1.

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.

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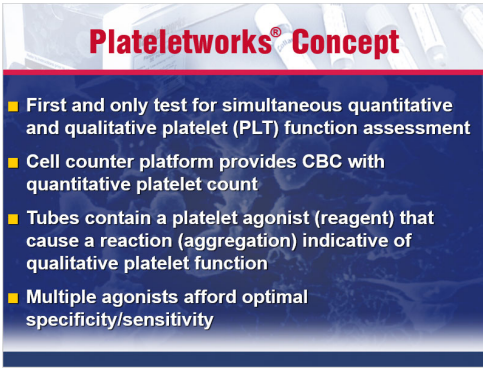
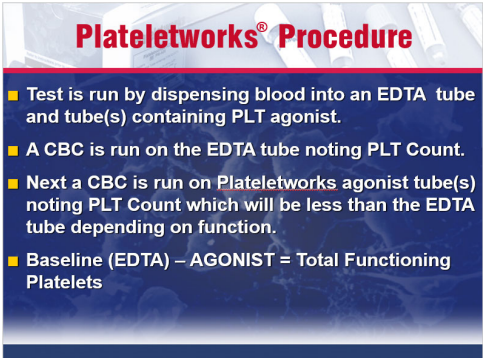


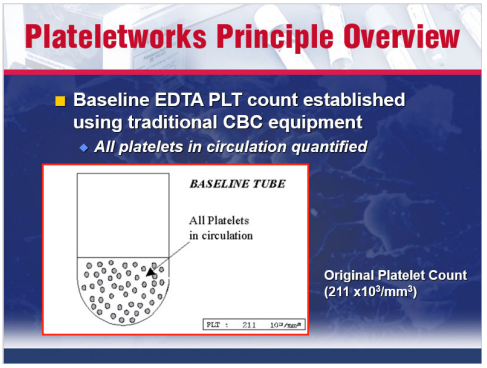
Plateletworks® is the first and only test to measure platelets both quantitatively and qualitatively. It is an economical and efficient screening tool. By using an impedance cell counter as the instrument platform, Plateletworks combines a CBC with a quantitative platelet count. The addition of a platelet 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.

3.



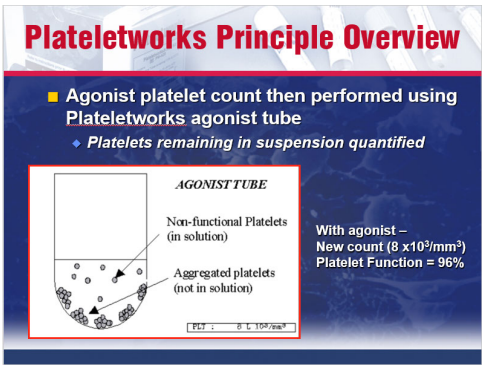
The Plateletworks procedure is very simply run with at least two tubes. One tube contains EDTA, which gives the baseline count, and the other tube or tubes utilize a traditional platelet agonist, such as ADP, collagen, or arachidonic acid. A quick mathematical calculation yields quantitation of functional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

4.



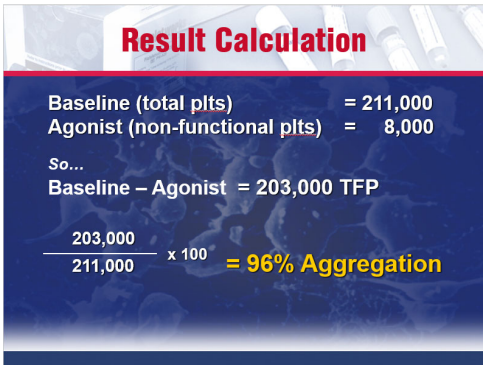
The first tube is the baseline EDTA platelet count also known as the total platelet count. EDTA is selected because often the end user will also like to use the other hematology results such as RBC, HCT etc. for additional patient assessment, and EDTA does not require volumetric correction as with sodium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

5.



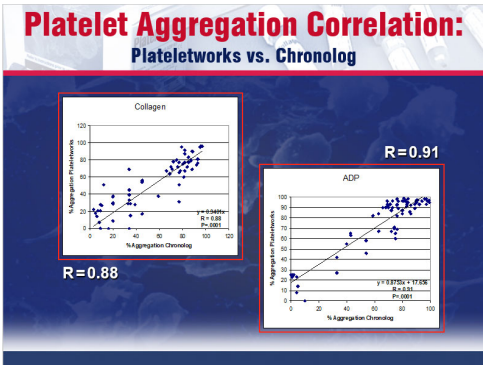
In the agonist tube, be it collagen, ADP or arachidonic acid, the functional platelets are aggregated and settle rapidly in the tube. When counted on an impedance hematology counter, the non-functional singlet platelets are counted while the functional platelets, in the form of platelet aggregates, are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

6.



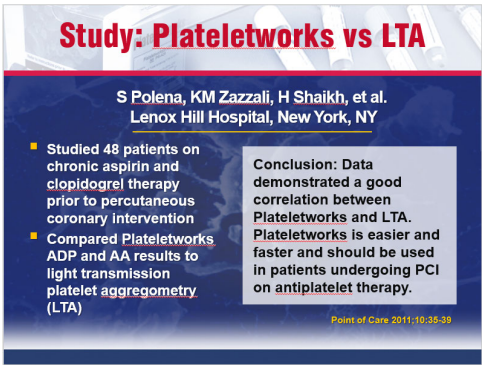
First the total functional platelets are determined by simply subtracting the agonist result from the baseline result. The percent aggregation is very quickly determined by dividing the total functional platelets by the baseline and multiplying by 100.

