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EFFECT OF RENIN ANGIOTENSIN SYSTEM INHIBITION ON CARDIOVASCULAR SEQUELAE IN ELDERLY HYPERTENSIVE PATIENTS WITH INSULIN RESISTANCE

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A Dissertation submitted in partial fulfillment of the requirements for the degree of Doctor of Philosophy at Virginia Commonwealth University.

by

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Dedication

This dissertation is dedicated to my son, Tareq Fadi Oweis. We are impatiently waiting to welcome him to this life. We love him more than anything in this world.

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This dissertation would not have been possible without the support of my beloved ones around me. My father and my mother, Hani and Ekhlas Zreikat, always surrounded me with the greatest love and care on earth. They sacrificed a lot for my sake. They encouraged me to pursue my dream in a foreign country, thousands of miles away from home, despite the difficulty and pain that we all went through. My husband, Fadi Oweis, always loved, supported and encouraged me. His presence by my side is a blessing that God offered me. With him, I spent the happiest moments of my life. I also believe that the best is yet to come. He is the love of my life. My sister, Yara, and my brother, Rami, are the best in the world. They surrounded me with their love and friendship and they always stood by my side. Yara, I will not forget the look on your face at the airport when we said our first goodbye. I love you!

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Table of Contents

List of Tables

List of Figures

Abstract

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CARDIOVASCULAR SEQUELAE IN ELDERLY HYPERTENSIVE PATIENTS

WITH INSULIN RESISTANCE

By Hala Hani Zreikat, PhD

A Dissertation submitted in partial fulfillment of the requirements for the degree of Doctor of Philosophy at Virginia Commonwealth University.

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Background: Insulin resistance may play a pathogenic role in cardiovascular disease (CVD). Resistance to insulin has been associated with obesity, hypertension, and abnormal glucose and lipid metabolism. The constellation of these features among insulin resistant subjects has been called the metabolic syndrome. Prevalence of the metabolic syndrome increases with age and is most common in the elderly. Different criteria have been proposed to define the metabolic syndrome (ATP, WHO, AACE, EGIR). Current management of metabolic syndrome focuses on the specific risk factors

that the patient may have without targeting the underlying insulin resistance. Angiotensin Converting Enzyme Inhibitors (ACEI) and Angiotensin Receptor Blockers (ARB) are widely used antihypertensive medications that may improve insulin sensitivity. We hypothesize that they can be used to reduce the long term cardiovascular complications in elderly hypertensive subjects with evidence of insulin resistance. In this study, we determined the effect of ACEI/ARB on the long term development of CVD in hypertensive non-diabetic elderly patients with the metabolic syndrome, as well as in patients with insulin resistance. **Methods:** Our research project utilizes the Cardiovascular Health Study (CHS) dataset. This dataset is a community based observational study where elderly participants were randomly selected and followed up for 11 years and the time to any cardiovascular event was recorded. In our project, we included hypertensive, non-diabetic individuals, with evidence of metabolic syndrome or insulin resistance, but had not experienced cardiovascular events at baseline. Cox regression model was used to evaluate the effect of ACEI/ARB on the time to the first cardiovascular event compared to the other antihypertensive medications adjusting for possible confounders such as age, race, gender, smoking status, triglycerides, LDL levels, systolic blood pressure, development of diabetes, congestive heart failure (CHF) and the number of anti-hypertensives. **Results:** In elderly hypertensive non-diabetic subjects with the metabolic syndrome according to the ATP and the WHO criteria, the hazard ratio for CVD associated with the use of ACEI/ARB was 0.65 or 0.68 (with 95 % C.I. of [0.45, 0.98], and [0.48, 0.96]) respectively when compared to the group exposed to the other anti-hypertensives. When the metabolic syndrome was defined

according to the AACE and EGIR, the use of ACE/ARB was associated with hazard ratios for CVD equal to 0.74 and 0.899, respectively (with 95 % C.I. of [0.54, 1.09] and [0.61, 1.34]) compared to the use of the other anti-hypertensives. Hypertensive non-diabetic elderly subjects who were insulin resistant as evidenced by a HOMA-IR in the upper quartile, had a hazard ratio for CVD of 0.78 (95 % C.I. [0.56, 1.09]) associated with the use of ACEI/ARB compared to the use of other anti-hypertensives. C**onclusions:** The effect of ACEI/ARB on the development of cardiovascular events differs according to the definition of the metabolic syndrome. Elderly hypertensive patients with the metabolic syndrome, defined by ATP and WHO, seem to have lower risk of CVD with ACEI/ARB compared to the other antihypertensive medications. However, this association is not significant in elderly hypertensive patients in the upper quartile of HOMA and in patients with the metabolic syndrome as defined by AACE and EGIR criteria.

CHAPTER I
Background

Overview of the Document

This dissertation describes a study designed to examine the effect of ACEI/ARB on the cardiovascular sequelae in hypertensive non-diabetic elderly subjects with the metabolic syndrome or evidence of insulin resistance. This chapter provides background information necessary to understand the significance of the project. The second chapter presents the objective, central hypothesis, rationale, specific aims and significance of the project. Chapter 3 describes the methodology used to conduct the study. The results are presented in chapter 4 followed by a discussion of the results and concluding remarks in chapter 5.

Definition of Metabolic Syndrome

The metabolic syndrome, or insulin resistance syndrome, is the constellation of different metabolic risk factors which promotes the risk for the development not only of diabetes but also of cardiovascular events as shown by several population based studies (1-8).

There is no uniform definition for the metabolic syndrome and different criteria have been proposed (9):

World Health Organization (WHO) Criteria

Based on the WHO, a diagnosis of the metabolic syndrome is made if the patient shows one of several markers of insulin resistance (10):

- impaired fasting glucose (fasting glucose level between 110-125 mg/dl),
- impaired glucose tolerance (2-hr post glucose level between 140-200 mg/dl),
- being in the upper quartile of the HOMA-IR level for the study population

AND

2 of the following additional risk factors:

- Obesity (waist to hip ratio > 0.9 in men or waist to hip ratio > 0.85 in women and/ or body mass index [BMI] > 30 kg/m^2), or
- High triglycerides level ≥ 150 mg/dl or
- HDL-C < 35 mg/dl in men or < 39 mg/dl in women, or
- Blood pressure ≥ 140 mm Hg for systolic blood pressure (SBP) and ≥ 90 mm Hg for diastolic blood pressure (DBP)
- Microalbuminuria (albumin excretion > 20 mcg/min).

European Group for Study of Insulin Resistance (EGIR) criteria

The EGIR proposed a modification of the WHO definition (11). By their criteria, plasma insulin level in the upper quartile of the study population plus 2 additional risk factors constitutes a diagnosis of the syndrome. The risk factors include:

- high waist circumference (≥ 94 cm in men or ≥ 80 cm in men), or

- high triglycerides level (≥ 150 mg/dl), or
- low HDL-C level (< 39 mg/dl in men or women), or
- high blood pressure (≥ 140/90 mm Hg or on hypertension medications), or
- impaired glucose metabolism (impaired glucose tolerance or impaired fasting glucose).

National Cholesterol Education Program (NCEP)'s Adult Treatment Panel III (ATP III) criteria

The most widely used definition for the metabolic syndrome was established by NCEP's ATP III report in 2001 (12). These guidelines were subsequently updated in 2005 by a scientific statement jointly published by the American Heart Association (AHA) and the National Heart Lung and Blood Institute (NHLBI) (9). A diagnosis of metabolic syndrome is defined in the updated guidelines as a person meeting 3 of the following 5 conditions: waist circumference > 102 cm in men or > 88 cm in women, triglycerides ≥ 150 mg/dl or on drug treatment for elevated triglycerides, HDL-C < 40 mg/dl in men or < 50 mg/dl in women or on drug treatment for reduced HDL-C, blood pressure ≥ 130 mm Hg for SBP or ≥ 85 mm Hg for DBP or on antihypertensive treatment in a patient with a history of hypertension, fasting glucose ≥ 100 mg/dl or on drug treatment for elevated glucose. The ATP criteria are simple to use in a clinical setting and have the advantage of avoiding emphasis on a single cause for the metabolic syndrome.

American Association of Clinical Endocrinologists (AACE) criteria

The AACE modified the ATP III criteria (13). According to AACE, a patient is defined to have the syndrome if he/she is at increased risk of insulin resistance by having any of the following risk factors based on clinical judgment:

- Family history of cardiovascular diseases (CVD) or
- a sedentary lifestyle (low or minimal exercise intensity) or
- high BMI (> 25 kg/m^2) or
- increased waist circumference (> 40 inches in men or > 35 inches in women)

And if he/she has 2 of the 4 identifying abnormalities:

- high triglycerides level (≥ 150 mg/dl),
- low HDL-C (< 40 mg/dl in men or < 50 mg/dl in women),
- high blood pressure (≥ 130/85 mm Hg),
- Impaired fasting glucose or impaired glucose tolerance.

International Diabetes Foundation (IDF) criteria

The IDF provided different criteria for the metabolic syndrome in 2005 (14). The IDF set out ethnic-specific criteria for increased weight circumference (≥ 94 cm in men or ≥ 80 cm in women for people of European origin; ≥ 90 cm in men or ≥ 80 cm in women in Asian populations, except for Japan, in whom the criteria were ≥ 85 cm in Japanese men or ≥ 90 cm in Japanese women). According to the IDF, a person is diagnosed with the metabolic syndrome if he/she has an increased waist circumference plus 2 additional risk factors:

- high triglycerides level (≥ 150 mg/dl or on medications for the hypertriglyceridemia),
- low HDL-C (< 40 mg/dl in men or < 50 mg/dl in women or on medications for the low HDL level),
- high blood pressure (≥ 130/85 or on hypertension medications),
- high fasting glucose level (≥ 100 mg/dl).

Prevalence of the Metabolic Syndrome

Estimates of the prevalence of the metabolic syndrome have varied substantially due to the variability of evaluated population and diagnostic criteria. The metabolic syndrome, as defined by the AHA/NHLBI/ATP III criteria, is estimated to be prevalent in 28% of the US adults aged ≥ 20 years, as found by a representative sample who participated in the cross-sectional NHANES III survey (1988-1994) (15). The prevalence increased significantly to 31.9 % in the NHANES (1999-2000) survey indicating that it continues to rise.

The prevalence of the metabolic syndrome increases with age, reaching peak levels in the sixth decade for men and the seventh decade for women (16). According to NHANES III survey, the prevalence of the metabolic syndrome was 6.7% among participants 20-29 years old, 43.9% among participants 60-69 years old, and 42% among participants 70 years and older. This increased prevalence of metabolic syndrome with age is paralleled with similar increases in the prevalence of obesity,

insulin resistance, dyslipidemia, high blood pressure and impaired glucose metabolism.

The prevalence of the metabolic syndrome, as defined by the ATP III criteria, was found to vary among ethnic groups ranging from a low 13.9 % in black men (mean age = 40.9 years) to a high of 27.2 % in Mexican American women (mean age = 38.9 years) (16). These findings suggest that Mexican Americans are more prone to develop insulin resistance, abnormal body fat distribution and metabolic syndrome (16-18). On the other hand, the African American population is known to have higher insulin resistance, higher CHD mortality rate and higher incidence of type 2 diabetes compared to the Caucasians. However, the metabolic syndrome prevalence was lowest in African American men accompanied with lower prevalence of large waist circumference, high triglycerides levels, low HDL levels but higher prevalence of high blood pressure (16). These findings may raise questions regarding the predictive validity of the ATP III criteria across different ethnic groups.

Pathogenesis of the Metabolic Syndrome

The pathogenesis of the metabolic syndrome is complex and incompletely understood but obesity and insulin resistance are known to contribute to its development (19). Insulin is normally responsible for the decrease in hepatic glucose production and the increase in insulin stimulated glucose uptake. In insulin resistance, the phosphatidyl inositol-3 (PI-3) kinase pathway, which is responsible for the

metabolic effects of insulin, is defective leading to hyperglycemia and compensatory hyperinsulinemia (20).

The P1-3 kinase pathway increases nitric oxide level which is a potent vasodilator. Thus, the impairment of this pathway in insulin resistance contributes to vascular endothelial dysfunction. Another signal transduction pathway of insulin involves the ERK-MAP kinase, which stimulates smooth muscle growth and proliferation, maintains its sensitivity to insulin. The overall effect may lead to atherogenesis (20;21). The atherogenic effects of insulin resistance may also result from increased production of very low density lipoproteins (VLDL), increased platelet activation and increased levels of coagulation factors such as fibrinogen and plasminogen activator inhibitor (22;23).

In insulin resistance, the adipocytes show resistance to the anti-lipolytic effects of insulin and results in an increase in the level of free fatty acids (FFA) in plasma. Overabundance of FFA exacerbates the existing insulin resistance by inhibiting insulin mediated glucose uptake in insulin sensitive tissues (22). In addition, these FFA cause an increased production of glucose, triglycerides and VLDL. High circulating glucose and FFA levels increase pancreatic insulin secretion resulting in hyperinsulinemia which may predispose to the development of high blood pressure by different mechanisms such as enhancing renal sodium and water reabsorption, and increasing sympathetic nervous system stimulation (22;23). Thus, the result would be the constellation of the metabolic abnormalities in an individual more than can be expected by chance.

Estimate of the Associated Risk of Cardiovascular Sequelae Associated with the Metabolic Syndrome

Numerous studies reported a significant increase in the hazard of CHD mortality, CVD mortality and all-cause mortality in patients with the metabolic syndrome (2-4). However, because of the different definitions of the metabolic syndrome, the magnitude and impact of cardiovascular risk is difficult to assess. Most estimates for the hazard for mortality associated with the metabolic syndrome ranged from 1.5 to 3 (2;4), although, higher estimates for CHD mortality (around 4) have also been reported (3). Increased risks of mortality were observed for diabetic subjects and in subjects with preexisting CVD (diseases that include coronary and non-coronary heart diseases such as stroke, and peripheral vascular diseases) with the highest risk among those with both diabetes and CVD. The risk of developing incident CHD in non-diabetic subjects with metabolic syndrome ranges from 1.3-2.9 (5;6;24).

Surrogate Measures of Insulin Resistance

Many investigators have used the diagnosis of the metabolic syndrome in individuals as an indicator of insulin resistance. Insulin resistance is also assessed by dynamic and static methods (25). Dynamic measures of insulin resistance, such as the euglycemic clamp, is labor intensive and are not suitable for studying large numbers of patients (25). In many epidemiological studies, the homeostatic model assessment (HOMA) was used (26). HOMA is a method used to assess insulin resistance from basal glucose and insulin concentrations (27). The relationship between fasting plasma

glucose and insulin reflects the balance between hepatic glucose output and insulin secretion, which is maintained by a feedback loop between the liver and the pancreatic β cells. Plasma glucose concentration in the basal state is regulated by hepatic glucose output, which is insulin dependent. Insulin concentration is dependent on the response of pancreatic cells to glucose. Insulin signals glucose uptake in the fat and muscle tissues, which depends on circulating glucose level as well. However, glucose uptake in the brain and urine depends solely on glucose (28).

HOMA can be calculated by multiplying fasting plasma glucose (mg/dl) and fasting plasma insulin (μU/ml) and dividing over 22.5 (27). Insulin sensitivity decreases as the HOMA value increases as shown in figure 1.1 below. There are good correlations between estimates of insulin resistance derived from HOMA and from the gold standard euglycemic clamp (26;27;29;30) and between HOMA and the minimal model (31;32). HOMA as well as the other measures (fasting insulin and fasting glucose/fasting insulin ratio) can indicate insulin resistance in subjects with normal glucose levels. As insulin resistance increases, fasting insulin and HOMA values increase, while the fasting glucose/insulin ratio decreases. On the other hand, HOMA but not fasting insulin or fasting glucose/insulin can reflect insulin resistance in diabetic subjects. Therefore, as the insulin resistance increases, HOMA value increases but no indicative changes are associated with fasting insulin or the fasting glucose/insulin ratio (table 1.1).

