Hemostasis in the Premature Neonate

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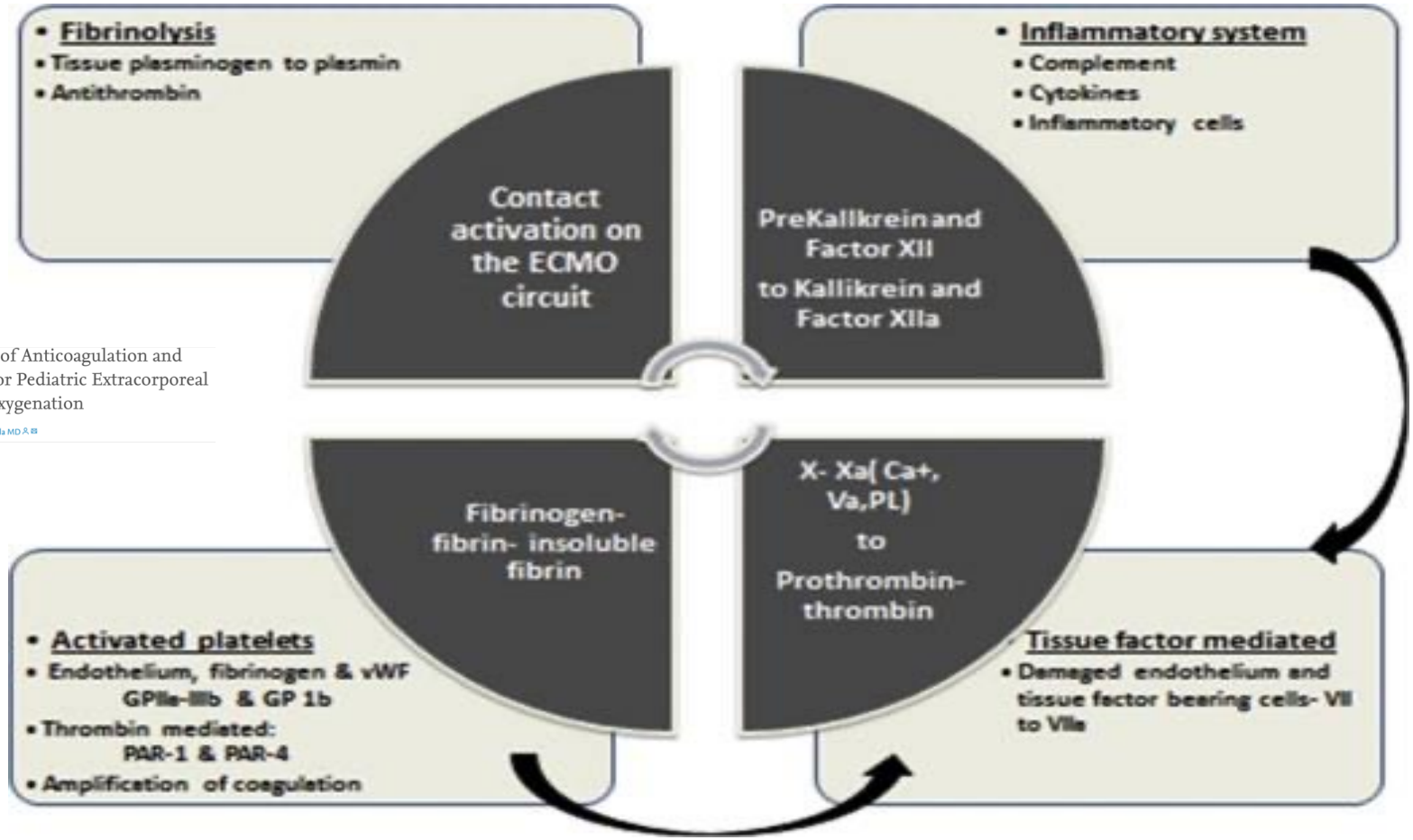
Slide courtesy of Patti Massicotte

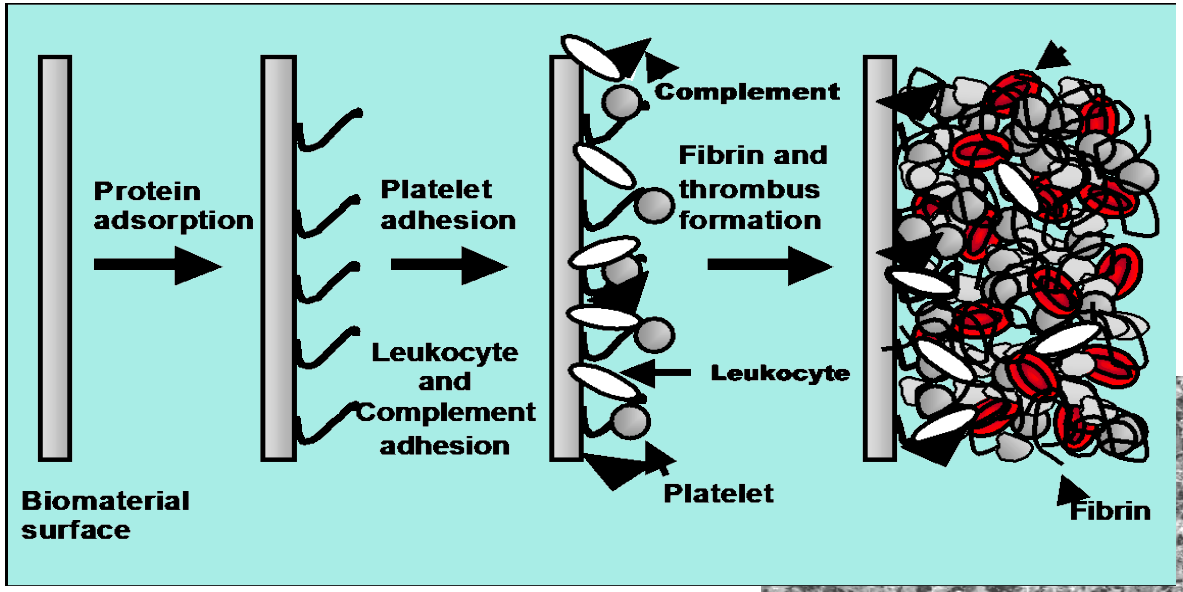
The Challenges of ECLS:

