Randomized, Multicenter trial to Compare antihypertensive Treatment with a β-Blocker-(metoprolol) and Procarida XL

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A. Introduction

As many as 50 million Americans have elevated blood pressure (systolic blood preasure of 140 mm. Hg or greater and/or diasotolic blood pressure 90 mm Hg *or* greater. The prevalence of high blood pressure increases with age, is greater for blacks than for whites, and in both races is greater in less educated than more educated people. In young adulthood and early middle age, high blood pressure prevalence is greater for men than for women. Nonfatal and fatal cardiovascular diseases - including coronary heart disease (CHD) and stroke - as well as renal disease and all cause mortality increase progressively with higer levels of both SBP and DBP. Higher levels of either SBP or DBP or both together are associated *with* increased risks *of morbidity,* disability, and mortality. Cardiovascular risks related to blood pressure elevation, dyslipidemia. cigarette use, diabetes melitus,-- physical inactivity and obesity. The *Fifih Report of the* Joint National Committee on Detection, Evaluation, and Treatment of High Blood Pressure outline hypertension as follows:

Category	Systolic, mm Hg	Diastolic, mm. HS
Normal	< 130	<85
High normal	130-139	85-99
Hypertension		
Stage I (mild)	140-159	90-99
Stage 2 (moderate)	160-179	100-109
&W 3 (severe)	190-209	110-119
Stage 4 (very severe)	> 210	>120

Calcium channel blockers (Diltiazem. Nifedipine, Verspamil) modify the entry of calcium into cells by blocking the slow or voltage dependent calcium channels resulting in vasodiltation and in the case of Nifedipine usually a reflex tacycardia. Currently there is controversy am shad acting Nifiedipme and possible association with increased morbidity and mortality in paients with hypertension and underlying CHD. A meta-analysis done by Furberg et al consisted of a dose-response analysis of nifedipine of 16 randomized (placebo vs nifedipine) cliniml trials of which 12 involved patients with myocardial infarction, three trials included patients with unstable angina. and one trial with unstable angina, one third of whom had a prior MI. The 30mm 40mg. and 50mg/day doses of nifedipine, showed no increase in relative risk when compared to placebo. The relative risk for mortality was 1.18 for 60mg/day dose and 2.83 (tripled risk) for the 80 mg/day dose. Short acting calcium antagonists not only increase sympathetic stimulation and cathecholamine but alos activate the renin angiotensin system. Packer suggested that "activation oft he renin angiotensin system may also predispose to occurrence of complex ventricular tachyarrhythmais, either by poteniating the development of calbecholamine -induced anhythmias or by increasing the production of mineralocorticords, which may exacerbate diurefic-induced potassium depletion." On the other hand a study done by Boyko et al (J of American College of Cardiology - July 1996)in patients (11,575) with chronic cardiac disease DOES NOT support the claim dad calcium antagonist therapy in patients with coronary artery disease, whether myocardial infarction. survivors or othes, harbours an increased risk of morality. The question pertaining to long acting Nifedipine (Procardia. XL) has not been addressed.

B. Aim oft he Study

The main aim of the study is to determine whether antibypedensive treatment with a β- blocker – metoprolol differs from treatment with Procardia XL. producing an equal reduction in blood pressure with with respect to the incidence of fatal and non-fatal myocardial infarction (MI), sudden death, stroke, and total morality in middle aged African-American men and women with mild to moderate hypertension.

C. Study design

A prospective randomized multicenter study with spproxhustely 7000 men and women with newly diagnosed hypertension will be divided into two treatment groups and will be followed for 60 months. It is probable that a 30% increase in tbe event rate – MI, stroke, and death in one group can be demonstrated with acceptable statistical certainly, power of about 80%. Logistic regression analysis will be performed on groups categorized by CAD risk factors - age, serum total cholesterol, smoking. and systolic, blood pressure (table 1). Kaplan-meyer survival curves will be used to analyze the mortality data. Chi square analysis will be done on the blood prearure measurements with calculation of means and standard deviation according to general. principles. Diffireaces of $P < 0.05$ will be concsidered statistically significant. Apprommately 15 national academic centers will collaborate. Patients will be recruited from The outpatient clinics. The corrdinating center will be CPMC. All eligible patients will be placed into a data base and will be randomly assigned to either arm of the study by the computer. At no point will patients receive both meloprolol and procardia XL.

Treatment is started with the first dose level; If this dose level does not produce a satisfactory reduction in blood pressure, the dose is then doubled (dose2). If dose 2 does not produce an adequate reduction in blood pressure, then a thiazide diuretic is added; therapeutic goal is SBP < 145 and DBP < 95. The physicians will be blinded as to which medication the patient is receiving; only if there is serious risk of hypertensive complications will a dose be adjusted within the first 2 weeks aficr starting therapy. Visits will be scheduled at two weeks. 2 months, 6th, 9th, 12th month and every 6 months thereafter. Side effects are asaessed at each visit. An annual EKG is recorded along with a chem. 7, urine analysis,

End points: The total mortality, cerebral hemorrhage and thrombosis, myocardial infarction and sudden death are recorded. New cases of heart failure and diabetes mellitus are noted. Each case which is suspected or considered by a center to have reached an end point is scrutinized centrally by an independent group - Safely committee. All possible iinformation needed to make an nomate diagnosis is collected, e.g. patient file, death certificate, and autopsy record.

