Screening Asymptomatic Diabetics for Coronary Artery Disease using Diabetic Autonomic Neuropathy as Selection Criteria

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A. Study Purpose and Rational

Diabetics with Autonomic Neuropathy (DAN), or disease of the involuntary nervous system, represent a population at especially high risk for cardiovascular mortality, including death from Myocardial Infarction (heart attack) and Sudden death [2]. They stand to derive a mortality benefit from surgical revascularization (a bypass operation), however due to neuropathy they often do not exhibit symptomatic angina, i.e. these patients often do not have the symptoms of cherst pain. In failing to have symptomatic coronary artery disease (CAD) they are not subject to the same diagnostic procedures that symptomatic patients undergo that are required for the diagnosis and ultimately the management of CAD, most notably a stress test [5]. We propose that screening asymptomatic diabetics, (diabetic patients without chest pain) who have autonomic neuropathy, we will identify a substantional amount of CAD, including that which may constitute a requirement for surgical revascularization.

It has been previously demonstrated that Type 2 Diabetics represent a population at significantly elevated risk for cardiovascular mortality and morbidity even in the absence of established Coronary artery disease. In fact their risk of cardiovascular events has been shown to be equivalent to patients with a history of MI, a mortality of 17% over 7 years of follow-up [1], and when limited to diabetics with autonomic neuropathy this number increases to 9% mortality over a 2 year period [6]. This may represent an association with more severe and long-standing diabetes, kidney disease and/or high blood pressure, or it may be reflective of independent pathological attributes of Cardiac autonomic dysfunction. Diabetics with an anginal syndrome and 3-vessel disease, or its equivalent, have previously been shown to derive a significant mortality benefit from surgical revascularization [3]. The enrollment criteria in the previously mentioned BARI trial included symptomatic angina, which itself excludes a substantial population of Diabetics at risk for Cardiovascular mortality. Previously published reports have identified that from 36 to 65% of Diabetics with Autonomic Neuropathy have silent ischemia i.e. these patients indeed had inadequate blood flow to supply their heart muscle, but failed to perceive the pain which can serve as a warning sign. However these studies failed to correlate the results of noninvasive testing with angiography, which is considered the gold standard in the diagnosis of CAD [4]. Unfortunately the prognosis of diabetics with DAN and silent ischemia has not been clearly identified, but the limited literature that has addressed this question has found a 30% event rate at 3 years [6]. By demonstrating an increased prevalence of CAD in asymptomatic diabetic patients with DAN we can resolve the results of studies done over a period of 20 years with varying sample size and methods. This study will be part of a two-part study with the latter portion aiming to randomize diabetics with DAN to observation or noninvasive examination for CAD and ultimately angiography and revascularization if indicated. The lack of reliable knowledge of the prevalence of 3-vessel CAD in this population precludes the design of a trial to identify a mortality benefit from screening asymptomatic diabetics with DAN. Here we aim to identify an estimate of 3 vessel CAD in this patient population and show that it is significantly larger than in diabetics without DAN. Therefore we hypothesize a 15% incidence of 3-vessel CAD in this population that will be significantly increased compared to appropriately matched diabetics without DAN.

B. Study Design and Statistical Analysis

Patients will be recruited by enrolling all newly diagnosed type 2 diabetic patients who are older than 35 years and have co-morbid hypertension. All patients agreeing to enrollment will undergo 24 hour

ambulatory electrocardiographic monitoring. Patients will be defined as having DAN if frequency analysis of heart rate variability (HRV) shows a leftward shift in LF central frequency (<5.5 ln) or if the number of interval differences of successive NN intervals measured over a 24-hour period are less than 500 [8]. A central Holter reading lab, blinded to patient selection will be responsible for the diagnosis of DAN. Patients will be excluded if they have a history of myocardial infarction, revascularization (defined as angioplasty or CABG), angina, or the inability to perform exercise stress testing. Information on traditional coronary risk factors will be recorded for all patients (presence of hypertension, hyperlipidemia, active smoking, family history). Each patient with DAN and a matched control with DM and without DAN will undergo noninvasive testing for CAD with exercise EKG monitoring by standard Bruce protocol with the addition of thallium scintigraphy. Silent myocardial ischemia will be defined as the presence of a reversible perfusion defect in the absence of anginal chest pain. A central nuclear cardiology lab unaware of presence or absence of DAN will determine if a reversible defect is present. All patients with reversible ischemia will undergo diagnostic coronary angiography; a central angiography lab blinded to presence or absence of DAN will interpret this. The primary endpoint being studied is the presence of 3-vessel CAD. Assuming a prevalence of 3 vessel CAD in the DAN group of 15%, 126 patients with DAN and 126 controls will need to be enrolled to show a significant difference with a 95% confidence interval, this was calculated using the Chi-Squared test for categorical variables. After patient enrollment and diagnostic testing a Yates-Corrected Chi Square for a 2 x 2 Contingency table will be computed and used to determine if the null hypothesis that the probability of 3 v CAD in the DAN group is = to the probability of 3 v CAD in the no DAN group. A Chi Squared test will be used to provide a point and interval estimation for the Odds Ratio (of CAD in DM with vs. without DAN).

C. Study Subjects

Patients with the previously mentioned inclusion and exclusion criteria will be recruited from all type 2 Diabetics at the Associates in Internal Medicine Clinic at CPMC. Any patient for whom the primary physician identifies Type 2 DM as a diagnosis will be approached and informed about the study. Risks will be disclosed, almost entirely consisting of the small but finite risk of undergoing diagnostic coronary angiography if indicated. Because no clear benefit has been proven of screening asymptomatic patients for CAD, this will not be used as incentive to enroll patients. Instead patients will be financially compensated for their time, depending on the extent of testing they require.

D. Bibliography

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