7.



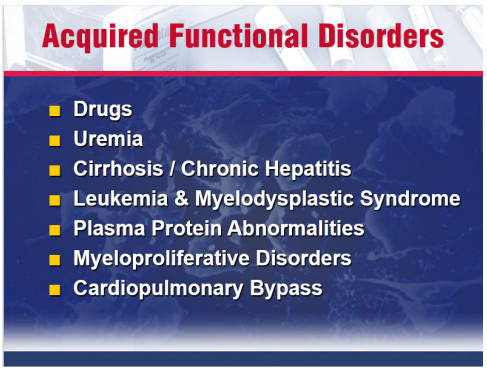
Plateletworks has been thoroughly tested against both PRP aggregation and whole blood aggregometry showing extremely good correlations at all levels.

8.



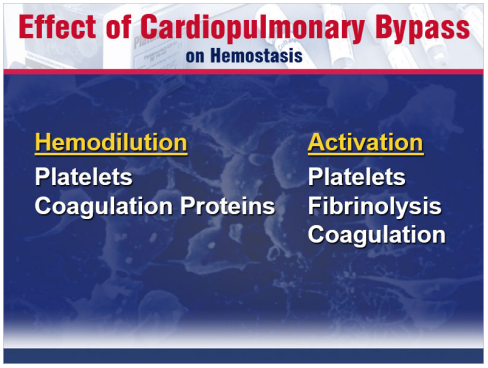
In a study performed at Lenox Hill Hospital, 48 patients on dual anti-platelet therapy prior to PCI were tested for platelet function using Plateletworks ADP and Arachidonic Acid, side by side with LTA. The study concluded Plateletworks performed as well as LTA and was more efficient and stress free.

9.



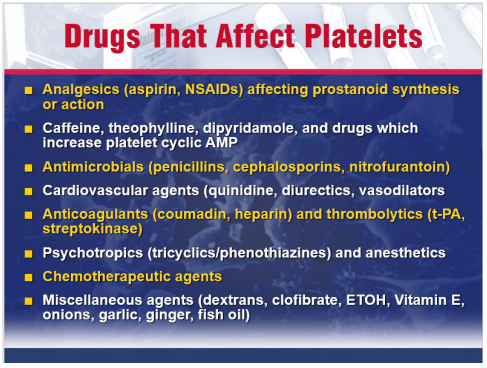
Most platelet problems seen in the clinical laboratory or clinically with patients are acquired functional disorders due to drugs, uremia, cirrhosis, leukemia, myelodysplastic disease, plasma protein disorders, and surgical therapies and procedures like cardiopulmonary bypass.

10.



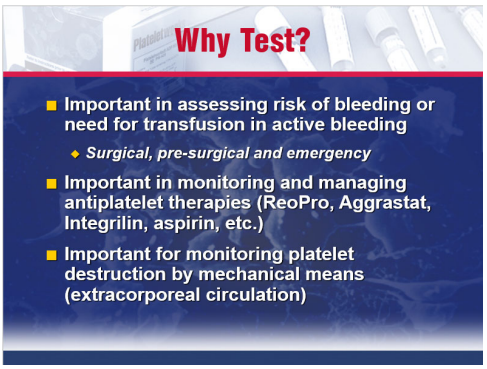
In cardiopulmonary bypass, there are two major effects on platelets. The first is hemodilution, which reduces the platelet count, as well as reducing coagulation proteins. The second is activation. Once the platelets are run through plastic tubing and exposed to oxygenator circuits, many of them are 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.



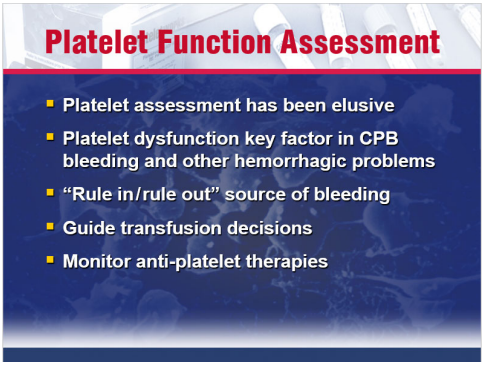
At least 900 drugs and compounds are known to affect platelet function either by up regulation or down regulation. Among these are analgesics, aspirin, nonsteroidal anti-inflammatory drugs (NSAIDs), caffeine, theophylline, dipyridamole, and drugs which increase cyclic AMP. There are antimicrobials, most 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. Psychotrophics, 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 dextrans, alcohol, high dose vitamin E, onions, garlic, ginger, fresh fish oil, dark chocolate, and dark beer also affect platelet function.

12.



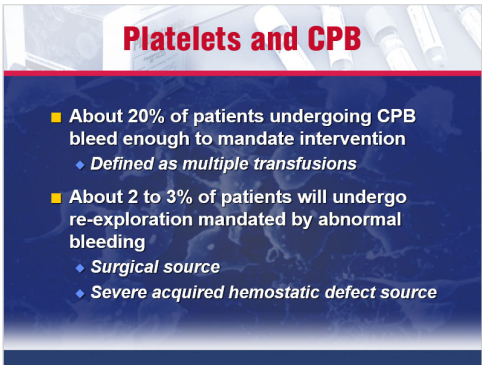
Why perform platelet aggregation testing? It is essential in assessing the risk of bleeding and/or the need for transfusion in actively bleeding patients. It is important in monitoring and managing antiplatelet therapy, especially in light of the tremendous increase in pharmacological intervention in 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.



