To use or not to use antithrombotics in unruptured cerebrovascular malformations? A systematic review focusing on this clinical and surgical dilemma

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OBJECTIVE Antithrombotic medications (ATMs), including antiplatelet therapy (APT) and oral anticoagulants (OACs), are widely used in current clinical practice for the prevention and treatment of a variety of cardiovascular diseases, deep vein thrombosis, and pulmonary thromboembolisms. The long-term usage of these drugs, associated with an inherent risk of bleeding, raises concerns for unruptured cerebrovascular malformations (UCVMs), such as arteriovenous malformations (AVMs), cerebral cavernous malformations (CCMs), and intracranial aneurysms (IAs), in which the bleeding risk also poses a major threat. The aim of this study was to assess the safety and risk-benefit ratio of ATMs in these various neurosurgical diseases and to give neurosurgeons a safe and reasonable choice regarding whether to administer ATMs to these patients during the course of the disease.

METHODS The authors conducted a systematic review of the literature (PubMed/MEDLINE and Embase) according to Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols (PRISMA-P) guidelines, which yielded 4 papers about CCMs, 2 about AVMs, and 9 about IAs. The risk of bias was assessed using the Cochrane Collaboration’s tool.

RESULTS For AVMs, only 2 studies with a total of only 14 patients were included. Data on AVMs and ATMs are limited and weak, relying on small case series. Nevertheless, there is no evidence for either an increased risk of intracranial hemorrhage in patients with AVMs who are receiving ATMs or the need to interrupt ATMs in those patients who have been diagnosed with sporadic, unruptured brain AVMs. With respect to CCMs, the literature search resulted in 4 cohort studies and 1 meta-analysis. These studies affirmed the absence of a correlation between ATMs and an increased risk of CCM bleeding while simultaneously suggesting a protective role of ATMs against bleeding. Concerning IAs, the topic is more complex and debated, despite larger case series on IAs than on AVMs or CCMs. The benefits of ATMs for IAs may vary according to the type of intervention and specific drug administered. Evidence supports the continuation of long-term APT for all patients newly diagnosed with an IA, whereas starting APT in patients with incidentally discovered IA as a means of prophylaxis against rupture is unclear.

CONCLUSIONS The findings of this review should be taken as a wide overview of UCVM and ATM. Future research should consider the relationship of AVM, CCM, and IA with APT and OAC independently.

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KEYWORDS antithrombotic; anticoagulant; aneurysm; cavernous malformation; arteriovenous malformation; antiplatelet; vascular
ANTITHROMBOTIC medications (ATMs), including antiplatelet therapy (APT) and oral anticoagulants (OACs), are widely used in current clinical practice for the prevention and treatment of a variety of cardiovascular diseases, deep vein thrombosis, and pulmonary thromboembolisms. The long-term usage of these drugs, associated with an inherent risk of bleeding, raises concerns for unruptured cerebrovascular malformations (UCVMs), such as arteriovenous malformations (AVMs), cerebral cavernous malformations (CCMs), and intracranial aneurysms (IAs), in which the bleeding risk also poses a major threat.

The increased risk of bleeding during neurosurgical procedures, both elective and emergent and leading to poor outcomes and deadly prognoses, is well established. Although with regard to aspirin, in particular, many studies have recently drawn attention to its safety in elective neurosurgical procedures. After hemorrhagic events, ATMs are suspended according to well-defined guidelines on timing and the need for ATM reversal agents. ATM discontinuation, however, does not apply to endovascular procedures, given that it may induce thromboembolic complications.

The current literature is unclear on how to manage the following two clinical scenarios: 1) a patient on ATMs who presents with an incidental finding of a UCVM, and 2) a patient with a known UCVM who needs to be placed on ATMs for various clinical reasons. Therefore, this systematic review of the literature aimed to assemble the current evidence concerning the safety of ATM usage in patients with conservatively managed UCVMs, such as AVMs, CCMs, and IAs. The primary objective of our review was to clarify whether there is an increased risk of bleeding for patients with UCVMs on ATMs, including the incidence of hemorrhagic events and the severity of the hemorrhagic event itself. Ultimately, the goal was to provide neurosurgeons with a risk-benefit analysis of ATMs in patients with UCVMs in order to facilitate the clinical decision-making process.