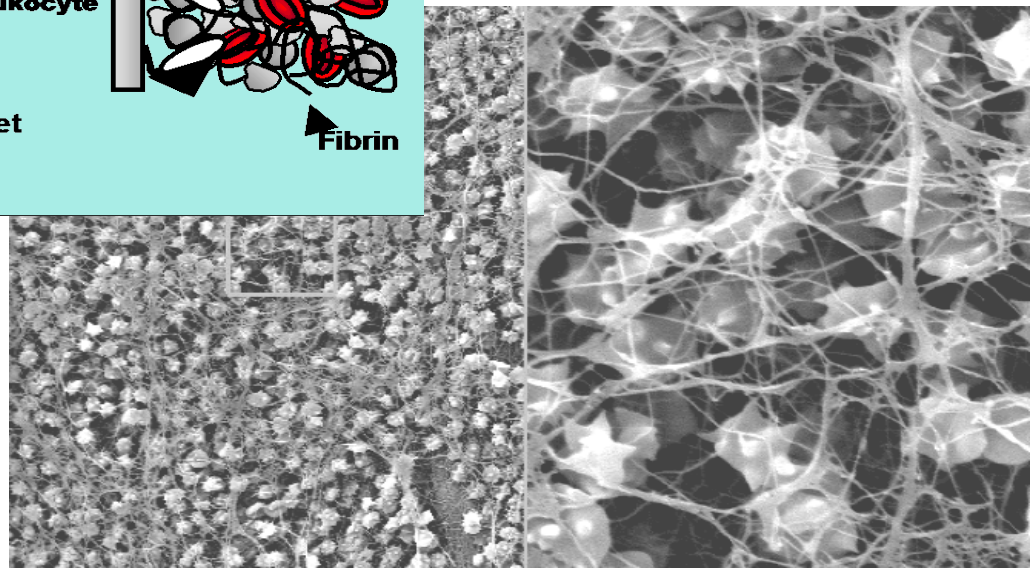


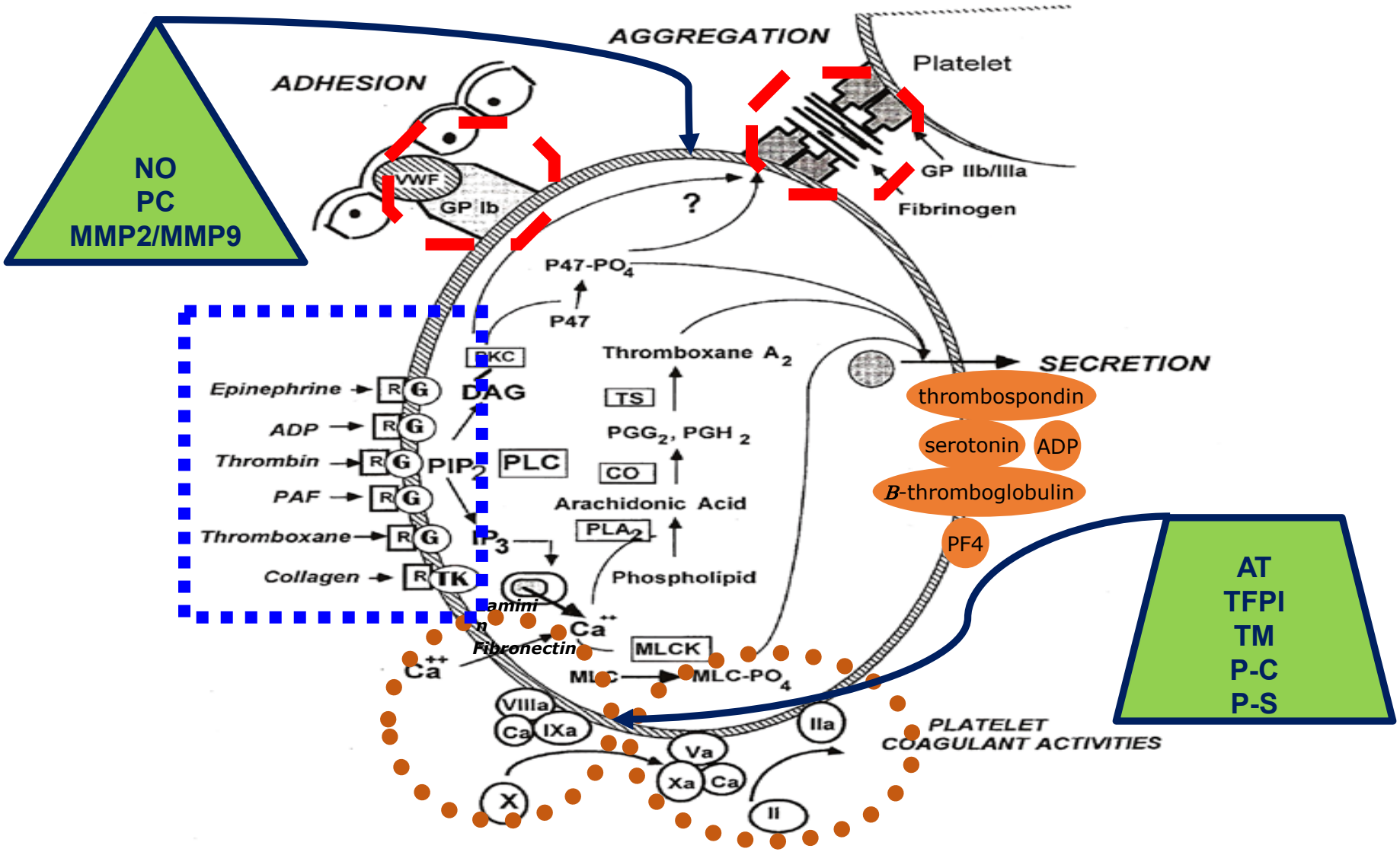
Management of Anticoagulation and Hemostasis for Pediatric Extracorporeal Membrane Oxygenation

