3: What are the risks of the procedure?*

*FAQ 4: How long does it take to recover?*

# Results

## Characteristics and Results of Critically Appraised Studies/Sources

*Note about terminology used in this report: This evidence report is intended to provide insight into the management of incidentally-discovered intracranial aneurysms. As noted by the 2015 guideline from the American Heart Association and American Stroke Association (hereafter 2015 AHA/ASA guideline), intracranial aneurysms are being discovered incidentally much more often now, likely as a result of an increase in neuroimaging studies being done for various other reasons. The 2015 AHA/ASA guideline also notes that most of these incidentally-discovered aneurysms will not cause problems, but how to manage them remains a difficult subject due to the potentially dire consequences of rupture (subarachnoid hemorrhage, which can cause death or permanent disability). In the strictest delineation of the condition, unruptured intracranial aneurysms (UIAs) can be either symptomatic or asymptomatic, and only asymptomatic UIAs would qualify as incidental intracranial aneurysms (IIAs). In several cases, however, the evidence base does not clearly differentiate UIAs from IIAs. However, as alluded to above, UIAs could technically include some patients who have aneurysmal symptoms (e.g., cranial nerve palsy). As noted in the 2015 AHA/ASA guideline, symptomatic UIAs may be at higher surgical/procedural risk (if managed with surgical or endovascular techniques) and higher rupture risk (if managed with watchful waiting) compared with IIAs/asymptomatic UIAs. To maintain fidelity of the sources we consider below, we use the terminology the source used, but unless the source clearly indicated otherwise, we consider UIAs to be mostly comprised of IIAs/asymptomatic UIAs. Additionally, we preferentially use IIA throughout the report unless using UIA to maintain fidelity of the phrasing used by an original source.*

**ALGRA 2019**

Algra AM, Lindgren A, Vergouwen MDI, Greving JP, van der Schaaf IC, van Doormaal TPC, Rinkel GJE. Procedural Clinical Complications, Case-Fatality Risks, and Risk Factors in Endovascular and Neurosurgical Treatment of Unruptured Intracranial Aneurysms: A Systematic Review and Meta-analysis. JAMA Neurol. 2019 Mar 1;76(3):282-293. PubMed

Relevant to FAQ3

- **Study design:** systematic review of observational studies
  - longitudinal studies with ≥ 50 adults reporting either clinical complications or case-fatality rate (within 30 days after procedure for both outcomes)
    - clinical complications defined as treatment complications that resulted in transient or permanent morbidity or mortality and that occurred ≤ 30 days after procedure
- **Population:** adults with saccular UIAs having elective endovascular treatment (standard coiling or advanced endovascular method) or neurosurgical treatment (including only clipping) between 2000 and 2017
- **Data extraction and synthesis:**
  - for each treatment modality, the authors separately extracted and synthesized
    - clinical complications and/or case-fatality rate data pooled using mixed-effects logistic regression models for dichotomous data
    - risk factor estimates (from odds ratios or risk ratios) pooled using weighted random-effects model
- **Study inclusion criteria:**
  - study report published between January 1, 2011 and January 1, 2017

- **Number of studies:** 114 total
    - 74 reported on endovascular treatment (including standard coiling only or advanced methods, such as stent- or balloon-assisted coiling or flow diversion methods)
    - 54 reported on neurosurgical treatment
- **Number of participants:** 106,433 patients with 108,263 aneurysms total
- **Duration of follow-up:** 30 days after operation

