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Bivalirudin vs Heparin

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Bivalirudin vs Heparin: Is there a Clear Winner?

Presented by

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Disclosures:

- I have no financial disclosures

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Contestant #1: Heparin

Anticoagulant or Cofactor?

- Heparin is a medication and a naturally occurring glycosaminoglycan.
- Heparin ACTS as a anticoagulant by binding to Antithrombin which occurs naturally in the blood
- The accelerated conformational change induced by heparin binding to Antithrombin leads to enhanced exposure of the reactive center in Antithrombin.
- This conformational change converts Antithrombin from a slow inactivator of coagulation factors Xa and IIa(**Thrombin**) to a rapid inactivator with over a 1000 fold increase in Antithrombin activity
- Also interacts with factors IXa, XIa, and XIIa
- Historically the main anticoagulant for ECMO
- 90%+ of ELSO centers worldwide report its use

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Heparin Advantages/ Disadvantages

Heparin advantages:

- Reversible with Protamine Sulfate(but alone has long half life 45-90 mins)
- low cost
- Clinician familiarity
- Ease of use in dosing
- Widespread availability
- Immediate affect after administration and usually predictable response

Heparin disadvantages:

- Not all IU of Heparin are bio-actively the same, unfractionated heparin needs an 18-chain minimum length and a specific pentasaccharide sequence to bind Antithrombin
- Heparin Induced Thrombocytopenia(HIT)
- Heparin is not a direct anticoagulant, but a cofactor to exhibit effect of anticoagulation
- Requires Antithrombin 3 (AT3) binding to exert its anticoagulant effects
  - 40-45% AT3 levels reported in literature
- Causes platelet activation and dysfunction
- Inhibits free THROMBIN ONLY, does not affect clot bound thrombin
- Heparin does not break down formed clots, it only prevents clot formation
- Disadvantages more pronounced in children due to qualitative and-quantitative deficiencies in both procoagulant and anticoagulant proteins in immature coagulation systems

Contestant #2 Bivalirudin

- Bivalirudin is a direct THROMBIN inhibitor (DTI) class of anticoagulant
- Chemically, it is a synthetic derivative of the naturally occurring drug hirudin, found in the saliva of a medicinal leech
- Growing support in last decade for DTI use in ECMO vs Heparin because Bivalirudin lacks many of the limitations seen with indirect thrombin inhibitors, such as heparin.
- Studies show increased reliability of labs results with Bivalirudin vs Heparin management

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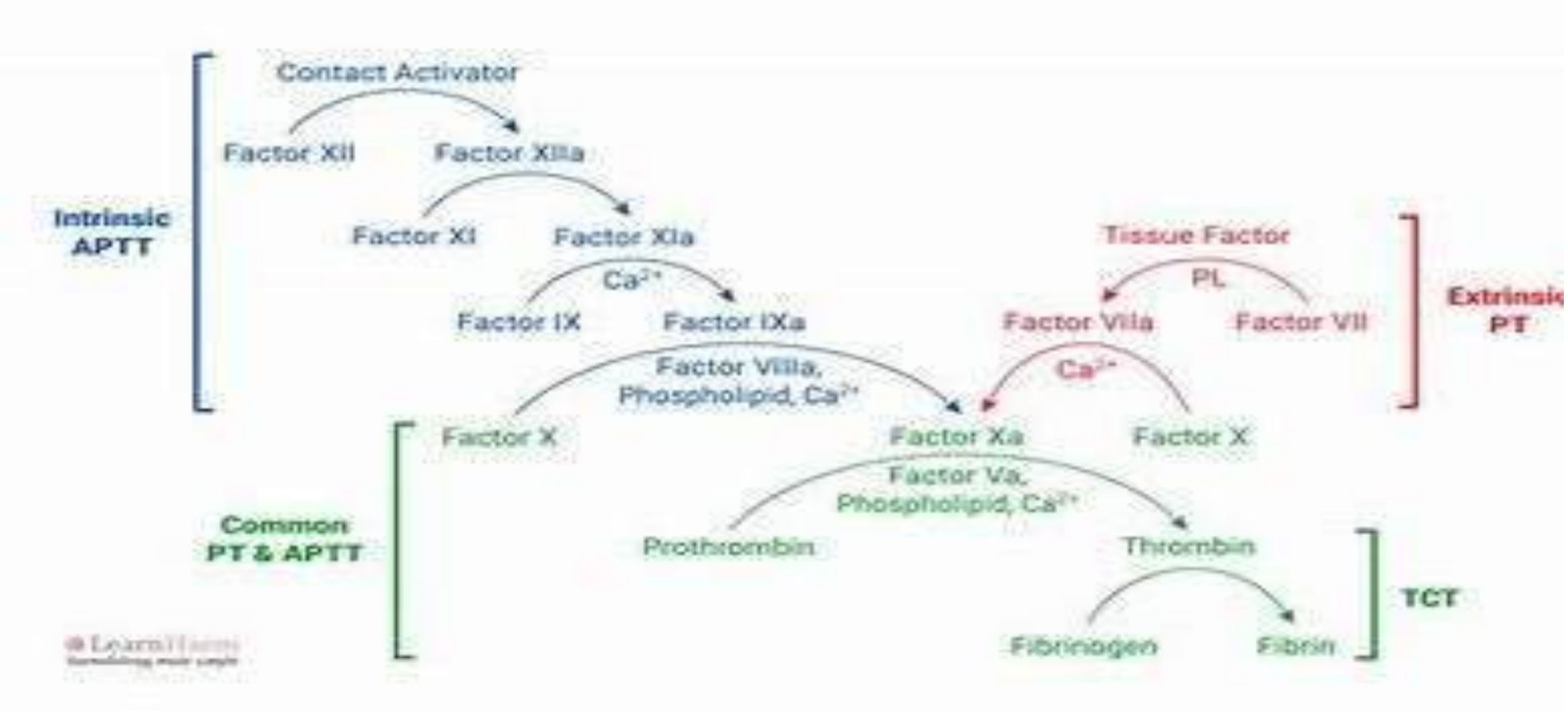
Bivalirudin Advantages/ Disadvantages

