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Thrombotic and Hemorrhagic Risk Following Cerebral Stent Placement

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Introduction

Antiplatelet therapy and flow diversion stents Aneurysms carry a high burden in the United States with an estimated six and a half million Americans living with an unruptured Aneurysm [1]. For these patients, the rate on rupture has been estimated to be 6-10/100,000 patients with a high fatality of 30-40% [2]. Thrombosis is common as one-third of Americans over the age of 40 are following some form of anti-platelet therapy to both reduce thrombotic risk and improve blood flow [3]. Patients who are on antiplatelet therapy experience the benefits of an overall reduced risk of thrombosis in normal vascular flow [4]. There are risks with antiplatelet therapy as these patients have an overall higher risk of bleeding [5]. This risk has been deemed necessary in some cases as there are a few procedures that require antiplatelet therapy in the post-operative setting. One of these procedures is cerebrovascular stent placement. These patients are generally prescribed a dual anti-platelet therapy (DAPT) regimen after stent placement to minimize the thrombotic risk. Recent research continues to expand upon the role of antiplatelet therapy in patients after placement of flow diversion stents, a procedure done to divert blood flow away from an aneurysm to decrease the chance of rupture While antiplatelet therapy can mitigate the risk of thrombosis, DAPT also leads to an increased risk of cerebral hemorrhage, a significant risk given that stents are often put in because an aneurysm is already present. As our understanding of the role of antiplanet therapy continues to grow, it is necessary to reevaluate how we manage patients post stent placement to balance the risks of thrombosis and hemorrhage [6]. Hemorrhagic and thrombotic complications with flow diversion stents. Flow diversion stents are an excellent therapy for management in select aneurysms. Moreover, the use of stents as a primary or adjuvant treatment for ischemic cerebrovascular diseases or cerebral aneurysms is rapidly increasing [7]. Stents are a way of both treating cerebral diseases as well as being a tool in treating difficult brain aneurysms [8]. Following stent placement, current standard of care is with DAPT, commonly employing drugs such as aspirin with clopidogrel, prasugrel, or ticagrelor [9], with the duration of therapy lasting anywhere from six to twelve months [10]. Patients are placed on DAPT because one of the major risks of stent placement is in-stent thrombosis.

These thrombi are associated with occlusion causing high mortality and morbidity rates [11,12]. Thrombotic events after stent placement are also not uncommon. Reports show that thrombotic complications occur anywhere from 2% to 9% following the placement of a cerebral stent [13,14]. What makes treating and predicting thrombotic episodes following stent placement problematic is the wide variety of presentations and onset of thrombi. These events can be acute, subacute, or delayed [15]. Prognosis of these events is highly variable and dependent on a host of factors including location of occluded blood vessel, the status of collateral circulation, and timely revascularization [16]. The way of reducing the risk of these events after stent placement is with anticoagulation therapy, but as stated, these medications come with their own hemorrhagic risks. Not only does DAPT increase the incidence of hemorrhages, but they can also increase the severity of them [17,18], particularly within the first three months [19]. The increased risk of bleeding combined with the severity means patients must take on a great risk when undergoing stent placement as, to date, there are not many screening procedures or alternative antiplatelet regimens for physicians to follow. The literature is unclear about the anticoagulation benefit when compared to the risks for elderly populations. Some studies have suggested that the anticoagulation benefit provided by DAPT is completely offset by its simultaneous increased risk of hemorrhage [20].

While there are certainly significant risks with cerebral stent placement, it still is widely used and the stroke and death rates in patients who have had a stent placed when compared to those who followed a natural course of their disease is considerably lower [21]. Stent placement is also a common procedure with upwards of one million Americans undergoing a stent placement each year [22]. With the American population continuing to age, it is likely that more and more people will need a stent placed as the effects of aging becomes more and more prominent. Because of this, it is necessary to both understand the biology behind the occurrence of thrombosis after stent placement, as well. as identifying individuals who are at high risk for developing a hemorrhage while on DAPT following cerebral stent placement.

