ANTIPLATLET AGENT REVERSAL IN ADULTS WITH TRAUMATIC INTRACRANIAL HEMORRHAGE

SUMMARY

The use of antiplatelet agents (such as clopidogrel or aspirin) has been steadily increasing. The use of these agents raises concern for inadequate platelet aggregation in the setting of acute hemorrhage, especially intracranial hemorrhage (ICH). The purpose of this guideline is to provide recommendations for the evaluation and management of patients on aspirin or ADP-inhibitors (e.g. clopidogrel, prasugrel, ticagrelor, etc…) who present with acute spontaneous or traumatic ICH.

RECOMMENDATIONS

- **Level 1**
  - **Discontinue antiplatelet agents when traumatic intracranial hemorrhage is suspected.**
- **Level 2**
  - **None**
- **Level 3**
  - **Aspirin therapy testing and/or reversal is NOT necessary.**
  - **Do NOT transfuse platelets for patients with antiplatelet-associated intracranial hemorrhage who will *NOT* undergo a neurosurgical procedure, regardless of type of platelet inhibitor, platelet function assay (PFA) results, hemorrhage volume, or neurologic exam.**
  - **In patients with traumatic brain injury (TBI) AND known history of ADP-inhibitor antiplatelet therapy (e.g. clopidogrel (Plavix), prasugrel (Effient), ticagrelor (Brilinta), ticlopidine (Ticlid), etc…) AND who have a planned neurosurgical procedure:**
    - **Check baseline PFA-Plavix® AND if POSITIVE:**
      - **Administer 1 unit of apheresis platelets (1 unit = 6-10 pack) IV x 1**
      - **Transfuse platelets at the time of maximal desired benefit**
  - **In patients with TBI AND unknown history of antiplatelet agents AND who have a planned neurosurgical procedure:**
    - **Assess risk for administration of ADP-inhibitors (See algorithm)**
      - **High Risk: Treat the same as known history of ADP-inhibitors**
      - **Low Risk:**
        - **Check STAT PFA-PLAVIX® assay**
        - **Administer 1 unit of apheresis platelets if the assay is positive**
      - **Minimal Risk: No further action**
  - **Consider the addition of one of the following options in patients with renal dysfunction (i.e. BUN > 20 and/or serum creatinine >2) AND active bleeding:**
    - **Desmopressin injection (dDAVP) 0.3 mcg/kg IV in 50mL NS x 1**
      OR Cryoprecipitate 1 unit IV STAT

EVIDENCE DEFINITIONS

- **Class I:** Prospective randomized controlled trial.
- **Class II:** Prospective clinical study or retrospective analysis of reliable data. Includes observational, cohort, prevalence, or case control studies.
- **Class III:** Retrospective study. Includes database or registry reviews, large series of case reports, expert opinion.
- **Technology assessment:** A technology study which does not lend itself to classification in the above-mentioned format. Devices are evaluated in terms of their accuracy, reliability, therapeutic potential, or cost effectiveness.

LEVEL OF RECOMMENDATION DEFINITIONS

- **Level 1:** Convincingly justifiable based on available scientific information alone. Usually based on Class I data or strong Class II evidence if randomized testing is inappropriate. Conversely, low quality or contradictory Class I data may be insufficient to support a Level I recommendation.
- **Level 2:** Reasonably justifiable based on available scientific evidence and strongly supported by expert opinion. Usually supported by Class II data or a preponderance of Class III evidence.
- **Level 3:** Supported by available data, but scientific evidence is lacking. Generally supported by Class III data. Useful for educational purposes and in guiding future clinical research.

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INTRODUCTION

The antiplatelet agents, including aspirin, clopidogrel prasugrel, ticagrelor, ticlopidine, and others have a number of clinical applications including decreasing risk of atherothrombotic events such as myocardial infarction and stroke (1). Aspirin and clopidogrel are the two most widely utilized agents today, frequently in combination therapy. Ticlopidine, due to a number of severe adverse events including neutropenia, agranulocystosis, and thrombotic thrombocytopenia purpura, is rarely used (2).

