Antiplatelet therapy guided by thrombelastography in patients with acute coronary syndromes (TEGCOR Study)

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A. INTRODUCTION

Platelet aggregation and activation mediated by various agonists are fundamental in the development of ischemia in patients with coronary artery disease.
Activated platelets mediate vessel wall inflammation, and thrombin generated by procoagulant factors and tissue injury initiates fibrin generation. Platelet-platelet aggregates cross-linked by fibrin and fibrinogen eventually mechanically obstruct the vessel lumen in patients with acute coronary syndromes. Dual antiplatelet therapy with aspirin and clopidogrel and more recently aspirin and prasugrel have become standard of care for patients undergoing percutaneous coronary intervention (PCI) and stent placement for acute coronary syndromes. Despite significant reduction in ischemic complications, concern remains regarding the occurrence of thrombotic events after coronary interventions and stenting. Specifically, high posttreatment platelet reactivity after coronary stenting measured by ex vivo platelet assays with clopidogrel have been repeatedly associated with high rates of stent thrombosis and myocardial infarction post PCI, events with high mortality and morbidity [1-3]. The significant interindividual variation in the extent of clopidogrel platelet inihibition is to a great degree founded in genetic interindividual differences in CYP450 metabolism or other drug-drug interactions that inhibit hepatic isoenzyme activity [4,5]. In particular reduced function polymorphisms of CYP 2C19 have been found to significantly impair the pharmacodynamic effects of clopidogrel and have been associated with worse clinical outcomes in several large studies of patients after coronary stent implantation [6]. These findings have supported the development of more efficacious and predictive P_2Y_{12} inhibitors, such as prasugrel and ticlopidine, both of which have been shown to be associated with reduced rates of stent thrombosis as compared to clopidogrel.
Thrombelastography (TEG) is an ex-vivo method that measures the viscoelastic properties of whole blood clot formation in response to various agonists [2] . In essence, the device features a stationary pin suspended by a torsion wire which is lowered into a rotating sample cup containing whole blood and various agonists. The device then measures the forces between the pin and the cup generated by the developing fibrin and platelet-fibrin clots.
Thus, the method enables the measurement of various parameters of coagulation and aggregation, including thrombin activity by measuring the time to fibrin generation, but also the relative contribution of platelet-platelet aggregate formation and fibrin generation on tensile clot strength. As we have shown previously, elevated whole blood clot strength appears to be a significant predictor for adverse ischemic events after coronary stenting with a relative adjusted OR of 22.6 for the occurrence of ischemic events in patients with highest quartile clot strength [2]. Inhibition of GpIIb/IIIa receptors by eptifibatide significantly reduces MA and also periprocedural myocardial infarctions associated with coronary stenting. It appears that high tensile whole blood clot strength on clopidogrel therapy appears to be a significant risk factor for recurrent ischemic events that may be only partially explainable by insufficient P_2Y_{12} receptor inhibition. The ex-vivo phenotype of high tensile clot strength is probably multifactorial, but may be due to release of tissue factor and increased velocity of thrombin generation in patients with acute coronary syndromes. Not surprisingly, it is these patients that are clinically known to be at highest risk for recurrent thrombotic events and cardiac death. Accordingly, we have previously demonstrated that high clot strength phenotype was associated with

