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Cerebrovascular Disease and Stroke (S Silverman, Section Editor)

Antithrombotic Management After Intracranial Hemorrhage

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Abstract

Purpose of review Intracranial hemorrhage remains one of the most feared acute neurological emergencies. However, apart from the acute management, secondary risk factor management and prevention of ischemic events remains ambiguous. We present a thorough review of the current data available regarding management of antithrombotics after intracranial hemorrhage.
Recent findings The most robust evidence comes from the investigators of the RESTART trial which reassured the safety of resuming antiplatelet therapy after ICH, namely in patients with prior indication and treatment with antithrombotics.
Summary We conclude that based on available data, the risk of recurrent ICH is probably too small to exceed the found benefits of antiplatelet therapy in the secondary prevention of ischemic vascular disease.

Introduction

Intracranial hemorrhage (ICH) refers to any bleeding inside of the intracranial vault and is characterized by extravasation of blood products into one or multiple intracranial compartments. It is subdivided on the basis of the anatomical location of the bleeding, either the brain parenchyma itself and/or the surrounding meningeal spaces. Intracranial hemorrhage is often associated with significant morbidity and mortality stratified by a number of clinical and radiological characteristics, including the size, location, etiology, and acuity of management.

Unfortunately, many patients presenting with ICH often have indications for antithrombotic treatment.

With the present data, it is often left to the discretion of the practitioner to determine indications for, and risks, benefits, and alternatives to antithrombotic medications. We present a review of the available data to assist in answering this difficult question.

Intra-axial hemorrhages

Intraparenchymal hemorrhage (IPH) is defined as bleeding within the brain parenchyma, etiologies of which can either be spontaneous or traumatic [1].

Spontaneous, or non-traumatic, IPH represents approximately 6.5 to 19.6% of cases of acute stroke and is generally associated with higher mortality when compared to its ischemic counterparts [2, 3]. One-year survival from IPH is approximately 40%, and 10-year survival is 24% [4–6]. Hypertension is the primary risk factor for spontaneous IPH.

Primary IPH accounts for 78 to 88% of those who present with IPH, and pathophysiologically is due to rupture of damaged small arteries or arterioles, most commonly as a consequence of hypertension or cerebral amyloid angiopathy (CAA) [7••]. Secondary IPH is more heterogeneous with various underlying etiologies including trauma, coagulopathy, cerebral venous sinus thrombosis, Moyamoya disease, vasculitis, tumor, hemorrhagic conversion of ischemic stroke, or due to a rupture of a mycotic aneurysm or vascular malformations [7••] (Table 1). Hemorrhage location, i.e., deep or lobar, is also an important differentiating factor not only for determination of etiology, but also for predicting recurrence of hemorrhage. This is discussed in detail in the section titled *Important Considerations in Antithrombotic Resumption.*

Intraventricular hemorrhage (IVH) occurs when there are blood products present within the ventricular system. An IVH may be primary or secondary,

Table 1. Primary and secondary causes of ICH

Primary Causes	Secondary Causes

• Hypertension
• Cerebral amyloid angiopathy
	• Hemorrhage transformation of ischemic stroke
	• Stimulant drugs
	• Vascular malformation
	  ○ Aneurysms
	  ○ Arteriovenous malformation
	  ○ Venous angioma
	  ○ Cavernoma
	  ○ Dural arteriovenous fistula
	• Coagulopathy
	  ○ Hereditary
	  ○ Acquired
	  ○ Iatrogenic (anticoagulants, antiplatelets)
	• Neoplasms
	• Trauma
	• Vasculitis
	• Moyamoya disease
	• Sinus venous thrombosis

such as when ventricular blood is present due to extravasation of blood from the parenchyma or the subarachnoid space. In cases of IVH, potential etiologies include rupture of arteriovenous malformations or fistulas, coagulopathy, choroid plexus tumor, and ependymal lesions [8•].

Extra-axial hemorrhages

The brain parenchyma is separated from the innermost layer of the calvarium by three layers of tissue. The potential spaces between the inner table of the calvarium and the dura is known as the epidural space, while the space between the dura and the arachnoid layer is referred to as the subdural space. The space between the arachnoid and the pia is called the subarachnoid space. Each of these cavities may be a site of accumulated blood products with varying mortality and morbidity, etiology, and management.

