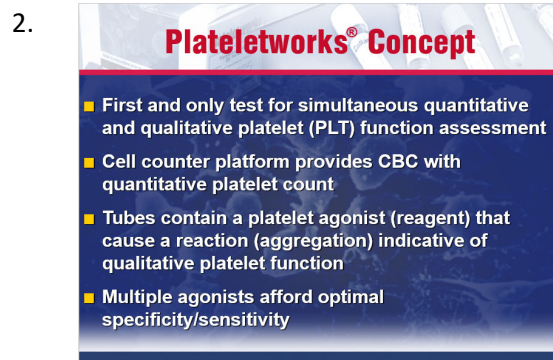
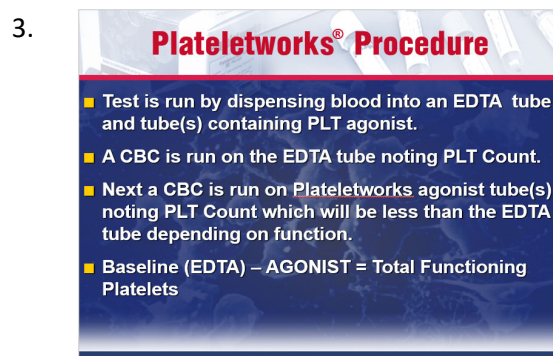




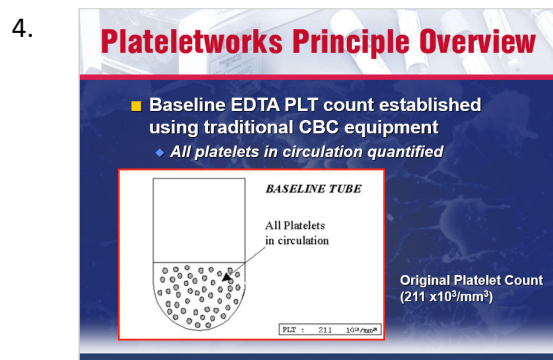
This slide series presents an overview of Plateletworks®, a whole blood platelet function test that can be performed in under 10 minutes at the point of care.



**Plateletworks®** is the first and only test to measure platelets both quantitatively and qualitatively. It is an economical and efficient screening tool. By using an impedance cell counter as the instrument platform, Plateletworks combines a CBC with a quantitative platelet count. The addition of a platelet agonist causes an aggregation reaction which precipitates out the functional platelets thus enabling a qualitative assessment of platelet function. The system offers individual agonists for optimal sensitivity to different clinical scenarios driven by acquired or congenital platelet defects.



The Plateletworks procedure is very simply run with at least two tubes. One tube contains EDTA, which gives the baseline count, and the other tube or tubes utilize a traditional platelet agonist, such as ADP, collagen, or arachidonic acid. A quick mathematical calculation yields quantitation of functional platelets.

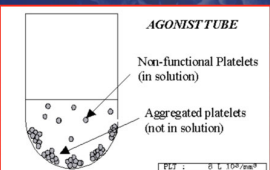


The first tube is the baseline EDTA platelet count also known as the total platelet count. EDTA is selected because often the end user will also like to use the other hematology results such as RBC, HCT etc. for additional patient assessment, and EDTA does not require volumetric correction as with sodium citrate tubes. Using a traditional CBC, Plateletworks is the only platelet function test that does not require additional capital purchase.

5.

## Plateletworks Principle Overview

- Agonist platelet count then performed using Plateletworks agonist tube
  - Platelets remaining in suspension quantified



**AGONIST TUBE**

Non-functional Platelets (in solution)

Aggregated platelets (not in solution)

With agonist –  
New count ( $8 \times 10^3/\text{mm}^3$ )  
Platelet Function = 96%

In the agonist tube, be it collagen, ADP or arachidonic acid, the functional platelets are aggregated and settle rapidly in the tube. When counted on an impedance hematology counter, the non-functional singlet platelets are counted while the functional platelets, in the form of platelet aggregates, are not. Any clumps that are counted are seen as a larger cell than a platelet and are thus insignificant.

6.

## Result Calculation

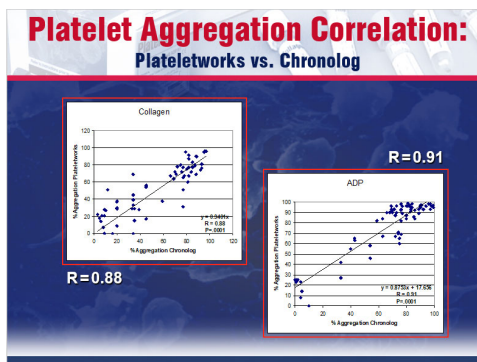
Baseline (total plts) = 211,000  
Agonist (non-functional plts) = 8,000

So...  
Baseline – Agonist = 203,000 TFP

$$\frac{203,000}{211,000} \times 100 = 96\% \text{ Aggregation}$$

First the total functional platelets are determined by simply subtracting the agonist result from the baseline result. The percent aggregation is very quickly determined by dividing the total functional platelets by the baseline and multiplying by 100.

7.



Plateletworks has been thoroughly tested against both PRP aggregation and whole blood aggregometry showing extremely good correlations at all levels.

8.

## Study: Plateletworks vs LTA

S Polena, KM Zazzali, H Shaikh, et al.  
Lenox Hill Hospital, New York, NY

- Studied 48 patients on chronic aspirin and clopidogrel therapy prior to percutaneous coronary intervention
- Compared Plateletworks ADP and AA results to light transmission platelet aggregometry (LTA)

**Conclusion:** Data demonstrated a good correlation between Plateletworks and LTA. Plateletworks is easier and faster and should be used in patients undergoing PCI on antiplatelet therapy.

Point of Care 2011;10:35-39

In a study performed at Lenox Hill Hospital, 48 patients on dual anti-platelet therapy prior to PCI were tested for platelet function using Plateletworks ADP and Arachidonic Acid, side by side with LTA. The study concluded Plateletworks performed as well as LTA and was more efficient and stress free.

9.