Methods
Search Strategy
A systematic review of the literature according to the Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols (PRISMA-P) guidelines was performed (Fig. 1). We searched two online databases—MEDLINE/PubMed and Embase—using the following free terms, keywords, or MeSH terms: “intracranial arteriovenous malformation,” “intracranial cavernous hemangiomas,” “cerebral cavernous malformation,” “intracranial aneurysm,” “anticoagulants,” “haemorrhage,” “intracranial bleeding,” “subarachnoid haemorrhage,” “antithrombotic agents/drugs,” and “delayed cerebral ischemia” with AND, OR, or NOT operators. All English-language papers published over a 20-year period from January 2001 to December 2021 were considered.

From the initial results page, we selected randomized and nonrandomized studies, as well as prospective and retrospective cohort studies. Due to limited data on the subject matter, we included case reports while excluding letters and editorials. Duplicates were removed. We did not request missing study data from the authors whose papers omitted such data. The titles and abstracts from the search results page were independently screened for eligibility by three review authors (A.B., P.F., and A.P.) to identify studies fulfilling the following inclusion criteria: inclusion of an adult population (> 18 years) on ATMs with a diagnosis of UCVM that reported the number of bleeding events. Studies in which ATMs were initiated after treatment (surgical or endovascular) were not considered, and only studies in which ATMs were ongoing at the time of UCVM bleeding were included. Due to the heterogeneity of UCVMs, we extrapolated and grouped data individually for each type of UCVM (AVM, CCM, and IA). Each paper’s full text was read and critically evaluated by the same three review authors. Disagreements were resolved through consensus after a thorough discussion of the conflicting article. The reference lists were also screened to identify additional relevant papers.

Outcome Definition
Two primary outcomes were reported for all UCVMs: 1) bleeding risk (number of bleeding cases/total cases), when both bleeding and nonbleeding cases were included; or 2) total number of bleeding cases, when only cases that bled were included. With respect to IAs, we noted an additional primary outcome of delayed cerebral ischemia (DCI) and secondary outcomes of morbidity, defined as major neurological deficits, and mortality. The findings of the risk of bias assessment are shown in Fig. 2.

Considering the heterogeneity of the pathologies addressed in this review, both the Results and Discussion have been divided into sections according to the specific underlying pathology: AVMs, CCMs, or IAs. Although there are significant differences between the mechanisms of action of APT and OACs, as well as between AVMs and CCMs in the literature, our results discussed these two therapies used in combination as ATMs. Meanwhile, for IAs, there were sufficient data to discuss APTs and OACs separately.

Results
The initial search resulted in a total of 660 papers. After the exclusion of duplicates, 126 papers published before 2001, and 36 non–English-language papers, the titles and abstracts of 425 studies were evaluated. An additional 156 studies were excluded, yielding 269 studies for full-text evaluation. Of these 269 papers, 254 were excluded as they did not fulfill the inclusion criteria (Fig. 1). In the end, 2 papers about AVMs, 10,11 4 about CCMs,12–15 and 9 about IAs16–24 were included in the systematic review.