elevated levels of fibrinogen, tissue factor, vWF, C-reactive protein, TNF-a and IL-8 and was found more frequent in patients with acute coronary syndromes as compared to patients with stable coronary artery disease [7,8]. These findings suggest that TEG may be a unique testing modality that is able to identify and specifically target patients at elevated clinical risk.
Although increased P_2Y_{12} receptor inhibition with prasugrel is more efficient in reducing ischemic events than clopidogrel, it also carries an increased risk for significant bleeding. Personalized treatment approaches should ideally be able to identify patients at need for higher or lower intensity of platelet P_2Y_{12} inhibition in an attempt to optimize the risk/benefit ratio for each patient. However, currently only one study prospectively compared a personalized dosing approach of clopidogrel vs. standard dosing in 162 patients prior to coronary stenting [9].
In addition to the currently available antiplatelet drugs that inhibit ADP mediated platelet aggregation by inhibiting P_2Y_{12}, several oral thrombin receptor protease-activated receptor-1 (PAR-1) inhibitors (platelet thrombin receptor) have been developed. Two oral PAR-1 inhibitors have completed phase 2 clinical trials and the eventual addition of these drugs to standard dual antiplatelet therapy may in the future further increase bleeding risk for patients on several antiplatelet drugs. Theoretically, thrombelastography may provide an ideal methodology to identify patients at highest risk for thrombin mediated ischemic events or identify patients at risk of bleeding. In the surgical field, thrombelastography has been used successfully to predict postoperative bleeding risk and guide post surgical and trauma related transfusion requirements.

Currently controversy exists as to the optimal method to identify patients at risk for ischemic events after coronary interventions and several point of care assays measuring platelet inhibition are currently in use in large prospective clinical trials. These currently employed methods focus on the specific amount of ADP mediated platelet aggregation measured ex-vivo to guide risk prediction and intensity of P_2Y_{12} inhibition by either dose adjustment of clopidogrel or switching therapy to prasugrel. Therefore, as a control group we will include a group of patients which will be assigned to prasugrel or clopidogrel therapy based on LTA measurements pre-cath using a cutoff that has been validated as a predictor of ischemic events in several other large studies [1].

The purpose of this study is to assess the pharmacodynamic effects of high intensity P_2Y_{12} receptor inhibition by prasugrel in patients with high clot strength and assess the interrelationship with clopidogrel non-response as defined by light transmittance aggregometry. Pharmacogenetic analyses will aid in understanding the impact of CYP450 metabolism and other polymorphisms in the coagulation cascade on the high clot strength phenotype.
Data from this study may be used in the design of personalized therapeutic trials of antiplatelet drugs and guide the use of next generation PAR-1 inhibitors.

B. SPECIFIC AIMS

The aim of the current study is to evaluate the impact of increased P_2Y_{12} inhibition by prasugrel on the physical properties of whole blood clot formation in patients with

persistent high fibrin-platelet clot strength on clopidogrel and compare the TEG guided treatment approach to a platelet aggregation guided approach of personalized antiplatelet therapy.
Pharmacogenetic analyses of revelant genetic polymorphisms and genes involved in thrombosis are intended to support pharmacodynamic conclusions drawn from the results of this study.

Primary hypothesis
High tensile clot strength as measured by TEG and defined as MA ≥ 69 on clopidogrel is partially due to inadequate P_2Y_{12} inhibition and can be overcome by switching to prasugrel

Primary Endpoint:
Persistence of high tensile clot strength measured by TEG 16-24 hours after reloading of either clopidogrel or prasugrel.

Secondary Endpoints:
a) Occurrence of ischemic events over 6 month follow-up period as defined by death, recurrent myocardial infarction, recurrent unstable angina, repeat coronary intervention (exclusion of staged interventions)
b) Occurrence of bleeding events according to TIMI minor/major criteria over 6 months follow-up.

C. METHODS

1.0 Inclusion/Exclusion Criteria

Inclusion Criteria:
- Patients admitted with acute coronary syndrome (unstable angina, non-ST elevation myocardial infarction) and referred for coronary angiography.
- Current therapy with clopidogrel (at least 300mg loading dose, or 75mg po daily for >5 days)
- Age range 21-75 years.