Arun Saini MD, Philip C. Spinella MD

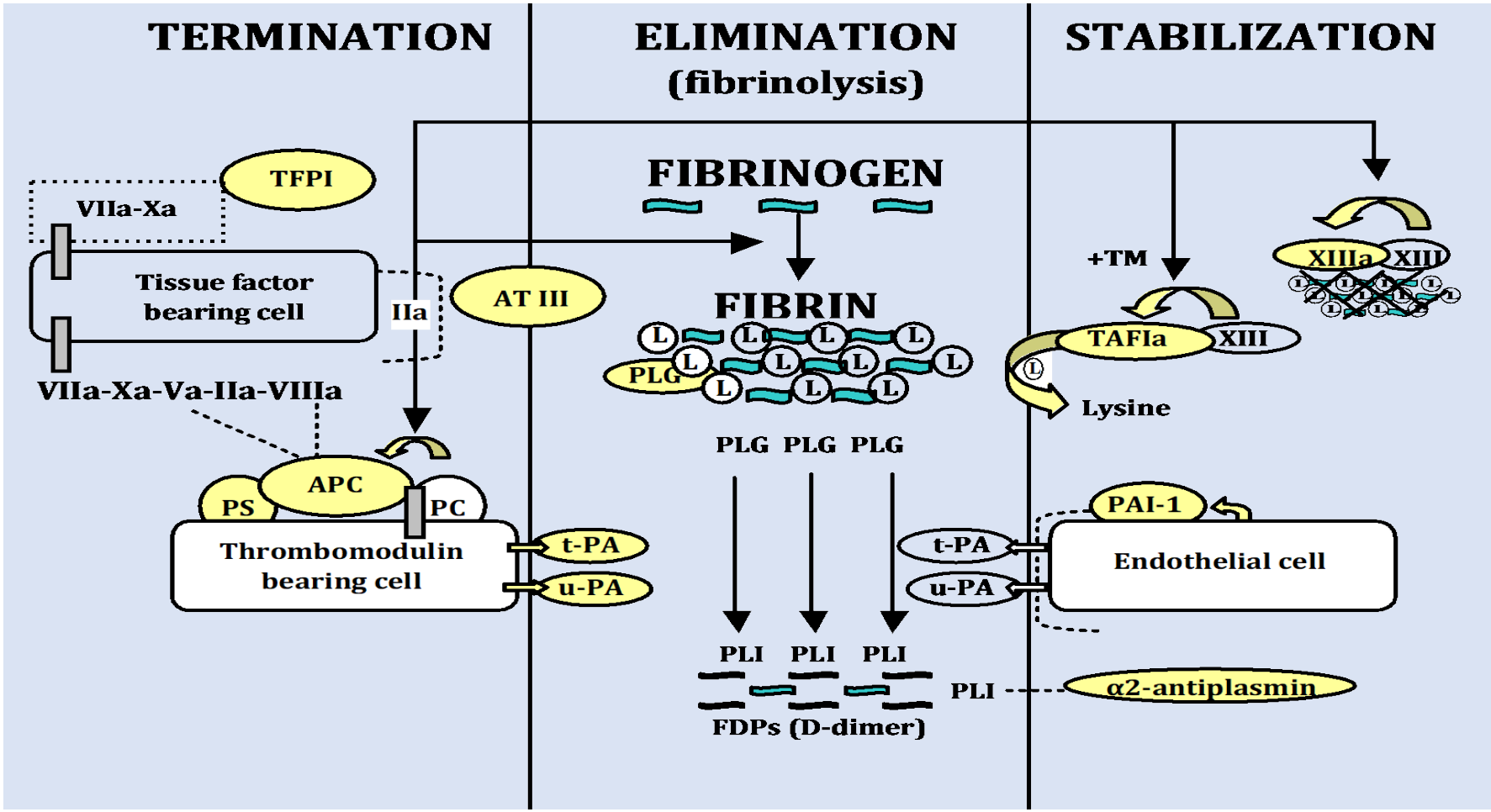
Blood Surface Interaction



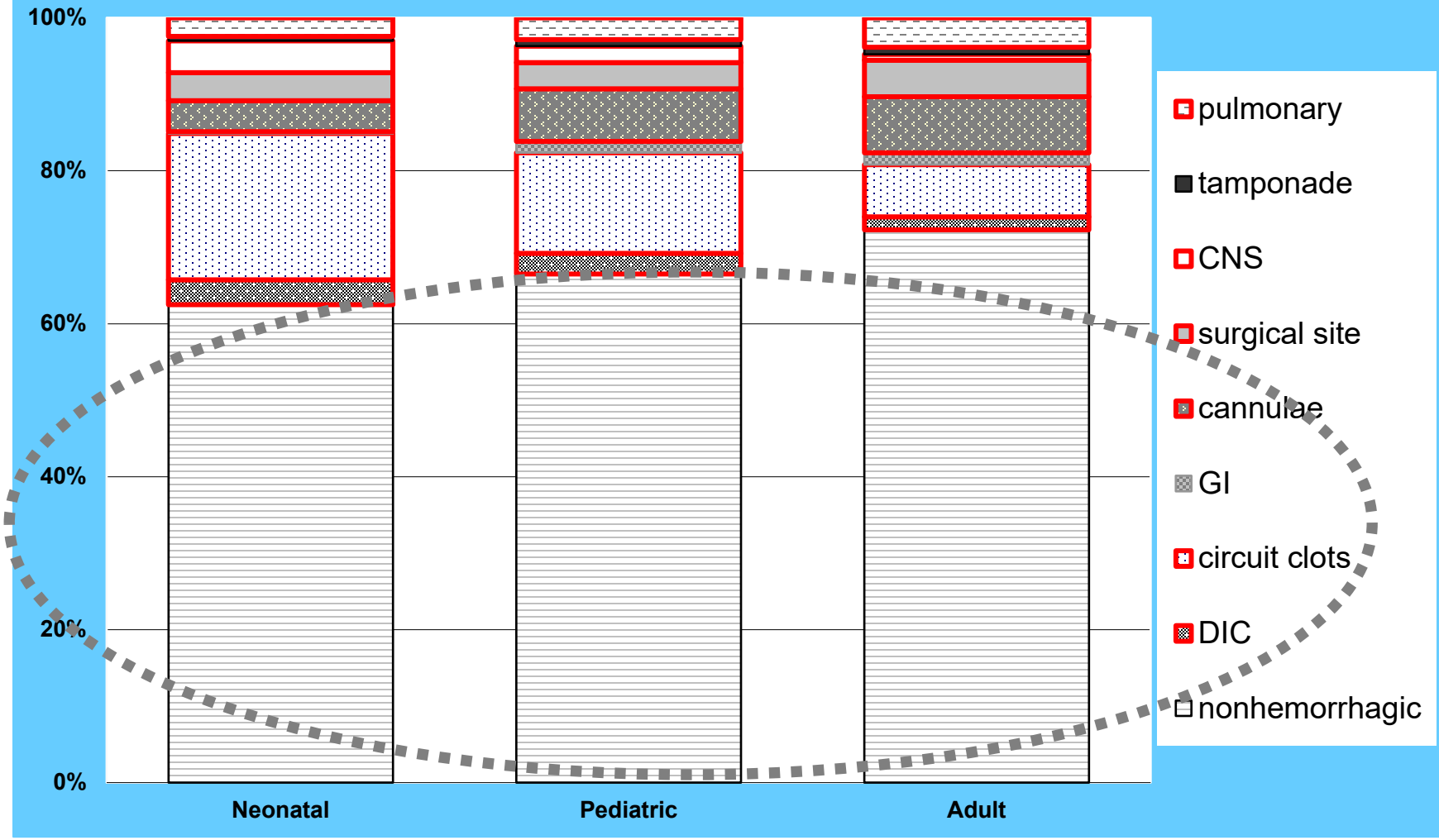



NO
PC
MMP2/MMP9
AGGREGATION
ADHESION
Platelet
VWF
GP Ib
?
GP IIb/IIIa
Fibrinogen
P47-PO4
P47
PKC
Epinephrine
ADP
Thrombin
PAF
Thromboxane
Collagen
R
G
TK
DAG
PIP2
PLC
IP3
Thromboxane A2
TS
PGG2, PGH 2
CO
Arachidonic Acid
PLA2
Phospholipid
SECRETION
thrombospondin
serotonin
ADP
B-thromboglobulin
PF4
amini
n
Fibronectin
Ca++
MLCK
MLC
MLC-PO4
VIIIa
Ca
IXa
Va
Xa
Ca
X
II
IIa
PLATELET
COAGULANT ACTIVITIES
AT
TFPI
TM
P-C
P-S