Subarachnoid hemorrhage can be grouped as either aneurysmal or non-aneurysmal. Separating traumatic causes, the most common etiology of SAH is a ruptured cerebral aneurysm (80–85%) [9, 10]. Aneurysms typically form at branch points along intracranial arteries due to hemodynamic stress on the wall between the two branches. Risk factors associated with an increased risk of aneurysmal rupture include black race, Hispanic ethnicity, hypertension, current smoking, alcohol abuse, use of sympathomimetic drugs, and having an aneurysm larger than 7 mm [9–11]. Other non-aneurysmal, non-traumatic causes of SAH include benign perimesencephalic hemorrhage, dural AV fistulas, AVMs, cortical venous sinus thrombosis, and vasculopathies including vasculitis, reversible vasoconstriction syndrome, and posterior reversible encephalopathy syndrome [10, 12].

Subdural hemorrhage results from stretching and tearing of bridging cortical veins which are present between the dura and the arachnoid. These hematomas are not limited by adherent periosteum and thus can cross suture lines. SDH are commonly seen in the elderly and may occur spontaneously owing to enlargement of the subarachnoid spaces seen with age-related cerebral volume loss, thus increasing tension on the bridging veins. Other more common etiologies of SDH include trauma, coagulopathic conditions, and in cases of dural metastases.

Epidural hemorrhage may be caused either by arterial injury (most commonly, the middle meningeal artery) or by injury to venous sinuses. Oftentimes, there is associated coexistent calvarial fracture, namely in adult populations.

Classes of antithrombotics

Antithrombotic agents have long been in clinical use and are among the most commonly prescribed classes of medications. With a long list to choose from, drug selection should be tailored to maintain a balance between preventing thromboembolic events and limiting potential side effects, the most concerning of which is ICH. The two most widely prescribed classes of antithrombotic drugs include antiplatelet agents and anticoagulants.

Antiplatelet drugs constitute a cornerstone of therapy for cardiovascular and cerebrovascular disease given the central role of platelets in

the formation and growth of thrombi in the arterial circulation. Aspirin is the most commonly used antiplatelet agent, interfering with thrombus formation through the selective and irreversible inhibition of platelet cyclooxygenase-1. The effectiveness of aspirin monotherapy has been demonstrated by a clear reduction in the risk of recurrent thrombotic events, independent of sex, age, or vascular risk factors [13–17]. This benefit comes with a small but definitive risk of ICH estimated as 0.2 events per 1000 patient-years [18].

Thienopyridines are another class of antiplatelet agents often used as monotherapy, or in combination with other antithrombotics. The active metabolites of these prodrugs reversibly or irreversibly block the P2Y12 receptor on the surface of platelets, inhibiting the pro-aggregatory actions of adenosine-5′-diphosphate. Clopidogrel, the most widely studied of its class, has shown improved patient outcomes over aspirin therapy alone, without a significant increase risk of ICH, 0.35% versus 0.49% [19]. However, unlike aspirin, plasma concentrations and antiplatelet effects between patients can vary with smoking, body mass index, gene polymorphisms, and co-administration of other agents metabolized by the CYP2C19 and CYP3A4 isoenzymes, most notably, proton pump inhibitors, lipophilic statins, and calcium channel blockers.

Newer agents have been developed to overcome these limitations. Prasugrel, another thienopyridine with a faster onset of action than clopidogrel and without significant evidence of metabolic variability, has been shown to reduce ischemic events in high-risk patients when compared to clopidogrel, albeit at the cost of an increased risk of ICH [20].

Yet another antiplatelet agent, ticagrelor, also acts on the P2Y12 receptor. However, unlike the thienopyridines, it is not a prodrug, and thus not dependent on CYTP450 metabolism for activation, producing less inter-individual variability. One study found monotherapy with ticagrelor significantly reduces the incidence of acute ischemic stroke, acute coronary syndrome, sudden cardiac death, and all-cause mortality in comparison with clopidogrel, with a negligible difference in ICH, 0.3% verse 0.2% [21]. A later comparison between ticagrelor and aspirin did not find ticagrelor to be superior to aspirin in reducing recurrent ischemic events, but the risk of ICH remained low [22].