Figure 1.1: Relationship between HOMA level, insulin sensitivity and pancreatic β cell function (28)

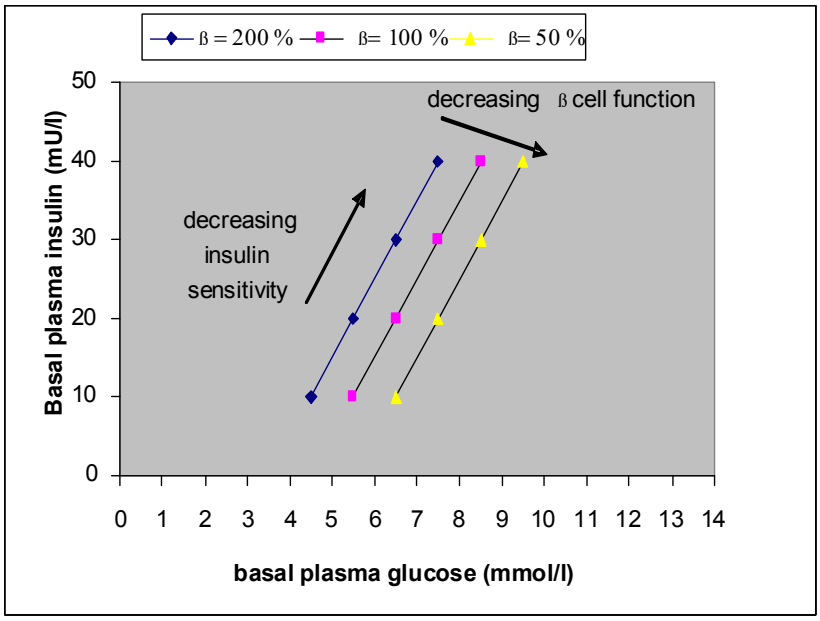


Table 1.1: Comparison between hypothetical HOMA level, fasting insulin and fasting glucose/insulin ratios in normoglycemic and diabetic subjects (33)

Patient	**Hypothetical fasting serum values**	**Fasting insulin measure**	**Fasting glucose/fasting insulin ratio**	**HOMA value**
A (normoglycemic)	Fasting insulin 20 (U/ml) Fasting glucose 100 (mg/dl)	20	5.0	4.94
B (normoglycemic)	Fasting insulin 30 (U/ml) Fasting glucose 100 (mg/dl)	30	3.33	7.41
C (diabetic)	Fasting insulin 30 (U/ml) Fasting glucose 150 (mg/dl)	30	5.0	11.11

Inhibition of Renin-Angiotensin-Aldosterone System and Insulin Resistance

Several lines of evidence suggest that Angiotensin Converting Enzyme Inhibitors (ACEI) and Angiotensin Receptor Blockers (ARB) may improve insulin sensitivity and decrease the risk of type 2 diabetes. Acute and chronic administrations of ACEI and/ or ARB have been shown to improve insulin sensitivity in several studies (34-54), although a few studies reported a metabolically neutral effect (55;56). Several different mechanisms have been suggested. A summary of the studies that investigated the effect of ACEI/ARB on the development of new onset diabetes are shown in table 1.2 below.

Table 1.2: Effect of ACEI/ARB on the development of diabetes

Author	Type of study	Sample size	Duration	Characteristics of subjects	Comparison	Development of Diabetes
Mcquen (57)	RCT (HOPE)	9,297	5 years	At risk for CVD	Ramipril vs. placebo	↓
Nikalson (58)	RCT (CAPP)	10,413	6.1 years	Hypertension	Captopril vs. diuretic &/or beta blocker	↓
Dahlof (59)	RCT (LIFE)	9,193	4.8 years	Hypertension	Losartan vs. Atenolol	↓
Yusuf (60)	RCT (CHARM)	5,436	2-4 years	Heart failure	Candesartan vs. placebo	↓
Cooper-Dehoff (61)	RCT (INVEST)	16,176	2.8 years	Coronary artery disease	Addition of Trandolapril to Verapamil	↓
Kjeldsen (62)	RCT (VALUE)	9,995	4.2 years	Hypertension	Valsartan vs. Amlodipine	↓
Barzilay (63)	RCT (ALLHAT)	18,411	4.9 years	Hypertension + 1 other risk factor	Lisinopril vs. Amlodipine vs. Chlorthalidone	↓
Bosch (55)	RCT (DREAM)	5,269	3 years	IFG, IGT	Ramipril vs. placebo	↔
Vermens (64)	Retrospective cohort (SOLVD)	291	——	Left Ventricular dysfunction	Enalapril vs. placebo	↓
Taylor (56)	Prospective cohort	41,193	8-16 years	Old women with hypertension	ACEI vs. others	↔

RCT = randomized controlled trial

A recent meta-analysis reviewed the literature until 2006 and included 22 clinical trials and 143,153 subjects (65). This meta-analysis found that ACEI/ARB were associated with the lowest incidence of diabetes compared to the other anti-hypertensives. The use of diuretics was used as the standard of comparison. The odds ratio for ARB was 0.57 (95% CI [0.46, 0.72], $p < 0.0001$), 0.67 for ACEI (95 % C.I. [0.56, 0.80], $p < 0.0001$), 0.75 for those using calcium channel blockers (95 % C.I.

[0.62, 0.90], p = 0.002), 0.90 for beta blocker (95 % C.I. [0.75, 1.09], p = 0.30), and 0.77 for placebo (95 % C.I. [0.63, 0.94], p = 0.009).

Different potential anti-diabetic mechanisms for ACEI and ARB have been suggested. Blockade of the renin-angiotensin system inhibition may lead to the reduced production of angiotensin Π, limiting its negative effects on insulin signaling, tissue blood flow, oxidative stress, sympathetic activity, and adipogenesis (66).

ACEI may reduce angiotensin Π mediated vasoconstriction and thus increase the perfusion of skeletal muscles and the pancreatic islet β cells leading to increased insulin wash out from the pancreas and improved delivery of glucose and insulin to periphery (67). In addition, ACEI can decrease the local pancreatic renin-angiotensin system activation caused by the toxic effects of hyperglycemia, obesity, hyperlipidemia, and hypertension on the islet pancreatic cells (68-70). These toxic effects may involve islet cell damage, fibrosis and apoptosis. ACEI and ARB inhibit NAPDH oxidase, an enzyme that promotes oxidative stress which is stimulated by angiotensin Π (71-73). Therefore, reduction of oxidative stress by reducing the formation and/ or the action of angiotensin Π can reduce the pancreatic fibrosis and preserve the islet cell architecture.

Angiotensin Π administration to rats has led to inhibition of the insulin stimulated PI-3 kinase activity, which is responsible for the metabolic effects of insulin signaling (74). It is therefore predicted that ACEI/ARB may improve the insulin sensitivity by abrogating these inhibitory effects of Angiotensin Π on insulin signaling.

Furthermore, the renin-angiotensin system inhibition might increase the levels of adiponectin and leptin. (75). These hormones are believed to enhance insulin sensitivity, promote the differentiation of adipocytes and possess complimentary and possible additive effects on weight reduction. In addition, ACEI and ARB have been shown to increase the cellular expression of glucose transporter protein (GLUT-4) which results in enhanced insulin stimulated glucose transport activity of the skeletal muscles (76;77).

Some molecules of the ACEI or ARB may have metabolic effects that differ between and within drug classes, suggesting anti-diabetic mechanisms that go beyond the effect on the inhibition of the renin-angiotensin system. It has been suggested that some ARB agents, such as telmisartan, have a partial agonistic activity of the peroxisome proliferator activated receptors (PPARγ) (78). PPARγ plays an important role in the regulation of carbohydrate and lipid metabolism and can improve insulin sensitivity (79;80).

Some of the effects of ACEI but not ARB may be explained by increased levels of bradykinin, which is a potent dilator and modulator of insulin action as a result of inhibiting angiotensin converting enzyme (67). It has been suggested that bradykinin enhances insulin signaling (81) and translocation of the glucose transporter (GLUT-4) in skeletal muscle (82;83). In addition, bradykinin directly increases NO levels which enhance insulin stimulated glucose oxidation and transport (84;85).

Inhibition of Renin-Angiotensin-Aldosterone System and Atherosclerosis/ CVD

Inhibition of the renin-angiotensin system has been definitely shown to reduce the morbidity and mortality associated with heart failure, myocardial infarction (MI) and to reduce cardiovascular events associated with diabetes (86). Currently, the use of ACEI or ARB is a well established treatment plan for hypertensive diabetic patients. The effect of the renin-angiotensin system on the progression of coronary atherosclerosis may be due to its influence on the fibrinolytic balance, vascular endothelial function, inflammation and plaque instability (86).

It is documented that renin-angiotensin system inhibition would ameliorate the risk of atherosclerosis in animal models. Treatment with different ACEI reduced endothelial dysfunction in atherogenic diet fed (87) and in hyperlipidemic rabbits (88). Similarly, ARB reduced blood pressure and atherosclerosis in different animal models (89-92). In a study of mice with the metabolic syndrome, treatment with ARBs inhibited development of hyperinsulinemia, hypertension, obesity, cardiac hypertrophy and atherosclerosis (93).

Beside the documented beneficial effect of ACEI in patients with reduced left ventricular function, ACEIs seem to have beneficial effects in decreasing cardiovascular events in stable patients without heart failure or left ventricular systolic dysfunction but with high risk coronary atherosclerosis as found in the HOPE and EUROPA studies (57;94). The HOPE study was a large randomized controlled trial that was designed to test the hypothesis that ACEI (Ramipril) would improve

morbidity and mortality in patients at high CVD risk (age > 55 years old, preexisting CVD, cigarette smoking, hypertension, or high cholesterol) compared to placebo. The trial was stopped early because of convincing evidence of the benefit of ACEI on the cardiovascular death, non fatal MI and stroke. The reduction in these endpoints far exceeded the modest reduction in blood pressure. The EUROPA study was a large double-blind placebo controlled multicenter trial that intended to investigate the effect of ACEI in the low risk population with stable CHD and no apparent heart failure. The results of the EUROPA study showed that among this subgroup of patients, ACEI can significantly improve the cardiovascular outcome including cardiovascular death, MI or cardiac arrest. Thus, treatment of ACEI should be considered in all patients with CHD.

A few clinical studies, such as the PEACE (95) and ALLHAT (96), found no significant decrease in the cardiovascular endpoint in subjects randomized to ACEI. A subgroup analysis of the ALLHAT study, a randomized double-blind hypertension treatment trial compared the effect of an ACEI (Lisinopril) to a thiazide type diuretic (Chlorthalidone) on the cardiovascular outcomes in hypertensive subjects with and without the metabolic syndrome. African American participants with the metabolic syndrome who were randomized to Lisinopril compared to Chlorthalidone were more likely to have higher rates of combined CHD, CVD, stroke, heart failure and ESRD, whereas non-African American participants with the metabolic syndrome had higher rates of only combined CVD and heart failure. There were no significant differences in endpoints for Lisinopril compared to Chlorthalidone in subjects without the

metabolic syndrome. The PEACE trial was a double blinded placebo controlled study that tested the hypothesis that the addition of ACEI in patients with stable coronary artery disease and normal or slightly reduced left ventricular function might reduce future cardiovascular complications. After a median follow-up of about 4.8 years, patients randomized to trandolapril (ACEI) showed no further benefit in terms of death from CVD, MI and coronary revascularization.

The ALLHAT study was the first and only study to report detrimental effects of ACEI/ARB on the cardiovascular clinical endpoints including heart failure, CVD, and CHD. A combined analysis of the three largest clinical trials (PEACE, HOPE and EUROPA) that investigated the effect of ACEI in patients with no evidence of heart failure was performed (97). This systematic review of these trials showed a clear benefit for the use of ACEI for a range of cardiovascular outcomes. It has been suggested that the apparent neutral effects of the PEACE trial could have been due to the inadequate power of that study.

A meta-analysis of most of the pertinent trials of ACEI in patients with coronary atherosclerosis found a modest beneficial effect of ACEI in patients with coronary artery disease and preserved ventricular function on combined cardiovascular outcome used in these studies (98). Compared to placebo, the use of ACEI was associated with a decrease in cardiovascular mortality (relative risk 0.83, 95% C.I. [0.72, 0.96]), non-fatal MI (relative risk 0.84, 95% C.I. [0.75, 0.94]), all cause mortality (relative risk 0.87, 95% CI [0.81, 0.94]) and revascularization rates (relative risk 0.93, 95% C.I. [0.87, 1.00]). Treatment of 100 patients at risk for CVD

with ACEI or ARB for an average of 4.4 years could prevent one death, or one MI, or one cardiovascular death or one coronary revascularization procedure.

Current Gaps of Knowledge in the Literature

Currently, antihypertensive medications, but no specific drug therapy, are recommended for elderly hypertensive non-diabetic patients with metabolic syndrome or insulin resistance. Most of the major clinical studies that investigated the effect of ACEI/ARB on incidence of diabetes or cardiovascular events had a mean age for participants less than 65 years old (99). Taking into consideration that the elderly population is at high CVD risk with a very high prevalence of the metabolic syndrome, there is a need for studies that are intended to investigate the effect of these medications specifically in the elderly population.

Most studies reported the effect of inhibition of renin-angiotensin system on the cardiovascular events in hypertensive patients at risk of CVD included diabetic subjects. The effect of ACEI/ARB in diabetic subjects is well-established. Thus, there is a need for studies designed to investigate the effect of ACEI/ARB in non-diabetic hypertensive subjects who are at high CVD risk such as the subjects with evidence of insulin resistance or metabolic syndrome. Few studies reported the effect of ACEI/ARB in subjects with the metabolic syndrome (100;101). These studies included small sample size that was followed up for a short duration of time. In addition, the effect of ACEI/ARB on the clinical cardiovascular endpoints was not assessed.

Summary of Background

The metabolic syndrome is a highly prevalent disorder that increases the CVD risk. Insulin resistance is hypothesized to be the major underlying risk factor for the development of metabolic syndrome. Current management of the metabolic syndrome focuses on the specific risk factors without targeting the underlying insulin resistance. Inhibition of the renin-angiotensin system by ACEI/ARB may decrease insulin resistance, reduce atherosclerosis and reduce CVD risk. The beneficial effects of ACEI/ARB are well established in diabetic patients; however whether this drug class also improves cardiovascular outcomes in non-diabetic hypertensive patients with insulin resistance is yet to be investigated. The metabolic syndrome is a highly prevalent disorder in subjects older than 65 years old which necessitates the investigation of the effect of ACEI/ARB in elderly hypertensive non-diabetic subjects with metabolic syndrome or evidence of insulin resistance.

CHAPTER II
Specific Aims and Significance

Goals and Objectives

Our long term goal is to find strategies to manage insulin resistance and to prevent its development in patients at risk which will lead to lower incidence of type 2 diabetes and cardiovascular events. The objective of this research project is to investigate the relationship between the use of renin-angiotensin-aldosterone system inhibitors such as ACEI or ARB and the incidence of cardiovascular events in elderly hypertensive, non-diabetic patients with the metabolic syndrome, or insulin resistance (defined as being in the upper quartile of the HOMA-IR)

Central Hypothesis

The central hypothesis is that ACEI/ARB will reduce incident cardiovascular events in elderly hypertensive non-diabetic individuals with the metabolic syndrome or insulin resistance, as compared to other anti-hypertensives.

Rationale

The rationale for the proposed research is that ACEI and ARB may have a beneficial effect on the insulin sensitivity. Clinical evidence also suggests that ACE and ARB, when compared to the other antihypertensive agents, may be associated with the lowest risk of incident diabetes. The HOPE study has further provided additional evidence that ACEI/ARB reduced the risk of cardiovascular events and new

onset diabetes in patients at risk. Currently, the use of ACEI or ARB is a well established treatment plan for hypertensive diabetic patients. However, the effect of ACEI or ARB is not established in hypertensive, non-diabetic elderly patients with evidence of insulin resistance.

Specific Aims

We tested our hypothesis with the following specific aims:

Specific aim 1: Identify the effect of ACEI /ARB on the long term development of cardiovascular events in elderly non-diabetic hypertensive patients with metabolic syndrome.

The working hypothesis here is that ACEI/ARB reduces incident cardiovascular events in elderly hypertensive patients with the metabolic syndrome. Several definitions of the metabolic syndrome were evaluated, including the WHO, EGIR, ATP III, and AACE criteria.

Specific aim 2: Identify the effect of ACEI /ARB on the long term development of cardiovascular events in elderly non-diabetic hypertensive patients with insulin resistance.

The working hypothesis here is that ACEI/ARB reduces incident cardiovascular events in elderly hypertensive patients with insulin resistance. Presence of insulin resistance was defined by HOMA-IR values in the upper 75th percentile of the study population.

The proposed work is important because it focuses on a specific treatment approach for hypertensive, non-diabetic elderly patients with evidence of insulin resistance. The combination of work proposed in aims 1 and 2 is expected to identify the effect of ACEI/ARB on the long term cardiovascular events in these patients. Such results will have a positive impact because it would propose a treatment approach that is expected to reduce the long term cardiovascular effects of insulin resistance.

