Role of Antiplatelet Therapy in Neurosurgery: Efficacy and Safety Profiles

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Review of Aspirin and Clopidogrel

It is vital to understand the pharmacokinetic profile of antiplatelet agents and the reason why patients take the agents. Knowing the reason for antiplatelet therapy helps to determine the risks of its discontinuation. A patient using antiplatelet therapy for primary or secondary prevention of vascular events will have a lower risk of vascular events than a patient who is using antiplatelet therapy to prevent stent thrombosis. Depending on how long it has been since stent placement, the risk of stent thrombosis may outweigh the risk of increased bleeding. Knowing the half-life of the drug and its metabolite(s) and the time required for platelet homeostasis to return after antiplatelet discontinuation is important. This information determines how far in advance to discontinue a drug prior to surgery. If there is still delayed platelet inhibition or pharmacologically active drug in a patient, they could still be at increased risk of bleeding despite having stopped the medication. Other studies have been dedicated solely to the pharmacokinetics of aspirin and clopidogrel and are widely available, and thus the intent of this chapter is to cover the important details that relate to the current surgery recommendations.

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Aspirin

The antiplatelet effect of aspirin results from the irreversible acetylation of an important serine moiety of cyclooxygenase (COX-1) on the platelet. This acetylation impairs the COX-1 mediated synthesis of thromboxane A_2, which is responsible for platelet aggregation and vasoconstriction [1]. Figure 6.1 depicts the mechanism of action of antiplatelet agents [2, 3]. Despite aspirin having a short terminal half-life of 0.4 h before being metabolized to salicylate, platelets are rapidly rendered unable to regenerate COX-1 and subsequently thromboxane A_2 [4, 5]. Although salicylate has a longer half-life than aspirin (2.1 h), it does not possess any inhibitory effects on platelet COX-1 [5, 6]. No antidote is available for aspirin because it binds irreversibly. Fresh platelets that have not been exposed to aspirin must be created to have functioning COX-1 and thromboxane A_2 activity. Although a platelet's life span is 7–10 days, some authors have claimed it may take 12–14 days for normal levels of platelet COX-1 and thromboxane A_2 to return [7, 8]. The mechanism proposed for the extended delay in normalization was that the freshly produced platelets were created from

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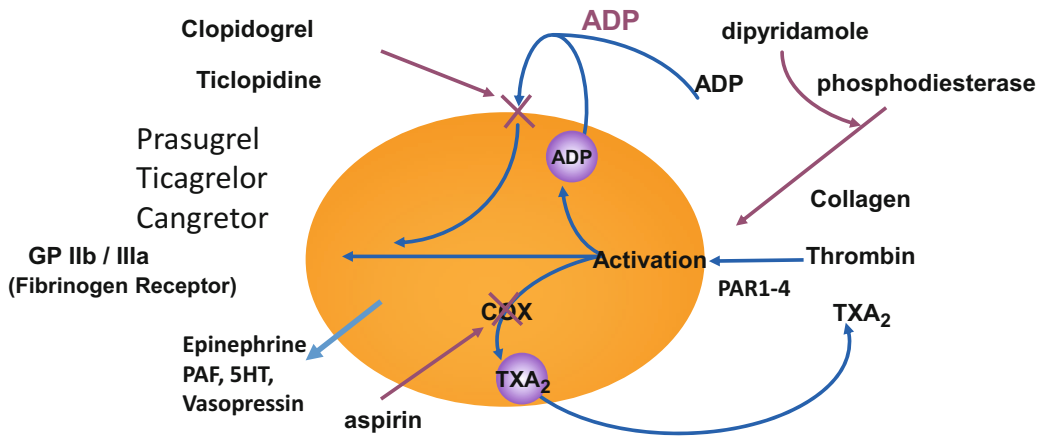

Fig. 6.1 Mechanism of action of antiplatelet agents

megakaryocytes with impaired COX-1 activity from prior aspirin exposure [7]. However, platelet aggregation recovers fully in 50 % of patients by day 3 and in 80 % of patients by day 4 [9]. Complete platelet function is achieved after approximately 7 days [8]. Recovery may have some variability between patients due to the dose ingested, bone marrow turnover, and the potential size of the platelet pool, determined by platelet count and patient size [10].

Clopidogrel

Clopidogrel is an oral, $P2Y_{12}$ receptor inhibitor. By irreversibly binding to the $P2Y_{12}$ receptor and modifying the adenosine diphosphate (ADP) receptor site, ADP is unable to bind, which prevents induction of platelet aggregation [11, 12]. Clopidogrel is a prodrug and requires hepatic activation to produce pharmacological activity. The antiplatelet efficacy is variable due to genetic variations in genes that are responsible for absorption and bio-activation of clopidogrel [13]. Maximum platelet aggregation inhibition of 40–60 % is achieved in 3–5 days [1]. Loading doses are often given to achieve therapeutic levels more rapidly [14]. Maximum platelet inhibition can be achieved within 6 h of a 300 mg loading dose [15]. Platelet inhibition can be seen within 2 h of ingestion [11]. Clopidogrel is concerning in surgery because some studies have reported carbon 14-labeled clopidogrel to have a half-life of >300 h at steady state [16]. However, the half-life of clopidogrel is roughly 6 h, and the active metabolite has a half-life of about 30 min [17]. Despite the concerning half-life of >300 h, normal platelet function returns after 7 days of discontinuation [18]. Similar to aspirin, there is no antidote for clopidogrel, which also binds irreversibly. A new pool of platelets must be created to replenish the platelets that have been irreversibly inhibited by clopidogrel. The week-long inhibition of platelet function can be problematic in patients who experience trauma or intracranial hemorrhage (ICH) because increased bleeding could potentially occur. Replenishing the platelet pool

with uninhibited platelets via platelet transfusions may be the only way to reduce excessive bleeding in emergency situations such as trauma or ICH.

Utility of Aspirin and Clopidogrel

Aspirin is used in both primary and secondary prevention of atherothrombotic vascular events, myocardial infarction (MI), stroke, and vascular death. However, the utility of aspirin in primary prevention has been questioned [19]. Clopidogrel is often used in conjunction with aspirin in patients at high risk for ischemic events [20]. Clopidogrel may also be used for patients with allergies or intolerances to aspirin. Aspirin and clopidogrel are also used for dual antiplatelet therapy (DAPT) after stent placement. The differing mechanisms of platelet inhibition provide synergy in helping to prevent stent thrombosis. The challenge in prescribing these medications lies in balancing their risks and benefits.

The vascular protection provided by antiplatelet therapy was clearly demonstrated in a 2002 meta-analysis of 287 studies in patients ($n = 135{,}000$) at high risk for occlusive vascular events [21]. Antiplatelet therapy reduced serious vascular events by 22 %, nonfatal MIs by 34 %, nonfatal stroke by 28 %, and vascular mortality by 15 %. Aspirin was the most commonly investigated drug in the meta-analysis. The authors concluded that aspirin in daily doses of 75–150 mg appeared to be as effective as larger doses of aspirin for long-term treatment. In addition, clopidogrel could be used as an effective alternative for patients who were unable to take aspirin.

Despite vascular protection benefits, antiplatelet therapy comes with risks. The increased risk of bleeding is worrisome with these agents, especially in the setting of neurosurgery where proper hemostasis is essential. One of the primary difficulties in determining the bleeding risk associated with low dose aspirin is the variable definition of "low dose" aspirin therapy. It has been defined as 75–162 mg daily in the CHARISMA trial [22], 50–325 mg daily by Berger et al. [23], 75–325 mg daily by Mills et al. [24], 75–150 mg daily by Rodríguez et al. [25], 75–100 mg daily by the American College of Chest Physicians [26], and 75 mg daily in the SALT trial [27]. Thus, great attention to detail must be used when assessing the risk-reducing benefits and bleeding risks associated with low dose aspirin.