Cilostazol, a phosphodiesterase 3 inhibitor, traditionally used in patients with peripheral artery disease, was recently found to be non-inferior to aspirin in reducing ischemic vascular events in Asian populations, with a lower rate of ICH observed with cilostazol [23]. Recent trials looking at combination therapy with cilastazol in secondary stroke prevention are pending publication.

Glycoprotein IIb/IIIa inhibitors are a group of potent antiplatelet agents that block the final common pathway in platelet aggregation. Agents in clinical use include abciximab, eptifibatide, and tirofiban. With a narrow range of clinical indications and an association with increased rates of ICH, glycoprotein IIb/IIIa inhibitors are generally used with caution [24–27].

With the assumption that inhibiting two pathways is better than one, attempts to combine antiplatelet agents have produced mixed results in both efficiency and bleeding risk. Dual antiplatelet therapy (DAPT) with clopidogrel plus aspirin has long been the standard of care in

cardiovascular disease, where the risk of thrombosis largely outweighs the risk of hemorrhage within cardiac tissue [28–30]. However, DAPT, when compared with clopidogrel alone, was found to increase the risk of bleeding, including a twofold increase in ICH [31]. However, exceptions to this have been found, notably, specific indication such as intracranial atherosclerosis or short term use following an acute ischemic event, was not found to be associated with an increased risk of ICH [32–34]. Dipyridamole was found to reduce the incidence of death from all vascular causes, as well as non-fatal stroke and non-fatal myocardial infarction. When used as a combination of aspirin and extended-release dipyridamole, study investigators found a slight increase in the incidence of ICH, 0.9 vs 0.5% [35, 36]. When compared to clopidogrel alone, there was no difference in primary outcomes and again at an increased risk of ICH [37]. Furthermore, the combination of cilostazol with aspirin or clopidogrel was found to be efficacious in high-risk patients when compared to long-term therapy with either aspirin or clopidogrel alone, without increase in ICH incidence [23, 38].

Anticoagulant drugs also play an integral role in the treatment and prevention of thrombotic events, however, as is the case with antiplatelet drugs, simultaneously increase the risk of bleeding.

Heparins act indirectly by catalyzing the actions of antithrombin to prevent thrombus formation and propagation. Although known to produce dose-dependent bleeding complications, the use of heparin has not been associated with a significant increase risk of ICH for most indications with the exception of patients receiving early treatment for an acute cardioembolic stroke [39].

Warfarin, an oral vitamin K antagonist that inhibits the hepatic synthesis of coagulation factors II, VII, IX, and X, was the mainstay of anticoagulant therapy for many decades. However, multiple observational studies and randomized trials have reported that even therapeutic levels, where the international normalized ratio (INR) is consistently between 2 and 3, the risk of ICH compared to the general population doubles with warfarin, with the annual risk in the range of 0.2 to 0.4% per person-years [40, 41]. In addition to an increased risk of ICH, retrospective evidence suggests that supratherapeutic warfarin therapy is an independent risk factor for larger initial hemorrhage volumes, as well as poor outcomes after ICH [42]. These limitations have restricted the use of warfarin and have led to the development of new medications for treatment and prevention of thrombotic events.

Dabigatran, apixaban, rivaroxaban, and edoxaban commonly referred to as the non-vitamin K oral anticoagulants (NOACs) modulate thrombus formation through the direct inhibition of either Factor Xa or thrombin. Studies have shown NOACs to have a favorable risk-benefit profile, with reductions in AIS, ICH, and mortality when compared to warfarin [43–46]. Despite this favorable comparison with warfarin, NOACs do confer a small increased risk of ICH when compared with patients who are not receiving an oral anticoagulant or are on aspirin monotherapy [47, 48].

The combined uses of anticoagulant and antiplatelet agents have been evaluated in multiple randomized clinical trials, with most showing an increase in ICH [49–52]. However, this risk may be acceptable in certain clinical settings. An exception to this was recently found in patients with stable atherosclerotic

disease, where adding low-dose rivaroxaban to aspirin was shown to be more effective than aspirin alone in reducing stroke reoccurrence without a significant difference in ICH incidence [53].