### Acquired Functional Disorders

- Drugs
- Uremia
- Cirrhosis / Chronic Hepatitis
- Leukemia & Myelodysplastic Syndrome
- Plasma Protein Abnormalities
- Myeloproliferative Disorders
- Cardiopulmonary Bypass

Most platelet problems seen in the clinical laboratory or clinically with patients are acquired functional disorders due to drugs, uremia, cirrhosis, leukemia, myelodysplastic disease, plasma protein disorders, and surgical therapies and procedures like cardiopulmonary bypass.

10.

### Effect of Cardiopulmonary Bypass on Hemostasis

<u>Hemodilution</u>	<u>Activation</u>
Platelets	Platelets
Coagulation Proteins	Fibrinolysis
	Coagulation

In cardiopulmonary bypass, there are two major effects on platelets. The first is hemodilution, which reduces the platelet count, as well as reducing coagulation proteins. The second is activation. Once the platelets are run through plastic tubing and exposed to oxygenator circuits, many of them are taken out or activated. Fibrinolysis comes into play because the plasminogen converts into plasmin, and coagulation will actually consume a number of the platelets.

11.


### Drugs That Affect Platelets

- Analgesics (aspirin, NSAIDs) affecting prostanoid synthesis or action
- Caffeine, theophylline, dipyridamole, and drugs which increase platelet cyclic AMP
- Antimicrobials (penicillins, cephalosporins, nitrofurantoin)
- Cardiovascular agents (quinidine, diuretics, vasodilators)
- Anticoagulants (coumadin, heparin) and thrombolytics (t-PA, streptokinase)
- Psychotropics (tricyclics/phenothiazines) and anesthetics
- Chemotherapeutic agents
- Miscellaneous agents (dextran, clofibrate, ETOH, Vitamin E, onions, garlic, ginger, fish oil)

At least 900 drugs and compounds are known to affect platelet function either by up regulation or down regulation. Among these are analgesics, aspirin, nonsteroidal anti-inflammatory drugs (NSAIDs), caffeine, theophylline, dipyridamole, and drugs which increase cyclic AMP. There are antimicrobials, most of which have antibody functions, and cardiovascular agents, such as quinidine and diuretics, which may actually be platelet poisons in some instances. Anticoagulants may also lead to antibodies, and thrombolytics, such as tPA and streptokinase, force the release of fibrinolysins. Psychotropics, such as Valium and Prozac, and certain anesthetics also disrupt function. Chemotherapeutic agents generally will kill platelets. A number of environmental factors and other miscellaneous agents, such as dextran, alcohol, high dose vitamin E, onions, garlic, ginger, fresh fish oil, dark chocolate, and dark beer also affect platelet function.



12.

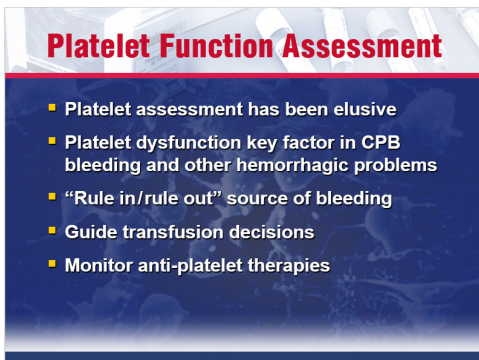


### Why Test?

- Important in assessing risk of bleeding or need for transfusion in active bleeding
  - ◆ *Surgical, pre-surgical and emergency*
- Important in monitoring and managing antiplatelet therapies (ReoPro, Aggrastat, Integrilin, aspirin, etc.)
- Important for monitoring platelet destruction by mechanical means (extracorporeal circulation)

Why perform platelet aggregation testing? It is essential in assessing the risk of bleeding and/or the need for transfusion in actively bleeding patients. It is important in monitoring and managing antiplatelet therapy, especially in light of the tremendous increase in pharmacological intervention in the treatment of thrombotic or clotting complications, such as myocardial infarctions. Also in emergency departments, where patients are frequently admitted with significant bleeding problems but unable to give a history because they are unconscious, platelet testing assists the attending physician to identify what may be the source of the bleeding.

13.

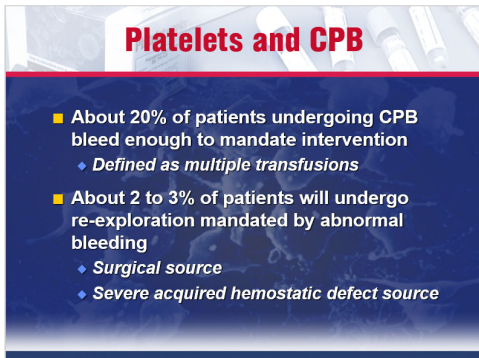


### Platelet Function Assessment

- Platelet assessment has been elusive
- Platelet dysfunction key factor in CPB bleeding and other hemorrhagic problems
- "Rule in/rule out" source of bleeding
- Guide transfusion decisions
- Monitor anti-platelet therapies

It is believed that platelet dysfunction is an important contributor to bleeding in cardiopulmonary bypass and other hemorrhagic problems. Near-patient monitoring of platelet function can contribute significantly to ruling in or ruling out the source of bleeding, can help guide transfusion decisions, and may be used to assess effectiveness of anti-platelet therapies.

14.



### Platelets and CPB

- About 20% of patients undergoing CPB bleed enough to mandate intervention
  - ◆ *Defined as multiple transfusions*
- About 2 to 3% of patients will undergo re-exploration mandated by abnormal bleeding
  - ◆ *Surgical source*
  - ◆ *Severe acquired hemostatic defect source*

In the hospital, there are many reasons to use Plateletworks. About 20% of all patients undergoing cardiopulmonary bypass surgery bleed enough to mandate intervention. In the United States, approximately 25% of all platelet donations go to patients who are undergoing bypass surgery. Two to three percent of these patients will undergo re-exploration mandated either by a surgical source of bleed or by an acquired hemostatic defect.

### 15. **Consequences of the Bleeding Patient**

- Re-operation
- Delayed chest closure
- Increased risk of mediastinitis or other infection
- Hypovolemia
- Biventricular cardiac function
- Blood product reactions (1.6% hepatitis A, 11.6% hepatitis B)
- Immunologic effects (anaphylaxis or acute lung injury)

In bleeding patients, the consequences can be significant: re-operation, delay in chest tube closure, increased risk of infections, volume issues, cardiac dysfunction, blood byproduct reactions and various immunological reactions. In cardio bypass surgery, there are proteins that are absorbed on a blood surface interface causing platelet adhesion to the surface. The platelets undergo sheer stress when going through the plastic tubing and through the bypass pumps and there are problems with surface contact activation and adhesion. Multiple factors increase the damage to hemostasis including release of thrombin, release of ADP, epinephrine, stress and hypothermia. Blood flow will also activate the platelets.