Arteriovenous Malformation
As far as AVMs are concerned, only 2 retrospective studies met the inclusion criteria (Table 1). In a 2018 retrospective study of 77 patients with an AVM, Sturiale et al.16 found that 10 of them were receiving long-term ATMs at the time of diagnosis. Not only did the authors find no significant difference in the rates of hemorrhagic onset between the ATM group and the non-ATM group (40% vs
55% hemorrhage rate, respectively), but also they discovered that none of the patients who continued taking ATMs after AVM diagnosis had hemorrhagic events over time. The other study, conducted by Edwards et al.,11 focused on hereditary hemorrhagic telangiectasia (HHT), which is a genetic disease often characterized by the presence of brain AVMs. Even though they showed that ATMs had a relatively safe drug profile in most of the patients with HHT, a solid comparison with sporadic brain AVMs cannot be made given the differing characteristics of HHT and AVM (e.g., bleeding rate, dimensions).25

Cerebral Cavernous Malformation

With respect to CCMs, the literature search yielded 4 cohort studies.12–15,26 These studies affirmed the absence of a correlation between ATM usage and increased risk of CCM bleeding, with a hemorrhage rate of 0%–2% in the ATM group and 2.5%–12.0% in the non-ATM group over an average 5-year follow-up period (Table 2). The 4 recent studies—1 prospective and 3 retrospective—are methodologically valid with reasonably long follow-up periods and large case series. The distinction between APT and OACs is not discussed within our article because there were no significant differences between the two therapies in any study. Of note, in the study by Zuurbier et al.,12 which was associated with the meta-analysis, a protective factor of ATMs was suggested in regard to CCM intracranial bleeding.

Aneurysms

Nine IA studies met the inclusion criteria: 1 prospective cohort study23 and 8 retrospective cohort studies.16–22,24,27,28 Of these, 6 focused on ruptured aneurysms and whether ATMs were previously administered or not.5 on follow-up

FIG. 1. PRISMA 2020 flow diagram illustrating study selection.
of patients with unruptured aneurysms, and 1 on both scenarios. Untreated and surgically or endovascularly treated patients were included. The results are summarized in Table 3. Most of the data on IAs address APT; there are only a few papers on OACs and they are predominantly concerned with the endovascular treatment period.

Taking into account only original studies, the risk of bleeding for unruptured and treated aneurysms on APT varied from 13% to 28% \(^{16,17}\), while the risk was estimated at 3% to 40% in the control group without APT. Similarly, the risk of presenting with subarachnoid hemorrhage (SAH) among those patients receiving APT ranged from 10% to 28% and in those not receiving APT from 40% to 51% \(^{22,24}\). In summary, 2 articles suggested a lower rate of hemorrhagic presentation with APT, 1 demonstrated augmented bleeding risk, and 1 was inconclusive.

In terms of secondary outcomes, the mortality rate ranged from 4% to 12.6% in patients not on ATMs and

### TABLE 1. Summary of the included studies on AVM

<table>
<thead>
<tr>
<th>Authors &amp; Year</th>
<th>Type of Study</th>
<th>No. of Patients</th>
<th>No. of Patients on ATM</th>
<th>Type of ATM</th>
<th>Hemorrhage Rate w/o ATM (%)</th>
<th>Hemorrhage Rate w/ ATM (%)</th>
<th>Follow-Up Time</th>
<th>Conclusions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sturiale et al., 2018(^{10})</td>
<td>Retrospective cohort</td>
<td>77</td>
<td>10</td>
<td>ACT, APT</td>
<td>55</td>
<td>40</td>
<td>4 yrs</td>
<td>No association between ATM &amp; AVM bleeding</td>
</tr>
<tr>
<td>Edwards et al., 2012(^{11})</td>
<td>Retrospective cohort</td>
<td>31</td>
<td>4</td>
<td>ACT, APT</td>
<td>0</td>
<td>0</td>
<td>Not available</td>
<td>No association between ATM &amp; AVM bleeding</td>
</tr>
</tbody>
</table>