Risk of ischemic stroke and bleeding: scoring tools

Patients with non-valvular atrial fibrillation have a higher risk of ischemic strokes when compared to control groups. Risk stratification scores for stroke events have been developed to appropriately assign an antithrombotic therapy. Most commonly used scoring tools are the $CHADS_2$ and CHA_2DS_2-VASc scores. Other variations of these scores have included renal dysfunction, such as the R_2CHADS_2 score to improve its prediction [54]. The ATRIA stroke risk score also includes renal dysfunction and proteinuria [55]. Of the commonly used scoring tools, the CHA_2DS_2-VASc score is the only available tool to select the patients with the lowest risk who do not warrant anticoagulation [56] (Table 2). Biomarkers for cardiac and renal dysfunction, as well as inflammation, have been used in scoring systems given their associated increase risk of stroke. The ABC stroke risk score is yet another scoring tool that includes cardiac troponin and B-type natriuretic peptide [57].

Oral anticoagulation is the most effective management for stroke prevention in patients with atrial fibrillation. However, the benefits of stroke risk reduction have to be weighed against the risk of major hemorrhage. Various tools have been developed to assess the risk of bleeding such as the HAS-BLED score, HEMORR2HAGES, ATRIA, ORBIT, and MBR factors score (Table 2). The 2016 European Society of Cardiology (ESC) guidelines provide a list of these risk factors including hypertension, labile INR, and medications that increase bleed risk and excess alcohol use defined as more than 8 drinks a week [58]. Each of these risk scores has been found to have a modest predictive value; however, when compared to the HAS-BLED score, it was found to have a lower predictive utility [59–62]. The clinical utility of these scores is to alert the clinician about patients that should be closely monitored in routine visits and not dissuade of the use of anticoagulation in the appropriate indication [59].

If and when antithrombotics should be initiated after hemorrhage

Given the cumulative risk of ICH recurrence is 1 to 5% per year in patients not on an antithrombotic agent [63–65], the decision to resume antithrombotic therapy following ICH requires careful consideration. It is paramount to weigh the risk of potentially fatal ICH progression or recurrence against the morbidity and mortality associated with thromboembolic events. This decision becomes even more challenging as evident by the variability seen in clinical practice. In patients suffering an ICH, the current American Heart Association/American Stroke Association recommendations are as follows: *If the indication for antithrombotic therapy is strong, anticoagulation or antiplatelet monotherapy can likely be restarted following a non-lobar ICH;* however, *in patients with non-valvular atrial fibrillation, long-term anticoagulation with warfarin is not recommended following a spontaneous warfarin-associated ICH* [66]. The most recent guidelines put forth by

Table 2. Ischemic and hemorrhagic stroke risk stratification scores

Ischemic Stroke Risk Scores					Hemorrhagic Stroke Risk Scores				
CHA_2DS_2-VASc	**$CHADS_2$**	**R_2CHADS_2**	**ATRIA stroke risk score**	**ABC stroke risk score**	**HAS-BLED**	**$HEMORR_2HAGES$**	**ATRIA bleeding score**	**ORBIT**	**ABC bleeding score**
Age	CHF	Renal dysfunction GFR<60 ml/min	Stroke	Age	Hypertension	Hypertension	Hypertension	Age>74	Age
Sex	Hypertension	Stroke, TIA	Age	Biomarkers: cTn-hs, NT-proBNP	Renal disease	Alcohol	GFR<30 or dialysis	Anemia	Biomarker: GDF-15, cTNT-hs, hemoglobin
CHF	Age>75	CHF	Female	Clinical history	Liver disease	History of malignancy	Age>75	History of hemorrhage	Clinical history (prior bleeding)
Hypertension	Diabetes	Hypertension	Diabetes		Stroke	Age>75	History of hemorrhage	Renal disease	
Stroke, TIA, Thromboembolism	Stroke, TIA	Age>75	CHF		Conditions predisposing to bleeding	Reduced platelet count or function	Anemia	Use of antiplatelet	
Vascular disease		Diabetes	Hypertension		Labile INR	History of hemorrhage			
Diabetes			Proteinuria		Age >65	Hepatic or renal disease			
			GFR<45		Medication predisposing to bleeding	Anemia			
					Alcohol	Genetic factors			
						Excessive fall risk			
						Stroke			

the European Society for Cardiology are equally as vague, stating: *Anticoagulation in patients with atrial fibrillation can be reinitiated after 4 to 8 weeks, when the cause of bleeding has been treated*, and *if anticoagulation is resumed, consider anticoagulants with low bleeding risks* [58]. In attempts to better define current recommendations, a number of recent meta-analyses have been conducted, and although limited by the observational nature of the data available, the results have been synonymous.