### 16. **Causes of Excessive Bleeding after CPB**

- Probable
  - ◆ Local bleeding site or acquired (mechanical or pharmaceutical) platelet dysfunction
- Possible
  - ◆ Preoperative drug-induced hemostatic dysfunction (aspirin, warfarin, IIb/IIIa)
  - ◆ Preoperative hemostatic dysfunction
  - ◆ Inherited hemostatic dysfunction (vWF, platelet defect)
  - ◆ DIC (sepsis, low-output state)
  - ◆ Primary fibrino(geno)lysis

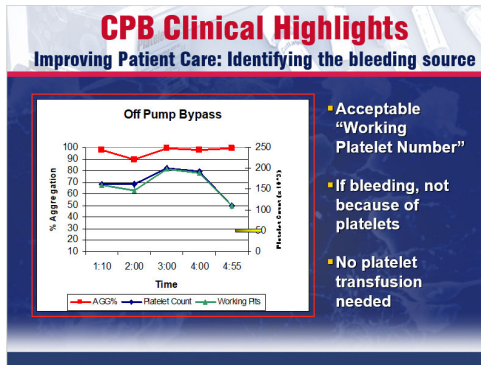
The most probable cause of excessive bleeding after cardiopulmonary bypass is local bleeding at the site, mechanical or pharmaceutical, due to platelet dysfunction. Possible causes that must be considered include: preoperative drug-induced hemostatic dysfunction (aspirin, warfarins, coumadin, anti-IIb/IIIa drugs), preoperative hemostatic dysfunction, inherited hemostatic dysfunctions, DIC, and primary fibrinolysis.

### 17. **Plateletworks® Value in CPB**

- Assess the extent of platelet dysfunction induced by CPB
- Monitor post-op recovery of platelet aggregation
- Monitor recovery/drop in platelet count
- Guide transfusion decisions
- Manage bleeding patients
- Evaluate emergency surgery Cath Lab patients with anti-platelet agents
- Manage anti-platelet agents given during beating heart procedures

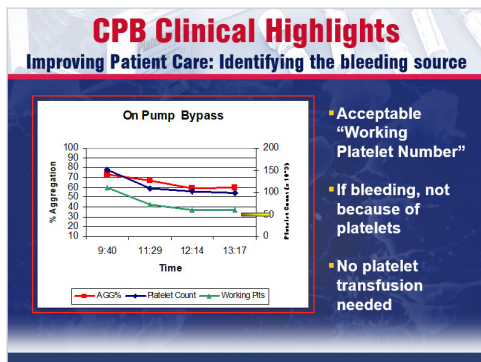
In cardiopulmonary bypass surgery, Plateletworks can be of value to assess the extent of platelet dysfunction caused by the procedure, monitor post-operative recovery, monitor recovery or drop in platelet counts, guide transfusion decisions, manage bleeding patients, and evaluate emergency surgery patients from the catheterization lab for anti-platelet drugs.

18.



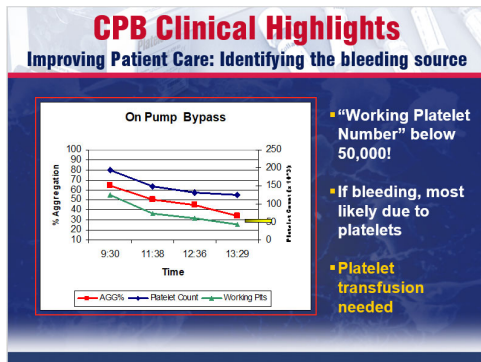
This shows a typical off-pump or beating heart procedure where the patient's percent aggregation never truly declines. While the number of working platelets does decline, the number of functional platelet is still within an acceptable range and the patient does not need to undergo any type of transfusion.

19.

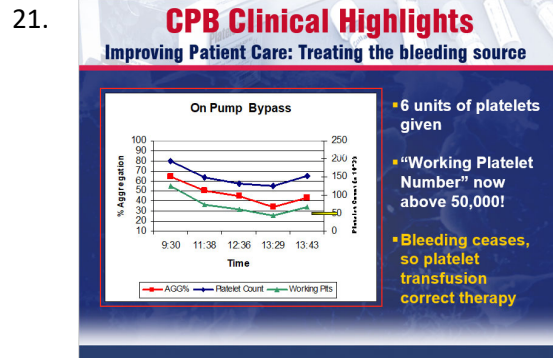


This illustrates what sometimes happens with an on-pump bypass procedure. The platelet count, percent aggregation, and even functional count are relatively good at the beginning of the procedure. Near the end of the procedure, the percent aggregation and total platelet count drop. The functional platelet count drops as well but remains above a functional level of 50,000. If this patient is bleeding, it is not likely because of platelets and would not require platelet transfusions. This patient should be investigated for plasma protein abnormalities which may require transfusion with fresh frozen plasma or cryoprecipitate.

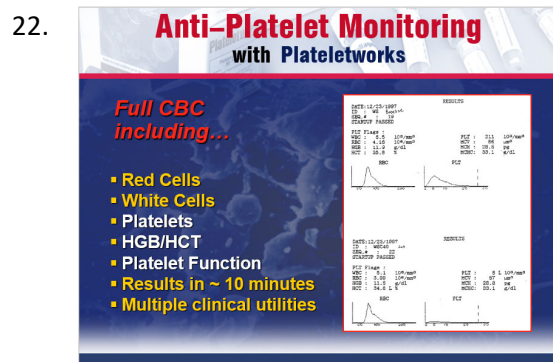
20.