Significance of the Proposed Research

The metabolic syndrome and insulin resistance are highly prevalent in the elderly. Currently the management of metabolic syndrome focuses on lifestyle modifications such as weight reduction, smoking cessation, exercise and reduced intake of atherogenic diet. Recommendations for drug therapy are based on current guidelines for the presence of specific metabolic risk factors according to the AHA, NHLBI, and American Diabetes Association (ADA). For the hypertension risk factor, anti-hypertensives are recommended. However, no specific drug therapy is recommended for the hypertensive patients with evidence of insulin resistance. Inhibition of the renin-angiotensin system by ACEI or ARB has been shown to be associated with improving insulin sensitivity. The beneficial effects of ACEI/ARB are well established in diabetic patients; however whether this drug class also improves cardiovascular outcomes in non-diabetic elderly patients with insulin resistance is yet to be investigated. By conducting our specific aims, we expect to provide evidence for the use of ACEI/ARB specifically in hypertensive, non-diabetic elderly patients with

evidence of insulin resistance. *The proposed research is significant because, if expected results on reduction in incident cardiovascular events are observed, ACEI and ARBs would be a valid antihypertensive option not only in diabetic patients, but also in non-diabetic hypertensive elderly patients with insulin resistance.* An important advance in the management of the metabolic syndrome is expected, along with reduced long term complications and health care costs. Furthermore, based on the expected results of this proposal, future studies may also assess the use of ACEI and/or ARB in preventing the development of metabolic syndrome in patients at risk.

CHAPTER III
Methods

Specific Aim 1

Identify the effect of ACEI /ARB on the long term development of cardiovascular events in elderly non-diabetic hypertensive patients with metabolic syndrome.

Introduction

Insulin resistance plays a pathogenic role in cardiovascular events. Better strategies to manage the insulin resistance may lower the incidence of the long term fatal complications. The *objective* of this aim is to investigate the relationship between the use of renin-angiotensin-aldosterone system inhibition by ACEI or ARB and the incidence of cardiovascular events in elderly hypertensive, non-diabetic patients with evidence of insulin resistance. To attain the objective of this section, we tested the *working hypothesis* that ACEI/ARB would reduce incident cardiovascular events in elderly hypertensive patients with the metabolic syndrome. Four different studies were conducted. Each of these studies included a different definition of the metabolic syndrome. We utilized the Cardiovascular Health Study (CHS) database which is a longitudinal observational study that followed up the participants for development of cardiovascular events over a period of 15 years. It was expected that the inhibition of the renin-angiotensin-aldosterone system would be associated with lower incidence of the long term cardiovascular complications of the metabolic syndrome. Such a finding

would be of importance because it would allow for the development of an effective approach to manage hypertensive patients with the metabolic syndrome and reduce their long term cardiovascular complications.

Rationale

The rationale behind testing this specific aim is that ACEI and ARB are known to have beneficial effects on insulin sensitivity and incidence of diabetes compared to other anti-hypertensives. Insulin resistance has been proposed as an important underlying cause for the metabolic syndrome and is associated with subsequent CVD (102;103). Thus, by reducing insulin resistance, ACEI and ARB may reduce CVD risk in hypertensive subjects with the metabolic syndrome. We are particularly interested in elderly subjects with the metabolic syndrome in this aim because the metabolic syndrome is highly prevalent in the elderly population. Therefore, we expect that the hypertensive elderly non-diabetic patients with metabolic syndrome who were prescribed ACEI or ARB to have a lower incidence of cardiovascular events when compared to the control group who were prescribed other antihypertensive drugs. Several definitions of the metabolic syndrome exist. Therefore, 4 separate studies were conducted; each of which used one of 4 different criteria proposed for the clinical diagnosis of the metabolic syndrome.

Design

This study was a retrospective cohort study that utilized the CHS Database. The subjects included in the analysis were non-diabetic and had been prescribed any

antihypertensive medication during any of the follow-up years. In addition, these subjects met one of 4 criteria for the metabolic syndrome. The subjects were identified based on their exposure to any ACEI or ARB. Hence, the exposed group was the subjects who had been exposed to ACEI/ARB alone or combined with other anti-hypertensives and the control group represented the subjects who were exposed to other anti-hypertensives other than ACEI/ARB. The primary endpoint was defined as the development of any incident cardiovascular event (described on page 31). The primary and secondary endpoints occurrence rates (see page 31) were compared between the ACEI/ARB group and the other anti-hypertensives control group adjusting for the possible confounding factors.

Data Source

The CHS is a National Institute of Health (NIH) sponsored community-based, longitudinal observational study of adults aged 65 and older at baseline to evaluate risk factors for the development and progression of CVD. Participants were randomly selected from Medicare eligibility lists in 4 U.S. communities in North Carolina, California, Pennsylvania and Maryland. Subjects eligible for the CHS included those who were: 1) 65 years or older; 2) non-institutionalized individuals; 3) expected to remain in the area for 3 years; 4) able to give informed consent. Participants were eligible whether or not they had a history of CVD (104). The complete dataset is available from the NHLBI without cost. The study received approval from

investigational review boards at each site and the Data Coordinating Center at the University of Washington.

An initial cohort of 5,201 was recruited between 1989 and 1990, and an additional 687 African Americans were recruited in 1992 and 1993. Of those contacted and eligible, 57.3% were enrolled. Self-reported health behaviors, history of disease, anthropometric measures, current medication use, seated blood pressure readings, electrocardiogram recordings, echocardiograms, and fasting blood chemistry measures were obtained during the baseline home interview or clinical examination. Blood was drawn in the morning after an overnight fast, and samples were analyzed in standardized fashion at the Central Blood Analysis Laboratory, University of Vermont. Follow-up interviews for cardiovascular events consisted of annual examinations and interim 6-month telephone calls for a total of 15 years. However, for the purpose of this study, we only used the first 11 years of event data (as explained in the section below). CVD included CHD, MI, angina pectoris, CHF, self-reported coronary artery bypass surgery (CABG), angioplasty, stroke and transient ischemic attack (TIA). For each cardiovascular condition, self-report was confirmed using components of the baseline examination or, if necessary, using a validation protocol that included review of medical records or surveys of treating physicians (105).

Initial classifications of events or deaths were made by the Coordinating Center and the Field Centers. Events initially classified as cardiac endpoints (MI, angina, CHF, claudication) were adjudicated by the cardiac subcommittee while events initially classified as cerebrovascular endpoints (stroke, TIA) were adjudicated by the

cerebrovascular subcommittee. The committee included CHS investigators from each of the four field centers, the coordinating center, and the project office from the NHLBI.

A packet of materials, with data summaries and support documents, for each event was prepared by the Coordinating Center and mailed to members of the appropriate review subcommittee prior to each meeting. If an event had been identified as both a cardiac and cerebrovascular endpoint, the packet for that event was sent to both review committees. During the adjudication meeting, the field center investigators presented the medical history, symptoms, course, and outcome of each event. The committee then discussed the case and determined the final classification.

Inclusion /Exclusion Criteria, Covariates and Endpoint Definition

Subjects included in the analysis for this proposal were based on the following inclusion and exclusion criteria to the CHS database.

Inclusion Criteria:

- Presence of the metabolic syndrome at baseline according to 4 different criteria explained below
- Subjects who have used any antihypertensive medication at baseline or during any of the follow-up years

Exclusion Criteria:

- Baseline diagnosis of diabetes (as defined by the ADA; fasting blood glucose > 126 mg/dl or a 2-hour serum glucose ≥ 200 mg/dl upon an oral glucose tolerance test with 75 gm glucose) or anti-diabetic medication use

including alpha glucosidase inhibitors, sulfonylureas, biguanides, thiazolinediones and insulin.

- Subjects with any prior history of cardiovascular events (defined as: MI, CHF, CHD, claudication, stroke, TIA, angina and arrhythmia). These subjects were predisposed to recurrent events. Therefore, they were excluded from the study.

Covariates and important variables to be considered:

The following major risk factors for CHD were considered: age ≥ 45 years for males and ≥ 55 years for females, cigarette smoking, low HDL (< 40 mg/dl), family history of premature CHD (male first degree relative < 55 years old, female first degree relative < 65 years), and hypertension (blood pressure >140/90 mmHg or on antihypertensive therapy). In addition to these CHD risk factors, we also considered other important cardiovascular risk factors as covariates. In consideration of all these risk factors, the list of covariates included:

- Age (age was recorded in the CHS dataset as a categorical variable with 13 levels, each level being a 2 year category, 1st level included age 65-66; 2nd level included age 67-68, etc, except for the last 2 categories) as shown in table 3.1 below.

Table 3.1: Age variable as recorded in the CHS dataset

Value	Age category
1	65 - 66
2	67- 68
3	69 - 70
4	71 - 72
5	73 - 74
6	75 - 76
7	77- 78
8	79 - 80
9	81- 82
10	83 - 84
11	85 - 86
12	87- 89
13	>= 90

- Smoking status (current, former or never smoker)
- Family history of cardiovascular events (present or absent)
- Gender (male/female)
- Alcohol use (defined as the number of alcohol beverages consumed per week): Different studies showed evidence indicating that moderate alcohol intake might be associated with a reduced incidence of CHD in diabetic and non-diabetic subjects (106;107). On the other hand, there is also substantial evidence that problem drinking (well beyond two drinks per day) is associated with increased cardiovascular mortality (106).
- Exercise intensity: Physically active individuals generally show a reduced risk of CHD compared to the sedentary population (108-110). This variable is categorical with 4 levels: no exercise, low, moderate or high exercise.

- Aspirin use (aspirin user or non user): A considerable number of subjects worldwide take aspirin on a daily basis for the prevention and treatment of CVD. Aspirin inhibits platelet activation by irreversibly inactivating cyclooxygenase-1, thereby blocking the generation of thromboxane A_2, a potent vasoconstrictor and platelet agonist. The 2009 version of the U.S. Preventive Services Task Force (USPSTF) recommendation encourages men who are between 45 to 79 years old and women between ages 55 to 79 years old to use aspirin when the potential benefit of a reduction in MI for men or stroke for women outweighs the potential harm of an increase in gastrointestinal hemorrhage (111).
- BMI and waist circumference: Total body fat and adipose tissue distribution, measured by BMI and waist circumference, are associated with cardio-metabolic risk, yet there are conflicting data regarding the better predictor of cardiovascular risk (112).
- Triglycerides: despite the debate regarding the role of triglycerides in CVD, some studies showed that the triglycerides level can serve as an independent cardiovascular risk factor after controlling for LDL, HDL (113).
- HDL cholesterol (continuous variable)
- LDL cholesterol (continuous variable)

- Race (white, African American or other): Due to the very small percent of subjects in the "other" category, the race variable was changed to a binary variable: African American or not.

African Americans have the highest overall CHD mortality rate and the highest out-of-hospital coronary death rate of any ethnic group in the United States, particularly at younger ages (114). Socioeconomics, racial disparity, and treatment access may lead to differential treatment and mortality according to race (115). In addition, research has begun to suggest that race and ethnic differences play a role in the metabolism of several medications, including anti-hypertensives (116).

- Income level: this variable is used to represent the socio-economic status of the subjects which might confound the results and thus needs to be adjusted for. This variable is divided into 8 different categories as shown in table 3.2 below:

Table 3.2: Eight levels of the income level variable

Value	Income level
1	Under $5,000
2	$ 5,000 to $7,999
3	$8,000 to $11,999
4	$12,000 to $15,999
5	$16,000 to $24,999
6	$25,000 to $34,999
7	$35,000 to $49,999
8	Over $50,000

- Time dependent covariates, the variables that may change in value over the course of the observation, including:
  - ACEI/ ARB use at baseline and throughout the duration of the study: We are interested in investigating the effect of the use of ACEI/ARB on the outcome. The use of any of these medications might change from one year to another which necessitates the inclusion of this variable in a time dependent manner. ACEI/ARB users who also used other anti-hypertensives concomitantly were also considered in the ACE/ARB exposed group. Individuals who used anti-hypertensives other than ACEI/ARB were considered not exposed to ACEI/ARB for that observation period.

- SBP at baseline and throughout the duration of the study: The high blood pressure is a known significant predictor of CVD. This variable was measured at baseline and then every follow-up until year 11 except for year 8. SBP was not collected in year 8. It was estimated by using year 7 readings.
- Total number of antihypertensive medications used: This variable might represent another indicator for the control of high blood pressure in the subjects. It was calculated at baseline and each follow-up year. The anti-hypertensives included the use of any beta blocker, any vasodilator, any ACEI, any ARB, any alpha blocker, any calcium channel blocker alone or combined with a diuretic in the same pill, plus, the use of any thiazide, loop diuretic, potassium sparing diuretic as single agents in the antihypertensive pill.
- Development of diabetes and CHF throughout the study: Hypertensive diabetic subjects and subjects who develop CHF in any of the follow-up years would have been prescribed ACEI/ARB according to established clinical guidelines. Therefore, the development of diabetes or CHF could confound the effect of ACEI/ARB on the cardiovascular outcome and a confounding by indication bias can be adjusted for by including these variables as time dependent variables.

At baseline, year 4, year 5 and year 9, fasting glucose levels were collected and diabetes was defined according to the ADA criteria (fasting glucose level higher than or equal to 126 mg/dl) or if they were on anti-diabetic medications. At baseline, oral glucose tolerance test data were available; therefore, 2-hour plasma glucose level higher than 200 mg/dl was also used to define diabetes at baseline. In years other than baseline, year 4, year 5, or 9, diabetes diagnosis was solely based on the use of anti-diabetic medications due to the fact that fasting labs and oral glucose tolerance tests were not performed at every follow-up year. We analyzed development of diabetes starting from baseline until year 11.

Starting from year 12, there were no reliable measurements of SBP, and fasting plasma glucose. In addition, the data for the development of diabetes and CHF were retrieved from patients' telephone self report with no validation from medical records. Therefore, in the analysis, the event follow-up data were limited to the first 11 years of the study.

Endpoint:

The primary endpoint was defined as the occurrence of *any* first incident CVD: MI, claudication, stroke, TIA, angina, angioplasty, CABG, ECG MI (silent MI) or death due to CHD. The incidence of *each* of these events was studied separately as secondary endpoints. The effects of ACEI/ARB on the incidence of cerebrovascular events and

CHD events were investigated separately. Cerebrovascular accident was defined as development of stroke or TIA. CHD included MI, angina, ECG MI and death due to coronary disease.

Statistical Analysis

A Cox hazards model with time dependent covariates was used to analyze the risk of developing cardiovascular events in users of ACE/ARB compared to non-users, adjusting for confounding and possible significant interactions. ACEI/ARB use, SBP, development of diabetes, number of antihypertensive medications and development of CHF were treated as time dependent annual observations. Subjects were censored if they did not develop any cardiovascular event during the follow-up period or if they did not make follow-up visits. Hazard ratios and their associated 95 % confidence intervals were calculated as the exponentiation of coefficients from the Cox model. In general a p-value ≤ 0.05 was considered as statistically significant unless stated otherwise.

Model Building Technique

The Cox regression analysis was performed for the use of ACEI/ARB (unadjusted model) and for each potential covariate separately in univariate analyses. Potential covariates that were of clinical interest (determined apriori) or those that reached a liberal significance level of 0.25 were kept. All these variables were included in the multivariable model. When adding each term, any variable that lost its significance were removed while checking that the model without the additional term did not result in a poorer fit by comparing the -2 log likelihood between the models. A

difference in the -2 log likelihood greater than 3.84 for 1 degree of freedom was considered as statistically significant. If the coefficients of the reduced model changed by more than 20% after elimination of a term, then the excluded variable may have been an important confounder and that term was included back to the model. Additionally, any discarded variable at the univariate stage was added to the multivariable model to evaluate again if addition of these eliminated variables improved the model significantly by comparing the -2 log likelihood and assessing the percent change in the coefficients in the model. The scale of the continuous variables in the model was checked for linearity as well. Clinically plausible interactions were included, including interactions between ACEI/ARB and age, ACEI/ARB and gender, and ACEI/ARB and race. We also assessed the proportional hazard assumption and the goodness of fit of the multivariable model.

Definition of the Metabolic Syndrome in the 4 Different Studies

Study number 1: The metabolic syndrome was defined based on the WHO criteria.

Study number 2: The metabolic syndrome was defined based on the EGIR criteria.

Study number 3: The metabolic syndrome was defined based on the ATP criteria.

Study number 4: The metabolic syndrome was defined based on the AACE criteria.