Aspirin exerts its effects through inhibition of cyclooxygenase-1 (COX-1) which prevents the conversion of arachidonic acid to thromboxane A_2 (3). Aspirin achieves platelet inhibition within 10 minutes following administration of a single dose. Aspirin results in an irreversible inhibition of platelet aggregation which persists for 5-7 days following discontinuation of aspirin (the time required for the body to release at least 20% new circulating platelets) (1).

In contrast to aspirin, clopidogrel, prasugrel, ticagrelor, and ticlopidine exert their antiplatelet effects by binding to the adenosine diphosphate (ADP) receptor on platelets preventing ADP from binding and activating glucoprotein GPIIB/IIIa which is necessary for platelet activation (2,4). Clopidogrel has a slightly slower onset and typically achieves maximal platelet inhibition (40-60%) at 7 days after initiation of therapy (1). If a loading dose of 300-400 mg of clopidogrel is administered, platelet inhibition occurs within 2-5 hours (4,5). The result of clopidogrel administration is irreversible inhibition of platelet aggregation that will remain effective for the lifespan of the platelet (7-10 days) (4). Prasugrel, similar to clopidogrel, is also an irreversible inhibitor of the ADP $P2Y_{12}$ receptor. It has an onset of ≤ 30 minutes after a loading dose and duration of effect based on the lifespan of the platelets (6). Ticagrelor reversibly binds ADP $P2Y_{12}$ receptor with an onset following loading dose of 30 minutes and duration of 24-60 hours (7).

The risk of mortality following intracranial hemorrhage in a patient on warfarin therapy has been estimated to range from 16-80% (8). Several retrospective trials have been conducted to assess the impact of antiplatelet therapy on mortality associated with intracranial hemorrhage. Ohm et.al. found that elderly patients (age > 50 years) who were receiving antiplatelet therapy (either monotherapy or dual therapy) at the time of their traumatic brain injury (TBI) had a significantly higher mortality rate (23% vs. 9% in the control group, p =0.016) (8). Similarly, Wong etal. found that elderly trauma patients (mean age 65-71 years) receiving clopidogrel alone had a higher mortality compared to a matched control group (29% vs. 14%) (9). For patients presenting with spontaneous intracranial hemorrhages, aspirin has been identified as an independent predictor of death (10).

LITERATURE REVIEW

Platelet Function Assays

There are a number of modalities available to evaluate platelet function. These include bleeding time, platelet aggregometry, platelet works, thromboelastographic platelet mapping, impact cone and plate(let) analyzer, PFA-100, VASP phosphorylation state and platelet function assays (9). Each of these modalities has a number of limitations and/or are time consuming to conduct. The most recently developed test, the VerifyNow® rapid platelet function analyzer, was specifically designed to allow point-of-care detection of aspirin or clopidogrel resistance (11).

The PFA-100 assay uses a membrane with a standardized aperture coated with either collagen/epinephrine or collagen/adenosine diphosphate (ADP) to active platelets and measures the time to formation of a platelet plug for the aperture. This test is insensitive to multiple inherited clotting disorders and is also unable to detect the presence of clopidogrel therapy (11,12).

The VerifyNow® Aspirin assay utilizes arachidonic acid converted to thromboxane A_2 to initiate platelet activation. The results of the aspirin assay are reported as aspirin reaction units (ARU). Patients not receiving aspirin were found to have ≥ 550 ARU (sensitivity 91.4%, specificity 100%) – therefore, the presence of aspirin is determined by values < 550 ARU (12,13).

The VerifyNow® P2Y12 assay (designated PFA-Plavix® at ORMC) assesses the impact of clopidogrel (Plavix®) or other P2Y12 inhibitors administration on platelet function. This assay assesses the rate of

platelet activation by ADP binding to the P2Y12 receptor (the inhibition target for clopidogrel). This assay differs from the aspirin assay in that there is a clear distinction between pre-clopidogrel therapy and post-clopidogrel therapy results. Results are reported as P2Y12 reaction units (PRU. A result of < 194 PRU is indicative of inhibition of platelet function by clopidogrel or other P2Y12 inhibitors. A result of 194-419 PRU correlates to normal platelet aggregation (12,14-16).