- **Results:**
    - endovascular treatment
        - pooled clinical complication risk: 4.96% (95% CI 4.00% to 6.12%); 74 studies, 4,995 events, 71,819 patients; $I^2$ 97.8%
            - if limiting to high-quality studies (as assessed by the authors, using a cutoff of 7 or greater on the Newcastle-Ottawa Scale as marking high quality): 4.30% (95% CI, 2.59% to 7.07%); 15 studies, 445 events, 10,412 patients; $I^2$ 95.6%
        - pooled ischemic complication risk: 2.82% (95% CI 2.29% to 3.47%)
        - pooled hemorrhagic complication risk: 0.90% (95% CI 0.64% to 1.27%)
        - pooled case-fatality rate: 0.30% (95% CI 0.20% to 0.40%); 71 studies, 379 events, 57,550 patients; $I^2$ 81.3%
            - if limiting to high-quality studies (as assessed by the authors, using a cutoff of 7 or greater on the Newcastle-Ottawa Scale as marking high quality): 0.12% (95% CI, 0.02% to 0.63%); 14 studies, 27 events, 9,352 patients; $I^2$ 84.4%
        - significant risk factors for complications in pooled analysis
            - female sex (OR 1.06, 95% CI 1.01 to 1.11)
            - diabetes (OR 1.81, 95% CI 1.05 to 3.13)
            - hyperlipidemia (OR 1.76, 95% CI 1.31 to 2.37)
            - cardiac comorbidity (OR 2.27, 95% CI 1.53 to 3.37)
            - wide aneurysm neck (> 4 mm or dome-to-neck ratio <1.5) (OR 1.71, 95% CI 1.38 to 2.11)
            - posterior circulation aneurysm (OR 1.42, 95% CI 1.15 to 1.74)
            - stent-assisted coiling (OR 1.82, 95% CI 1.16 to 2.85)
            - stenting (OR 3.43, 95% CI 1.45 to 8.09)
    - neurosurgical treatment
        - pooled clinical complication risk: 8.34% (95% CI 6.25% to 11.10%); 54 studies, 6,501 events, 34,614 patients; $I^2$ 99.0%
            - if limiting to high-quality studies (as assessed by the authors, using a cutoff of 7 or greater on the Newcastle-Ottawa Scale as marking high quality): 6.89% (95% CI, 3.80% to 12.16%); 11 studies, 303 events, 4,059 patients; $I^2$ 95.8%
        - pooled ischemic complication risk: 2.52% (95% CI 1.62% to 3.91%)
        - pooled hemorrhagic complication risk: 1.23% (95% CI 0.71% to 2.15%)
        - pooled case-fatality rate: 0.10% (95% CI 0.00% to 0.20%); 49 studies, 156 events, 24,901 patients; $I^2$ 91.4%
            - if limiting to high-quality studies (as assessed by the authors, using a cutoff of 7 or greater on the Newcastle-Ottawa Scale as marking high

quality): 0.30% (95% CI, 0.00% to 0.94%); 11 studies, 5 events, 4,059 patients; $I^2$ 73.4%

- significant risk factors for complications in pooled analysis
  - age (OR per year increase, 1.02, 95% CI 1.01 to 1.02)
  - female sex (OR 0.43, 95% CI 0.32 to 0.85)
  - coagulopathy (OR 2.14, 95% CI 1.13 to 4.06)
  - use of anticoagulation (OR 6.36, 95% CI 2.55 to 15.85)
  - smoking (OR 1.95, 95% CI 1.36 to 2.79)
  - hypertension (OR 1.45, 95% CI 1.03 to 2.03)
  - diabetes (OR 2.38, 95% CI 1.54 to 3.67)
  - congestive heart failure (OR 2.71, 95% CI 1.57 to 4.69)
  - posterior circulation aneurysm (OR 7.25, 95% CI 3.70 to 14.20)
  - aneurysm calcification (OR 2.89, 95% CI 1.35 to 6.18)