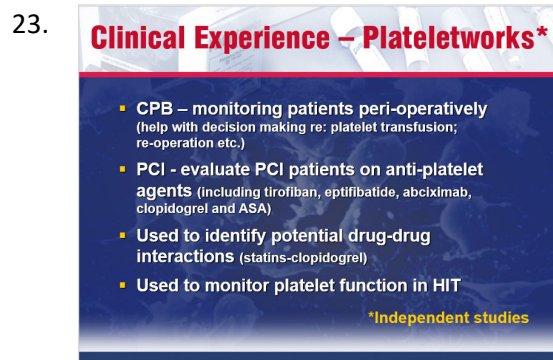
This slide indicates an on-pump or a bypass patient whose total platelet count decreased, the percent aggregation decreased substantially, and the working or functional platelet count has gone below 40,000. If this patient is bleeding, it is most likely due to a lack of quantity of functional platelets, and this would be an indicator for a platelet transfusion particularly if bleeding.



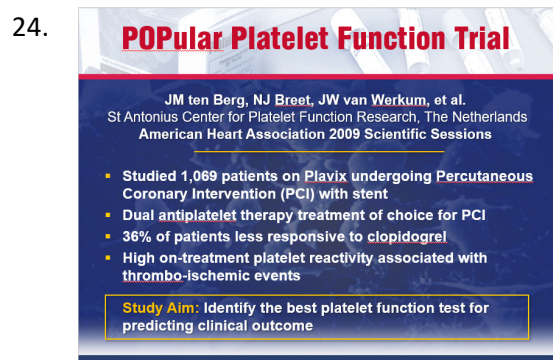
This shows the previous patient, post-transfusion. The platelet count, functional platelet count, and percent have all gone back up, and so the platelet transfusion did correct the problem.



While Plateletworks includes the Complete Blood Count, the real key to the efficacy of the Plateletworks assay is the ability to provide the functional platelet count, the % aggregation / inhibition, PLUS the red blood cells, hemoglobin and hematocrit, all in one assay in less than 10 minutes.



A variety of independent clinical studies have shown the utility of the Plateletworks assay in cardiopulmonary bypass (CPB) and coronary interventions (PCI), in identifying potential drug-drug interactions, and even in monitoring platelet function in the presence of heparin-induced thrombocytopenia (HIT).



A study called the POPular trial examined the different platelet function tests to determine the best way to predict clinical outcomes. The study included 1,069 patients on Plavix undergoing PCI. The treatment of choice for PCI is dual anti-platelet therapy consisting of aspirin regimen combined with a platelet inhibitor such as clopidogrel, better known as Plavix. In this study 36% of the patients were found to be less responsive to clopidogrel and were at a high risk for platelet reactivity associated thrombo-ischemic events.



25.

### POPular Platelet Function Trial

- Assays included:
  - Light transmittance aggregometry (LTA) with ADP
  - Helena Plateletworks®
  - Accumetrics VerifyNow® P2Y12
  - Matis Medical IMPACT-R
  - Matis Medical IMPACT-R ADP
  - Dade PFA-100 Collagen and ADP
  - Siemens INNOVANCE® PFA P2Y
- Primary composite endpoint at one year to predict death, MI, stent thrombosis, and stroke
- Primary safety endpoint to predict TIMI, major and minor bleeding

JM ten Berg, et al.  
 AHA 2009 Scientific Sessions  
 Poster Session 1022-1023

The POPular study looked at multiple methods, compiling data over the span of a year, to try to identify the possibility of death, myocardial infarction, stent thrombosis, or stroke. They also looked at predicting major and minor bleeding events.

26.

### POPular Platelet Function Trial

#### Conclusions


- Only LTA, Plateletworks and VerifyNow P2Y12 able to identify patients at higher risk of cardiovascular event.
- None able to identify those at risk of bleeding complications.

JM ten Berg, et al.  
 AHA 2009 Scientific Sessions  
 JAMA 2010; 303(8): 754-762

While none of the methods were able to predict the risk of bleeding complications, it was concluded that only LTA, Plateletworks, and VerifyNow P2Y12 were able to identify patients at high risk for cardiovascular event.

27.

### Nationwide Plateletworks Study



- 12 major hospitals across Canada
- 7,402 patients undergoing cardiac surgery
  - Intervention group of 3,847
  - Control group of 3,555
- POC hemostatic testing including Plateletworks as an integrated transfusion algorithm significantly reduced RBC and platelet transfusions as well as major bleeding

Karoubi K, et al. Circulation. 2016; 134: 1152-62.

Another study published in 2016 included data from 12 major hospitals and 7,402 patients undergoing cardiac surgery. The study concluded that implementing point of care testing, including Plateletworks as an integrated transfusion algorithm, significantly reduced RBC and platelet transfusions as well as major bleeding events.

28.

### Nationwide Plateletworks Study

Reduced usage of blood products using algorithm with Plateletworks to guide transfusion decisions  
 n = 3847 in intervention group

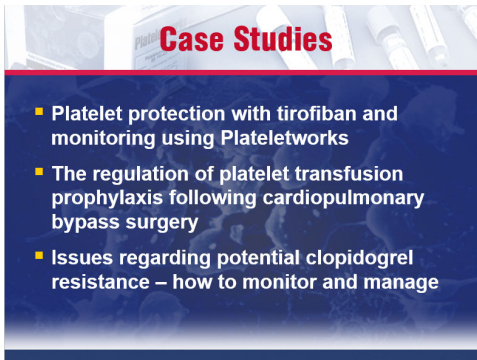
Product	Reduction
Platelets	24%
Packed RBC	13%

Estimated annual savings in USA: \$582,500

Reductions of platelet transfusions of 24% and PRBC transfusions of 13% were seen. This is not only a great savings to the hospitals, but to the patients as well. The benefits are not just in monetary value either. Fewer transfusions means less risk exposure for patients, shorter hospital stays, and less strain on the already short-supplied blood banks.



29.

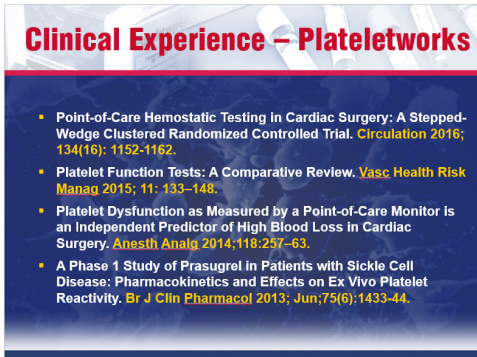


**Case Studies**

- Platelet protection with tirofiban and monitoring using Plateletworks
- The regulation of platelet transfusion prophylaxis following cardiopulmonary bypass surgery
- Issues regarding potential clopidogrel resistance – how to monitor and manage

The case studies presented in the following slides exemplify the real-life usefulness of Plateletworks in the clinical setting.