Interpretation of Platelet Function Assays (13,14,16-18)

Test	***Abnormal ("Positive")***	***Normal ("Negative")***
Platelet Function Assay **(PFA-100®)**	> 180 seconds = abnormal > 200 seconds = Aspirin effect > 300 = GP IIb/IIIa inhibitor effect	63 – 180 seconds*
Platelet Function Assay ASPIRIN **(VerifyNow® Aspirin Assay)**	< 550 ARU	≥ 550 ARU
Platelet Function Assay PLAVIX **(VerifyNow® P2Y12 Assay)**	< 194 PRU	194-419 PRU†

GP IIb/IIIa inihibitor = glycoprotein IIb/IIIa, ARU = aspirin reaction units, PRU = P2Y12 reaction units
*Orlando Regional Medical Center (ORMC) Clinical Laboratory normal range

†Data from the package insert for the *VerifyNow® P2Y12 assay* suggests that a PFA Plavix > 194 PRU (formerly designated as < 20%) is associated with low risk of perioperative bleeding (14); a single center study in trauma patients with acute TBI targeted a PFA Plavix of ≤10% (now designated as ≥ 194 PRU) as a threshold at which platelets would not be transfused based on literature suggesting that levels of ≤10% (≥ 194 PRU) are indicative of clopidogrel resistance (15,19,20).

Test Comparison (12-14,17)

Tests	**Indications**	**Comments**
Platelet Function Assay **(PFA-100®)**	• Replaced bleeding closure time • Nonspecific test for platelet function • Use when history of anti-platelet therapy unknown • Collagen-epinephrine is tested first; if abnormal, collagen-ADP will be done automatically	• Often abnormal in vWF disease • Results can be affected by low vWF, low platelets (<100K), hematocrit (<30%) & use of GP IIb/IIIa inhibitors • Insensitive to Plavix (P2Y12) effect but can screen for suspected ASA use (Epi abnormal but ADP normal) • Effective to monitor DDAVP therapy • **Cost**: ~$8/test (not including tubes; supplies etc.)
Platelet Function Assay ASPIRIN **(VerifyNow® Aspirin Assay)**	• Specific test for platelet inhibition due to aspirin	• Results can be affected by NSAIDs, GP IIb/IIIa inhibitors • **Cost**: ~$30/test (not including tubes; supplies etc.)
Platelet Function Assay PLAVIX **(VerifyNow® P2Y12 Assay)**	• Specific test for platelet inhibition due to P2Y12 inhibitors such as clopidogrel (Plavix®)	• Results can be affected by low platelets or hematocrit; and use of GP IIb/IIIa • **Cost**: ~$56/test (not including tubes; supplies etc.)

NSAIDs = non-steroidal anti-inflammatory agents; ADP = adenosine diphosphate; Epi = epinephrine, DDAVP = desmopressin, GP IIb/IIIa = glycoprotein IIb/IIIa,

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Thromboelastography (TEG)
The use of standard TEG to assess platelet inhibition by antiplatelet agents has not been well delineated. The TEG will provide a picture of clot strength which includes platelet aggregation. There is a TEG platelet mapping (TEG PM) module, but it is not universally available. Cattano et al. utilized TEG PM to evaluate 57 patients on home dual-antiplatelet therapy who were scheduled for elective non-cardiac surgery. Their study demonstrated a predictable model of inhibition and a decrease in platelet inhibition based on time since last dose of aspirin or clopidogrel (21). This information provides some initial data to help guide interpretation of the TEG PM. Further studies on the utilization of the TEG PM module in the traumatic brain injury setting are needed. Please see the "Thromboelastography (TEG) in Trauma" guideline for additional information on current place in care and interpretation of the values.

Reversal Strategies for Antiplatelet Agents
There are several reversal strategies available for patients on antiplatelet therapy who present with an acute ICH (spontaneous or traumatic) (1). These strategies include administration of platelets, desmopressin, conjugated estrogens, and/or recombinant factor VII (1,22).

Ohm et al. conducted a retrospective review of 90 patients 50 years or older admitted with a diagnosis of ICH and known pre-admission antiplatelet administration (aspirin, clopidogrel or both). The treatment patients were matched to 89 controls with similar injuries, but no pre-injury antiplatelet therapy. The most common mechanism of injury was fall and patients receiving antiplatelet therapy had significantly more co-morbid conditions (71.1% vs. 34.8%, $p<0.001$). Platelet transfusions were administered to 24 of 90 study patients and 5 of 89 control patients ($p=0.001$). No mention was made of the quantity of platelets transfused. Platelet function assays were not routinely performed. There were no statistically significant differences in disposition of patients at discharge (8).