Exclusion Criteria:
- Unable to give consent
- Age younger than 21 years, greater than 75 years
- History of stroke
- Body weight <60 kg
- Acute STEMI,
- Thrombocytopenia<100’000,
- requirement for chronic warfarin therapy

2.0 Enrollment/Randomization

The current study will be an open label study. Subjects will be enrolled among patients who are admitted with an acute coronary syndrome (unstable angina, non-STEMI) and who are being referred for coronary angiography and possible percutaneous coronary intervention. All study candidates must have received at least 300mg of clopidogrel loading dose since admission, or have been on clopidogrel 75mg daily for >5 days at time of enrollment.
Subjects will be enrolled before undergoing diagnostic angiography using written informed consent after screening for appropriate candidates. Patients will have the first study blood draw performed prior to coronary angiography. In case significant coronary disease is found and the patient proceeds with percutaneous coronary intervention, the patient will be randomized to either a TEG guided or LTA guided strategy. The subject with then be switched to prasugrel or continue on clopidogrel according to the results of the pre-cath TEG or LTA measurements. Patients in the TEG guided arm with high physical clot strength (MA≥69) will be assigned to prasugrel, whereas patients with lower clot strength (MA<69) will continue on clopidogrel. This cutoff reflects the 50^{th} percentile of clot strength based on data from a prior cohort of patients undergoing PCI and was determined as cutoff for ischemic risk in prior studies.
Patients in the LTA guided arm with high on treatment platelet reactivity to ADP (PA>42.9%) will be assigned to prasugrel, whereas patients with low on treatment platelet reactivity (PA≤42.9%) will continue on clopidogrel. This value was determined as a significant cutoff for ischemic risk in prior studies. If the decision is made to proceed with percutaneous revascularization, patients assigned to remain on clopidogrel will receive 300mg clopidogrel loading dose in the cath lab, and then remain on 75mg po daily. Patients assigned to prasugrel will receive 60mg po loading dose, and then remain on 10mg po daily.

Telephone follow-up will be conducted after 6 months to assess for ischemic and bleeding events.

The enrollment and study process is depicted in a Fig 1.

We plan on enrolling 100 subjects, with 50 subjects randomized to each arm:

3.0 Study Procedures

After signing of informed consent, patients are asked to fill out a short questionnaire regarding demographics, risk factors, family history and dietary history that will take 5 minutes to complete.

Venous blood will be collected through peripheral venous puncture (~ 20ml) prior to cardiac catheterization and again 16-24 hours post PCI.

Thrombelastography measurements and light transmittance aggregometry will be performed using several agonists on both occasions.
The remaining buffy coat will be collected and frozen at -80°C for DNA extraction and analysis. Analysis of candidate genes involved in metabolism of thienopyridines, platelet aggregation, and coagulation will be performed.

Patient records from the Indiana Network for Patient Care (INPC) will be accessed for analysis of cardiovascular outcomes.
Data that will be collected for database analyses includes the following (not exclusive):

Demographics	Age Gender Weight Height
Race/ Ethnicity	Self reported
Risk factors/Co-morbidities	Diabetes mellitus Hypertension Hyperlipidemia PVD COPD/Asthma Renal failure/Dialysis Smoking history Valvular disease Hx of arrhythmias
Nutritional History	Caffeine consumption Alcohol use
Medications	Current medication list
History of Present Illness	Reason for referral for cardiac cath
Laboratory	Most recent laboratory data prior to stress test will be obtained from INPC to include: Cardiac markers (troponin, CK, CKMB) Complete blood count Basic metabolic profile Liver function tests (if available) Lipid profile
Electrocardiogram	As per standard of care
Cardiac catheterization	Cines/Images from cardiac catheterizations performed

4.0 Reporting of Adverse Events or Unanticipated Problems involving Risk to Participants or Others

4.1 Data Safety Monitoring Board

A data safety monitoring board consisting of two physicians not directly involved with the study will monitor the progress of the study at least annually.

4.2. Reporting mechanisms for adverse events to the IRB, FDA, NIH.

The principal investigator and study coordinator will review the clinical course for immediate adverse events directly related to the study procedure. Unanticipated serious adverse events as defined below or loss of anonymity will be reported to the IRB within 10 days after discovery in writing. Anticipated adverse events of coronary interventions will be reported during continuing annual review to the IRB.