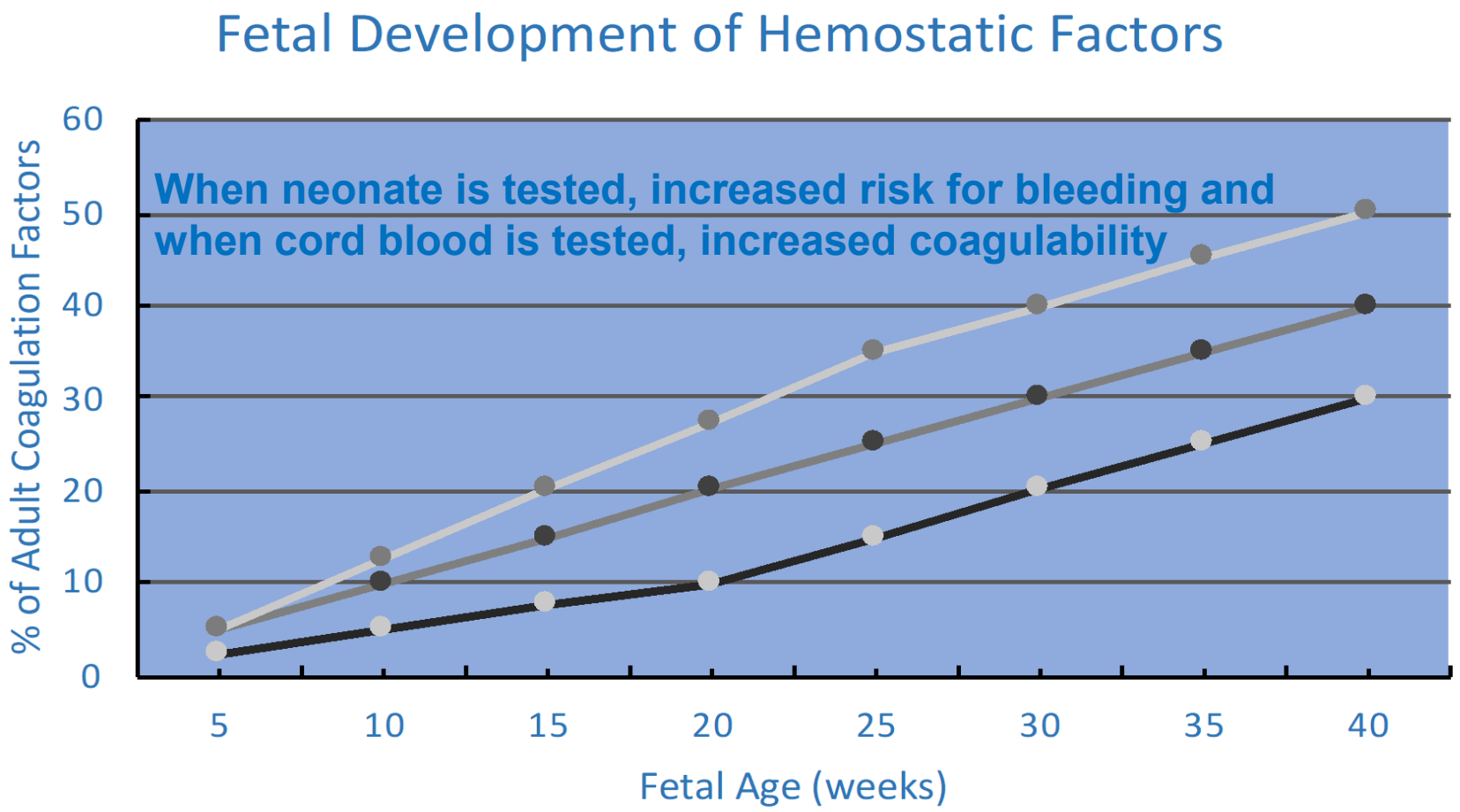
Fibrinolytic Pathway



Hemorrhagic Complications of ECLS



In Utero Development of Coagulation Factors



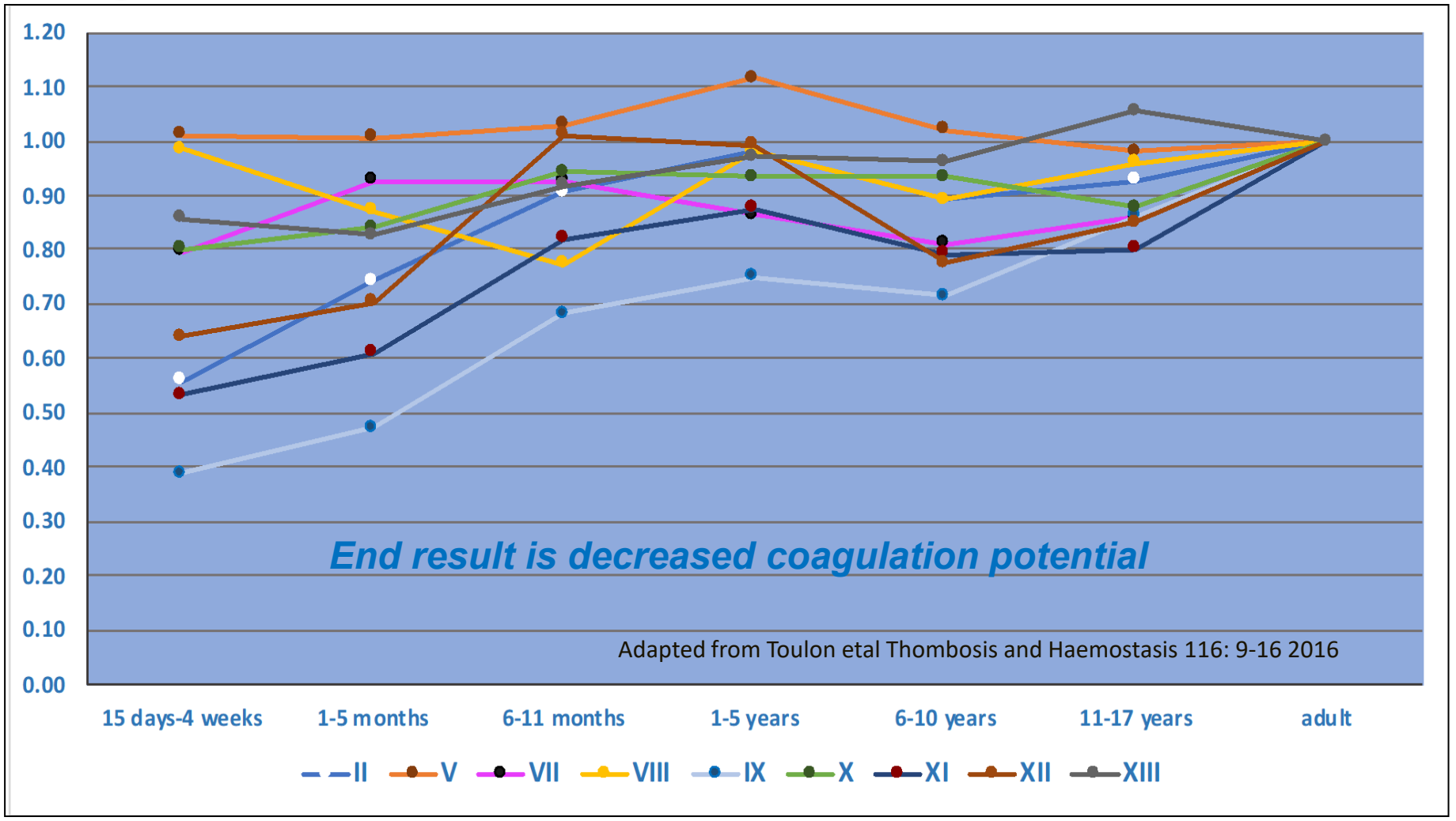
Adapted from Toulon etal Thombosis and Haemostasis 116: 9-16 2016

