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A thrombolytic protocol of bivalirudin for giant coronary artery aneurysms and thrombosis in patients with Kawasaki disease

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Introduction

Kawasaki disease (KD) is considered a rare condition but is the most common form of acquired heart disease in children in the United States. KD occurs worldwide, with the highest incidence in Japan and its etiology remains unknown. It is characterized by fever and systemic inflammation associated with rash, conjunctival injection, swollen hands and feet, dry, cracked lips, and enlarged cervical lymph nodes. The standard treatment is intravenous immunoglobulin (IVIG) and aspirin. When administered within 10 days of fever onset, treatment reduces the risk of coronary artery aneurysms (CAA) from 25% to ~ 5%. Almost all morbidity and mortality in KD occurs in KD patients with large or giant coronary aneurysms, defined as having a maximum coronary z score of ≥ 10 or absolute diameter greater than 8 mm. In patients with giant aneurysms in the early weeks after KD onset, coronary thrombosis often progresses to myocardial infarction and thus requires emergent medical intervention.

Thrombolysis: Addition of bivalirudin to tPA in acute Kawasaki disease

In this Grand Rounds, we present successful use of bivalirudin and tissue plasminogen activator (tPA) for thrombolysis in a high-risk infant with KD and thrombus in giant coronary artery aneurysms. We propose a protocol for these rare and high-risk patients, with the understanding that final management decisions must be individualized for each patient's particular clinical status

Case Vignette

A previously healthy 6-month-old Egyptian male infant presented with four days of fever associated with one day of rash, red eyes, red lips and swollen fingers. Initial physical examination identified bilateral conjunctival injection with limbic sparing, a generalized maculopapular rash, erythematous oral mucosa and vermillion border, and swollen digits of all four extremities. Laboratory investigation at presentation was significant for elevated inflammatory markers (C-reactive protein: 20.4 mg/dL, white blood cells (WBC): 14.1×10^3/μl with 68% neutrophils), normocytic anemia for age (hemoglobin: 8.3 g/dL, age-adjusted Z-score: -4.7); elevated alanine transaminase (112 IU/L) and sterile pyuria (urine WBC: 7/hpf, urine culture: no bacterial growth). He was diagnosed with complete Kawasaki disease (KD), admitted to a local children's hospital, and treated with a single dose of IVIG (2 g/kg) followed by infliximab (5 mg/kg) because of his young age and high risk of coronary artery aneurysms (CAAs). His initial echocardiogram on admission was interpreted as normal, as was a follow-up study on day three of hospitalization. He was discharged on low dose aspirin on day nine of illness.

He was readmitted from clinic three days later for recurrent fever with worsening anemia (hemoglobin: 7.2 g/dL, age-adjusted Z-score: -6.3), thrombocytosis (935×10^3/μl), and leukocytosis (WBC: 19.1×10^3/μl with 42% neutrophils). An echocardiogram was performed and was reportedly normal. Following a negative infectious work-up including blood and urine culture, respiratory viral PCR panel, and chest X-ray, he was started on oral prednisolone (2 mg/kg/day followed by a tapering course). As the dose was tapered, the fever recrudesced, and the CRP started to rise.

The infant was admitted again on day 23 of illness to the local pediatric intensive care unit (PICU) after an echocardiogram revealed multiple aneurysms of the left main coronary artery (LMCA) (4.5 mm, body surface area-adjusted Z-score: 8.1 using the Dallaire method), mid-left anterior descending (LAD) artery (4.7 mm, Z-score: 10.6) and right coronary artery (RCA, 4.7 mm, Z-score: 9.2). These were consistent with the findings of a cardiac computed tomography (CT) angiogram two days later showing fusiform CAAs of the LAD (4.8 mm, Z-score: 11.0), left circumflex artery (LCx, 3.5 mm, Z-score: 6.7) and RCA (4.9 mm, Z-score: 10.6). (Figure 1) The anti-inflammatory treatment was changed from prednisolone to anakinra (10 mg/kg/day) and cyclosporine (1.5-2 mg/kg/day, serum peak levels 101.6-604.5 ng/ml). An evaluation was negative for other vasculitides including anti-neutrophil cytoplasmic antibodies, myeloperoxidase and proteinase-3 autoantibodies.