Modeling Cerebral Blood Flow

Considerations in patient management There are multiple distinguishing characteristics of the cerebral vasculature that provide relatively unique hemodynamic considerations that must be considered within the scope of diagnostics and interventions, both surgically and medically. In general, the volume and variability of cerebral blood flow is a key factor that has physiological, and in some cases pathological, ramifications. Blood flow is tightly regulated to meet the metabolic demands of the brain. In an adult, cerebral blood flow generally makes up roughly 15-20% of the cardiac output, and excess blood flow can lead to raised intracranial pressure (ICP) and damage to the brain [24]. Irregular geometry between different commuting branches, such as in the circle of Willis, high pressure sensitivity, and relatively high flow rate, poses the inherent risk of embolisms mediated occlusion in cerebral arteries, and the formation of aneurysms [25], which may result in ischemic and hemorrhagic strokes. The cerebral blood flow is tightly regulated to maintain a constant supply of oxygen and nutrients to the brain chiefly through a combination of neural control and autoregulation. The former, neural control involves both the sympathetic and parasympathetic division of nervous system [26]. The sympathetic nervous system causes vasoconstriction of cerebral blood vessels, which can increase blood pressure and reduce cerebral blood flow, while the parasympathetic nervous system cause vasodilation of cerebral blood vessels, which can decrease blood pressure and blood flow [27]. Conversely, autoregulation of the cerebral vasculature responds directly through a variety of mechanisms [28]. All of which encompass a direct baroreflex. Like with the rest of the circulatory system, as pressure increases, vessels constrict; however, rather than purely relying on intravascular pressure, autoregulation of cerebral vasculature relies on changes in cerebral perfusion pressure (CPP), which is the difference between mean arterial pressure (MAP) and ICP [29]. For this reason, maintaining an appropriate CPP is critical in managing patients with intracranial pathology, including traumatic brain injury [30]. In addition to autoregulation and Neural control, metabolic activity and carbon dioxide level have a notable effect on cerebral blood flow. Specifically, increased carbon dioxide levels and increased metabolic activity induce vasodilation [31]. In terms of modeling, these all represent non-linear systems and therefore require more complicated analysis and pose more difficulty to accurately simulate [32]. Cerebral anatomy flow vulnerabilities Anatomically, the venous portion of the cerebral vascular system contains the cerebral sinuses that are distinct in shape, being formed by the dura mater [33]. The veins in cranium and in the surrounding structures notably lack valves allowing for bidirectional communication. This poses two main vulnerabilities: the risk of thromboembolism formation, which may lead to an ischemic attack, or infection via that can be directly introduced by the local vasculature, most infamously via the ophthalmic veins in the colloquially named “Danger Triangle” [34,36]. Further, the cavernous sinus holds the unique position of being the only venous structure penetrated by both a nerve (CN VI) and an artery (the internal carotid artery) [37]. Physiologically, this means that thrombosis within this area can lead to CN VI palsy as well as partial or complete occlusion of the cavernous segment of the adjacent internal carotid artery, and subsequent stroke. However, in a general sense, the cerebral vasculature follows similar hemodynamics to the rest of the body and can be modeled using similar parameters. Estimations of blood flow can be attained through numerical fluid dynamic models that follow Navier-Stokes dynamics [38]. However, basic closed form models such as the Wind Kessel model, fail to account for the non-linear flow resistance that occurs in cerebral vasculature [39]. This added level of complexity has pushed computational models of cerebral blood flow towards numerical solutions 39 and in vitro applications of fluid dynamic simulations [40]. Luckily, with advancements in computational power and finiteelementmultiphysics modeling, complex numerical solutions are attainable as an effective and bio-accurate model of cerebral hemodynamics [41] as shown in figure 1. It should be noted when developing such a model for the intracranial space, special attention needs to be paid to irregular structures such as the Circle of Willis and the cavernous sinus, the dramatic effects that regulation plays on local blood pressure, and geometric features of the cerebral venous sinus systems as well as the changes in viscosity that occurs due to the drainage of cerebrospinal fluid. Additionally, complex network-based models have started to appear to capture and effectively represent this complexity [42]. The flow dynamics of the cerebral venous system make it a unique environment and as will be discussed, special attention must be given when trying to mitigate thrombotic risk in this area of the vasculature (Figure 1). Exemplar simulation of blood flow through the Circle of Willis as adapted from Kim et al. [43]

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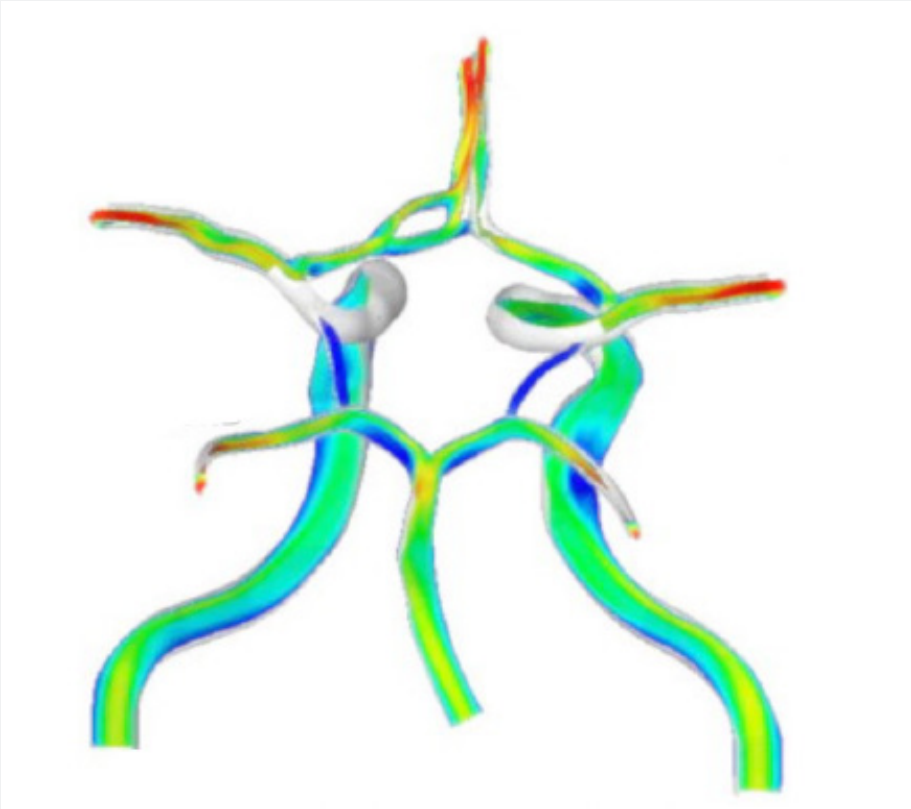

