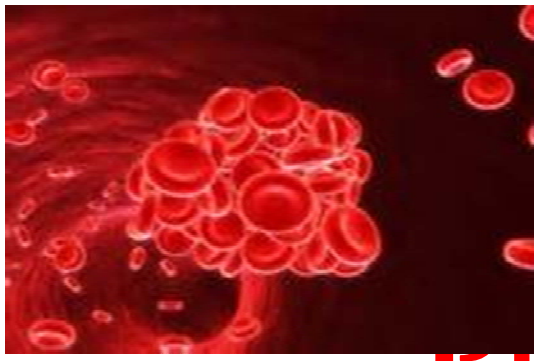
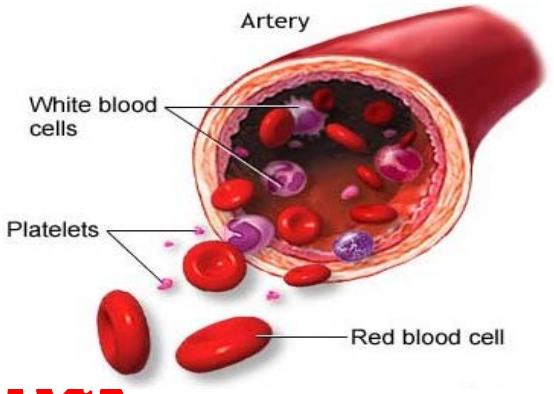




Platelets, Traun..., Hemorrhage: What should we do to help?

Douglas Paul D.O. FACOS
Medical Director Trauma Services
Kettering Health Network

Overview

- Platelet function and dysfunction
- Platelet Function Tests
- Platelet Function Testing on Antiplatelet Medication
- POC testing for neurosurgery
- Transfusion in TBI
- Desmopressin use in ICH

Patient Scenario

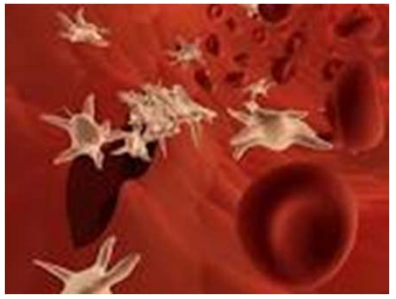
- 75 YO Male fell down the steps
- GCS 13
- Vitals Stable
- PMHx:
  - CAD with stent placement, PVD
- Meds:
  - Plavix and ASA
- CT Scan shows Intracerebral Hemorrhage

Patient Scenario

- Next steps?
- What antiplatelet medications?
- Do they need the medications?
- How do we assess medication effect?
- What do we do to maximize patient outcome?
- What literature is out there to support our approach?

Platelets

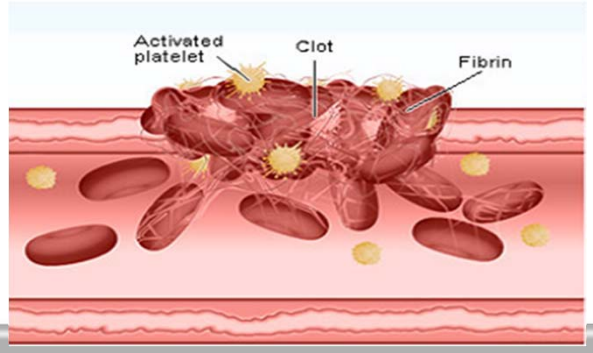
- Circulating anucleate disc shaped cell
- Responsible for initiating hemostatic mechanisms that repair injury to vascular endothelium
- 4 functions
  - Adherence
  - Activation & secretion
  - Aggregation
  - Interaction with coagulation factors



TRAUMA

Platelets

- Endothelial break exposes collagen
- Stimulates platelets to adhere & secrete Thromboxane A2 & ADP into circulation
- This activates other platelets to also secrete
- Activated platelets bind to circulating fibrinogen



TRAUMA

Platelet Function Tests

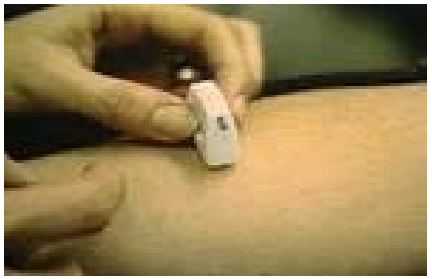
- Developed for bleeding disorders
- Increasingly used in basic research
  - Platelet physiology
  - Phenotype/ Genotype association
  - Drug development
  - Monitoring antiplatelet therapy

Platelet Function Tests

- Past 50 years golden era for PFT
- Understanding platelet targets for thrombotic inhibition led to wide arsenal of medications
- Assays developed to assess
  - Risk of thrombosis & hemorrhage
  - Monitor efficacy of drugs
  - Peri-procedural tool for prediction & management of hemorrhage in trauma patients

Platelet Function Tests
Duke Ivy Bleeding Time

- 1901- Milian initially described
- 1910 – Duke first correlated platelet dysfunction
- 1941 – Ivy Refined the test
  - BP cuff to 40 mm Hg
  - 5 mm long & 1mm deep incision on ventral forearm



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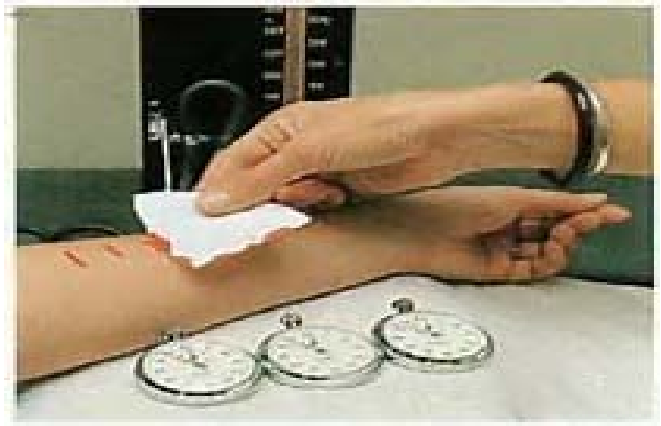
TRAUMA

Platelet Function Tests
Duke/Ivy

- 1961 – Mielke developed spring-loaded device with sterile blades
- Simple test
- No special equipment / lab
- Poorly reproducible
- Invasive
- Insensitive to mild platelet defects
- Time consuming



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TRAUMA

Platelet Function Tests
Light Transmission Aggregometry

- Light transmission through platelet rich plasma
- Non-physiological test: platelets isolated from other whole blood components
- As platelets aggregate to agonist, turbidity decreases & light transmission increases
- Modified technique: use pre-coated well plates to trigger aggregation upon addition of PRP. More rapid test, screening tool.

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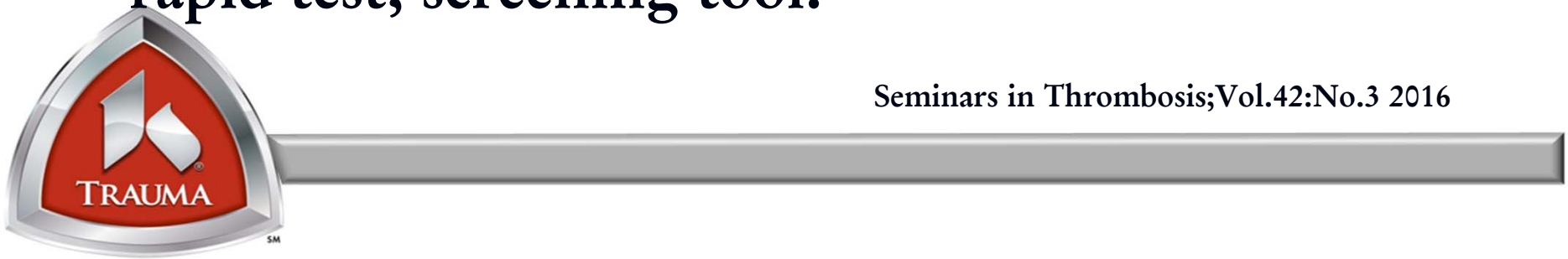

Whole Blood Aggregometry

- Performed on whole blood, small sample
- Based on change in electrical impedance resulting from platelet aggregation in response to classical agonists onto 2 electrodes immersed directly into saline diluted whole blood
- Delay between collection & test can influence result

