The aspirin and plavix cardiovascular disease reduction in diabetics trial (APCRT)

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A. Study Purpose and Rationale

In 2005, the Centers of Disease Control (CDC) reported an estimated 20.8 million Americans, or seven percent of the U.S. population, had diabetes. Of this number, a purported 6.2 million persons were unaware that they carried this diagnosis. Diabetes is associated with accelerated atherosclerosis, and hence the link between diabetes and cardiovascular disease (CVD) is a well established one. Compared to their non-diabetic counterparts, diabetics (type 2) are two-to four times at increased risk for CAD (Diabetes. 2005; 54: 2430). Additionally, diabetics are at increased risk for recurrent ischemic events than non-diabetics. It is believed that platelet dysfunction plays a salient role in augmenting the incidences of atherothrombotic complications among diabetics.

According to national statistics, in 2003, 5.2 million Americans with diabetes aged 35 years and older self-reported being diagnosed with a cardiovascular disease condition (ie, coronary heart disease, stroke, or other heart condition). Of this group, 3.5 million reported being diagnosed with coronary heart disease (self-reported coronary heart disease, angina, or heart attack) and 1.5 million reported being diagnosed with a stroke (CDC

Recently, the April 20th issue of the New England Journal of Medicine published the CHARISMA trial comparing dual antiplatelet therapy with low-dose aspirin plus plavix versus placebo plus low-dose aspirin among a population of 15,603 patients at high risk for atherothrombotic events, that is persons with either clinically evident cardiovascular disease or multiple risk factors. The study found no significant benefit associated with plavix plus aspirin as compared with placebo plus aspirin in reducing the incidence of the primary end point of myocardial infarction, stroke, or death from cardiovascular causes. Furthermore, among asymptomatic patients they found a 20 percent relative increase in the rate of primary events in the dual therapy arm.

The COMMIT trial, another randomized placebo-controlled multicenter trial looking at plavix plus aspirin versus aspirin plus placebo in 45, 852 patients hospitalized for an acute myocardial infarction found a reduced risk for the composite outcomes of death, reinfarction, or stroke within a 28 day period.

The landmark U.K. Prospective Diabetes Study found a 16% reduction in myocardial infarction and a 12% reduced risk of any diabetes related deaths (defined as fatal MI or sudden death, fatal stroke, death from peripheral vascular disease, death from renal disease and death from hyper/hypoglycemia) with just intensive glucose control among subjects without the addition of dual anti-platelet therapy.

This study proposes to look at the "asymptomatic" arm of the CHARISMA study, that is specifically diabetics with no prior history of MI, strokes, PAD, or microvascular complications and assess whether dual antiplatelet therapy with aspirin and plavix will lead to a reduced risk in the primary composite endpoint of cardiovascular (CVD) mortality, non-fatal myocardial infarction, and non-fatal stroke. The study's designated secondary endpoints will be first MI, stroke, TIA, hospitalization for unstable angina, CVD mortality, and revascularization (with either PCI or CABG). A subgroup analysis of the event rates of the primary endpoints for diabetics with the metabolic syndrome will also be performed. We hypothesize that dual antiplatelet therapy with aspirin and plavix will prove successful in reducing our study's composite primary endpoints of CVD mortality, non-fatal MI, and non-fatal stroke. As prior studies have shown, individuals with the metabolic syndrome are at greater risk for cardiovascular events, we, therefore, anticipate a more impressive reduction in primary outcome measures among the subgroup of diabetics who meet criteria for the metabolic syndrome.

B. Study Design

This study is proposed to be a six year prospective, interventional, randomized, placebo-controlled, double-blinded (patient, investigators, and patient clinicians will be blinded to study arm), multi-center trial. The participants will be randomized either to the interventional arm of the study plavix plus aspirin or the control arm aspirin plus placebo, with the primary endpoint being a composite of cardiovascular disease mortality (CVD mortality defined as fatal MI and/or fatal stroke), non-fatal myocardial infarction (MI), non-fatal stroke. Study participants will be type 2 diabetics between the ages of 35 years and 79. A subset of patients with both diabetes and the metabolic syndrome as defined by the national cholesterol education program criteria which includes the following risk factors: individuals with truncal obesity in men a waist of 102 cm and in women 88 cm, HDL of < 40 in men and <50 in women, elevated fasting triglycerides of >150, and BP >1301>80 will be studied. As diabetics the subjects will have already met the criteria for impaired fasting glucose.