The infant was treated with intravenous heparin infusion, but the therapeutic level of activated Partial Thromboplastin Time (aPTT) was not achieved consistently and the antithrombin 3 (ATIII) level was low (78%). Therefore, given the increased risk of thrombus in the giant aneurysms, he received three days of bivalirudin (0.15-0.26 mg/kg/hr) dosed for standard thrombosis risk (targeted aPTT: 60-80 seconds), which was switched to subcutaneous enoxaparin on day 28 of illness. While on bivalirudin infusion, he developed a left facial nerve palsy, a rare neurological complication of KD. An urgent CT scan of the brain identified no intracranial bleeding. A subsequent brain MRI also showed no abnormalities.

Despite these therapies, serial follow-up echocardiographic studies suggested enlarging CAAs over the following week with concerns for coronary artery thrombi, and the patient was transferred to the PICU at Rady Children's Hospital-San Diego on day 32 of illness for further management.

On arrival, a cardiac CT angiogram revealed giant fusiform CAAs of the LAD (8.3 mm, Z-score: 20.3), LCx (8 mm, Z-score: 18.3) and mid-RCA (9.1 mm, Z-score: 22.9), as well as multiple mural thrombi in the distal LAD, LCx and RCA causing vascular wall irregularity and near-total occlusion. (Figure 1) Anticoagulation and thrombolytic therapies were initiated including intravenous heparin infusion (10 U/kg/hr) with tissue plasminogen activator (tPA) at 0.05 mg/kg/hr for 8 hours/day for three days alternating with high dose bivalirudin (0.5 mg/kg/hr) (targeted aPTT: 80-100 seconds). Aspirin (5 mg/kg/day) was continued, and platelet responsiveness testing was confirmed with the VerifyNow test of 350 ARU with target level of <550 ARU. Beta-adrenergic blockade with propranolol was initiated and the anti-inflammatory regimen of anakinra (10 mg/kg/day) and cyclosporine (5 mg/kg/day) was continued.

The infant responded well to treatment, with normalized D-dimer levels implying that maximal thrombolysis had been achieved. A repeat cardiac CT angiogram after thrombolytic therapy demonstrated reduced size of the mural thrombi within the RCA and LAD, as well as interval decrease in the dimensions of the CAAs as compared to the CT upon transfer six days earlier. The patient was discharged on day 42 of illness on a weaning schedule of oral cyclosporine, oral magnesium/protein supplement, daily aspirin, three times daily propranolol and twice daily subcutaneous enoxaparin with an anti-Factor Xa level of 0.7 IU/ml. During follow-up clinic visits one week and one month after discharge, the infant remained clinically well with normal global LV systolic function, no obvious thrombus in the CAAs, and stable CAA sizes on echocardiography.

We describe an infant with KD complicated by multiple giant CAAs and intracoronary thrombosis. The initial regimen of anticoagulation and thrombolysis was unsuccessful in attaining the desired level of aPTT or preventing progression of thrombosis. This failure was

attributed to several factors, including the low ATIII level that was not replaced, the absence of concomittant use of tPA with heparin, and an inadequate bivalirudin dose and target aPTT range.

Pharmacology of Bivalirudin

Bivalirudin is a synthetic direct thrombin inhibitor (DTI) that binds reversibly to thrombin, engaging both the active/catalytic site and the exosite 1/fibrinogen binding site, independently of antithrombin.[1] With a molecular weight of approximately 4,000 Da, this small peptide is susceptible to cleavage by proteases, including thrombin. It exhibits a brief half-life of 19 minutes under normal renal function conditions, with about 80% undergoing enzymatic clearance and the remainder being eliminated by the kidneys. This characteristic allows its administration in patients with mild-to-moderate renal dysfunction without necessitating dose adjustment. However, in patients with renal failure requiring hemodialysis, the half-life may extend to 2 hours.