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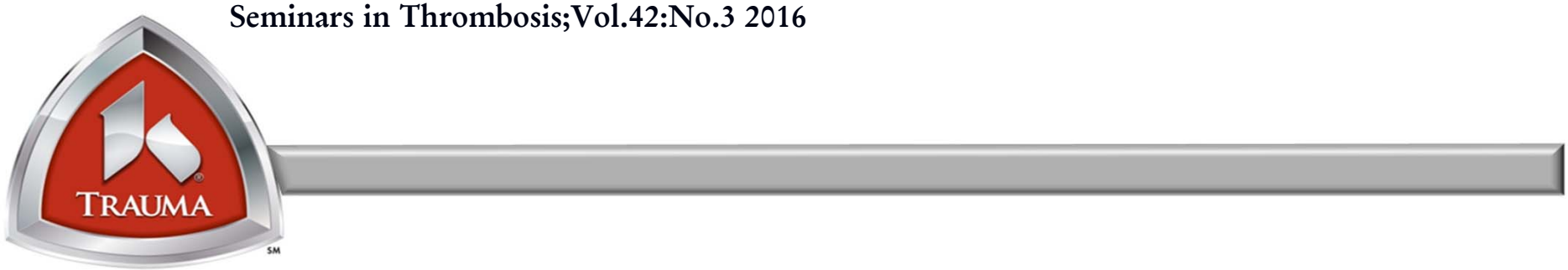
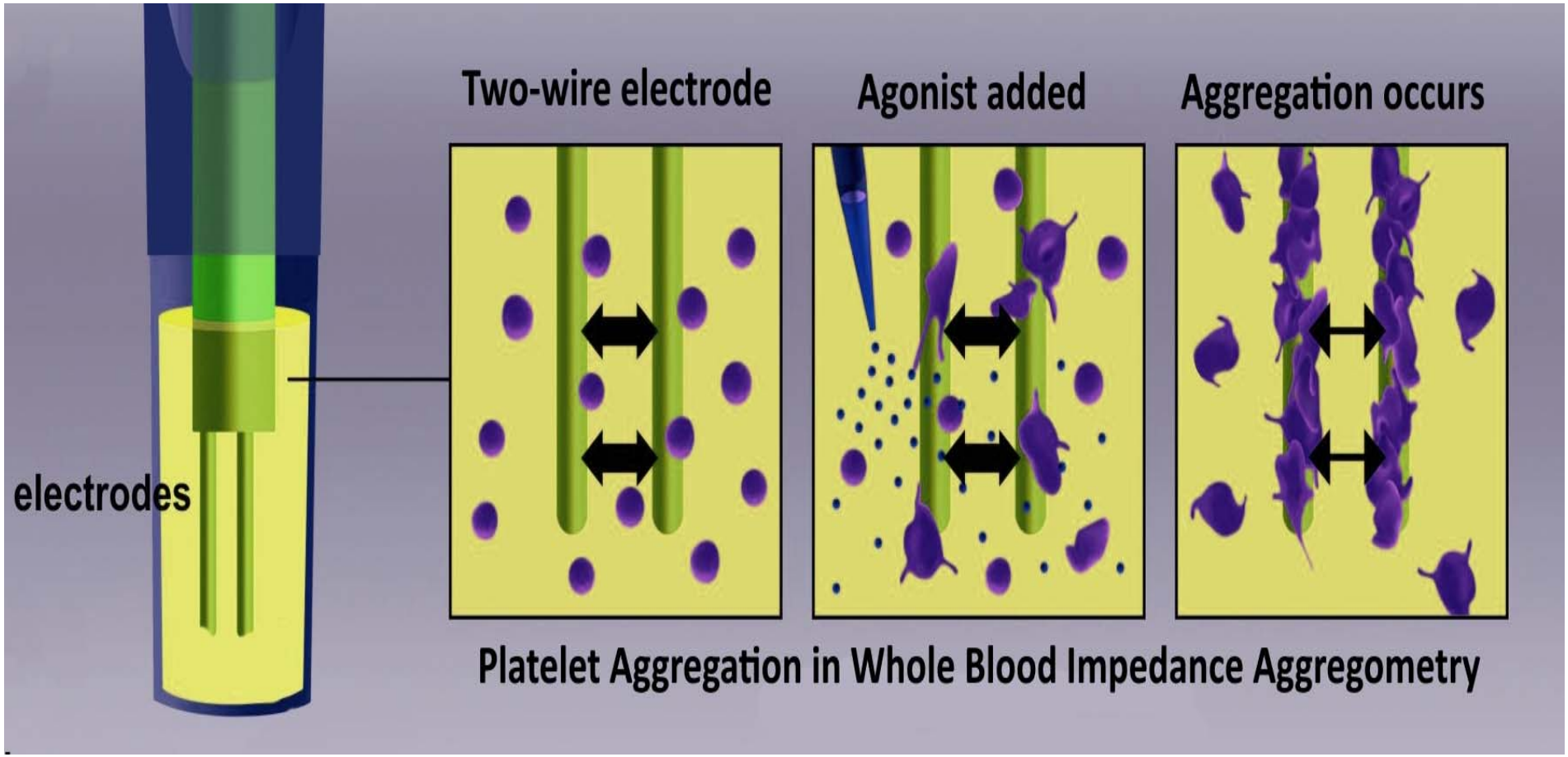
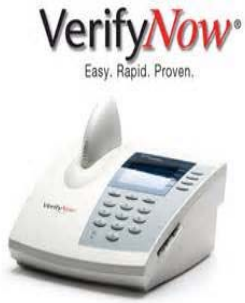



Two-wire electrode
Agonist added
Aggregation occurs
electrodes
Platelet Aggregation in Whole Blood Impedance Aggregometry

TRAUMA
SM

Verify Now

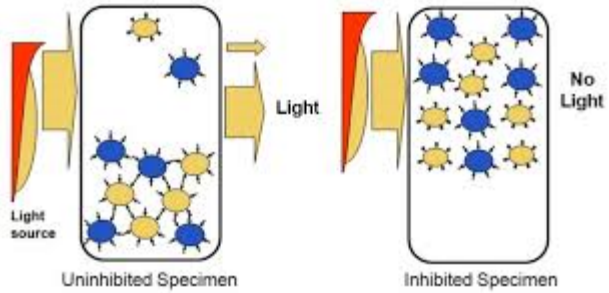
- Developed to monitor anti-platelet therapy
- POC test Using Light aggregometry
- Fibrinogen coated polystyrene beads
- Agglutinate in whole blood in response to
  - Arachadonic acid (ASA cartridge)
  - ADP & Prostaglandin E1(P2/Y12)
  - Thrombin receptor activating peptide
    - (GIIbIIIa cartridge)



TRAUMA

Verify Now

- Factors influencing assay:
  - Fibrinogen levels
  - HCT
  - Platelet count
  - Triglyceride levels
  - Time from sample to testing



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Platelet Function Analyzer (PFA-100/200)

- Cartridge based assay
- Small volume blood aspirated through aperture in membrane coated with platelet agonists
- "Closure time" is when aper[illegible]o platelet plug

Platelet Function Analyzer (PFA-100/200)

- Easy to use, rapid, small volume (0.8ml)
- Minimal training
- Factors influencing test:
  - < 50,000 platelet count
  - < 25% Hematocrit
  - VWF level
- Limited in detecting mild platelet defects