4.3. Plan for unanticipated AE reporting

Unanticipated serious adverse events must be reported to the IRB within 10 days of discovery. Unanticipated serious adverse events are events (including adverse events, injuries, side effects during a study) that caused harm to one or more subjects or others, or placed one or more subjects or others at increased risk of harm, **AND** were unexpected (the frequency or severity of the event is not accurately reflected in the informed consent document for the cardiac catheterization or is inconsistent with available literature, e.g. drug brochure, protocol) , **AND** were related (e.g. > 51% chance) to the research procedures, **AND** require revision to the informed consent document.

4.4. Plan for annual reporting of AEs

Based upon continuing review, all adverse events will be reported to the Clarian IRB annually in writing.

4.5 Study Withdrawal/Discontinuation

Participants may withdraw from the participation in the study at any time. This requires a written request to the principal investigator.

5 Statistical Considerations

Sample size calculation was performed assuming an estimated prevalence of 50% of MA ≥ 69 in the general patient population with ACS on clopidogrel referred for cardiac catheterization according to previous studies. It was assumed that switching to prasugrel would reduce the maximal clot strength in 60% of these patients with baseline MA ≥ 69 resulting in 20% prevalence of high tensile clot strength. Assuming a power of 0.8 and alpha 0.05 with a loss of 5% of follow-up, a sample size of 50 in each arm and a total sample size of n=100 was calculated accordingly.

6 Privacy/Confidentiality Issues

All information will be collected and kept on a customized database on computers of the investigators and on a secure network server at the Krannert Institute of Cardiology. Access to the database is password protected and computers will be kept in locked offices at the Krannert Institute and Wishard Hospital. Access to the offices housing the information is only available via keys possessed by the investigators. Only the listed investigators of the study will have access to review information and to analyze data. Data sent for analysis will be de-identified. The names of the patients will not be revealed if the results of this study lead to a publication.
The genetic information found through the course of the study will not be revealed to the study participants or their family members.
Blood samples are stored in a secured biospecimen storage facility that has secured access. Biospecimens are deidentified and do not allow identification of patients.

7 Follow-up and Record Retention

The study will last for at least 6 months after enrollment of the last study subject. Records and samples will be kept as required by the IRB and federal legislation and until completion of all study related analyses.

D. FACILITIES AVAILABLE

The cardiac catheterization laboratories at Wishard Hospital and Methodist Hospital will be used as study locations as required for the clinical care of the patients. Standard hospital care will be provided.
Laboratory analyses including platelet studies, thrombelastography, as well as DNA analysis will be performed in the laboratories of the Division of Clinical Pharmacology, Indiana University School of Medicine.

E. SUPPORTING INFORMATION

The proposed research strives to further the cause of delivering personalized care to patients undergoing invasive and high risk procedures in the cardiac catheterization laboratory. Personalizing antiplatelet drug therapy by adjusting drugs and dosing according to measurements of platelet inhibition has been proposed as a future approach to optimally balance desired therapeutic effects as well as unwanted adverse effects and thus deliver optimal patient care. Patients enrolled in this study will benefit from advanced laboratory testing and likely improved outcomes after coronary stenting compared to standard treatment. Findings from this study may be useful in the design of future clinical research studies.