Bivalirudin possesses several distinctive characteristics that render it especially suitable for highly thrombogenic conditions in the pediatric population, as compared to the use of unfractionated heparin.[2–6] Firstly, unlike unfractionated heparin that only inhibits circulating thrombin, bivalirudin inhibits both circulating and clot-bound thrombin, thereby diminishing clot stability and fostering thrombolysis. Secondly, bivalirudin has little to no effect upon other serine proteases and does not require ATIII to enhance thrombin inhibition, a crucial requirement for heparin's effectiveness in inhibiting thrombin. In the case presented here, the ATIII level was initially low and the desired aPTT range was not achieved with the heparin infusion. The ATIII-independent effect of bivalirudin holds particular significance in pediatric patients due to developmental hemostasis—physiological changes in the hemostatic system from fetal to

adulthood.[7,8] In children under 6 months of age, ATIII levels are less than 50% of adult levels, primarily because it is a potent antiangiogenic protein. The physiologically low levels of ATIII necessitate higher doses of heparin to achieve therapeutic levels, leading to a non-linear dose-response curve, as ATIII can potentiate thrombin inhibition by a thousand-fold. Bivalirudin does not bind other circulating plasma proteins, ensuring a more predictable activity profile. Lastly, bivalirudin is not influenced by platelet factor 4 (PF4) and potentially inhibits platelet activation by suppressing thrombin, consequently impeding the activation of factors V, VIII, and X. Noteworthy is bivalirudin's intrinsic anti-inflammatory properties, complementing its anti-platelet effects, rendering it well-suited for conditions such as KD.

As with all anticoagulants, bleeding is the primary adverse event related to bivalirudin use. While there is no antidote to reverse bivalirudin effect, the half life is short secondary to proteolytic degradation at 19 min with preserved renal function and up to 2 hours with severe renal impairment secondary to ~ 20% renal excretion. Herein, we describe a protocol (Figure 2), based on first principles of the current understanding of the pharmacokinetics and pharmacodynamics of bivalirudin in children[9] and apply it to the pro-inflammatory and pro-thrombogenic state of KD. There are currently no data from clinical trials to guide the use of bivalirudin in this patient population.

Prior to initiation of antithrombotic therapy

We recommend that all patients have baseline cardio-hematological risk assessment for bleeding and thrombosis. This includes: (1) past medical history and family history of bleeding or thrombosis; (2) physical examination for bleeding (mucosal bleeding, blood in secretions, stool, urine, epistaxis, bruising, petechiae, menses, etc.) and symptomatic thrombosis (venous:

swelling, purpura, erythema; arterial: cool, blue, pulseless), and baseline neurological exam, or baseline neuroimaging (head ultrasound, MR or CT) if reassuring neurological exam cannot be obtained; and (3) baseline laboratory data of hemolysis and inflammatory markers (lactate dehydrogenase (LDH), plasma free hemoglobin, D-dimer, factor 8 activity, von Willebrand Factor vWF antigen and activity), coagulation studies (aPTT, prothrombin time (PT)/international normalized ratio (INR), fibrinogen, thrombin time), complete blood count (CBC) and differential, complete metabolic profile including creatinine and blood urea nitrogen for glomerular filtration rate estimation and liver function test (LFTs) including albumin, and cardiac biomarkers (high sensitivity troponins, brain natriuretic peptide).

Other optional laboratory work includes thromboelastography with platelet mapping (TEG-PM) to assess clot strength (maximal amplitude, MA), or rotational thromboelastrometry (ROTEM) with assessment of A10, A20 and MCF for clot strength in EXTEM, INTEM and FIBTEM based on center availability. Genetic thrombophilia work-up is warranted in the setting of significant history of thrombosis or familial history of thrombophilia. Note that bivalirudin will cause a false positive lupus anticoagulant.

Thrombolytic administration (tPA)

Timing of initiation of thrombolytic therapy should be prompt to treat and prevent thrombosis progression and compromise of coronary perfusion. Active bleeding or large territory ischemic stroke within the past 2 weeks, and intracranial hemorrhage or other major bleeding event within the last 48 hours, would generally preclude administration of tPA and/or other antithrombotic agents, unless the benefit of thrombolysis overweighs its risk regardless.

Coagulopathy needs to be corrected prior to initiation of tPA when: (1) fibrinogen < 150 mg/dL with cryoprecipitate 1 unit/10 kg of body weight (increase fibrinogen by 60-100 mg/dL) or fresh frozen plasma (FFP) 10-20 ml/kg and recheck 1 hour after infusion; (2) aPTT or PT > 1.5× upper limit of normal with FFP 10-20 ml/kg and recheck 1 hour after infusion; (3) platelet count < 50×10^3/μl. Because thrombocytopenia (platelet count < 150 K) is uncommon in KD except in the 5% of children with KD shock syndrome, other etiologies should be investigated. Platelet administration should be reserved for active bleeding. It is necessary to have blood products on hold and available. For neonates we recommend infusion of 10 units/kg FFP to replete plasminogen prior to initiation of tPA and consideration of FFP administration for infants 3 months to 1 year of age, if there is evidence of impaired fibrinolysis on adjunctive testing.

