STUDY PROTOCOL

Official title: Polypill Strategy for Evidence-Based Management of Patients with Acute Coronary Syndrome Undergoing Percutaneous Coronary Intervention in an Underserved Patient Population

NCT number: NCT05514938

IRB Approved date: 04/25/2025

Form A

IRB #	STU-2022-0604

PROTOCOL FORM / RESEARCH DESCRIPTION

If an item does not apply to your research project, indicate that the question is "**not applicable**" – do not leave sections blank

Click once on the highlighted entry in each box to provide your response. Click the item number/letter or word, if hyperlinked, for detailed instructions for that question. If your response requires inserting a table, picture, etc, you may need to first delete the box that surrounds the answer and then insert your table or other special document.

1. Purpose and objectives. *List the purpose and objectives:*

Objective: Investigate the utility of a polypill-based strategy for patients with acute coronary syndrome (ACS) with drug eluting stent (DES) placement. Polypill therapy will consist of a high-intensity statin (rosuvastatin 40 mg daily), aspirin 81 mg daily, and a P2Y12 inhibitor, either prasugrel 10 mg daily or clopidogrel 75 mg daily.

Primary Aim: To determine whether the use of a polypill consisting of aspirin 81 mg, prasugrel 10 mg or clopidogrel 75 mg, and rosuvastatin 40 mg daily for patients who undergo percutaneous coronary intervention (PCI) after acute coronary syndrome (ACS) is feasible and leads to improved medication adherence compared with usual care.

Hypothesis: We hypothesize that the use of a polypill is feasible in a low SES setting for patients with ACS after PCI and stent implantation. We hypothesize that its use will be associated with improved platelet inhibition as measured by platelet function assay, greater LDL reduction, and improved medication adherence as compared to usual care.

2. Background.

- Describe past experimental and/or clinical findings leading to the formulation of your study.
- For research involving investigational drugs, describe the previously conducted animal and human studies.
- For research that involves FDA approved drugs or devices, describe the FDA approved uses of this drug/device in relation to your protocol.
- Attach a copy of the approved labeling as a product package insert or from the Physician's Desk Reference.

You may reference sponsor's full protocol or grant application (section number and/or title) or if none, ensure background includes references.

Please respond to all components of this item, or clearly indicate which components are not applicable.

a. Background

Acute coronary syndromes (ACS) represent a large contributor to patient morbidity and mortality and healthcare costs. Patients with suspected ACS are referred for diagnostic coronary angiography, and if obstructive coronary disease is found, percutaneous coronary intervention (PCI) with a drug-eluding stent (DES) has been proven to reduce mortality and reduce recurrent myocardial infarction. Medical therapy for ACS involves treatment with a statin and dual antiplatelet drug therapy with aspirin and P2Y12 inhibition.[1,2]

Dual antiplatelet therapy (DAPT) is a vital aspect of post-PCI care and ensures stent patency.[2] Aspirin blocks metabolism of arachidonic acid and production of thromboxane A2 through irreversible inhibition of cyclooxygenase 1.[3] Prasugrel and clopidogrel are irreversible inhibitors of the platelet P2Y12 ADP receptors, while ticagrelor is a reversible inhibitor of the platelet P2Y12 ADP receptor. Current guidelines recommend dual antiplatelet therapy for at least 1 month and ideally up to 1 year for patients treated medically, and at least 1 year for patients treated with DES after hospitalization for ACS.[4,5]

Additionally, lipid lowering therapy is a cornerstone of post-ACS care. Multiple studies have demonstrated a direct correlation between low-density lipoprotein cholesterol (LDL-C) levels and ASCVD risk.[6] Statins (3-hydroxy-3-methylgultaryl-coenzyme A reductase inhibitors) are first-line therapies used to achieve LDL-C reductions. High-intensity statins, such as atorvastatin 40 mg or 80 mg or rosuvastatin 20 mg or 40 mg, can lower LDL-C by > 50%, and patients with history of ACS have greater benefit from high-intensity statins versus low-intensity statins.[7] Importantly, administration of a high-intensity

statin is a Class 1 recommendation from the AHA/ACC Non-ST-Elevation ACS guidelines and the ST-Elevation ACS guidelines.