For a diagnosis of myocardial infarction to be recorded at least two of the following three criteria are to be fulfilled.

1 Central chest pain of more than 15 minutes in duration with onset during the previous 48 hrs or pulmonary edema without previously known valvular disease, or shock without suspicion of acute hyporvolemia or intoxication.
2 Transient elevation of serial creatine kinease (CPK) above normal limits for the lab, with a peak within 24 hours of infarction and an MB fraction of greater than 1.8 %
3 ECG series with the presence of pathological Q-waves and/or the developmeml or disappearance of localized ST elevation combined with the development of T wave inversion in at least 2 ofthe 12 routine standard leads (I, II, III, aVR, aVF, V1, V2, V3, V4, V5, V6)

For a diagnosis of acute fatal MI to be recorded it is either to be stated on the death certificate or in the event ofthe death cedificate being uncertain, macroscopic or microscopic myocardial necrosis is to be demonstrated at the post mortem examination.

Cerebrovascular disease is recorded when there are unequivocal signs of focal, or global neurological deficits of sudden onset with a duration of at least 24 hrs, these findings will be confirmed by non - contrast CT of the head. Fatal cerebrovascular disease is recorded when stated on the death certificate.

Patients who discoutinue the treatment, do not cooperate, or fail to attend follow up sessions are not excluded from the study, analysis will be done on an intent to treat basis.

Randomization - After randomization subjecis are divided into 3 groups according to risk for MI and sudden death (low, medimn, and high). based an risk - smoking. systolic blood pressure, total serum cholesterol (Table 1). Each risk group is divided into three age strata 40-49-, 50-59; 60-64 (table 2)

Table 1:

Systolic- BP	Cholesterol (mmol/L)	Nonsmoker	Ex-smoker	Smoker
> 160	> 8.7	H	H	H
	7.0 – 8.6	M	H	H
	< 7.0	L	M	H
< 160	> 8.7	M	H	H
	7.0-8.6	M	M	H
	< 7.0	L	L	H

Table I

Age	40-49	50-59	60-64
M	medium risk groups		
L	low risk groups		
H	high riA groups		

D. Study drugs

Both procardia XL and metoprolol will be administered orally.

Dosage regimen	Dose I	Dose 2
Metoprolol	100 mg/day	200mg/day
procardia XL	30 mg/day	60 mg /day

Known side effects include sexual dysfunction, orthostasis, pomble bronchospasm in asthmatics, dyslipidemia, bradycardia, and dizziness with beta blockers. Nefidpine XL can cause orthostais, lower extremity edema, dizziness.

E. Description of study procedures

Thee will be strict criteria. for the measurement of blood pressure. Subjects referred by ther clinic phynciam will be suspected of having hypertension. At the initial screening examination the blood pressures obtained will not be used for data analysis. The mean of rour subsequent readings will be obtained. The following protocol will be used: Patients should be seated with their arm bared. supported. and at heart level; They kould not have smoked or injested caffeine within 30 minutes before measurement, Measurement should begin after 5 minutes of rest; The cuff bladder should nearly (at least 80%) or completely encircle the arm; Measurements will be taken with a calibrated electronic device - Hawskley Random Zero- which permits blind registration of the blood pressure; The first two madings me taken at 15 minute intervals, the remaining are taken with the same interval 14 days later.

All eligible patients will be asked standardized questions about prevuois diseases, cardiovascular symptoms and smoking habits. Patients are given a physical exam and a 12 lead EKG, fasting chem. 7, total cholesterol, height, weight, along with tests for albuminuria, glycosuria, hematuria are obtained.. Each year the patient will undergo the same barrage of tests for comparison to baseline.

F. Inclusion/exclusion criteria

African - American mm and women aged 40-65 years old wdh diastolic blood pressure between 90-109 or systolic between 140-179 (mean of four readings) wilt be ernolled in the study. Patients with a

history of CVA, prior MI, verified angina pectoris, or patients with cancer or other diseases with a poor prognosis, cirrhosis of the liver, known alcoholics, AIDS, asthma, COPD, and diabetes will be excIuded. Patients with secondary or maligant hypertension, are also excluded. Patients will be referred by their primary care doctors from the 15 academic centers. The study is limited to African - Americans because of the increased incidence of mortality and morbidity due to hypertension and CHD in this population and the lack of clinical tials to evaluate anti-hypetesive therapy in this group of patients.