tPA dosing and monitoring (Alteplase)

The suggested pediatric dosing is 0.03-0.10 mg/kg/hr for 6-12 hours (max dose 2 mg/hr). We suggest starting at 0.05 mg/kg/hr for 8 hours as standard dosing. It is reasonable to consider shorter or longer durations of tPA based on patient's specific risk of thrombosis and bleeding. For standard risk, we chose the mid-range of both dose and duration. In setting of increased risk of bleeding such as lower platelet count or history of bleeding, then starting dose is lower at 0.03 mg/kg/hr. The initial dose should be determined according to patient-specific risks for bleeding and thrombosis based on baseline evaluation from medical history, physical exam, laboratory data and imaging. We recommend two sources of access (peripheral IV or central line) for tPA administration.

To enhance the overall effectiveness of thrombolytic therapy, and to reduce the risk of re-occlusion, concomitant administration of low dose anticoagulation should be considered. Early

in our experience, we utilized low dose unfractionated heparin (UFH) at 10 U/kg/hr given that there is more literature on the safety of concomitant UFH with tPA. However with expanding experience, it is also reasonable to consider starting low dose bivalirudin at 0.25 mg/kg/hr with normal renal function or 0.07 mg/kg/hr for severe renal dysfunction.[10,11] This dosing is half of the standard initiation dose for bivalirudin as shown in Table 1 and adjusted based on renal impairement. Bivalirudin based approach with concomitant tPA may be more simple and streamlined then transitioning between anticoagulants, but limited data in children currently exists.

During infusion, patients should be monitored with laboratory tests (CBC, PT, aPTT, fibrinogen, D-dimer, LDH, plasma free hemoglobin) every 4 hours or at the discretion of the managing team based on stability, and clinical assessment of the following: (1) hourly vital signs and neurological status (may be decreased in frequency for stable patients based on managing team's discretion), (2) continuous cardio-respiratory monitoring for infusion and 8 hours post-infusion, (3) urine and stool for blood with each void during infusion and 8 hours post infusion, (4) neuroimaging as needed for any change in neurological status.

Additional cycles of tPA may be repeated based on the response to treatment as determined by echocardiographic evaluation of coronary arteries and laboratory data.

Bivalirudin dosing and monitoring

Infusion of bivalirudin can be initiated or increased to therapeutic level immediately after completion of tPA or between cycles of tPA, through peripheral IV or central venous line (CVL). If bivalirudin is to be infused via CVL, we suggest priming the line to ensure systemic delivery

in a timely fashion. UFH should be discontinued when infusing bivalirudin and may transition directly to bivalirudin after stopping UFH. The initial therapeutic dosing (Table 1) and maintenance titration (Tables 2 and 3) of bivalirudin are determined based on risk of thrombosis. Changes in renal function may impact bivalirudin metabolism and necessitate dose adjustments (Tables 1 and 3).

aPTT, INR and thrombin time (or dilute thrombin time based on center availability) should be checked 2 hours after initiation of infusion. Further laboratory monitoring frequency can be reduced from 4 hours post-dose titration, to daily at the discretion of the managing team based on patient's stability. Although bivalirudin administration will prolong/elevate the INR in a linear dose-dependent fashion, absolute INR values vary among patients. As such, each patient will have individual aPTT-INR correlation, which is useful to rule out contamination of samples from heparin. For example; bivalirudin at 0.5 mg/kg/hr may result in aPTT of 65s and INR of 1.8 in one patient, and aPTT of 65s and INR of 2.4 in another patient. The aPTT to INR ratio will be relatively consistent in each patient such that a dramatic rise in aPTT to >200 with stable INR would suggest contamination of the sample with UFH and/or traumatic blood draw. One can also use heparinase PTT in the setting of possible heparin contamination.