Figure 1: Exemplar simulation of blood flow through the Circle of Willis as adapted from Kim et al. 2006 (43).

Thrombotic Complications with Stent Placement

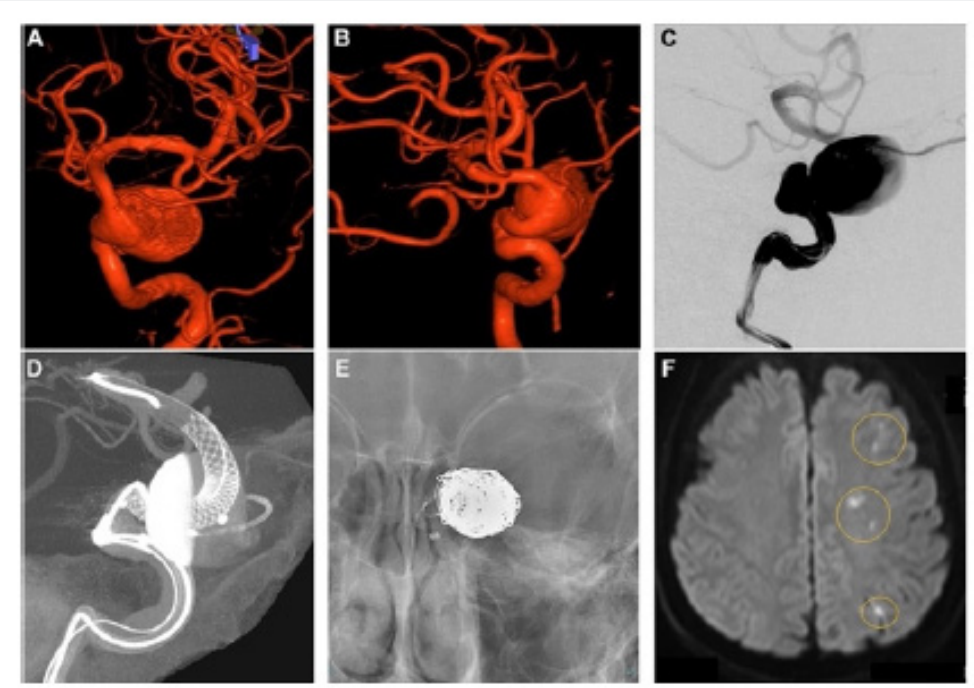

Figure 2: Example patient case exhibiting effects of perioperative thromboembolic events following Pipeline Embolization Device (PED) placement for intracranial aneurysm treatment.

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Procedure Correlations with Increased Thrombosis As previously described above, serious complications such as thrombotic events, can occur following flow diversion techniques via stent placement without antiplatelet therapy. Indeed, it is well-established that there exists a risk of thromboembolic events when surgically managing intracranial aneurysms via endovascular means, a risk shared by both coil embolism and stent flow diversion. These complications necessitate the utmost care during evaluation of device placement in patients, as they can potentially result in symptomatic ischemic strokes and brain lesions if not detected and managed accordingly (Figure 2) [44,45]. Thromboembolic events comprise the most common complications associated with coil embolism, at a rate determined to be approximately 10.9% of treated patients [46], with multiple studies describing an incidence rate range of approximately 2% to 9% of patients [47-53]. Further adding to the severity of these complications, the same study additionally attributed thromboembolic events to be the most associated postoperative complication with permanent neurological deficits because of ischemic stroke [46]. In a similar vein, thromboembolic events occur.

