Antiplatelet Strategies for

Paracorporeal VADs

**BACKGROUND**

Antiplatelet initiation and titration plans should be driven by the VAD team and/or dedicated hematology service with special expertise in MCS to maintain consistency and continuity of care.

**ACTION REVISED DATE:** 07/02/2020

**OBJECTIVES**

No approach to antiplatelet therapy initiation, monitoring, nor titration has been evaluated.  There is wide variation among institutional experience and practice with minimal data to support any one method.  This document is intended to serve as a guide for suggested approaches to antiplatelet therapy in children supported by paracorporeal VADs. Paracorporeal VADs are defined as pumps outside of the body with either temporary or durable cannula. Thrombogenicity varies by device type, cannula type, and number of connectors, as such variations in antiplatelet therapy may be required for different types of paracorporeal devices. The most common paracorporeal VAD include: Berlin Heart EXCOR with EXCOR cannula and Centrimag/Pedimag/Rotaflow with EXCOR cannula.

In this document, we strive to provide a summary and harmonization of institutional practices that appear reasonable based on the current clinical experience surrounding antiplatelet therapy in the pediatric paracorporeal population.

**PROTOCOL**

**Aspirin (acetylsalicylic acid)**

Aspirin induces its platelet inhibitory effect via COX-1 inhibition by irreversibly blocking the arachidonic acid (AA) binding site and reducing the expression of platelet surface GP IIb/IIIa receptors.  This effect is irreversible for the life of the platelets exposed (7-10 days in healthy persons, may be shorter in children with inflammation and exposure to extracorporeal circuits due to inflammation-induced COX-2 activation resulting in high on-aspirin platelet reactivity).

**Dosing preparations:**

* Immediate release (oral 75 mg, 100 mg, 162 mg, 325 mg, non-enteric coated/chewable 81 mg; rectal suppositories 300 or 600 mg)
* Delayed release (oral enteric coated 81 mg, may have lower efficacy when compared to the chewable tablet)
* *Starting dose: 3-5 mg/kg/day once daily (minimum 20.25 mg)*
* *Maximum total daily dose: 30 mg/kg/day up to 325 mg per dose*

**Adverse effects:**

* Tinnitus, diminished auditory acuity
* GI intolerance/ulcers (6-31%)
* Sensitivity/allergies have been described: skin reaction, urticaria, angioedema, agitation, confusion, acidosis, hyperkalemia, hypoglycemia, acetabular bone destruction, rhabdomyolysis, weakness, anemia, DIC, prolonged PT
* There are many medications and foods that can diminish or enhance salicylate effect, see Special Considerations
* No specific antidote

**Special considerations:**

* Ibuprofen, naproxen and other NSAIDS can reduce the cardioprotective effect of ASA [[Capon 2005](https://www.ncbi.nlm.nih.gov/pubmed/?term=Pharmacodynamic+Interaction+of+Naproxen+With+Low-Dose+Aspirin+in+Healthy+Subject); [Catella-Lawson 2001](https://www.ncbi.nlm.nih.gov/pubmed/11752357)].
* If absolutely needed, NSAIDS should be administered 2 or more hours after aspirin [[MacDonald 2003](https://pubmed.ncbi.nlm.nih.gov/12598144/?from_term=Effect+of+ibuprofen+on+cardioprotective+effect+of+aspirin&from_pos=2)].
* Does not require renal dosing, but cautious use if CrCl <10 for worsening nephropathy
* Avoid in severe liver disease
* ASA has been associated to prolong PT and can be a cause of thrombocytopenia
* ASA can enhance the nephrotoxic effects of ACE-I (*Risk C: Monitor therapy*)
* ASA can diminish the therapeutic effect of ACE-I (*Risk C: Monitor therapy*)
* Calcium channel blockers (CCB) can enhance the antiplatelet effect of ASA
* ASA may enhance the adverse effects of corticosteroids related to GI bleeding
* ASA can decrease the absorption of ascorbic acid
* ASA can diminish the effect of spironolactone
* The following foods can cause salicylate accumulation: prunes, raison, tea and gherkins, curry powder, paprika, licorice as they contain additional salicylate... DID YOU KNOW the average American diet contains 10-200mg/day of salicylates?
* The following foods can increase urinary excretion of salicylates: Vit C containing fruits
* Unable to achieve “therapeutic ASA” and/or thrombosis in setting of ASA:
	+ Pharmacogenomics testing for CYP2C9 polymorphism
	+ Consider BID dosing (should also be considered in setting of significant thrombocytosis)
	+ Consider rectal administration if enteral access (gastric or jejunal) is not feasible or in smaller infants where crushing and diluting the medication leads to loss of some of the needed dose to the tube or cup.
	+ Consider adding or transitioning to alternate antiplatelet agents (Clopidogrel, Ticagrelor, Dipyridamole)
* Bleeding events/supratherapeutic on ASA:
	+ Pharmacogenomic testing for CYP2C9 polymorphism
	+ Review medications or foods that may lead to accumulation of salicylate effect
	+ Change formulation (from chewable to enteric coated, or PR)
	+ Consider changing to lower BID dosing