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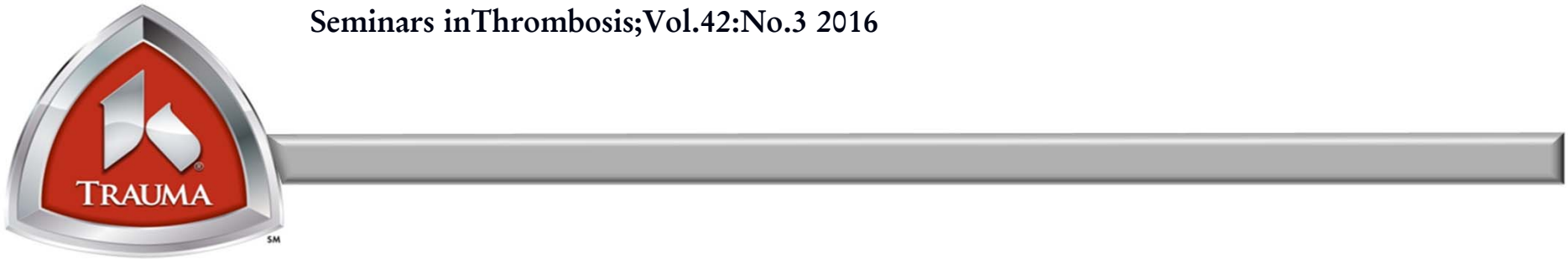
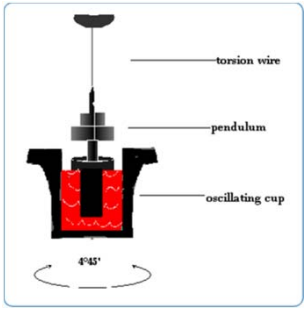
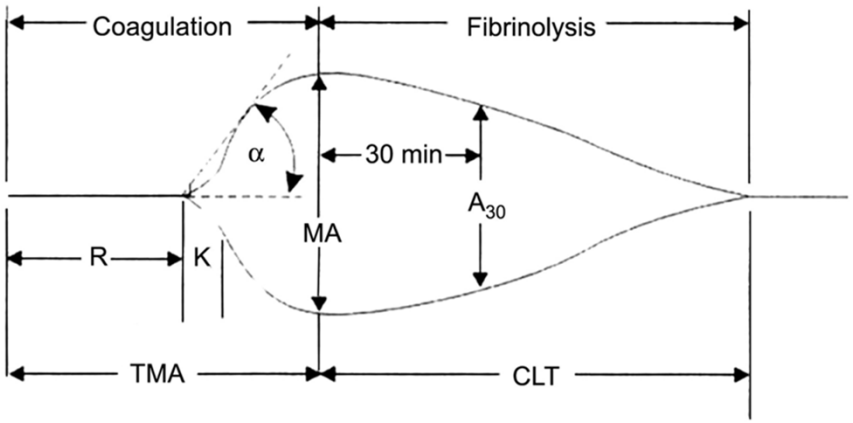


TEG/Rotem



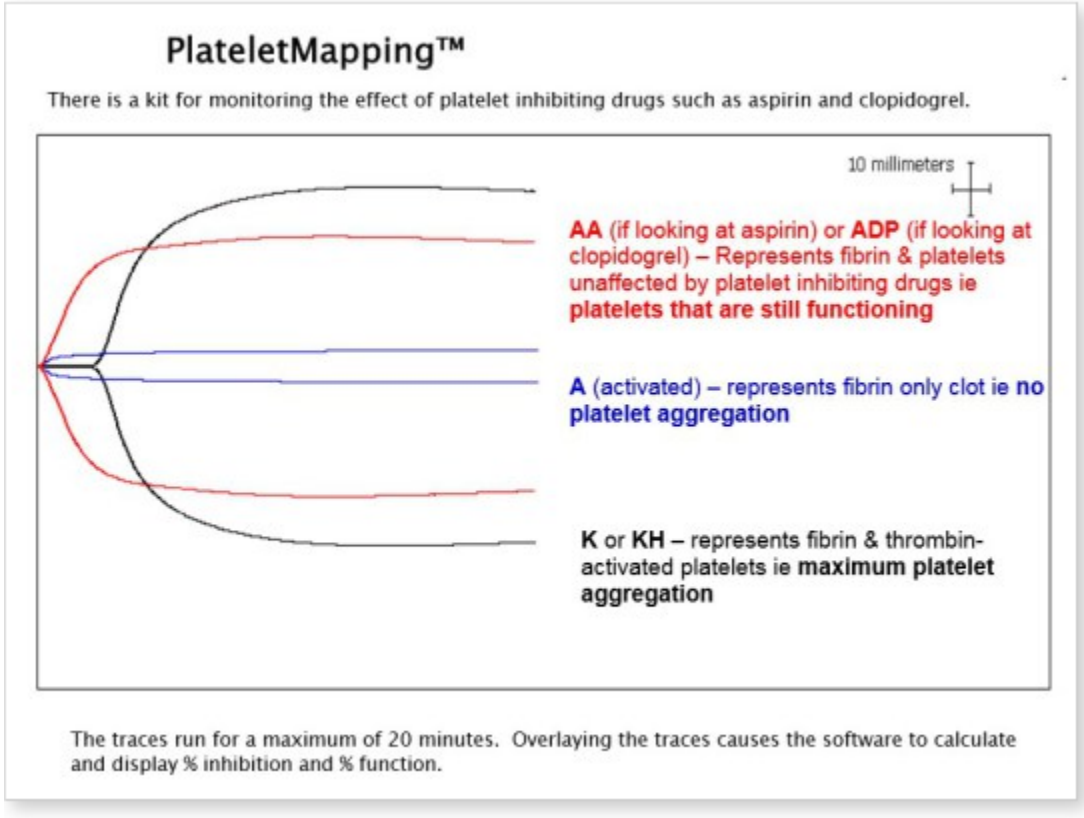


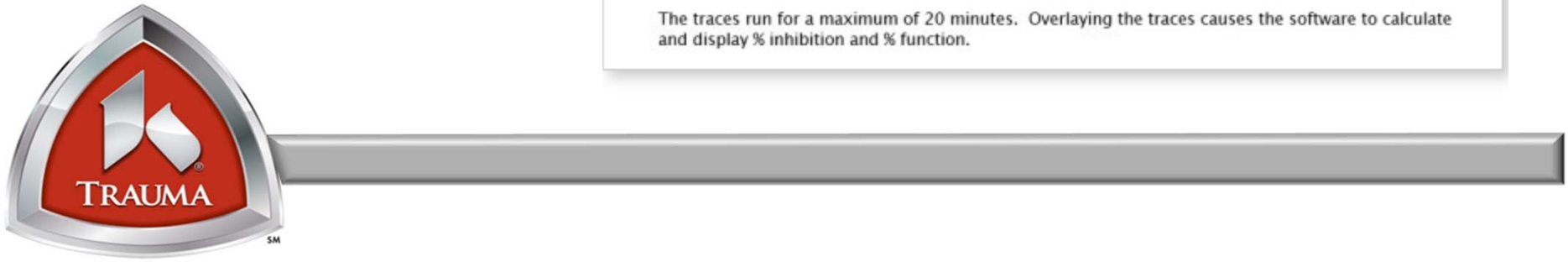
- Both tests exhibit relative insensitivity to various aspects of platelet function
- Not routinely recommended for platelet function testing

TRAUMA
SM

TEG-Platelet Mapping

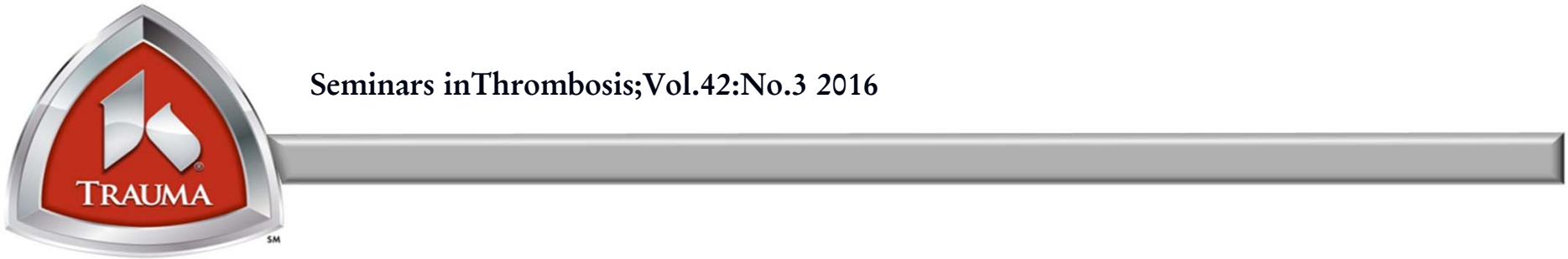
- Arachadonic acid or ADP
- Whole blood





Flow Cytometric Analysis of Platelet Function

- Laser based technology
- Analysis based on scatter of light produced as they cross light source
- Diluted anticoagulated whole blood incubated with variety of reagents
  - Antibodies
  - Dyes that bind to specific proteins, granules & lipid membranes