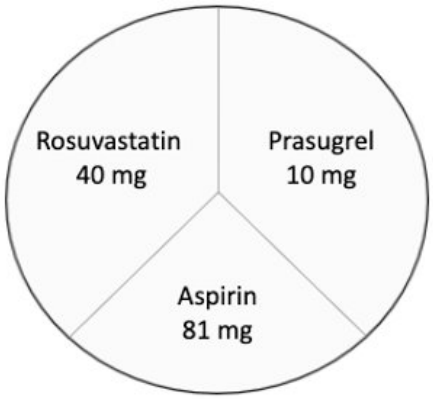
The combination of prompt diagnosis of ACS, management with coronary angiography with possible DES placement, and medical therapy including DAPT has led to improvements in ACS mortality. However, nonadherence to cardiovascular medications is common. Data from the US Veteran's Affair's hospitals show that nearly 30% of patients did not refill clopidogrel after index hospitalization for ACS. [8] In a study of the PREMIER registry, one in seven patients stopped taking clopidogrel therapy after 1 month, and those who stopped had ninefold elevated risk of death within 1 year.[9] Poor adherence to antiplatelet therapy with either aspirin or P2Y12 inhibitors can lead to in-stent thrombosis, a particularly morbid occurrence characterized by high patient morbidity and mortality. Early stoppage of dual antiplatelet therapy increases risk of stent thrombosis 90-fold.[10]

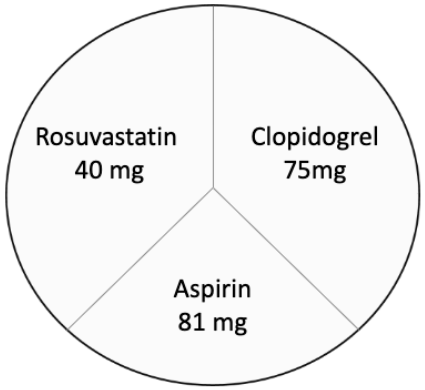
Nonadherence to statins is also well documented. Roughly 1/3 of ischemic heart disease is related to dyslipidemia, and statins are the mainstay of treatment. However, roughly 25-50% of patients discontinue their statin therapy within the first year after treatment initiation.[11] Lipid reduction is a proven strategy to prevent further cardiovascular events, however, medication nonadherence is a significant barrier.

The polypill is a potential strategy for increasing utilization of proven ACS therapies. The polypill refers to a fixed-dose combination of once-daily medication with proven benefits. The feasibility of a polypill-based strategy has been demonstrated for the primary prevention of cardiovascular events. Among patients with hypertension at a federally qualified community health center, the polypill led to a reduction in systolic blood pressure (-7 mm Hg, 95% CI: -2 to -12; p=0.003) and low-density lipoprotein cholesterol (-11 mg/dl, 95% CI: -5 to -18; p=0.0003) [12]. Multi-drug combinations have additionally been employed in the Indian Polycap Study, HOPE-3 trial, UMPIRE trial and most recently in the PolyIran study, which demonstrated high rates of adherence, and low rates of adverse events.[13-16] In PolyIran, the largest of these studies, more than 6500 healthy individuals were enrolled and randomized to treatment with a polypill containing low doses of a thiazide diuretic, aspirin, statin, and ACE/ARB versus no pharmacologic intervention for primary prevention of cardiovascular disease. Among those receiving the polypill, a 34% risk reduction in major cardiovascular events was observed compared to standard treatment.[13] In the smaller UMPIRE trial, moreover, adherence among participants receiving a polypill formulation was more than three-fold higher than in those receiving usual care.[15] Few studies have enrolled disadvantaged U.S populations to date and no study to our knowledge has evaluated a polypill strategy for treatment of heart failure, where pill burden and adherence continue to present obstacles to improving care.