with almost identical frequency with the use of the Pipeline Embolization Device (PED) [49,54]. In one study, it was determined that these thromboembolic complications occurred more frequently immediately following the PED placement (6.5% of patients), but their rate of occurrence substantially decreases over time, well beyond the point of the cessation of antiplatelet therapy [52]. Despite the relatively low rate of incidence, the authors caution that long-term surveillance is still required in patients to further prevent additional thromboembolic events from occurring [52]. Factors Leading to Increased Thrombotic Risk On a grand scale, exact peri-operative conditions that potentially give rise to thromboembolic events remain to be completely elucidated. One study conducted by Tan et al. performed a multivariate analysis on PED placement outcomes in seventy-four patients to determine risk factors associated with thromboembolic events [53]. In this study, it was determined that PED placement procedure times exceeding 116 minutes and multiple placements of PED devices are significantly associated with the development of peri-operative thromboembolic events [53]. In essence, these results corroborate practical findings associated with many endovascular procedures. Namely, a longer procedural time correlates with a longer catheter placement and manipulation, both of which can activate platelet action and cause thrombosis. Furthermore, more complex cases that require longer procedural time may additionally contribute. to the higher risk of developing thrombosis. In addition to this, multiple PED placements increase the surface area of which platelets can activate upon, thus increasing the risk of thromboembolic events [53]. It is important to note that thromboembolic events associated with flow diversion include the phenomena of both within-stent thrombus formations and distal embolization [45]. Regardless of the manifestation, it is thought that the formation of the events is resultant of the physical nature of the flow diversion devices [55]. In particular, the PED, comprised of platinum tungsten and cobalt chromium, potentially provides sufficient metallic surface area to inadvertently activate thrombosis more than the intended goal [56]. Like studies related to coronary artery stents, it is thought that excessive thrombogenesis may be related to multiple factors related to the coagulation cascade. For example, possibilities include metal exposure to subendothelial tissue that results in activation of the extrinsic coagulation cascade, poor responsive inhibition to the activation of platelets, or intrinsic coagulation cascade activation due to lowered shear stress secondary to reduced blood flow [57]. In combination, these factors can lead to inappropriate amounts of thrombogenesis, thus causing the formation of thromboembolic events following PED placement. (Figure 2). Example patient case exhibiting effects of perioperative thromboembolic events following Pipeline Embolization Device (PED) placement for intracranial aneurysm treatment. A, B,C. Images depicting the original intracranial aneurysm formed on the left internal carotid artery. D. The deployed PED device at the location of the neck of the aneurysm to achieve flow diversion. E. Adjuvant coil placement. F. Magnetic resonance image (MRI), taken one day post-operation, depicting asymptomatic frontoparietal lesions resultant of perioperative thromboembolism [45]. Variations in Dual Antiplatelet Therapy Response In addition to vasculature-based pathophysiology, it is also believed that variable patient responses to DAPT during treatment contribute to thromboembolism [53,56]. As mentioned previously, DAPT is a combination of aspirin and another antiplatelet medication, commonly clopidogrel. The variability of the treatment is largely a consequence of the variability observed in the pharmacokinetic and metabolic profile of the second medications [58]. Further complicating this situation is the fact that there lacks a standard protocol for this antiplatelet medication during PED deployment [56]. Nevertheless, point-of-care platelet function tests, such as Verify Now, that measure P2Y12 (ADP receptor) inhibition are commonly used as tools for risk assessment for developing thromboembolic events [59]. Measured in P2Y12 reaction units (PRU), these tests can quantifiably group patients into low-responders and high-responders to clopidogrel. In one study conducted by Delgado Almandoz et al. [60] it was determined that inadequate (PRU < 60) preoperative PRU values were significantly associated with thromboembolic events 60. It is recommended by the authors that patients are maintained within a range between [60] to 240 PRU before undergoing PED placement, and patients outside of this range should be rescheduled until the target PRU range is achieved [60]. Thrombotic risks are evident with sent placement and their variability can make them difficult to manage. Identifying markers and patients who are at higher risk of thrombus may allow a more personalized medicinal approach to DAPT therapy that can lead to better outcomes and reduced adverse events.

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Hemorrhagic Complications with Antiplatelet Therapy