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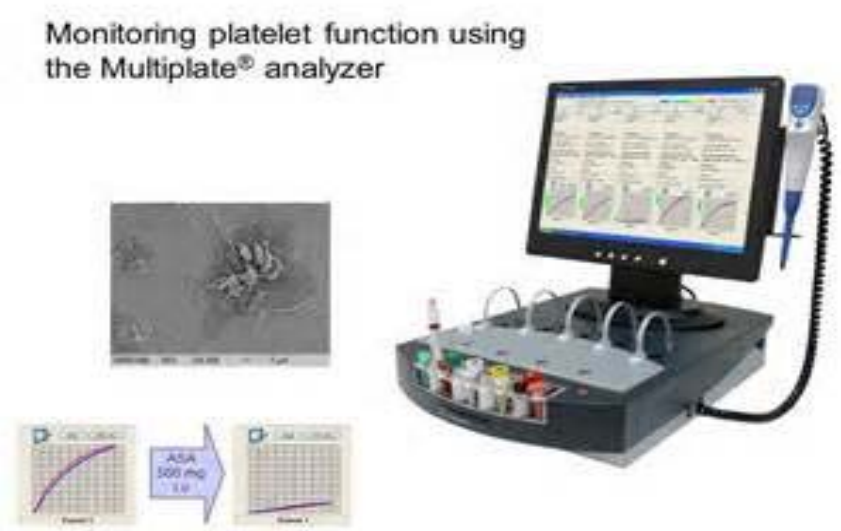
Multiplate Analyzer

- Multiple electrode aggregometry
- AA/ADP added
- Alteration in electrical impedance due to platelet aggregation is measured and quantified



TRAUMA

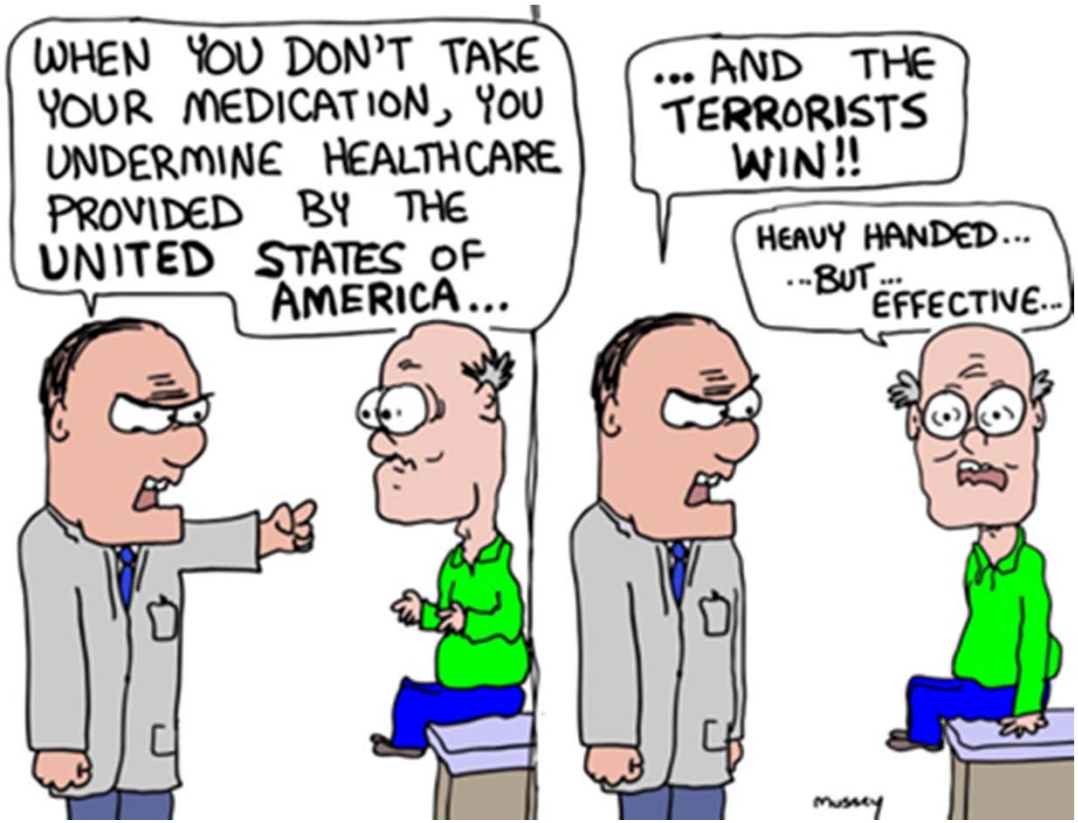
PFT in Patients on Antiplatelet Medications

- Largest literature is with patients undergoing percutaneous coronary intervention (PCI)
- Class 1A evidence for dual antiplatelet therapy in PCI
- Individual variability in response seen
- ~ 40% pts. on antiplatelet meds may not have expected inhibitory effect!!!

PFT in Patients on Antiplatelet Medications

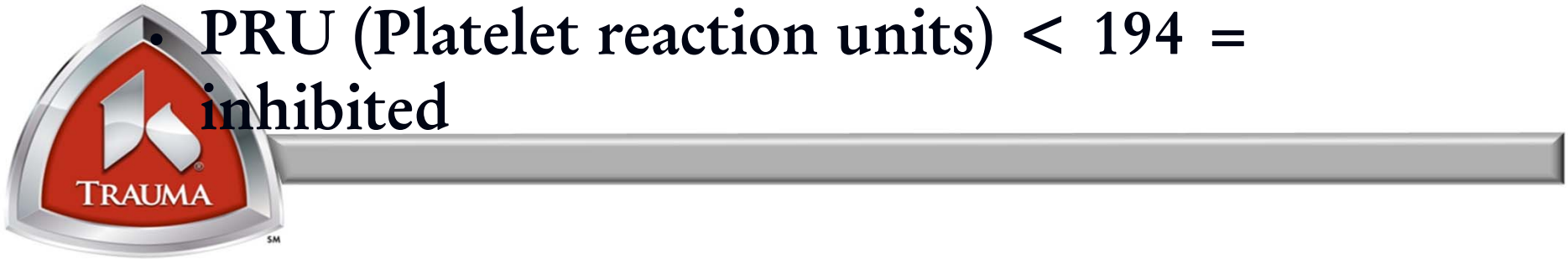
- Inadequate response to antiplatelet meds:
  - Drug interactions
    - Proton pump inhibitors
  - Genetic differences
  - Diabetes & other pre-existing conditions
  - Noncompliance

