Laboratory Medicine in the Era of Disruptive Technology
LMCE 2017 & KSLM 58th Annual Meeting
October 18-20, 2017
Grand Walkerhill Seoul, Korea
www.lmce-kslm.org

Practical role of lab hematology in precision medicine and targeted therapies: focus on warfarin pharmacogenetics and thromboelastography guided transfusions in severe trauma

Charles Eby M.D.

Department of Pathology and Immunology, Washington University School of Medicine in St. Louis, Missouri, USA

Providing Precision, or Personalized, medical care to patients is based on a longstanding principle: to maximize outcomes patient care about while minimizing those outcomes patients most fear based on as much knowledge about the individual's state as is available.

Pharmacogenetics (PGx) is a source of new knowledge about how some patients will react to certain medications. Warfarin has been used for over 60 years for primary and secondary prevention of arterial and venous thromboembolic events. The anticoagulant effect of warfarin is unpredictable: stable doses range from < 1.0 mg/day to ≥ 15 mg/day: and the "therapeutic window" between inadequate anticoagulation and increased risk of clotting and excessive anticoagulation and increased risk of bleeding is narrow. The period of greatest risk for these complications is during the initiation of warfarin therapy by "trial and error" dosing combined with frequent INR monitoring.

Almost two decades of pharmacogenetic and translational research efforts have clearly established the importance of polymorphisms in two genes on patients' stable warfarin dose, CYP2C9 and VKCORC1, across many ethnic and racial populations. Polymorphisms in several other genes, including CYP 4F2, may have modest effects on warfarin dose in some groups.

However, several clinical trials to assess the clinical utility of warfarin PGx when compared to strategies to estimate initial warfarin dose without PGx have been inconclusive. Meanwhile, direct oral anticoagulants which do not require routine therapeutic drug monitoring are replacing warfarin for stroke prevention in patients with non-valvular atrial fibrillation and treatment of venous thrombo-emboli. In the United States the Center for Medicaid and Medicare Services (CMS) does not pay for warfarin PGx testing, even though the USA Food and Drug Administration encourages using the information when available for initial dose selection.

However, warfarin may not be ready to retire yet. The results of the recently published GIFT TRIAL (Genetics InFormatics Trial of Warfarin to Prevent Deep Venous Thrombosis) will be presented during this presentation. Patients undergoing hip or knee replacement therapy were randomized to receive warfarin for DVT prophylaxis based on either clinical dosing algorithms or clinical + pharmacogenetic dosing algorithms (Fig. 1). The primary outcome was a composite of: major bleeding, INR ≥4, DVT or PE, or death. Patients randomized to the pharmacogenetic dosing arm had a significantly lower rate of the composite outcome (Table 1), primarily due to fewer INRs ≥ 4. Warfarin continues to be an important oral anticoagulant for selected indications including patients with prosthetic heart valves, severe kidney disease, and body mass extremes, and warfarin is more affordable than DOACs in many countries. Improving the accuracy and safety of initial warfarin treatment is an example of how Hematology Laboratories can contribute to precision medicine.

Figure 1. GIFT Trial Patient Participation and Follow up after Hip or Knee Replacement Surgery