Center variability on coagulation assays may result in slight modification of goal ranges. Dilute thrombin time is a more sensitive test for bivalirudin, but is not obtainable at all centers, with variability in assays across centers. If available at your center, it can be used in place or in addition to aPTT for monitoring. In the setting of acute thrombosis treatment, bivalirudin dosing may require larger dose escalation to achieve therapeutic ranges (upwards of 100-200% dose escalation over the course of 24-48 hours). If there are 2 dose escalations with no change in aPTT or INR, we recommend considering larger dose increments by 50-100% and/or bolus of

0.25-0.5 mg/kg over 5 min with follow up coagulation labs in 2 hours to ensure that therapeutic levels are achieved promptly and safely.

Antiplatelet therapy

Antiplatelet therapy should be initiated at time of diagnosis pending no acute bleeding and platelet count > 50 $\times 10^3/\mu l$. If able to tolerate enteral administration, acetylsalicylic acid (aspirin) at 5 mg/kg/day rounded up to 20.25mg, 40.5mg or 81 mg tablet is the first line agent. Both TEG-PM and point-of-care platelet responsiveness testing (e.g. VerifyNow) are acceptable to assess aspirin effect with targets as: (1) arachidonic inhibition on TEG-PM > 70%; or (2) VerifyNow for acetylsalicylic acid < 500 ARU.[12]

In the setting of large coronary thrombosis, progression of thrombosis despite treatment (treatment failure) or high on treatment platelet reactivity to aspirin, consider adding or transitioning to clopidogrel 1 mg/kg/day with target of : (1) ADP inhibition on TEG-PM > 70%; or (2) VerifyNow P2Y12 assay for clopidogrel < 121 PRU. Rule out modifiable causes of high on treatment platelet reactivity to aspirin by avoiding other NSAID use (ibuprofen) or considering twice daily dosing if there is high platelet turnover. If non-responsive to clopidogrel based on platelet responsiveness testing, ensure that there is no co-administration of medications that alter metabolism such as omeprazole. Other antiplatelet agents can be considered for treatment failure such as ticagrelor at a starting dose of 0.06 mg/kg/dose twice daily that can be titrated up to a maintenance dose of 1.2 mg/kg/dose twice daily based on available platelet responsiveness testing such as the VerifyNow P2Y12 assay.

If enteral administration and/or absorption is not established, intravenous antiplatelet agents should be utilized. Eptifibatide is an intravenous glycoprotein IIb/IIIa receptor antagonist

given as bolus of 180 mcg/kg (maximum 22.6 mg) followed by infusion of 2 mcg/kg/minute (maximum of 15mg/hour). A second bolus of the same dose can be administered 10 minutes after the first bolus. Infusions typically continue for 18-24 hours, but can be continued longer pending ongoing hematological stability. Other intravenous glycoprotein IIb/IIIa agents include tirofiban at 0.075-0.15 mcg/kg/min.

Increased risk of bleeding with dual antiplatelet therapy should be anticipated. Therefore, it is necessary to consider preventive strategies for epistaxis (e.g. bacitracin or petroleum jelly to inside nares twice daily, Afrin spray as needed, conjugated estrogen cream to inside nares three times daily for 7 days) as needed. We also suggest daily screening for clinical signs of bleeding, including changes in menses if applicable.

Duration of therapy

Following completion of tPA, duration of bivalirudin is dependent upon response to therapy, which includes: (1) echocardiographic resolution or reduction in thrombosis burden; (2) laboratory data suggestive of thrombolysis (normalized or downtrending LDH, plasma free hemoglobin, D-dimer), trend in high-sensitivity troponins and trend in inflammatory markers (CRP, erythrocyte sedimentation rate, Factor 8 activity, wWF antigen as indicated).

After stabilization of coronary thrombosis (reduction or resolution), it is advisable to consider transition to long-term outpatient antithrombotic regimen and antiplatelet therapy for indefinite thromboprophylaxis. Historically, standard of care was low molecular weight heparin for 6-12 weeks, followed by vitamin K antagonists if ongoing CGA or thrombosis. However, there is expanding experience with the use of direct oral anticoagulants, and increased use of primary apixaban therapy starting at ~ 0.1 mg/kg/dose twice daily rounded to quarters of

commercially available 2.5 and 5 mg tablets.[13,14] We measure peak apixaban levels (apixaban-specific anti-Xa chromogenic analysis level) 4 hours after the 3rd to 5th dose, and trend levels every 3-6 months pending stability with a therapeutic target of 200-320 ng/ml for high risk thrombosis conditions. For ongoing GCA, many experts use oral anticoagulation together with dual antiplatelet therapy in the form of low dose aspirin (~ 5 mg/kg/day) and clopidogrel 1 mg/kg/day for ~3-6 months after coronary thrombosis. Intensity of antithrombosis is assessed every 3-6 months pending resolution and evolution of coronary thrombosis and aneurysms, with transition from dual antiplatelet to single antiplatelet +/- anticoagulation. In the setting of bleeding adverse events, antiplatelet agents may be suspended or discontinued, and/or levels of anticoagulation adjusted.