ACT = anticoagulant therapy.
The rates of in-hospital mortality and poor outcomes in patients with SAH appear to be higher among long-term ATM users;\textsuperscript{29} however, other studies show that correct use of aspirin is associated with lower adjusted odds of aneurysmal SAH (aSAH).\textsuperscript{38} Given that inflammation is considered an important player in the formation and rupture of brain aneurysms and AVMs, these latter studies suggest the importance of the anti-inflammatory properties of aspirin in protecting against AVM hemorrhage.\textsuperscript{39,40} As previously stated, this review found only 2 AVM studies, of which 1 included only a subset of AVM patients with HHT, for a total of only 14 patients receiving ATMs. With such a small number of AVM patients on ATMs—even though an increased risk of neither hemorrhagic presentation nor rebleeding was demonstrated—it is impossible to express strong conclusions regarding the safety of long-term ATM use. For the same reason, it was also impossible to report a difference in management between AVMs with previous bleeding and those without, nor a difference between APT and OACs. In light of the fact that AVMs have an increasingly longer clinical course, involving radiosurgery rather than surgery itself, further studies are needed to define the impact of ATMs on the risk of bleeding in the natural history of this disease.

Cerebral Cavernous Malformations

CCM is the second most common incidental vascular finding after aneurysm on brain MRI, with a prevalence of 1 in 625 neurologically asymptomatic people. Overall, CCMs have a prevalence of 0.1%–0.5%, representing 10%–20% of all cerebrovascular lesions, and may arise in either sporadic or autosomal dominant forms.\textsuperscript{26} These patients can be asymptomatic, symptomatic with seizures or stroke caused by CCM-related ICH, or symptomatic with focal neurological deficits without radiological signs of recent bleeding. Similar to other neurovascular pathologies, the use of ATMs in CCMs is burdened by the theoretical risk of bleeding; however, unlike AVMs and IAs, CCMs are less likely to have a surgical indication and thus more likely to be managed conservatively over long periods of time. Even in the event of a CCM bleed, this is usually of little concern and causes relatively minor neurological deficits to the patient. The bleeding rates of CCMs are approximately 0.5% and 2.8% per patient-year for supratentorial and brainstem lesions, respectively.\textsuperscript{26}

### Discussion

**Arteriovenous Malformations**

Brain AVMs are high-flow cerebrovascular malformations characterized by abnormal connections between different arteries and draining veins, without an interposing capillary net, and a high risk of severe intracranial bleeding. Prior reviews on brain AVMs have noted an incidence of 1.12–1.42/100,000 person-years\textsuperscript{29–32} and described the most common presenting symptoms as hemorrhage (occurring in as many as 50% of patients), headache, or seizures.\textsuperscript{33} AVMs carry a risk of spontaneous bleeding of up to 2%–4% per year, or up to 78% in a lifetime. Of note, this risk depends on several AVM characteristics such as previous rupture, location of the malformation nidus, type of venous drainage, and presence of a concurrent aneurysm.\textsuperscript{33–35}

Unfortunately, there is limited information in the literature about ATMs and their role in the risk of AVM-related intracranial hemorrhage (ICH). Management of these patients is often determined by surgeons and neuro-radiologists on the basis of personal experience and opinions. The first randomized controlled trial (A Randomized Trial of Unruptured Brain Arteriovenous Malformations [ARUBA]) demonstrated increased rates of stroke and mortality associated with intervention compared with medical management.\textsuperscript{36,37} Therefore, this translated to an increasing number of patients entering conservative management and regular neuroradiological follow-up instead of surgery, leading to a greater number of patients reaching an age where they may develop cardiovascular diseases requiring ATMs. Despite this scenario becoming more frequent, the association between ATMs and risk of intracranial bleeding still remains poorly understood for any kind of cerebrovascular malformation.