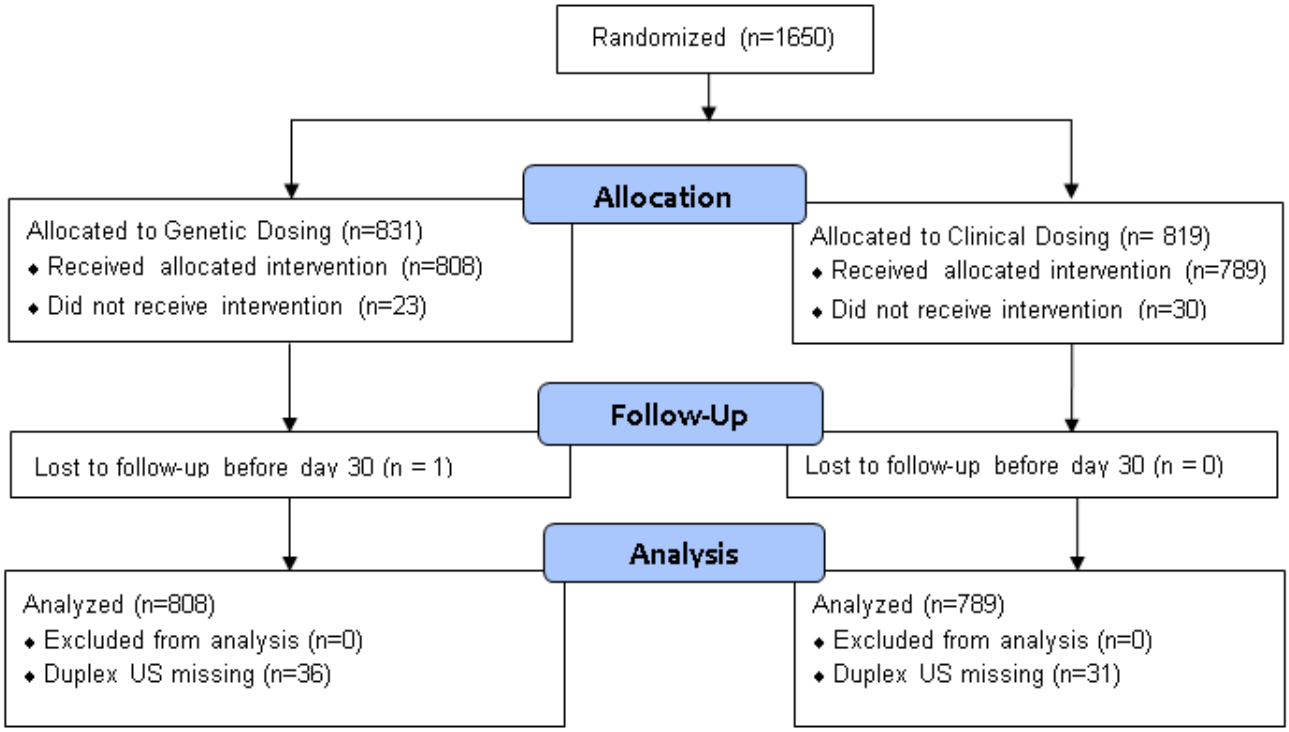

Table 1.

Primary Results (N = 1597)

Endpoint	Genotype Group, N = 808, % (N)	Clinical Group, N = 789, % (N)	P-value
Major bleed (days 1-30)	**0.25% (2)**	**1.01% (8)**	**0.062**
INR ≥ 4 (days 1-30)	**6.9% (56)**	**9.8% (77)**	**0.041**
VTE (days 1-60)	**4.1% (33)**	**4.8% (38)**	**0.48**
Death (days 1-30)	**0.0% (0)**	**0.0% (0)**	**1.00**
Total	10.8% (87)	14.7% (116)	0.018

The second part of this presentation will focus on thromboelastography testing in the setting of major trauma. Emergency management of major traumatic injuries has undergone dramatic changes in the past 10-15 years with a major focus on rapid reversal of coagulopathy by replacing the hemostasis components of blood (clotting factors, platelets, fibrinogen) in addition to red blood cells. Much of the attention has been on how quickly transfusions are started and the ideal ratio of red cells: plasma: platelets in each box of massive transfusion protocol (MTP) blood products.

Clinical researchers are now examining the potential clinical utility of precision transfusion support of severe traumatic hemorrhage guided by rapid hemostasis information provided by thromboelastography instruments. While Hematology laboratory experts may not directly supervise these instruments or interpret the results, it is important that they understand the principles underlying this technology and the current gaps in evidence supporting its use in management of trauma in order to provide a balanced assessment of thromboelastography's value to precision medicine.