A meta-analysis by Serebruany et al. [28] included 51 randomized, controlled trials of 338,191 patients and divided antiplatelet therapy into 6 groups based on drug and dose. The data showed there was no difference in Thrombolysis in Myocardial Infarction (TIMI) major bleeds between the aspirin <100 mg daily group (1.7 %, 95 % CI [1.4–1.9 %]) and the aspirin 100–325 mg daily group (1.7 %, 95 % CI [1.5–1.85 %]). There was an increase in TIMI major bleeds in the aspirin >325 mg daily group (2.5 %, 95 % CI [1.7–3.3 %]) vs. the aspirin 100–325 mg daily group (1.7 %, 95 % CI [1.5–1.85 %]), but no *P* value was calculated. When looking at total bleeds (both major and minor), aspirin <100 mg daily was the safest option (3.6 %, 95 % CI [3.3–3.9 %]). Aspirin 100–325 mg daily and aspirin >325 mg were much more problematic in regard to total bleeds (9.1 %, 95 % CI [8.7–9.4 %] and 9.9 %, 95 % CI [8.4–11.4 %], respectively). It appears there is no difference in major bleeding between aspirin <100 mg daily and aspirin 100–325 mg daily, while doses >325 mg daily may lead to increased bleeding. For all bleeds, aspirin <100 mg daily was the safest while 100–325 mg daily and >325 mg daily were similar for total bleeds. For neurosurgery patients who need to be on aspirin, less than 100 mg daily is likely the safest option.

The rates of bleeding for clopidogrel use were less clear in the Serebruany et al. meta-analysis. Major bleeds were recorded in patients taking thienopyridines—a major bleeding rate of 2.1 % (95 % CI [1.9–2.3 %]). For total bleeds, the rate of bleeding was 8.5 % (95 % CI [8.1–8.8 %]) [28]. No *P* values were reported between aspirin and clopidogrel. However, given the increase in both major and total bleeds, it appears reasonable to use aspirin over clopidogrel whenever possible especially when

one antiplatelet agent must be used for prevention of stent thrombosis during surgery.

Perioperative Use of Antiplatelet Agents

There are two primary concerns with antiplatelet therapy in the perioperative setting: continued use of antiplatelet agents during surgery could lead to increased bleeding during surgery and discontinuation of antiplatelet agents could result in the occurrence of vascular complications. A review by Korte et al. [29] reported that several studies showed an increase of bleeding and transfusion of blood products with the perioperative use of aspirin. However, there is a lack of studies that have investigated the use of aspirin in neurosurgery. A meta-analysis by Burger et al. [30] reported that aspirin at relatively higher doses possibly increased the risk of bleeding-related fatalities, and relatively "low-dose aspirin neither increases the level of the severity of bleeding complications nor the perioperative mortality because of bleeding complications." Palmer and colleagues reported that aspirin was not associated with any bleeding fatalities [31]. But they reported that the combination of such agents with certain pathologies may lead to an increased risk of postoperative hematomas. It is unclear if age, reason for first surgery, or other patient characteristics contributed to postoperative hematomas. Also, anticoagulants were not excluded, and it is unclear how many patients may have been on both anticoagulants and aspirin.

Suddenly discontinuing antiplatelet therapy can result in a rebound effect. There is a temporary period of increased thromboxane A_2 production and decreased fibrinolysis, which leads to increased prothrombotic activity [32–34]. A prospective study reported that patients who had recently discontinued aspirin, primarily for elective surgery, were responsible for 5.4 % of all patients admitted for acute coronary syndrome (ACS) [35]. The average time for ACS onset after aspirin withdrawal was 12 days. Recent aspirin withdrawers (patients who discontinued aspirin within 3 weeks prior to ACS) had significantly higher rates of death or myocardial infarction (21.9 % vs. 12.4 %, $P=0.04$) and bleeding complication (13.7 % vs. 5.9 %, $P=0.03$) than patients who discontinued aspirin earlier than 3 weeks prior to ACS. Retrospective studies have also seen increases in number of cardiovascular events ranging from 2.3 to 6.1 %. The timing from aspirin withdrawal and incidence of cardiovascular events was on average 8.5 days for ACS, 14.3 days for stroke, and 25.8 days for peripheral vascular events [36–38].

A meta-analysis of 50,279 patients taking aspirin for secondary prevention reported a threefold increase (OR = 3.14) in major cardiovascular events in aspirin withdrawers compared to those who remained on aspirin therapy [39]. The risk was even greater in patients with coronary stents (OR = 89.78). The average time from aspirin discontinuation to a thrombotic cardiovascular event was 10.7 days. The authors concluded that aspirin withdrawal in patients with ischemic heart disease or other apparent cardiovascular disease was associated with obvious, prognostically adverse consequences. They recommended only discontinuing aspirin therapy if the risk of bleeding far surpassed the risk of atherothrombotic consequences.

Clearly, there are risks associated with both the continued use of antiplatelet agents during surgery and the discontinuation of antiplatelets prior to surgery. Although it is likely that aspirin and other antiplatelet agents may lead to increased bleeding in neurosurgery, the real risk has not been determined. The high risk and consequences associated with excessive bleeding in a closed system have led researchers to rely on the results of continued aspirin use in other surgical studies. Guidelines for antiplatelet use in neurosurgery are also scarce. The guidelines for the perioperative use of antiplatelet agents typically come from The American College of Chest Physicians (CHEST), The American College of Cardiology (ACC), The American Heart Association (AHA), and The American Stroke Association (ASA), although they do not specifically address neurosurgery. The guidelines are clearer for patients who are on antiplatelet therapy and have planned surgery than for patients on antiplatelet therapy

who require immediate surgery due to trauma or spontaneous ICH.

Patients who require antiplatelet therapy for prevention of stent thrombosis pose a challenging dilemma because the risk of stent thrombosis may outweigh the risk of bleeding even during neurosurgery. The type of stent used is also important. Bare metal stents are fully endothelialized in 4–6 weeks, however, drug-eluting stents require up to a year. The highest risk of thrombosis occurs during the endothelialization, and the risk is further increased when antiplatelet therapy is abruptly discontinued [40]. The 2014 ACC/AHA guidelines are very specific to patients with a previous percutaneous coronary intervention (PCI) and stent placement because they include both timing to surgery and antiplatelet use [41]. For timing of elective non-cardiac surgery in patients with previous PCI, the ACC and AHA made the following recommendations [41]:

Class I

1. "Elective non-cardiac surgery should be delayed 14 days after balloon angioplasty (*Level of Evidence:* C) and 30 days after bare metal stent (BMS) implantation. (*Level of Evidence:* B)"
2. "Elective non-cardiac surgery should be optimally delayed 365 days after drug-eluting stent (DES) implantation. (*Level of Evidence:* B)"

Class IIa

1. "In patients in whom non-cardiac surgery is required, a consensus decision among treating clinicians as to the relative risks of surgery and discontinuation or continuation of antiplatelet therapy can be useful. (*Level of Evidence*: C)"

Class IIb

1. "Elective non-cardiac surgery after DES implantation may be considered after 180 days if the risk of further delay is greater than the expected risks of ischemia and stent thrombosis. (*Level of Evidence*: B)"

Class III: HARM

1. "Elective non-cardiac surgery should not be performed within 30 days after BMS implantation or within 12 months after DES implantation in patients in whom dual antiplatelet therapy (DAPT) will need to be discontinued perioperatively. (*Level of Evidence*: B)"
2. "Elective non-cardiac surgery should not be performed within 14 days of balloon angioplasty in patients in whom aspirin will need to be discontinued perioperatively. (*Level of Evidence*: C)"

In addition to timing, the agent used can also influence the risk of bleeding. As stated before, clopidogrel may be associated with higher rates of bleeding and reversal of platelet inhibition occurs at a slower rate than with aspirin [9, 18, 28]. It is not surprising that the guidelines developed by the ACC and the AHA favor aspirin over clopidogrel. For the antiplatelet agent used in the perioperative setting, they made the following recommendations [41].