Rational of Dual Antiplatelet Therapy As stated above, DAPT is the current standard following flow diversion stent placement. While the use of antiplatelet agents carries hemorrhagic risk, especially in patients with intracranial aneurysms, DAPT is considered mandatory in the context of flow diversion stenting [61]. Patients with unruptured intracranial aneurysms are often placed on aspirin alone for anti-inflammatory effects. This treatment is only associated with a small, short-term risk of hemorrhage and is associated with decreased risk of aneurysm rupture with continued, long-term treatment [2]. In contrast, DAPT carries a 40-50% increase in hemorrhage risk when compared treatment with aspirin alone [62]. Flow diversion stenting procedures often involve use of anticoagulants, such as heparin, in conjunction with DAPT in the perioperative period. Use of anticoagulant agents in patients at risk of stroke is also associated with a 7-10-fold increase in risk of intracranial hemorrhage [19]. The use of these drugs in cases that require flow diversion all contribute. to the risk of hemorrhagic complications in patients with unruptured aneurysms. Their necessity complicates the use of flow diverters in cases of acute aneurysm rupture. Risks involved with flow diversion stent placement include hemorrhage, both intraparenchymal and subarachnoid [61]. One institutional study analyzed outcomes of 47 patients with anterior circulation aneurysms who were. treated with flow diversion. Four of these patients experienced intraparenchymal hemorrhage ipsilateral and anatomically distal to the treated aneurysm. These hemorrhagic events all were likely directly related to the procedure, as they occurred within hours or days postoperatively and were in the vascular distribution of the parent artery. The rate of intraparenchymal hemorrhage in This cohort is 8.5% (4 out of 47 patients) compared to the annual risk of 1.1%-1.8% in patients undergoing DAPT for stroke prevention [63]. These hemorrhagic events did notepaper to have an association with the type of aneurysm nor with a complication during the procedure. The increased incidence compared to patients solely on DAPT further indicates the risk of hemorrhage as a complication of flow diversion. While the above example demonstrates the increased risk of hemorrhage post-flow diversion, other studies have suggested that this risk may not be quite as high. One meta-analysis found that the rate of subarachnoid hemorrhage and the rate of intraparenchymal hemorrhage were both 3% after deployment of flow diversion stents [64]. In a multicenter trial of endovascular treatment for intracranial aneurysms, delayed.

Intraparenchymal hemorrhage occurred at a rate of 2.4% and was a much more common complication compared to delayed aneurysm rupture [65]. Additional studies found that the rate of intraparenchymal hemorrhage after flow diversion was 1.1%, in line with the annual risk in patients on DAPT alone and significantly lower than the rate of 8.5% in the study [66]. Though there is some conflicting data regarding the risk of hemorrhage after use of flow diversion in patients with unruptured aneurysm, it is generally accepted that the procedure comes with enough risk to warrant concern, but not enough to discourage use of DAPT in fear of thrombotic complications (Figure 3). Hematoma following flow diversion in right ICA, adapted from Cruz et al63 A, right supraglenoid ICA aneurysm before flow diversion B, right ICA AP angiogram 3 months later, with persistent early aneurysm filling (indicatedby asterisk). C, angiogram after deployment of 2 more flow diversions to reduce aneurysm filling. D, noncontract CT 1 day later shows acute right lobar hematoma. The mechanism of delayed hemorrhage remains unclear, but a few hypotheses do exist. Some propose that the reduction in arterial compliance at the site of flow diversion could lead to increased pressure distal to the aneurysm [63]. Additionally, it is possible that thrombus induced autolysis could serve as a mechanism for delayed aneurysm rupture after flow diversion procedures, as thrombosis is an important step in occlusion of the treated aneurysm [67]. Consideration with Antiplatelet Protocols With regards to the drugs used for DAPT, most studies have used aspirin and clopidogrel daily leading up to stent placement and for several months following the procedure [61]. Stopping of clopidogrel was often done as a measure to prevent hemorrhagic complications, but in patients with flow diversion stents, thrombotic complications were generally more severe and often occurred with premature termination of clopidogrel administration. Thus, a minimum of 6 months of DAPT is. recommended, with clopidogrel only being discontinued if angiography indicates no stenosis of the artery at 6-month follow up [68]. In the event of hemorrhage, there is a lack of consensus on DAPT management. While clopidogrel is generally stopped, aspirin is often continued to prevent thrombosis, which remains an equally significant clinically complication of flow diversion [65]. This need for DAPT further illustrates the complicated nature of flow diversion in acute aneurysm rupture, which is discussed much less here relative to unruptured aneurysm treatment [68]. Clopidogrel is generally accepted as the secondary agent in DAPT in most studies, though it is subject to “antiplatelet resistance” in a significant proportion of patients. Ticagrelor and prasugrel are alternatives to clopidogrel used to prevent DAPT resistance in some patients [11]. One concern with use of ticagrelor and prasugrel, which may be subject to less antiplatelet resistance in some patients, is an increased incidence of hemorrhage. However, multiple studies demonstrated that DAPT regimens using ticagrelor were associated with better survival and were not associated with higher hemorrhagic risk compared with regimens using clopidogrel [69 70].