In 2017, a large meta-analysis of 8 studies examined the relationship between anticoagulation therapy and ICH recurrence. About 38% of who were restarted on anticoagulation, did it within 10 to 39 days from ICH. In the population that resumed, thromboembolic events were less compared to those who did not resume anticoagulation and both groups had similar ICH recurrence [67].

Another systematic review and meta-analysis that was conducted in 2017 included 10 observational studies on 7799 patients who survived VKA associated ICH, where warfarin was the only agent re-prescribed [68]. ICH recurred in 6.7% of patients who resumed warfarin compared to 7.7% of patients who did not resume anticoagulant therapy. Similar findings were observed in a number of other meta-analyses [69, 70]. The consensus being that reinitiation of antithrombotic therapy following a primary ICH is associated with a lower risk of ischemic and thromboembolic events, with no apparent additional risk of ICH recurrence if started after the first 2 weeks following ICH, with the appropriate time frame for anticoagulant resumption being around 4 weeks [67–72]. The most robust data comes from a recent publication of the RESTART trial, a prospective, randomized, open-label, blinded endpoint trial completed in the UK. Five hundred thirty-seven participants were recruited at a median of 76 days after intracranial hemorrhage, with one to one randomization to start or avoid antiplatelet therapy. The median follow up was 2 years. Twelve of the 268 participants in the antiplatelet arm had recurrence of ICH compared with 23 of the 268 in the stop antiplatelet group (hazard ratio 0.51, $p = 0.060$). Thirty-nine patients in the antiplatelet arm had major occlusive vascular events compared to 38 in those allocated to avoid antiplatelet therapy. To the best of our knowledge and review of the existing literature, this is the only randomized controlled trial to date which has reassured the safety of resuming antiplatelet therapy after ICH, namely in patients with prior indication and treatment with antithrombotics. The authors conclude that the risk of recurrent ICH is probably too small to exceed the found benefits of antiplatelet therapy in the secondary prevention of ischemic vascular disease [73••].

Important considerations in antithrombotic resumption

While the summation of recent literature suggests antithrombotic therapy should be reintroduced following a primary ICH, the multifactorial nature of ICH recurrence necessitates a number of factors be taken into consideration prior to resuming therapy, including the etiology, size, and anatomical location of the hemorrhage. Certainly, one should consider the class of medication to be resumed, as well as the indication for antithrombotic treatment, and the individual risk factors of each patient [70].

Multiple non-modifiable risk factors such as old age, male sex, CAA, and Asian ethnicity should be taken into consideration when assessing the risk of ICH recurrence. In the elderly, the increased risk of ICH can be attributed to a higher prevalence of CAA and more observed comorbidities. However, given the increase burden of comorbid disease, the indication for antithrombotic therapy may be even more indicated, and thus age alone should not be the ultimate deciding factor [74]. In addition to age, ethnicity has been shown to play a role in ICH recurrence. In two of the major trials comparing VKAs and NOACs, Asian populations were found to have a higher risk of ICH with warfarin, dabigatran, and apixaban when compared with non-Asian populations, possibly suggesting a more cautious approach to anticoagulation in this population. Furthermore, according to a large, international case-control study, modifiable risk factors were found to account for 88.1% of the population-attributable risk of ICH [75]. Thus, comorbid factors that should be addressed prior to resuming antithrombotic agents post-ICH include hypertension, hyperlipidemia, obesity, tobacco use, excessive alcohol consumption, and illicit drug use [76–80].