**Plavix (clopidogrel)**

Clopidogrel prevents platelet activation and aggregation by irreversibly blocking the P2Y12 component of adenosine diphosphate (ADP) receptor on the platelet surface.  The half-life of the parent drug is 6 hours, but the active metabolite has a half-life of 30 minutes. CYP2C19 inhibitors may reduce the concentration of active metabolites and CYP2C19 polymorphism may affect efficacy.

**Dosing preparations:**

* Suspension oral 5 mg/ml or film coated tablet 75 mg
* *Starting dose: 0.2 mg/kg/day once daily.*
* *Maximum: 1.2 mg/kg/day up to 75 mg per day*

**Special considerations**

* No renal or hepatic dosing adjustment necessary
* Unable to achieve “therapeutic Plavix effect” and/or thrombosis in setting of Plavix:
	+ Pharmacogenomics testing for CYP2C19 poor metabolizer (CYP2C19\*2 or \*3 carriers)
	+ Assess for medications that will decrease effect of Plavix: amiodarone, CCB, erythromycin, fentanyl, grapefruit juice, lansoprazole, omeprazole, pantoprazole, morphine
	+ Change to alternative antiplatelet agents (ticagrelor, dipyridamole, or ASA)
* Bleeding events/supratherapeutic on Clopidogrel:
	+ Pharmacogenomics testing for CYP2C19 hypermetabolizer

**Dipyridamole (Persantine)**

Dipyridamole synergistically modifies several biochemical pathways, including: a) inhibition of platelet cAMP-phosphodiesterase; b) potentiation of adenosine inhibition of platelet function by blocking reuptake by vascular and blood cells, and subsequent degradation of adenosine; and possibly, c) potentiation of PGI2 antiaggregatory activity and enhancement of PGI2 biosynthesis.

*\*Note that dipyramidole has vasodilatory properties including the coronary arteries.*

**Dosing preparations:**

* IV infusion not generally used, rather 10 mg/ml oral suspension
* *Starting dose: 1 mg/kg every 6 hours.*
* *Maximum: 4 mg/kg every 6 hours (usual adult maximum dose 100 mg/dose)*

**Adverse effects:**

* Headaches, dizziness, flushing

**General considerations for initiation of antiplatelet drugs:**

*Prior to starting antiplatelet therapies, these suggested criteria should be considered:*

1. *Patient is tolerating anticoagulation without excessive bleeding as agreed upon by surgical and medical teams.*
2. *Evolution of chest tube output from sanguinous to serosanguinous.*
3. *Suggest stable platelet count over 80 x 103/mL.*
4. *Maximum amplitude by heparinase TEG is not below 50 mm and/or does not already exhibit 70% AA or ADP ­­inhibition prior to starting either aspirin or clopidogrel respectively*