The IDF criteria for the metabolic syndrome may not be valid for the diagnosis of the metabolic syndrome in the elderly (117-119); therefore, it was not considered in our analysis as the dataset contained only elderly subjects. The IDF criteria included obesity as an obligatory parameter in the metabolic syndrome. This means that if a subject showed an increase of all the parameters involved in the diagnosis of the metabolic syndrome but had a waist circumference in the normal range, that subject would not be defined as a metabolic syndrome patient although he/she was at high risk for CVD. The IDF cutoff points especially for the waist circumference were lower than the other criteria resulting in the inappropriateness of the use of these criteria in the elderly (high waist circumference for men according to the IDF is defined as a waist circumference > 94 cm while other criteria defines high waist circumference if greater than 102 cm). Some studies found that IDF-metabolic syndrome patients constituted about half of the general population; thus it should be considered as a "normal variant" (120).

Specific Aim 2

Identify the effect of ACEI /ARB on the long term development of cardiovascular events in elderly non-diabetic hypertensive patients with insulin resistance.

Rationale

It has been suggested that making the diagnosis of the metabolic syndrome based on specific number of risk factors, as shown in the definitions of metabolic syndrome above, might not be a sensitive measure of insulin resistance (121). One of the most commonly used surrogate measures of insulin resistance in epidemiological research is the HOMA-IR derived from the product of fasting insulin and fasting glucose. Individuals with HOMA-IR values above 75th percentile of the study population are usually considered insulin resistant (11). We expect that elderly hypertensive patients with evidence of insulin resistance who were prescribed ACEI or ARB to have a lower incidence of cardiovascular events when compared to the control group who were prescribed other anti-hypertensives.

Design

This study was a retrospective cohort study that utilized the CHS database. The subjects included in the analysis were non-diabetic and had been prescribed antihypertensive medication at baseline or during any of the follow-up years. In addition, these subjects had evidence of insulin resistance. Insulin resistance was defined by being in the upper quartile of the HOMA level of the study population. The

exposed group was identified based on their exposure to ACEI or ARB, and the control group consisted of individuals who used anti-hypertensives other than ACEI or ARB. The incidence rate for the primary and secondary endpoints was compared between the exposed and the non-exposed groups adjusting for the possible confounding factors.

Data Source

The data source for Specific Aim 2 was the same as Specific Aim 1.

Inclusion /Exclusion Criteria, Covariates and Endpoint Definition

The inclusion and exclusion criteria for Specific Aim 2 were as follows:

Inclusion Criteria:

- Evidence of insulin resistance by being in the upper quartile of the HOMA level for non-obese, non-diabetic subjects in the cohort.
- Subjects who had used any antihypertensive medication during any of the follow-up years.

Exclusion criteria, covariates and endpoint for Aim 2 were the same as Aim 1.

Statistical Analysis

The statistical analyses employed for aim 2 were the same as aim 1.

Chapter IV
Results

Introduction

This chapter begins with a presentation of descriptive statistics followed by the results of each specific aim.

Of the original 5888 subjects enrolled in the CHS dataset, the numbers of subjects who met the inclusion criteria are: 990, 749, 777, and 1102 respectively for study 1-4 of the first specific aim. On the other hand, 1216 subjects satisfied the inclusion/ exclusion criteria for specific aim 2. Table 4.1 below shows the sample size, entry and follow-up time data for both specific aims.

Table 4.1: Sample size, entry and follow-up time, number of events for both specific aims

Study	# subjects	Entry time (days)	Follow-up time (days)			# of events
			minimum	maximum	median	
Specific aim 1						
WHO	990	0	12	4035	3361.5	339
EGIR	749	0	28	4035	3602	248
ATP	777	0	20	4035	3484	254
AACE	1102	0	20	4035	3489	368
Specific aim 2						
Upper quartile Of HOMA	1216	0	28	4035	3683	402

Cohort Characteristics

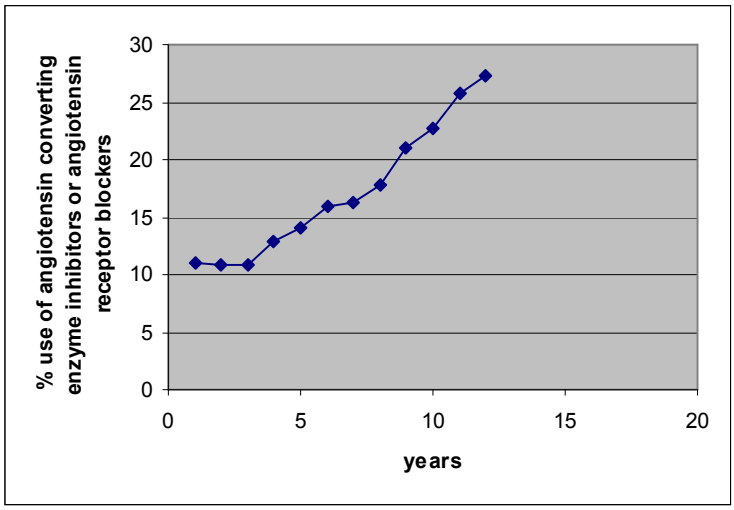
Specific Aim 1

Study Number 1: The metabolic syndrome was defined based on the WHO criteria

A) The Use of Angiotensin Converting Enzyme Inhibitors and/or Angiotensin Receptor Blockers

At entry into the study, 109 out of the 990 subjects (11%) were taking ACEI. None of the subjects at entry used ARBs. The use of ACEI/ARB increased from baseline until year 11 where 27.3 % used ACEI and/ or ARB as shown in figure 4.1 below. The average duration of use of ACEI/ARB was 2.1 years.

Figure 4.1: Percentage of use of ACEI and/or ARB over the follow-up years using the WHO definition for the metabolic syndrome



B) Baseline Characteristics of Subjects

Baseline characteristics of subjects were compared between the exposed group (exposed to ACEI/ARB) and the control group. At baseline, there were no statistically significant differences between the 2 groups regarding their age, gender, smoking habits, triglycerides, HDL, LDL levels, BMI, total number of antihypertensive medications used or fasting glucose level. However, the ACEI/ARB group contained a higher percentage of African Americans and had a higher SBP compared to the control group. The use of different antihypertensive medications (thiazides, loop diuretics, potassium sparing diuretics, calcium channel blockers, vasodilators as single agents) was similar between the 2 groups. However, the exposed group was prescribed less beta blockers and alpha blockers as presented in table 4.2 below.

However, it should be taken into consideration that the subjects included in the exposed and the control groups changed consistently at each follow-up year. Therefore, these comparisons did not reflect the differences between the 2 groups at any other follow-up year.

Table 4.2: Baseline comparisons between the exposed and the control groups using the WHO definition for the metabolic syndrome

Covariate	ACEI/ARB users	Control group	p value
Gender (% males)	47%	43%	0.41
Smoking 1=never 2=former 3=current	1 40.4% 2 47.7% 3 11.9%	1 47.7% 2 41.5% 3 10.8%	0.35
Black	23.85%	12.49%	0.0011
Triglycerides (mg/dl)	142.7	150.6	0.2091
HDL (mg/dl)	51.9	51.8	0.91
LDL (mg/dl)	130.6	133.3	0.45
Age	72.1	72.98	0.104
BMI	27.8	27.9	0.84
# HTN medications among hypertensive subjects	1.80	1.71	0.28
SBP	145.9	141.7	0.047
Fasting glucose (mg/dl)	103.4	102.8	0.45
Drug use at baseline			
Beta blockers	8.26%	18.84%	0.0063
Thiazides	12.84%	18.84%	0.125
Loop diuretics	7.34%	5.56%	0.45
K sparing diuretic	0.00%	1.59%	0.185
Calcium channel blocker	17.40%	11.12%	0.054
Vasodilators	12.84%	10.67%	0.49
Alpha blockers	0.00%	4.54%	0.023
Angiotensin receptor blockers	0.00%	0.00%	

C) Characteristics of Subjects throughout the Study

The percent of hypertensive subjects with uncontrolled blood pressure was compared between the exposed and the control groups at baseline and each follow-up year as shown in table 4.3 below. We noticed that in the 11 years of follow-up, the percentage of subjects with uncontrolled blood pressure was not significantly different between those who used ACE/ARB and those who did not use any of these 2 classes of drugs. These blood pressure data suggested that any difference in incident cardiovascular events between the two groups during the follow-up period would not probably be due to a difference in blood pressure control.

Table 4.3: Percentage of hypertensive subjects with uncontrolled blood pressure (>140/90) in both the exposed and the control groups using the WHO definition for the metabolic syndrome

Covariate	ACEI/ARB users (%)	Control group (%)	p value
Baseline	58.7	60.3	0.75
Year 1	94.12	92.98	0.728
Year 2	89.71	92.4	0.4398
Year 3	47.62	52.89	0.274
Year 4	52.9	54.57	0.718
Year 5	54.55	59.38	0.2718
Year 6	52.9	59.48	0.135
Year 7	52.44	58.57	0.155
Year 8	55.38	59.57	0.3011
Year 9	60	65.32	0.175
Year 10	51.29	55.11	0.328
Year 11	59.91	63.01	0.42

As noted previously, there might be a possible bias due to the recommended prescribing of ACEI/ARB for CHF patients that might confound the results. The percentage of subjects with CHF in both the exposed and control groups over the 11 years of follow-up are shown in table 4.4 below. It appears that those prescribed ACEI/ARB were more likely to have CHF. Using Cox regression model, where the outcome of interest was defined as the time to develop CHF, we observed that there was no statistically significant difference between those exposed to ACEI/ARB and the control group in terms of incident CHF that developed during the study as shown in table 4.5 below. However, this did not eliminate the possibility of prevalent CHF that would have led to the use of ACEI/ARB, as suggested by data in table 4.4. CHF as a time dependent covariate was therefore included in the multivariable model.

Table 4.4: Percentage of subjects with CHF at baseline and each follow-up year in both the exposed and the control groups using the WHO definition for the metabolic syndrome

Covariate	ACEI/ARB users (%)	Control group (%)	p value
Baseline	0	0	-
Year 1	0	1.36	0.38
Year 2	0.93	1.25	1.00
Year 3	1.85	2.72	0.00019
Year 4	9.45	2.2	0.031
Year 5	10.07	5.17	0.0308
Year 6	12.74	6.36	0.0076
Year 7	13.04	8.2	0.0691
Year 8	15.91	9.58	0.0214
Year 9	21.15	10.61	0.00016
Year 10	24.89	11.37	< 0.0001
Year 11	23.14	12.52	< 0.0001

Table 4.5: Cox regression model results for the effect of the use of ACEI/ARB on the time to develop CHF using the WHO definition for the metabolic syndrome

Analysis of Maximum Likelihood Estimates								
Variable	DF	Parameter Estimate	Standard Error	Chi-Square	p-value	Hazard Ratio (HR)	95% HR Confidence Limits	
Use of ACEI And/or ARB	1	0.11381	0.21261	0.2865	0.5925	1.121	0.74	1.70

Similarly, there was a possible confounding by indication bias for ACEI/ARB in diabetic patients. The percentage of subjects who developed diabetes in both the exposed and the control groups over the 11 years of follow-up were similar for the most part as shown in table 4.6. Cox regression analysis showed that the time to develop diabetes for the most part was not different between those who used ACEI/ARB and the control groups, as shown in table 4.7 below. These data suggested that any difference in incident cardiovascular events between the two groups during the follow-up period would not probably be due to a difference in the development of diabetes during the study.

Table 4.6: Percentage of subjects diagnosed with diabetes at each follow-up year in both the exposed and the control groups using the WHO definition for the metabolic syndrome

Diabetes diagnosis	ACEI/ARB users (%)	Control group (%)	p value
Baseline	0	0	-
Year 1	0.93	0.11	0.2064
Year 2	0.93	0.23	0.2931
Year 3	1.57	0.35	0.1258
Year 4	1.44	1.18	0.6803
Year 5	5.1	2.52	0.1149
Year 6	3.11	0.84	0.0321
Year 7	3.98	1.47	0.0605
Year 8	5.29	1.79	0.01
Year 9	6.22	4.44	0.2898
Year 10	4.71	2.72	0.1486
Year 11	5.56	3.19	0.0951

Table 4.7: Cox regression model results for the effect of the use of ACEI and/or ARB on the time to develop type 2 diabetes using the WHO definition for the metabolic syndrome

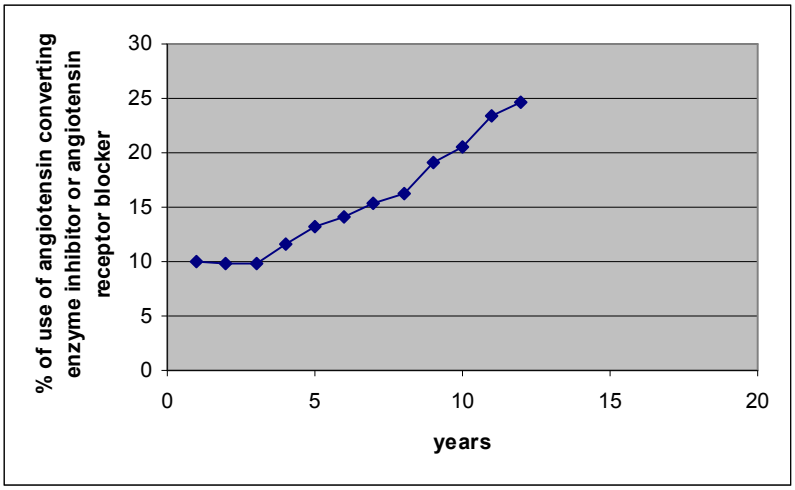
Analysis of Maximum Likelihood Estimates								
Variable	DF	Parameter Estimate	Standard Error	Chi-Square	p-value	Hazard Ratio (HR)	95% HR Confidence Limits	
Use of ACEI and/or ARB	1	0.17022	0.37839	0.2024	0.6528	1.186	0.57	2.489

Study number 2: The metabolic syndrome was defined based on the EGIR criteria

A) The Use of Angiotensin Converting Enzyme Inhibitors and/or Angiotensin Receptor Blockers

At entry into the study, 75 out of the 749 subjects (10.01%) were taking ACEI and none of the subjects at entry used ARB. The use of ACEI/ARB increased from baseline until year11 where 24.7 % used ACEI and/ or ARB as shown in figure 4.2 below. The average duration of use of ACEI and/ or ARB was 1.9 years.

Figure 4.2: Percentage of use of ACEI and/or ARB over the follow-up years using the EGIR definition for the metabolic syndrome



B) Baseline Characteristics of Subjects

The baseline characteristics of subjects were compared between those exposed to ACEI and/or ARB and the control group. At baseline, there were no significant differences between the 2 groups regarding their gender, age, smoking habits, triglycerides, HDL, LDL levels, BMI, total number of antihypertensive medications used, and fasting glucose level. On the other hand, the exposed group contained a higher percentage of African Americans and they had higher SBP at baseline. The use of different antihypertensive medications (beta blockers, thiazide diuretics, loop diuretics, potassium sparing diuretics, vasodilators, alpha blockers) was similar between the 2 groups. However, the exposed group was prescribed more calcium channel blockers compared to the control group as shown in table 4.8 below.

However, it should be taken into consideration that the subjects included in the exposed and the control groups changed significantly at each follow-up year. Therefore, these baseline comparisons do not reflect the differences between the exposed and the control groups at any other follow-up time.

Table 4.8: Baseline comparisons between the exposed and the control groups using the EGIR definition for the metabolic syndrome

Covariate	ACEI/ARB users	Control group	p value
Gender (% males)	42.6	40.36	0.699
Smoking 1=never 2=former 3=current	38.7 52.00 9.33	50.3 38.58 11.13	0.078
Black	30.67	13.65	0.0001
Triglycerides (mg/dl)	138.87	142.70	0.5893
HDL (mg/dl)	50.5	52.5	0.2506
LDL (mg/dl)	130.95	133.70	0.5091
Age	72.1	72.4	0.6516
BMI	28.07	27.60	0.3462
# HTN medications among hypertensive subjects	1.77	1.72	0.59
SBP	143.9	138.4	0.023
Fasting glucose (mg/dl)	101.3	99.9	0.1877
Drug use at baseline			
Beta blockers	9.33	13.65	0.2951
Thiazides	13.33	16.91	0.4287
Loop diuretics	6.67	4.01	0.2798
K sparing diuretic	0.00	1.78	0.244
Calcium channel blocker	21.33	10.09	0.0034
Vasodilators	12.00	8.01	0.2378
Alpha blockers	0.00	3.26	0.1123
Angiotensin receptor blocker	0.00	0.00	

C) Characteristics of Subjects throughout the Study

The percent of hypertensive subjects with uncontrolled blood pressure was compared between the exposed and the control groups at baseline and each follow-up year as shown in table 4.9 below. We notice that in the 11 years of follow up, the percentage of subjects with uncontrolled blood pressure was not significantly different between those who used ACEI/ARB and those who did not use any of these 2 classes of drugs. These blood pressure data suggest that any difference in incident cardiovascular events between the two groups during the follow-up period would probably not be due to a difference in blood pressure control.