C. Statistical Analysis

There will be 1,314 subjects in each arm of the study. Chi-square analysis will be used to analyze all categorical data, whereas continuous variable will be analyzed using a t-test. Multivariable Cox proportional-hazards regression, adjusted for age, gender, race, smoking, glycemic control will be used to examine the risk of CVD mortality, non-fatal MI, non-fatal stroke. The study was powered to see a 25% reduction in the risk of the primary endpoint (composite outcome of CVD mortality, nonfatal MI, and nonfatal stroke) in the plavix plus aspirin arm (especially given evidence-based medicine interventions). As in the CHARISMA trial, our group anticipates a 3.1 percent annual event rate in the control group during the 60 to 72 month follow-up. A sub-group analysis of those participants with the metabolic syndrome will be performed to see if there is an increased risk of the primary endpoints in such individuals. Data will be analyzed according to the intention to treat principles. During the six year study periods, five preplaimed interim analyses will be conducted with an independent data safety monitoring board evaluating for adverse events in the aspirin plus plavix arm. As in similar studies using dual antiplatelet therapy, the primary safety end point was severe bleeding according to the "GUSTO (Global Utilization of Streptokinase and Tissue Plasminogen Activator for Occluded Coronary Arteries) definition, which will include fatal bleeding and intracranial hemorrhage, or bleeding that caused hemodynamic compromise requiring blood or fluid replacement, inotropic support, or surgical intervention. Also according to the GUSTO criteria, moderate bleeding (defined as bleeding that led to transfusion but did not meet the criteria for severe bleeding) will be evaluated (CHARISMA, 1709)." Any individuals who experience such events will be unblended and removed from study.

D. Study Procedure (Conceptual and Operational Definitions)

As stated in the previous section, the primary study endpoint will be the composite outcome of CVD mortality (defined as fatal MI and/or fatal stroke), non-fatal MI, and non-fatal stroke. At the time of death, the patient's data will be censored. Mortality data is to be ascertained by using computerized matching of two national databases, the National Death Index and the Social Security Administration' Death Master File. CHD mortality data will be identified by the International Classification of Diseases, ninth revision (codes 410 through 414). CVD mortality was defined by codes 390 through 459. Mortality information will also be extracted from death certificates. Regarding non-fatal outcomes, data will be ascertained by patient interview and questionnaires during follow-up visits and will be further confirmed by computerized patient chart review and/or contacting the patient's primary physician, and again by using ICD-9 codes. Principal secondary outcomes will include: revascularization (PCI or CABG), TIA, hospitalization for unstable angina, non-fatal MI, non-fatal stroke, and CVD mortality.

The following baseline data will be obtained from each subject: age; gender; self-reported race/ethnicity (with race classified as non-Hispanic white, non-Hispanic black, Asian/Pacific Islander, Native American, and other. Ethnicity classified as Mexican-American and all others Hispanic

American); premature family history of coronary artery disease (CAD), presence of hypertension (the mean blood pressure after 3 sifting readings; with hypertension defined as a blood pressure >130/>80); smoking history (never, former, current); fasting HDL (with patients meeting criteria for metabolic syndrome if HDL is <40 in males and <50 in females); fasting triglycerides (with patients meeting criteria for metabolic syndrome if triglyceride levels are >150); HgbAlc (with values above >6.5% indicating poor glycemic control and values <6.5% indicating good glycemic control); presence of microalbuminuria; insulin therapy (yes or no); listing of all current medications (anti-hypertensives, diuretics, statins); and hip to waist measurements (with patients meeting criteria for metabolic syndrome if they are a man with waist >102 cm or a woman with a waist circumference of >88 cm). Following the initial visit, follow-up visits will be at 3mos, 6mos, 9mos in the first year and every 6mos thereafter. Of the laboratory values listed, lipid profiles, microalbumin (albumin: creatinine ratios) will be collected yearly and Hgb Ale levels will be collected biannually. Although this information does not pertain directly to the primary endpoints, several of these data will be used to identify subjects with the metabolic syndrome. These patients will then be further assessed in a subgroup analysis. All laboratory data will be analyzed at a central lab.