Downey et al. conducted a retrospective study to assess the impact of platelet transfusions in elderly TBI patients who were on chronic antiplatelet therapy prior to injury. They identified 328 patients at two different institutions who were greater than 50 years old, receiving chronic antiplatelet therapy (aspirin or clopidogrel) and sustained a TBI. Of these patients, 166 received a platelet transfusion (the majority at one hospital that had a protocol to transfuse if the platelet function assay was abnormal). There was no difference in the mortality rate between the two groups (17.5% vs. 16.7%, p=0.85). This study was limited by its retrospective nature and did not include an assessment on the impact of time from injury to platelet transfusion on mortality (23).

Vilahur et al. conducted a study in healthy volunteers to assess the efficacy of platelet transfusions in reversing the platelet inhibition caused by the combination of aspirin and clopidogrel. They established that the administration *ex vivo* of platelets could overcome the inhibition demonstrated following standard loading and maintenance doses of aspirin and clopidogrel in patients previously naïve to either agent. Their *ex vivo* model provides a guideline for the number of units of pooled platelets necessary to overcome a certain percentage of inhibition. The number of units is calculated off of the baseline platelet count and the amount of inhibition. They demonstrated normalization of platelet aggregation by the addition of as little as 20% of platelet rich plasma (PRP) to the study subjects' plasma, but patients who received a 600 mg clopidogrel loading dose followed by three days of 75 mg per day required more donor platelets to normalize platelet aggregation (5).

% added pooled PRP*	Platelet units†	Platelet pools‡
20	5	1
40	10	2
50	12.5	2-3
60	15	3

*PRP = platelet rich plasma – the percent of normal platelets added to the aspirin / clopidogrel patient's plasma to reverse the effects of anticoagulation
†Platelet units – increased platelet counts by 10,000 μL
‡Platelet pool = 5 platelet units

Powner et al. reviewed the options presently available to reverse antiplatelet agents. Their recommendation was a minimum of 5 units or equivalent of platelets to offset the effects of routine aspirin or clopidogrel/ticlopidine administration. This combined with discontinuation of aspirin/ clopidogrel/ticlopidine (19).

In 2011, Bachelani et al. conducted a retrospective review of 84 trauma patients with TBI to assess the need for platelet transfusion based on PFA-ASA and then re-analyze the PFA-ASA for response. Of the 84 patients, 64% (54/84) had a (+) PFA-ASA on arrival. All of these patients received one unit of apheresis platelets. Forty-five of the 54 PFA(+) patients had post-transfusion PFA-ASA, of which only 64% had a PFA-ASA > 550 post-transfusion. For the total group analysis, the authors noted that a history of aspirin therapy was not associated on logistic regression with ICH progression. Additionally, transfusion of platelets had no impact on mortality, progression of ICH or need for surgery (24).

In 2013, the Surgical Critical Care team at ORMC conducted a retrospective review of all adult patients with a documented TBI on Head CT and a PFA test ordered on admission. A total of 127 patients were evaluated and 65% had a positive PFA. Logistic regression revealed that a positive PFA did not predict worsening of the ICH, need for operative intervention or mortality. Additionally, it was determined that the PFA-ASA assay only has a sensitivity of 0.72 and a specificity of 0.73 to detect platelet inhibition due to aspirin in TBI patients (25,26).

In 2015, Leong et al. conducted a meta-analysis of four retrospective trials evaluating the effect of platelet transfusions in patients with TBI on clinical outcomes. In the pooled analysis, there were a total of 711 patients (316 received platelets and 395 did not receive platelets). In general, the patients were of similar age, admission GCS, admission injury severity score (ISS), mechanism of injury and hospital LOS. The forest plot for in-hospital mortality demonstrated a trend toward increased mortality in the patients who received platelets (OR 1.77 compared to the non-transfused patients, 95% CI 1-3.13). The authors found no difference in rates of neurologic or medical decline, need for neurosurgical intervention, or progression of ICH between the two groups (27).