Class I

1. "In patients undergoing urgent non-cardiac surgery during the first 4–6 weeks after BMS or DES implantation, DAPT should be continued unless the relative risk of bleeding outweighs the benefit of the prevention of stent thrombosis. (Level of Evidence: C)"
2. "In patients who have received coronary stents and must undergo surgical procedures that mandate the discontinuation of $P2Y_{12}$ platelet receptor-inhibitor therapy, it is recommended that aspirin be continued if possible and the $P2y_{12}$ platelet receptor be restarted as soon as possible after surgery. (Level of Evidence: C)"
3. "Management of the perioperative antiplatelet therapy should be determined by a consensus of the surgeon, anesthesiologist, cardiologist, and patients, who should weigh the relative risk of bleeding with that of stent thrombosis. (Level of Evidence: C)"

Class IIb

1. "In patients undergoing nonemergency/non-urgent non-cardiac surgery who have not had previous coronary stenting, it may be reasonable to continue aspirin when the risk of potential increased cardiac events outweigh the risk of increased bleeding. (Level of Evidence: B)"

Class III: No Benefit

1. "Initiation or continuation of aspirin is not beneficial in patients undergoing elective non-carotid surgery who have not had previous coronary stenting (Level of Evidence: B), unless the risk of ischemic events outweighs the risk of surgical bleeding. (Level of Evidence: C)"

These recommendations could apply for patients taking aspirin for primary and secondary prevention of cardiovascular events because their recommendations rely on the risk vs. benefit of antiplatelet therapy. In neurosurgery, it is unlikely that the risk of cardiac events will outweigh the risk of bleeding, especially in patients without stents. In the 2012 CHEST supplement to The Antithrombotic Therapy and Prevention of Thrombosis Evidence-Based Clinical Practice Guidelines [26], a review of primary stoke prevention with aspirin, there was no significant reduction in number of strokes including nonfatal ischemic and hemorrhagic strokes in low, moderate, or high cardiovascular risk patients. The CHEST guidelines were similar to the ACC/AHA guidelines, however, they specifically mentioned secondary prevention: "For patients with established CAD including patients after the first year post-ACS and/or with prior CABG surgery: We recommend long-term single antiplatelet therapy with aspirin 75–100 mg daily or clopidogrel 75 mg daily over no antiplatelet therapy (Grade 1A). We suggest single over dual antiplatelet therapy with aspirin plus clopidogrel (Grade 2B)" [26].

Once again, risk vs. benefit applies to these recommendations. *In the setting of neurosurgery, discontinuation is likely the right decision nearly every time*. The risk of increased bleeding is more dangerous than the risk of a cardiovascular event while on the short discontinuation from antiplatelet therapy during surgery. The patients who experienced increased vascular events had discontinued aspirin and had remained off therapy. Patients who must take a short antiplatelet therapy hiatus for surgery may not see an increase in vascular events because resuming therapy may counteract the time of increased prothrombotic activity. The average time to vascular events after discontinuing antiplatelet therapy ranged from 8.5 to 25.8 days [35–39]. Patients would likely discontinue antiplatelet therapy for only 5–7 days, depending on the agent, prior to surgery and resume therapy shortly after surgery. Initiation of antiplatelet therapy would likely occur before the average time of increased vascular events. Quickly reinitiating antiplatelet therapy after surgery may prevent the occurrence of these vascular events.

As the guidelines recommend, timing of elective surgeries in patients with stents is important. In patients at high risk for surgical bleeding, $P2Y_{12}$ platelet receptor inhibitors should be discontinued, however, aspirin should be continued throughout surgery. The $P2Y_{12}$ platelet receptor inhibitor should be resumed as soon as possible after surgery. The management of the patient's antiplatelet therapy should be carefully discussed between the cardiologist, neurosurgeon, anesthesiologist, patient, and pharmacist. Pharmacists can provide a wealth of knowledge about mechanism of action, half-life, time form discontinuation to platelet normalization, and possible alternative options in the perioperative setting. Aspirin is the drug of choice when the patient must remain on one antiplatelet agent during surgery. Any antiplatelet medications discontinued prior to surgery should immediately be restarted once the patient is out of surgery and stabilized.

Does Antiplatelet Therapy Increase the Risk of Hematoma Expansion?

Thrombocytopenia and coagulopathy are common after traumatic brain injury and the occurrence of these abnormalities increases as severity of injury increases [42]. Potentially exacerbating hematoma expansion is the use of antiplatelet agents prior to head injury. The limited number of platelets remaining in the thrombocytopenic patient could potentially be irreversibly inactivated by aspirin or clopidogrel, leading to a further inability to prevent excessive bleeding.

The primary concern with hematoma expansion is its direct link to increased morbidity and mortality [42–47]. Some studies have

associated anticoagulants, specifically warfarin, with increased hematoma expansion and mortality [43–45, 47, 48–50, 51]. It is reasonable to question if antiplatelet therapy would also have a similar association. Unfortunately, the data is less clear. The 2010 AHA and ASA guidelines developed for patients suffering ICH recommended warfarin reversal in INR-elevated patients [52]. They also recommended replacement therapy for severe coagulation factor deficiency patients. However, no recommendations regarding the reversal of antiplatelet therapy were provided because of limited and conflicting studies. When closely inspected, there is no surprise why there are no guidelines written based on the studies that have investigated the effect of antiplatelet therapy on hematoma expansion. There were large variations between studies as far as the definition of hematoma expansion, the inclusion window from symptom onset to hospital admission, and time from symptom onset until first computed tomography (CT) scan. Several studies contained significant flaws in data recording, lack of patient demographics, and poor study design. In the defense of some of these studies, the researchers were assessing other factors or agents besides antiplatelets on hematoma expansion and decided to include an analysis of their patients on antiplatelet therapy. Another common issue was that several studies failed to exclude patients who were on prior anticoagulants. Failing to exclude these from the study contaminates the results because anticoagulants are known to contribute to hematoma expansion and increase mortality. It would have been prudent to exclude warfarin from the studies because warfarin is well known to increase bleeding. Exclusion is particularly important in the studies that are directly investigating the effect of antiplatelet agents on hematoma expansion. Table 6.1 is a summary of some of the most substantial and relevant studies on the impact of antiplatelet therapy on hematoma expansion.

Flibotte and colleagues [53] were primarily assessing the risk of hematoma expansion and mortality in patients on warfarin, and determined that 40 % of the study population was on antiplatelets (more than were on warfarin). Although this study supports that antiplatelet therapy does not increase hematoma expansion, its limitations were a small sample size, contamination of results with data from patients on warfarin, and a lack of patient demographics. It was also unclear how many patients on antiplatelet therapy were also on warfarin.

Saloheimo and colleagues [54] did not report the exact time to first CT scan after symptom onset in their study. The first CT imaging was done in 73 % (32/44) of aspirin users and 70 % (97/138) of non-aspirin or warfarin users on day one of symptom onset. However, large variations can occur between groups because hematoma expansion occurs early and rapidly. Thus it is prudent to include time to first CT scan because most expansion occurs within 6 h of symptom onset. Although aspirin users had the smallest median volume of ICH (16 mL) compared with non-aspirin and warfarin users (20 mL), there was no significant difference in median volume between nonusers and aspirin users. The study did not find an association between aspirin and hematoma enlargement. However, the exclusion of numerous deaths and emergent surgeries in a small population may have accounted for lack of significance because these patients did not have a second CT. Only 56.5 % (78/138) of nonusers of aspirin or warfarin and 47.7 % (21/44) of aspirin users received a second CT scan. Age and comorbid conditions may also have impacted the results of the study because aspirin users were older than non-aspirin or warfarin users.

Toyoda and colleagues [55] recorded both the agent and dose of the antiplatelet for the three agents used at various doses and combinations. Of the 57 patients on antiplatelet therapy, 33 were included in calculating the influence of antiplatelet therapy on hematoma enlargement. Patients who were excluded from the analysis had died ($n=4$) or required surgery ($n=20$); the study may have been underpowered. A greater percentage of the patients in the antiplatelet group were over 70 years of age, had suffered more symptomatic ischemic strokes, and had higher rates of diabetes mellitus and heart disease than those patients not on antiplatelet agents.

Table 6.1 Studies on the role of antiplatelet therapy (APT) on hematoma expansion