Conclusion

KD patients with giant coronary artery aneurysms are at high risk of thrombosis and myocardial infarction, resulting in major morbidity and mortality. Bivalirudin is a reversible direct thrombin inhibitor and offers intrinsic anti-platelet and anti-inflammatory effects, making it a suitable adjunct to conventional tPA treatment for this pediatric condition when thrombolytic therapy is indicated. Dosing and aPTT-targeted titration of bivalirudin is based on clinical assessment of each patient's individual thrombosis/bleeding risks and renal function. Antiplatelet treatment with aspirin should be continued after adequate platelet inhibition effect is ensured.

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Figure 1: Three-dimensional reconstruction of the aorta and coronary arteries demonstrating multiple giant fusiform aneurysms of the right and left coronary arteries, left anterior descending coronary, and circumflex coronary.

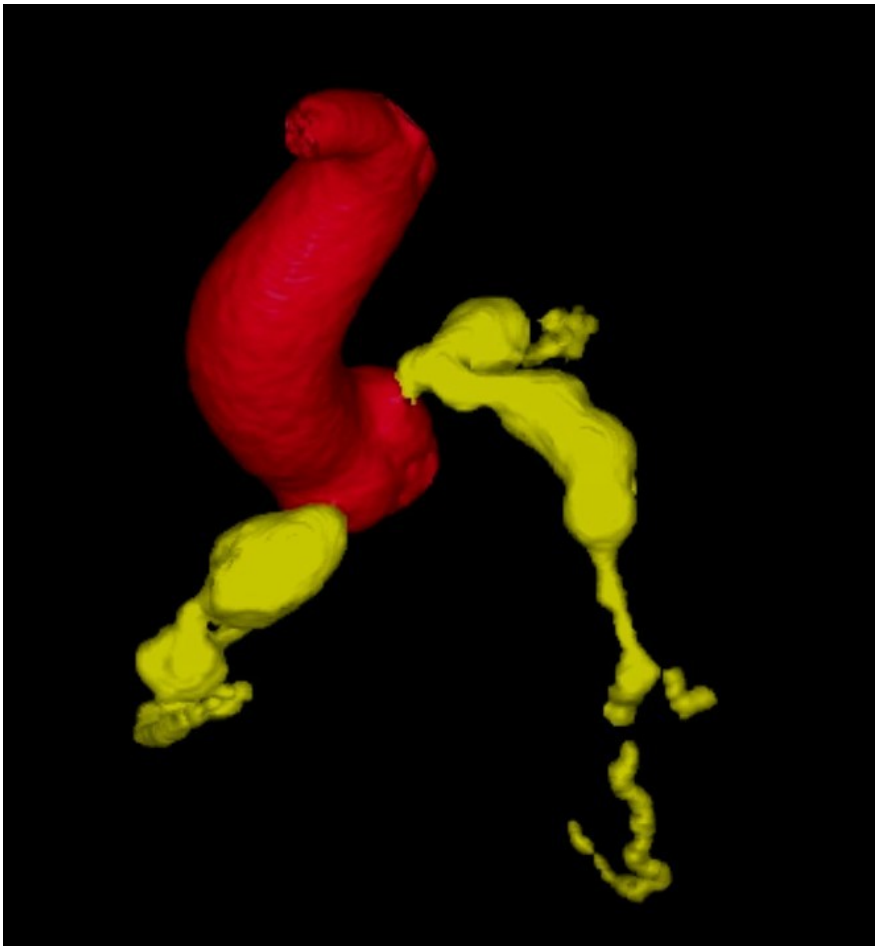

Table 1: Bivalirudin starting dose

Renal function (glomerular filtration rate, ml/min/1.73 m^2)	**Initial dosing** (IV infusion)