Primary Hemostasis of the Preterm Neonate

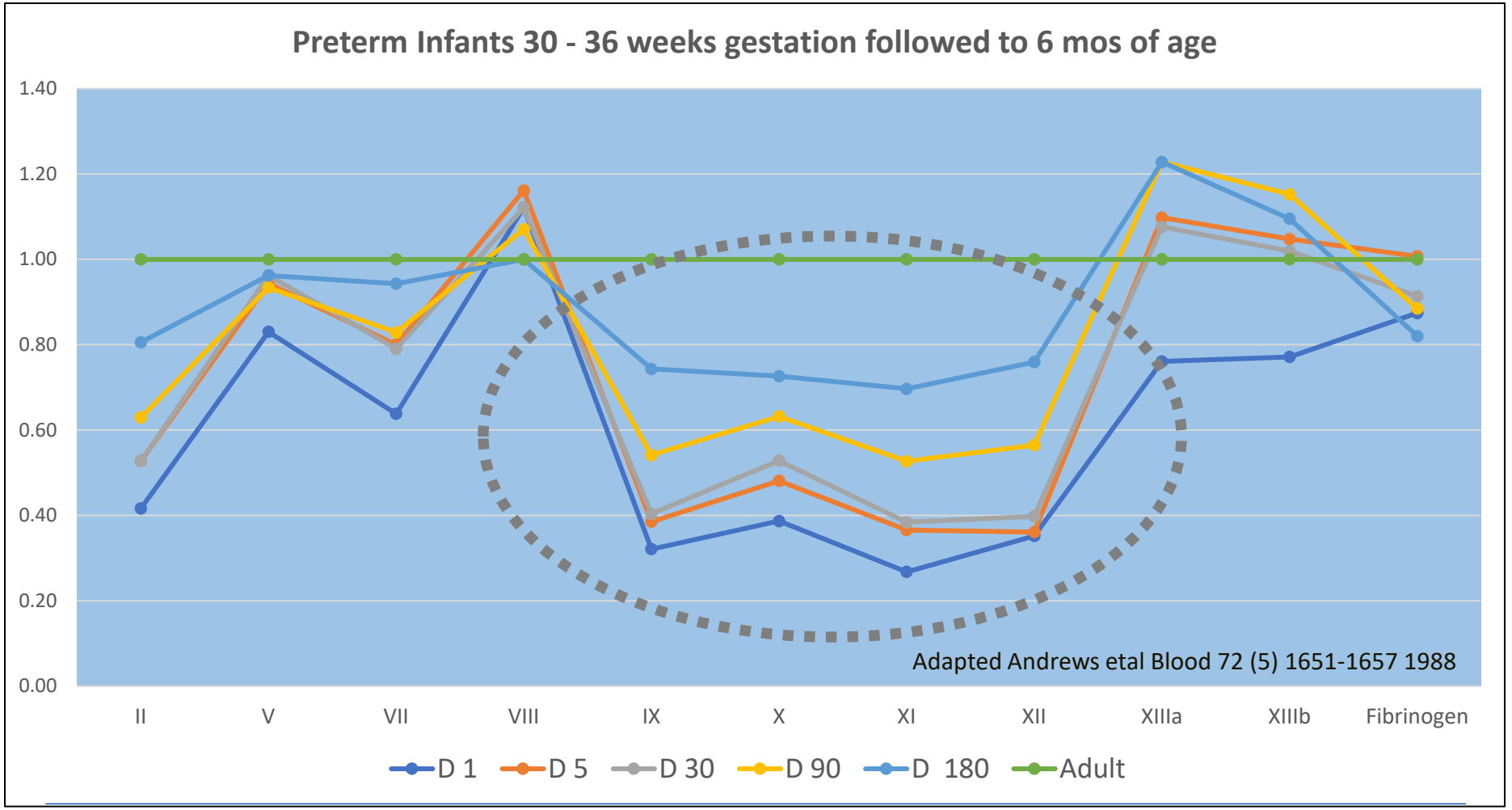
- Platelets exist by 5 weeks gestation
- Platelet count is usually normal (adult) levels by 22 weeks gestation
- Platelets are hyporeactive the more premature due too lack of alpha adrenergic receptors.
- Also have low, high molecular weight kininogen (HMWK)
- Compensatory to this they have higher levels of vWF and thus they seem to have a relatively normal primary response to hemorrhage.