Study	Population	APT agents + daily dose (mg)[a] + no. of patients (n)	ACT excluded? If not, no. of patients on ACT	Results
Flibotte 2004	183 patients <72 h of symptom onset prior to hospital admission and CT scan evidence of non-traumatic ICH	None specified	No; study designed to determine risk of hematoma expansion in W patients	APT not associated with increased initial hematoma volume, APT use 34.8 mL ± 40.5 mL vs. non-APT use 35.4 mL ± 38.7 mL, $P = 0.92$ APT not associated with hematoma expansion OR 0.42, 95 % CI [0.12–1.46]
Saloheimo 2005	44 ASA patients CT evidence of ICH or death record confirming ICH Control group = 138 patients not on ASA or W with CT evidence of ICH or death record confirming ICH	ASA median dose 250 (range 50–500)	No W users had their own group ($n = 26$)	No difference in hematoma expansion between non-ASA users (8 % [6/78]) and ASA users (19 % [4/21], no P value provided Significant increase in mean enlargement of hematomas by percentage in ASA users (12.8 % ± 22.6) vs. non-ASA users (4.8 % ± 16.1), $P = 0.006$
Toyoda 2005	57 patients on APT with non-traumatic ICH hospitalized within 24 h of stroke onset Control group = 194 patients not on APT with non-traumatic ICH hospitalized within 24 h of stroke onset	ASA 81 ($n = 15$) ASA 100 ($n = 16$) ASA 162 ($n = 1$) ASA 200 ($n = 1$) T 100 ($n = 2$) T 200 ($n = 9$) T 300 ($n = 1$) Cilostazol 100 ($n = 3$) ASA 100 + T 100 ($n = 2$) ASA 81 + T 200 ($n = 5$) ASA 100 + cilostazol 100 ($n = 1$) T 200 + cilostazol 200 ($n = 1$)	Yes	Hematoma enlargement >40 % within 2 hospital days was greater in patients on APT (27 % [9/33]) vs. patients not on APT therapy (8 % [12/147]), $P < 0.005$ On multivariate analysis, APT was associated with hematoma enlargement OR 7.67, 95 % CI [1.62–36.4], $P = <0.01$ Multivariate analysis of the 31 patients on ASA 81–100 mg and the 194 patients not on APT showed that ASA was an independent predictor of hematoma enlargement, OR 5.81, 95 % CI [1.01–33.3], no P value provided
Sorimachi 2007	8 patients hematoma enlargement ≥20 % 180 patients no hematoma enlargement ≥20 %	Hematoma enlargement group ASA 80 or 100 ($n = 5$, 1 also on W) No hematoma enlargement no ASA dose specified, ($n = 14$)	No Hematoma enlargement group ($n = 1$ on W alone, $n = 1$ on ASA + W) No hematoma enlargement group ($n = 14$)	Hematoma expansion ≥20 %, observed in 26.3 % (5/19) of patients on ASA therapy

(continued)

Table 6.1 (continued)

Study	Population	APT agents + daily dose (mg)[a] + no. of patients (n)	ACT excluded? If not, no. of patients on ACT	Results
Toyoda 2008	180 patients on APT hospitalized within 24 h of non-traumatic ICH Control group=738 patients not on APT or ACT hospitalized within 24 h of non-traumatic ICH	ASA 81 ($n=62$) ASA 100 ($n=41$) ASA other doses ($n=5$) T 100 ($n=9$) T 200 ($n=29$) T 300 ($n=3$) Cilostazol 100 ($n=3$) Cilostazol 200 ($n=3$) Various other single agents ($n=6$) DAPT (mainly ASA 81 and T 100) ($n=19$)	No W users were in a separate study group	APT associated with increase in hematoma expansion, OR adjusted for age and sex: 1.71, 95 % CI [1.04–2.81], $P=0.036$ APT associated with increase in hematoma expansion, multivariate adjusted odds ratio: 1.92, 95 % CI [1.10–3.34], $P=0.022$ Multivariate analysis showed APT did not increase the risk of large hematomas ASA alone associated with increase in hematoma expansion, OR adjusted for age and sex: 1.80, 95 % CI [1.02–3.17], $P=0.044$ ASA alone associated with increase in hematoma expansion, multivariate adjusted OR: 1.99, 95 % CI [1.05–3.79], $P=0.035$
Moussouttas 2009	17 patients on APT with a spontaneous supratentorial ICH diagnosed within 6 h of onset and a follow-up CT ~48 h later Control group=53 patients not on APT with a spontaneous supratentorial ICH diagnosed within 6 h of symptom onset and a follow-up CT ~48 h later	ASA ($n=15$) C ($n=2$) No doses specified	Yes	Antiplatelet therapy not a predictor of ICH expansion >25 %, >33 % or >50 %, $P=0.81$, 0.93, 0.64, respectively No difference in initial CT scan volume (mL) between APT patients (13.8 ± 11.4) vs. non-APT patients (19.2 ± 15.4), $P=0.25$ No difference in second CT scan volume (mL) between APT patients (21.5 ± 24.6) vs. non-APT patients (24.6 ± 25.1), $P=0.50$ No difference in hematoma expansion (mL) between APT users (7.7 ± 22.7) vs. non-APT users (5.5 ± 14.3), $P=0.94$ No difference in hematoma expansion (%) between APT users (110.4 ± 363.4) vs. non-APT users (20.8 ± 47.9), $P=1.0$.
Sansing 2009	70 patients on APT with CT diagnosis of ICH within 6 h of symptom onset Control group=212 patients not on APT with CT diagnosis of ICH within 6 h of symptom onset	ASA ($n=56$) C ($n=5$) D ($n=1$) ASA + C ($n=3$) ASA + D ($n=2$) Triflusal ($n=2$) Indobufen ($n=1$) No doses specified	Yes	The relative risk with any hematoma expansion in APT patients was 0.85, UCI=1.03, $P=0.16$ No difference in initial ICH volume in patients on APT (median [IQR]: 13.1 [7.9–27.3]) vs. patients not on APT (median [IQR]: 15.7 [7.9–31.4]), $P=0.037$ No difference in percentage of patients with ICH growth >33 % in APT patients (24.2 %) vs. non-APT patients (26.2 %), $P=0.75$ No difference in percentage of patients with any ICH growth in APT patients (59.1 %) vs. non-APT patients (67.3 %), $P=0.18$

(continued)

Table 6.1 (continued)

Study	Population	APT agents + daily dose (mg)[a] + no. of patients (n)	ACT excluded? If not, no. of patients on ACT	Results
Yildiz 2011	52 patients on APT with CT diagnosis of ICH within 12 h of symptom onset and a follow up CT 72 h later Control group = 101 patients not on APT with diagnosis of ICH and a CT within 12 h of symptoms and a follow-up CT 72 h later	ASA (n = 49) C (n = 1) ASA + C (n = 2) No doses specified	Yes	APT patients had hematoma expansion 42.9 % (15/35) vs. non-APT patients 17.5 % (10/57), P < 0.01 More APT patients had hematoma expansion (42.9 % [15/35]) vs. non-APT patients (17.5 % [10/57]), P < 0.01 APT patients had more increase between baseline and follow-up hematoma volume (3.6 mL [median IQR: 0.3–14.3]) vs. non-APT patients (0.0 mL [median IQR: 0.0–5.7]), P < 0.01
Fabbri 2013	201 patients with mild, moderate or severe head trauma that worsened on follow-up head CTs Control group = 1357 patients with mild, moderate, or severe head trauma with stable or improved follow-up head CTs	Study group = 106 on APT Control group = 431 on APT ASA = 439 (usual dose 100 mg daily) T (n = 69) C (n = 28) No doses specified for T and C	No	APT patients at increased risk of worsening CT vs. those not treated, RR 2.09, 95 % CI [1.63–2.71] In mild head trauma, APT increased risk of worsening CT in patients with ≤2 lesions vs. no APT, RR 1.86, 95 % CI (1.06–3.30), P = 0.032 In mild head trauma, APT increased risk of worsening CT in patients with ≥3 lesions vs. no APT, RR 3.34, 95 % CI (1.74–6.40), P = 0.003 In moderate-severe head trauma, APT increased risk of worsening CT in patients with ≤2 lesions vs. no APT, RR 1.72, 95 % CI (1.21–2.45), P = 0.002 In moderate-severe head trauma, APT increased risk of worsening CT in patients with ≥3 lesions vs. no APT, 33 %, [13/39] vs. 22.7 % [15/66], no RR or P calculated Neurosurgical intervention was required more often in APT patients (21.2 %) vs. non-APT patients (11.2 %), RR 1.90, 95 % CI (1.35–2.66), P < 0.001

[a]Daily dose

ACT anticoagulant therapy, *APT* antiplatelet therapy, *ASA* aspirin, *C* clopidogrel, *CT* computed tomography, *D* dipyridamole, *DAPT* dual antiplatelet therapy, *ICH* intracerebral hemorrhage, *IQR*, interquartile range *OR* odds ratio, *T* ticlopidine, *UCI* upper limit of confidence interval, *W* warfarin

Despite using a smaller increase in percentage (≥20 %) to define increase in hematoma expansion compared to other studies, Sorimachi and colleagues [56] found eight patients who experienced hematoma expansion. They found that hematoma expansion occurred in 26.3 % of the patients on antiplatelet agents prior to the ICH, which might be due to warfarin.

