# Anticoagulant and antiplatelet therapy in patients with an unruptured intracranial aneurysm

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**INTRODUCTION —** Unruptured intracranial aneurysms are detected in up to 2 to 3 percent of older adults who undergo high-quality noninvasive intracranial arterial imaging (eg, magnetic resonance angiography, computed tomographic angiography). Subarachnoid hemorrhage from a ruptured intracranial aneurysm is associated with a short-term mortality of 40 percent, with one-half of survivors sustaining permanent neurologic injury. Thus, detection of an asymptomatic unruptured aneurysm creates a management dilemma in patients who have indications for antithrombotic therapy. (See "Unruptured intracranial aneurysms".)

This topic review will discuss issues related to anticoagulant and antiplatelet therapy in patients with an unruptured intracranial aneurysm.

**RATE OF RUPTURE —** Rates of rupture for previously detected unruptured aneurysms vary according to their size (ie, there is a greater risk of rupture in larger aneurysms), specific location (eg, higher rates of rupture with posterior circulation aneurysms) [1], as well as history of prior subarachnoid hemorrhage from a separate aneurysm [2]. This subject is reviewed in depth separately, and will only be reviewed briefly here (see "Unruptured intracranial aneurysms", section on 'Risk of aneurysm rupture'):

- For patients with small (<7 mm) aneurysms in the anterior circulation and without a history of subarachnoid hemorrhage, the rupture rate is very low, below 0.1 percent per year.
- For similar patients who have moderate-sized aneurysms (7 to 12 mm), the rupture rate averages 2.5 percent per year.
- For those with larger aneurysms (>13 mm) or those with aneurysms involving the posterior communicating artery, rupture rates range from 3 to 20 percent per year or even higher in giant aneurysms.

Other factors influencing rupture rates of previously unruptured intracranial aneurysms include patient age (relative risk 2.0 for those >60 years), female sex (relative risk 1.6) and tobacco smoking (relative risk 1.7) [1].

It is not known whether antithrombotic therapies influence the rate of rupture of intracranial aneurysms. By reducing thrombus formation in the aneurysmal sac, it is possible that antithrombotic therapy could **increase** rates of aneurysm rupture. In about 30 percent of cases of subarachnoid hemorrhage from aneurysm rupture there is a history of recent symptoms attributable to the aneurysm and thought to be caused by intramural or minor subarachnoid hemorrhage, also known as "warning leaks." Major aneurysmal subarachnoid hemorrhage typically follows these symptoms within a few weeks in most patients. (See "Clinical manifestations and diagnosis of aneurysmal subarachnoid hemorrhage", section on 'Clinical presentation'.) Antithrombotic and antiplatelet therapies could exacerbate the severity of the hemorrhage in case of rupture, perhaps even converting intramural or minor subarachnoid hemorrhages into major, life-threatening bleeding.

Conversely, aspirin could **reduce** the risk of rupture by inhibiting inflammatory mediators (such as matrix metalloproteinases and tumor necrosis factor-alpha) that might play a role in the evolution and eventual rupture of intracranial aneurysms [3]. Clinical data on these points are sparse, as summarized below.

**EFFECT OF ANTIPLATELET THERAPY —** Available clinical data are limited and conflicting regarding the influence of aspirin on rates of aneurysm rupture.

- In the Nurses' Health Study, a large prospective longitudinal cohort study, middle-aged women who used >15 aspirin per week had twice the rate of all-cause subarachnoid hemorrhage compared with nonusers [4]. The excess risk was particularly pronounced among older and hypertensive women, and it was not observed among those taking lower doses of aspirin. In this study, there were an unduly large number of subarachnoid hemorrhages relative to ischemic strokes and intraparenchymal hemorrhages, although the fraction of subarachnoid hemorrhages that were due to ruptured aneurysms was not reported. Despite multivariate statistical adjustments, imbalances in other vascular risk factors between aspirin users versus nonusers in observational trials leave etiologic associations unproven.

- In contrast, aspirin use at least three times weekly was associated with a lower risk of aneurysm rupture in a nested case-control study of the untreated cohort of patients in the International Study of Unruptured Intracranial Aneurysms (ISUIA) (adjusted OR 0.27; 95% CI 0.11–0.67) [3]. A possible protective effect of chronic aspirin use on the risk of aneurysm rupture deserves further investigation.

Regarding the severity of subarachnoid hemorrhage, data from two selected surgical case series have shown no apparent increase in the initial severity of bleeding and no adverse effect on long term outcome in patients presenting with aneurysmal subarachnoid hemorrhage who were taking aspirin prior to rupture [5,6]. There are no studies assessing the effect of other antiplatelet agents or combination antiplatelet therapy on the risk of intracranial aneurysm rupture or the severity of subarachnoid hemorrhage in case of aneurysm rupture.