**Table of strategy options:**

|  |  |  |
| --- | --- | --- |
| **Weight-based strategy** | **Circuit appearance** | **Titration based on responsiveness testing** |
| Antiplatelet medications are usually started shortly after achieving a therapeutic PTT.**Medication goals:****Aspirin*** Double dose each day until achieving target
* Target dose: 30 mg/kg-day divided BID

**Plavix*** Double dose each day until achieving target
* Target dose: 0.8-1 mg/kg-day, once daily

**Caveats:** * The above maximum target doses are typical for Berlin Heart patients that eventually are transitioned to enoxaparin as a chronic anticoagulation agent. While on Bivalirudin, due to its innate antiplatelet effect we consider lower antiplatelet medication doses (usually half of the maximum above and sometimes no plavix)
* Target TEG MA heparinase of 55-65 but do not titrate on any sliding scale based on those numbers. If greater than 65, assess the clinical picture to see if there is a source of inflammation or if medications can be weight adjusted, at times also add Omega 3 fatty acids as well 500 mg BID as well as in extreme cases with excessive pump thrombosis can go to as high as 1.8/kg of plavix
* Optimize GI prophylaxis, especially in continuous flow pumps to prevent bleeding, at times dual therapy is needed.
* Clarify your route of administration of these medications. ASA in particular is tough to give to small babies effectively by mouth/tube as it does not compound and can be gritty and clog up tubes. If possible to have patients chew their ASA or if babies consider crushing multiple small dose tablets to increase the amount of powder or rectal ASA for more precise dosing and assurance that what you order is what the patient gets.
 | Antiplatelet therapy initiation is suggested once anticoagulation therapy has been therapeutic and stable, based on the appearance of the circuit and bleeding risk profile.**Clean Circuit:*** Patient is therapeutic and stable on anticoagulation infusion, with no signs of increased bleeding and risk is low
* Initiate ASA therapy
* Monitor for signs of increased bleeding, especially if chest drains still in place, and other sites

**Circuit with early postoperative fibrin/thrombus deposition within 24-48 hours of VAD implantation** (inflammation, infection, shearing):* Patient should be on an anticoagulation infusion, based on bleeding risk profile.
* If not on anticoagulation, consider starting anticoagulation prior to ASA therapy
* If patient is subtherapeutic on anticoagulation, optimize therapy and monitor VAD and bleeding
* If available, send TEG/ROTEM, coagulation profile and platelet function assay to assess reason for fibrin/thrombus deposition.
* If anticoagulation is optimal, and bleeding appropriate, start ASA therapy irrespective of hardware/tubing, and titrate to target ranges (see monitoring and titration) in discussion with clinical team.
* If available, repeat platelet function assay to assess response.

**Circuit with delayed fibrin/thrombus deposition, and not on ASA therapy*** If available, Send TEG/ROTEM or platelet function assay to assess platelet activity
* Initiate ASA therapy and repeat platelet function assay to assess response

 **On stable anticoagulation and aspirin therapy, with signs of increased fibrin/thrombus deposition:*** Check anticoagulation parameters with labs, TEG/ROTEM, and platelet function assay
* Optimize/increase anticoagulation goals if necessary
* Increase aspirin dose per dosing titration table until either platelet function assay indicates improved response or max dose reached

**Subtherapeutic anticoagulation, not on ASA and evidence of fibrin/thrombus deposition:*** If anticoagulation therapy is subtherapeutic, continue to titrate to target goals
* Obtain TEG/ROTEM and platelet function assay
* Assess for any bleeding (chest tubes, cannula sites, airway, etc.)
* Initiate ASA therapy at starting dose and titrate to goal dose