### TABLE 2. Summary of the included studies on CCM

<table>
<thead>
<tr>
<th>Authors &amp; Year</th>
<th>Type of Study</th>
<th>No. of Patients</th>
<th>No. of Patients on ATM (%)</th>
<th>Median Follow-Up (yrs)</th>
<th>Annual Hemorrhage Rate w/o ATM</th>
<th>Annual Hemorrhage Rate w/ ATM</th>
<th>Conclusions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Zuurbier et al., 2019\textsuperscript{12}</td>
<td>Retrospective cohort &amp; metaanalysis</td>
<td>300</td>
<td>61 (20.3)</td>
<td>7.4</td>
<td>12</td>
<td>2</td>
<td>Association btw ATM &amp; lower risk of CCM hemorrhage</td>
</tr>
<tr>
<td>Bervini et al., 2019\textsuperscript{13}</td>
<td>Retrospective cohort</td>
<td>408 (492)</td>
<td>91 (22.3)</td>
<td>3.9</td>
<td>2.5</td>
<td>0.7</td>
<td>No association btw ATM &amp; CCM bleeding</td>
</tr>
<tr>
<td>Fleming et al., 2013\textsuperscript{15}</td>
<td>Retrospective cohort</td>
<td>292</td>
<td>40</td>
<td>Not available</td>
<td>Not available</td>
<td>0.41</td>
<td>No association btw ATM &amp; CCM bleeding</td>
</tr>
<tr>
<td>Schneble et al., 2012\textsuperscript{14}</td>
<td>Prospective cohort</td>
<td>87 (738)</td>
<td>16 (18)</td>
<td>3.9</td>
<td>Not available</td>
<td>0</td>
<td>No association btw ATM &amp; CCM bleeding</td>
</tr>
</tbody>
</table>
TABLE 3. Summary of the included studies on IA