**EFFECT OF ANTICOAGULATION —** No data supporting higher rupture rates following the use of anticoagulants are available from randomized clinical trials or large cohort studies. However, available studies do not convincingly exclude higher rates of aneurysmal subarachnoid hemorrhage in anticoagulated patients due to the infrequency of subarachnoid hemorrhage, which is typically combined with other causes of hemorrhagic strokes in reports of clinical trials. Evidence that intravenous thrombolysis with the administration of recombinant tissue plasminogen activator (rtPA) appears safe in patients with unruptured intracranial aneurysms who have an acute ischemic stroke argues against an increased risk of rupture from the use of drugs that affect coagulation [7].

Anticoagulation appears to worsen the clinical outcome of aneurysmal subarachnoid hemorrhage. Death or dependency following aneurysmal subarachnoid hemorrhage occurred in 93 percent (14 of 15) of anticoagulated patients versus 49 percent of those not receiving anticoagulants in the only reported case series [8]. This was due to the worse clinical status at the time of admission of anticoagulated patients, as a consequence of more severe initial bleeding.

**MANAGEMENT —** Available clinical guidelines [9,10] and major reviews [11] concerning management of unruptured intracranial aneurysms do not address the use of antiplatelet agents or anticoagulants. Given the available information as summarized above, it is not clear that antithrombotic therapies increase the risk of aneurysm rupture. However, the following observations have been made:

- Anticoagulation with oral vitamin K inhibitors augments the severity of initial bleeding if rupture does occur.

- There is no evidence that aspirin worsens the clinical outcome of aneurysmal subarachnoid hemorrhage, but the existing data are meager [5,6]. Consequently, at present, detection of an unruptured intracerebral

aneurysm should not be regarded as a contraindication to antiplatelet therapy for patients who have a clear indication for such medication.

The apparent doubling (from about 50 percent to nearly 100 percent) of the rates of death or disability associated with rupture of an intracranial aneurysm should be considered in weighing the benefits versus risks of anticoagulation in patients known to harbor an unruptured intracranial aneurysm.

As an example, for an elderly patient with atrial fibrillation and prior stroke or transient ischemic attack who has a 10 mm unruptured aneurysm involving the anterior communicating artery, treatment with warfarin would be expected to produce an absolute reduction in the rate of stroke of about 6 percent per year (half of which are likely to be fatal or disabling) [12], but would augment the risk of fatal or disabling subarachnoid hemorrhage by about 0.25 percent per year [2,8]. In the absence of other risks, this analysis would lead one to favor anticoagulation in this particular patient.

For those patients with larger aneurysms or those whose absolute benefits from anticoagulation are smaller, the estimated harm from anticoagulation may substantially mitigate its benefits. Thus, the decision must be individualized according to the best estimates of benefits versus risks.

It is unclear how the need for chronic anticoagulation should influence the complex benefit/risk equation regarding repair of unruptured intracranial aneurysms [8,9,13,14]. Anticoagulation appears to double the mortality associated with rupture of intracranial aneurysms, and hence this is a relevant factor in the decision. Most experts do not consider a requirement for anticoagulation therapy to be an indication for aneurysm repair [15].

**SUMMARY AND RECOMMENDATIONS**

- Unruptured intracranial aneurysms are detected in 2 to 3 percent of older adults and hemorrhage from a ruptured intracranial aneurysm is associated with a short-term mortality of 40 percent, with one-half of survivors sustaining permanent neurologic injury. (See "Unruptured intracranial aneurysms".)
- Antiplatelet or anticoagulant therapy could potentially increase the risk of an intracranial aneurysm by one or more of the following effects (see 'Effect of antiplatelet therapy' above and 'Effect of anticoagulation' above):
  - By reducing thrombus formation in the aneurysmal sac, anticoagulation and excessive aspirin use could increase rates of rupture. However, based on current evidence, daily use of regular doses of aspirin is safe and there is preliminary evidence that it might even decrease the risk of aneurysm rupture.
  - Anticoagulation can exacerbate the degree of hemorrhage in case of rupture. This adverse effect has not been clearly observed with aspirin use. The risks associated with other antiplatelet agents or with combination of antiplatelet agents are not known.
  - Anticoagulation appears to worsen the clinical outcome of aneurysmal subarachnoid hemorrhage
- Management of a patient with an unruptured intracranial aneurysm who requires treatment with an antiplatelet agent or anticoagulation for another indication is problematic. Two general principles apply to these patients (see 'Management' above):
  - Detection of an unruptured intracerebral aneurysm should not be regarded as a contraindication to antiplatelet therapy for patients who have a clear indication for such medication.
  - For patients with larger aneurysms or those whose absolute benefits from anticoagulation are smaller, the estimated harm from anticoagulation may substantially mitigate its benefits. Thus, the decision must be individualized according to the best estimates of benefits versus risks.

- Issues to be considered include the following (see 'Management' above):
  - Risk of spontaneous rupture of the aneurysm (eg, size, location)
  - Risk of thrombosis/stroke if antiplatelet/anticoagulant treatment is not given
  - Risk of exacerbated bleeding from an aneurysmal rupture if anticoagulant treatment is given



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## Contributor Disclosures

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