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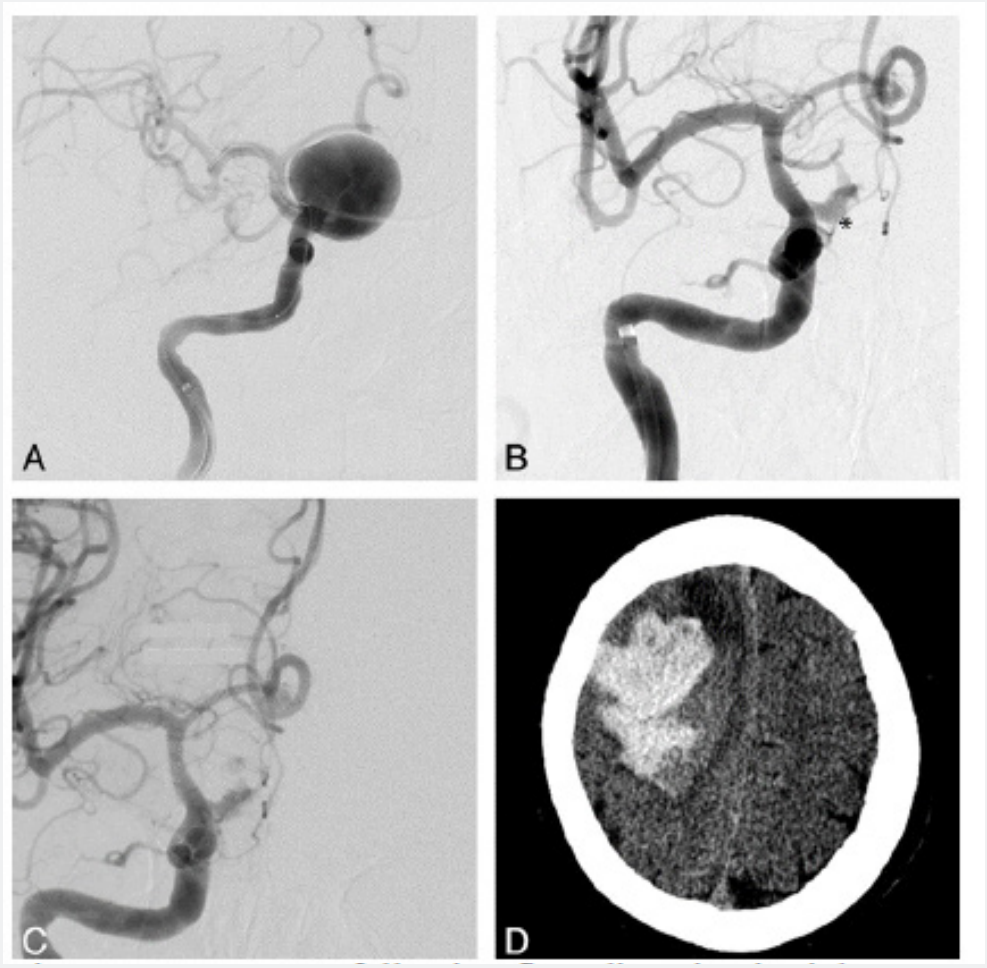

Figure 3: Hematoma following flow diversion in right ICA, adapted from Cruz et al63 A, right supraglenoid ICA aneurysm before flow diversion B, right ICA AP angiogram 3 months later, with persistent early aneurysm filling (indicated by asterisk). C, angiogram after deployment of 2 more flow diversions to reduce aneurysm filling.

Coming into focus in recent research is the use of platelet response assays, which can discern patients who are DAPT hypo responders and hyper responders, which is relevant to the antiplatelet resistance already mentioned. Specific to hemorrhagic complications of endovascular aneurysm treatment, DAPT hyper responders have been shown to be at increased risk of delayed hemorrhage post procedure [11,71]. The notion of using an individual patient's platelet response to adjust DAPT has been explored in some research, and its benefits are currently under scrutiny by further studies. Nevertheless, DAPT remains the standard of care following stent placement and the hemorrhagic risk remains. The results of future studies on individualized DAPT therapy should be considered and a possible safer alternative for some patients.

Thrombus Formation and Potential Targets

Pathological Cerebral Flow Cerebral blood flow (CBF) is typically tightly regulated, but its normal dynamics can be disrupted by pathophysiology. Strokes, aneurysms, vertebral stenosis, carotid stenosis, and vascular malformations are examples of cerebrovascular diseases associated with abnormal CBF [72]. Thrombus formation and platelet aggregation can play an important role in cerebrovascular diseases by disrupting normal CBF. Thrombus formation begins when damaged blood vessels express the von-Willebrand factor to activate platelets. Activated platelets then activate phospholipase C (PLC), which hydrolyzes bonds in inositol trisphosphate (IP3) and 1,2-diacylglycerol (DAG). This leads to a rise in intracellular calcium levels and the subsequent release of arachidonic acid. Arachidonic acid is converted to prostaglandin products with the enzymes COX1 and COX2. The prostaglandins become pro-aggregatory molecules, such as thromboxane A2 (TXA2), which further activate more platelets [73]. In cerebrovascular disease, antiplatelet therapy is used to increase CBF. Common antiplatelet drugs include acetylsalicylic acid (primarily aspirin), clopidogrel, Aggrenox, and Glib-IIIa receptor antagonists such as ticagrelor [74]. Each of these medications affects distinct steps in thrombus formation, has different ranges of benefits on CBF, and has various