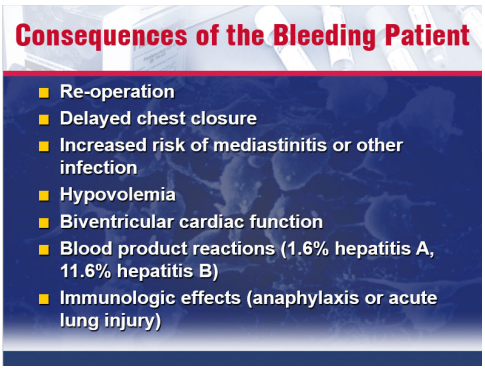
It is believed that platelet dysfunction is an important contributor to bleeding in cardiopulmonary bypass and other hemorrhagic problems. Near-patient monitoring of platelet function can contribute significantly to ruling in or ruling out the source of bleeding, can help guide transfusion decisions,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

14.



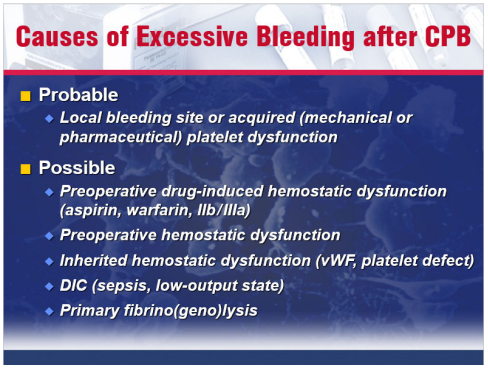
In the hospital, there are many reasons to use Plateletworks. About 20% of all patients undergoing cardiopulmonary bypass surgery bleed enough to mandate intervention. In the United States, approximately 25% of all platelet donations go to patients who are undergoing bypass surgery. Two to three percent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

15.



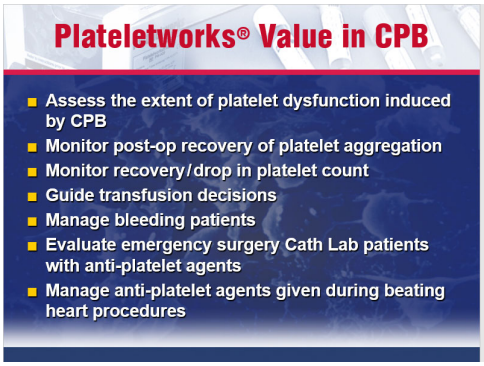
In bleeding patients, the consequences can be significant: re-operation, delay in chest tube closure, increased risk of infections, volume issues, cardiac dysfunction, blood byproduct reactions and various immunological reactions. In cardio bypass surgery, there are proteins that are absorbed on a blood 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.



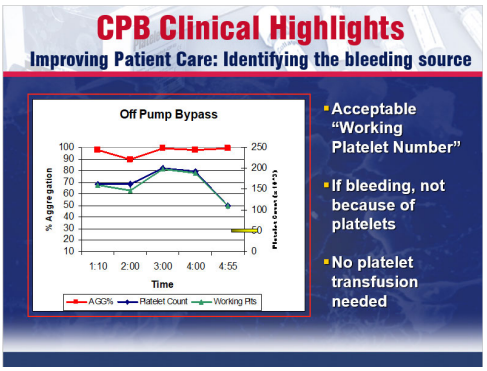
The most probable cause of excessive bleeding after cardiopulmonary bypass is local bleeding at the site, mechanical or pharmaceutical, due to platelet dysfunction. Possible causes that must be considered include: preoperative drug-induced hemostatic dysfunction (aspirin, warfarins, coumadin, anti-IIb/IIIa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

17.



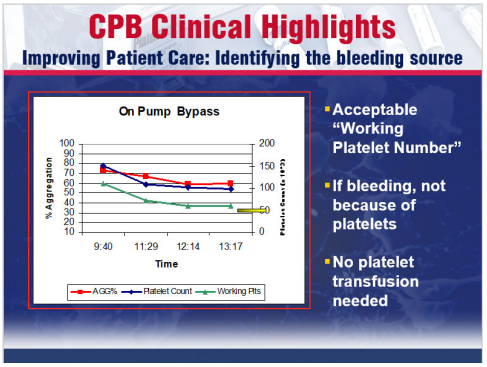
In cardiopulmonary bypass surgery, Plateletworks can be of value to assess the extent of platelet dysfunction caused by the procedure, monitor post-operative recovery, monitor recovery or drop in platelet counts, guide transfusion decisions, manage bleeding patients, and evaluate emergency surgery patients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

18.



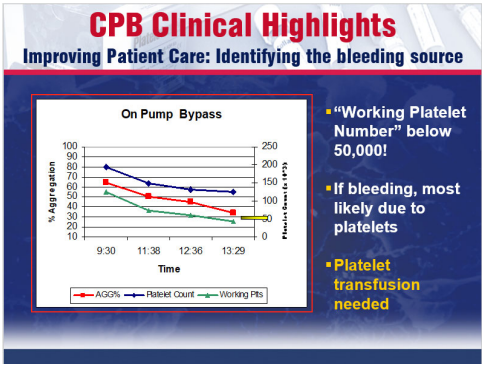
This shows a typical off-pump or beating heart procedure where the patient's percent aggregation never truly declines. While the number of working platelets does decline, the number of functional platelet is still within an acceptable range and the patient does not need to undergo any type of transfusion.