No randomized trial has evaluated a polypill strategy for the treatment of ACS. Given the significant pill burden and challenges with adherence, a polypill strategy may have substantial advantages. Thus, we propose a single-center, open-label, pragmatic pilot study of a polypill-based strategy for the treatment of ACS. The polypill will consist of a high-intensity statin (rosuvastatin 40 mg daily), aspirin 81 mg daily, and either clopidogrel 75 mg or prasugrel 10 mg daily. The rationale for the trial is summarized as follows:

- Acute coronary syndromes represent a major contributor to mortality, morbidity, and healthcare costs
- Effective therapies are widely available; however, adherence is low. This contributes to worse patient outcomes and increased risk of morbidity and mortality.
- The once-daily polypill leverages a population-based strategy that has previously demonstrated efficacy in improving adherence and access to therapy in low-resource settings, making it an innovative approach for improving post-ACS care.





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b. Current practice

Local practice follows current ACS guidelines through the AHA/ACC, which recommend dual antiplatelet therapy with aspirin and a P2Y12 inhibitor for 1 year after drug eluting stent placement for ACS. Guidelines also recommend a high intensity statin to treat hyperlipidemia and reduce the risk of future atherosclerotic events. Traditionally, aspirin 81 mg is given in conjunction with either prasugrel 10 mg daily, clopidogrel 75 mg daily, or ticagrelor 90 mg twice daily, in conjunction with either atorvastatin 40 mg or 80 mg or rosuvastatin 20 mg or 40 mg daily. In many facilities, clopidogrel and prasugrel are preferentially used as they are dosed daily.

3. Study Design.
Describe the study design (e.g., single/double blind, parallel, crossover, etc.) Consider inserting a scheme to visually present the study design.

We propose a single-center, open-label, pragmatic, pilot study of 40 patients randomized to the polypill therapy and 40 patients randomized to standard of care. Duration of follow up will be 1 month. The target population is patients receiving care at Parkland Hospital or UT Southwestern Medical Center for an ACS event in which a drug eluting stent is placed, and the patient is treated

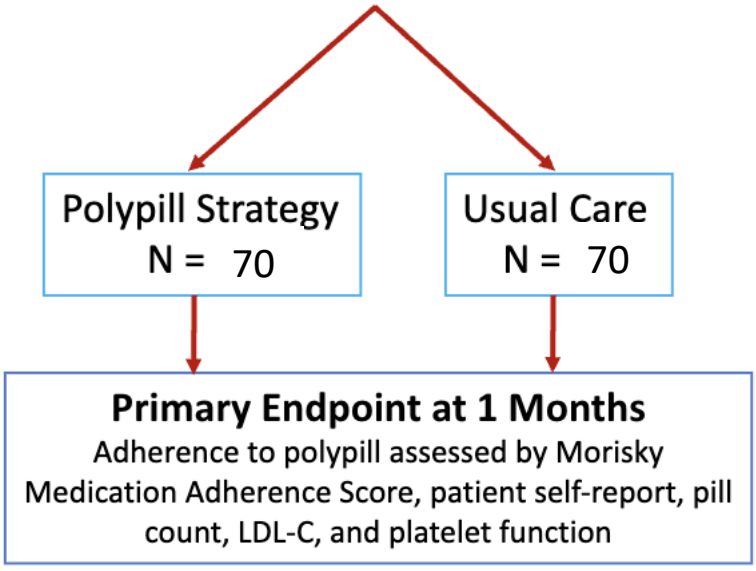
with prasugrel or clopidogrel, aspirin, and a high-intensity statin. The polypill will depend on which P2Y12 inhibitor is used between prasugrel or clopidogrel.

Eligibility

Patients admitted with acute coronary syndrome who undergo percutaneous coronary intervention with drug eluting stent placement.

Exclusion:

1. Age < 18
2. Estimated glomerular filtration rate < 30 mL/min/1.73 m^2 as measured by the simplified MDRD formula
3. Current need for inotropes or with cardiac index < 2.2 L/min/m^2
4. Current need for systemic anticoagulation
5. Contraindication to receive any components of the polypill
6. History of allergic reaction or intolerance to aspirin, prasugrel or clopidogrel, or rosuvastatin
7. Comorbidities that might be expected to limit lifespan within the 1-month study period
8. Inability to provide written informed consent
9. Pregnancy



4. Research Plan / Description of the Research Methods:

4.a. Provide a **comprehensive narrative** describing the **research methods**.