Bivalirudin advantages:

- Binds directly to thrombin, no Antithrombin activity required
- Binds both free circulating and clot bound thrombin
- Bivalirudin also inhibits thrombin-mediated platelet activation and aggregation
- Not associated with Heparin induced Thrombocytopenia Short half life (15-25 mins)
- 80% metabolized in blood, 20% hepatic/renal
- Immediate onset and predictable response
- Relatively ease of monitoring
- Binding is reversible

Bivalirudin disadvantages:

- No reversible agent
- Clotting risk in stagnant areas, low flow areas
- Higher cost, but cost neutral when compared to Antithrombin replacement and Heparin



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What does the current research show?

Survival to discharge and 6 months follow up

Safety for pediatric use

Heparin may increase the rate for blood transfusion through phlebotomy

Lower rate of Neurologic events in the Bivalirudin groups

Time to reach target anticoagulation level was quicker in Bivalirudin vs Heparin groups

Bivalirudin is associated with significantly fewer overall circuit related thrombotic events, pump and circuit component exchanges

Transfusion: Reported a significant decrease in composite transfusion requirement in the first 24 hours in pediatric Bivalirudin group

Cost comparison: Lower vs heparin when Antithrombin 3 (thrombate) replacement and lab monitoring cost factored in, especially in children age 1 year and less.

Monitoring: ACT, aPTT, TEG, Thrombin time

Is there a Clear Winner?

- Current research shows Bivalirudins' adoption of use and clinical acceptance is becoming the main anticoagulant for Extracorporeal Life Support modalities outside the operating room setting.
- Bivalirudin has a better mode of action by binding Thrombin also inhibiting thrombin activation of platelets.
- Bivalirudin can break down clot burden in the ECMO circuit helping eliminate component exchange
- Bivalirudin has a short half life advantageous for any bleeding complication, and has a reversible binding action to release Thrombin
- Surgical procedures reported in literature favored with Bivalirudin at low dose

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The Arnold Palmer approach to ECLS Anticoagulation

What if you utilized both drugs?

- Current practice is to start on Heparin at cannulation and add in Bivalirudin to be come the primary anticoagulant provider with low dose Heparin continued infusion.
- This practice has been our model for 2+ years with excellent results.

But WHY both?

- Our practice incorporates the use of ECMO Specialists for staffing and not always a perfusionist in house.
- This combination has proven to be effective at minimizing blood product transfusions, increasing circuit life longevity and providing a safety layer if a loss of flow event were to happen.
- Current practice aligns with literature to reduce platelet transfusion, anecdotal natural rise in Antithrombin with no replacement and safe transition with weaning circuit flows