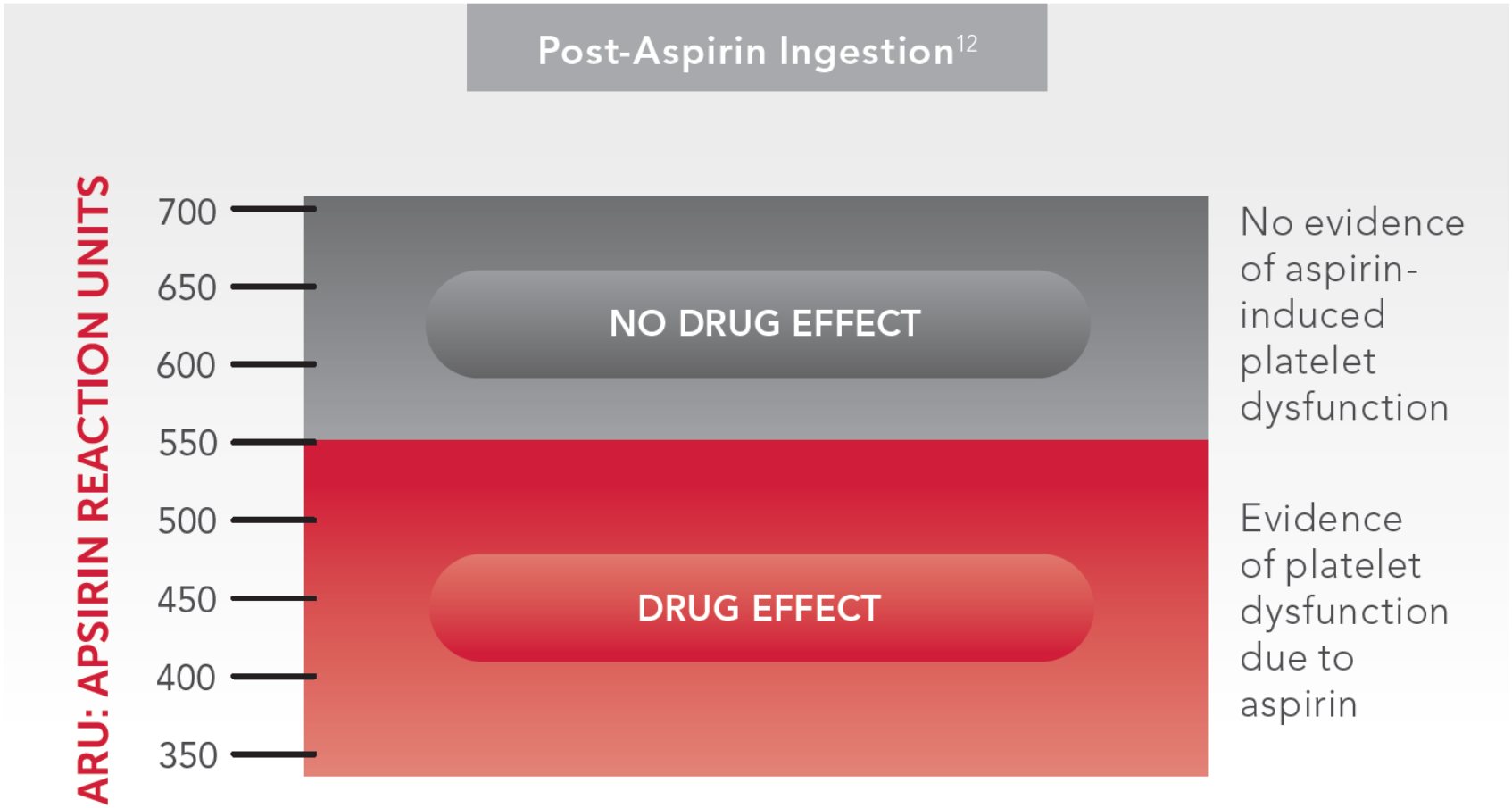
Non Compliance



Platelet Reactivity

- High reactivity indicates NO therapeutic inhibition
- Low reactivity indicates Presence of therapeutic inhibition
- Verify Now
  - ARU (aspirin reaction units) <549 = inhibited
  - PRU (Platelet reaction units) < 194 = inhibited





Interpretation of Verify Now - Aspirin

TRAUMA

High Platelet Reactivity

- Relationship between HPR & thrombotic events in PCI well established
- POPular study
  - 422 pts. assessed by Verify Now or AA LTA all cause death significant in HAPR at 1 year follow up
- ISAR-ASPI (Intracoronary PI & antithrombotic regimen)
  - 7,090 pts. HPR independent predictor of death

Breet et al J Thromb Haemost 2010;8(10):2140-2148
Mayer et al J Am CollCardiol 2014;64(9):863-871

High Platelet Reactivity

- Adapt DES 8,449 pts
  - VN > 550 inversely related to bleeding

- Aspirin Non-responsiveness & Clopidogrel Endpoint Trial (ASCET) 1,001 pts.

Stone et al Lancet 2013;382(9892) 614-23

Low Platelet Reactivity

- LPR key determinant of major bleeding & entry site complications in PCI pts.
- Adapt-DES registry LPR had more clinically relevant bleeding
- Cusset identified platelet inhibition as strongest predictor of bleeding when on Prasugrel

Stone et al Lancet 2013;382(9892) 614-23
Cusset et al JACC Cardiovasc Interv 2013; 6(8):854-63

GRAVITAS

Gauging Responsiveness with Verify Now Assay Impact on Thrombosis & Safety

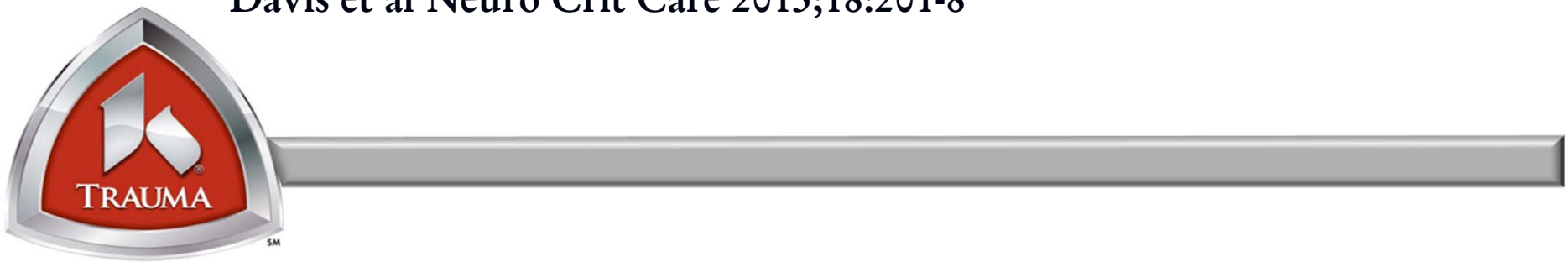
- Blinded randomized controlled trial PCI pts.
- Stable angina or ACS
- HPR patients randomized to
- additional loading dose of Clopidogrel (600 mg)
- Increase MTC dose 150 mg or standard 75mg

- Among HPR pts. with drug-eluding stents high dose did not reduce incidence from death from CV causes, nonfatal MI or stent thrombosis

POC Testing in Neurosurgery

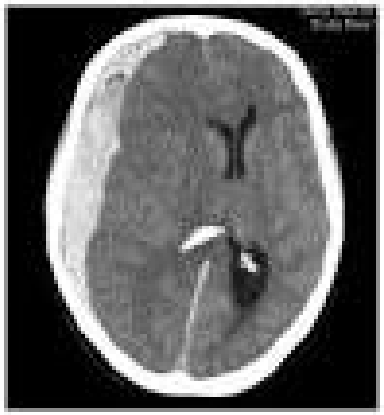
- 50 NS Pts.
- Severe TBI
- TEG PM utilized
- Decreased platelet function associated with increased mortality

Davis et al Neuro Crit Care 2013;18:201-8



POC Testing in Neurosurgery

- PFA-100 screened 58 pts. with subdural hematoma

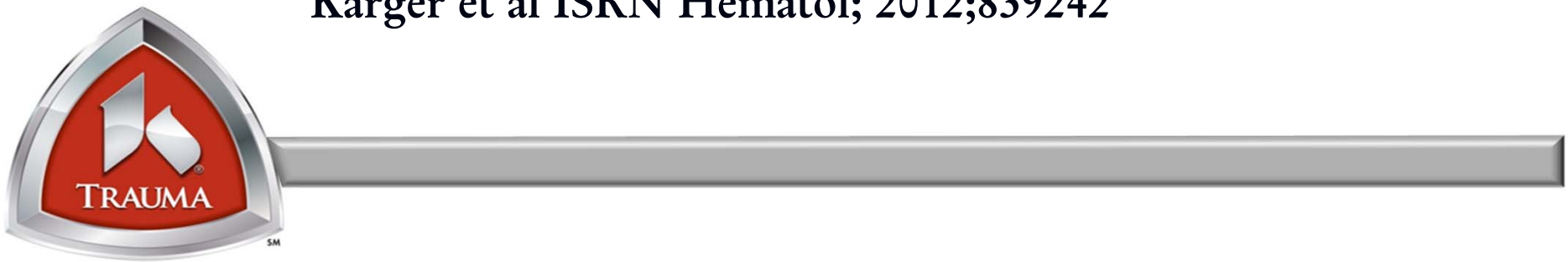


- 38% had impaired platelet function

POC Testing in Neurosurgery

- PFA-100 screening tool in elective neurosurgery procedures
- 15/93 had abnormal findings

Karger et al ISRN Hematol; 2012;839242

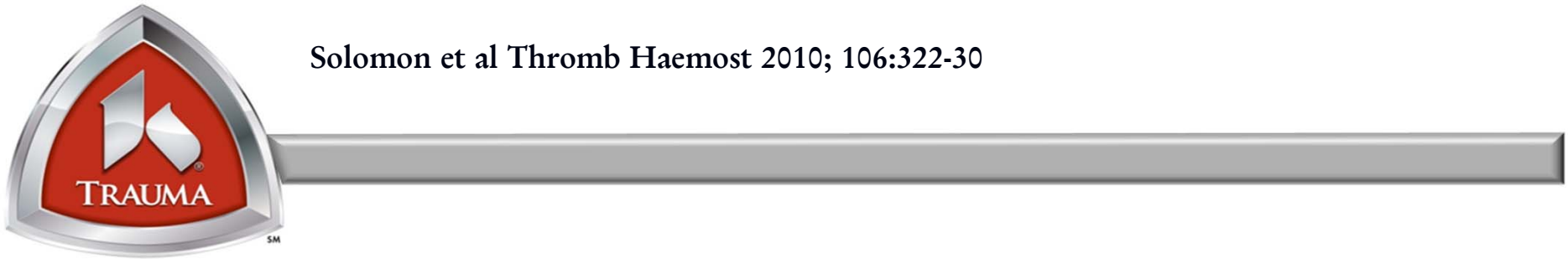


POC Testing in Neurosurgery

- Multiplate analyzer used in 163 trauma pts.