19.



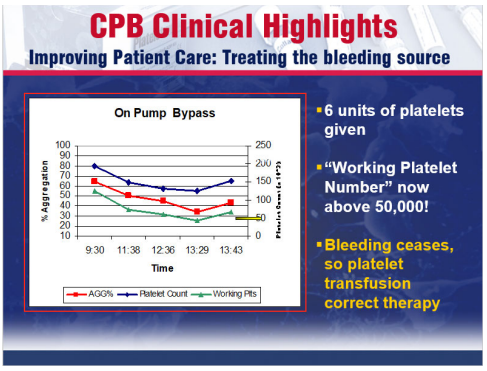
This illustrates what sometimes happens with an on-pump bypass procedure. The platelet count, percent aggregation, and even functional count are relatively good at the beginning of the procedure. Near the end of the procedure, the percent aggregation and total platelet count drop. The functional platelet 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.



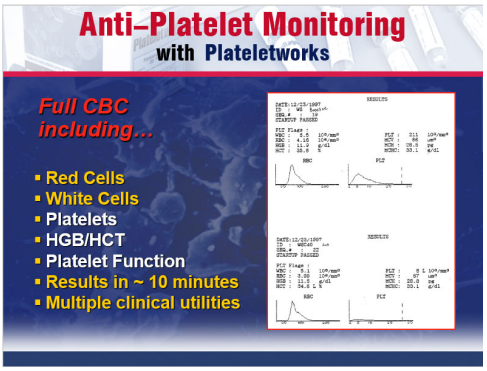
This slide indicates an on-pump or a bypass patient whose total platelet count decreased, the percent aggregation decreased substantially, and the working or functional platelet count has gone below 40,000. If this patient is bleeding, it is most likely due to a lack of quantity of functional platelets,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

21.



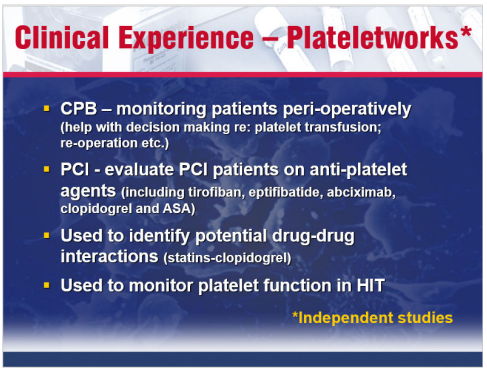
This shows the previous patient, post-transfusion. The platelet count, functional platelet count, and percent have all gone back up, and so the platelet transfusion did correct the problem.

22.



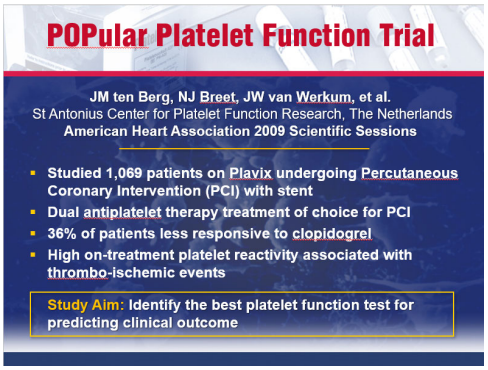
While Plateletworks includes the Complete Blood Count, the real key to the efficacy of the Plateletworks assay is the ability to provide the functional platelet count, the % aggregation / inhibition, PLUS the red blood cells, hemoglobin and hematocrit, all in one assay in less than 10 minutes.

23.



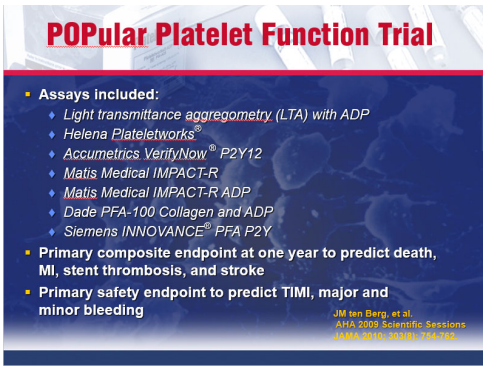
A variety of independent clinical studies have shown the utility of the Plateletworks assay in cardiopulmonary bypass (CPB) and coronary interventions (PCI), in identifying potential drug-drug interactions, and even in monitoring platelet function in the presence of heparin-induced thrombocytopenia (HIT).

24.



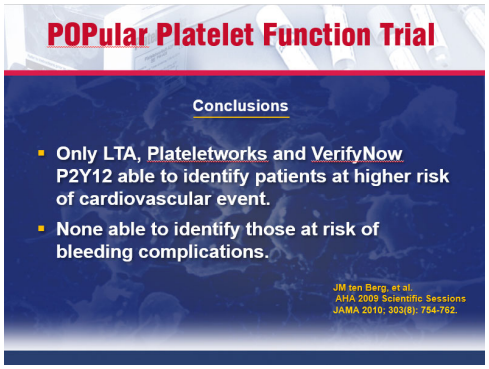
A study called the POPular trial examined the different platelet function tests to determine the best way to predict clinical outcomes. The study included 1,069 patients on Plavix undergoing PCI. The treatment of choice for PCI is dual anti-platelet therapy consisting of aspirin regimen combined with 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.



