Clopidogrel and lansoprazole versus aspirin and lansoprazole to prevent recurrent ulcer bleeding

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A. Rationale

Use of aspirin, plavix or both has been on the rise for primary prevention MI, CVA and PVD. The increase use of anti-platelet agent increases the incidence of upper gastrointestinal bleed.

Aspirin doubles the risk of gastrointestinal bleeding. It inhibits prostaglandin production in the stomach thereby disrupting its mucosal integrity. Plavix or clopidogrel inhibits platelet aggregation. It binds to platelet ADP receptor which prevents ADP dependent activation of Gp2b3a which fibrinogen needs to bind to platelet. Plavix causes less damage to the gastric mucosa and has a lower incidence of GI bleed compare to aspirin. In addition, history of GIB increases your risk of subsequent GIB.

In the Caprie trial which span 2 years, the incidence of UGI bleed was 2.48% on plavix and 3.31% on aspirin. Based on the CAPRIE trial, ACC-AHA recommended that patients who could not tolerate aspirin because of UGIB take plavix instead. In response, Chan et al did a prospective randomized double blinded clinical trail that looks the incidence of recurrent UGIB on clopidogrel and aspirin with proton pump inhibitor. They looked at patient admitted with UGIB from aspirin induced ulcer and randomized them to receive aspirin and esomeprazole and clopidogrel alone and looked at the rate of recurrent bleed in each group. In the study, the clopidogrel arm had higher incidence of rebleed of 8.6% compare to aspirin and proton pump inhibitor with an incidence of 0.7%. Base on these results, Chan concluded that patients admitted with upper GIB should receive aspirin and a protein pump inhibitor to prevent recurrent bleed.

The purpose of my study is to look at the incidence of recurrent UGIB in patients with documented UGIB on aspirin and lansoprazole compare to clopidogrel and lansoprazole. Since clopidogrel alone has a lower incidence of GIB, the treatment arm on clopidogrel and lansoprazole should have even lower incidence of bleed.

B. Study Design

Multi center 24 month prospective randomized double blind trial

Randomization will be carried out using computer generated list of random numbers. A blinded staff member will then assign the treatment according to consecutive numbers that ae kept in sealed envelope. All medications are re-packaged with aspirin and plavix in identical red capsule and corresponding prevacid tablets.

The power for the study is set at 80% with alpha set at 5%. The sample size is determined using the 2 proportion chi square test. We are looking for an incidence rate of 1% in the aspirin and lansoprazole group based on the Chan study and looking for a 50% reduction in the clopidogrel and lansoprazole group. A sample size of 5066 in each treatment arm will be needed to sufficiently power this study. Assuming 10% will not follow up, we will recruit 11000 patients for the study. The study will use an intention to treat analysis with survival analysis using the Kaplan Meir curve and Cox proportional hazard regression model.

We will enroll patients presenting to the emergency room with upper GIB on aspirin or plavix or both medications wih symptoms of hematemasis or melena or drop in hemoglobin by 2g/dl from baseline. All patients will be placed on prevacid drip on admission and transition over to po bid within 72 hrs. All patients will also have Esophagogastroduodenoscopy or EGD within 24 hours of admission to document an ulcer. During the EGD, biopsy will be taken at 3 sites from the antrum and 2 from the body. They were

will be stained for helicobacter pylori. Patient with HP infection wwill be treated with 2 weeks of prevacid and antibiotics.

On day 7, patients are trandomized to receive plavix 75mg and prevacid 30mg po bid or aspirin 81mg and prevacid 30mg po BID. After 1 month of the study, the prevacid will be changed to once a day.

Follow up:

Month 1, then Month 2 then every three month for 2 year.

On each visit, patients are asked symptoms of GIB like melena, hematemesis and CBC was drawn in each visit. Compliance is measure by filling out monthly pill box and then counting the pill left. Also we will make monthly phone calls to assess for compliance

In addition, patients are asked to fill out monthly questionnaires regarding NSAID use and other new medications.

Primary End Point: Recurrent UGIB define by hematemasis, melena, ulcer or bleeding erosion on EGD, and drop in hemoglobin by 2 points. Ulcer is defined at least 0.5cm in diameter with some depth. Bleeding erosion is defined by flat mucosal break with presence of blood in the stomach

Secondary End Point: Lower GIB defined by hemoglobin drop by 2, bright red blood per rectum or melena. All patients with lower GIB will receive colonoscopy to locate the source of bleed. If colonoscopy is negative, a capsule study will be performed. The study will also look at extra-gastrointestinal bleed like intracranial bleed.