- Decreased platelet function was significantly more frequent in non-survivors than survivors

Solomon et al Thromb Haemost 2010; 106:322-30



POC Testing in Neurosurgery

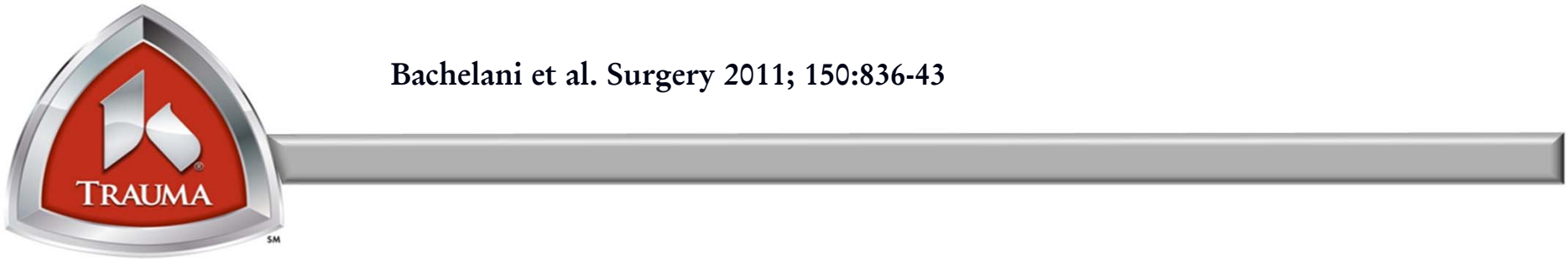
- Multiplate analyzer used in 22 pts. on antiplatelet medication
- Required urgent neurosurgical intervention
- Administration of desmopressin, TXA & platelet concentrate doubled platelet activity as measured by repeated analysis

Benyon et al J Clin Neurosci 2013; 20:1805-6
Benyon Clin Neurol Neurosurg 2013;115:2003-8

POC Testing in Neurosurgery

- 84 pts. With TBI
- Verify Now assay
- Demonstrated failure to normalize platelet function through platelet transfusion
- Associated with trend towards higher mortality

Bachelani et al. Surgery 2011; 150:836-43

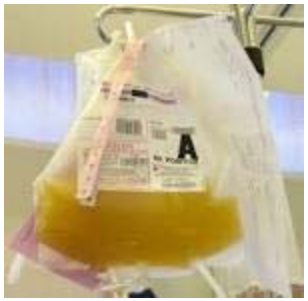


Transfusion in TBI

- PRBC

- FFP

- Platelets



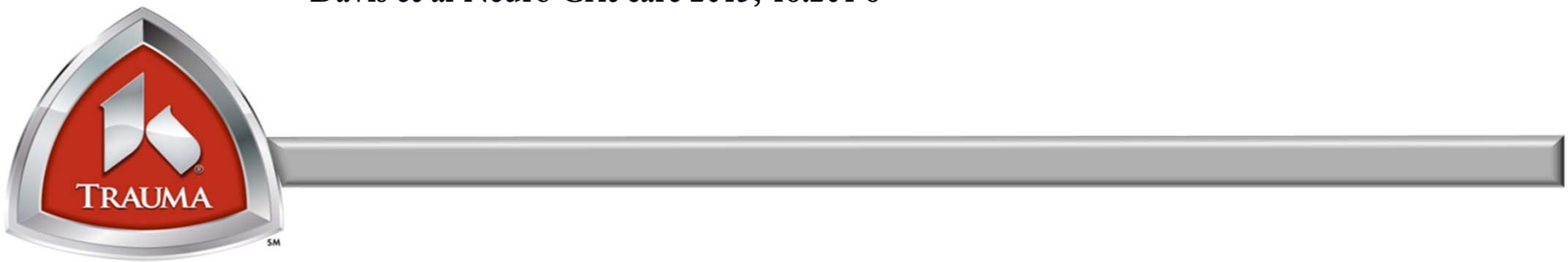
- A deficiency in any of these leads to worse clinical outcome

Transfusion in TBI

- TBI pts. Can develop platelet dysfunction even without antiplatelet therapy

- Mechanism unknown

Davis et al Neuro Crit care 2013; 18:201-8



Transfusion in TBI

- > 35% of adult population is on some form of antiplatelet medication

  Am J Prev Med 2006; 30:74-7

- TBI Pts. on antiplatelet therapy worse outcomes

  J Trauma 2008; 65:303-8
  J Trauma 2008; 65: 785-8

AAST Multicenter Trial (2016) – in press

- Prospective, observational trial
- Hypothesis: Patients on NOA have higher rates of ICH, ICH progression, and death compared to patients on traditional anticoagulant and antiplatelet agents
- 1,844 patients – 16 Trauma Centers including KMC

Kobayashi, Leslie et al. (2016) In press.

AAST Multicenter Trial (2016) – in press

- Overall mortality was 7%. No significant difference between groups. NOA's did not have increased risk of death on multivariate analysis.
- Patients on aspirin had highest rate and risk of ICH
  - Kobayashi, Leslie et al. (2016) In press

Benefits of Platelet Transfusion? Dysfunction

- Platelet Transfusion an Unnecessary Risk for Mild TBI

  Washington et al J Trauma ACS 2011;71:358-63

- Nishijima et al – No benefit in transfusion

  J Trauma ACS 2012;72:1658-63

- Worsened outcome seen

  OHM et al. J Trauma 2005;58:518-22

Benefits of Platelet Transfusion? Dysfunction

- Improved outcome seen

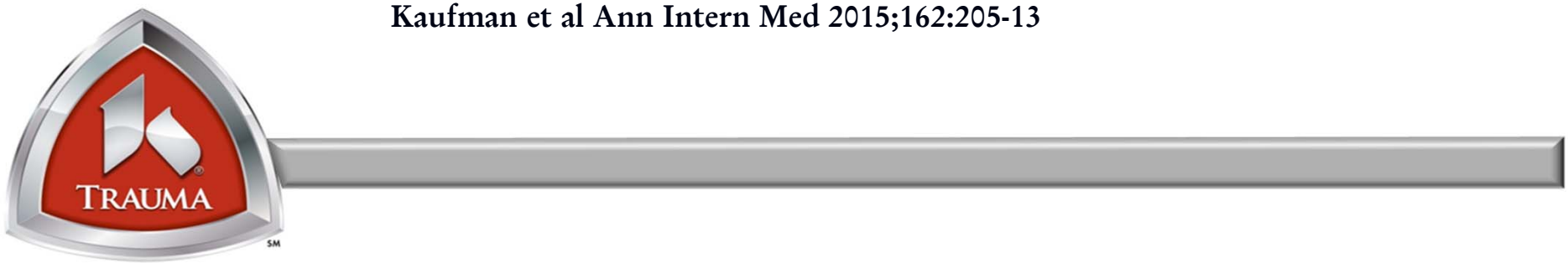
  Wong et al J Trauma 2008;65:1303-8

- American Academy of Blood Bank Guidelines

  Advancing Transfusion and Cellular Therapies Worldwide

  - Insufficient evidence to recommend for or against platelet transfusion in TBI

  Kaufman et al Ann Intern Med 2015;162:205-13

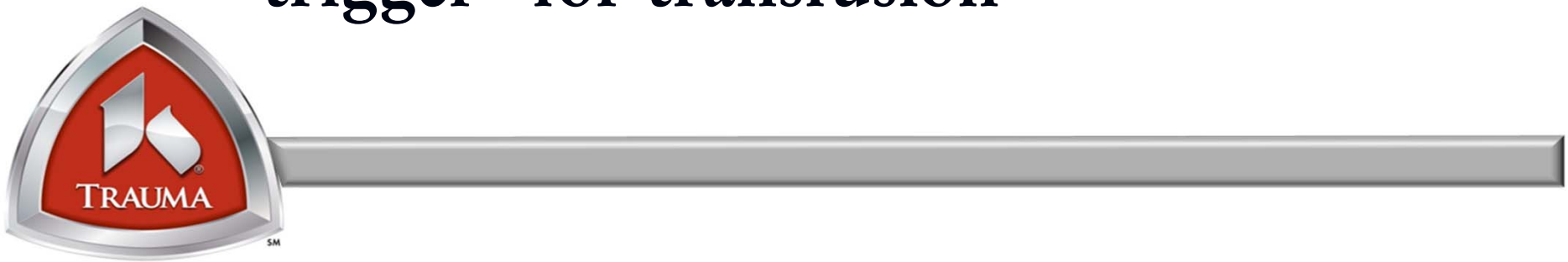


Benefits of Platelet Transfusion? Thrombocytopenia

- Studies showing ability to predict progression of hemorrhage in TBI
- Often due to DIC from severe TBI