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.



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.

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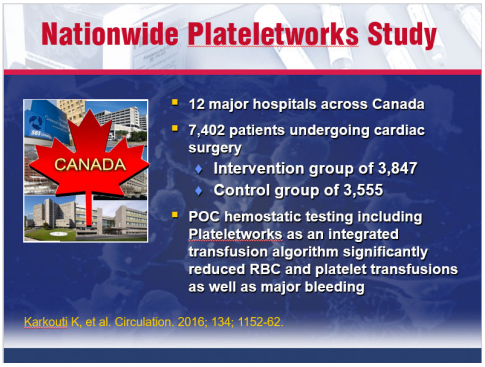
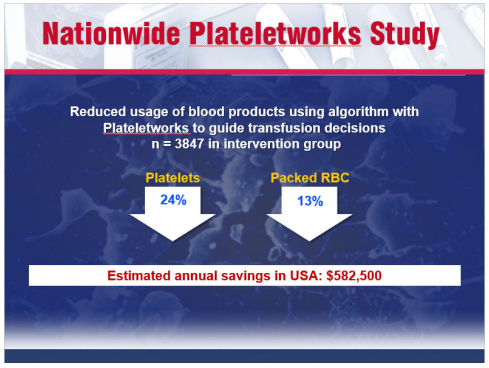


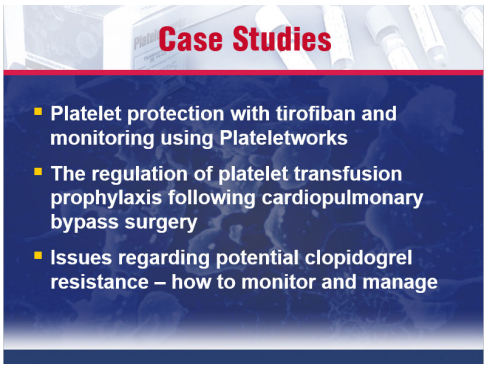
Another study published in 2016 included data from 12 major hospitals and 7,402 patients undergoing cardiac surgery. The study concluded that implementing point of care testing, including Plateletworks as an integrated transfusion algorithm, significantly reduced RBC and platelet transfusions as well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

28.



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.

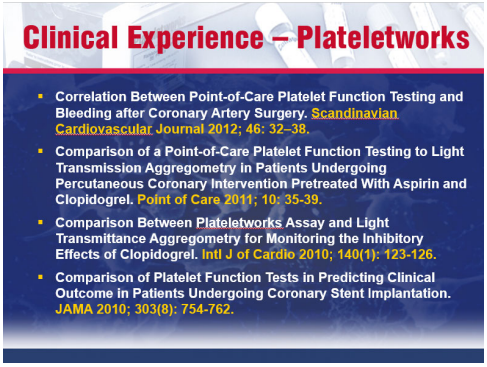


The case studies presented in the following slides exemplify the real-life usefulness of Plateletworks in the clinical setting.

30.

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

31.



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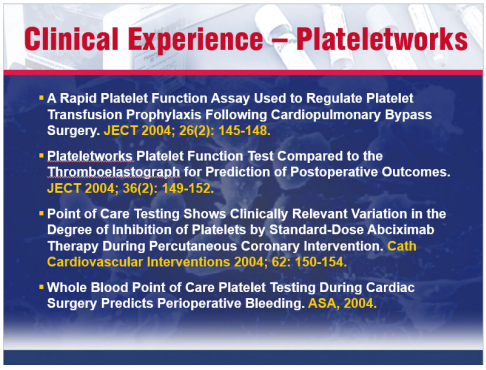

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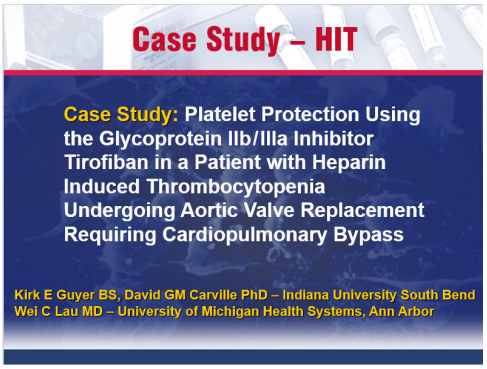
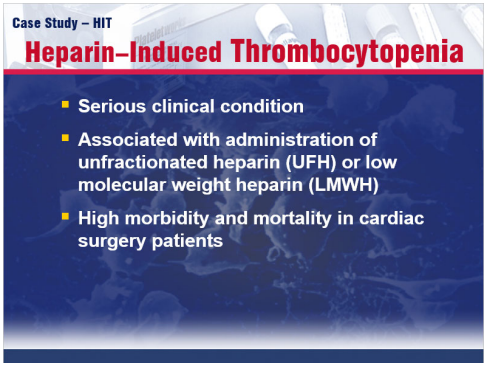


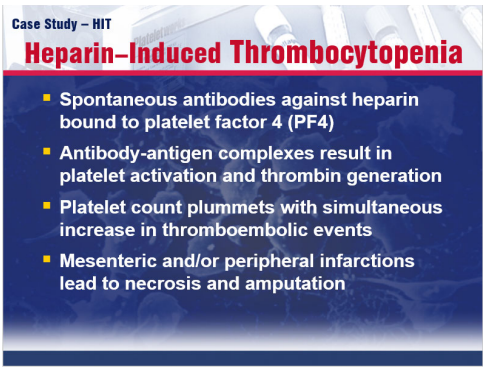
This case study delineates the use of the glycoprotein IIb/IIIa inhibitor, Tirofiban, in a patient with heparin-induced thrombocytopenia who did have to undergo coronary bypass intervention. The abstract was presented at the AACC Symposium on Critical Care and Point of Care Testing, September 2002, Monterey,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

36.