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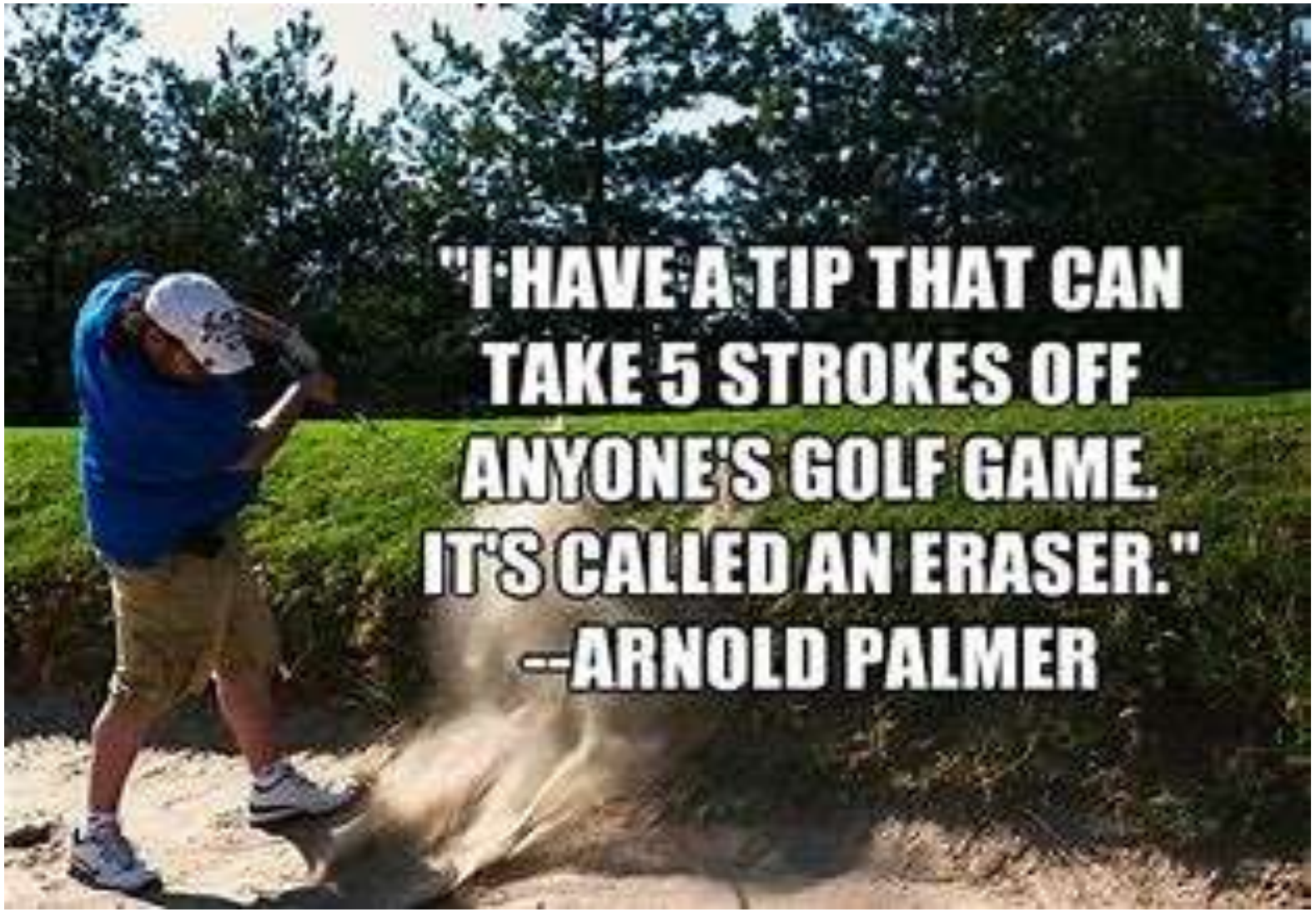
Thank you!



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Surgical site bleeding was most common and earliest complication, occurring most frequently in central cannulation(post cardiotomy)
Rates of thrombotic and hemorrhagic were not statically significant, rates of therapeutic Aptt were again not statically significant
However blood product transfusion was significantly lower in Bivalirudin group. This included all blood products PRBC, PLT, FFP, Cryo (Rannuci)
Notably 6 episodes of intracardiac thrombus ALL occurred in the Heparin only group vs ZERO in the Bivalirudin group

Thromboembolic and Hemorrhagic complications occur in up to 30% of ECMO cases

The choice of anticoagulant and concomitant monitoring VA ECMO has been associated with the prevalence of major bleeding, thromboembolic events and MORTALITY

Machado et al:

Phlebotomy associated blood loss in Heparin cohort seems to be directly related to the monitoring strategy, ie: hourly ACT vs q6 Aptt in Bivalirudin cohort

"Simply put, the UFH patients received dramatically more laboratory tests requiring phlebotomy determined not based upon efficacy of the anticoagulant agent but rather by the protocol utilized for monitoring".

Recent evidence supports the application of multiple anticoagulation tests as opposed to reliance on a single assasy. This concept is reinforced by reports of anti-Xa being most specific for heparin levels but less specific for coagulation factor levels that are better detected Aptt.

Routine lab surveilence for hemolysis using plasma free Hgb with LDH assessment