vWF and HMWK of the Preterm Neonate

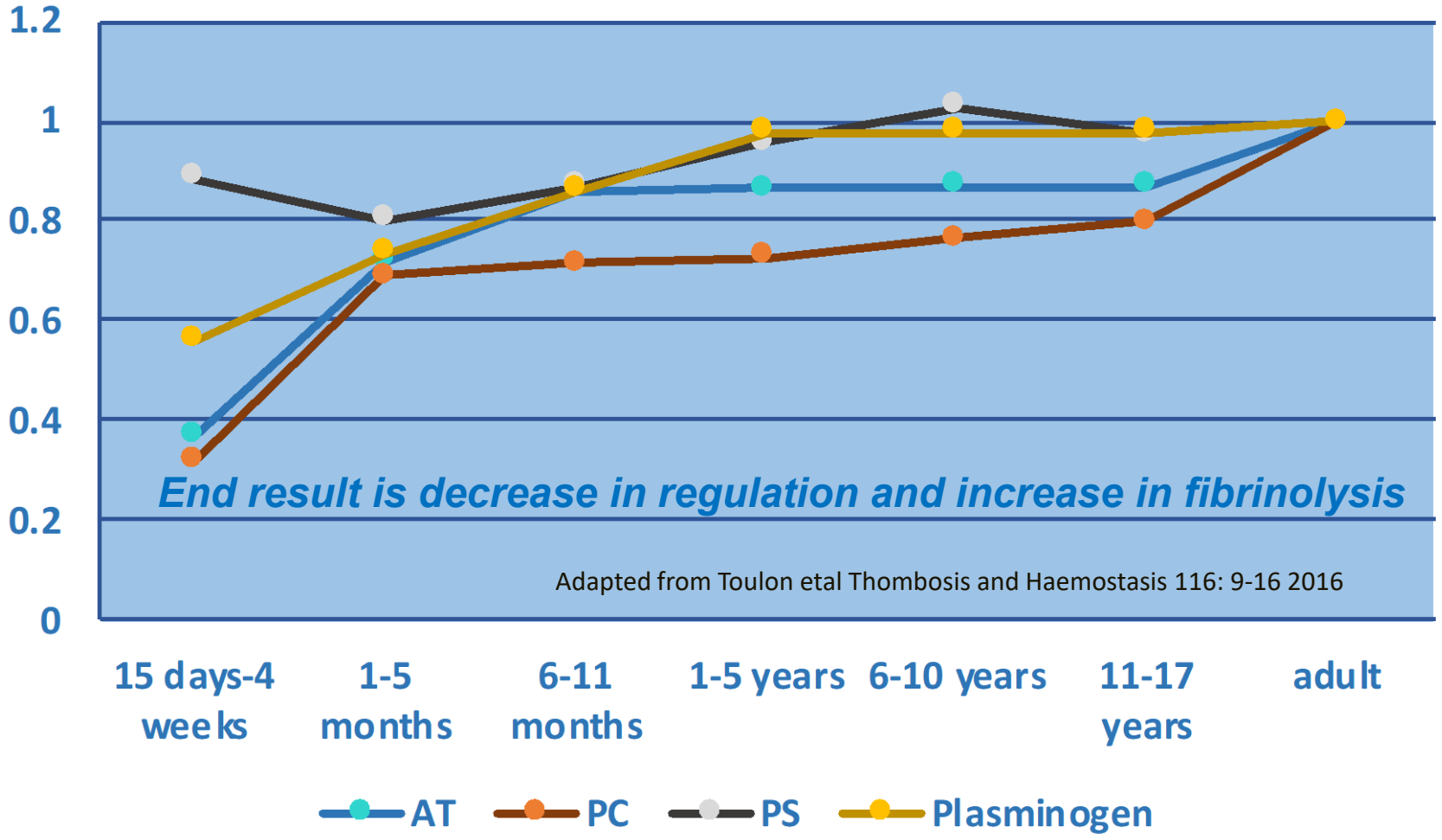
Coagulation Factor Levels from Neonate to Adult



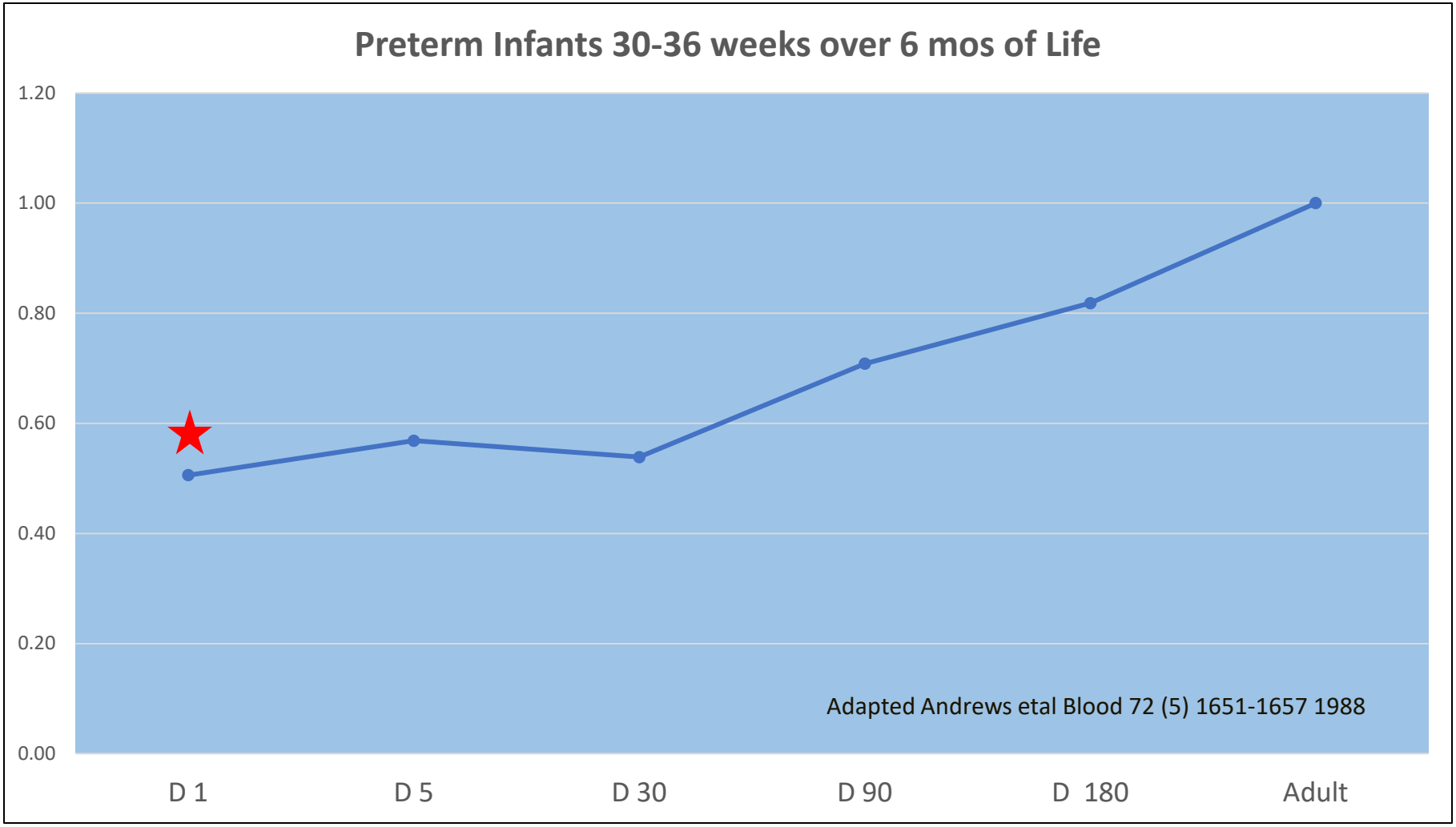
Coagulation Factor Levels in Preterm Infants Over 6 Mos