30.

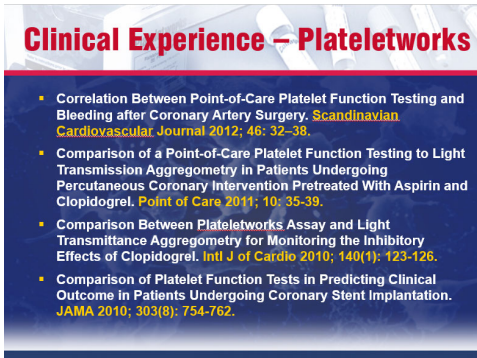


**Clinical Experience – Plateletworks**

- Point-of-Care Hemostatic Testing in Cardiac Surgery: A Stepped-Wedge Clustered Randomized Controlled Trial. *Circulation* 2016; 134(16): 1152-1162.
- Platelet Function Tests: A Comparative Review. *Vasc Health Risk Manag* 2015; 11: 133-148.
- Platelet Dysfunction as Measured by a Point-of-Care Monitor is an Independent Predictor of High Blood Loss in Cardiac Surgery. *Anesth Analg* 2014;118:257-63.
- A Phase 1 Study of Prasugrel in Patients with Sickle Cell Disease: Pharmacokinetics and Effects on Ex Vivo Platelet Reactivity. *Br J Clin Pharmacol* 2013; Jun;75(6):1433-44.

The next few slides show published data relevant to platelet function monitoring with Plateletworks.

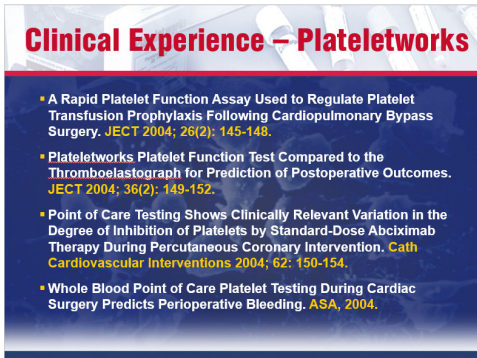
31.



**Clinical Experience – Plateletworks**

- Correlation Between Point-of-Care Platelet Function Testing and Bleeding after Coronary Artery Surgery. *Scandinavian Cardiovascular Journal* 2012; 46: 32-38.
- Comparison of a Point-of-Care Platelet Function Testing to Light Transmission Aggregometry in Patients Undergoing Percutaneous Coronary Intervention Pretreated With Aspirin and Clopidogrel. *Point of Care* 2011; 10: 35-39.
- Comparison Between Plateletworks Assay and Light Transmittance Aggregometry for Monitoring the Inhibitory Effects of Clopidogrel. *Intl J of Cardiol* 2010; 140(1): 123-126.
- Comparison of Platelet Function Tests in Predicting Clinical Outcome in Patients Undergoing Coronary Stent Implantation. *JAMA* 2010; 303(8): 754-762.

32.



**Clinical Experience – Plateletworks**

- A Rapid Platelet Function Assay Used to Regulate Platelet Transfusion Prophylaxis Following Cardiopulmonary Bypass Surgery. *JECT* 2004; 26(2): 145-148.
- Plateletworks Platelet Function Test Compared to the Thromboelastograph for Prediction of Postoperative Outcomes. *JECT* 2004; 36(2): 149-152.
- Point of Care Testing Shows Clinically Relevant Variation in the Degree of Inhibition of Platelets by Standard-Dose Abciximab Therapy During Percutaneous Coronary Intervention. *Cath Cardiovascular Interventions* 2004; 62: 150-154.
- Whole Blood Point of Care Platelet Testing During Cardiac Surgery Predicts Perioperative Bleeding. *ASA*, 2004.

33.

### Clinical Experience – Plateletworks

- Efficacy of High-Dose Bolus Tirofiban Compared to Regular-Dose Glycoprotein IIb/IIIa Inhibitors on Platelet Aggregation Inhibition in Myocardial Infarction Patients Treated with Primary Angioplasty. *ESC, August 2003.*
- Impact of Angina Class on Inhibition of Platelet Aggregation Following Clopidogrel Loading in Patients Undergoing Coronary Intervention. *Cath Cardiovascular Interventions 2003, 59: 21-25.*
- Monitoring Platelet Function During Cardiopulmonary Bypass in the Presence of Tirofiban. *Soc Cardiovasc Anest, April 2003.*
- Clopidogrel Poor Responders Discovered During Point-of-Care Platelet Aggregation Testing. *ACC, March 2003*

34.

### Clinical Experience – Plateletworks

- Atorvastatin Reduces the Ability of Clopidogrel to Inhibit Platelet Aggregation: A New Drug-Drug Interaction. *Circulation 2003; 107: 32 - 37.*
- Contribution of Hepatic Cytochrome P450 3A4 Metabolic Activity to the Phenomenon of Clopidogrel Resistance. *Circulation 2004; 109: r1 – r6.*
- Evaluation of Platelet Count and Function in Patients Administered Tirofiban or Eptifibatide Undergoing Percutaneous Coronary Intervention. *Point of Care: The Journal of Near-Patient Testing & Technology 2004; 3(2): 66-70.*

35.

### Case Study – HIT

**Case Study:** Platelet Protection Using the Glycoprotein IIb/IIIa Inhibitor Tirofiban in a Patient with Heparin Induced Thrombocytopenia Undergoing Aortic Valve Replacement Requiring Cardiopulmonary Bypass

Kirk E Guyer BS, David GM Carville PhD – Indiana University South Bend  
Wei C Lau MD – University of Michigan Health Systems, Ann Arbor

This case study delineates the use of the glycoprotein IIb/IIIa inhibitor, Tirofiban, in a patient with heparin-induced thrombocytopenia who did have to undergo coronary bypass intervention. The abstract was presented at the AACC Symposium on Critical Care and Point of Care Testing, September 2002, Monterey, California.

36.

