The Effect of Dapagliflozin on platelet function testinG profiles in Diabetic PatiEnts: The EDGE Study.

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Rationale and Background:

Dual antiplatelet therapy (DAPT) with aspirin and clopidogrel represents the standard of care for the prevention of recurrent ischemic events in patients undergoing percutaneous coronary intervention (PCI). For more than 20 years, dual antiplatelet therapy with aspirin and Clopidogrel has remained the cornerstone of treatment for patients with acute coronary syndrome (ACS). However, some patients have impaired clopidogrel response and thus persist with high on-treatment platelet reactivity (HPR) resulting in an increased risk of atherothrombotic events. The boxed warning added to the clopidogrel label underscoring the potential risk of adverse cardiovascular outcomes among patients with a "poor metabolizer" genotype and advocating the use of other antiplatelet medications or alternative dosing strategies for these patients has led to investigations of treatment options associated with more optimal platelet inhibition. These include switching to a novel generation P2Y12 inhibitor (e.g. prasugrel or ticagrelor).

Sodium GLucose Transport 2 inhibitors (SGLT2I), including dapagliflozin, reduce the likelihood of hospitalization for heart failure and death in persons with type 2 diabetes, of which the mechanism has not been fully elucidated. The mechanical effects of dapagliflozin on platelet function profiles have not yet been ascertained. It remains unclear if this reduction in cardiovascular death is mediated by decreased platelet reactivity.

Hypothesis:

1. Dapagliflozin attenuates platelet reactivity in patients with diabetes mellitus.
2. Dapagliflozin decreases platelet reactivity by 10%.

Null Hypothesis:

There is no difference in response in patients with stable coronary artery disease on DAPT concerning PRUs on dapagliflozin.

Study Goals and Objectives:

1. To describe platelet function profiles of patients with stable coronary artery disease on DAPT on dapagliflozin.

Study Design:

The study will be of a prospective, randomized, parallel trial design over 2 years. Patients at the Eric Williams Medical Sciences Complex (EWMSC), Mt. Hope, Trinidad and Tobago will be screened for potential eligibility.

Methodology:

Inclusion criteria

Patients will be screened and considered eligible for the study if they are:

1. between 18 and 74 years of age,
2. have stable coronary artery disease and diabetes mellitus, already on DAPT with aspirin and clopidogrel for at least 6 months,
3. not on any physician-prescribed medications or complementary/alternative therapies,

Exclusion criteria

Patients are ineligible to participate if any of the following criteria are met:

1. presence of active internal bleeding or history of bleeding diathesis or clinical findings associated with an increased risk of bleeding,
2. history of ischemic or hemorrhagic stroke, transient ischemic attack, intracranial neoplasm, arteriovenous malformation, or aneurysm,
3. history of clinical and/or hemodynamic instability,
4. within 1 month of placement of a bare metal stent,
5. within 30 days of coronary artery bypass graft surgery or PCI without a stent placed,
6. planned coronary revascularization,
7. treatment with fibrin-specific fibrinolytic therapy <24 h or non-fibrin-specific fibrinolytic therapy <48 h,
8. use of an oral anticoagulation agent or international normalized ratio >1.5,
9. body weight <60 kg,
10. age >75 years,
11. hemoglobin <10 g/dL,
12. platelet count $<100\times10^6/\mu L$,
13. creatinine >2 mg/dL,
14. hepatic enzymes >2.5 times the upper limit of normal,
15. pregnancy and/or lactation.

The study will undergo a formal approval process by the Campus Ethics Committee (CEC) of the University of the West Indies (UWI) and all patients are to provide written informed consent before participating in the study. The trial will be conducted by the Declaration of Helsinki and the International Conference on Harmonization (ICH) Guidelines for Good Clinical Practice

(GCP). Two clinical research associates (CRAs) will secure and assess the quality of the data and the university biostatistician will perform the data analysis after data lock. The CRAs will then deliver the database and the analysis results to the principal investigator (PI). Data will be coded per patient by first letter of first name, first letter of last name followed by numerical date of birth in the order of day, month, and year in a password-protected and encrypted database program in the office of Lecturer Dr. Naveen Seecheran at the Department of Clinical Medicine office, 2nd Floor, Building 34, Eric Williams Medical Sciences Complex.

Patient Interview and Case Report Form

If a patient satisfies the selection criteria from the initial screening process, a physician or CRA-directed interview will then be administered. Demographic and anthropometric data will be recorded on a case report form (CRF). This will comprise the patient's medical and procedural history including any active medications.

Each patient will then be allocated via a computerized randomization program. Patients on DAPT for at least 6 months will be tested for platelet function testing with the P2Y12 VerifyNow assay at baseline. The patients will then undergo at least a 2-week course of dapagliflozin 10mg, followed thereafter by platelet function testing. The study will be randomized via a computer randomization program with a permuted block design and concealment allocation. It is also a controlled, prospective trial design, as group A serves to act as a baseline comparator group and group B has the desired antiplatelet strategy to be investigated over the longitudinal 2-week period. The study will also be blinded as patients will be unaware of their treatment assignments as well as the CRA or physician (Interventional Cardiologist) that performs the platelet function testing.