In 2016, the Neurocritical Care Society published antithrombotic reversal guidelines (22). The recommendations for reversal of antiplatelet agents for any type of ICH are as follows:

Recommendation	Quality of Evidence
Recommend discontinuing antiplatelet agents when intracranial hemorrhage is suspected.	Good practice statement
Suggest ***against*** platelet transfusion for patients with antiplatelet-associated intracranial hemorrhage who will ***not*** undergo a neurosurgical procedure, regardless of the type of platelet inhibitor, platelet function testing, hemorrhage volume, or neurological exam	Conditional recommendation, low-quality evidence
Suggest platelet transfusion for patients with aspirin- or ADP inhibitor- associated intracranial hemorrhage who ***will*** undergo a neurosurgical procedure.	Conditional recommendation Low-quality evidence
Suggest platelet transfusion for patients with aspirin- or ADP inhibitor- associated intracranial hemorrhage who ***will*** undergo a neurosurgical procedure.	Conditional recommendation Moderate quality of evidence
Recommend platelet function testing prior to platelet transfusion if possible.	Strong recommendation Moderate quality evidence
When platelet function testing is not readily available, empiric platelet transfusion may be reasonable.	Conditional recommendation Low-quality evidence
Recommend against platelet transfusion for patients with laboratory documented platelet function within normal limits or documented antiplatelet resistance.	Strong recommendation Moderate quality evidence

Adapted from Frontera JA, et.al. *Neurocrit Care.* 2016:24:6-46. (22)

Based on the literature published to date, the known risks of platelet transfusion (transfusion –associated acute lung injury [TRALI], infection, etc…), and the lack of documented benefit on survival or functional outcomes, it is recommended that platelet transfusions be utilized only as recommended by the currently published guidelines.

Uremic Bleeding and Platelet Dysfunction
Cryoprecipitate can be considered as a treatment option in patients with uremic bleeding. Each unit of cryoprecipitate contains variable amounts of von Willebrand factor (vWf), factor VIII, and fibrinogen. It is postulated that administration of cryoprecipitate may increase the amount of circulating functional clotting factors in the patient's plasma. It may be beneficial in acute bleeding due to its relatively quick onset of action (one hour), but overall response may vary from patient to patient. Administration of cryoprecipitate does carry the same risks as other blood product transfusions (29).

Estrogens decrease circulating levels of antithrombin III and protein S and increase factors VII, VIII, IX, X, and prothrombin. In addition, platelet counts may also be increased (30). Livio et al. administered conjugated estrogens to six patients (age range 29-61 years) with chronic renal failure and a history of bleeding and prolonged bleeding time (≥ 20 minutes; normal range 5-7 minutes for adults). None of the patients were taking aspirin or other agents known to decrease platelet aggregation for at least 20 days. Patients were given conjugated estrogens in a dose of 0.6 mg/kg IV daily for 5 days (some patients received as many as 10 days of therapy). All patients demonstrated a decrease in bleeding time following administration of the estrogens (31).

Desmopressin (DDAVP), a vasopressin analog, is indicated for control of hemorrhage in patients with mild-to-moderate hemophilia A and von Willeband's disease. It's primary mechanism of action is to increase circulating levels of factor VIII and von Willebrand factor (vWf) leading to secondary improvements in platelet adhesion to endothelial defects (28,29,32,33). It has also been considered for use in patients with uremia and prolonged bleeding time due to decreased expression of vWF and decreased activity of the vWF-factor VIII complex (29,30). Two advantages to DDAVP are its relatively quick onset of action (one hour), similarity to cryoprecipitate, and lack of transfusion-related side effects. However, the effects of DDAVP do not last more than 24 hours and patients are likely to develop tachyphylaxis after a single dose of DDAVP limiting its utility for repeated dosing (29).

There have been two randomized, double-blind, placebo controlled trials using DDAVP (either 0.3 mcg/kg/dose or 0.4 mcg/kg/dose) for the treatment of uremic bleeding. Mannucci et al. studied 21 patients with chronic renal failure – 12 patients were randomly assigned to either DDAVP (0.3 mcg/kg/dose) or placebo; the other nine patients were treated with DDAVP prior to nephrectomy. They demonstrated a decrease in bleeding time for all patients who received DDAVP (compared to baseline) and also one patient who received placebo. Statistical analysis was not available (32). Koehler et al. administered DDAVP 0.4 mcg/kg/dose subcutaneous to 8 patients on hemodialysis with consistently prolonged bleeding times. The administration of DDAVP resulted in statistically significant decreases in bleeding time. Interestingly, the total platelet count decreased significantly following administration of DDAVP; the clinical significance of this decrease was unclear (35).