Table 4.9: Percentage of hypertensive subjects with uncontrolled blood pressure (>140/90) in both the exposed and the control groups using the EGIR definition for the metabolic syndrome

Covariate	ACEI/ARB users (%)	Control group (%)	p value
Baseline	57.33	58.88	0.7991
Year 1	91.30	91.35	0.9909
Year 2	84.78	89.63	0.3228
Year 3	48.84	56.19	0.2061
Year 4	55.10	57.83	0.6190
Year 5	57.84	60.67	0.5966
Year 6	58.18	61.72	0.4937
Year 7	53.10	59.91	0.1871
Year 8	55.56	60.74	0.2841
Year 9	61.36	62.82	0.7626
Year 10	54.19	54.68	0.9176
Year 11	61.84	61.03	0.8609

The percentage of subjects with CHF in both the exposed and the control group over the 11 years of follow-up are shown in table 4.10 below. It appears that subjects prescribed ACEI/ARB were more likely to have CHF. Cox regression model, where the outcome of interest was defined as the time to develop CHF, showed statistically significant difference between those exposed to ACEI/ARB and the control groups in terms of incident CHF as shown in table 4.11 below. Subjects who were exposed to ACEI/ARB had higher risk to develop CHF, suggesting that subjects at risk for CHF could have been prescribed more ACEI/ARB. Thus, development of CHF needs to be adjusted for in our analysis.

Table 4.10: Percentage of subjects with CHF at baseline and each follow-up year in both the exposed and the control groups using the EGIR definition for the metabolic syndrome

Development of CHF	ACEI/ARB users (%)	Control group (%)	p value
Baseline	0	0	-
Year 1	0	1.04	1.00
Year 2	1.37	0.89	0.5137
Year 3	1.37	2.2	1.00
Year 4	8.05	1.66	0.0025
Year 5	12.12	4.0	0.0021
Year 6	16.19	4.97	0.000124
Year 7	14.78	6.15	0.0031
Year 8	16.39	7.66	0.005
Year 9	21.68	8.75	< 0.0001
Year 10	23.38	9.41	< 0.0001
Year 11	21.14	10.45	0.00046

Table 4.11: Cox regression model results for the effect of the use of ACEI and/or ARB on the time to develop CHF using the EGIR definition for the metabolic syndrome

Analysis of Maximum Likelihood Estimates								
Variable	DF	Parameter Estimate	Standard Error	Chi-Square	p-value	Hazard Ratio (HR)	95% HR Confidence Limits	
Use of ACEI and/or ARB	1	0.50496	0.25022	4.0727	0.0436	1.657	1.02	2.71

The percentage of subjects who developed diabetes over the 11 years of follow-up in both the exposed and the control groups are presented in table 4.12 below. The percentage of subjects with diabetes was not significantly different between subjects who used ACEI/ARB and those who did not used any of these 2 classes of drugs except for 2 years (year 5 and year 8). The Cox model showed that the time to develop diabetes was not significantly different between those who used ACEI/ARB and the control group, as shown in table 4.13 below. However, this did not eliminate the possibility that developing diabetes during the study would have led to the use of ACEI/ARB, as suggested by data in table 4.12. Development of diabetes as a time dependent covariate was therefore included in the multivariate model.

Table 4.12: Percentage of subjects diagnosed with diabetes at each follow-up year in both the exposed and the control groups using the EGIR definition for the metabolic syndrome

Diabetes diagnosis	ACEI/ARB users (%)	Control group (%)	p value
Baseline	0	0	-
Year 1	1.37	0.15	0.1855
Year 2	1.37	0.15	0.1855
Year 3	1.15	0.45	0.3904
Year 4	1.01	1.08	1.00
Year 5	4.76	1.55	0.0463
Year 6	2.61	0.79	0.1102
Year 7	3.28	1.12	0.0877
Year 8	4.20	0.99	0.0147
Year 9	4.55	2.69	0.2906
Year 10	4.57	1.92	0.0583
Year 11	4.32	2.30	0.1957

Table 4.13: Cox regression model results for the effect of the use of ACEI and/or ARB on the time to develop type 2 diabetes using the EGIR definition for the metabolic syndrome

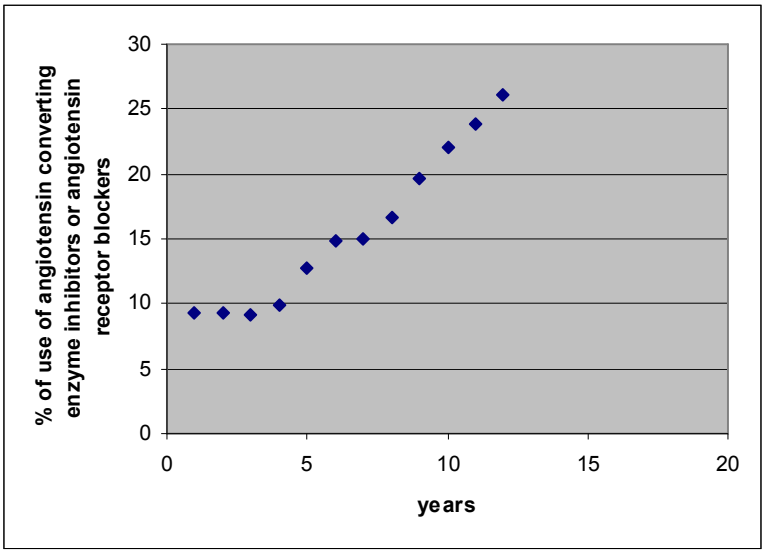
Analysis of Maximum Likelihood Estimates								
Variable	DF	Parameter Estimate	Standard Error	Chi-Square	p-value	Hazard Ratio (HR)	95% HR Confidence Limits	
Use of ACEI and/or ARB	1	-0.10049	0.60553	0.0275	0.8682	0.904	0.28	2.96

Study number 3: The metabolic syndrome was defined based on the ATP criteria

A) The Use of Angiotensin Converting Enzyme Inhibitors and/or Angiotensin Receptor Blockers

At baseline, 72 out of the 777 subjects (9.3%) were taking ACEI and none of the subjects at entry used ARB. The use of ACEI/ARB increased from baseline until year11 where 26.1 % used ACEI and/ or ARB as shown in figure 4.3 below. The average duration of use of ACEI/ARB was 1.9 years.

Figure 4.3: Percentage of use of ACEI and/or ARB over the follow-up years using the ATP definition for the metabolic syndrome



B) Baseline Characteristics of Subjects

Baseline characteristics of subjects were compared between those exposed to ACEI and/ or ARB and the control group. At baseline, there were no statistically significant differences between the 2 groups regarding their age, gender, smoking habits, triglycerides, HDL, LDL levels, BMI, total number of blood pressure medications used, fasting glucose or SBP. However, the exposed group contained a higher percentage of African Americans. The use of the different antihypertensive medications (thiazide diuretics, potassium sparing diuretics, vasodilators and alpha blockers) was similar between the 2 groups. However, the exposed group was prescribed significantly less beta blockers but more loop diuretics and calcium channel blockers compared to the control group as shown in table 4.14 below.

However, it should be taken into consideration that the subjects included in the exposed and the control groups changed consistently at each follow-up year. Therefore, these baseline comparisons did not represent the differences between the exposed and the control groups at any other follow-up year.

Table 4.14: Baseline comparisons between the exposed and the control groups using the ATP definition for the metabolic syndrome

Covariate	ACEI/ARB users (%)	Control group (%)	p value
Gender (% males)	42	33	0.1214
Smoking 1=never 2=former 3=current	1 40 2 47 3 13	1 51 2 37 3 12	0.1937
Black	21	11	0.015
Triglycerides (mg/dl)	165.4	160.2	0.5
HDL (mg/dl)	47.6	49	0.38
LDL (mg/dl)	130.0	136.2	0.15
Age	71.8	72.5	0.29
BMI	28.7	28.6	0.9
# HTN medications among hypertensive subjects	1.85	1.70	0.207
SBP	143.8	140.0	0.2
Fasting glucose (mg/dl)	105.3	104.4	0.37
Drug use at baseline			
Beta blockers	5.56%	18.70%	0.0051
Thiazides	9.7%	16.7%	0.122
Loop diuretics	11.1%	4.4%	0.0129
K sparing diuretic	0.0%	1.4%	0.31
Calcium channel blocker	18.1%	8.7%	0.0096
Vasodilators	13.9%	9.4%	0.22
Alpha blockers	0.00%	3.97%	0.09
Angiotensin receptor blocker	0.00%	0.00%	

C) Characteristics of Subjects throughout the Study

The percent of hypertensive subjects with uncontrolled blood pressure was compared between the exposed and the control groups at baseline and each follow-up year as shown in table 4.15 below. We noticed that in the 11 years of follow-up, the percentage of subjects with uncontrolled blood pressure was not significantly different between those who used ACEI/ARB and those who did not use any of these 2 classes of drugs except for year 3. In year 3, higher percentage of hypertensive subjects had uncontrolled blood pressure in the control group. To account for any possible difference in the control of blood pressure between the exposed and the control groups, SBP and the "total number of anti-hypertensives used" were included in the model as time dependent variables.

Table 4.15: Percentage of hypertensive subjects with uncontrolled blood pressure (> 140/90) in both the exposed and the control groups using the ATP definition for the metabolic syndrome

Covariate	ACEI/ARB users (%)	Control group (%)	p value
Baseline	57	62	0.37
Year 1	96	93	0.51
Year 2	89	92	0.38
Year 3	38	55	0.0038
Year 4	47	56	0.098
Year 5	55	59	0.43
Year 6	50	60	0.052
Year 7	51	60	0.074
Year 8	53	61	0.088
Year 9	57	64	0.082
Year 10	50	56	0.18
Year 11	58	62	0.43

The percentage of subjects with CHF in both the exposed and control group over the 11 years of follow-up are shown in table 4.16 below, suggesting that there was a difference between groups in some years. It appears that those prescribed ACEI/ARB were more likely to have CHF. Cox regression model, where the outcome of interest was defined as the time to develop CHF, showed no statistically significant difference between the exposed and the control groups in terms of incident CHF that developed during the study as shown in table 4.17 below. However, this did not eliminate the possibility of prevalent CHF that would have led to the use of ACEI/ARB, as suggested by data in table 4.16. CHF as a time dependent variable was therefore included in the multivariable model.

Table 4.16: Percentage of subjects with CHF at baseline and each follow-up year in both the exposed and the control groups using the ATP definition for the metabolic syndrome

Development of CHF	ACEI/ARB users (%)	Control group (%)	p value
Baseline	0	0	-
Year 1	0%	1.42%	0.611
Year 2	0%	1.42%	0.611
Year 3	0%	2.27%	0.3857
Year 4	2.6%	2.29	0.6966
Year 5	6.06%	4.72%	0.6152
Years 6	10.43%	5.44%	0.0559
Year 7	12.07%	6.66%	0.0535
Year 8	13.08%	8.8%	0.1406
Year 9	19.61%	9.3%	0.00089
Year 10	21.05%	11.06%	0.0013
Year 11	21.08%	11.99%	0.0035

Table 4.17: Cox regression model results for the effect of the use of ACEI and/ or ARB on the time to develop CHF using the ATP definition for the metabolic syndrome

Analysis of Maximum Likelihood Estimates								
Variable	DF	Parameter Estimate	Standard Error	Chi-Square	p-value	Hazard Ratio (HR)	95% HR Confidence Limits	
Use of ACEI and/or ARB	1	0.03200	0.26446	0.0146	0.9037	1.033	0.615	1.7

Similarly, the percentage of subjects who developed diabetes over the 11 years of follow-up in both the exposed and the control group are shown in table 4.18 below. Cox model showed that the time to develop diabetes was not different between those who used ACEI/ARB and the control group, as shown in table 4.19 below. Thus any difference in incident cardiovascular events between the two groups during the follow-up period would not probably be due to a difference in the development of diabetes.

Table 4.18: Percentage of subjects diagnosed with diabetes at each follow-up year in both the exposed and the control groups using the ATP definition for the metabolic syndrome

Diabetes diagnosis	ACEI/ARB users (%)	Control group (%)	p value
Baseline	0	0	-
Year 1	0	0.14	1.00
Year 2	0	0.14	1.00
Year 3	1.3	0.29	0.2691
Year 4	1.01	1.18	1.00
Year 5	6.09	3.02	0.1017
Year 6	2.59	0.76	0.103
Year 7	4.62	1.24	0.0184
Year 8	4.58	1.76	0.064
Year 9	7.02	4.95	0.3369
Year 10	4.86	2.87	0.2387
Year 11	5.91	3.48	0.1506

Table 4.19: Cox regression model results for the effect of the use of ACEI and/ or ARB on the time to develop type 2 diabetes using the ATP definition for the metabolic syndrome

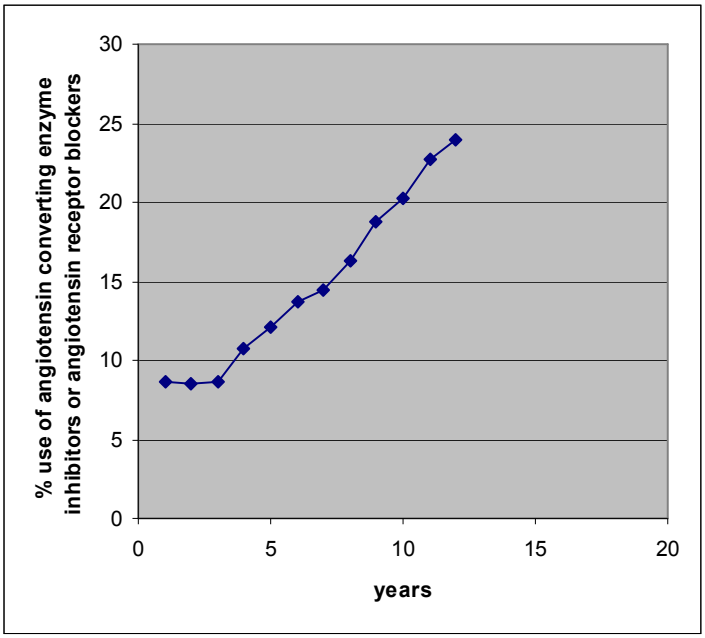
Analysis of Maximum Likelihood Estimates								
Variable	DF	Parameter Estimate	Standard Error	Chi-Square	p-value	Hazard Ratio (HR)	95% HR Confidence Limits	
Use of ACEI and/or ARB	1	0.18609	0.43251	0.1851	0.6670	1.205	0.516	2.812

Study number 4: The metabolic syndrome was defined based on the AACE criteria

A) The Use of Angiotensin Converting Enzyme Inhibitors and/or Angiotensin Receptor Blockers

At entry into the study, 95 out of the 1102 subjects (8.6 %) were taking ACEI and none of the subjects at entry used ARB. The use of ACEI/ARB increased from baseline until year 11 where 23.96 % used ACEI and/ or ARB as shown in figure 4.4 below. The average duration of use of ACEI/ARB was equal to 1.8 years.

Figure 4.4: Percentage of use of ACEI and/or ARB over the follow-up years using the AACE definition for the metabolic syndrome



B) Baseline Characteristics of Subjects

Baseline characteristics of subjects were compared between those exposed to ACEI and/or ARB and the control group. At baseline, there were no statistically significant differences between the 2 groups regarding their age, smoking habits, triglycerides, HDL, LDL levels, BMI, the total number of antihypertensive medications used and fasting plasma glucose. However, the exposed group had higher percentage of males and African Americans and they had higher SBP. The use of different antihypertensive medications (thiazide diuretics, potassium sparing diuretics, calcium channel blockers, vasodilators and alpha blockers) were similar between the 2 groups.

However, the exposed group was prescribed significantly less beta blockers but more loop diuretics compared to the control group as shown in table 4.20 below.

However, it should be taken into consideration that the subjects included in the exposed and the control groups changed consistently at each follow-up year. Therefore, these baseline comparisons did not reflect the differences between the 2 groups at any other follow-up year.