1) Provide the **order in which tests/procedures will be performed**,
2) Provide the **setting** for these events and a description of the **methods used to protect privacy** during the study.
3) Provide the **plan for data analysis** (include as applicable the **sample size calculation)**

Please respond to all components of this item, or clearly indicate which components are not applicable.

Study sites and participants: All participants will be recruited from UT Southwestern Medical Center – Clements University Hospital and Parkland Hospital. We will perform pre-screening using EHR data after obtaining permission from the primary physician teams. We have a study coordinator with extensive experience performing clinical trials at Parkland Health and Hospital Systems and UT Southwestern Medical Center. Patients will be approached prior to discharge from their ACS hospitalization. Patients will be introduced to the study and be given a copy of the study consent form. Patients will be informed about the study, its goals, and the risks and benefits of participating and will be invited to participate. If patients express interest, they will be contacted within 7 days of hospital discharge. Patients will receive standard of care upon discharge from the hospital.

The initial visit will serve as a formal screening and baseline visit. Patients will be randomized at this visit. The polypill will be substituted for the individual component medications, with other medicines continued as prescribed. Potential participants will be asked to fill out a demographic questionnaire and survey regarding medication use, health status, and other characteristics in-person to assess potential eligibility. Based on our initial experience, we estimate that we will need to contact 200 patients over a 4-month enrollment period to enroll 150 patients in the study. In our prior polypill trial, conducted in an outpatient setting, we observed a 45% response rate to the initial invitation, of which ~50% met eligibility criteria and consented to randomization. We will record all contact attempts and responses to determine recruitment rates and reasons for entry or non-entry into the trial. The study team has substantial experience with recruiting participants for clinical trials and observational studies.

Participants who meet eligibility criteria will be invited to enroll in the trial. The study will be open label. For this initial pilot study, we will create a random sequence randomization table. The investigational drug service at Aston in the UT Southwestern Medical Center will randomize patients to either the polypill or control arm. The study investigators will prescribe the polypill to those in the intervention arm. In response to the initial polypill prescription, participants will receive an initial pill vial containing a 30-day supply of medication at the initial visit. Participants will be instructed to take one pill per day for the duration of the study. All polypill medications, including unopened or partially used containers, will be maintained at the study site for eventual return to the vendor. As this is an open-label trial, there will be no placebo provided in the usual care arm. Patients will be informed to bring their medications to the baseline visit. The research team will confirm that patients picked up the initial prescription of aspirin, prasugrel or clopidogrel, and rosuvastatin prescribed by discharging physicians. Patients in the usual care arm can provide receipt of payment and will be reimbursed for drug costs and/or co-payments for aspirin, prasugrel or clopidogrel, and statin.

This project will utilize REDCap and the Clinical Data Pull (CDP) via FHIR (Fast Healthcare Interoperability Resource) module of REDCap. The Clinical Data Pull (CDP on FHIR) is a special feature for importing data into REDCap from an external source system. It provides an adjudication process whereby REDCap users can approve all incoming data from the source system before it is officially saved in their REDCap project. The CDP will only allow people with access to PHI use it as it has a built-in check each time it is accessed. The CDP can only be enabled by a REDCap administrator who serves as a honest broker to PHI. Using the CDP on FHIR requires using the Medical Record Number (MRN) as a key to automatically gathering demographics and Laboratory data and reduces data entry errors.

Baseline Study Visit:

Patients will undergo a baseline history and physical at time of enrollment. The screening and baseline visits will be combined into a single visit to reduce the total number of visits. Informed consent will be obtained at the visit. A study coordinator will review responses to baseline questionnaire as a final check on inclusion and exclusion criteria and current medication use.

- A medical and social history will be obtained such as demographic data, health history, smoking and alcohol use, level of education, a questionnaire about their health and living arrangement. Vital signs will be measured in seated participants according to standardized protocols.
- A baseline assessment of quality of life (Seattle Angina Questionnaire)
- A baseline survey to understand of the medical uses of statin medications
- A 15 mL blood sample will be obtained for eligibility laboratories, including a complete metabolic panel and complete blood count, platelet function testing, and lipid levels. If results of any of this testing is present within 14 days, the labs will not be rechecked at the baseline visit. The blood sample will be drawn, processed, refrigerated, and transported to the core laboratory for storage.
- Pre-menopausal women will undergo a rapid urine pregnancy test.