### Case Study – HIT

### Heparin-Induced Thrombocytopenia

- Serious clinical condition
- Associated with administration of unfractionated heparin (UFH) or low molecular weight heparin (LMWH)
- High morbidity and mortality in cardiac surgery patients

Heparin-induced thrombocytopenia or HIT is a serious clinical scenario that occurs with the administration of unfractionated heparin (UFH) and, to a lesser extent, with low molecular weight heparin (LMWH). HIT has a high incidence of morbidity and mortality, particularly in patients undergoing cardiac surgery.

37. **Case Study – HIT**  
**Heparin-Induced Thrombocytopenia**

- Spontaneous antibodies against heparin bound to platelet factor 4 (PF4)
- Antibody-antigen complexes result in platelet activation and thrombin generation
- Platelet count plummets with simultaneous increase in thromboembolic events
- Mesenteric and/or peripheral infarctions lead to necrosis and amputation

HIT patients spontaneously generate antibodies against heparin bound to platelet factor 4 (PF4) with the subsequent formation of antibody-antigen complexes which result in platelet activation and thrombin generation. This physiological sequence of events elicits a significant decrease in platelet count with a simultaneous increase in thromboembolic events including venous thromboembolism (VTE), pulmonary embolism (PE), stroke or myocardial infarction (MI). Such thromboembolic events may result in either mesenteric and/or peripheral infarctions leading to necrosis and amputation.

38. **Case Study – HIT**  
**Strategies to Prevent HIT**

Alternative modes of anticoagulation needed:

- Danaparoid sodium
- Recombinant-hirudin (bivalirudin/refludan)
- Argatroban
- Anti-GPIIb/IIIa agents

The problem is that patients undergoing CPB must be anticoagulated, but unfractionated and/or low molecular weight heparins are not an optimal therapeutic strategy for patients with HIT. Alternative modes of anticoagulation are required. These include the use of danaparoid sodium, recombinant-hirudin (bivalirudin/refludan) or argatroban. Other suggested strategies include the administration of anti-GPIIb/IIIa agents to protect the platelets.

39. **Case Study – HIT**  
**AntiGPIIb/IIIa Agents for HIT**

- **Abciximab** – Fab’ – sustained anti-platelet and potential thrombocytopenic responses at therapeutic levels - not suitable
- **Eptifibatide** – heptapeptide – good pharmacokinetic profile with a short-half life
- **Tirofiban** – non-peptide – good pharmacokinetic profile with a short-half life

Koster et al. *Anesthesiology* 2001; 94(2): 245-251  
 Jeske et al. *Thromb Haemost* 1999; 82 (suppl): 389

Among the anti-GP IIb/IIIa agents, studies have demonstrated that tirofiban is a safe adjunctive therapy in the management of CPB patients with HIT.



40.

Case Study – HIT

### Monitoring AntiGP IIb/IIIa Agents

- Not an approved use of anti-GP IIb/IIIa agents
- Need to monitor patient's response in OR
- Can't use gold standard (PRP aggregometry) or flow cytometry (centralized tests) in OR
- Need near-patient analyzer to monitor

Plateletworks used in this study for OR monitoring

At this point in time, anti-GP IIb/IIIa agents are not approved for this type of patient therapy. Therefore, the patient's response to these agents must be monitored very closely. Although PRP aggregometry is the gold standard for assessing platelet function, neither PRP aggregometry nor flow cytometry performed in the central laboratory can provide the turnaround time necessary for monitoring the patient in the Operating Room. This case study used Plateletworks to provide an assessment of platelet count and function in four minutes in the surgical suite.

41.

Case Study – HIT

### Case Report

- 84 year old female admitted for aortic valve replacement
- Previously diagnosed with HIT
- GP IIb/IIIa antagonist, tirofiban, administered to protect patient's platelets and prevent HIT
- UFH @ 300 units/kg with an ACT of  $\geq 480$  secs
- Tirofiban infusion stopped 30 minutes prior to termination of CPB

An 84-year-old female patient with severe aortic stenosis, and previously diagnosed with HIT, was admitted to the University of Michigan Medical Center for aortic valve replacement. To protect the patient's platelets and prevent HIT, the short-acting GP IIb/IIIa antagonist, tirofiban, was administered using a 10 mg/kg loading dose with 0.15 mg/kg/min infusion. To anticoagulate during CPB, unfractionated heparin (UFH) in the standard dosing of 300 units/kg was given to maintain an ACT of 480 seconds or greater. Thirty minutes prior to termination of CPB, the tirofiban infusion was stopped.

42.

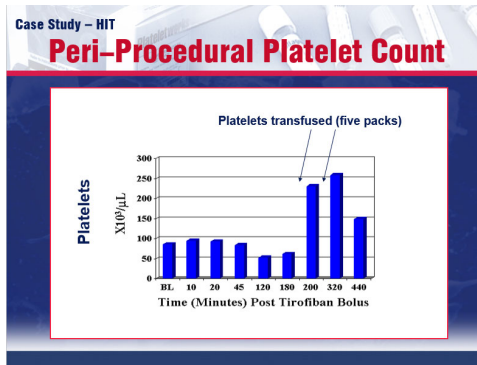
Case Study – HIT

### Patient Monitoring

- Patient's platelet count and function evaluated with Plateletworks
- Reference platelet count performed and compared with platelet count in the presence of 20mM ADP
- Ratio of ADP to reference tube platelet count calculated as percent platelet aggregation
- 4 minute TAT

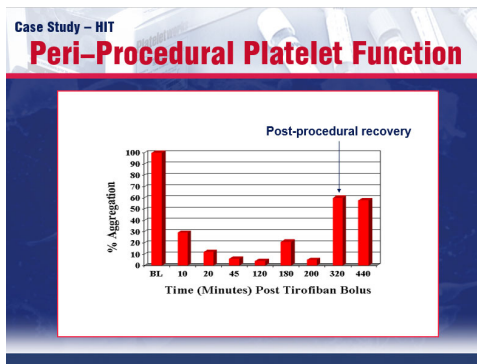
The patient was evaluated for both platelet count and platelet function using Helena's Plateletworks. Plateletworks uses traditional electronic impedance principles. A reference value for the platelet count was established using 1 mL of the patient's fresh whole blood and the Plateletworks EDTA baseline tube. This reference value was then compared to a platelet count using the Plateletworks ADP tube. A ratio of the two values provided the percent platelet aggregation. Results are available in just four minutes.