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long-term consequences. Aspirin is the most used antiplatelet medication to increase CBF, especially in the case of ischemic stroke [74]. Aspirin works by acetylating the active site of COX1 to prevent the conversion of arachidonic acid to prostaglandins and ultimately block the production of TXA2 [75]. Paradoxically, many studies have found that aspirin reduces CBF and increases the risk of ischemic stroke when used in low-risk individuals [76]. There are also other aspects of aspirin that make it difficult to use in patients with cerebrovascular disease. For example, 95% of TXA2 production must be inhibited by aspirin to successfully inhibit platelet aggregation [75]. Aspirin also has a very short half-life in vivo ranging between 2-3 hours, making it difficult to successfully inhibit TXA2 production without unintended side effects. Around one-quarter of patients prescribed aspirin are also resistant to the aspirin and show no significant benefit from it [77]. For these reasons, aspirin alone is often not used to treat cerebrovascular disease; it is typically combined with other antiplatelet agents. Combination Antiplatelet Therapy effects on CBF One antiplatelet drug used in combination with aspirin is clopidogrel. Clopidogrel is a pro-drug activated by cytochrome P450 in the liver; therefore, it is much slower acting than aspirin and can take 3-7 days to have an effect. Once clopidogrel is activated, it binds to an ADP receptor on platelet membranes, which prevents the ADP-binding and the subsequent activation of platelets [75]. Clopidogrel increases cerebral blood flow, but its effects are minimal. Clopidogrel and aspirin combined have a much more significant effect in increasing CBF without major differences in side effects [78]. Various studies have assessed the impact of the impacts of these combined drugs and have found a wide range of results, which are outlined in table 1 below. While the exact effects of aspirin and clopidogrel are debated, there are other antiplatelet therapies used to treat abnormal CBF. For instance, GPIIb-IIIa inhibitors inhibit the binding of the von-Willebrand factor, hindering platelet activation. A study by Kawano et al. reviewed the impact of ME3277, a GPIIb-IIIa inhibitor, in resolving middle cerebral artery occlusion. The study found that ME3277 reduced thrombus formation and improved CBF significantly, especially when compared to aspirin, but more research needs to be done regarding its clinical utility [79].

Table 1: Summaries of clinical trials exploring the role of dual antiplatelet therapy with aspirin and clopidogrel in stroke.

Clinical Trial	Patients (n)	Patient Demographics	Groups	Endpoint	Outcome
ACTIVE A	7,554	Atrial fibrillation and increased risk of stroke	A) Dual therapy - 75 mg clopidogrel/d + 75-100 mg aspirin/d B) Monotherapy - 75-100mg aspirin/d	Major vascular event	Dual therapy was found to be better than monotherapy
CHANCE	5,170	Chinese cohort who suffered from transient ischemic attack or minor ischemic stroke within 24 hours of enrollment	A) Dual therapy - 75-300 mg loading dose aspirin followed by 75 mg aspirin/d from days 2 to 21 and 300 mg loading dose clopidogrel followed by 75 mg clopidogrel/d from days 2 to clopidogrel/d from days 2 to 90 B) Monotherapy - 75-300 mg loading dose aspirin followed by 75 mg aspirin/d from days 2 to 90	Ischemic or hemorrhagic stroke	Dual therapy was found to be better than monotherapy
CHARISMA	15,603	Atherothrombotic risk factors, coronary disease, cerebrovascular disease, or peripheral artery disease	A) Dual therapy - 75 mg clopidogrel/d + 75-162 mg aspirin/d B) Monotherapy - 75-162 mg aspirin/d	MI, stroke, or death by cardiovascular causes	No difference between dual therapy and monotherapy
MATCH	7,599	Transient ischemic attack/ischemic stroke with risk factors for recurrence	A) Dual therapy - 75 mg aspirin/d and 75 mg clopidogrel/d B) Monotherapy - 75 mg aspirin/d	Ischemic stroke, myocardial infarction, or vascular death	Increased bleeding (major or minor) in dual therapy group
SPS3	3,020	Lacunar stroke within 180 days of enrollment	A) Dual therapy - 325 mg aspirin/d + 75 mg clopidogrel/d B) Monotherapy - 325 mg aspirin/d	Recurrent stroke (ischemic or hemorrhagic)	Increased rate of death, extracranial bleeding, and GI bleeding in dual therapy group

(Adapted from 75)

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Another antiplatelet medication that was recently investigated is Aggrenox, a drug that combines aspirin and dipyridamole. Dipyridamole increases intracellular cAMP levels, prevents the breakdown of adenosine, and amplifies the effects of proteinoids, each of which works to decrease platelet activation [75]. Aggrenox has proven effective in secondary stroke prevention [80], but more clinical trials are needed to provide clear recommendations for Aggrenox use. Antiplatelets have significantly improved clinical outcomes in patients with cerebrovascular disease, notably stroke. Between 1997 and 2007, antithrombotic agents were increasingly used as an effective therapy for stroke, decreasing the stroke death rate from 44.8% to 14.7% [72]. Antiplatelet therapy has also increased health-related quality of life for patients in chronic stages of ischemic or hemorrhagic stroke [81]. Many clinical trials have assessed the effects of specific antiplatelet therapy drugs, such as aspirin, but more research is needed to fully understand the impacts of combination therapy on cerebral flow.