Assignment to Study Groups:

- Subjects will be randomized at this visit to either the polypill or usual care arm.
  - The Polypill will be in addition to or in place of similar medications that participants may be currently taking
  - The usual care group will have no changes to their current coronary artery disease medications.
- We anticipate that relatively few participants will have unexpected laboratory abnormalities meeting exclusion criteria (e.g., electrolyte abnormalities, renal failure, LFT abnormalities) given the pre-screening protocols using the EHR. If any exclusion criteria are identified, the participant will be contacted and withdrawn from the study.

Follow-Up:

There will be one follow up appointment at the 1-month time period. At this visit, the study coordinators will review:

- Questionnaires for completeness
- Assess vital signs
- Collect a blood sample to assess platelet function testing, lipid levels, statin drug levels.
- Assess medication adherence by pill count
- MMAS-8 questionnaire
- Assess for medication safety, tolerance, and side effects.
- Assess statin myopathy questionnaire
- Seattle Angina Questionnaire to assess quality of life

Compensation and Reimbursement:. Subjects will receive $50 at the baseline visit and at the 1-month follow-up visit. Patients will also receive travel vouchers and/or transportation reimbursements for their follow-up visits. Finally, patients randomized to the usual care arm may bring receipt to be reimbursed for cost of prasugrel or clopidogrel, aspirin, and statin medication.

Data Analysis:

Our primary outcome will be adherence, which will be assessed by the Morisky Medication Adherence Score – 8 (MMAS-8), pill count, and via circulating statin drug levels.. Secondary outcomes will include platelet function and LDL-C. The MMAS-8 ranges from 0 to 8, with scores as follows: low adherence, <6; medium adherence, 6 to <8; and high adherence, 8. Adherence will be assessed at 1 month by grouping scores within the above strata and comparing adherence across the polypill group and usual care group. A risk ratio will be calculated as the probability of high treatment adherence as compared with low or medium adherence in the polypill group as compared with the usual-care group. We will compare platelet function levels with the student t-test or Kruskal-Wallis test. We will compare mean change in LDL-C with the student t-test or Kruskal-Wallis test.

As this is a pilot study, sample size will include 150 participants, enrolled in 1:1 fashion alternating between intervention (polypill) group and the control group.

4.b. List of the study intervention(s) being tested or evaluated under this protocol

☐ **N/A -** this study does not test or evaluate an intervention.

#	Study intervention(s) being tested or evaluated under the protocol *Add or delete rows as needed*	Affiliate Place a check next to institution(s) where the intervention will be performed	Local Standard Practice? Indicate whether the intervention is considered acceptable practice locally for applicable institutions
1	**Polypill –** The medication will be supplied as an inert, hollow gel-capsule containing each component medication (aspirin 81 mg, prasugrel 10 mg, rosuvastatin 40 mg OR aspirin 81 mg, clopidogrel 75 mg, rosuvastatin 40mg) without the need for chemical combination or compounding. Each of the FDA-approved component medications will come from FDA-registered production facilities. We have received an exemption from the FDA for this combination polypill (IND # 163137).	☒ UTSW	☐ Yes
		☒ PHHS	☐ Yes
		☐CMC	☐ Yes
		☐THR	☐ Yes
		☐TSRH	☐ Yes
		☐ Other: _____	☐ Yes

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4.c. Risk:Benefit Analysis of study interventions being tested or evaluated under this protocol

For each study intervention identified in section 6b above, complete a risk:benefit analysis table.

(Two tables are provided, copy & paste additional tables as needed or delete both tables if this study does not test an intervention)

4.c.
Study Intervention #1
Polypill

List each group exposed to this intervention on a separate line. (e.g., experimental, control, Arm A, Arm B, etc) **Or** state All Groups/Subjects	For each group, list the **benefits** of this intervention. (Benefits can be directly from the intervention or from a monitoring procedure likely to contribute to the subject's well being). If there are no benefits, state "none".
Polypill Group	None

If you are requesting a Waiver of Informed Consent, complete the table below.