Blood Sampling, Phlebotomy

Blood samples for platelet function testing will be collected at baseline before the patients are administered dapagliflozin (baseline sample). Blood will be drawn via an antecubital vein using a 21-gauge needle. The initial 5 mL of all blood samples will be discarded as medical waste as per the institution's policy (to avoid spontaneous platelet activation). Several laboratory tests will be performed including:

1. Complete Blood Count
2. Renal Function Profile
3. Hepatic Function Profile
4. VerifyNow P2Y12 PRU test assay - which will also be performed at the 2nd-week time point after patients have completed their assigned treatment schedules.

Overall, there will be 2 separate instances in which blood sampling/phlebotomy will be performed.

Aggregation Testing, Platelet Function Testing

Citrated blood samples are processed by CRAs and study investigators. The platelet function assay to be utilized is the VerifyNow P2Y12 (VN-P2Y12) assay (Accriva, San Diego, California). In brief, the VN-P2Y12 assay is a rapid whole blood point-of-care device that reports results as P2Y12 reaction units (PRU) and percent inhibition of platelet aggregation (%IPA). Assays will be performed as per the instructions of the manufacturer previously described. Please see attached:

- http://www.accriva.com/uploads/assets/clsi-procedures/14983-revf.docx
- http://www.accriva.com/uploads/assets/clsi-procedures/14982-revk.doc

Safety Considerations:

Overall, patient risk would be considered minimal.

The risks of phlebotomy coupled with treatment and management are:

1. Arteriospasm, Hematoma – sterile compression bandage will be done to achieve hemostasis monitoring of vital signs digital pulse oximetry to ensure perfusion of tissues, blood transfusions, Vascular Surgeon consultation for brachial artery repair, and/or luminal dilatation.
2. Nerve damage/injury- Orthopaedic management of possible injury to median nerve, evaluation, and follow-up in the clinic, and possible anti-inflammatory medications for nerve inflammation.
3. Infection- Debridement, microscopy, culture, and sensitivity as well as initiating empirical broad-spectrum antibiotics, and monitoring for signs of sepsis. If febrile or septic shock admission to hospital and commencement of intravenous fluids, intravenous antibiotics with possible ICU intervention.
4. Low risk: Phlebotomy: Vascular spasm, hematoma, local infection, Medium Risk Phlebotomy: nerve damage/injury (unlikely), Dapagliflozin: urinary tract infections, fungal infections, (rare-occasional, usually not life-threatening), Serious Risk Phlebotomy: hand surgery (exceedingly rare), Dapagliflozin: diabetic ketoacidosis, Fournier's gangrene, and hypoglycemia (very rare).

The study will be by the summary of risks and risk-reduction strategies outlined in Table 8 in the WHO Guidelines on Drawing Blood: Best Practices in Phlebotomy. Any serious adverse events (SAEs) will be recorded as per the Bleeding Academic Research Consortium (BARC) group definitions and reported to the Ethics Committee of the University of the West Indies within 24 hours. The patient will receive health care per the participating institution’s guidelines and policies i.e. Cardiology Department at EWMSC, Mt. Hope, Trinidad & Tobago.

Follow-up:
Patients will be informed of their results in person, or if unavailable via telephone. They will also be provided with a hard-copy report of their platelet function profiles. They will also be informed on a scheduled basis of the management plan for any serious adverse events (SAEs) that may have unfortunately occurred as a result of their direct participation in the study.

Data Management and Statistical Analysis:
The patient information will be initially recorded on CRFs which will be stored in the Adult Medicine Unit locking file cabinets, located at the Department of Clinical Medical Sciences, University of the West Indies, St. Augustine. Data will be coded per patient by first letter of first name, first letter of last name followed by numerical date of birth in the order of day, month, and year in a password-protected and encrypted database program in the office of Lecturer Dr. Naveen Seecheran at the Department of Clinical Medicine office, 2nd Floor, Building 34, Eric Williams Medical Sciences Complex. Each CRF and study database will be reviewed by 2 CRAs to minimize error, and clean and reconcile any conflicting data. We will aim for *n* of least 16 patient profiles, see sample size calculations. Any missing information will be censored and thus, not imputed. The study biostatistician will perform routine statistical analyses with SPSS v. 11.0 software (SPSS, Chicago, IL). Continuous variables are expressed as means ± SD. Categorical variables are to be expressed as frequencies and percentages. Student's t-test will be used to compare continuous variables. Comparisons between categorical variables will be performed using the two-tailed Fisher's exact test or the Pearson's $\chi 2$ test, as appropriate. A p-value of < 0.05 will be considered statistically significant. No adjustments for multiple comparisons will be made. Results will be reported as least-square mean ± SEM for the detailed analyses.