**For institutions who give consideration to chest tubes prior to starting ASA therapy:*** Patient is therapeutic and stable on an anticoagulation infusion and bleeding risk is not high. If bleeding risk is high, discuss with team best and safest next steps
* If available, obtain TEG/ROTEM or platelet function assay to assess platelet function
* Discuss with team initiation of ASA therapy
* After initiation of ASA therapy, monitor chest tube output for increased bleeding
* Consider removing CT when bleeding remains stable or improves.
 | Two-step aspirin titration to ensure (1) responsiveness and (2) 24-hour antiplatelet effect:**STEP 1 – responsiveness testing (“peak” effect):*** Obtain TEG with platelet mapping at 4 hours after first aspirin dose.
* If platelet inhibition is adequate at 4-hours (>70% AA inhibition), continue to STEP 2.
* If platelet inhibition is inadequate at 4-hours (<70% AA inhibition), increase aspirin dose (up to 30 mg/kg/dose).
	+ Re-test TEG with platelet mapping at 4-hours after this increased dose.
	+ >70% arachidonic acid inhibition demonstrates adequate “peak” effect of platelet inhibition by aspirin via the AA pathway, proceed to STEP 2.

**STEP 2 – 24-hour antiplatelet effect:*** To ensure long-lasting 24-hour platelet inhibition with aspirin (once responsiveness is established in STEP 1), re-test TEG with platelet mapping at 24 hours after the first dose (prior to the next dose)
* If platelet inhibition is adequate at 24 hours (>70% AA inhibition), continue once daily aspirin dosing.
* If platelet inhibition is inadequate and waned at 24 hours (<70% AA inhibition), increase dosing frequency to twice daily (same dose from STEP 1 that demonstrated adequate “peak” inhibition of AA pathway).

**Note**: A similar strategy can be utilized with either ROTEM or VerifyNow testing for aspirin responsiveness. The use of multiple modes of testing should be considered; however, fair discordance exists between assays [[Lordkipanidzé 2007](https://pubmed.ncbi.nlm.nih.gov/17569678/)] |
| **IT IS REASONABLE TO START ANTIPLATELET THERAPY WITH ASPIRIN WITHIN 2-4 DAYS POST-OPERATIVE.****SUGGESTED USUAL SEQUENCE OF ANTIPLATELET THERAPY INITIATION: ASPIRIN, FOLLOWED BY CLOPIDOGREL OR DIPYRAMIDOLE.** |

**Circuit appearance-based strategy:**

Recommendations for aspirin initiation in the post-operative pediatric VAD patient, primarily based on circuit appearance and taking into consideration bleeding risk profiles of the patient. Below are recommendations based on circuit appearance, at different clinical times in the patient’s course. Always monitor for increase in oozing or bleeding as you add or increase anticoagulation/antiplatelet therapy, assess the VAD frequently per unit protocol, and increase frequency if any fibrin or clots detected. [[Steiner 2016](https://www.ncbi.nlm.nih.gov/pubmed/27556152) and [Rosenthal 2017](https://www.ncbi.nlm.nih.gov/pubmed/28606584)]