Table 4.20: Baseline comparisons between the exposed and the control groups using the AACE definition for the metabolic syndrome

Covariate	ACEI/ARB users	Control group	p value
Gender (% males)	51.58	41.1	0.048
Smoking 1=never 2=former 3=current	40.00 46.32 13.68	49.06 40.02 10.92	0.2327
Black	17.89	10.43	0.0266
Triglycerides (mg/dl)	142.5	145.7	0.6059
HDL (mg/dl)	50.37	52.18	0.2296
LDL (mg/dl)	130.45	134.40	0.2809
Age	72.63	72.70	0.8689
BMI	27.6	27.7	0.8158
# HTN medications among hypertensive subjects	1.78	1.72	0.5255
SBP	145.295	139.497	0.0078
Fasting glucose (mg/dl)	104.4	102.65	0.0771
Drug use at baseline			
Beta blockers	5.26	15.49	0.007
Thiazides	15.79	16.58	0.842
Loop diuretics	9.47	4.47	0.0308
K sparing diuretic	0.00	0.89	0.3548
Calcium channel blocker	13.68	9.04	0.1386
Vasodilators	11.58	8.64	0.336
Alpha blockers	0.00	3.57	0.061
Angiotensin receptor blockers	0.00	0.00	

C) Characteristics of Subjects throughout the Study

The percent of hypertensive subjects with uncontrolled blood pressure was compared between the exposed and the control groups at baseline and each follow-up year as shown in table 4.21 below. In year 3, 6, 7, 8, 9 and 10, the p value was less than 0.05. In these years, the percentage of subjects with uncontrolled blood pressure was higher in the control group compared to the group who were prescribed ACEI/ARB. We adjusted for the control of blood pressure in our analyses by including the SBP and the total number of anti-hypertensives used as time dependent variables in the statistical models.

Table 4.21: Percentage of hypertensive subjects with uncontrolled blood pressure (>140/90) in both the exposed and the control groups using the AACE definition for the metabolic syndrome

Covariate	ACEI/ARB users (%)	Control group (%)	p value
Baseline	56.84	62.14	0.316
Year 1	94.83	93.91	0.7803
Year 2	89.83	92.91	0.3921
Year 3	44.44	55.84	0.0215
Year 4	49.62	56.31	0.1541
Year 5	52.35	60.71	0.0592
Year 6	49.67	62.04	0.0048
Year 7	48.50	59.39	0.0108
Year 8	50.52	60.34	0.015
Year 9	55.90	65.57	0.0142
Year 10	48	57.4	0.0156
Year 11	58.30	63.37	0.1853

The percentage of subjects with CHF in both the exposed and the control groups over the 11 years of follow-up are shown in table 4.22 below. It appears that those

prescribed ACEI/ARB were more likely to have CHF. Cox regression model where the outcome of interest was defined as the time to develop CHF showed no statistically significant difference between the exposed and the control groups in terms of incident CHF as shown in table 4.23. However, this did not eliminate the possibility of prevalent CHF that would have led to the use of ACEI/ARB, as suggested by data in table 4.22. CHF as a time dependent covariate was therefore included in the multivariate model.

Table 4.22: Percentage of subjects with CHF at baseline and each follow-up year in both the exposed and the control groups using the AACE definition for the metabolic syndrome

Development of CHF	ACEI/ARB users (%)	Control group (%)p	p value
Baseline	0	0	-
Year 1	0	1.09	0.613
Year 2	0	1.09	0.613
Year 3	1.05	2.58	0.723
Year 4	5.93	2.54	0.072
Year 5	6.72	5.27	0.54
Year 6	11.26	5.99	0.0223
Year 7	12.58	7.64	0.044
Year 8	16.76	9.1	0.0044
Year 9	20.77	9.94	< 0.0001
Year 10	23.77	10.69	< 0.0001
Year 11	22.4	11.74	< 0.0001

Table 4.23: Cox regression model results for the effect of the use of ACEI and/or ARB on the time to develop CHF using the AACE definition for the metabolic syndrome

Analysis of Maximum Likelihood Estimates							
Variable	DF	Parameter Estimate	Standard Error	Chi-Square	p-value	Hazard Ratio (HR)	95% HR Confidence Limits
Use of ACEI and/or ARB	1	0.09585	0.22221	0.1861	0.6662	1.101	0.71 1.701

The percentage of subjects who developed diabetes over the 11 years of follow-up was for the most part similar in both the exposed and the control groups as presented in table 4.24 below. Cox regression model showed that the time to develop diabetes was not different between those who used ACEI/ARB and the control group, as shown in table 4.25 below. Thus any difference in incident cardiovascular events between the two groups during the follow-up period would not probably be due to a difference in the development of diabetes.

Table 4.24: Percentage of subjects diagnosed with diabetes at each follow-up year in the exposed and the control groups using the AACE definition for the metabolic syndrome

Covariate	ACEI/ARB users (%)	Control group (%)	p value
Baseline	0	0	-
Year 1	0	0.1	1.00
Year 2	0	0.2	1.00
Year 3	0.85	0.41	0.433
Year 4	0.75	1.14	1.00
Year 5	3.97	2.84	0.44
Year 6	1.89	1.06	0.42
Year 7	2.79	1.63	0.35
Year 8	4.35	1.90	0.044
Year 9	5.83	4.55	0.48
Year 10	4	2.82	0.404
Year 11	5.30	3.34	0.145

Table 4.25: Cox regression model results for the effect of the use of ACEI and/or ARB on the time to develop type 2 diabetes using the AACE definition for the metabolic syndrome

Analysis of Maximum Likelihood Estimates								
Variable	DF	Parameter Estimate	Standard Error	Chi-Square	p-value	Hazard Ratio (HR)	95% HR Confidence Limits	
Use of ACEI and/or ARB	1	-0.03953	0.42628	0.0086	0.9261	0.961	0.42	2.22

Specific Aim 2

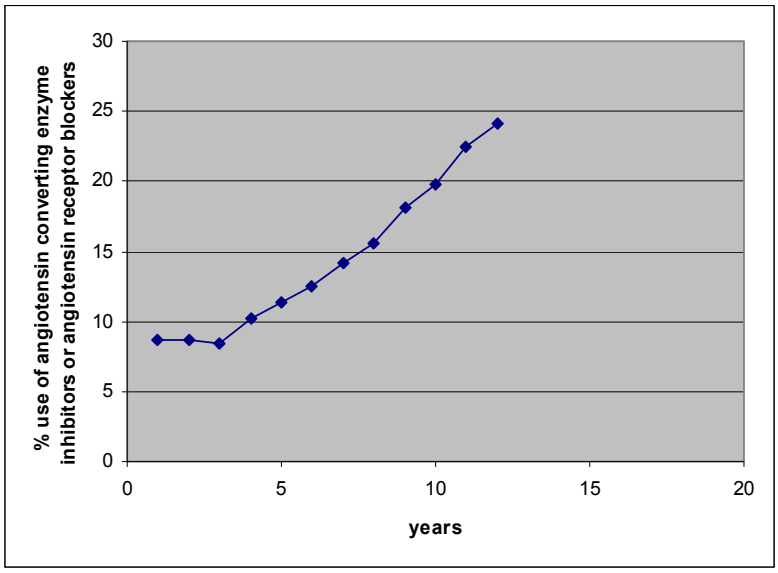
A) The Use of Angiotensin Converting Enzyme Inhibitors and/or Angiotensin Receptor Blockers

For the second specific aim, the study population consisted of elderly hypertensive non-diabetic subjects in the upper quartile of HOMA. The cut off point for

the upper quartile of HOMA was found to be 2.52. Thus, a subject was considered to be insulin resistant if the HOMA was equal to or greater than 2.52.

At entry into the study, 105 out of the 1216 subjects (8.63%) were taking ACEI and none of the subjects at entry used ARB. The use of ACEI/ARB increased from baseline until year 11 where 24.2 % used ACEI and/ or ARB as shown in figure 4.5 below. The average duration of use of ACEI/ARB was equal to 1.7 years.

Figure 4.5: Percentage of use of ACEI and/or ARB over the follow-up years for specific aim 2



B) Baseline Characteristics of Subjects

Baseline characteristics of subjects were compared between those exposed to ACEI and/or ARB and the control group. At baseline, there were no statistically significant differences between the 2 groups regarding their age, gender, smoking habits, triglycerides, HDL, LDL levels, BMI, total number of blood pressure

medications used, and fasting plasma glucose. However, the exposed group had a higher percentage of African Americans and higher SBP. The use of different antihypertensive medications (thiazide diuretics, potassium sparing diuretics, vasodilators and alpha blockers) was similar between the 2 groups. However, the exposed group was prescribed significantly more loop diuretics and calcium channel blockers as shown in table 4.26.

Table 4.26: Baseline comparisons between the exposed and the control groups for specific aim 2

Covariate	ACEI/ARB users	Control group	p value
Gender (% males)	43.81	39.69	0.41
Smoking 1=never 2=former 3=current	39.05 48.57 12.38	48.51 40.23 11.25	0.17
Black	22.86	12.06	0.0017
Triglycerides (mg/dl)	142.3	141.8	0.9314
HDL (mg/dl)	50.86	52.98	0.1434
LDL (mg/dl)	132.6	134.7	0.5617
Age	72.08	72.44	0.4725
BMI	27.80	27.66	0.6804
# HTN medications among hypertensive subjects	1.83	1.7	0.1193
SBP	144.05	137.85	0.0024
Fasting glucose (mg/dl)	103.4	102.2	0.1918
Drug use at baseline			
Beta blockers	9.52	13.41	0.2587
Thiazides	13.33	15.39	0.5746
Loop diuretics	8.57	4.05	0.0316
K sparing diuretic	0.00	1.17	0.2651
Calcium channel blocker	20.00	7.65	<0.0001
Vasodilators	12.38	7.47	0.0745
Alpha blockers	0.00	2.88	0.078
Angiotensin receptor blockers	0.00	0.00	

C) Characteristics of Subjects throughout the Study

The percent of hypertensive subjects with uncontrolled blood pressure was compared between the exposed and the control groups at baseline and each follow-up

year as shown in table 4.27 below. The percentage of subjects with uncontrolled blood pressure was higher in the control group compared to the group who was prescribed ACEI/ARB in some of the follow-up years. We adjusted for the control of blood pressure in our analyses by including the SBP and the total number of anti-hypertensives used as time dependent variables in the statistical models.

Table 4.27: Percentage of hypertensive subjects with uncontrolled blood pressure (>140/90) in both the exposed and the control groups for specific aim 2

Covariate	ACEI/ARB users (%)	Control group (%)	p value
Baseline	56.19	60.76	0.37
Year 1	92.19	93.05	0.799
Year 2	88.52	92.29	0.308
Year 3	45.53	57.25	0.015
Year 4	50	56.68	0.148
Year 5	53.02	62.57	0.029
Year 6	48.8	62.16	0.0015
Year 7	47.46	59.4	0.0039
Year 8	50.48	60.23	0.0125
Year 9	57.97	63.66	0.1377
Year 10	49.59	53.59	0.285
Year 11	57.02	61.18	0.2605

The percentage of subjects with CHF in both the exposed and the control groups over 11 years of follow-up are shown in table 4.28 below. It appears that those prescribed ACEI/ARB were more likely to have CHF. Cox regression model, where the outcome of interest was defined as the time to develop CHF, showed no statistically significant difference between the exposed and the control groups in terms of incident CHF that developed during the study as shown in table 4.29. However, this did not eliminate the possibility of prevalent CHF that would have led to the use of ACEI/ARB,

as suggested by data in Table 4.28. CHF as a time dependent covariate was therefore included in the multivariable model.

Table 4.28: Percentage of subjects with CHF at baseline and each follow-up year in both the exposed and the control groups for specific aim 2

Development of CHF	ACEI/ARB users (%)	Control group (%)	p value
Baseline	0	0	-
Year 1	0	1.08	0.614
Year 2	1.9	0.9	0.278
Year 3	1.96	2.42	1.00
Year 4	8.06	2.2	0.0013
Year 5	9.42	4.64	0.024
Year 6	13.82	5.45	< 0.0001
Year 7	15.03	6.71	0.0006
Year 8	17.37	8.09	0.0002
Year 9	21.27	9.25	< 0.0001
Year 10	24.07	10.15	< 0.0001
Year 11	22.63	11.04	< 0.0001

Table 4.29: Cox regression model results for the effect of the use ACEI and/or ARB on the time to develop CHF for specific aim 2

Analysis of Maximum Likelihood Estimates								
Variable	DF	Parameter Estimate	Standard Error	Chi-Square	p-value	Hazard Ratio (HR)	95% HR Confidence Limits	
Use of ACEI and/or ARB	1	0.23203	0.21372	1.1788	0.2776	1.261	0.83	1.92

Similarly, the percentage of subjects who developed diabetes over the 11 years of follow-up in both the exposed and the control group are presented in table 4.30. It appears that there was for the most part no statistically significant difference between the 2 groups in terms of development of diabetes during the study. Cox model showed

that the time to develop diabetes was not different between those who used ACEI/ARB and the control group, as shown in table 4.31 below. These data suggested that any difference in incident cardiovascular events between the two groups during the follow-up period would not probably be due to a difference in development of diabetes during the study.

Table 4.30: Percentage of subjects diagnosed with diabetes at each follow-up year in both the exposed and the control groups for specific aim 2

Diabetes diagnosis	ACEI/ARB users (%)s	Control group (%)	p value
Baseline	0	0	-
Year 1	0.95	0.09	0.165
Year 2	0.98	0.18	0.231
Year 3	0.81	0.37	0.417
Year 4	0.71	1.02	1.00
Year 5	3.95	2.54	0.290
Year 6	2.31	0.86	0.1003
Year 7	3.16	1.27	0.10
Year 8	4.52	1.41	0.0059
Year 9	5.81	3.79	0.207
Year 10	4.38	2.23	0.0594
Year 11	5.10	2.71	0.059

Table 4.31: Cox regression model results for the effect of the use of ACEI and/or ARB on the time to develop type 2 diabetes for specific aim 2

Analysis of Maximum Likelihood Estimates								
Variable	DF	Parameter Estimate	Standard Error	Chi-Square	p-value	Hazard Ratio (HR)	95% HR Confidence Limits	
Use of ACEI and/or ARB	1	0.15416	0.39809	0.1500	0.6986	1.167	0.54	2.55

Results

Specific Aim 1: Identify the effect of ACEI/ARB on the long term development of cardiovascular events in elderly non-diabetic hypertensive patients with metabolic syndrome

Study Number 1: The metabolic syndrome was defined based on the WHO Criteria

A) Consideration of Age as an Independent Variable

In order to test for the linearity of this variable, the -2 log likelihood value was compared between the model with age as categorical variable and the model with age as a linear variable. The difference in -2 log likelihood was equal to 21.9 which is larger than ($\chi^2_{11,\ 0.05}$= 19.68) suggesting a trend for non-linearity. Therefore, age was added in the model as three levels according to the classical geriatric classification: 65 to 74 years, 75 to 84 years, and 85 years and older.

B) Univariate Analyses of the Independent Variables

The results of the univariate analyses are shown in table 4.32 below. The variables that were found to have a statistically significant effect on the time to incidence of cardiovascular event included: age, gender, smoking status, race, number of alcohol beverages, exercise intensity level, BMI and HDL (p-value < 0.25). Among the time dependent variables, the use of ACEI/ARB, SBP, development of CHF and the

total number of antihypertensive medications were significantly associated with the outcome.

Table 4.32: Univariate analyses using the WHO definition for the metabolic syndrome

Variable	DF	Parameter Estimate	Standard Error	Chi-Square	p-value	Hazard Ratio
Age (75-84) vs. (65-74)	1	0.356	0.117	9.259	0.0023	1.4
Age (≥ 85) vs. (65-74)	1	1.114	0.277	16.21	<0.0001	3.05
Gender (male vs. female)	1	0.54629	0.10891	25.1585	<.0001	1.727
Smoking(former vs. never)	1	0.27339	0.11758	5.4060	0.0201	1.314
Smoking(current vs. never)	1	0.65925	0.16650	15.6768	<.0001	1.933
Race (black vs. other)	1	-0.39833	0.19866	4.0202	0.0450	0.671
# alcohol beverages	1	0.01053	0.00699	2.2686	0.1320	1.011
Aspirin use	1	0.01881	0.11748	0.0256	0.8728	1.019
Exercise intensity level	1	0.08456	0.07055	1.4366	0.2307	1.088
BMI	1	-0.02344	0.01381	2.8817	0.0896	0.977
Income level	1	0.00438	0.02783	0.0248	0.8749	1.004
Family hx of MI	1	0.08371	0.11718	0.5103	0.4750	1.087
Triglycerides	1	0.0006823	0.0008630	0.6251	0.4292	1.001
HDL	1	-0.01012	0.00414	5.9671	0.0146	0.990
LDL	1	0.0005222	0.00160	0.1059	0.7449	1.001
Time dependent covariates						
ACEI/ARB use	1	-0.23604	0.16588	2.0248	0.1548	0.790
SBP	1	0.00857	0.00250	11.7398	0.0006	1.009
Development of diabetes	1	0.20660	0.36106	0.3274	0.5672	1.229
Development of CHF	1	1.84290	0.14976	151.4211	<.0001	6.315
Number of HTN medications	1	-0.12568	0.05359	5.4989	0.0190	0.882

C) The Multivariable Model

We included the variables that were statistically significant in the univariate analysis. We then tested the variables that lost their significant effect upon inclusion in the multivariable model as well as the variables that were not significant in the

univariate analysis for any confounding effect. Tests for interactions between the exposure variable and age, race, gender were also conducted (for details, see model building technique section in chapter 3). However, none of these interactions were found to be statistically significant. The final model is presented in table 4.33 below.