Sample Size Calculation:
Assuming:
1. A 75 mg/d clopidogrel maintenance dose required at least 5 days and a 600 mg loading dose of clopidogrel required up to 8 hours to achieve ~50% steady state of inhibition of ADP-induced platelet aggregation.
2. An estimated decrease of 10%, thus achieving a steady state inhibition of ADP-induced aggregation of 55% in patients with dapagliflozin.
3. Type 1 error rate 5%
4. Statistical power of 80%

n = **25**
(http://hedwig.mgh.harvard.edu/sample_size/js/js_parallel_quant.html)

Quality Assurance:
The study will be by GCP and the Declaration of Helsinki. In addition, it will only commence after official approval from the Ethics Committee of the University of the West Indies. There will be no Data Safety and Monitoring Board (DSMB). Patient Informed Consent Forms (ICFs) and Case Report Forms (CRFs) will each be quality-controlled by 2 CRAs and recorded in triplicate (1 for patient records, 2 for the study team).

Expected Outcomes of the Study:
The information obtained from the study would be integral in developing antiplatelet strategies for patients with impaired platelet reactivity. It will advance knowledge in the field i.e. useful for baseline information and hypothesis generation for further studies within the scientific community. It will also determine if dapagliflozin is an adjunct for non-response to the current armamentarium of antiplatelet therapies available in Trinidad and Tobago. This information can then reliably inform regulatory bodies e.g. Ministry of Health (MOH) to make additions to the national Chronic Disease Assistance Medication Program (CDAP) to include this as a possible adjunct to facilitate a more potent antiplatelet effect.

Dissemination of Results and Publication Policy:
The patients will be informed of their results in person, or if unavailable via telephone. They will also be provided with a hard-copy report of their platelet function profiles. The results and conclusion of the study will be published for the scientific community for further analysis and discussion. The aforementioned study team, including collaborators, will be acknowledged on any publications. The principal investigator (PI) will determine the order of author contributorship.

Duration of the Project:
Please see the Project Management and Gantt Table below. The estimated duration for the study is approximately 2 years.

Problems Anticipated:
1. Financial: The resources (see outlined budget below) required for the study are relatively expensive and thus, would require funding to ensure successful completion.

Project Management:

	ICF	CRF	Sample Collection	VN POC Analysis	Database Entry	Statistical Analysis	Manuscript Preparation

Timeline/months	20m	20m	20m	20m	2m	2m	2m
CRA 1	X	X	X	X	X		
CRA 2	X	X	X	X	X		
Bio-Statistician						X	
NS						X	X

Ethics:

The final version of the protocol will be submitted to the Ethics Committee of the University of the West Indies, located at the University of the West Indies, St. Augustine, Trinidad and Tobago. The study team will await official approval before any study-related activities can commence. There are no significant ethical concerns about conducting the study. All patient samples (blood) that are surplus to requirements will be discarded as per the participating institution's medical waste protocol. The study will be stringently conducted by the Declaration of Helsinki.

Informed Consent Forms:

Please see the attached Ethics Committee of the University of the West Indies file for the final version of ICF. ICFs will be physician or CRA-administered and available only in English. They will undergo an approval process by the Ethics Committee of the University of the West Indies before the study can commence. Each ICF will be done in triplicate (1 for patient records and 2 for the study team). The ICF will comprise the important aspects that are in accordance with the international guidelines outlined in the references.

Budget:

Item	Quantity	Purpose/Justification	Total/USD
VerifyNow ASA and P2Y12 PRU Test Kits	2	Test Kits for collected blood samples	~21,000 TTD
Maintenance	N/A	Analyzer needs to be maintained as per Company's policy (located in US - shipping, handling & insurance)	~0 TTD

Stationery	25	25 Informed Consent Forms & Case Report Forms (Triplicate)	~0 TTD
Total			~$2,000 USD

Other support for the Project:
The study will be financed via grant support from the University of the West Indies, St. Augustine. Applications to other sources of funding will be submitted to the respective agencies.

Financing and Insurance:
The study will be financed via grant support from the University of the West Indies, St. Augustine. No specific insurance coverage will be provided to the study participants; however, they will receive health care as per the participating institution's guidelines and policies i.e. the Cardiology Department at the EWMSC, Mt. Hope, Trinidad & Tobago.

Collaboration with other scientists or research institutions:

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Key Words:

- antiplatelet drugs
- Clopidogrel
- Dapagliflozin
- high on-treatment platelet reactivity
- platelet function

Abbreviations and Acronyms:

HOT-PR	High on-treatment Platelet Reactivity
LTA	Light Transmission Aggregometry
MPA	Maximal Platelet Aggregation
PD	Pharmacodynamic
PRI	Platelet Reactivity Index
PRU	Platelet Reactivity Units
VN-P2Y12	VerifyNow P2Y12

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