If you have a consent form, **list the reasonably foreseeable risks in the consent form (and do not complete this section).**

List the risks according to the probability (likely, less likely or rare) and magnitude (serious or not serious).
(include: 1) expected adverse events; 2) rare and serious adverse events; 3) all other psychological, social, legal harms)
Do not delete frequency. Frequency must be estimated because it will assist you with determining which adverse events will require prompt reporting.

	Not serious	**Serious**
Likely These risks are expected to occur in more than **20** out of **100** subjects.	•	•
	Not serious	**Serious**
Less likely These risks are expected to occur in **5-20** subjects or less out of **100** subjects.	•	•
		Serious
Rare These risks are expected to occur in less than **5** subjects out of **100**		•

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	4.d. List ALL other research procedures or components not listed in table 4.b. ***The combination of Tables 4b and 4d should account for all of the research procedures that will take place during this study.*** Consider grouping similar procedures under a single component (e.g., blood work, CT = safety assessments)			
#	**Research component** • **individual procedures** *example:* **Eligibility Assessments** • History and physical • Questionnaire • Laboratory tests *Add or delete rows as needed*	**Column A** **Local Standard Practice** Indicate the number of times each procedure will be performed as stipulated in the research plan **that would be performed if the participant were not participating in the study.**	**Column B** **Research Only** Indicate the number of times each procedure will be performed solely for research purposes *(meaning that the participant would not undergo the same number of procedures or would not undergo the procedure(s) at the same frequency if they were not participating in the study)*	**Column D** **Risks** **If you are requesting a Waiver of Informed Consent, complete the table below.** List the reasonably expected risks for each procedure or group of procedures under the following categories as appropriate: • Serious and likely; • Serious and less likely; • Serious and rare; • Not serious and likely; • Not serious and less likely
1	**Eligibility Assessments**			
	Medical History	0	1	Loss of confidentiality, not serious and less likely
	Physical exam	0	1	Temporary discomfort; not serious and less likely
	Questionnaires	0	1	Loss of confidentiality; not serious and less likely
	Laboratory tests via blood draw	0	1	Not serious and less likely: The risks of drawing blood are uncommon and may include bleeding, minor infection, and bruising. Commonly, having blood drawn is painful, and rarely can lead to infection at the site of the blood draw. The amount of blood drawn is small and represents an exceedingly small percentage of the total blood volume and will not represent a significant risk to the subject.
2	**Research Component**			
	MMAS-8	0	1	Loss of confidentiality; not serious and less likely
	Medical History and	0	1	Loss of confidentiality, not serious and less likely
	Physical Exam	0	1	Temporary discomfort; not serious and less likely
	Questionnaires	0	1	Loss of confidentiality, not serious and less likely
	Laboratory tests via blood draw	0	1	Not serious and less likely:

				The risks of drawing blood are uncommon and may include bleeding, minor infection, and bruising. Commonly, having blood drawn is painful, and rarely can lead to infection at the site of the blood draw. The amount of blood drawn is small and represents an exceedingly small percentage of the total blood volume and will not represent a significant risk to the subject.
3	**Insert component 4 here**			
	Insert procedure here			
	Insert procedure here			
	Insert procedure here			
4	**Insert component 4 here**			
	Insert procedure here			
	Insert procedure here			
	Insert procedure here			

5. Safety Precautions. *(Describe safeguards to address the serious risks listed above.)*

a. Describe the procedures for protecting against or minimizing any potential risks for each of the more than minimal risk research procedures listed above.

Greater than minimal risk (also described in the consent form):
There are potential risks and side effects from each drug in the Polypill:

Prasugrel-Containing Polypill:

Aspirin – This drug is used for the treatment of acute coronary syndrome. Doses of aspirin vary, but this study will utilize low-dose 81 mg aspirin administered daily. Aspirin is one of the oldest medications utilized and is the cornerstone of therapy for acute coronary syndrome. Aspirin produced statistically significant and clinically important reductions in the risk of subsequent myocardial infarction, stroke, and vascular death. The drug is an antiplatelet medication.