- **Certainty: Very low**
  - **Risk of bias:** No serious concern for overall complications and case fatality, Serious concern for ischemic and hemorrhagic complications
    - Although estimates included a mixture of higher- and lower-quality studies, analyses limited to higher-quality studies suggest the addition of lower-quality studies may not have substantially influenced estimates. Additionally, the influence was mostly to increase the estimate of risk if including lower-quality studies (rather than decrease it, which would be of greater concern). The apparent exception to this pattern is the case-fatality estimate for neurosurgical clipping, where the pooled estimate was 0.10% vs. 0.30% for the overall estimate and the estimate limited to higher-quality studies. However, we judged this not to be a large enough difference to justify a full downgrade. We also note the wider 95% CI for the estimate of 0.30% (0.00% to 0.94%) is entirely consistent with the point estimate of 0.10% and its 95% CI (0.00% to 0.20%).
    - The assessment above was only possible for overall complications and case fatality (not for ischemic or hemorrhagic complications). Although some may consider it reasonable to infer the same pattern would hold for ischemic and hemorrhagic complications, we are not sufficiently assured this would be true and favor downgrading, though we recognize others might reasonably disagree.
  - **Imprecision:** No serious concern for any outcome
  - **Indirectness:** Very serious concern for all outcomes other than case-fatality, Serious concern for case-fatality – The authors were unable to differentiate transient from permanent complications, and this makes a large difference in the importance of the complication; the authors also allowed up to 25% of the UIAs to be symptomatic rather than asymptomatic
  - **Inconsistency:** Very serious concern for all outcomes – In addition to other evidence suggesting that the risk of complications is linked to various characteristics (e.g., Dasenbrock 2019, Ji 2016, and the 2015 guideline from the American Heart Association and American Stroke Association), Algra 2019 also found risk could be substantially influenced by various patient factors. Perhaps the most striking instance of this in Algra 2019 is the OR for clinical complication from neurosurgical clipping if the aneurysm was in the posterior location vs the internal carotid: OR 7.25 (95% CI 3.70 to 14.20). Additionally, the authors only present $I^2$ values for their univariate estimates of risk, and $I^2$ can and often does prove insufficient or even misleading when assessing heterogeneity of univariate estimates. Therefore, we consider this report to provide insufficient information to assess heterogeneity. Considering

all these things together, we are very concerned that a meta-analytic estimate could be importantly misleading for any individual patient, even if it provides some sense of an "average" risk.

- **Other considerations**
  - the authors' inclusion criteria allowed up to 25% of the aneurysms to be symptomatic
    - per the supplement to Algra 2019 (eTable 5, physical page 24 of the appendix), only 1 study each for endovascular methods and neurosurgical clipping reported risk factor data based on presence/absence of symptoms; however, this does not necessarily mean only 2 studies included symptomatic aneurysms, but rather, that only 2 studies allowed assessment of how the presence/absence of symptoms might have impacted outcomes
  - *transient* and *permanent* clinical complications could not be disentangled from heterogeneous outcome definitions across studies, and they were combined for pooled clinical complication risk measure
    - suggests need for cautious interpretation of
      - pooled clinical complication risk estimate
      - pooled analysis of risk factor data (because analysis specific to overall complications outcome measure)
  - assessment of effect of aneurysm size as risk factor
    - authors did not pool risk factor data on aneurysm size for either endovascular treatment or neurosurgical treatment and the relevant forest plots suggest this may have been due to high heterogeneity (eFigure 4, for both)
    - authors pointed out in Discussion section that previous studies have identified aneurysm size as a risk factor for neurosurgical treatment but not as risk factor for endovascular treatment

**DASENBROCK 2019**

Dasenbrock HH, Rudy RF, Smith TR, Gormley WB, Patel NJ, Frerichs KU, Aziz-Sultan MA, Du R. Adverse events after clipping of unruptured intracranial aneurysms: the NSQIP unruptured aneurysm scale. J Neurosurg. 2019 Mar 15:1-10. PubMed

Relevant to FAQ3

- **Study design:** observational study
  - development and validation of predictive scale to identify patients at greatest risk of postoperative adverse events
- **Population:** data on patients who had surgical clipping of an UIA were extracted from the prospective National Surgical Quality Improvement Program registry (NSQIP)
  - only patients having surgical clipping were included because NSQIP does not systematically collect data on patients having endovascular procedure
- **Development of score:**
  - NSQIP for years 2007-2014 was used as study population
  - multivariable analysis identified predictors of adverse event outcomes
    - screening of potential predictor variables to include in model with univariate logistic regression
      - screened variables related to patient demographics, comorbidities, functional status, preoperative laboratory values, aneurysm location/complexity, and operative time