An excellent 2008 study by Toyoda and colleagues [57] investigated the role of antiplatelet therapy on hematoma expansion. They included a very specific definition of hematoma expansion

and included the specific dose of each agent used. There were detailed patient demographics and a multivariant adjustment based on risk factors and comorbidities. The authors prevented contamination of the data with warfarin by creating separate categories for antiplatelet agents, warfarin, and for patients on both antiplatelet agents and warfarin. The authors also recorded time from symptom onset to first CT scan, in which there was no difference between the control group and the antiplatelet group. One of the best aspects of the study was that the antiplatelet groups were differentiated into three groups: aspirin alone, antiplatelet agent other than aspirin, and dual antiplatelet agents. Multivariate-adjusted analysis was done on these groups to provide the best analysis on this highly controversial topic. The study limitations were reported as the study being retrospective and that hematoma expansion was not assessed in every patient because some patients died or received surgery before a second CT scan. This likely reduced the reported number of patients experiencing hematoma expansion. Despite these limitations, this study was one of the most carefully designed and well reported studies to date in analyzing the effect of antiplatelet therapy on hematoma expansion. One possible disadvantage is that the study population may be homogenous because the study was conducted in Japan.

Moussouttas and colleagues [58] recorded time to first CT scan, time between initial and second CT, as well as hematoma volumes and changes. Patient demographics were included, however, hypertension was the only comorbidity included. It is impossible to determine if any factors besides age and hypertension may have contributed to the results of the study. The main disadvantage of the study is that it was likely unpowered because the study consisted of 70 patients, of which only 17 were on antiplatelet therapy.

Data from the prospective, placebo arm of the Cerebral Hemorrhage and NXY-059 Treatment (CHANT) trial was analyzed by Sansing and colleagues [59]. This is one of the larger and more properly designed studies with attention to imaging timing, baseline demographics, and exclusion of anticoagulants. The authors differentiated the antiplatelet agents, however, no doses were recorded. This study was one of the few studies to conduct a power analysis. They reported an 80 % power to detect a 6.5 mL difference in hematoma expansion between study groups, using an alpha of 0.05 and a standard deviation of 16 mL. The majority of the studies reviewed up to this point lacked a power analysis. The authors concluded that aspirin, compared to the other antiplatelet agents, had comparable hemorrhage volumes and rates of hematoma expansion, although no analysis was shown. The population size was still not large enough to confidently make a generalized determination that antiplatelets do not contribute to hematoma expansion.

Yildiz and colleagues [60] provided excellent patient demographics, which included timing to first CT scan and an analysis of the agents used. However, no doses were recorded, even though 94 % of the antiplatelet patients were on aspirin monotherapy alone. Patients on aspirin had larger admission hematoma volumes, which would have required larger growth to qualify as expansions. The definition of expansion in this study was growth >12.5 mL or >33 % from baseline ICH volumes. Antiplatelet agents were determined to cause hematoma expansion, however, a large portion (33 %) of patients did not have a second CT scan. It is difficult to make a strong conclusion regarding the remaining patients because small changes have much more dramatic changes in percentages and *P* values. The study was likely underpowered, and a large portion of patients not being included in analysis only further eroded the ability to detect differences between the groups. The lack of a substantial population in this study makes it difficult to make a determination if antiplatelet therapy contributes to hematoma expansion.

Fabbri and colleagues [61] had a substantially sized study, with a primary interest in determining the short-term and long-term outcomes in subjects with head injuries. Their study

included data about worsening lesions, however, they did not define what constituted a hematoma expansion. Worsening was defined as a "change of at least one point in Marshall Category between initial and follow up CT scan performed during serial controls within 24 h and the need for neurosurgical intervention because of clinical and/or radiological deterioration during the observation period (first 7 days after diagnosis)." No patient demographics were included comparing patients on antiplatelet therapy and those not on antiplatelet therapy. It is unclear if there were any significant differences between patients on antiplatelet therapy who had favorable outcomes vs. those who had unfavorable outcomes because no demographics of these groups were disclosed. It is unclear if patients on antiplatelets were older and/or sustained more severe injuries. These factors could have influenced the results of the study. The only demographics provided compared patients with worsening or stable/improved conditions between initial and follow up CT. Of the 201 patients who had worsening outcomes, 106 were on antiplatelet therapy. Patients in the worsening category had significantly lower Glasgow Coma Scale (GCS) scores (65.2 %) than those in the stable/improved group (22.7 %, $P<0.001$). Patients in the worsening group also had significantly more basal skull fractures (13.9 %) than those in the stable/improved group (8.6 %, $P=0.019$). Throughout this paper there were some inconsistencies in numbers reported when referring to the same value.

Several factors can determine if a researcher will conclude if hematoma expansion occurred. These factors include the definition of hematoma expansion and time to first CT scan. Several of the studies had differing definitions of hematoma expansion, as listed in Table 6.2, thus it may be difficult to directly compare the studies' results. An exaggeration of hematoma expansion may exist if a significant number of small hematomas enlarged slightly but due to increasing >33 %, qualified as an expanded hematoma. Substantial hematoma expansions of this nature could misrepresent the true risk. Future studies investigating hematoma expansion should adopt a uniform definition that prevents over-representation of small hematoma expansions. A more specific definition should include two qualifiers such as an increase >33 % and >12.5 mL. This definition was used in two of the studies reviewed. A double qualifier definition would exclude small hematomas that expanded only slightly but still surpassed the 33 % benchmark.

Table 6.2 Different trials' definitions of hematoma expansion

Author, year	Definition of hematoma expansion
Fabbri 2013	No clear definition. Head CTs were retrospectively reviewed by a blinded, independent, expert neurologist. No percentage or volume requirements given.
Flibotte 2004	≥33 %
Moussouttas 2009	No specific definition. Directly compared APT patients' hematomas vs. non-APT patients' hematomas volume.
Saloheimo 2005	≥33 %
Sansing 2009	>33 %
Sorimachi 2007	≥20 %
Toyoda 2005	>40 %
Toyoda 2008	>33 % or >12.5 mL
Yildiz 2011	≥33 %

APT Antiplatelet therapy

Data regarding hematoma growth indicates that most growth occurs within 6 h of symptom onset [62]. Studies that had extended time between onset of symptoms and first CT scan may have missed the opportune time to accurately determine hematoma expansion. Table 6.3 lists the inclusion criteria window that the studies discussed above allowed from symptom onset to admission. The lack of consistency in timing of the first CT could be a potential reason for the unknown role of antiplatelet therapy on hematoma expansion. Only three studies required patients to be diagnosed with ICH by CT scan within 6 h of onset. Interestingly, none of these studies showed an increase in hematoma growth with antiplatelet therapy.

One major event that cannot be overlooked in the role of antiplatelets (or any drug) in hematoma expansion is that patients may not receive a

Table 6.3 Inclusion window from time of first symptom onset until admission

Study	Inclusion window from symptom onset to admission (h)
Fabbri 2013	24
Flibotte 2004	72
Moussouttas 2009	6
Saloheimo 2005	No time period (any patient with documented ICH included)
Sansing 2009	6
Sorimachi 2007	24
Toyoda 2005	24
Toyoda 2008	24
Yildiz 2011	12

ICH intracerebral hemorrhage

second CT scan due to their prognosis. If a patient presents with a substantial hematoma and the decision by the medical staff and family is to withdraw care or proceed with surgery, a second CT may not be performed. In cases of surgery or death, it is likely that hematoma expansion occurred because the patient required surgery to prevent further expansion or died from the severity of the expanding hemorrhage. The amount of data that goes unrecorded by this mechanism may prevent detection of hematoma expansion in certain patient populations. An analysis of patients with a second CT scan should be conducted as well as a separate analysis that assumes that patients who required surgery or died also qualified as having hematoma expansion. In these studies, it may be clearer to determine the true risk of hematoma expansion in patients on antiplatelet therapy prior to traumatic brain injury or ICH.

Clearly, larger, multicenter studies need to be performed to determine the actual risk of hematoma expansion with prior antiplatelet use. Too many studies have been unpowered and were unable to determine the true risk. If several large hospitals agreed to prospectively follow patients and combine their data, the true risk may finally be determined. In order for such a trial to work, there needs to be an established definition of hematoma expansion. A consensus should be established on how long the inclusion window should be from symptom onset to first CT scan. With windows that extend up to 24 h, the hematoma may have already experienced its primary growth before a CT could be obtained. As several studies have shown, the most expansion occurs in the first 6 h after symptom onset [62]; limiting the inclusion window to patients having a CT scan within 6 h of symptom onset may be best. To ensure a large population for the study, anticoagulants may not necessarily have to be excluded from the analysis if they have their own study group. Patients who are on both anticoagulants and antiplatelet therapy should also be their own study group and not grouped into either the anticoagulant or antiplatelet groups. Names and doses of each antiplatelet therapy should also be recorded to potentially determine the safest antiplatelet agent.