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.

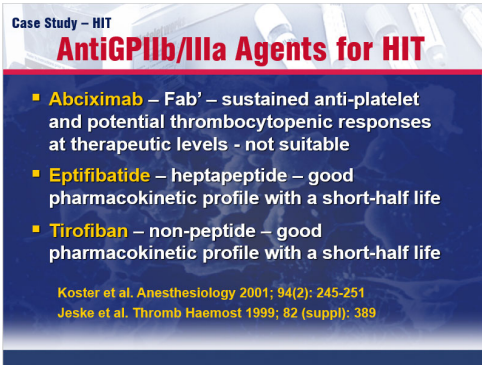


HIT patients spontaneously generate antibodies against heparin bound to platelet factor 4 (PF4) with the subsequent formation of antibody-antigen complexes which result in platelet activation and thrombin generation. This physiological sequence of events elicits a significant decrease in platelet count 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.

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.



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.

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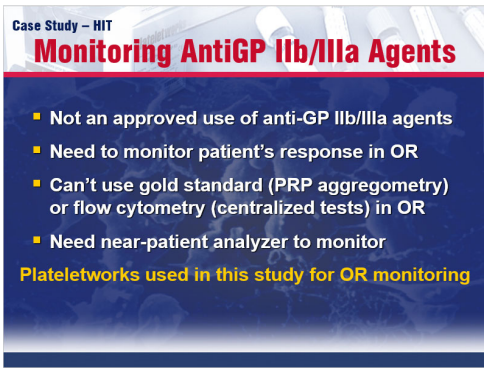
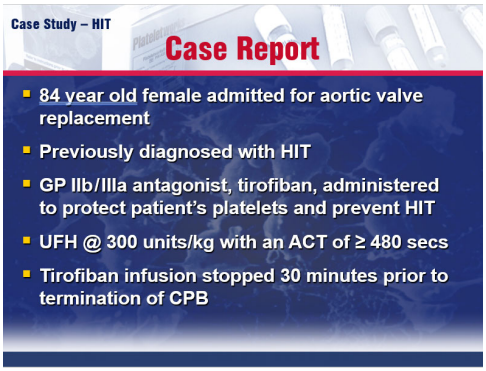


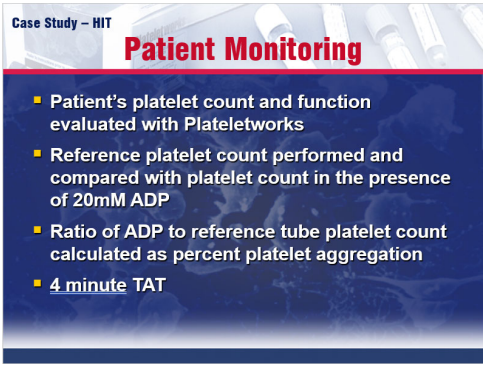
At this point in time, anti-GP IIb/IIIa agents are not approved for this type of patient therapy. Therefore, the patient's response to these agents must be monitored very closely. Although PRP aggregometry is the gold standard for assessing platelet function, neither PRP aggregometry nor flow cytometry 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.



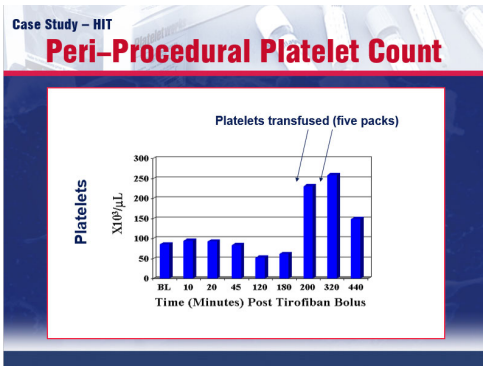
An 84-year-old female patient with severe aortic stenosis, and previously diagnosed with HIT, was admitted to the University of Michigan Medical Center for aortic valve replacement. To protect the patient's platelets and prevent HIT, the short-acting GP IIb/IIIa antagonist, tirofiban, was administered 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.



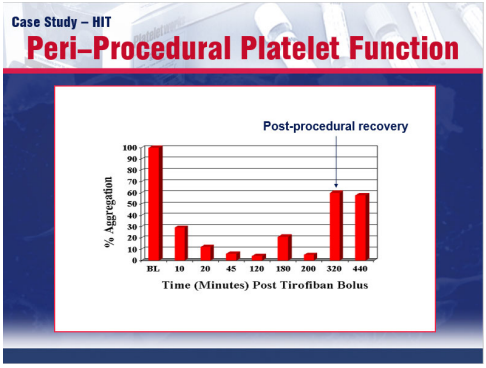
The patient was evaluated for both platelet count and platelet function using Helena's Plateletworks. Plateletworks uses traditional electronic impedance principles. A reference value for the platelet count was established using 1 mL of the patient's fresh whole blood and the Plateletworks EDTA baseline 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.