C. Study Procedure

Esophagogastroduodenoscopy (EGD)

All patients enrolled in the study on initial presentation of upper GIB will receive an EGD to document a bleeding ulcer. During the procedure which last about 30-60 minutes, the patient will be given a sedative and an analgesic for mild sedation. A local anesthetic is then given in the mouth and mouth piece given to protect the teeth. The patient is then placed on their side and the endoscope inserted into the mouth and advanced until the stomach and duodenum is visualized. During the procedure, biopsy of the gastric mucosa will be performed.

D. Study Drug

Clopidogrel / Plavix

- approved drug especially for primary prevention in patient at risk for atherosclerotic disease
- given at 75mg by mouth per day, the recommended daily dose

Side effect: >10%: Gastrointestinal: The overall incidence of gastrointestinal events (including abdominal pain, vomiting, dyspepsia, gastritis and constipation) has been documented to be 27% compared to 30% in patients receiving aspirin.

3% to 10%:
Cardiovascular: Chest pain (8%), edema (4%), hypertension (4%)
Central nervous system: Headache (3% to 8%), dizziness (2% to 6%), depression (4%), fatigue (3%), general pain (6%)
Dermatologic: Rash (4%), pruritus (3%)
Endocrine & metabolic: Hypercholesterolemia (4%)
Gastrointestinal: Abdominal pain (2% to 6%), dyspepsia (2% to 5%), diarrhea (2% to 5%), nausea (3%)
Genitourinary: Urinary tract infection (3%)
Hematologic: Bleeding (major 4%; minor 5%), purpura (5%), epistaxis (3%)
Hepatic: Liver function test abnormalities (<3%; discontinued in 0.11%)
Neuromuscular & skeletal: Arthralgia (6%), back pain (6%)

Respiratory: Dyspnea (5%), rhinitis (4%), bronchitis (4%), cough (3%), upper respiratory infection (9%)
Miscellaneous: Flu-like syndrome (8%)

1% to 3%:
Cardiovascular: Atrial fibrillation, cardiac failure, palpitation, syncope
Central nervous system: Fever, insomnia, vertigo, anxiety
Dermatologic: Eczema
Endocrine & metabolic: Gout, hyperuricemia
Gastrointestinal: Constipation, GI hemorrhage, vomiting
Genitourinary: Cystitis
Hematologic: Hematoma, anemia
Neuromuscular & skeletal: Arthritis, leg cramps, neuralgia, paresthesia, weakness
Ocular: Cataract, conjunctivitis

<1% (Limited to important or life-threatening): Acute liver failure, agranulocytosis, allergic reaction, anaphylactoid reaction, angioedema, aplastic anemia, bilirubinemia, bronchospasm, bullous eruption, erythema multiforme, fatty liver, fever, granulocytopenia, hematuria, hemoptysis, hemothorax, hepatitis, hypersensitivity, hypochromic anemia, interstitial pneumonitis, intracranial hemorrhage (0.4%), ischemic necrosis, leukopenia, lichen planus, maculopapular rash, menorrhagia, neutropenia (0.05%), ocular hemorrhage, pancreatitis, pancytopenia, pulmonary hemorrhage, purpura, retroperitoneal bleeding, serum sickness, Stevens-Johnson syndrome, stomatitis, thrombocytopenia, thrombotic thrombocytopenic purpura (TTP), toxic epidermal necrolysis, urticaria, vasculitis

Aspirin

- approved drug for anti-inflammatory, acute MI, CABG, stent, carotid endarterectomy, stroke prevention/ TIA,
- 81mg by mouth daily, approved for primary prevention of atherosclerotic disease

Side Effect: Central nervous system: Fatigue, insomnia, nervousness, agitation, confusion, dizziness, headache, lethargy, cerebral edema, hyperthermia, coma

Cardiovascular: Hypotension, tachycardia, dysrhythmias, edema

Dermatologic: Rash, angioedema, urticaria

Endocrine & metabolic: Acidosis, hyperkalemia, dehydration, hypoglycemia (children), hyperglycemia, hypernatremia (buffered forms)