Proposed Antiplatelet Regimen

The current standard of care to prevent the development of in-stent thrombosis following endovascular stenting favors a standard regimen of aspirin plus a single P2Y12 inhibitor (usually clopidogrel). While there are variations among institutions for how to load these medications, as well as varying length of treatment, standard regimen based on the original trials of the pipeline device is generally as follows: patients are pre-treated up to 10 days pre-procedure with daily low-dose aspirin (81mg) and a standard dose of clopidogrel (75mg). Following the procedure, patients are then placed on an increased dose of daily aspirin (100mg) for six months or more, with continued use of clopidogrel (75mg) for usually a month or greater [82]. A later pipeline study used a higher loading dose of aspirin 325mg for 2 days pre-procedure, as well as either clopidogrel (75mg) for a week pre-procedure versus a single 600 mg loading the day before stenting. This was then followed by 3 months of standard clopidogrel (75mg) and high-dose aspirin (325mg) for at least 6 months [83]. Despite the use of anti-platelet therapy following stent placement, up to 9% of patients may have ischemic complications, and part of this issue could be from poor individual patient response to agents like clopidogrel (however this remains controversial) [84,85]. Given that the literature shows that up to nearly one third of all patients that undergo flow-diversion have resistance to clopidogrel as measured on platelet function assay testing, newer studies have looked at the use of agents like ticagrelor as an alternative P2Y12 inhibitor, which reportedly does not have a known resistance rate [86]. Ticagrelor has its limitations, including twice-daily dosing (which may impede patient compliance), and is a reversible inhibitor, however, overall can serve as an effective alternative clopidogrel for patients that are resistant. Similarly, prasugrel therapy has been suggested as an alternative to poor clopidogrel responders, but also may have a higher risk of post-procedure hemorrhagic events [87]. There is no current literature consensus on what constitutes the most optimal DAPT regimen, especially given controversy over which patients even need platelet testing [85]. Additionally, there is the question of the efficacy of using both platelet reactivity unit testing alongside platelet thromboelastographic with platelet mapping, as the two testing methods have shown poor agreement in prior studies [88]. With these limitations in mind, an ideal DAPT regimen should likely attempt to tailor to individual patient response and would adjust dosing and medication choice respectively. An example regimen that tailors to individual patient response can be proposed as follows: patients should undergo pre-procedure loading with DAPT, for example with high-dose aspirin (325mg) and standard clopidogrel (75mg) daily for a week, followed by pre-procedure platelet function testing to assess for individual patient response. Using the Verify Now point-of-care platelet function assay as an example, should patients fall within the target PRU range of 70-150, they likely have good response and will have a lower chance of ischemic or hemorrhagic complications as per a retrospective analysis by Badih et al. [88] The PRU range in their study, however, was limited to a small subset of patients, and so a PRU range of 60-240 was generally felt to be a safe window to perform the procedure with the caveat that patients in this range may need follow-up testing to ensure that they stay within therapeutic ranges post-operatively, and that later agent change or dosing adjustments can be made to keep them in the therapeutic window if indicated. Additionally, platelet thromboelastographic with platelet mapping could be used as an alternative test. Should patients be hypo-responders to clopidogrel pre-procedure, they can be loaded with ticagrelor, followed by switching to ticagrelor or prasugrel as the P2Y12 inhibitor of choice post procedurally. Platelet testing assays should then be repeated post-procedure to ensure that they maintain adequate response, and all patients should be maintained on some DAPT regimen (based on what they respond appropriately to) of either high- or low dose aspirin daily for at least 6 months, as well as a P2Y12 inhibitor for at least 3 months [89,90].

Discussion and Conclusion

Flow diversion with intracranial stent placement is becoming an increasingly more common technique to secure unruptured aneurysms. There is consensus in the literature on the need for DAPT following stent placement, at least in the short term. The exact optimal pharmacotherapy and duration remain to be fleshed out in randomized control trials, and the moment, should likely be tailored to each patient on an individual basis to maximize benefits while reducing the risk of hemorrhagic consequences. Clopidogrel has been the standard drug of choice for physicians, but as highlighted, some patients have poor response to clopidogrel [84,85]. Continual use of Clopidogrel without individual patient considerations may put an unnecessary burden on patients and could lead to lower compliance. Further studies will need to look at other antiplatelet medications, such as Ticagrelor, and compare the efficacy and complication rate as compared to the current standard of care. As further studies also look at individualized

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DAPT regimens, special consideration should be given to patients who are known to be at a higher risk for hemorrhagic complications. Ultimately, as the field continues to progress, taking an individualized approach toward each patient's unique pharmacodynamic profile will likely be an important measure to lowering the complications associated with flow-diverting devices, while minimizing adverse drug related complications.

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