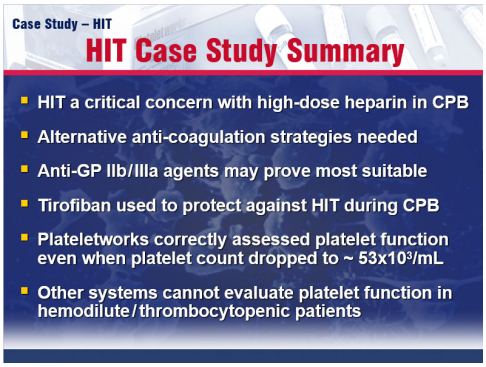
Note here that during surgery at approximately 120 to 180 minutes there was a significant drop in the platelet count due to hemodilution. After the patient was transfused, the counts rebounded well and stayed elevated.

44.



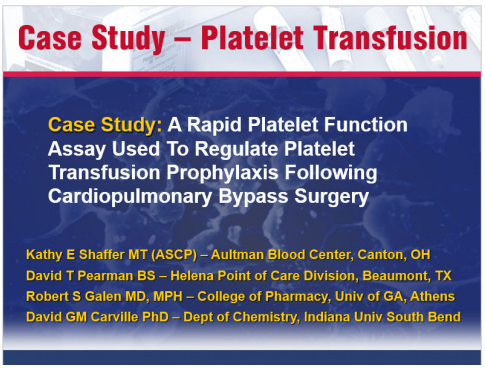
At twenty minutes post-tirofiban bolus, platelet aggregation was reduced to approximately 12% and remained low throughout the procedure, even after the tirofiban infusion was stopped. The decrease in platelet function was also a protective mechanism for the platelets. At 180 minutes, transfused platelets 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.



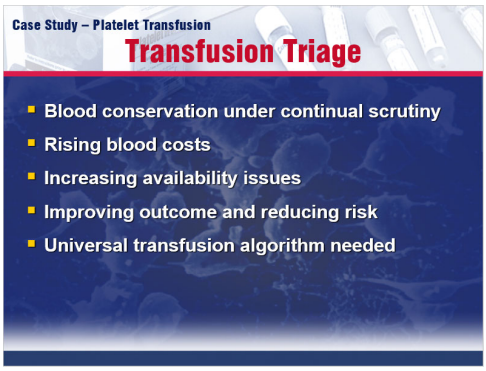
HIT is of major clinical concern in patients who receive high-dose heparin while undergoing cardiac procedures such as cardiopulmonary bypass. Alternative anti-coagulation strategies must be considered (prostacyclins, prostaglandins, DTIs). Anti-GPIIb/IIIa agents, especially the shorter-acting agents 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 $53x10^3$/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.



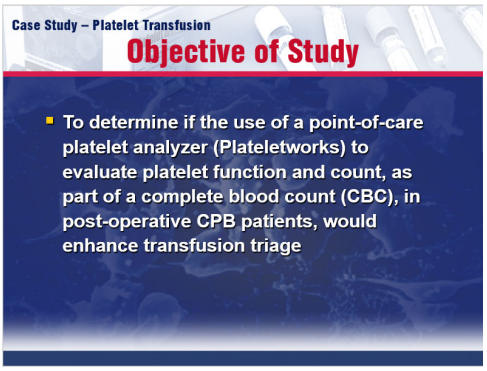
These next slides show the results of a six-month clinical study of cardiopulmonary bypass patients at Aultman Hospital by Shaffer and others and the effectiveness of near-patient platelet function monitoring on transfusion outcome. In summary, a significant reduction in platelet transfusions was achieved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

47.



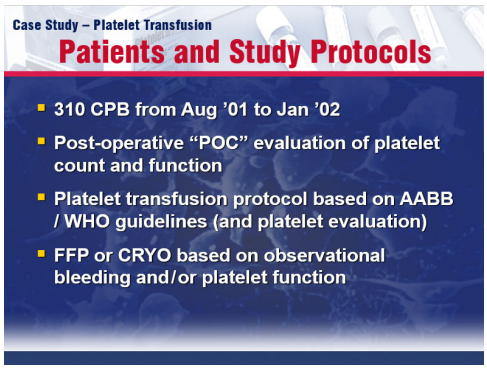
The rising cost of blood coupled with concerns about blood supply availability and contamination put blood conservation under constant scrutiny. Institutions can reduce expenditures and patient risk by evaluating transfusion practices. A major goal for the regulatory bodies and healthcare providers should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

48.



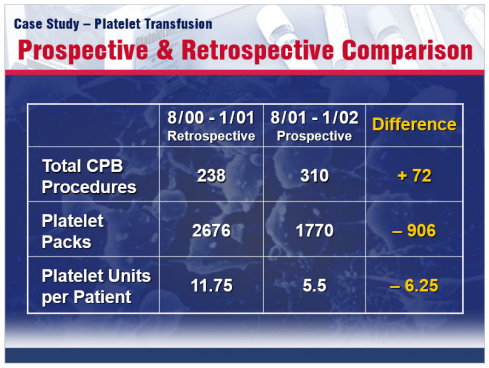
The purpose of the study conducted by Shaffer et al was to determine if the use of a point-of-care platelet analyzer (Plateletworks) to evaluate platelet function and count as part of a complete blood count (CBC) in post-operative CPB patients, would enhance transfusion triage.