Watson et al. conducted a small observational study on the effect of DDAVP (0.4 mcg/kg/dose over 12 minutes) on bleeding time in 12 patients with chronic renal failure and a history of bleeding. All 12 patients demonstrated a significant decrease in bleeding time following administration of DDAVP (36).

Use of Desmopressin (DDAVP) in Patients on Anti-Platelet Agents
With the increasing use of anti-platelet agents such as clopidogrel and aspirin, interest has been raised for a potential role of DDAVP in the setting of acute bleeding in these patients. The use of desmopressin in patients with normal renal function who have active hemorrhage and a history of recent (within the past seven days) of aspirin or clopidogrel (Plavix®) administration is mentioned in a number of review articles, however, there is a paucity of randomized controlled trials evaluating its safety and efficacy in this population (18).

Ranucci et al. reported a single case on the use of DDAVP to reverse the effects of clopidogrel in a patient undergoing emergent carotid endarterectomy (CEA). They described the abnormal results of PFA-100 consistent with clopidogrel therapy. These results improved following administration of a single dose of 0.3 mcg/kg of DDAVP but did not return completely to normal. The patient underwent an uneventful CEA (37).

Gratz et al. enrolled 65 patients (DDAVP n=29, Placebo n=30) in a randomized, double-blind, placebo-controlled trial looking at the effect of DDAVP administration on bleeding in patients on aspirin undergoing coronary artery bypass grafting (CABG). They included all patients who had taken aspirin within the seven days prior to surgery. Patients in the DDAVP group received 0.3 mcg/kg/dose in 50mL NS infused over 30 minutes immediately after heparin reversal with protamine. Patients in the DDAVP group had significantly less chest tube and total blood loss compared to placebo ($p<0.05$). There were no differences between groups with regard to transfusion requirements. Complications were similar between groups with three myocardial infarctions (MI) in the DDAVP group (one fatal) and one fatal MI in the placebo group (33).

Floradal et al. investigated the use of DDAVP on bleeding time in 18 patients (12 aspirin patients and six control patients) undergoing elective cholecystectomy. All patients underwent open cholecystectomies. Six of the aspirin patients were randomized to receive two doses of DDAVP (0.3 mcg/kg/dose over 30 minutes) at induction of anesthesia and then six hours later. The patients in the DDAVP group had a significantly longer preoperative bleeding time compared to placebo. DDAVP did shorten this bleeding time to a time comparable to placebo. There was no difference in postoperative bleeding time. All of the bleeding complications in this study occurred in the aspirin alone group (38).