<table>
<thead>
<tr>
<th>Authors &amp; Year</th>
<th>Type of Study</th>
<th>No. of Aneurysms on ATM (%)</th>
<th>Ruptured or Unruptured Aneurysm</th>
<th>Treatment</th>
<th>Type of Medication</th>
<th>Mortality</th>
<th>Morbidity</th>
<th>IB or DCI</th>
<th>Conclusions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nakamizo et al., 2017</td>
<td>Retrospective cohort</td>
<td>42 (11.2)</td>
<td>Unruptured</td>
<td>Surgical</td>
<td>APT, ACT</td>
<td>No difference</td>
<td>8.9% (ATM) vs 3.9% (no ATM)</td>
<td>IB in 13.3% (ATM) vs 3.9% (no ATM)</td>
<td>IB incidence increased in ATM group</td>
</tr>
<tr>
<td>Gross et al., 2014</td>
<td>Retrospective cohort</td>
<td>114 (15.3)</td>
<td>Unruptured</td>
<td>Not available</td>
<td>APT</td>
<td>Not available</td>
<td>Not available</td>
<td>IB in 40% (no ATM) vs 28% (ATM)</td>
<td>Lower rate of hemorrhagic presentation w/ APT</td>
</tr>
<tr>
<td>Simard et al., 2013</td>
<td>Retrospective cohort</td>
<td>43 (50)</td>
<td>Ruptured</td>
<td>Surgical &amp; endovascular</td>
<td>ACT, intravenous LDH 1 (no ACT) vs 0 (ACT)</td>
<td>25 (58%) (no ACT) vs 16 (37%) (ACT) discharged to rehabilitation centers</td>
<td>DCI in 9 (21%) (no ACT) vs 0 (0%) (ACT)</td>
<td>Postprocedural LDH use may be safe &amp; beneficial in patients w/ ruptured aneurysms</td>
<td></td>
</tr>
<tr>
<td>Fuji et al., 2020</td>
<td>Retrospective cohort</td>
<td>8 (5.16)</td>
<td>Ruptured</td>
<td>Endovascular</td>
<td>APT, ACT</td>
<td>Not available</td>
<td>Not available</td>
<td>IB in 0 (0%) (ACT) vs 5 (3.4%) (no ACT), delayed aneurysm rupture in 2 (25%) (ACT) vs 0 (0%) (ACT)</td>
<td>Additional ACT before flow diverter placement does not reduce ischemic complications compared w/ dual APT but does increase hemorrhagic complications</td>
</tr>
<tr>
<td>Toussaint et al., 2004</td>
<td>Retrospective cohort</td>
<td>29 (9.5)</td>
<td>Ruptured</td>
<td>Surgical &amp; endovascular</td>
<td>APT</td>
<td>0</td>
<td>62.5% w/ rebleeding vs 31.3% w/o rebleeding</td>
<td>Not available</td>
<td>No significant effect of previous aspirin use on overall outcome after aSAH</td>
</tr>
<tr>
<td>Narata et al., 2019</td>
<td>Retrospective cohort</td>
<td>113</td>
<td>Unruptured</td>
<td>Endovascular</td>
<td>ACT (HGH vs LDH) 3 (4.2%) (HDH) vs 1 (1.2%) (LDH)</td>
<td>Symptomatic neurological complications in 8 (11.1%) (HDH) vs 1 (12%) (LDH)</td>
<td>IB in 5 (6.9%) (HDH) vs 1 (12%) (LDH)</td>
<td>LDH administered during endovascular procedure decreased the overall number of symptomatic neurological complications</td>
<td></td>
</tr>
<tr>
<td>Nisson et al., 2020</td>
<td>Retrospective cohort</td>
<td>347</td>
<td>Ruptured &amp; unruptured</td>
<td>Surgical</td>
<td>ACT, APT</td>
<td>4% (no ATM) vs 2% (ATM)</td>
<td>No difference</td>
<td>IB in 10% (clopidogrel) vs 46% (control) &amp; 16% (ASA) vs 51% (control)</td>
<td>Patients receiving APT were less likely to present w/ ruptured aneurysms; no difference w/ ACT</td>
</tr>
<tr>
<td>Hasan et al., 2011</td>
<td>Prospective cohort</td>
<td>271</td>
<td>Ruptured</td>
<td>Surgical &amp; endovascular</td>
<td>APT</td>
<td>Not available</td>
<td>Not available</td>
<td>Odds ratio 0.40–0.87 for IB in aspirin group vs control group</td>
<td>Aspirin use may confer a protective effect against risk of IA rupture</td>
</tr>
<tr>
<td>Dasenbrock et al., 2017</td>
<td>Retrospective cohort</td>
<td>353</td>
<td>Ruptured</td>
<td>Surgical &amp; endovascular</td>
<td>ACT, APT (aspirin) 19.4% (ACT) vs 12.6% (no ACT) &amp; 13.5% (APT) vs 12.6% (no APT)</td>
<td>Poor outcomes in 53.6% (ACT) vs 37.6% (no ACT) &amp; 36.1% (APT) vs 37.8% (no APT)</td>
<td>IB in 9.8% (APT) vs 9.7% (no APT) &amp; 10.2% (ACT) vs 9.7% (no ACT)</td>
<td>APT &amp; ACT were not associated w/ differential mortality or complication rates after SAH</td>
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</table>

ASA = acetylsalicylic acid; HDH = high-dose heparin; IB = intracranial bleeding; LDH = low-dose heparin.
Thus, greater attention should be paid to these patients with untreated CCMs who may require ATMs for future medical reasons during their long follow-up period.

ATMs may play a protective role in regard to intracranial bleeding caused by CCM rupture. The association between long-term ATM use and lower risk of ICH is based on the theory that these bleeding events may be triggered by thrombus formation either in an associated developmental venous anomaly or within the dilated caverns of a CCM caused by slow or stagnant blood flow. Nonetheless, this relationship could also be due to the fact that CCM hemorrhage is more common in younger than older patients, and older patients are more likely to require ATMs. To address this potential confounding variable, Zuurbier et al. adjusted for age and still found a statistically significant association between ATM use and lower rates of CCM rupture. As such, ATMs may improve outcomes and reduce the risk of recurrent bleeding in CCMs.

Aneurysms
Accounting for almost 85% of nontraumatic SAH cases, IAs affect nearly 3.2% of the population. In patients harboring unruptured IAs, the use of ATMs, especially after bleeding, is controversial and must be addressed. A protective role of aspirin has been reported in the context of SAH; however, the risk of devastating bleeding events is still a concern for patients with IAs on ATMs.