43.



Note here that during surgery at approximately 120 to 180 minutes there was a significant drop in the platelet count due to hemodilution. After the patient was transfused, the counts rebounded well and stayed elevated.

44.



At twenty minutes post-tirofiban bolus, platelet aggregation was reduced to approximately 12% and remained low throughout the procedure, even after the tirofiban infusion was stopped. The decrease in platelet function was also a protective mechanism for the platelets. At 180 minutes, transfused platelets were given and immediately there was some function, but the residual of the tirofiban kept some of those platelets from being active. It took about 320 minutes for post-procedural recovery.

45.

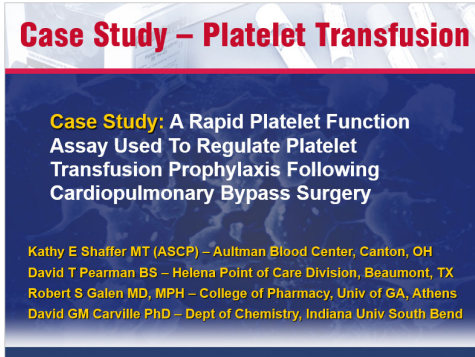
Case Study – HIT

## HIT Case Study Summary

- HIT a critical concern with high-dose heparin in CPB
- Alternative anti-coagulation strategies needed
- Anti-GP IIb/IIIa agents may prove most suitable
- Tirofiban used to protect against HIT during CPB
- Plateletworks correctly assessed platelet function even when platelet count dropped to ~ 53x10<sup>3</sup>/mL
- Other systems cannot evaluate platelet function in hemodilute/thrombocytopenic patients

HIT is of major clinical concern in patients who receive high-dose heparin while undergoing cardiac procedures such as cardiopulmonary bypass. Alternative anti-coagulation strategies must be considered (prostacyclins, prostaglandins, DTIs). Anti-GPIIb/IIIa agents, especially the shorter-acting agents tirofiban and eptifibatide, may prove most suitable. In this study, tirofiban was used to protect against HIT during CPB. Also when the platelet count dropped to approximately 53x10<sup>3</sup>/mL the Plateletworks test platform was still capable of monitoring platelet function. Other systems are not able to accurately evaluate platelet function in the hemodilute or thrombocytopenic patient.

46.



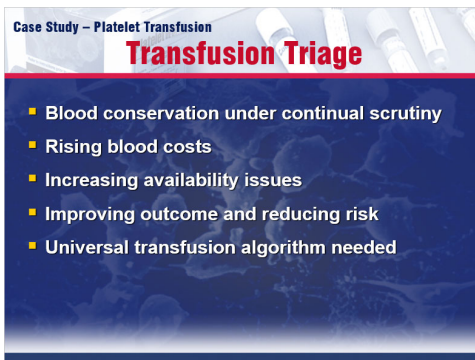
### Case Study – Platelet Transfusion

**Case Study:** A Rapid Platelet Function Assay Used To Regulate Platelet Transfusion Prophylaxis Following Cardiopulmonary Bypass Surgery

Kathy E Shaffer MT (ASCP) – Aultman Blood Center, Canton, OH  
David T Pearman BS – Helena Point of Care Division, Beaumont, TX  
Robert S Galen MD, MPH – College of Pharmacy, Univ of GA, Athens  
David GM Carville PhD – Dept of Chemistry, Indiana Univ South Bend

These next slides show the results of a six-month clinical study of cardiopulmonary bypass patients at Aultman Hospital by Shaffer and others and the effectiveness of near-patient platelet function monitoring on transfusion outcome. In summary, a significant reduction in platelet transfusions was achieved with no adverse outcomes noted.

47.



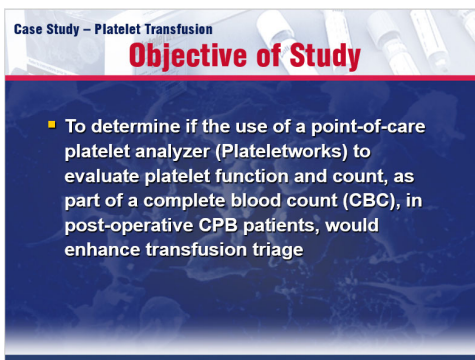
### Case Study – Platelet Transfusion

#### Transfusion Triage

- Blood conservation under continual scrutiny
- Rising blood costs
- Increasing availability issues
- Improving outcome and reducing risk
- Universal transfusion algorithm needed

The rising cost of blood coupled with concerns about blood supply availability and contamination put blood conservation under constant scrutiny. Institutions can reduce expenditures and patient risk by evaluating transfusion practices. A major goal for the regulatory bodies and healthcare providers should be to establish a universal transfusion algorithm based on “all” available current technologies.

48.



### Case Study – Platelet Transfusion

#### Objective of Study

- To determine if the use of a point-of-care platelet analyzer (Plateletworks) to evaluate platelet function and count, as part of a complete blood count (CBC), in post-operative CPB patients, would enhance transfusion triage

The purpose of the study conducted by Shaffer et al was to determine if the use of a point-of-care platelet analyzer (Plateletworks) to evaluate platelet function and count as part of a complete blood count (CBC) in post-operative CPB patients, would enhance transfusion triage.



49.

**Case Study – Platelet Transfusion**

### Patients and Study Protocols

- 310 CPB from Aug '01 to Jan '02
- Post-operative “POC” evaluation of platelet count and function
- Platelet transfusion protocol based on AABB / WHO guidelines (and platelet evaluation)
- FFP or CRYO based on observational bleeding and/or platelet function

This prospective study was conducted at Aultman Hospital in Canton, Ohio between August 2001 and Jan 2002 used the Plateletworks point-of-care system to post-operatively assess platelet count and function in 310 cardiopulmonary bypass patients. Samples were drawn from an arterial line. The protocol for platelet transfusion was based upon the AABB/WHO guidelines ( $<50 \times 10^3/\mu\text{L}$  or  $<100 \times 10^3/\mu\text{L}$  with concomitant microvascular bleeding). The decision to transfuse FFP or CRYO was based on observational bleeding and/or the platelet function result.

50.