E. Study Drugs

The patients in the study will be given two of three medications. All patients will be asked to take 81 mg of aspirin by mouth daily and either 75 mg of plavix by mouth daily OR placebo which will be similar in appearance to plavix. The known side effect of active medications increased risk of bleeding.

F. Medical Device

No medical devices will be studied in this trial.

G. Study Subjects/Recruitment of Subjects

Eligible patients will be defined as men and women between the ages of 35 and 79 with type two diabetes mellitus, without evidence of significant end-organ damage. Subjects will be recruited from outpatient clinic sites. Exclusion criteria will include individuals with contraindications to aspirin or plavix therapy (ie aspirin allergies), persons w/ a recent history of PUD +/- gastrointestinal bleed, patients with longterm NSAID and antithrombotic medication (ie coumadin) use, persons already requiring plavix therapy, persons with a known CAD (ie, past MI, revascularization either CABG or PCI, persons w/ unstable angina), persons with prior stroke, known PAD, ESRD, and microvascular complications of diabetes, or patients with non-cardiac related morbidity which would prevent them from completing the six year follow-up study period (ie patients with cancer).

Written informed consent will be obtained from all participants once the study institutions 1RB's have approved the study. Patients will be randomized to either receive aspirin and plavix versus aspirin plus placebo. Patients will be recruited from the satellite affiliate outpatient clinic sites.

To reiterate, patients will have a comprehensive evaluation the first month of the study where baseline demographic information (HTN, family history of CAD, past or present tobacco history, level of activity, race/ethnicity, gender, age). Baseline laboratory data will be obtained as well as waist circumference will be collected for our subset analysis of patients who meet criteria for the metabolic syndrome. Following the initial visit, subjects will be seen at three month intervals during the first year, and then every six months thereafter.

Compliance with medical therapy will be assessed by pill count and patient questionnaire and interview during follow-up periods.

H. Confidentiality of Study Data

All study subject information/data will be coded using a unique code number generated at random by a study computer programmer which will not be known any investigators, primary physicians. Code will be broken in the event of a severe or moderate adverse event.

I. Potential Conflict of Interest

At the time of the writing of this proposal, neither the investigators nor the University have a proprietary interest in either plavix or aspirin nor does any individual investigator stand to benefit financially in any other way from the results of this investigation. If at any time during the six years that this study is being conducted there arises a conflict of interest, the study investigator in question will be asked to remove him or herself from his/her involvement in this trial.

J. Location of the Study

This study is designed as a multicenter trial to be conducted at all institutions whose IRB's have approved this trial. CPMC will be one of several sites.

K. Potential Risks

Has been already discussed in the statistical analysis section of this packet.

L. Potential Benefits

If the experimental arm does indeed demonstrate a statistically significant reduction in the study primary endpoint, all participants randomized to the aspirin plus plavix arm will potentially experience a benefit from their participation in the study. Likewise, if aspirin therapy shows a greater benefit these subjects will stand to benefit.

M. Altrenative Therapies

his study does not involve the use of any experimental therapies; therefore, there is no need to discuss alternative therapies.

N. Compensation to Subjects

There will be no form of monetary compensation provided to the study subjects.

O. Costs to Subjects

The only additional costs patients will incur during their participation in the study is the cost of transportation to and from the study site.

P. Minors as Research Subjects

This study WILL NOT INVOLVE minors as study participants.

Q. Radiation or Radioactive Substances

There will be no use of radiation or radioactive substances in this study.