- aneurysm size was not included because it is not collected in NSQIP
- adverse events outcome used for building main model
  - 30-day postoperative adverse events that are included in NSQIP algorithm (death, complications, and any reoperation)
    - complications defined as
      - postoperative cerebrovascular accidents
        - stroke with dysfunction (motor, sensory, or cognitive) that persists for ≥ 24 hours;
        - new postoperative coma that persists for ≥ 24 hours;
      - other complications
        - airway (extubation failure or prolonged mechanical ventilation)
        - cardiac (cardiac arrest or acute myocardial infarction)
        - infectious (surgical site infections, pneumonia, urinary tract infections, and sepsis)
        - symptomatic venous thromboembolism
        - packed red and blood cell transfusions
- predictors for 30-day postoperative adverse events outcome identified with univariate logistic regression with $p < 0.20$ were considered for inclusion in final multivariable model, which was generated using stepwise backward selection with exit criteria $p > 0.05$
  - secondary multivariable model developed based on neurological complications as outcome
- scale score calculated based on assigning points to variables that were significantly associated with risk of outcome in multivariable models
  - number of points assigned related to magnitude of odds ratio of association (in model with any adverse event as outcome)
    - 2 points for variables with OR 2.0 to 2.99
    - 3 points for OR 3.0 to 3.99
    - 4 points for OR > 4.0
  - 1 point for variables significantly associated only with neurological complications as outcome (but not any adverse event as outcome)
  - number of points assigned for each included variable provided in table below

**Components of the NSQIP unruptured aneurysm scale score**

| Variable | Stratum | Number of points |
|---|---|---|
| patient age | 51 to 60 years of age | 2 |
| | 61 to 70 years of age | 4 |
| | > 70 years of age | 4 |
| anticipated operative time* | 240 to 330 minutes | 2 |
| | > 330 minutes | 3 |
| body mass index (BMI) | BMI > 35 kg/m$^2$ (WHO class II or III obesity) | 2 |

| | | |
|---|---|---|
| *comorbidity-related variables* | | |
| bleeding disorder† | bleeding disorder present | 1 |
| cardiac‡ | coronary artery disease or congestive heart failure present | 2 |
| diabetes mellitus | diabetes mellitus present | 2 |
| *lab value-related variables* | | |
| anemia (hematocrit < 36%) | anemia present | 2 |
| leukocytosis (white blood cell count > 12,000/µl) | leukocytosis present | 3 |

* While the actual operative time is not known prior to surgery, surgeon may anticipate operative time based on aneurysm size, morphology, and planned surgical approach

† Combines several hypothrombotic conditions (vitamin K deficiencies, hemophilias, thrombocytopenia, and long-term anticoagulation), but does not include aspirin or other antiplatelet use

‡ Defined by NSQIP as congestive heart failure exacerbation or angina within 30 days, myocardial infarction within 90 days, or previous cardiac revascularization (percutaneous or surgical)

- **Validation of score:**
  - predictive capability of NSQIP unruptured aneurysm scale to classify adverse event-related outcomes in other populations was evaluated
    - populations
      - two validation
        - internal validation population: NSQIP (2015-2016)
        - external validation population: Nationwide Inpatient Sample (2002–2011)
      - study population - NSQIP (2007-2014)
    - increasing NSQIP unruptured aneurysm scale score was predictive of all adverse events (except reoperation) in both validation populations evaluated
      - results were generally consistent in sensitivity analysis that removed operative time as a variable
        - performed on internal validation population because external validation population did not include operative time as variable (which is reason for sensitivity analysis)
        - found that C-statistic was lower than score that included operative time, but discrimination remained good (other than no longer being predictive for mechanical ventilation)
  - scores on NSQIP unruptured aneurysm scale were divided into risk strata by points allocated and risk of major adverse event-related outcomes from the NSQIP validation population (2015–2016) were reported for each risk strata (included in table below)

**Risk of outcome in NSQIP validation population (2015–2016) stratified by the NSQIP unruptured aneurysm scale divisions**

| | **Very low risk** | **Low risk** | **Medium risk** | **High risk** |
|---|---|---|---|---|
| NSQIP unruptured aneurysm scale score | 0–3 | 4–5 | 6–7 | ≥ 8 |
| % patients | 31.2% | 34.4% | 21.0% | 13.4% |
| **Outcome** | | | | |
| Any adverse event | 7.0% | 15.7% | 19.7% | 38.1% |

| | | | | |
|---|---|---|---|---|
| Major complication* | 6.1% | 12.0% | 18.2% | 31.0% |
| Coma or stroke | 3.0% | 3.7% | 9.1% | 19.1% |
| Mechanical ventilation | 0.6% | 2.8% | 3.0% | 9.5% |
| Medical complication† | 1.0% | 2.8% | 10.6% | 9.5% |
| Infectious complication | 2.0% | 2.8% | 6.1% | 11.9% |
| Extended hospitalization‡ | 5.1% | 17.0% | 28.8% | 45.2% |
| Nonroutine hospital discharge§ | 4.1% | 10.2% | 21.2% | 45.2% |