Antiplatelet Therapy
The protective role of APT, such as aspirin, has been suggested in several studies that have shown a reduced risk of SAH of 33%–73%; this has been attributed to the anti-inflammatory effects of these molecules. Attention should instead be focused on the timing of APT intake.

In the International Study of Unruptured Aneurysms, Hasan et al. found that 271 patients who were taking aspirin at least 3 times per week to daily had decreased risk of aSAH. Moreover, long-term use (>1 year) of low-dose aspirin was found to be protective against SAH by Cea Soriano et al. This finding was corroborated by Dassenbrock et al. who, in a 2017 retrospective analysis of 1509 patients, also demonstrated that patients on APT had significantly lower odds of a cardiac complication or a venous thromboembolic event and patients on long-term APT had shorter hospital length of stay and fewer nonroutine discharges. In a retrospective series of 63 patients taking APT, Nisson et al. highlighted the protective role of APT in contributing to a significantly lower risk of IA rupture and subsequent SAH. In the present study, however, the timing of APT intake was not specified. Another 2014 retrospective analysis of 717 patients with IAs performed by Gross et al. showed a greater risk of hemorrhage in patients not taking aspirin compared with patients taking aspirin (40% vs 28%). Furthermore, of the 274 patients who presented with aSAH, 81 were taking aspirin and no significant difference in presenting clinical or radiographic grade was found. In a 2013 study by García-Rodríguez and colleagues involving 1340 patients with SAH, long-term low-dose aspirin therapy was found to have a protective effect against SAH, especially for patients on long-term aspirin therapy (>3 years). Equally important was the finding that aspirin did not increase the risk of ICH. The results from an early 2004 retrospective study by Toussaint et al. indicated that the overall clinical outcomes after aSAH in patients taking aspirin before hemorrhage were not different from those who were not taking aspirin. However, trends toward an increased risk of rebleeding and a decreased risk of a permanent neurological deficit from vasospasm were seen in patients who used aspirin before they had SAH. In contrast to these abovementioned findings, a 2017 meta-analysis by Phan et al. of 226 patients demonstrated that those who received aspirin had an increased risk of SAH in the first 3 months of use.

Although long-term APT use was associated with some benefits in terms of the prevention of aneurysmal rupture and lack of worsening outcomes in cases of SAH, care needs to be taken in the perioperative period for the neurosurgical treatment of unruptured IAs. Nakamizo et al. analyzed 401 patients and showed no particular risks in terms of mortality, morbidity, or symptomatic brain infarction; however, ICH occurred more frequently in the ATM group than in the non-ATM group. Conversely, a 2003 meta-analysis by Dorhout Mees et al. demonstrated that the administration of APT after aSAH reduced the risk of DCI, while the ICH risk was not substantially higher if APT was started before surgery.

OACs and Heparin
Regarding the use of OACs in patients with IAs, there are less data in the literature, but most articles support the evidence of an increased risk of bleeding and worse outcomes. In the study by Dassenbrock et al., long-term use of OACs was associated with a higher rate of complications after SAH, nonroutine discharge, and longer length of stay. In the same manner, systemic anticoagulation with warfarin therapy has been associated with poor outcomes after aSAH. In only one retrospective analysis were OACs not associated with an increased risk of aSAH; this was the case for the subgroup of 12 patients taking OACs in the study by Nisson et al. Overall, ATMs are relatively safe in patients harboring IAs, with APT performing better than OACs, as demonstrated by Fuji et al. In this study, 155 patients with unruptured IAs received dual APT before endovascular treatment. Patients on long-term OACs were more likely to have delayed aneurysm ruptures with hemorrhagic complications and no reductions in the incidence of ischemic complications, additional treatment, and incomplete obliteration at final follow-up.