Physiologic Regulation of Coagulation & Fibrinolysis



Plasminogen Levels in Preterm Infants Over 6 Mos



Hemostasis of the Preterm Neonate

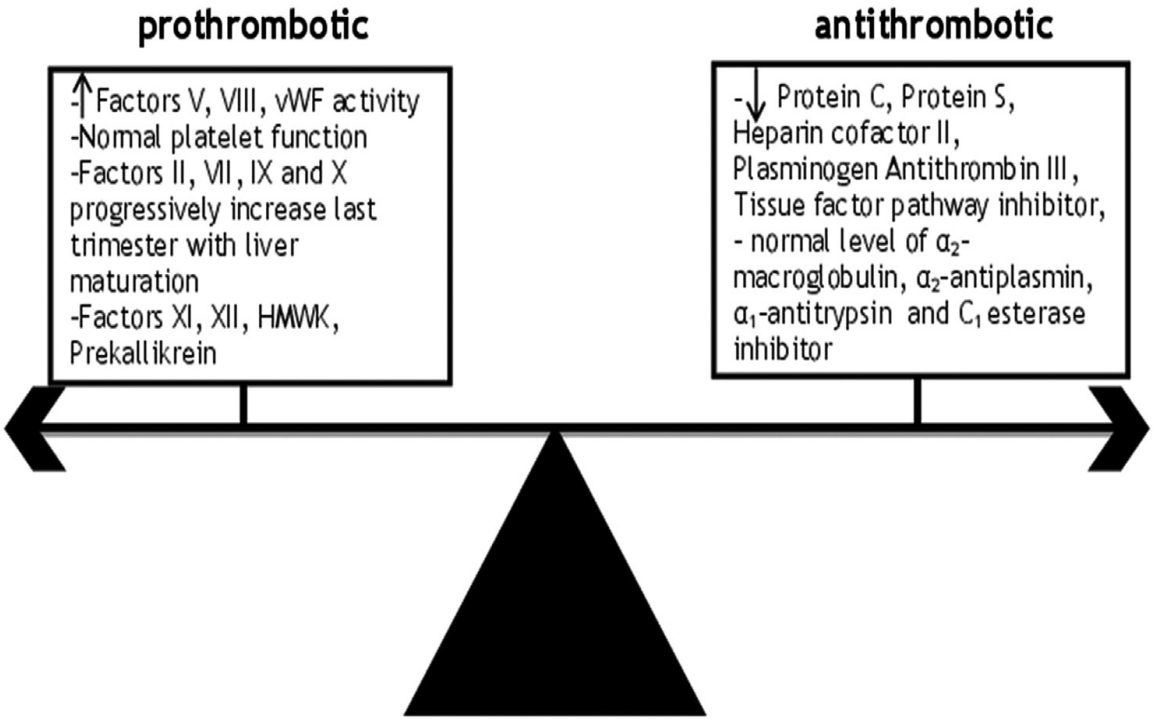
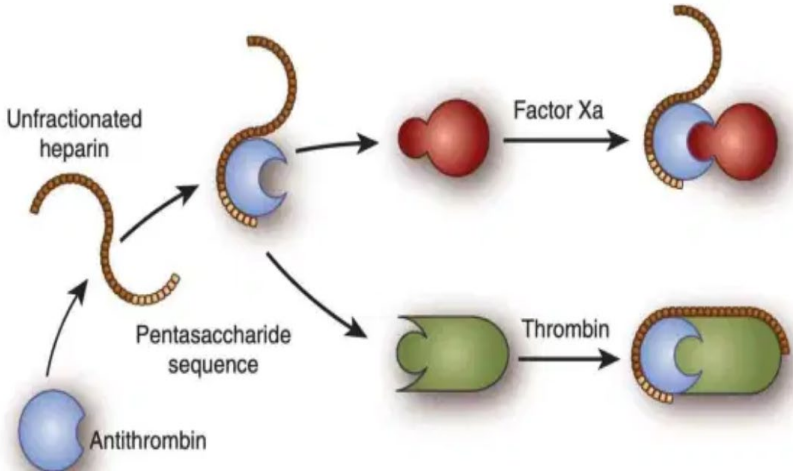
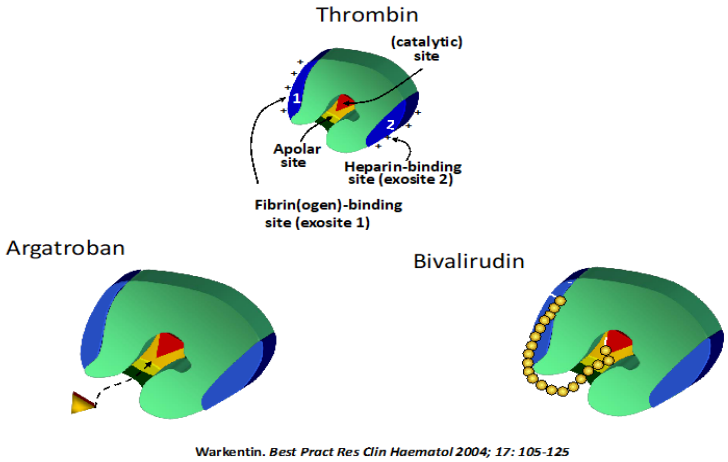


Fig. 1. Components of the hemostatic system in preterm infants compared with adults. The overall outcome appears to be balanced as spontaneous thrombosis or bleeding are rare in the absence of blood flow or vessel wall disturbances. vWF, von Willebrand factor; HMWK, high-molecular-weight kininogen.