* includes death, stroke or coma, reoperation, airway complication (extubation failure or prolonged mechanical ventilation), cardiac complication (cardiac arrest or acute myocardial infarction), venous thromboembolism, sepsis, or surgical site infections
† includes cardiac complication (myocardial infarction or cardiac arrest), venous thromboembolism (pulmonary embolism or deep venous thrombosis), sepsis, urinary tract infection, or pneumonia
‡ defined as length of stay > 6 days (the upper quartile of length of stay in NSQIP study population)
§ defined as discharge from hospital as any disposition other than to home

- **Certainty: Moderate for discrimination, Low for calibration**
    - Although the authors describe derivation, internal validation, and external validation, all data came from databases in the United States, so there may be some uncertainty about this model's ability to be generalized to international populations.
    - Predicted risks are not accompanied by any measure of precision.
    - Their description of calibration is considered suboptimal. They describe Hosmer-Lemeshow (HL) testing, but: (1) providing graphical representation of predicted vs. observed would be more informative than HL testing in isolation and (2) it is not clear that the HL testing is applied to the strata they created (as shown in the above table) and calibration itself can be measured at several levels (i.e., the overall population/mean calibration, different groups of patients based on predicted risk, or different groups of patients based on different combinations of predictors). It is also not clear how the strata themselves were created.
- **Other considerations:**
    - limitations of scale due to limitations of NSQIP dataset used to develop it
        - scale is only applicable to patients who have surgery (NSQIP dataset does not systematically collect data on patients who have endovascular treatment)
        - does not include aneurysm size (data not collected by NSQIP)
    - location of aneurysm not included in final scale
        - two sensitivity analyses evaluated location as binary variable
            - carotid vs. vertebrobasilar circulation
                - not associated with adverse events in univariable analysis (p = 0.34) so not evaluated in multivariable analysis
            - simple vs. complex (classified by CPT coding)
                - significant in univariable analysis (p = 0.04) but did not meet criteria for inclusion in final multivariable model of adverse events
                    - location of aneurysm variable ('simple vs. complex') may have been no longer significant in the multivariate model – which included operative time -- if there was high collinearity between increased complexity of surgery and increased length of operative time
    - authors acknowledge in Background and Discussion that size and location (along with age) are consistency reported predictors of morbidity and mortality from intervention

but that the expected operative time may be a suitable surrogate measure of these; however, there appear to be potential limitations with this approach

- operative time is not known before the surgery so this item on the scale is based on an *expected* operative time
- key evidence-based predictive aneurysm characteristics based on the patient data (size and location) are not used and in their place is the surgeon's subjective and holistic assessment based on these variables (as well as other variables related to the aneurysm characteristics and the planned surgical approach)

**NEWMAN 2016**

Newman WC, Neal DW, Hoh BL. A new comorbidities index for risk stratification for treatment of unruptured cerebral aneurysms. J Neurosurg. 2016 Sep;125(3):713-9. PubMed

Newman 2016 describes a novel scoring system using a patient's comorbidities to predict poor outcome, mortality, length of stay, and hospital charges, seeking to outperform other comorbidity-based scoring systems (namely the Charlson Comorbidity Index and the Elixhauser Comorbidity Index). Although the article describes derivation of the model and cites c statistics and areas under the curve that suggest it may discriminate better than the CCI or ECI, it does not clearly describe how it assessed discriminatory capacity (i.e., how patients were classified into higher or lower risk based on their novel scoring system). Additionally and perhaps more importantly for purposes of this evidence report, it also does not provide any information on how the score might be used (or whether it can be used) to estimate an individual patient's risk; accordingly, it does not describe calibration of this model. Therefore, although this article was progressed to Part 3 for full text appraisal, only a brief summary is provided here, and we do not advance it to Part 4.

**PHASES RISK PREDICTION METHOD – GREVING 2014 & BIJLENGA 2017**

Greving 2014 derived and internally validated the PHASES risk prediction method (hereafter "PHASES") and Bijlenga 2017 externally validated its discrimination. These studies are summarized separately below, but considering them together impacts overall certainty, as we describe here.