J Neurotrauma 2005;22:291-6

- < 100,000 platelet count often used a "trigger" for transfusion



Thrombocytopenia < 100,000

- 9 fold increase in morbidity
  - "The impact of platelets on the progression of traumatic intracranial hemorrhage

Schnuriger et al. J Trauma 2010;68:881-5

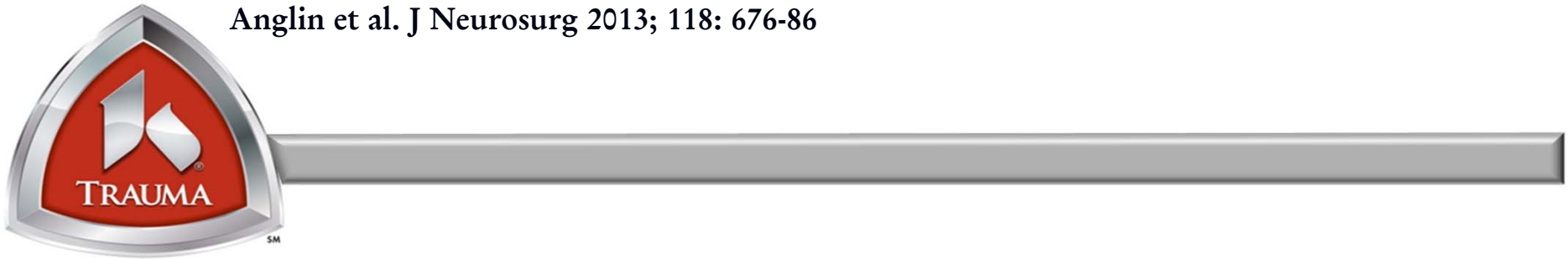
- Increased likelihood of hemorrhage progression

Allard et al J Trauma 2009;67:959-67

Risk: Benefit of Platelet Transfusion in TBI &Thrombocytopenia

- Retrospective analysis of TBI pts. with platelet count 50,00-100,000
- Did not result in any improvement in outcome at 6 months
- Suggests that 100,000 is TOO HIGH threshold for transfusion

Anglin et al. J Neurosurg 2013; 118: 676-86



Plavix & TBI

- 46 Plavix medicated trauma patients

- 28% had no measurable effect of platelet inhibition

- Platelet transfusion would unnecessarily increased transfusion related risks and waste product

Bansal et al J Trauma 2011;70:65-9

TRAUMA

Recent Metaanalysis

- Failed to prove that transfusion of platelets to reverse antiplatelet effects in pts. with traumatic ICH was beneficial

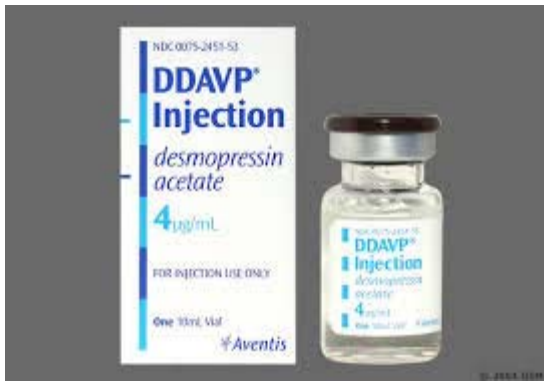
Campbell et al. World Neurosurg 2010;74:279-85

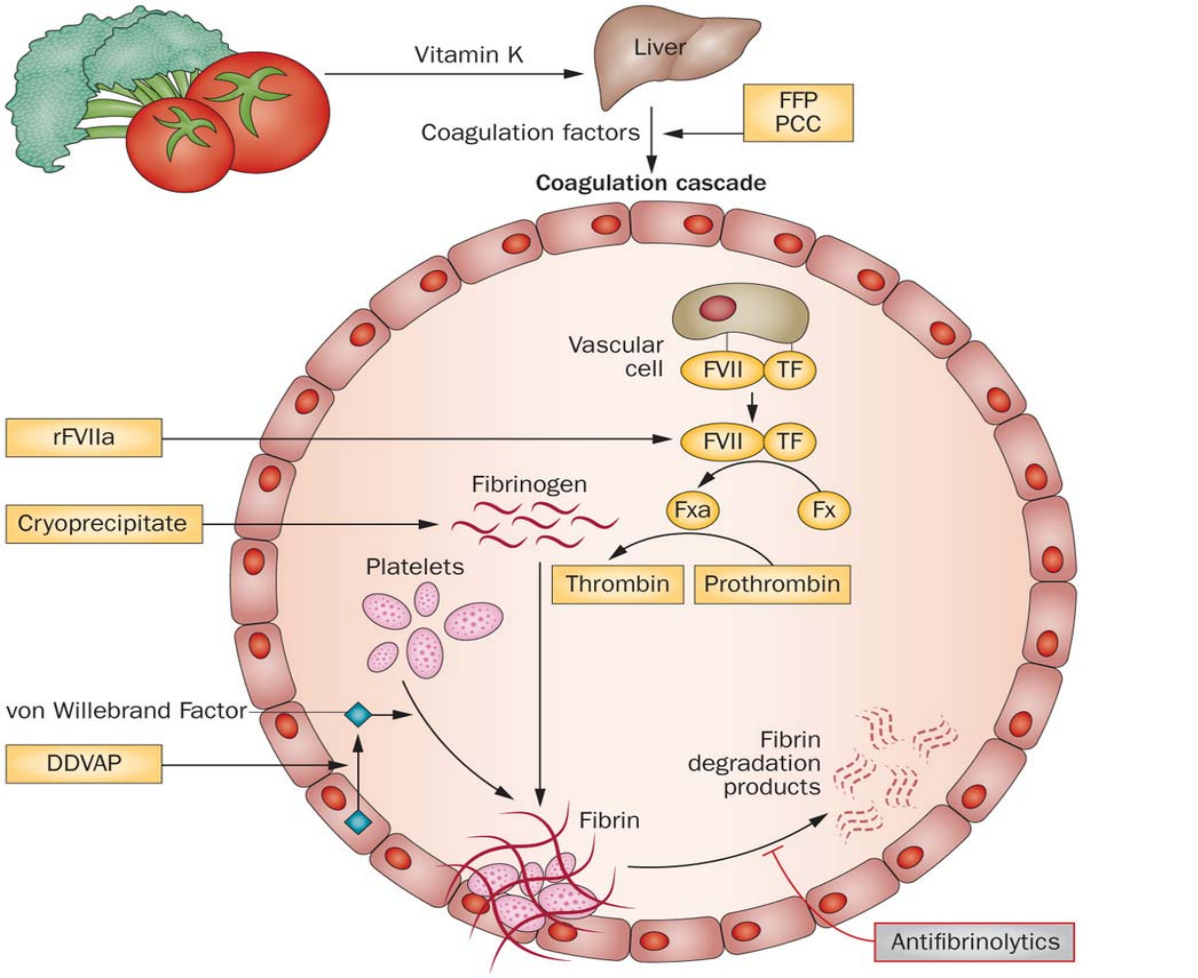
Nishijima et al. J Trauma ACS 2013;72:1658-63

PATCH: platelet transfusion in cerebral haemorrhage: study protocol for a multicentre, randomised, controlled trial

- The primary objective is whether platelet transfusion improves outcome in intracerebral haemorrhage patients who are on antiplatelet treatment.
- Patients randomised to receive platelet transfusion within six hours or standard care.
- The primary endpoint is functional health after three months.
- The main secondary endpoints are safety of platelet transfusion and the occurrence of haematoma growth.

What about Desmopressin ??