Gastrointestinal: Nausea, vomiting, dyspepsia, epigastric discomfort, heartburn, stomach pain, gastrointestinal ulceration (6% to 31%), gastric erosions, gastric erythema, duodenal ulcers

Hematologic: Anemia, disseminated intravascular coagulation, prolongation of prothrombin times, coagulopathy, thrombocytopenia, hemolytic anemia, bleeding, iron-deficiency anemia

Hepatic: Hepatotoxicity, transaminases increased, hepatitis (reversible)

Neuromuscular & skeletal: Rhabdomyolysis, weakness, acetabular bone destruction (OA)

Otic: Hearing loss, tinnitus

Renal: Interstitial nephritis, papillary necrosis, proteinuria, renal failure (including cases caused by rhabdomyolysis), increased BUN, increased serum creatinine

Respiratory: Asthma, bronchospasm, dyspnea, laryngeal edema, hyperpnea, tachypnea, respiratory alkalosis, noncardiogenic pulmonary edema

Miscellaneous: Anaphylaxis, prolonged pregnancy and labor, stillbirths, low birth weight, peripartum bleeding, Reye's syndrome

Lansoprazole

- approve for GERD, peptic ulcer disease, NSAID associated gastric ulcer, erosive esophagitis
- given 30mg by mouth daily

Side Effect

1% to 10%:
Central nervous system: Headache (children 1-11 years 3%, 12-17 years 7%)
Gastrointestinal: Abdominal pain (children 12-17 years 5%; adults 2%), constipation (children 1-11 years 5%; adults 1%), diarrhea (4%; 4% to 7% at doses of 30-60 mg/day), nausea (children 12-17 years 3%; adults 1%)

<1% (Limited to important or life-threatening): Abnormal vision, agitation, allergic reaction, ALT increased, anaphylactoid reaction, anemia, angina, anxiety, aplastic anemia, arrhythmia, AST increased, chest pain, convulsion, depression, dizziness, dry eyes, dry mouth, erythema multiforme, esophagitis, gastrin levels increased, gastrointestinal disorder, glucocorticoids increased, globulins increased, hemolysis, hemolytic anemia, hepatotoxicity, hyperglycemia, LDH increased, maculopapular rash, pancreatitis, photophobia, rash, RBC abnormal, taste perversion, Stevens-Johnson syndrome, thrombocytopenia, tinnitus, toxic epidermal necrolysis (some fatal), tremor, vertigo, visual field defect, vomiting, WBC abnormal

E. Study Questionnaires

1) How many times have you used Motrin, Aleve, Excedrin or other types of NSAIDs this month?
2) Have you experience any vomiting of blood or noticed any blood in your stool? Have you noticed any black tarry stool?
3) Have you started any new drugs lately?
4) How much alcohol have you drunk in the past month?
5) Are you taking all of the prescribe medication?

F. Study Subjects

Enrollment Criteria:

Patient presenting to the emergency room with upper GIB in the setting of aspirin or plavix or both medications with symptoms of hematemasis or melena or drop in hemoglobin by 2g/dl from baseline. All patients must have eophagogastroduodenoscopy or EGD within 24 hours of admission to document an ulcer.

Exclusion Criteria:

Pt on other anticoagulation, history of gastric cancer, history of gastric surgery, allergy to aspirin or plavix, with recent drug eluting stent placement requiring plavix, thrombocytopenia.

G. Recruitment of subject

All hospital or emergency room admissions with a diagnosis of upper gastrointestinal bleed and taking aspirin, plavix or both and needing an EGD

H. Confidentiality of Study Data

All patients will be assign a number and all patient identifier will be removed from the file. The number and name of patient assignment will be kept in a secure location.

I. Conflict of Interest

There is no conflict of interest

J. Location of the study

All major academic centers in NYC, Philadelphia and Boston

K. Potential Risk

There is still a potential risk of GIB when taking aspirin or plavix although the risk should decrease with the lansoprazole. In addition, there is a risk of extra gastrointestinal bleed with taking plavix or aspirin.

L. Potential Benefit

You may not benefit from participation in this study if you happen to develop a recurrent bleed

M. Compensation

There will be no monetary compensation for this study. The patient will receive free proton pump inhibitor for the 2 years. In addition, they will have free lab draws and physical with each clinic visit.