Finally, the use of low-dose heparin in patients with IAs was investigated by only a few articles. Narata et al. demonstrated that the administration of low-dose heparin during endovascular treatment decreased the overall number of symptomatic neurological complications without any statistically significant association with hemorrhagic complications. Meanwhile, Simard et al. showed that patients who were administered a low-dose intravenous heparin infusion within 48 hours of SAH experienced significantly fewer occurrences of symptomatic vasospasm and infarcts compared with controls. Likewise, Hoh et al. found that heparinization for cerebral aneurysm coiling can be safely performed even after external ventricular drain placement within 24 hours.
Limitations

As previously mentioned in the specific subsections, the currently available data in the literature on this topic are extremely limited and heterogeneous, particularly with regard to study design, inclusion criteria, and outcome definition. For these reasons, a proper quantitative analysis could not be performed. Almost all of the included studies were retrospective cohort studies (13 of 15), with only 2 prospective and no randomized controlled trials. Furthermore, the risk of bias assessment of the included studies highlighted a high or unclear risk of bias in more than 50% of them.

Future Perspectives

The findings of this review should be taken as a wide overview of the topic of UCVMs and ATMs. Future research should consider the relationship of AVMs, CCMs, and IAs with APT and OACs independently. In particular for CCMs, further studies should focus on discovering a possible protective role of ATMs against CCM bleeding. The management of ATMs in patients with IAs needs to be further investigated, with prospective studies focusing separately on APT and OACs, as well as distinguishing between ruptured and unruptured aneurysms and between surgical and endovascular treatment.

Conclusions

Data on AVMs and ATMs are limited and weak, relying on small case series. Nevertheless, there is no evidence for either an increased risk of ICH in patients with AVMs who are receiving ATMs or the need to interrupt ATMs in those patients who have been diagnosed with sporadic, unruptured brain AVMs.

With respect to CCMs, the literature review suggested the safety of ATMs in these patients. As far as IAs are concerned, the use of ATMs is more complex and debated because the benefits of ATMs may vary according to the type of intervention and specific drug administered. Evidence supports the continuation of long-term APT in patients newly diagnosed with an IA \(^{17,41}\), whereas starting APT in patients with incidentally discovered IAs as a means of prophylaxis against rupture is unclear.

Appendix

Search string for PubMed/MEDLINE: (“brain arteriovenous malformation” or “cavernous haemangiomas” or “cerebral cavernous malformation” or “aneurysm”) and (“anti-coagulants” or “antithrombotic agents” or “antiplatelet” or “anti-thrombotic” or “antithrombotic drug”) and (“haemorrhage” or “intracranial bleeding” or “subarachnoid haemorrhage” or “delayed cerebral ischemia”). Search string for Embase: (“brain arteriovenous malformation” or “intracranial arteriovenous malformation”) and (“anticoagulants” or “antiplatelet”) and “haemorrhage”; “intracranial aneurysm” and (“anticoagulants” or “antiplatelet”) and “subarachnoid hemorrhage” and “delayed cerebral ischemia”; and (“cavernous haemangioma” or “brain cavernous malformation”) and (“anticoagulants” or “antiplatelet”) and (“bleeding” or “haemorrhage”).

References


Disclosures
The authors report no conflict of interest concerning the materials or methods used in this study or the findings specified in this paper.

Author Contributions
Conception and design: Bianconi, Ceraudo, Prior, Fiaschi. Acquisition of data: Bianconi, Minardi, Allevi. Analysis and interpretation of data: Bianconi, Ceraudo, Minardi, Allevi. Drafting the article: Bianconi, Ceraudo, Minardi, Allevi. Critically revising the article: Ceraudo, Nico, Zona, Fiaschi. Reviewed submitted version of manuscript: Bianconi, Nico, Zona, Fiaschi. Approved the final version of the manuscript on behalf of all authors: Bianconi. Administrative/technical/material support: Allevi. Study supervision: Bianconi, Garbossa, Fiaschi.

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