The development and internal validation of PHASES involved a systematic review of all published data for aneurysm rupture available worldwide, and therefore it could not be externally validated for either discrimination or calibration at the time of its publication. However, they did internally validate it with bootstrapping methods, and its inclusion of studies from different centers and different countries may offer some reassurance of external validity compared to if this score had been developed at a single center. Additionally, Bijlenga 2017 showed PHASES gives Moderate certainty in the discriminatory capacity of PHASES (the ability to stratify people into higher and lower risk categories), but it did not evaluate calibration (the accuracy/precision of estimated risks). Therefore, we judge PHASES to have Moderate certainty for discrimination and Low certainty for calibration.

**GREVING 2014**

Greving JP, Wermer MJ, Brown RD Jr, Morita A, Juvela S, Yonekura M, Ishibashi T, Torner JC, Nakayama T, Rinkel GJ, Algra A. Development of the PHASES score for prediction of risk of rupture of intracranial aneurysms: a pooled analysis of six prospective cohort studies. Lancet Neurol. 2014 Jan;13(1):59-66. PubMed

Relevant to FAQ2

- **Study design:** systematic review of observational studies for development PHASES
  - meta-analysis of individual patient data from 6 prospective cohort studies to
    - determine predictors of aneurysm rupture
    - establish risk prediction chart to estimate 5-year cumulative aneurysm risk of rupture by patient risk factor status
- **Population:** patients with unruptured intracranial aneurysms

- **Study inclusion criteria:**
  - ≥ 50 patients
  - aneurysm rupture as outcome
  - prospective study design
  - studied risk factors for aneurysm rupture

- **Number of studies:** 6
- **Number of participants:** 8,382
- **Duration of follow-up:** median across 6 studies ranged from 1 year to 21 years

- **Results:**
  - mean risks of aneurysm rupture
    - 1.4% (95% CI 1.1% to 1.6%) at 1 year
    - 3.4% (95% CI 2.9% to 4.0%) at 5 years
    - rate of rupture decreased during first five years of follow-up

- significant independent predictors of aneurysm rupture included higher age, hypertension, history of subarachnoid hemorrhage, aneurysm size, aneurysm location, and geographical region (Finland and Japan associated with increased risk)

**Risk prediction charts for aneurysm rupture within the next 5 years by aneurysm size and aneurysm location in patients aged < 70 years from North America and European countries (other than Finland)**

*For patients with no hypertension and no history of subarachnoid hemorrhage*

| | **aneurysm size** | | | |
|---|---|---|---|---|
| **aneurysm location** | ≥ 20 mm | 10 to 19.9 mm | 7 to 9.9 mm | < 7 mm |
| internal carotid artery | 5% | 1% | 1% | 0% |
| middle cerebral artery | 9% | 2% | 1% | 0% |
| anterior cerebral arteries* | 15% | 4% | 2% | 1% |
| posterior communicating artery or posterior circulation† | > 15% | 5% | 2% | 1% |

* Includes the anterior cerebral artery, anterior communicating artery, and pericallosal artery

† Posterior circulation includes the vertebral artery, basilar artery, cerebellar arteries, and posterior cerebral artery

*For patients with hypertension but no history of subarachnoid hemorrhage*

| | **aneurysm size** | | | |
|---|---|---|---|---|
| **aneurysm location** | ≥ 20 mm | 10 to 19.9 mm | 7 to 9.9 mm | < 7 mm |
| internal carotid artery | 7% | 2% | 1% | 0% |
| middle cerebral artery | 12% | 3% | 1% | 1% |
| anterior cerebral arteries* | > 15% | 6% | 2% | 1% |
| posterior communicating artery or posterior circulation† | > 15% | 7% | 3% | 1% |

* Includes the anterior cerebral artery, anterior communicating artery, and pericallosal artery

† Posterior circulation includes the vertebral artery, basilar artery, cerebellar arteries, and posterior cerebral artery