49.



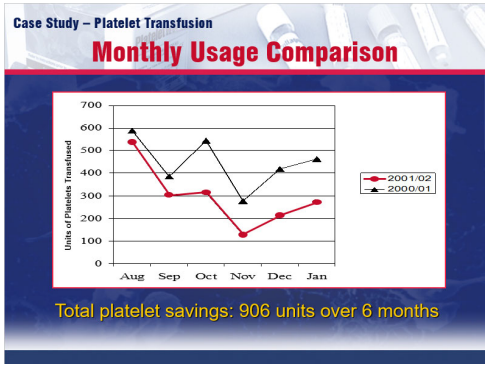
This prospective study was conducted at Aultman Hospital in Canton, Ohio between August 2001 and Jan 2002 used the Plateletworks point-of-care system to post-operatively assess platelet count and function in 310 cardiopulmonary bypass patients. Samples were drawn from an arterial line. The protocol for platelet transfusion was based upon the AABB/WHO guidelines (<50x10^3/µL or <100x10^3/µL with concomitant microvascular bleeding). The decision to transfuse FFP or CRYO was based on observational bleeding and/or the platelet function result.

50.



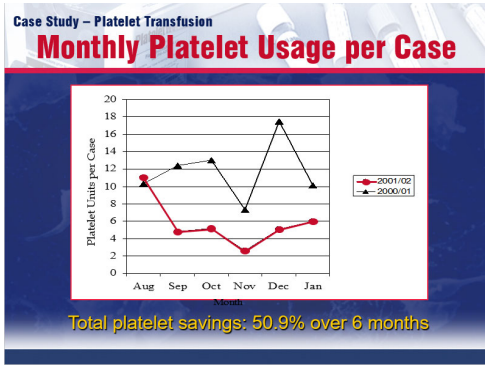
Results were compared retrospectively to the same time period the previous year. It showed a 25% increase in caseload with an additional 72 CPB surgeries being performed for a total of 310 procedures in the prospective period. In this same patient group, a total of 1,770 platelet packs were transfused 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.



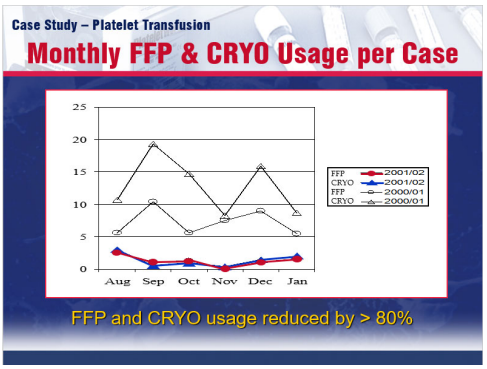
This graph represents a month-by-month comparison of prospective and retrospective platelet transfusion data. Even with a 25% increase in CPB procedures, platelet usage was reduced by 906 packs during the 6-month period. All apheresis platelets that were transfused were counted as seven random donor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

52.



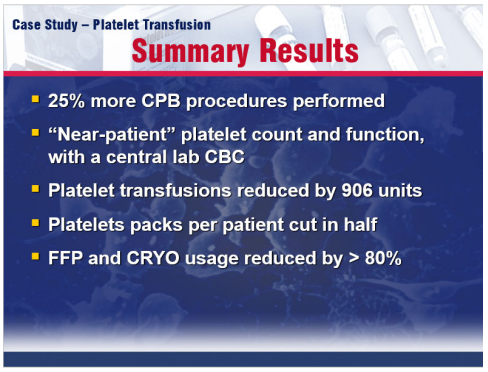
Here is a monthly representation of platelet transfusions per case. The total reduction of platelets transfused per patient was greater than 50%.

53.



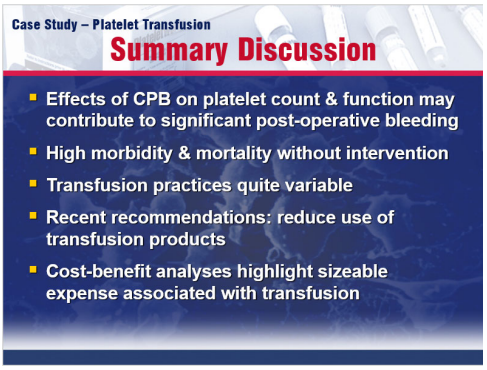
Monthly comparative data as retrieved from blood bank records showed a total savings of 82% for FFP and 88% for CRYO during the study period.

54.



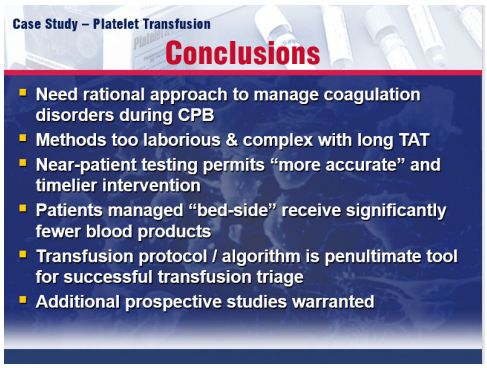
In the prospective study (Aug 2001 to Jan 2002) 25% more cardiopulmonary bypass procedures were performed over the same time period as the previous year (Aug 2000 to Jan 2001). In the study period, all patients had platelet count and function evaluated "near-patient" in addition to a CBC performed in 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.



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.