Anticoagulant Choice





Warkentin. *Best Pract Res Clin Haematol 2004; 17: 105-125*

Unfractionated Heparin (UNFH)

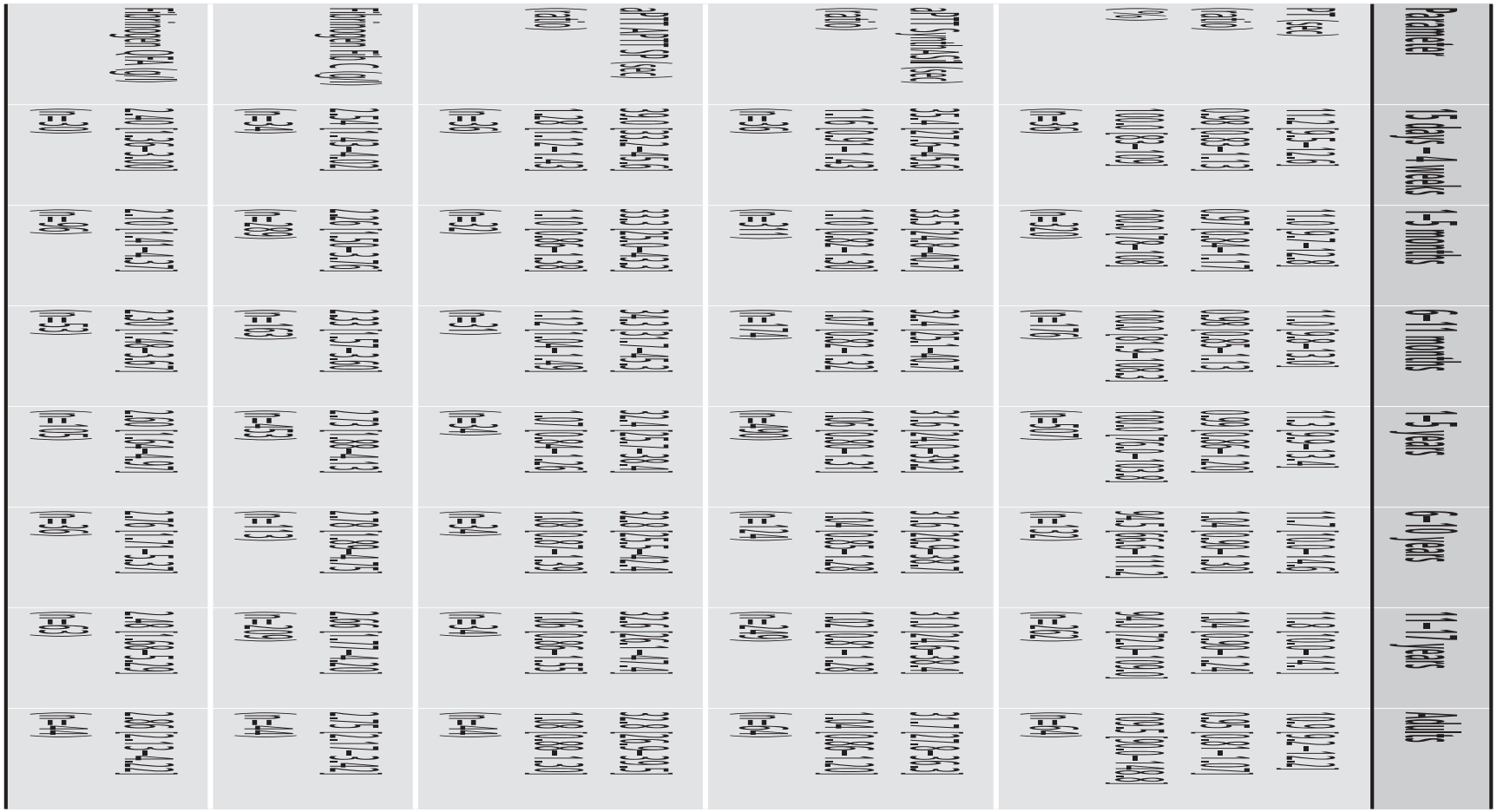
- Default anticoagulant for ECLS
- Derived from bovine and porcine intestine and lung
- ~ 1/3 of UNFH molecules contain the pentasaccharide sequence that allows for binding to AT
- AT – Thrombin - UNFH complex produces 1000 X increase in AT activity
- Hepatic metabolism, renal excretion
- Rapidly neutralized by protamine (salmon)

Slide courtesy of Patti Massicotte

Direct Thrombin Inhibitor General Guide to Dosing

DRUG	DOSE		MONITORING**		BLEEDING**	
	CHILD	ADULT	CHILD	ADULT	CHILD	ADULT
Argatroban Hepatic clearance	0.1-10 ug/kg/min In HIT*; 0.75 ug/kg/min Adjust dose by 0.1–0.25 ug/kg/min In hepatic compromise 0.2 ug/kg/min	0.2ug/kg/min* in HIT; 2.0 ug/kg/min and adjust re PTT	PTT 1.5- 3X (<100 sec) 2 hr post initiation ACT 160-200	PTT 40-120 2 hr post initiation ACT 170-200 Esper et al 2014 Phillips &Khoury 2014	FVIIa 30-90 ug/kg	FVIIa 30-90 ug/kg
Bivalirudin Proteolysis 75% renal 25% Clearance	Bolus 0.125-0.25 mg/kg Infusion 0.125-0.2 mg/kg/h (if initial drug) Infusion 0.1-0.8, if tx from UFH	Infusion 0.08-0.2 mg/kg/h Dose increase up to 0.03 mg/kg/h	PTT 50-70 2 hr post initiation ACT160-200	PTT 40-120 2 hr post initiation ACT 200-220	FVIIa 30-90 ug/kg **<10 case reports	FVIIa 30-90 ug/kg

Coagulation and Anticoagulation Testing Variability



Toulon etal Thombosis and Haemostasis 116: 9-16 2016

Challenges with Present Monitoring Tests

ACT	Least related to heparin dose on ECMO Least responsive to heparin dose changes More frequent sampling Results influenced by reagent used Influenced by thrombocytopenia, hematocrit, and hypothermia
APTT	Over 300 reagents available Reagent changes heparin sensitivity No difference in bleeding or thrombosis risk compared to Anti-Xa Influenced by plasma free hemoglobin and hyperbilirubinemia
Anti-Xa	Assay results influenced by assay type - Exogenous antithrombin - Dextran sulfate additive - Neither Influenced by plasma free hemoglobin, hyperbilirubinemia, and hypertriglyceridemia
TEG/ROTEM	High interoperator variation Results influenced by assay used and plasma free hemoglobin

Hematologic concerns in extracorporeal membrane oxygenation

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Classification of Surface Modifications

Surface Passivation

phosphorylcholine

albumin

Biomimetic Surface Functionalization

heparin

nitric oxide

direct thrombin inhibitor

Endothelialization

in vitro preseeding

in situ capture

VV extracorporeal life support for the Third Millennium: will we need anticoagulation?

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Table 2 Characteristics of ideal extracorporeal surface modification

Characteristics	Heparin bonded	PPC	No releasing	No generating	Combination NO and DTI	EDC
Cover entire circuit	✓	?	×	✓	±	✓
Longevity	✓	✓	✓	✓	✓	?
No systemic anticoagulation	×	×	✓	✓	✓	✓
Normal manufacture	✓	✓	×	×	×	×
Prevent thrombosis	×	×	✓	✓	✓	✓
Preserve platelet function	×	×	✓	✓	✓	✓
Reduce inflammation	±	±	✓	✓	✓	✓

PPC, phosphorylcholine; EDC, endothelialization; DTI, direct thrombin inhibitor; NO, nitric oxide.

Thank You