*For patients with both hypertension and history of subarachnoid hemorrhage*

| | **aneurysm size** | | | |
|---|---|---|---|---|
| **aneurysm location** | ≥ 20 mm | 10 to 19.9 mm | 7 to 9.9 mm | < 7 mm |
| internal carotid artery | 10% | 3% | 1% | 0% |
| middle cerebral artery | > 15% | 5% | 2% | 1% |
| anterior cerebral arteries* | > 15% | 8% | 3% | 2% |
| posterior communicating artery or posterior circulation† | > 15% | 9% | 4% | 2% |

* Includes the anterior cerebral artery, anterior communicating artery, and pericallosal artery

† Posterior circulation includes the vertebral artery, basilar artery, cerebellar arteries, and posterior cerebral artery

- Other considerations:
    - prediction reliable over first 5 years after aneurysm detection, and cannot be extrapolated over remaining lifetime because risk of aneurysm growth and rupture are not constant over time
    - risk chart has applicability to patients with previous subarachnoid hemorrhage from another aneurysm and patients with incidentally found aneurysms because both types of patients included in scale development
    - many patients received treatment during follow-up and in some cases this may have been because of increase in aneurysm size or development of new symptoms, both of which are associated with increases in rupture; as a result, patients with aneurysms that may have been likely to burst have been removed from the cohort resulting in a selection bias that affects the calculation of risk of rupture
    - in each of the 3 risk prediction charts above, rupture risks are similar in the aneurysm location categories "anterior cerebral arteries" and "posterior communicating artery or posterior circulation"; Greving 2014 suggested these 2 categories could be combined when discussing their simplified version of PHASES, and Bijlenga does this as well; due to the similarity in estimates, we have also combined them into single category in the modified versions of the risk prediction charts included in Part 4 for simplicity
    - the final mathematical method to generate estimates is included in Greving 2014's appendix, and although online calculators exist (e.g., https://qxmd.com/calculate/calculator_464/phases-score, http://www.kockro.com/calculators/calculator-phases/?lang=en), these use the approximation offered by Greving 2014 in their Table 4 and Figure 3; Greving 2014 specify their Table 4 and Figure 3 give only "approximate predictions", and we note these approximations can yield estimates different from the above risk prediction tables (which are based on the full method in the appendix)

**BIJLENGA 2017**

Bijlenga P, Gondar R, Schilling S, Morel S, Hirsch S, Cuony J, Corniola MV, Perren F, Rüfenacht D, Schaller K. PHASES Score for the Management of Intracranial Aneurysm: A Cross-Sectional Population-Based Retrospective Study. Stroke. 2017 Aug;48(8):2105-2112. PubMed

Relevant to FAQ2

- **Study design:** population-based cohort of prospectively recruited and consecutive patients diagnosed with intracranial aneurysm used for discrimination validation study of PHASES
- **Population:** patients diagnosed with intracranial aneurysm
    - among 1,164 patients in cohort, 323 were excluded leaving a total population of 841 patients for whom PHASES was calculated retrospectively
        - patients were excluded if positive familial history of intracranial aneurysm or subarachnoid hemorrhage (n = 119), polycystic kidney disease (n = 40), aneurysm-related symptoms (including cranial nerve compression, embolization from an aneurysm, or sentinella headaches) (n = 26), or missing information.
- **Study inclusion criteria:**
    - patients recruited between 2006 and 2014

- **Number of studies:** not applicable
- **Number of participants:** 1,164

- **Duration of follow-up:** mean 3.2 years
- **Classification of patients into four groups:**
  - observed and stable IIA
  - observed and growing IIA
  - immediately treated IIA
  - patients diagnosed in context of aneurysmal subarachnoid hemorrhage

- **Pooling of groups for analysis:**
  - follow-up IIA group: observed and stable IIA or observed and growing IIA
  - high risk of rupture: observed and growing IIA, immediately treated IIA, and aneurysmal subarachnoid hemorrhage
- **Comparisons assessed to evaluate PHASES**
  - follow-up vs. immediate treatment of incidentally diagnosed IIA
    - comparison assessed: follow-up IIA group vs. immediately treated IIA group
  - classification of unruptured vs. ruptured aneurysms
    - comparison assessed: IIA group (observed and stable IIA, observed and growing IIA, or treated) vs. aneurysmal subarachnoid hemorrhage group
  - discrimination of patients at low risk vs. high risk
    - comparison assessed: observed and stable IIA vs. high risk of rupture