1. **Clean circuit:**
	1. Patient is therapeutic and stable on anticoagulation infusion as set by clinical team, with no signs of increased bleeding and bleeding risk is low
	2. Initiate ASA therapy
	3. Continue monitoring for any signs of new onset oozing or bleeding, especially if chest drains in place
	4. If oozing or bleeding noted after ASA initiation, refer to “monitoring”
2. **Circuit with early postoperative fibrin/thrombus deposition within 24-48 hours of VAD implantation** (inflammation, infection, shearing)
	1. Patient should be on an anticoagulation infusion, based on bleeding risk.
		* + If not on anticoagulation, consider starting anticoagulation prior to ASA therapy
	2. If patient is not therapeutic on anticoagulation, optimize therapy and monitor VAD and bleeding deposition [[Feldman 2013](https://www.ncbi.nlm.nih.gov/pubmed/23352391)].
	3. If anticoagulation is optimal, and bleeding is within expected, start ASA therapy irrespective of hardware/tubing, and titrate to target ranges (see monitoring and titration) in discussion with clinical team
	4. If available, repeat platelet function assay to assess response.
3. **Circuit with delayed fibrin/thrombus deposition**
	1. If patient is not on ASA therapy and fibrin or thrombi deposition noted
	2. If available, Send TEG/ROTEM or platelet function assay to assess platelet activity
	3. Initiate ASA therapy and repeat platelet function assay to assess response
4. **Special Considerations**
	1. On stable anticoagulation and ASA therapy, with signs of increased fibrin/thrombus deposition
		1. Check anticoagulation parameters with labs, TEG/ROTEM, and platelet function assay
		2. Optimize/increase anticoagulation goals if necessary
		3. Increase aspirin dose per dosing titration table until either platelet function assay indicates improved response or max dose reached
	2. Subtherapeutic anticoagulation, while not on ASA and evidence of fibrin/thrombus deposition
		1. If IV anticoagulation therapy is subtherapeutic, continue to titrate to target goals
		2. Obtain TEG/ROTEM and platelet function assay
		3. Assess for any bleeding (chest tubes, cannula sites, airway, etc)
		4. Initiate aspirin therapy at starting dose and titrate to goal dose
	3. For institutions who give consideration to chest tubes prior to initiation of ASA therapy:
		1. Patient is therapeutic and stable on an anticoagulation infusion and bleeding risk is not high
			* If bleeding risk is high, discuss with team best and safest next steps
		2. If available, obtain TEG/ROTEM or platelet function assay to assess platelet activation
		3. Discuss with team initiation of ASA therapy
		4. After initiation of aspirin therapy, monitor for signs of increased bleeding while chest tubes are in place
		5. Consider removing CT when bleeding remains stable or improves

**Titration based on responsiveness testing (TEG with platelet mapping):**

Thrombelastography (TEG) is a whole blood viscoelastic hemostatic assay (VHA) that characterizes the life-span of clot formation from the initiation of fibrin cross-link formation through clot breakdown and fibrinolysis.  Another commonly-used VHA is rotational thrombelastometry (ROTEM) that produces comparable whole blood hemostatic data merely with altered terminology.  The maximal amplitude of the TEG oscillogram (or maximum clot firmness of ROTEM) demonstrates the maximal clot strength achieved by the platelet linking via the interaction of fibrin and platelet surface GP IIb/IIIa receptors.  Platelet mapping is performed by comparison of 3 samples from the same patient.  MAthrombin demonstrates the maximal clot strength (MA from standard TEG oscillogram) via activation with Kaolin to induce a thrombin response to maximally activate all platelets and convert all fibrinogen to fibrin.  MAA (aka. MAfibrin) demonstrates the complete blockade of thrombin (platelets inhibited, fibrin activation only).  MAAA samples have arachidonic acid (AA) added (conversion inhibited by aspirin) to demonstrate the ability of non-inhibited platelets to activate.  The comparison of the AA-bathed MAAA tracing to the difference between the fully activated MAthrombin and fully-inhibited MAA tracings demonstrates the % platelet inhibition via the AA pathway in the presence of aspirin. [[Whiting 2014](https://www.ncbi.nlm.nih.gov/pubmed/24123050) and [Luddington 2005](https://www.ncbi.nlm.nih.gov/pubmed/15784122)]

The antiplatelet effect of acetylsalicylic acid has a half-life of 20 minutes and, thus, remains effective in the circulation for just over an hour (anti-inflammatory effect maintains a longer half-life).  New platelets generated after clearance of aspirin will likely remain uninhibited (and thus able to induce thrombosis) until the next dose of aspirin arrives. The increase in aspirin dosing frequency has been demonstrated to provide consistent platelet inhibitory effect in adult patients with inflammation associated with type 2 diabetes [[Spectre 2011](https://www.ncbi.nlm.nih.gov/pubmed/21800009) and [Rocca 2012](https://www.ncbi.nlm.nih.gov/pubmed/22471290)].