- There are no common serious side effects associated with this medication. However, as with all antiplatelet drugs, bleeding is associated with aspirin, and hemorrhage may occur at virtually any site.
- **Rare and serious side effects:** Dyspepsia, gastrointestinal ulcer, bleeding.
- Patients who are trying to become pregnant or are pregnant should avoid aspirin.

Prasugrel – This drug is used for treatment of acute coronary syndrome and is an antiplatelet medicine. This drug is used to prevent clots forming in blood vessels after a procedure called percutaneous coronary intervention. This medication has been FDA approved and has been shown to be efficacious after myocardial infarction.

- Prasugrel can cause significant, sometimes fatal, bleeding. Prasugrel should not be used in patients with a history of transient ischemic attack (TIA) or stroke.
- **Rare and serious side effects:** The most common side effect is bleeding. Other side effects include hypertension (8%), headache (6%), nausea (5%), nosebleed (6%).
- Because fetal risk cannot be ruled out with the use of this medication, patients who are pregnant or trying to become pregnant should not take this medication.

Rosuvastatin– This drug is a statin that regulates the amount of cholesterol and other lipids made by your body and helps reduce the risk of heart disease and repeat heart attack. Rosuvastatin is FDA approved and belongs to a class of medications known as statins.

- **Less Likely, some may be serious effects:** All statin medications can cause myalgias, or muscle aches. The highest risk is within the first year of use. Incidence ranges from 2% to 13%. **Rare and serious side effects:** Liver function test abnormalities. Upon discontinuation or dose reduction, liver test levels return to or near pretreatment levels (2%). New onset diabetes can occur in 3% of the patient population.
- Because fetal risk cannot be ruled out with the use of this medication, patients who are pregnant or trying to become pregnant should not take this medication.

Clopidogrel-Containing Polypill:

Aspirin – This drug is used for the treatment of acute coronary syndrome. Doses of aspirin vary, but this study will utilize low-dose 81 mg aspirin administered daily. Aspirin is one of the oldest medications utilized and is the cornerstone of therapy for acute coronary syndrome. Aspirin produced statistically significant and clinically important reductions in the risk of subsequent myocardial infarction, stroke, and vascular death. The drug is an antiplatelet medication.

- There are no common serious side effects associated with this medication. However, as with all antiplatelet drugs, bleeding is associated with aspirin, and hemorrhage may occur at virtually any site.
- **Rare and serious side effects:** Dyspepsia, gastrointestinal ulcer, bleeding.
- Patients who are trying to become pregnant or are pregnant should avoid aspirin.

Clopidogrel – This drug is used for treatment of acute coronary syndrome and is an antiplatelet medicine. This drug is used to prevent clots forming in blood vessels after a procedure called percutaneous coronary intervention. This medication has been FDA approved and has been shown to be efficacious after myocardial infarction.

- Clopidogrel can cause significant, sometimes fatal, bleeding.
- **Rare and serious side effects:** The most common side effect is bleeding, with major bleeding ≤4%, life-threatening ≤2, minor bleeding 4% to 5%. Other side effects include a hemorrhagic stroke or intracranial hemorrhage.
- Because fetal risk cannot be ruled out with the use of this medication, patients who are pregnant or trying to become pregnant should not take this medication.

Rosuvastatin– This drug is a statin that regulates the amount of cholesterol and other lipids made by your body and helps reduce the risk of heart disease and repeat heart attack. Rosuvastatin is FDA approved and belongs to a class of medications known as statins.

- **Less Likely, some may be serious effects:** All statin medications can cause myalgias, or muscle aches. The highest risk is within the first year of use. Incidence ranges from 2% to 13%. **Rare and serious side effects:** Liver function test abnormalities. Upon discontinuation or dose reduction, liver test levels return to or near pretreatment levels (2%). New onset diabetes can occur in 3% of the patient population.
- Because fetal risk cannot be ruled out with the use of this medication, patients who are pregnant or trying to become pregnant should not take this medication.

Minimizing Confidentiality Risks
Consent forms, medical history data, and study data are stored in secured files, either in locked file cabinets or in a locked room separate from medical records and coded such that all subject identifiers have been removed. As an additional precaution all HIPAA regulated information is stored in an electronic file separate from other study data. Only approved study staff (Drs. Wang and Pandey) will be given authorization to access the database. Blood samples are processed and labeled with barcode labels that include the subjects electronically generated study code and date of sample collection. The blood samples are stored in locked freezers in the study Laboratory; only approved study staff has access to the keys for each freezer. Access to the electronic freezer inventory of the specimens is kept on a secure password protected computer.