The underlying etiology of the primary ICH should also be considered. It was suggested that patients resuming anticoagulation after a traumatic ICH experienced a lower rate of ICH recurrence compared to patients who suffered a spontaneous ICH [71]. On the contrary, patients with underlying CAA have a substantially increased risk of subsequent ICH, with a direct correlation observed between the number of microbleeds on gradient echo MRI and the risk of recurrence [81, 82]. Furthermore, ICH associated with CAA are more likely to be lobar, which are additionally more prone to recurrence than those in the deep cortical structures, 5–14.3% compared to 1.3–2.9% [83]. These hemorrhages also tend to have larger volumes and worse outcomes [70, 83–86].

Regarding the indication for restarting antithombotics, the majority of studies listed atrial fibrillation as the most common reason for anticoagulation prior to the initial ICH, followed by prosthetic heart valve, venous thromboembolism, and previous ischemic stroke or myocardial infarction; patients with prosthetic heart valve were noted to be the most likely indication for resumption of antithrombotic agents following ICH [67, 87]. Of these indications, reinitiation of anticoagulation in atrial fibrillation was found to have the most significant benefit in mortality [87].

Which agent to resume

Arguably as difficult as the initial decision to resume an antithrombotic agent following ICH may be, the decision of what antithrombotic agent to resume and when is equally important. In the acute setting following ICH, the decision to initiate a temporary parenteral anticoagulant for DVT/PE prophylaxis has largely been agreed upon as safe, assuming there has been cessation of bleeding and stable hematoma volume on imaging [88]. In line with this, current American guidelines support the initiation of prophylactic LMWH or unfractionated heparin in patients at risk of DVT/PE between day 1 and 4 from ICH onset [4]. Furthermore, in patients that develop a proximal DVT or non-fatal PE in the acute period following an ICH and do not receive therapeutic anticoagulation, the risk of fatal PE is significantly increased [89].

In patients with prosthetic heart valves and valvular atrial fibrillation, there is only one guideline based option for anticoagulation, VKAs. While multiple

retrospective studies and meta-analysis have suggested that VKAs are safe to resume following an ICH, medication compliance and routine monitoring is essential, thus resumption should be considered on a patient to patient basis. Patients that maintained a well-controlled INR following VKA resumption were found to have less major bleeding and thromboembolism compared with patient not taking any anticoagulant [72]. Inversely, patients with supratherapeutic INRs experienced a higher incidence of ICH and as expected, patients who were maintained at a target INR lower than guideline recommendations were at higher risk for thromboembolism [90]. The timing of anticoagulant initiation is also of particular importance in this patient population given their increased risk of thromboembolic events. With this in mind, it has been suggested that VKAs be resumed at 2 weeks after the onset of ICH, and possibly earlier if the hematoma volume is small and the etiology treated [72, 91]. However, an association was found between early VKA initiation and increased ICH in patient that resumed treatment sooner than 10 days from onset [92].

For all other indications necessitating long-term anticoagulation, there are a number of approved anticoagulants available and even less consensuses on when they should be initiated. Considering the majority of research on this topic focuses on resuming treatment with VKAs and patients with previous ICH were excluded from the NOAC trials, little is known about the outcomes of patients resumed on NOACs. As suggested during their initial clinical trials, ICH associated with NOACs seem to be less severe than that VKAs, with smaller initial hematoma volumes, less hematoma expansion, and better functional outcomes [93, 94]. Additionally, a recently published article suggests that patients that resumed a NOAC verse warfarin following ICH had a lower incidence of both ischemic stroke and recurrent ICH during the first year of treatment [71]. Furthermore, the availability of rapid, agent specific, anticoagulant reversal suggests NOACs may be the optimal choice for anticoagulation resumption; however, the question of when still remains. The reviewed literature suggests resuming anticoagulation between 3 days and 30 weeks post-ICH [95].

Regarding antiplatelet use following ICH, some consensus exists. In patients who were taking APT for primary prevention of coronary or ischemic cerebrovascular disease, there is no clear indication to resume antiplatelet therapy [96–98]. Prior to 2019, there was limited data on the risks of resumption of antithrombotics in patients with prior intracerebral hemorrhage [99]. With recent data, as demonstrated in the RESTART trial, resuming antiplatelet at a median of 2.5 months did not increase the risk of intracranial hemorrhage [73••].