Table 4.33: Multivariable model using the WHO definition for the metabolic syndrome

Parameter	DF	Parameter Estimate	Standard Error	Chi-Square	p-value	Hazard Ratio (HR)	95% HR Confidence Limits	
Use of ACEI/ARB	1	-0.33210	0.17586	3.5664	0.0590	0.717	0.508	1.013
SBP	1	0.00667	0.00251	7.0548	0.0079	1.007	1.002	1.012
Development of CHF	1	1.80697	0.15552	134.9960	<.0001	6.092	4.491	8.263
Development of diabetes	1	0.52760	0.36572	2.0812	0.1491	1.695	0.828	3.471
# HTN medications	1	-0.09475	0.05534	2.9317	0.0869	0.910	0.816	1.014
Age (75-84) vs. (65-74)	1	0.27609	0.12010	5.2847	0.0215	1.318	1.042	1.668
Age (≥ 85) vs. (65-74)	1	0.90380	0.28359	10.1570	0.0014	2.469	1.416	4.304
Gender (male vs. female)	1	0.56275	0.11602	23.5264	<.0001	1.755	1.398	2.204
Former smoker vs. never	1	0.18128	0.12278	2.1801	0.1398	1.199	0.942	1.525
Current smoker vs. never	1	0.68065	0.17053	15.9315	<.0001	1.975	1.414	2.759
Race (black vs. not)	1	-0.39441	0.20183	3.8189	0.0507	0.674	0.454	1.001
LDL	1	0.00321	0.00168	3.6718	0.0553	1.003	1.000	1.007

The hazard ratio for the incidence of any cardiovascular event in the exposed group was found to be equal to 0.72 compared to the control group suggesting that the hazard for cardiovascular events for those exposed to the drug of interest was only about 72% of the hazard for those who were not exposed to ACEI or ARB. The 95%

C.I. (0.51, 1.01) suggested that the exposure to either ACEI/ARB had a non-statistically significant effect on the time to develop CVD.

D) Testing the Proportional Hazard Assumption

1) We included interactions between each independent variable and log (time) to test for the proportional hazard assumption. Table 4.34 below presents the estimated coefficients, standard errors, Wald statistics and p-values for the Wald statistics of the interactions with log-time.

Table 4.34: Testing the proportional hazard assumption by including interactions of independent variables with time using the WHO definition for the metabolic syndrome

Parameter	DF	Parameter Estimate	Standard Error	Chi-Square	p-value	Hazard Ratio (HR)	95% HR Confidence Limits	
Age level (65-74)*log(time)	1	0.18529	0.24622	0.5663	0.4517	1.204	0.743	1.950
Age level (75-84)*log(time)	1	0.02832	0.24517	0.0133	0.9080	1.029	0.636	1.663
Use of ACEI/ARB*log(time)	1	-0.09601	0.21330	0.2026	0.6526	0.908	0.598	1.380
SBP*log(time)	1	-0.00284	0.00273	1.0809	0.2985	0.997	0.992	1.003
Development of CHF*log(time)	1	-0.23373	0.16673	1.9650	0.1610	0.792	0.571	1.098
Development of diabetes *log(time)	1	0.40027	1.23926	0.1043	0.7467	1.492	0.132	16.932
Gender*log(time)	1	-0.20369	0.13168	2.3927	0.1219	0.816	0.630	1.056
Never smoking*log(time)	1	-0.14138	0.19661	0.5171	0.4721	0.868	0.591	1.276
Former smoking*log(time)	1	-0.21399	0.18802	1.2953	0.2551	0.807	0.558	1.167
Race*log(time)	1	-0.08465	0.22570	0.1407	0.7076	0.919	0.590	1.430
LDL*log(time)	1	-0.00062	0.00179	0.1216	0.7273	0.999	0.996	1.003
Number of HTN medications*log(time)	1	0.19008	0.06576	8.3542	0.0038	1.209	1.063	1.376

As can be seen from the table above, the "number of antihypertensive medications" variable seemed to have a significant interaction with time, suggesting that this variable might violate the proportional hazard assumption. Therefore, the interaction of this variable with log (time) needed to be added to the model.

2) The proportional hazard assumption was also tested by examining a plot of the scaled Schoenfeld residuals from the model without the interactions terms with time. Each subplot had a slope essentially equal to zero suggesting that the proportional hazard assumption was met for all the variables except for the "number of antihypertensive medications" variable (see appendix B for details).

3) Testing the proportional hazard assumption using the rank test as shown in table 4.35.

Table 4.35: Testing the proportional hazard assumption by the rank test using the WHO definition for the metabolic syndrome

Variable	Rho	Chi	DF	p-value
Use of ACEI/ARB	-0.036	0.47	1	0.495
Development of CHF	-0.026	0.25	1	0.619
Development of diabetes	0.0198	0.13	1	0.715
SBP	-0.06762	1.47	1	0.2261
Number of HTN medications	0.14515	8.21	1	0.0042
Age (75-84) vs. (65-74)l	-0.064	1.45	1	0.2292
Age (≥ 85) vs. (65-74)	-0.0976	3.33	1	0.0679
Gender	-0.09958	3.46	1	0.063
Past smokers vs. never smokers	-0.0525	0.96	1	0.3274
Current smokers vs. never smokers	0.04508	0.7	1	0.4043
Race	-0.05702	1.08	1	0.2995
LDL	-0.01173	0.06	1	0.8138
Global test		23.88	12	0.021

The p-value for the global test of the rank test was statistically significant suggesting that the proportional hazard assumption might be violated. However, after including the interaction between the "number of antihypertensive medications" and time to the model, the overall global test was no longer statistically significant as shown in table 4.36.

Table 4.36: Testing the proportional hazard assumption by the rank test for the modified model using the WHO definition for the metabolic syndrome

Variable	Rho	Chi	DF	p-value
Use of ACEI/ARB	-0.0328	0.4	1	0.5262
Development of CHF	-0.0247	0.23	1	0.634
Development of diabetes	0.0162	0.09	1	0.7662
SBP	-0.065	1.39	1	0.239
Number of HTN medications	-0.0004	0.00	1	0.9932
Age (75-84) vs. (65-74)	-0.063	1.41	1	0.2353
Age (≥ 85) vs. (65-74)	-0.0927	2.99	1	0.0835
Gender	-0.097	3.28	1	0.0708
Past smokers vs. never smokers	-0.0517	0.93	1	0.334
Current smokers vs. never smokers	0.043	0.65	1	0.419
Race	-0.0504	0.83	1	0.3616
LDL	-0.013	0.07	1	0.788
Number of HTN medications *log(time)	0.0063	0.02	1	0.899
Global test		15.04	13	0.305

E) The Modified Multivariable Model

The interaction between the "number of anti-hypertensives used" and log "time" was added to the multivariable model. The result is presented in table 4.37 below.

Table 4.37: Modified multivariable model using the WHO definition for the metabolic syndrome

Parameter	DF	Parameter Estimate	Standard Error	Chi-Square	p-value	Hazard Ratio (HR)	95% HR Confidence Limits	
Use of ACEI/ARB	1	-0.38385	0.17840	4.6296	0.0314	0.681	0.480	0.966
SBP	1	0.00627	0.00253	6.1579	0.0131	1.006	1.001	1.011
Development of CHF	1	1.82024	0.15620	135.7942	<.0001	6.173	4.545	8.385
Development of diabetes	1	0.50311	0.36598	1.8897	0.1692	1.654	0.807	3.389
Number of HTN medications	1	-1.41579	0.45350	9.7465	0.0018	0.243	0.100	0.590
Age (75-84) vs. (65-74)	1	0.28217	0.12001	5.5280	0.0187	1.326	1.048	1.678
Age (≥ 85) vs. (65-74)	1	0.94021	0.28360	10.9913	0.0009	2.561	1.469	4.464
Gender (male vs. female)	1	0.56108	0.11614	23.3405	<.0001	1.753	1.396	2.201
Former smoker vs. never	1	0.18516	0.12292	2.2691	0.1320	1.203	0.946	1.531
Current smoker vs. never	1	0.67930	0.17057	15.8603	<.0001	1.972	1.412	2.756
Race (black vs. not)	1	-0.35993	0.20223	3.1678	0.0751	0.698	0.469	1.037
LDL	1	0.00328	0.00168	3.8061	0.0511	1.003	1.000	1.007
Number of HTN medications*log (time)	1	0.18356	0.06201	8.7617	0.0031	1.201	1.064	1.357

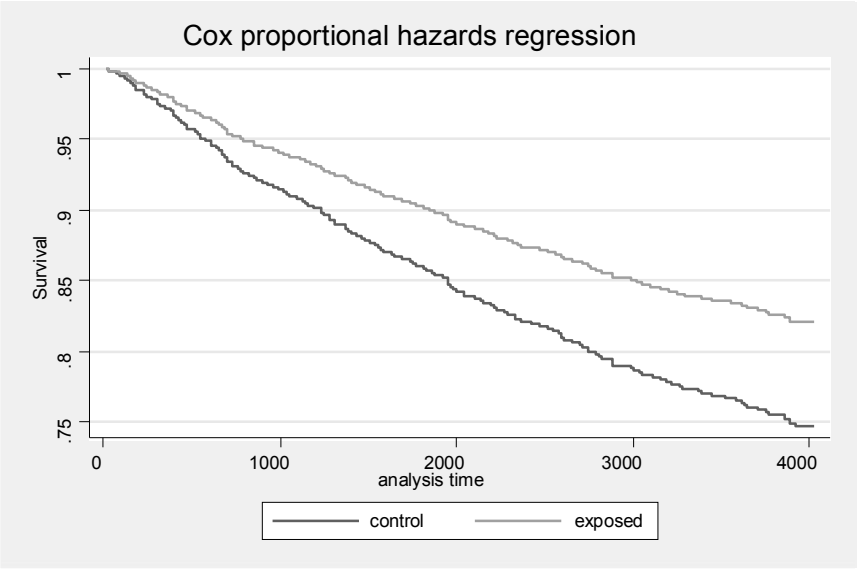
As can be seen from table 4.37, exposure to either ACEI/ARB had a significant effect on the time to develop CVD. The hazard for cardiovascular events for those exposed to the drug of interest was only about 68% of the hazard for those who were not exposed to ACEI or ARB when using the WHO definition.

F) Survival Plot

Cox regression survival plot for the multivariable model is presented in figure 4.6 below. Survival estimates for the exposed group (exposed to ACEI/ARB) were

significantly higher than the control group; suggesting that the exposure to ACEI/ARB in hypertensive non-diabetic subjects with the metabolic syndrome according to the WHO criteria, had a significant protective effect against the development of CVD.

Figure 4.6: Cox regression survival plot using the WHO definition for the metabolic syndrome



G) Influence Diagnostics

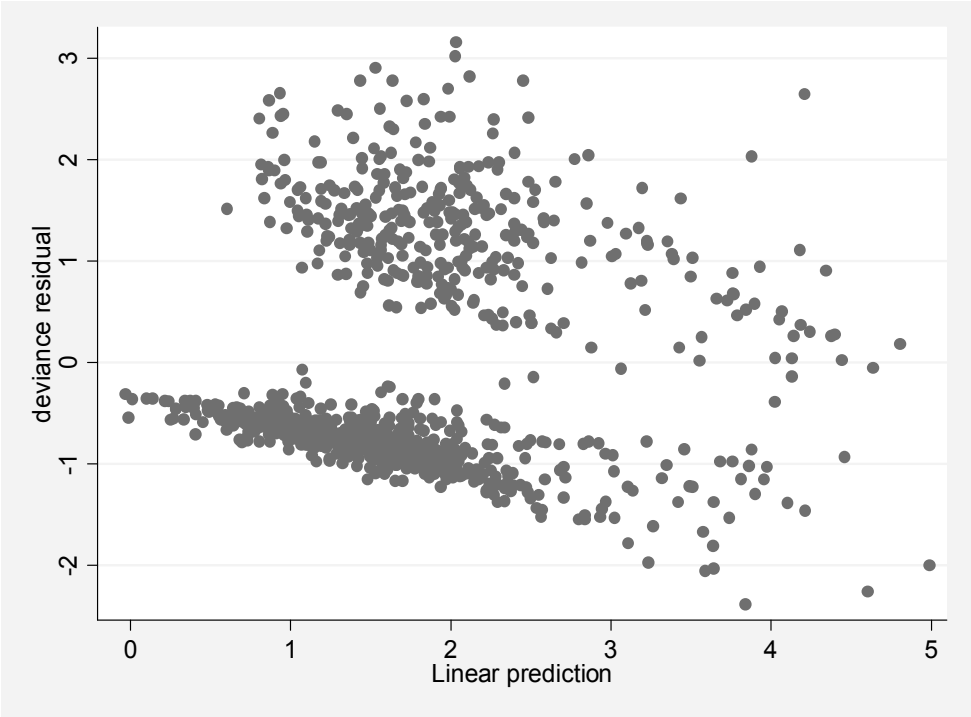
G.1 Deviance residuals:

Deviance residuals behave like residuals from the ordinary least squares regression: they are symmetrically distributed around zero and have an approximated standard deviation of one. They are negative for observations that have longer survival times than expected and positive for observations with survival times shorter than

expected (122). Therefore, very high or low values suggest that the observation may be an outlier and needs special attention.

Deviance residual plot is shown in figure 4.7 below. We noticed the 2 clusters that were due to censoring; the upper portion represented the uncensored subjects and the lower portion represented the censored subjects. None of the observations seemed to be of a striking distance between the other points indicating that there did not appear to be any outliers.

Figure 4.7: Deviance residuals plot using the WHO definition for the metabolic syndrome



G.2 DFBETA statistic

DFBETA statistics tell us how much each coefficient changes by removal of a single observation from the sample (122). DFBETA was calculated for each variable

and none of the variables had exceptionally large values (DFBETA ≥ 2) for any of the DFBETAs. DFBETA for the use of ACEI/ARB ranged from -0.0179 to 0.0299; -0.0147 to 0.023 for CHF; -0.05 to 0.13 for diabetes; -0.00034 to 0.0004 for SBP; -0.063 to 0.17 for the number of antihypertensive medications; -0.036 to 0.028 for age; -0.012 to 0.012 for gender; -0.011 to 0.0099 for former smoking; -0.0147 to 0.0245 for current smoking; -0.013 to 0.037 for race; -0.0002 to 0.00028 for LDL; -0.022 to 0.01 for the interaction between the number of antihypertensive medications and time. Thus, we may conclude that there were no unusually influential observations.

Study Number 2: The metabolic syndrome was defined based on the EGIR criteria

A) Consideration of Age as an Independent Variable

The difference in -2 log likelihood between the model that included age as a categorical variable and the model where age was treated as continuous was equal to 19.568 which is smaller than $\chi^2_{11,\,0.05} = 19.68$ suggesting that there was no trend for non-linearity. Thus age was treated as a continuous variable. Sensitivity analysis using age as a categorical variable was also performed (see Appendix A for details).

B) Univariate Analysis of the Independent Variables

Table 4.38 below presents the results of the univariate analyses for all the independent variables. The variables that were found to have a statistically significant effect on the time to incidence of cardiovascular event included: age, gender, current smokers vs. never, race, HDL level, and the triglycerides level. Among the time

dependent variables, SBP, the "total number of antihypertensive medications" and the development of CHF were significantly associated with the outcome.

