Presentation Title: Correlation between CYP2C19 Allele Status and P2Y12 Assay in Patients Receiving Clopidogrel after Acute Ischemic Stroke (CASPA-AIS)

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Background Information: Stroke is a leading cause of death in Americans, with up to 25% of fatalities occurring in people who have had a previous stroke. As such, secondary prevention in this population is critical. Dual antiplatelet therapy (DAPT) with aspirin and clopidogrel is the current standard of care for secondary prevention in non-cardioembolic minor acute ischemic stroke (AIS) [(NIHSS score ≤3)] and high-risk transient ischemic attack (TIA) [(ABCD2 score ≥4)]. However, because clopidogrel is a pro-drug metabolized to its active form by CYP2C19, its efficacy can be significantly impacted by a patient's CYP2C19 phenotype. Unfortunately, CYP2C19 genotype testing is not routinely available to patients initiated on DAPT following an ischemic event. P2Y12 assays reporting the amount of P2Y12 receptor-mediated platelet aggregation are more widely accessible and can be used to characterize a patient's response to clopidogrel therapy; however, it is unclear if this assay correlates with a patient's CYP2C19 allele status.

Objective: The goal of this research project is to investigate a correlative relationship between CYP2C19 allele status and P2Y12 receptor-mediated platelet aggregation as measured by the VerifyNow P2Y12 Assay in the setting of clopidogrel therapy. Ultimately, this study aims to evaluate this assay as a potential alternative to CYP2C19 genotyping for identifying suboptimal responders to clopidogrel therapy. Secondary objectives are to examine the relationship between CYP2C19 allele carrier status and stroke-free status at 30 days in the same population, as well as to assess any impact of time interval between clopidogrel loading dose and P2Y12 assay draw on platelet reactivity units.

Methods: This is a prospective, observational study enrolling subjects $\geq$ 18 years of age presenting with minor AIS or high-risk TIA for which they are being discharged on dual antiplatelet therapy with clopidogrel/aspirin per the indication supported by the POINT/CHANCE trials. Whole blood samples will be collected from consenting patients at least 12 hours after the clopidogrel loading dose is administered but within 7 days of DAPT initiation. The VerifyNow P2Y12 assay will be performed by clinical laboratory services in-house at UVA Health and PRUs < 204 will be considered indicative of optimal platelet reactivity response. CYP2C19 genotyping will be completed off-site at RPRD Diagnostics utilizing a CLIA-certified genotyping panel. P2Y12 assay results will be blinded to both the patient and the care team in the Electronic Health Record so as not to influence clinical decision making.

Preliminary Results: Enrollment is ongoing, and CYP2C19 genotyping will occur offsite in batch after the target population of 30 subjects is identified. Therefore, the final analysis of the primary objective cannot yet be performed. However, an interim analysis of the data associated with the secondary aim of assessing the impact of time between clopidogrel load and P2Y12 assay draw has been completed. No statistically significant relationship was found between the number of hours separating clopidogrel load from serum draw and the instance of PRUs being less than 204 [OR: 1.041 (95% CI 0.969-1.119)].

Conclusion: Evaluation of the primary objective is ongoing. However, there does not appear to be a statistically significant correlation between the time period from clopidogrel load to P2Y12 assay and platelet reactivity units. This supports the methodology employed in this study of attaining the P2Y12 assay as early as 12 hours after the clopidogrel load to evaluate the likely pharmacodynamic activity of clopidogrel at steady state.