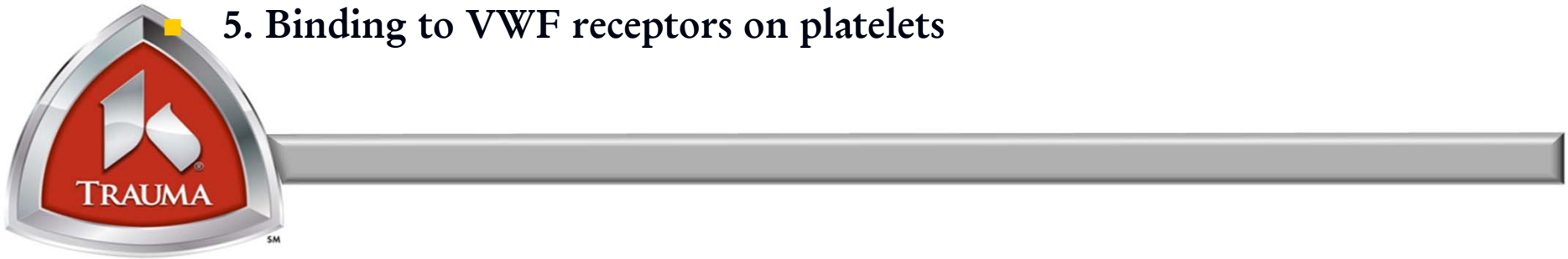




TRAUMA

Desmopressin exerts its haemostatic effect by:

- 1. Inducing synthesis of the von Willebrand factor (VWF) by endothelial cells
- 2. Stimulating release of the VWF from its storage sites in endothelial cells
- 3. Cleaving the large VWF multimers circulating in plasma into smaller multimers
- 4. Enhancing interaction between platelets and the VWF
- 5. Binding to VWF receptors on platelets



Desmopressin Improves Platelet Activity in Acute Intracerebral Hemorrhage

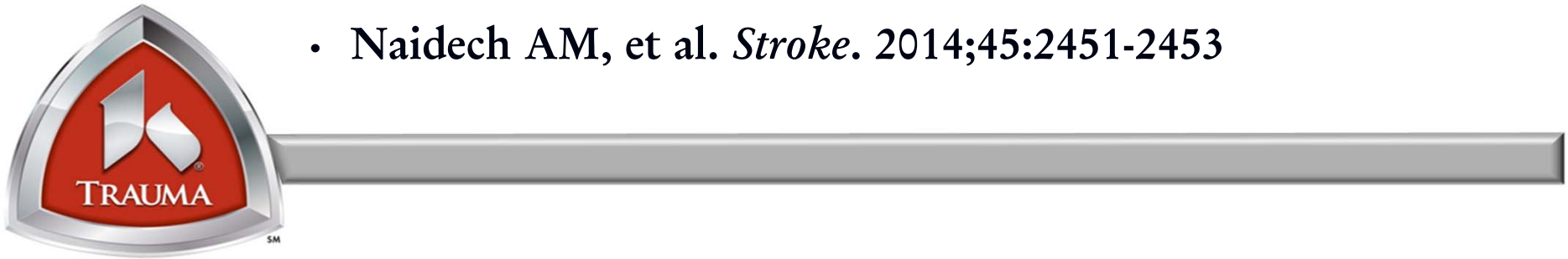
- Study Design Prospective, single-center study
- Population: Patients with acute ICH confirmed with CT scan and known aspirin use or reduced platelet activity
- Intervention: DDAVP 0.4 mcg/kg IV over 30 minutes and other
- routine care
- Primary Endpoint: Change in the platelet function at T = 1 hour after the start of DDAVP
- Secondary Endpoints
  - -vWF antigen
  - -Serum sodium
  - -Hematoma volume

Naidech AM, et al. *Stroke*. 2014;45:2451-2453

TRAUMA

Desmopressin Improves Platelet Activity in Acute Intracerebral Hemorrhage Author's Conclusion

- DDAVP improved measures of platelet activity, vWF antigen, and decreased hematoma volume
- Given its safety, low cost DDAVP is an attractive pharmacological treatment for acute ICH
- Further larger randomized control trials are needed



- Naidech AM, et al. *Stroke*. 2014;45:2451-2453

Desmopressin Acetate in Intracranial Hemorrhage

- Study Design Prospective, single-center study
- Population Patients with acute ICH confirmed with CT scan and aspirin within 24 hours prior to admission
- Intervention DDAVP 24mcg IV over 30 minutes
- Primary Endpoint Platelet function half an hour after DDAVP administration
- Secondary Endpoints Platelet function 3 hours after DDAVP administration

Kapapa T, et al. *Neurol Res International*. 2014;2014:298767

Desmopressin Acetate in Intracranial Hemorrhage

- Author's Conclusion:
- DDAVP can improve platelet function after 30 minutes in ICH patients,
- Coagulation status can be restored to normal between 30 minutes to 3 hours

Kapapa T, et al. *Neurol Res International*. 2014;2014:298767

The Effect of Platelet and Desmopressin Administration of Early Radiographic Progression of Traumatic Intracranial Hemorrhage

- Study Design 3-year retrospective analysis at a level I trauma center
- Population Adult trauma patients admitted with a diagnosis of traumatic ICH
- Intervention Platelets and DDAVP (0.3mcg/kg IV or 0.15mcg/kg IV in elderly patients) vs. No platelets and No DDAVP
- Primary Endpoint Hemorrhage progression defined as 25% increase in volume
- Secondary Endpoints
  - In hospital mortality
  - Length of stay

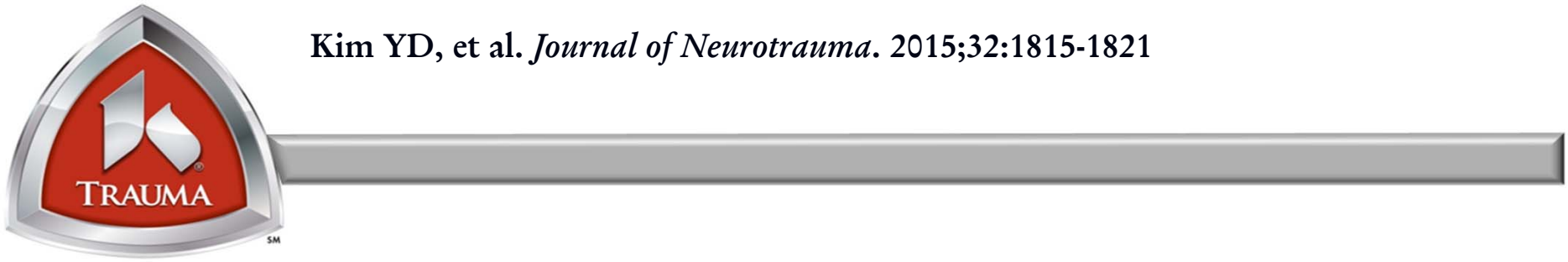
Kim YD, et al. *Journal of Neurotrauma*. 2015;32:1815-1821

The Effect of Platelet and Desmopressin Administration of Early Radiographic Progression of Traumatic Intracranial Hemorrhage

- ICU and hospital length of stay were increased in the Platelet/DDAVP (+) group

- Patients in the Platelet/DDAVP (+) group had increased mortality (p=0.03) and more health services upon discharge
  - After controlling for baseline characteristics no difference in mortality

Kim YD, et al. *Journal of Neurotrauma*. 2015;32:1815-1821



The Effect of Platelet and Desmopressin Administration of Early Radiographic Progression of Traumatic Intracranial Hemorrhage

- Platelets and DDAVP administration are not associated with statistically significant decreased early radiographic hemorrhagic progression
- It is not known whether long-term neurological function is improved by platelet and DDAVP administration

Kim YD, et al. *Journal of Neurotrauma*. 2015;32:1815-1821

Cost of Desmopressin

- A 100kg patient receiving 0.4 mcg/kg = 40 mcg

- $168.34

DDAVP Summary

- Current literature is not conclusive of recommendations for management and reversal of patients with ICH on antiplatelet therapy
- DDAVP can be considered in patients who have taken anti-platelet therapy and have severe ICH
- New Guidelines for Reversal of Antithrombotics in Intracranial Hemorrhage recommend consideration of DDAVP in patients with ICH

What Have We Learned Today?

- Numerous platelet function tests
- 35% of population on antiplatelet therapy
- 40% of those taking antiplatelet therapy are non-responders
- 28% of TBI patients have platelet dysfunction not due to antiplatelet therapy
- Dysfunctional and deficient #'s (?) of platelets likely to show progression of traumatic hemorrhage

What Have We Learned Today ?

- The decision to transfuse platelets in traumatic ICH has no strong evidenced based literature to support it.
- The decision to use Desmopressin also has no strong evidence for use in traumatic ICH

Clear as Mud

Questions ??

TRAUMA
SM