Alternatives to antithrombotics

For patients with atrial fibrillation who are high risk of bleeding, non-pharmacological management may be considered. Anticoagulation treatment in a patient with recurrent bleeding, excess risk of falling, or thrombocytopenia poses a high risk of intracranial and systemic hemorrhage. The left atrial appendage (LAA) is a common location for thrombus formation, accounting for nearly 90% of the presumed origin of thrombi in patients with atrial fibrillation, and therefore procedures like amputation, ligation, or occlusion of this area have been shown to reduce thromboembolic risk [100].

The WATCHMAN device was studied in two randomized trials, PROTECT AF and PREVAIL, which demonstrated the efficacy of percutaneous closure of the left atrial appendage with 40% relative risk reduction of strokes and cardiovascular events [101, 102]. This device is a self-expanding, nickel titanium-framed structure which comes in various diameters to fit different appendage sizes. Complications from device implantation have decreased from 8.7 to 4.5% as operators become more experienced [103]. Another endovascular device is the Amplatzer Cardiac Plug device (Amulet) that has been used in European countries, but is not yet FDA approved for use within the USA. Currently, the Amulet IDE Trial will be the first randomized head-to-head trial between the WATCHMAN device and AMPLATZER Amulet device [103]. Both devices have shown similar annual stroke risk in retrospective studies [104]. Currently, patients that benefit from the WATCHMAN device require short-term anticoagulation; however, there is some data that antiplatelet therapy may be used in patients that are ineligible for anticoagulation. The ASAP study concluded that the WATCHMAN device could safely be implanted without warfarin transition and instead use antiplatelet therapy for 6 months [105].

Another FDA approved device is the LARIAT system which consists of percutaneous suture ligation of the left atrial appendage with pericardial and trans-septal access [106]. A study that included 154 patients reported a < 5-mm residual leak in 94%, major bleeding in 9%, peri-procedural pericardial effusion in 16%, and left atrium thrombus in 4.8% [107].

Surgical exclusion of the left atrial appendage can be performed endocardially or epicardially. The procedure can include resection, ligation, or stapling and can be performed during cardiothoracic surgery or thoracoscopically [108]. Meta-analysis of cases has shown reduction in neurological events including stroke [109].

Catheter ablation is a procedure performed for patients with symptomatic atrial fibrillation. However, atrial fibrillation is reported to recur in 20 to 40% of patients post procedure [110]. This procedure should not be considered as a cure of atrial fibrillation but rather for symptomatic treatment. The recent CABANA trial showed no significant reduction of strokes or deaths in patients treated with catheter ablation compared to medical therapy [111].

Finally, another cohort of patients that may particularly benefit from LAA closure devices are patients with atrial fibrillation and cerebral microhemorrhages noted on brain MRI. Cerebral microbleeds in cortical areas are common in patients with cerebral amyloid angiopathy. These findings have a higher risk for recurrent intracranial hemorrhage. The CROMIS-2 was an observational prospective study that found that therapeutic anticoagulation had 3 times higher risk for symptomatic ICH in patients who had atrial fibrillation, recent stroke/TIA, and microbleeds vs those who did not have microbleeds [112].

Conclusion

While thorough review of observational retrospective studies can assist in the management of patients necessitating antithrombotic therapy following ICH, high-quality evidence regarding this decision as well as the optimal timing for resumption of these agents is better addressed by randomized clinical trials. The most robust data comes from the investigators of RESTART, a PROBE design trial in which the authors concluded that the risk of recurrent ICH is small and

likely exceeded by the benefits of antiplatelet therapy in the secondary prevention of vascular occlusive disease [73••]. The decision for anticoagulant resumption still remains unanswered, for which randomized controlled trials are needed to better assess risks and benefits for recurrent ICH.

Compliance with Ethical Standards

Conflict of Interest

Christian E. Cajavilca, Destiny Hooper, and Rajeel Imran each declare no potential conflicts of interest.
Rajan R. Gadhia reports personal fees from Abbott Pharmaceuticals for speaking for PFO Closure.

Human and Animal Rights and Informed Consent

This article does not contain any studies with human or animal subjects performed by any of the authors.

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- •• Of major importance

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