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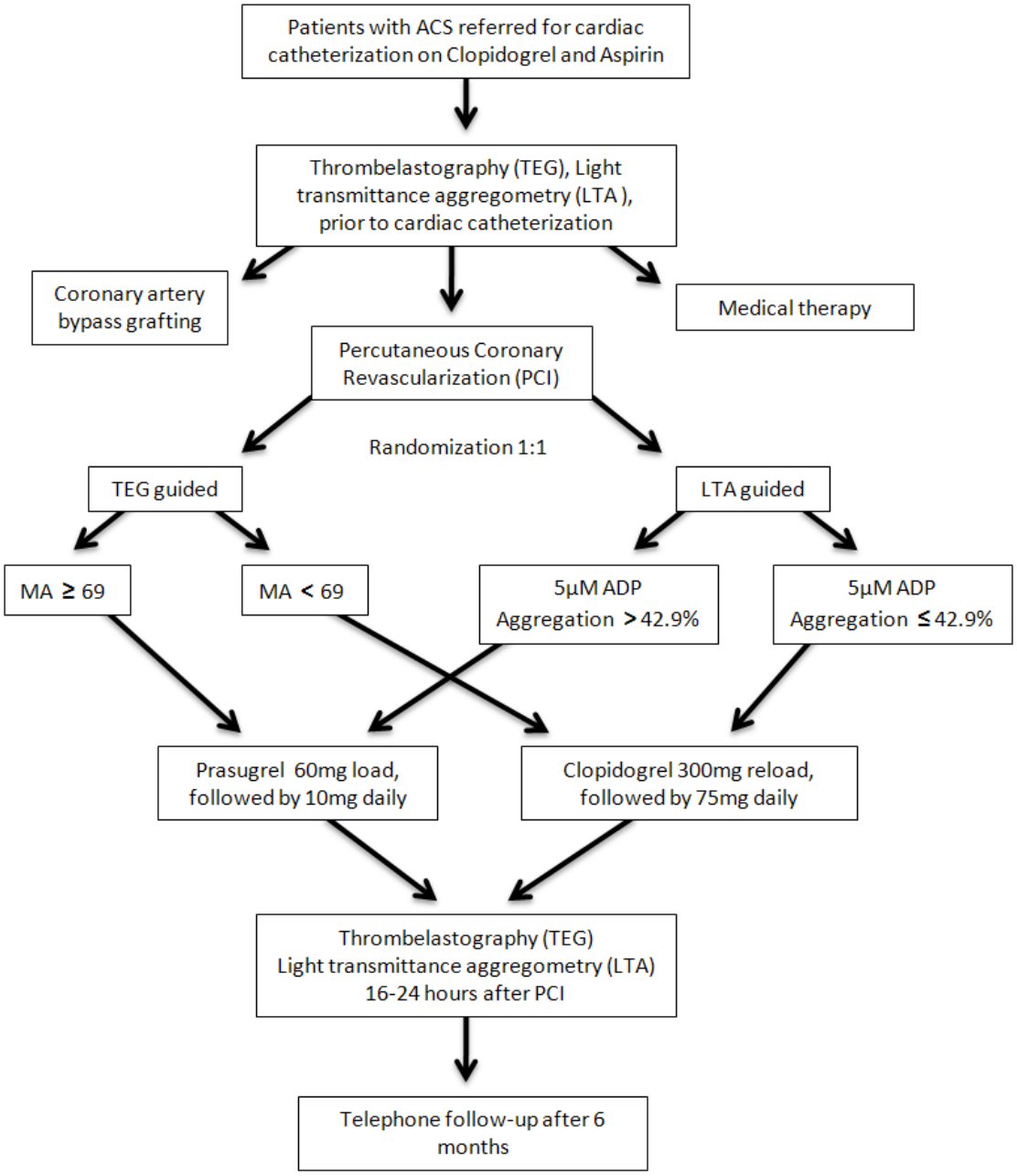
Fig 1.


Patients with ACS referred for cardiac catheterization on Clopidogrel and Aspirin
Thrombelastography (TEG), Light transmittance aggregometry (LTA), prior to cardiac catheterization
Coronary artery bypass grafting
Medical therapy
Percutaneous Coronary Revascularization (PCI)
Randomization 1:1
TEG guided
LTA guided
MA ≥ 69
MA < 69
5µM ADP Aggregation > 42.9%
5µM ADP Aggregation ≤ 42.9%
Prasugrel 60mg load, followed by 10mg daily
Clopidogrel 300mg reload, followed by 75mg daily
Thrombelastography (TEG) Light transmittance aggregometry (LTA) 16-24 hours after PCI
Telephone follow-up after 6 months