- **Results:**

**Median (first and third quartile values) of the phases score distributions for each group***

| | n | median | quartile 1 | quartile 2 | p-value |
|---|---|---|---|---|---|
| Full cohort | 841 | 4 | 2 | 6 | < 0.001 |
| observed and stable IIA | 277 | 2 | 1 | 4 | not significant |
| follow-up IIA group | 302 | 2 | 1 | 4 | reference group |
| observed and growing IIA | 25 | 3 | 2 | 4 | not significant |
| IIA (stable, growing, or treated) | 598 | 4 | 2 | 6 | < 0.001 |
| immediately treated IIA | 296 | 5 | 3 | 7 | < 0.001 |
| high risk of rupture | 564 | 5 | 4 | 7 | < 0.001 |
| aneurysmal subarachnoid hemorrhage | 243 | 5 | 4 | 8 | < 0.001 |

*Distribution of PHASES scores is not Gaussian and is highly skewed

- **Other considerations**
  - Authors pointed out that to be able to balance risks associated with natural history vs. risks associated with intervention, the development of a similar score on interventions would be required and that the development of an Unruptured Intracranial Treatment Score has been initiated.

**JI 2016**

Ji W, Liu A, Lv X, Kang H, Sun L, Li Y, Yang X, Jiang C, Wu Z. Risk Score for Neurological Complications After Endovascular Treatment of Unruptured Intracranial Aneurysms. Stroke. 2016 Apr;47(4):971-8. PubMed

Relevant to FAQ3

- **Study design:** observational study
  - development and internal validation of scale to quantify individual patient risk of postoperative adverse events after endovascular treatment of UIAs

- **Population:** data on consecutive patients who had endovascular treatment (including standard coiling only or advanced methods, such as stent- or balloon-assisted coiling or flow diversion methods)
- for UIAs between 2012 and 2015 at hospital in China
    - 1060 patients
        - 636 in derivation group
        - 424 in validation group
- **Development and validation of score:**
    - patients randomly divided into derivation group (60%) and validation group (40%)
    - outcome ("neurological complications") was defined as any transient or permanent increase in modified Rankin Scale score after aneurysm embolization
        - outcome was a composite that combined transient neurological deficits that resolved within 1 month and deficits considered permanent at 1-month evaluation
    - multivariable logistic regression model with backward stepwise variable selection found that 3 variables were significantly associated with neurological complications and had reached a previously defined odds ratio threshold of 1.2 (all 3 had odds ratios about 3)
        - size (dichotomized at $\geq$ 10 vs. < 10)
        - core area (Yes/No)
            - core area defined as perforator-rich vessels and important cerebrovascular branches supplying the brain stem and basal ganglia region
                - perforator-rich vessels included A1 segment of anterior cerebral artery, M1 segment of middle cerebral artery, P1 segment of posterior cerebral artery, internal carotid artery bifurcation, and basilar artery
                - important cerebrovascular branches included posterior inferior cerebellar artery and anterior choroidal artery
        - cerebral ischemic comorbidities (Yes/No)
            - defined as transient ischemic attack, cerebral infarction, or cerebral vascular stenosis
    - risk score for neurological complications was derived by assigning 1 point to each of the 3 independent predictors
    - validation of risk score
        - in derivation group
            - score showed significant discrimination
                - C-statistic, 0.714 (95% CI 0.624 to 0.804)
            - calibration
                - McFadden $R^2$, 0.102
        - in validation group, discrimination and calibration properties were reproduced (C-statistic 0.721, 95% CI 0.618 to 0.824; McFadden $R^2$ 0.136)

**Risk of neurological complications by clinical score in validation group***

| | **Clinical score** | | | |
|---|---|---|---|---|
| | **0** | **1** | **2** | **3** |
| neurological complications | 2% | 11% | 18% | 33% |

*For all 4 clinical scores, consistent proportions with neurological complications were reported in the derivation group and in the combined validation and derivation groups.

- **Certainty: Low**
  - Absence of external validation; additionally, the outcome used for the development of this risk score is a composite of transient and permanent neurological complications, and an outcome that instead limits to permanent complications may be more clinically relevant and useful.

# Evidence report for watchful waiting vs. surgical or endovascular treatment for patients with unruptured intracranial aneurysm

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