Do Platelet Transfusions Reduce Mortality in Patients with Spontaneous or Traumatic Intracranial Hemorrhage?

Patients with inhibited platelet function may experience excessive bleeding. Correcting for platelet inhibition may reduce hematoma expansion in trauma and ICH patients. As previously discussed, platelets are irreversibly inhibited by aspirin and clopidogrel for the life of the platelet. The only way to reverse platelet inhibition would be to create new platelets. However, in a trauma situation, patients do not have a week to replenish platelets. Quick replenishment with new platelets appears to be a reasonable option to reverse the platelet inhibition. However, platelet transfusions are not a procedure to be taken lightly because they are associated with inherent risk. These risks prevent platelet transfusions from being performed in every patient who has been on antiplatelet therapy prior to an ICH or who has suffered severe trauma.

One of the most feared complications of platelet transfusions is transfusion-related acute lung injury (TRALI). Globally, TRALI is the primary

mechanism for transfusion-related morbidity and mortality [63]. In the FDA's fatality summary report investigating blood collection and transfusions, TRALI was responsible for 47 % of all transfusion-related fatalities disclosed to the Center for Biologics Evaluation and Research (CBER) [64]. The incidence of TRALI is frequently reported as 1 in every 5000 recipients of blood products, although several recent studies have proposed that the true incidence may be closer to 1 in every 1000 recipients [65, 66]. Although the definition of TRALI has changed several times, it is characterized by acute onset of severe dyspnea, tachypnea, fever, new or worsening hypoxemia, occasional hypotension, cyanosis, and bilateral infiltrates on frontal chest radiographs that occur within 6 h of transfused blood products [63].

Due to the inherent risks associated with platelet transfusions, it is important to establish the usefulness of such a procedure. Currently, there are no guidelines recommending a platelet transfusion to a patient suffering an ICH who had previously been on antiplatelet therapy. Platelet transfusions are regarded as investigational and their usefulness is unknown in patients on antiplatelet therapy prior to an ICH [52]. One of the reasons for the lack of recommendations is the conflicting results from studies that have investigated the role of platelet transfusions in patients taking antiplatelet therapy prior to an ICH or head trauma. Additionally, many of the studies were plagued by poor design and lacked substantial study populations. Table 6.4 summarizes the results from the most substantial, relevant, and commonly referenced studies on the impact of platelet transfusion reducing mortality in patients on antiplatelet therapy prior to an ICH or head trauma.

Ohm and colleagues [67] designed a study to investigate the role of antiplatelet agents in mortality in the elderly, and the paper contained some information on platelet transfusions. Demographics were not given for patients on antiplatelet therapy who received a platelet transfusion vs. those on antiplatelet therapy who did not receive a platelet transfusion or for the antiplatelet therapy patients who received a platelet transfusion and the control patients. Patients on antiplatelet therapy had significantly more comorbid conditions. It is not known if the patients on antiplatelet therapy who received the platelet transfusions were older, had more comorbid conditions, or sustained more severe injuries vs. the control patients who received platelet transfusions. Without a comparison between groups it is hard to determine the actual relationship between platelet transfusions and mortality in this study.

Ivascu and colleagues [68] clearly differentiated which antiplatelet agents the study population was taking. However there were no demographics given for the patients on antiplatelet therapy who received or did not receive a platelet transfusion, or between the antiplatelet therapy patients who received a platelet transfusion and the control patients who received a platelet transfusion. It is hard to establish if there were any factors that may have contributed to increased mortality such as age, GCS scores, and injury severity score. Given the small number of patients who received platelet transfusions ($n=40$) in this study and the uncertainty of how many of these patients were on antiplatelet therapy, it is impossible to make any general recommendations on platelet transfusions based on this study.

In the study by Fortuna and colleagues [69] platelet transfusions were determined on a case-by-case basis. Platelet transfusion patients were significantly older (73 ± 2 years vs. 69 ± 1, $P=0.02$), were injured more severely (injury severity scale (ISS) 28 ± 1 vs. 24 ± 1, $P=0.001$) and had a lower GCS (11 ± 1 vs. 13 ± 0.2, $P=0.007$). Although this study was somewhat larger than the previous studies, the information is contaminated by anticoagulant data and lacks a strong platelet transfusion analysis. These reasons make it difficult to confidently make any recommendation about platelet transfusions and mortality based on this study.

Extensive demographics were provided by Creutzfeldt and colleagues [70] about patients in their study as to receiving antiplatelet therapy or not and whether receiving a platelet transfusion or not. Antiplatelet therapy patients had significantly more comorbid conditions in comparison to the

Table 6.4 The role of platelet transfusions (PT) on mortality in patients on antiplatelet therapy (APT)

Study	Class of ICH	No. patients on APT, in control group	No. of patients transfused	ACT excluded? If not, no. of patients on ACT	Results
Ohm 2005	TR	APT ($n=90$) ASA ($n=50$), C ($n=12$), ASA + C ($n=20$) Control ($n=89$)	APT ($n=24$) Control ($n=5$)	No W + ASA ($n=6$) W + C ($n=2$) W + ASA + C ($n=2$) 6/10 W + APT patients had normal INRs No patients in control group on ACT	Increased mortality in PT group (47.6 %, 10/21) vs. the non-PT group (25 %, 2/8), no *P* value calculated
Ivascu 2008	TR	ASA ($n=61$) C ($n=17$) ASA + C ($n=31$) Control ($n=42$)	$n=40$, unclear how many patients from each ACT group were transfused	Unclear, no exclusion criteria listed and INR was recorded	No difference in mortality between PT patients and non-PT patients, 28 % [11/40] vs. 13 % [9/69], respectively, $P=0.064$
Fortuna 2008	TR	APT ($n=126$) ASA ($n=91$), C ($n=17$), ASA + C ($n=18$) Control ($n=250$)	66/166 CAW	No W ($n=29$) W + ASA ($n=10$) H ($n=1$)	Increased mortality in patients on CAW who received PT (30 %) vs. those on CAW who did not receive PT (16 %), $P=0.01$ Multivariate analysis suggested that mortality was impacted by age (OR 1.07, 95 % CI [1.03–1.10]) and ISS (OR 1.04, 95 % CI [1.01–1.08]) but not CAW use (OR 0.56, 95 % CI [0.28–1.14]) or PT, P not calculated
Creutzfeldt 2009	SP	All ($n=368$) APT ($n=121$) ASA ($n=105$) ASA + C ($n=11$) ASA + D ($n=2$)	53/121 APT	No, only patients with INR <1.5 excluded	No difference in mortality in APT patients who received PT (26 %, 14/53) vs. APT patients who did not receive PT (38 %, 26/68), $P=0.17$ PT likely associated with hospital death (OR 1.25, 95 % CI 0.28–5.54) and APT likely associated with hospital death (OR 2.44, 95 % CI 1.07–5.56) when adjusted for prognostic and propensity score Unadjusted data showed APT likely associated with a favorable outcome (OR 2.01, 95 % CI 0.97–4.17) and unlikely to result in hospital death (OR 0.58, 95 % CI 0.27–1.27) Unadjusted data showed APT likely associated with favorable outcomes (OR 1.20, 85 % CI 0.78–1.86) and APT unlikely to be associated with hospital death (OR 2.44, 95 % CI 1.07–5.56).