Reporting Adverse Events: Each subject will be evaluated for any adverse events. Any event that is reported to either the principal Investigator or his designated research associates by the subject or medical staff caring for the subject and which meets the criteria will be documented as such. Any event that is reported will then generate an adverse event report, which will be submitted to the UTSW IRB, and FDA. The report will include a description of the event, when and how it was reported, as well as any official chart records or documentation to corroborate the event or the reporting of the event. All adverse events will be graded as mild, moderate, or severe, in accordance with the grading scale below. Any severe and/or unanticipated adverse event will be immediately reported to the safety officer, IRB, and FDA. All other adverse events will be reported in a timely fashion to the safety officer, IRB, and FDA preferably within 2 weeks of the date of the event. All adverse events will be summarized annually and submitted to the IRB and FDA.

b. Where appropriate, discuss provisions for ensuring necessary medical or professional intervention in the event of adverse events, or unanticipated problems involving subjects.

Reporting Adverse Events: Each subject will be evaluated for any adverse events. Any event that is reported to either the principal investigator or his designated research associates by the subject or medical staff caring for the subject and which meets the criteria will be documented as such. Any event that is reported will then generate an adverse event report, which will be submitted to the local institutional IRB, and FDA. The report will include a description of the event, when and how it was reported, as well as any official chart records or documentation to corroborate the event or the reporting of the event. All adverse events will be graded as mild, moderate, or severe, in accordance with the grading scale below. Any severe and/or unanticipated adverse event will be immediately reported to the IRB, and FDA. All other adverse events will be reported in a timely fashion to the IRB, and FDA preferably within 2 weeks of the date of the event. All adverse events will be summarized annually and submitted to the IRB and FDA.

The UTSW IRB requires that the following events be reported to the IRB:

a) Any event that requires prompt reporting (e.g. serious adverse events);
b) Accidental or unintentional change to the IRB-approved protocol that involves risks or has the potential to recur;
c) Deviation from the protocol taken without prior IRB review to eliminate apparent immediate hazard to a research participant;
d) Publication in the literature, safety monitoring report including a Data and Safety Monitoring Report, Interim result, or other finding that indicates an unexpected change to the risk/benefit ratio of the research;
e) Adverse event that is both a serious adverse event and an unexpected adverse event, which is in the Investigator's opinion is more likely than not to be related to the research procedures;

Adverse event reporting: It is proposed that events possibly related to the study will be graded by the investigators in the following manner:

Adverse Event (AE) Grading Scale:

0 = No Adverse Event or within normal limits

1 = Mild Severity: Transient laboratory test alterations indicating injury without long-term risk; discomforts noted but no disruption of daily activities; no therapy, or only symptomatic therapy required

2 = Moderate Severity: Laboratory test alterations indicating injury without long-term risk; discomfort sufficient to modify normal daily activity; specific therapy required (i.e., more than symptomatic)

3 = Serious Severity: Laboratory test indicating a serious health threat or permanent injury; incapacity, inability to work, inability to perform normal daily activity; hospitalization required or prolonged; emergency treatment required; life threatening events; death

f) Breech in confidentiality that may involve risk to that individual or others;
g) Complaint of a participant that indicates an unanticipated risk or which cannot be resolved by the research staff; or
h) Other event that is unanticipated, involved risk to participants or others and was possibly related to the research procedures.

Adverse events of a serious severity thought to be related to the research protocol will be reported to the UTSW IRB and Drs. Wang and Pandey within 24 hours of occurrence and the specific study will cease to perform the suspect procedure under review. The IRB will have the responsibility to confirm the severity of the adverse event, determine if it is likely that the adverse event was related to the study, and make recommendations for continuation, modification or cessation of the study. Data monitoring will routinely be performed by Drs. Pandey and Wang and in response to the reports of serious adverse events.

c. Will the safeguards be different between/among groups?

☐ Yes ☒ No

N/A