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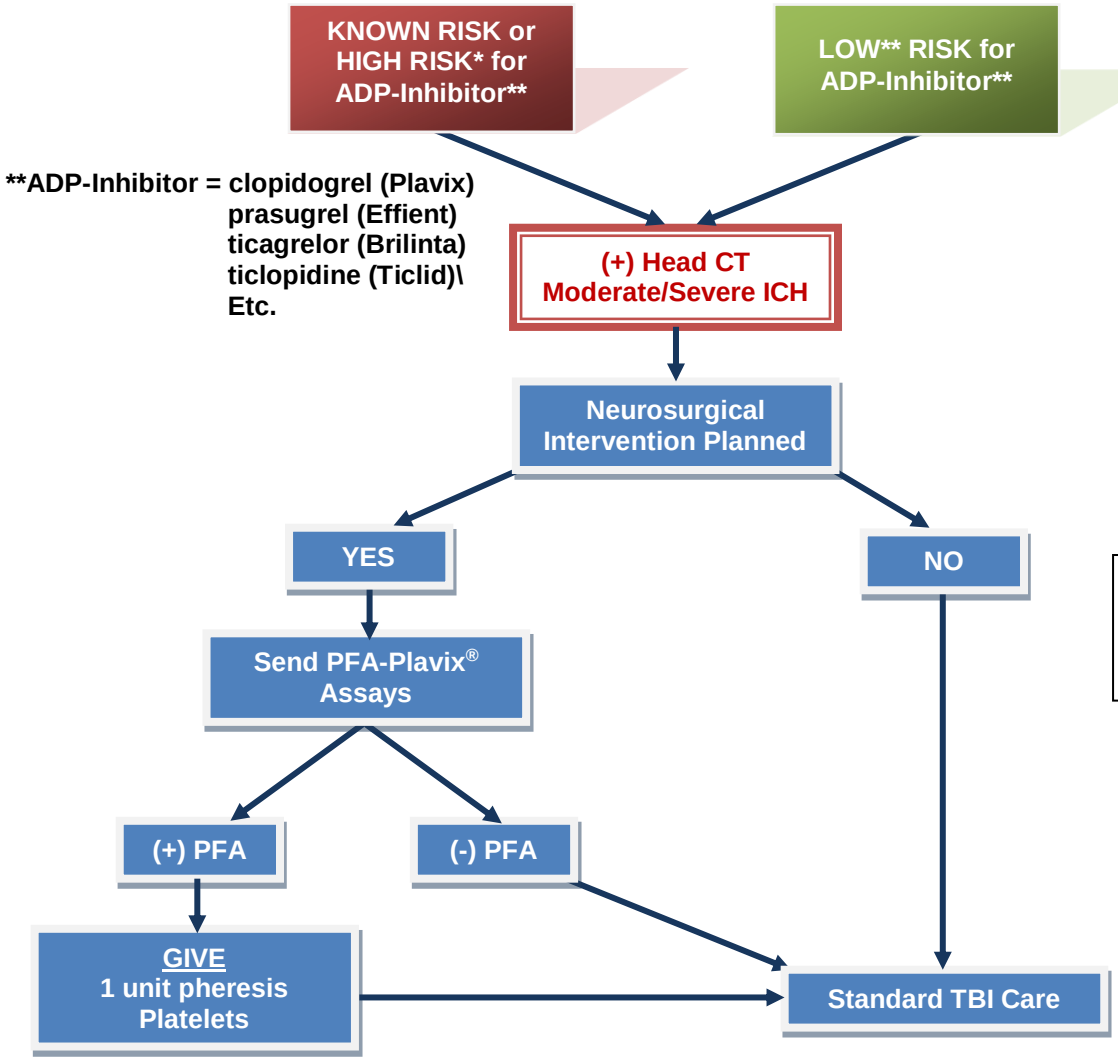
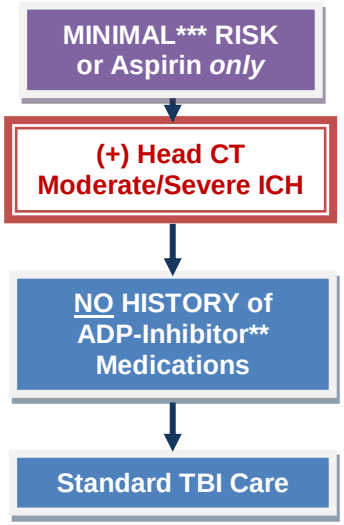
ASSESSING RISK of PLATELET DYSFUNCTION in TRAUMATIC INTRACRANIAL HEMORRHAGE





Comment: at present, there is no information available regarding the ability of PFA assays to assess for the presence of alternative medications that may also be causing platelet dysfunction (such as ginkgo, willow bark, dong quai, danshen, etc).

KNOWN RISK = Patient is on antiplatelet agents such as clopidogrel, prasugrel, ticagrelor, ticlopidine, etc.

****DOES NOT INCLUDE ASPIRIN****

***HIGH RISK**
- Sternotomy scar
- Atrial fibrillation on the monitor
- Elderly
- Sequelae of peripheral vascular disease

****LOW RISK**
- Age > 40 AND diabetes

*****MINIMAL RISK**
- Age < 40
- No known cardiovascular disease

1 unit pheresis platelets (single donor) = 6-10 random/pooled platelet packs

PFA = Platelet Function Assay (Plavix Assay = VerifyNow P2Y12 Assay)

Interpretation:
PFA Plavix > 194 PRU = NO clopidogrel-induced platelet dysfunction detected