(continued)

Table 6.4 (continued)

Study	Class of ICH	No. patients on APT, in control group	No. of patients transfused	ACT excluded? If not, no. of patients on ACT	Results
Downey 2009	TR	All ($n=328$)	$n=166$: ASA ($n=92$), ASA + C ($n=74$) No PT ($n=162$): ASA ($n=139$), ASA + C ($n=23$)	No PT: W ($n=147$) non-PT: W ($n=130$)	No difference in mortality between PT (17.5 % [29/166]) and non-PT (16.7 % [27/162], $P=0.85$)
Bachelani 2011	TR	All ($n=84$) ASA ($n=36$) No ASA ($n=48$)	45 with an initial ART of <550	Yes	No difference in mortality between PT 11 % (4/36) vs. those non-PT 6.4 % (3/48), $P=0.442$ Trend toward increased mortality in non-responders to PT, $P=0.09$
Washington 2011	TR	All ($n=108$) on APT APT: ASA, C, or both	44	Yes	No difference in mortality rates between PT (5 %, 2/44) vs. non-PT (0 %, 0/64)
Suzuki 2014	SP	All ($n=432$) APT ($n=66$) ASA ($n=50$), ASA + C ($n=12$), C ($n=2$), T ($n=2$) non-APT ($n=366$)	APT = 6/66 non-APT = 10/366	No	Increased mortality at 7 days in APT patients who did not receive PT (50 %, 30/60) vs. APT patients who received PT (0 %, 0/6), $P=0.03$ Increased mortality at 90 days in APT patients who did not receive PT (77.5 %, 31/60) vs. APT patients who received PT (0 %, 0/6), P not calculated

ACT anticoagulant therapy, *APT* antiplatelet therapy, *ART* The Aspirin Response Test (ART;VerifyNow), *ASA* aspirin, *C* clopidogrel, *CAW* clopidogrel, aspirin and warfarin, *D* dipyridamole, *H* heparin, *ICH* intracranial hemorrhage, *MTBI* mild traumatic brain injury, *PT* Platelet transfusion, *SP* spontaneous, *T* ticlopidine, *TR* traumatic, *W* warfarin

control group and higher GCS score than the control patients. There were no significant differences between patients on antiplatelet therapy who received platelet transfusions and patients on antiplatelet therapy who did not receive platelet transfusions. However, there were significantly more women in the platelet transfusion group. Knowing that the groups were similar makes determining the benefit of platelet transfusions easier. Platelet transfusions were associated with likely favorable outcomes in every category (unadjusted, adjusted for prognostic score, adjusted for propensity score, and adjusted for both prognostic and propensity score). Platelet transfusions were likely associated with hospital death when adjusted for prognostic score and prognostic and propensity score combined, while hospital death was unlikely when the data was unadjusted and adjusted for propensity. The unadjusted data suggested that platelet transfusions were beneficial because of the unlikelihood of hospital death according to their odds ratio (Table 6.4), yet the authors did not report a benefit from platelet transfusions. All the patients in the platelet transfusion group who died, died after life support was withdrawn. However, six patients in the non-platelet transfusion group died from causes other than the removal of life support.

Downey et al. [71] provide demographics between the transfused and non-transfused patients that showed that patients in the platelet transfusion group were significantly older (77 ± 10.4 years) than non-platelet transfusion patients (73.0 ± 10.8 years, $P<0.001$). There were significantly more patients on warfarin in the platelet transfusion group (147 [89 %]) than patients in the non-platelet transfusion group (130 [80 %]). Warfarin may have affected the

results of the study because mortality rates of patients on warfarin were higher (27.5 % [42/277]) than those not on warfarin (15.2 % [14/51]). The higher percentage of patients on warfarin should have put the platelet-transfused group at a disadvantage, however mortality rates were similar. The authors stated that there was no standardization of timing of platelet transfusion. Platelets took an average of 34 min to arrive once ordered, and more time was required to perform laboratory tests for abnormal platelet function. Transfusions performed earlier, possibly upon admission to the hospital, may have limited hemorrhage expansion and may have prevented mortality. The utility of this study is that it included a large number of patients and included many who were on warfarin, but this latter fact makes it difficult to confidently make a decision regarding platelet transfusions.

Excellent patient demographics were provided by Bachelani et al. [72]. Patients with platelet inhibition were significantly older (81 years, interquartile range (IQR) [74-86]) compared to patients without platelet inhibition (76 years, IQR [59-85]; $P=0.010$). All other factors were similar between groups including comorbid conditions, injury severity, and admission GCS. There was no significant difference in mortality between transfused and non-transfused patients. Because all factors besides age were similar, this is one of the few studies in which transfused patients were not worse off than non-transfused patients. However, the small size of the study made it difficult to find significant changes between groups. The authors conducted some additional analysis of platelet transfusions. Repeat Aspirin Response Tests (ARTs) were conducted after each platelet transfusion. In patients who received a platelet transfusion, 29 of 45 had a correction of their platelet inhibition, as evidenced by an ART of ≥550 aspirin response units. Of the 16 non-responders to the first platelet transfusion, nine were transfused again. Of the nine patients, six had reversal of their platelet inhibition. An additional patient was able to reverse platelet inhibition after a third transfusion. The remaining two patients were unable to correct their platelet inhibition with >3 transfusions. A trend toward increased mortality in patients who were non-responders to platelet transfusions was observed. Patients who did respond to platelet transfusion were given larger quantities/volumes (median, 6 [IQR 5–10] vs. 8 [IQR 6–10]; $P=0.13$). This likely represented a dose–response relationship for platelet transfusions. The authors reported an average increase of 70 ± 50 aspirin response units per 6-pack of platelets. The data showed that not every patient will respond to a single platelet transfusion.

The benefit of platelet transfusions in mild traumatic brain injury was investigated by Washington and colleagues [73]. The attending neurosurgeon made the decision to transfuse because there was no protocol for the initiation of transfusion. It appeared that platelet transfusions were reserved for worse-off or declining patients. The demographics showed that the patients who received platelet transfusions were more likely to be on clopidogrel (52 % [23/44] vs. 20 % [13/64]; $P=0.0005$), have a Marshall class VI hemorrhage (32 % [14/44] vs. 11 % [7/64]; $P=0.043$), and have larger ICH volumes (20.6 mL ± 26.5 vs. 8.2 mL ± 13.7; $P=0.02$) than patients who did not receive a platelet transfusion. Interestingly, there was no difference in any of the other outcome results (neurological decline, surgical intervention, cardiac event, respiratory event, Glasgow outcomes, or hematoma expansion) between groups. Patients who received platelet transfusions did experience more medical decline (14 % [6/44]) than those who did not receive a platelet transfusion (3 % [2/6]), however, this did not reach statistical significance ($P=0.06$). The medical decline may have been related to the fact that the patients who received platelet transfusions were in worse medical condition. There were no deaths in the non-transfused group and two deaths in the platelet transfusion group; both deaths occurred after platelet transfusions, one from a myocardial infarction and the other from a congestive heart failure exacerbation. It is unclear if these were directly related to platelet transfusions because the authors did not elaborate on the deaths.

Detailed demographics were also given in the study by Suzuki and colleagues [74]. They provided several excellent multivariate analyses investigating the role of antiplatelet therapy on mortality, as well as platelet transfusions on mortality. However, the study only included data on platelet transfusions in six patients on previous antiplatelet therapy prior to ICH. It would be impossible to discover any meaningful, significant differences between groups with such a small population.

A Dutch study, the Platelet Transfusion Intracerebral Hemorrhage (PATCH) trial [75], was designed to investigate the role of platelet transfusion in improving outcomes in patients previously on antiplatelet therapy who have a spontaneous ICH. This trial would be one of the largest studies to date, planned to have a sample size of 95 patients in the study group. Study patients would receive a platelet transfusion within 6 h of onset of intracerebral hemorrhage and within 1.5 h of CT scan, and 95 patients in the control group would receive the standard of care. Patients would be excluded if they are on vitamin K antagonists, if surgery was planned within 24 h after admission, or if death was imminent. These important exclusion criteria eliminate the influence of warfarin on results and try to ensure data outcomes for as many patients as possible. Many prior studies lacked substantial populations because patients who received surgery or died were not included in result outcomes. No information regarding the study results has been published yet.

It is clear that more extensive studies with larger populations need to be conducted. With some conflicting results from the studies reviewed here and small sample sizes in some cases, it is obvious why the AHA and the ASA consider platelet transfusions in patients with a history of antiplatelet use to be investigational and their role unclear [52]. One of the primary reasons why their benefit is unknown is that most platelet transfusion studies do not compare similar groups. Frequently, platelet transfusion patients had worse injuries or were in poorer medical condition than the patients who did not receive platelet transfusion. These patients were more likely to die, which could skew the results toward platelet transfusions not being beneficial in reducing mortality. When the decision to transfuse is left to the neurosurgeon, they may want to wait to transfuse patients who are in poorer health, declining, or more severely injured because platelet transfusions come with inherent risks. The concern with administering a platelet transfusion to a patient who is not critically ill or declining is the possibility of having the patient suffer complications from the transfusion. These complications could result in increased morbidity or death. A protocol similar to the one in the Bachelani study [72], in which the patient's condition did not affect the decision to transfuse, may be a good approach. Using a more objective test to determine when to initiate a platelet transfusion would help to reduce the tendency to only treat patients who are more likely to die. Using an aspirin response test in prior aspirin users may help determine which patients are initial responders and which require additional transfusions. The knowledge that all patients may not initially respond to the first transfusion is an important key to help reduce mortality. Similar testing for clopidogrel can also be done using the flow cytometric vasodilator-stimulated phosphoprotein phosphorylation (VASP)-assay and the VerifyNow $P2Y_{12}$ assay. Better designed trials should investigate the true role of platelet transfusions in reducing mortality. This is an important area of research that needs to be addressed because of the many patients on antiplatelet therapy and the high rate of mortality associated with ICH.