**Two-step aspirin titration to ensure (1) responsiveness and (2) 24-hour antiplatelet effect:**

1. **STEP 1 – responsiveness testing:**
	1. Obtain TEG with platelet mapping at 4 hours after first aspirin dose.
		1. Initial 4-hour post-aspirin testing is meant to establish adequacy of response to aspirin dose and meant to evaluate the “peak” effect on arachidonic acid (AA) inhibition.
		2. Aspirin (anti-platelet effect) has a short half-life of 20 minutes (anti-platelet effect). Early post-dosing testing will demonstrate the effect of that initial aspirin dose on the circulating platelets at that time.
	2. If platelet inhibition is adequate at 4-hours (>70% AA inhibition), continue to STEP 2.
	3. If platelet inhibition is inadequate at 4-hours (<70% AA inhibition), increase aspirin dose to next deliverable dose (up to 30 mg/kg/dose).
		1. Re-test TEG with platelet mapping at 4-hours after this increased dose.
		2. >70% arachidonic acid inhibition demonstrates adequate “peak” effect of platelet inhibition by aspirin via the AA pathway, proceed to STEP 2.
2. **STEP 2 – 24-hour antiplatelet effect:**
	1. Children after VAD implant are likely to have more-rapid platelet turnover (wound healing, circuit exposure, inflammation, infection).  Platelets produced after aspirin has been cleared (t ½ = 20 min) will not be inhibited by the initial aspirin dose.
	2. To ensure long-lasting 24-hour platelet inhibition with aspirin, re-test TEG with platelet mapping at 24 hours after the first dose (prior to the next dose):
		1. Waning of platelet inhibition prior to the second dose demonstrates less-than-24-hour platelet inhibition with once-daily dosing of aspirin.
		2. Platelet turnover results in production of new (AA pathway not inhibited) platelets after the clearance of the prior aspirin dose.
	3. If platelet inhibition is adequate at 24 hours (>70% AA inhibition), continue once daily aspirin dosing.
	4. If platelet inhibition is inadequate and waned at 24 hours (<70% AA inhibition), increase dosing frequency to twice daily (same dose from STEP 1 that demonstrated adequate “peak” inhibition of AA pathway).

*Note: A similar strategy can be utilized with ROTEM or VerifyNow testing for aspirin responsiveness.*

**VerifyNow Testing for Aspirin Resistance/Responsiveness:**

* The VerifyNow test is a qualitative test to aid in the detection of platelet dysfunction due to aspirin ingestion.
	+ Test results are reported in Aspirin Reaction Units (ARU) – Aspirin Reaction Units (ARU) indicate the amount of thromboxane A2-mediated activation of GP IIb/IIIa receptors involved in platelet aggregation.
	+ ARU is calculated as a function of the rate and extent of platelet aggregation. Expected values are in the range of 350-700 ARU. The cut-off to determine if a patient is receiving the therapeutic benefit of aspirin is 549.
* Use VerifyNow point of care test alone or in conjunction with TEG /PM to assess AP therapeutic range:
	+ For aspirin <549 ARU denotes responsiveness:
		- If >550 ARU, consider increasing ASA dose, changing to BID dosing, reviewing medication or food that may diminish effect, and/or adding or converting to another AP agent
	+ For Plavix <194 RU denotes responsiveness:
		- If >195 RU, consider increasing plavix dose, changing to BID dosing, reviewing medication or food that may diminish effect and/or adding or converting to a

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***Disclaimer:*** *The ACTION network is focused on quality improvement efforts such as harmonizing best practice protocols, disseminating them among institutions, and helping centers to improve care practices at the local level. This protocol was developed as a consensus tool for pediatric VAD programs. The information in the protocols are based on center practices, individual opinions, experiences, and, where available, published literature. Centers may choose to adapt this protocol to include in their center-specific protocols with reference to ACTION with the understanding that these are meant as guidelines and not standard of care. (Revised: 07/02/2020)*