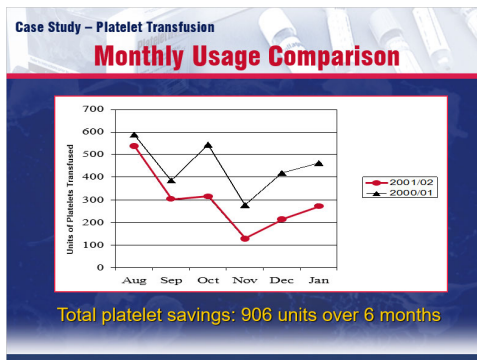
**Case Study – Platelet Transfusion**

### Prospective & Retrospective Comparison

	8/00 - 1/01 Retrospective	8/01 - 1/02 Prospective	Difference
Total CPB Procedures	238	310	+ 72
Platelet Packs	2676	1770	- 906
Platelet Units per Patient	11.75	5.5	- 6.25

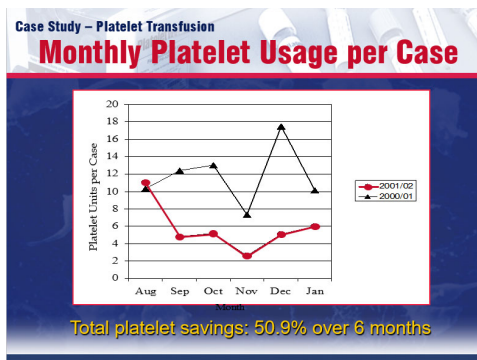
Results were compared retrospectively to the same time period the previous year. It showed a 25% increase in caseload with an additional 72 CPB surgeries being performed for a total of 310 procedures in the prospective period. In this same patient group, a total of 1,770 platelet packs were transfused as compared to 2,676 platelet packs for a savings of 906 packs. A reduction in units per patient from 11.75 to 5.5 was also realized.

51.



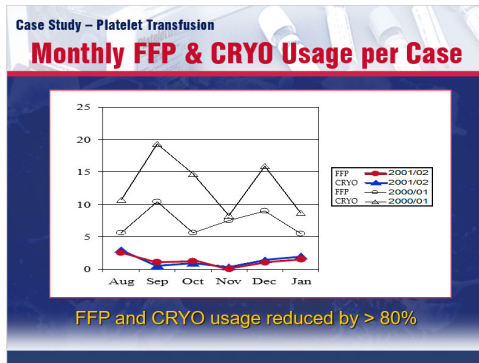
This graph represents a month-by-month comparison of prospective and retrospective platelet transfusion data. Even with a 25% increase in CPB procedures, platelet usage was reduced by 906 packs during the 6-month period. All apheresis platelets that were transfused were counted as seven random donor packs.

52.



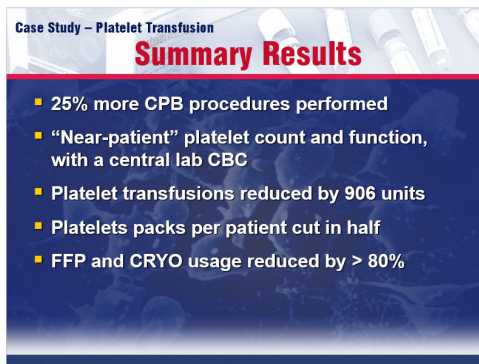
Here is a monthly representation of platelet transfusions per case. The total reduction of platelets transfused per patient was greater than 50%.

53.



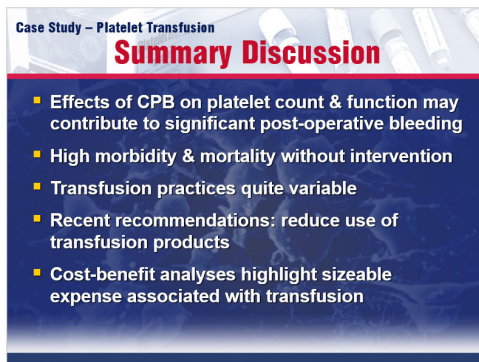
Monthly comparative data as retrieved from blood bank records showed a total savings of 82% for FFP and 88% for CRYO during the study period.

54.



In the prospective study (Aug 2001 to Jan 2002) 25% more cardiopulmonary bypass procedures were performed over the same time period as the previous year (Aug 2000 to Jan 2001). In the study period, all patients had platelet count and function evaluated “near-patient” in addition to a CBC performed in the central laboratory. The total reduction in platelet transfusions was 906 units or a per patient reduction of 6 units (from 11.75 platelet units/patient to 5.75 units/patient) or 50.9%. FFP usage was reduced by 82% and CRYO by 88% during this six-month time period.

55.



The effects of cardiopulmonary bypass on both platelet count and function contribute to clinically relevant post-operative bleeding. In the absence of appropriate intervention, there is significant morbidity and mortality. Transfusion practices vary greatly from institution to institution. Recent recommendations are to reduce the use of transfusion products which pose an unnecessary risk and expense to patients who do not require them.

56.

Case Study – Platelet Transfusion

### Conclusions

- Need rational approach to manage coagulation disorders during CPB
- Methods too laborious & complex with long TAT
- Near-patient testing permits “more accurate” and timelier intervention
- Patients managed “bed-side” receive significantly fewer blood products
- Transfusion protocol / algorithm is penultimate tool for successful transfusion triage
- Additional prospective studies warranted

A rational approach to the management of coagulation during CPB is essential. Most methods are too labor-intensive, require highly-trained personnel and have too long of a turnaround time to be of practical use. The recent development of near-patient systems permits “more accurate” and timelier intervention. Multiple studies have demonstrated that those patients managed “bed-side” received significantly fewer blood products. This study showed a substantial reduction in transfusions with no adverse outcomes (patients actually experienced less adverse chest drainage than patients randomized to standard therapy) and supports the establishment of a transfusion protocol/algorithm for improved transfusion triage.

57.



**Plateletworks®** and the **Mindray BC3600®** hematology counter or any impedance cell counter can provide whole blood evaluation of platelet function (aggregation and inhibition) and platelet count in the near-patient setting. Testing is simple to perform with results available in under 10 minutes. Plateletworks systems are currently in use in emergency departments, cardiac surgery and cath labs, neurology and ICUs, providing a fast and economical means of giving physicians better information for better patient care.