Review of Novel Antiplatelet Agents

Several novel antiplatelet agents have been developed that have improved pharmacokinetic properties and potential clinical benefits over the traditional antiplatelet agents like aspirin and clopidogrel. Some of these new antiplatelet agents are reversible, have shorter half-lives, and have more consistent inhibition than clopidogrel. These characteristics may provide a safer option for patients who require antiplatelet therapy

during neurosurgery. However, these medications have not been tested in neurosurgery and bleeding risks must be evaluated based on non-neurosurgery studies.

Prasugrel

Prasugrel is an oral, third generation theinopyridine that selectively and irreversibly inhibits the $P2Y_{12}$ receptor [76]. Prasugrel, like clopidogrel, is a prodrug, but it is more potent than clopidogrel. In a study of a single oral dosing of prasugrel, there was a tenfold increase in the anti-aggregatory ability of prasugrel compared to clopidogrel [77]. Prasugrel has a faster onset and a greater and more consistent platelet inhibition compared with clopidogrel at the approved dose and as compared to clopidogrel.

Several trials have compared prasugrel and clopidogrel for bleeding risk and cardiovascular outcomes. In the TRILOGY-ACS trial ($n=9326$), fewer cardiovascular deaths, myocardial infarctions, or strokes were in the prasugrel arm than in patients who took clopidogrel based on angiographic analysis [78]. Prasugrel did not significantly increase the risk of Global Use of Strategies to Open Occluded Arteries (GUSTO) severe or life-threatening bleeds or TIMI major bleeds [79].

In another large study ($n=13{,}608$), prasugrel was compared to clopidogrel for death and bleeding risk for patients with moderate-to-high risk for acute coronary syndrome with a scheduled percutaneous coronary intervention. Prasugrel significantly reduced the number of nonfatal MIs (7.3 % vs. 9.5 %, $P<0.001$), urgent target-vessel revascularizations (2.5 % vs. 3.7 %, $P<0.001$), and stent thrombosis (1.1 % vs. 2.4 %, $P<0.001$) compared with clopidogrel. However, prasugrel was associated with more non-CABG-related TIMI major bleeding (2.4 % vs. 1.8 %, $P=0.03$), life-threatening bleeds (1.4 % vs. 0.9 %, $P=0.01$), fatal bleeding (0.4 % vs. 0.1 %, $P=0.002$), and CABG-related TIMI major bleeding (13.4 % vs. 3.2 %, $P<0.001$) [80].

Given the increased risk of bleeding and only minor improvements in protective effects, prasugrel is likely not a practical choice for neurosurgery.

Ticagrelor

Ticagrelor is an orally active adenosine triphosphate analog that reversibly binds the $P2Y_{12}$ receptor. Interestingly, ticagrelor is not a prodrug and does not need metabolic activation to effectively inhibit the $P2Y_{12}$ receptor, but approximately 1/3 of an administered ticagrelor dose undergoes hepatic conversion into an active metabolite that is essentially equipotent to the parent compound [81–83]. When ticagrelor binds to the $P2Y_{12}$ receptor, it almost completely inhibits platelet aggregation induced by adenosine diphosphate [81, 84]. A quicker and more extensive inhibition of platelet inhibition is achieved with ticagrelor compared with clopidogrel [81, 85]. However, there are similar concerns in the perioperative setting for ticagrelor as for prasugrel. First, the half-life of ticagrelor is 7 h (and 9 h for the active metabolite), which is similar to clopidogrel [86]. Second, the greater extent of platelet inhibition may also lead to increased bleeding. One large study investigated the role of cardiovascular events and bleeding risks in patients admitted to the hospital with acute coronary syndrome. In the ticagrelor PLATO study ($n=18{,}624$), ticagrelor reduced death vs. clopidogrel from vascular causes, MI, or stroke (9.8 % vs. 11.7 %, $P<0.001$) and occurrence of definite stent thrombosis (1.3 % vs. 1.9 %, $P=0.009$) [87]. There was no significant difference in major bleeding between ticagrelor vs. clopidogrel by study criteria (11.6 % vs. 11.2 %, $P=0.43$) or TIMI criteria (7.9 % vs. 7.7 %, $P=0.57$), or life-threatening or fatal bleeding (5.8 % vs. 5.8 %, $P=0.70$). There was a small increase in intracranial bleeding in the ticagrelor group compared to the clopidogrel group but it was not statistically significant. Patients who did have an intracranial bleed were more likely to have a fatal bleed while on ticagrelor vs. on clopidogrel (0.1 % vs. 0.001 %, $P=0.02$). The increased risk of intracranial bleeding and fatality associated

with intracranial bleeds is a major concern with ticagrelor. Ticagrelor also appears not to be a possible alternative to clopidogrel for patients requiring neurosurgery.

Cangrelor

Cangrelor is an intravenous, short-acting, potent, reversible, competitive inhibitor of the $P2Y_{12}$ receptor. One of the most desirable characteristics of cangrelor is its short half-life of 3 min [76]. Platelet homeostasis can occur within 60 min of cangrelor discontinuation [88]. A shorter duration of platelet inhibition should allow for more manageable episodes of bleeding and hopefully fewer bleeding fatalities. Cangrelor can achieve steady state in 30 min and inhibits platelet aggregation more than clopidogrel [85, 88]. Despite these advantages, two cangrelor studies (CHAMPION PLATFORM [89] and CHAMPION PHOENIX [90]) were terminated early because cangrelor failed to achieve efficacy. In the CHAMPION PHOENIX study ($n=11,145$), cangrelor use led to fewer primary endpoints: death from any cause, MI, ischemia-driven revascularization, or stent thrombosis vs. clopidogrel (4.7 vs. 5.9 %, $P=0.005$). There was no difference in GUSTO-defined severe or life threatening bleeding for cangrelor vs. clopidogrel (0.2 % vs. 0.1 %, $P=0.44$) or TIMI-defined major bleeding (0.1 % vs. 0.1 %, $P>0.999$). However, there was an increase in GUSTO-defined severe or moderate bleeding in the cangrelor group vs. the clopidogrel group but without statistical significance. Given the lack of efficacy and the lack of reduction of bleeding risk associated with cangrelor, it also may not be the best alternative option to use in neurosurgery unless future studies can show a clear benefit.

Other novel agents are still in development and lack any substantial patient population studies. The data for prasugrel, ticagrelor, and cangrelor as replacement agents for the typical antiplatelet agents, aspirin and clopidogrel, is weak at best right now. The best option now may be to rely on aspirin and clopidogrel because they have the most data and have been used the longest. Knowing more about the bleeding threat that exists with aspirin or clopidogrel may be better than the unknown bleeding risks associated with the novel agents, especially in the setting of neurosurgery.

Conclusion

There are still many questions left unanswered by this review chapter, because there is little data regarding the use of antiplatelets in neurosurgery. Better designed studies in the future may help to discover the role of antiplatelet therapy in hematoma expansion as well as the benefit of platelet transfusions in patients with a prior history of antiplatelet therapy who experience an ICH or traumatic head injury. Although there is a lack of neurosurgical guidelines regarding the use of antiplatelet therapy, The American College of Chest Physicians, The American Heart Association, and The American Stroke Association provide the best guidance on antiplatelet therapy in the perioperative setting. In neurosurgery, discontinuation of all antiplatelet therapy agents is likely the best option unless the patient has recently had a stent placed. In these situations, discontinuation of all agents except aspirin appears to be the best recommendation at this time. More studies must be performed to determine the true benefit of the novel antiplatelet agents prasugrel, ticagrelor, and cangrelor. Although some of the novel agents may not be inferior, they may be associated with higher bleeding risks. Until more data is available, it appears that aspirin is the antiplatelet agent of choice when antiplatelet therapy must be continued during neurosurgery because aspirin has been extensively studied and the risks are well known. Using aspirin at doses <100 mg per day may help reduce the risk of bleeding in patients who require antiplatelet therapy during neurosurgery.

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