Normal: > 60	0.5 mg/kg/hr
Mild-moderate dysfunction: 30-60	0.25 mg/kg/hr
Severe dysfunction: < 30	0.15 mg/kg/hr

Table 2: Target aPTT ranges based on patient specific risk of thrombosis and bleeding

Clinical assessment	**aPTT**
[a]High risk of thrombosis	2.5-3× baseline (~80-100s)
Standard risk	2-3× baseline (60-80s)
[b]High risk of bleeding	1.5-2× baseline (45-60s)

Table 3: Bivalirudin maintenance dose titration based on aPTT

aPTT result	**Dose adjustment**
5-15 seconds out of range	Increase or decrease by 15%
≥ 15-30 seconds out of range	Increase or decrease by 25%
> 120 seconds out of range with commensurate change in INR	• Normal renal function: hold 15 min and reduce by 30%. • Mild-moderate dysfunction: hold 45 min and reduce by 40%. • Severe dysfunction: hold 2 hours and recheck aPTT before restart of infusion.

Figure 2: Thrombolytic protocol using bivalirudin for Giant Coronary Aneurysms (GCA) and thrombosis in Kawasaki Disease (KD)

KD GCA Bleeding and Thrombosis Risk Assessment/Work-up

Laboratory test:

-Basic metabolic profile (BUN, creatinine, CBC, liver function tests)

-baseline hemolysis markers (LDH, plasma free hemoglobin, D-dimer)

-Coagulation profile (PT/INR, aPTT, fibrinogen, thrombin time TEG/ROTEM with platelet mapping

-Cardiac biomarkers (brain natriuretic peptide, high

Thrombolytic administration (tPA); 6- 12 hour infusion

tPA infusion monitoring

Ad hoc:

-urine and stool for blood during infusion and 8 hours post infusion

-neuroimaging if change in neurological status

Bivalirudin and Antiplatelet Dosing and monitoring

-Bivalirudin can start immediately after completion of tPA or between cycles

Renal function (GFR, ML/min/1.73m^2)	**Starting dose (IV infusion rate)**
Normal: >60	0.5 mg/kg/hour
Mild-moderate dysfunction: 30-60	0.25 mg/kg/hour
Severe Dysfunction: <30	0.15 mg/kg/hour

-monitor aPTT, INR, thrombin time or dilute thrombin time 2 hours after starting and then 4 hours after dose change or at the discretion of the provider to achieve the goal level for risk of bleeding and thrombosis outlined below:

High risk thrombosis	aPTT 2.5-3x baseline (80-110sec)
Standard risk thrombosis	aPTT 2-3x baseline (60-80sec)
High risk bleeding	1.5-2x baseline (45-60 sec)

Antiplatelet	**Dose**	**Platelet responsiveness testing**
Aspirin	5 mg/kg/day rounded to 20.25 mg, 40.5mg, 81 mg tablet	VerifyNow <550ARU
Clopidogrel	0.5-1 mg/kg/day	VerifyNow P2Y12 <121 ARU
Ticagrelor	Starting 0.06 mg/kg/dose BID up to 1.2 mg/kg/dose BID	VerifyNow P2Y12 <121 ARU
Eptifibatide	IV bolus 180 mcg/kg, infusion 2 mcg/kg/min x 18-24 hours	

Patient admitted to hospital with KD, at risk or proven thrombosis of GCA

History:
-Past medical history of thrombosis or known thrombophilia
-Family history of thrombosis or known thrombophilia

Physical Exam:
-baseline neurological exam
-exam for signs of bleeding

Imaging:
-echocardiogram
-ECG
-cardiac CT
- neuro-imaging if neurological exam not reassuring/obtainable (head ultrasound or CT)

Start tPA at 0.05 mg/kg/hr (dosing range 0.03-0.10 mg/kg/hr) if:

- no active bleeding or large territory stroke within past 2 weeks, or major bleeding in last 48 hours
-Platelet count >50,000/mm^3; fibrinogen >150 mg/dl; aPTT or PT <1.5 x upper limit of normal
-correct coagulopathy prior to administration of tPA
-**Infusion duration 6-12 hours (recommend 8 hours) and can be repeated x 2 additional days**

Hourly:
-vital signs & cardiorespiratory monitoring during infusion and 8 hrs post
-neurological status hourly

Every 6 hours:
-CBC, aPTT, PT/INR, fibrinogen, D-dimer, LDH, plasma free Hgb