Table 4.38: Univariate analyses using the EGIR definition for the metabolic syndrome

Variable	DF	Parameter Estimate	Standard Error	Chi-Square	p-value	Hazard Ratio
Age	1	0.05643	0.01271	19.7063	<.0001	1.058
Gender (male vs. female)	1	0.38279	0.12720	9.0564	0.0026	1.466
Smoking(former vs. never)	1	0.12462	0.13881	0.8060	0.3693	1.133
Smoking(current vs. never)	1	0.73898	0.18651	15.6979	<.0001	2.094
Race (black vs. other)	1	-0.31306	0.21641	2.0927	0.1480	0.731
# alcohol beverages	1	0.00431	0.00884	0.2380	0.6257	1.004
Aspirin use	1	0.13614	0.13590	1.0034	0.3165	1.146
Exercise intensity level	1	0.05048	0.08130	0.3856	0.5346	1.052
BMI	1	-0.01340	0.01671	0.6430	0.4226	0.987
Income level	1	-0.00497	0.03342	0.0221	0.8819	0.995
Family hx of MI	1	0.12877	0.13785	0.8726	0.3502	1.137
Triglycerides	1	0.00178	0.00102	3.0013	0.0832	1.002
HDL	1	-0.01207	0.00479	6.3663	0.0116	0.988
LDL	1	0.0005307	0.00190	0.0783	0.7796	1.001
Time dependent covariates						
ACEI/ARB use	1	0.06298	0.18340	0.1179	0.7313	1.065
SBP	1	0.00857	0.00313	7.4916	0.0062	1.009
Development of diabetes	1	0.33991	0.45428	0.5599	0.4543	1.405
Development of CHF	1	1.64961	0.18367	80.6611	<.0001	5.205
Number of HTN medications	1	-0.07516	0.06013	1.5623	0.2113	0.928

C) The Multivariable Model

We included the variables that were statistically significant in the univariate analysis. We then tested the variables that lost their significant effect upon inclusion in the multivariable model as well as the variables that were not significant in the univariate analysis for any confounding effect. Tests for interactions between the exposure variable and age, race, gender were also conducted (see model building

technique section in chapter 3 for details). However, none of these interactions were found to be statistically significant. The final model is presented in table 4.39 below.

Table 4.39: Multivariable model using the EGIR definition for the metabolic syndrome

Parameter	DF	Parameter Estimate	Standard Error	Chi-Square	p-value	Hazard Ratio (HR)	95% HR Confidence Limits	
Use of ACEI/ARB	1	-0.07112	0.19951	0.1271	0.7215	0.931	0.630	1.377
SBP	1	0.00698	0.00311	5.0262	0.0250	1.007	1.001	1.013
Development of CHF	1	1.58336	0.18915	70.0710	<.0001	4.871	3.362	7.057
Development of diabetes	1	0.67224	0.46090	2.1273	0.1447	1.959	0.794	4.834
Number of HTN medications	1	-0.10036	0.06482	2.3971	0.1216	0.905	0.797	1.027
Age	1	0.04805	0.01254	14.6774	0.0001	1.049	1.024	1.075
Gender (males vs. females)	1	0.30685	0.13385	5.2558	0.0219	1.359	1.046	1.767
Former smoker vs. never	1	0.07297	0.14562	0.2511	0.6163	1.076	0.809	1.431
Current smoker vs. never	1	0.75934	0.19119	15.7735	<.0001	2.137	1.469	3.108
Race (black vs. other)	1	-0.36477	0.22018	2.7446	0.0976	0.694	0.451	1.069

As can be seen, exposure to either ACEI/ARB had no significant effect on the incidence of cardiovascular events. The hazard ratio for the incidence of any cardiovascular event in the exposed group was found to be equal to 0.93 compared to the control group with a 95% C.I. (0.63, 1.377) suggesting that the hazard for cardiovascular events for those exposed to the drug of interest was not statistically different from the hazard for those who were not exposed to ACEI or ARB.

D) Testing the Proportional Hazard Assumption

1) We included interactions between each variable and log (time) to test for the proportional hazard assumption as presented in table 4.40 below. The table shows the interactions as well as the estimated coefficients, standard errors, Wald statistics and p-

values (the main effects alone are not shown). Wald test for each interaction with time was not statistically significant suggesting that the proportional hazard was most likely met for all the variables except for the "total number of anti-hypertensives" variable.

Table 4.40: Testing the proportional hazard assumption by including interactions of independent variables with time using the EGIR definition for the metabolic syndrome

Parameter	DF	Parameter Estimate	Standard Error	Chi-Square	p-value	Hazard Ratio (HR)	95% HR Confidence Limits	
Use of ACEI/ARB *log(time)	1	-0.01096	0.24665	0.0020	0.9646	0.989	0.610	1.604
SBP*log(time)	1	-0.00421	0.00351	1.4395	0.2302	0.996	0.989	1.003
Development of CHF*log(time)	1	0.48713	0.38753	1.5801	0.2087	1.628	0.762	3.479
Development of diabetes*log(time)	1	0.07233	1.21649	0.0035	0.9526	1.075	0.099	11.665
Number of HTN medications *log(time)	1	0.16075	0.07946	4.0928	0.0431	1.174	1.005	1.372
Age *log(time)	1	-0.03043	0.01329	5.2461	0.0220	0.970	0.945	0.996
Gender*log(time)	1	-0.16581	0.15451	1.1516	0.2832	0.847	0.626	1.147
Former smoking*log(time)	1	0.00787	0.22297	0.0012	0.9719	1.008	0.651	1.560
Past smoking*log(time)	1	-0.21904	0.21596	1.0287	0.3105	0.803	0.526	1.227
Race*log(time)	1	-0.18014	0.25158	0.5127	0.4740	0.835	0.510	1.367

2) The proportional hazard assumption was also tested by examining a plot of the scaled Schoenfeld residuals from the model without the interactions terms with time. Each subplot had a slope essentially equal to zero except for the "total number of antihypertensives" suggesting that the proportional hazard assumption was met for all the variables except this variable (see appendix B for details).

3) Testing the proportional hazard assumption using the rank test as shown in table 4.41 below.

Table 4.41: Testing the proportional hazard assumption by the rank test using the EGIR definition for the metabolic syndrome

Variable	Rho	Chi	DF	p-value
Use of ACEI/ARB	-0.031	0.25	1	0.619
Development of CHF	0.122	3.58	1	0.059
Development of diabetes	0.0097	0.02	1	0.8778
SBP	-0.0886	1.73	1	0.189
Age	-0.116	3.22	1	0.073
Number of HTN medications	0.125	4.0	1	0.046
Gender	-0.079	1.6	1	0.206
Former smoker vs. never smoker	-0.092	2.27	1	0.132
Current smoker vs. never smoker	0.014	0.05	1	0.829
Race	-0.089	1.95	1	0.163
Global test		18.6	10	0.0455

From the previous analysis to test the proportional hazard assumption, we noticed that one variable might violate this assumption "the total number of antihypertensive medications". Therefore, the final modified multivariable model included the previously mentioned variables and the interaction between the total number of anti-hypertensives with time.

E) The Modified Multivariable Model

The final modified multivariable model included the interaction between the total number of anti-hypertensives with time as shown in table 4.42.

Table 4.42: Modified multivariable model using the EGIR definition for the metabolic syndrome

Parameter	DF	Parameter Estimate	Standard Error	Chi-Square	p-value	Hazard Ratio (HR)	95% HR Confidence Limits	
Use of ACEI/ARB	1	-0.10970	0.20204	0.2948	0.5872	0.896	0.603	1.331
SBPI	1	0.00677	0.00311	4.7522	0.0293	1.007	1.001	1.013
Development of CHF	1	1.58319	0.18986	69.5356	<.0001	4.870	3.357	7.066
Development of diabetes	1	0.64936	0.46179	1.9773	0.1597	1.914	0.774	4.733
Number of HTN medications	1	-1.19545	0.54971	4.7292	0.0297	0.303	0.103	0.889
Age	1	0.04939	0.01259	15.3776	<.0001	1.051	1.025	1.077
Gender (male vs. female)	1	0.30223	0.13399	5.0880	0.0241	1.353	1.040	1.759
Former smoker vs. never	1	0.08302	0.14582	0.3242	0.5691	1.087	0.816	1.446
Current smoker vs. never	1	0.76748	0.19120	16.1129	<.0001	2.154	1.481	3.134
Race (black vs. other)	1	-0.33256	0.22084	2.2678	0.1321	0.717	0.465	1.105
Number of HTN medications *log (time)	1	0.15060	0.07451	4.0853	0.0433	1.163	1.005	1.345

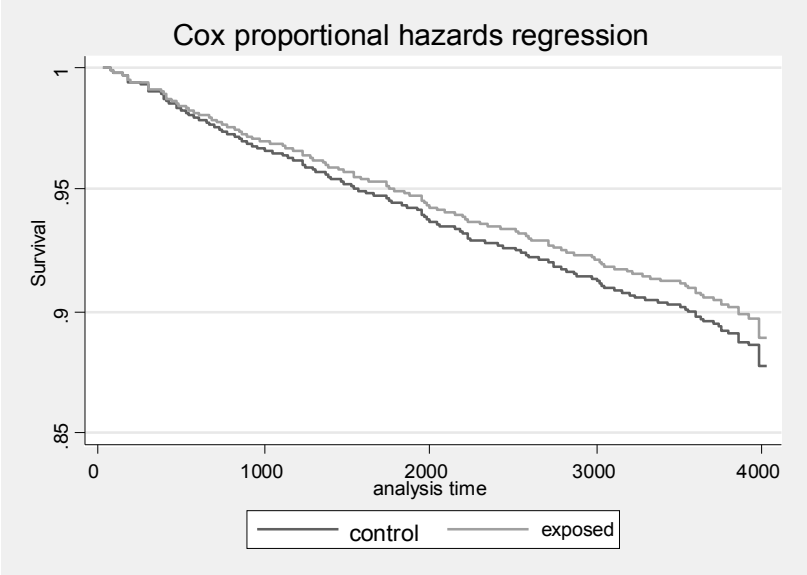
Exposure to either ACEI/ARB had no statistically significant effect on the incidence of cardiovascular events using the EGIR definition of metabolic syndrome. The hazard ratio for the incidence of any cardiovascular event in the exposed group was found to be equal to 0.89 compared to the control group with a 95% C.I. (0.6, 1.33) suggesting that the hazard for cardiovascular events for those exposed to the drug of

interest was not statistically different from the hazard for those who were not exposed to ACEI or ARB for the EGIR definition.

F) Survival Plot

Cox regression survival plot for the multivariable model is presented in figure 4.8 below. Survival estimates for the exposed group (exposed to ACEI/ARB) were not significantly higher than the control group; suggesting that the exposure to ACEI/ARB in hypertensive non-diabetic subjects with the metabolic syndrome according to the EGIR criteria, had no significant protective effect against the development of CVD.

Figure 4.8: Cox regression survival plot using the EGIR definition for the metabolic syndrome

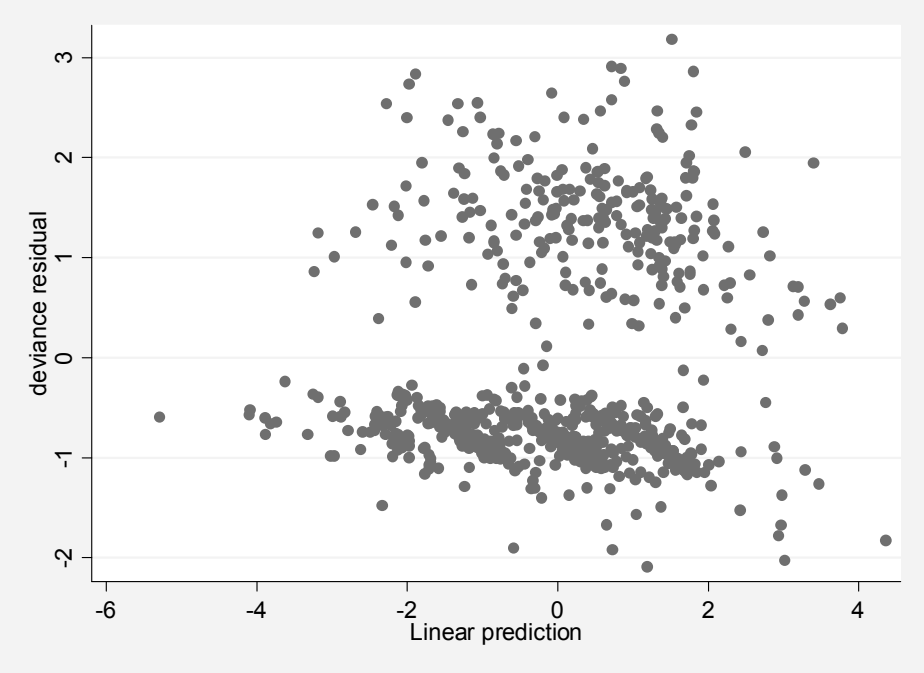


G) Influence Diagnostics

G.1 Deviance residuals

Figure 4.9 shows that none of the observations seem to be of a striking distance from the other points indicating that there did not appear to be any outliers.

Figure 4.9: Deviance residuals plot using the EGIR definition for the metabolic syndrome



G.2 DFBETA statistic

DFBETA was calculated for each variable and none of the variables had exceptionally large values for any of the DFBETAs; none of the DFBETAs was ≥ 2. DFBETA for the use of ACEI/ARB ranged from -0.0197 to 0.039; -0.0166 to 0.035 for CHF; -0.023 to 0.199 for diabetes;-0.00055 to 0.00055 for SBP;-0.08 to 0.193 for the number of anti-hypertensives used; -0.042 to 0.038 for age; -0.013 to 0.015 for gender; -0.016 to 0.016 for former smoking; -0.017 to 0.031 for current smoking; -0.013 to 0.046 for race; -0.025 to 0.0125 for the interaction between the number of anti-hypertensives and time. Thus, we may conclude that there were no unusually influential observations.

Study Number 3: The metabolic syndrome was defined based on the ATP Criteria

A) Consideration of Age as an Independent Variable

The -2 log likelihood for the model where age was treated as a continuous variable was equal to 3236.283, -2 log likelihood for the model with age as a 13 level categorical variable was equal to 3221.402. The difference between the -2 log likelihood for the 2 models was equal to 14.88 which is less than $\chi^2_{11,\ 0.05} = 19.68$ suggesting no trend for non-linearity. Thus, age was included in the model as a continuous variable. Sensitivity analysis using age as a categorical variable was also performed (see Appendix A for details).

B) Univariate Analysis of the Independent Variables

The results of the univariate analyses are shown in table 4.43 below. Most of the independent variables had a statistically significant effect on the time to develop CVD except for the following: BMI, income level, family history of MI and LDL level. Among the time dependent variables, only one variable "development of diabetes" had no statistically significant effect on the outcome of interest.

Table 4.43: Univariate analyses using the ATP definition for the metabolic syndrome

Variable	DF	Parameter Estimate	Standard Error	Chi-Square	p-value	Hazard Ratio
Age	1	0.05025	0.01227	16.7605	<.0001	1.052
Gender (male vs. female)	1	0.71269	0.12598	32.0021	<.0001	2.039
Smoking(former vs. never)	1	0.30989	0.13745	5.0830	0.0242	1.363
Smoking(current vs. never)	1	0.76511	0.18055	17.9580	<.0001	2.149
Race (black vs. other)	1	-0.47588	0.25239	3.5550	0.0594	0.621
# alcohol beverages	1	0.01646	0.00825	3.9804	0.0460	1.017
Aspirin use	1	0.16044	0.13212	1.4746	0.2246	1.174
Exercise intensity level	1	0.11705	0.08143	2.0662	0.1506	1.124
BMI	1	-0.01151	0.01637	0.4949	0.4817	0.989
Income level	1	0.02912	0.03296	0.7808	0.3769	1.030
Family hx of MI	1	0.01301	0.13451	0.0094	0.9230	1.013
Triglycerides	1	0.00194	0.0009438	4.2173	0.0400	1.002
HDL	1	-0.01376	0.00549	6.2759	0.0122	0.986
LDL	1	0.00137	0.00181	0.5755	0.4481	1.001
Time dependent covariates						
Use of ACEI/ARB	1	-0.24629	0.20481	1.4461	0.2292	0.782
SBP	1	0.00814	0.00299	7.4268	0.0064	1.008
Development of diabetes	1	0.02940	0.41767	0.0050	0.9439	1.030
Development of CHF	1	1.96322	0.17102	131.7789	<.0001	7.122
Number of HTN medications	1	-0.08069	0.05998	1.8100	0.1785	0.922

C) The Multivariable Model

In the multivariable model, the level of HDL at baseline, aspirin use, exercise intensity level, the number of alcohol beverages and the total number of anti-hypertensives lost their significant p value and were removed from the multivariable model. However, LDL level at baseline was found to be significantly associated with the time to develop any cardiovascular event after adjusting for other variables (for details on our approach to determine the final model, see model building technique

section in chapter 3). The final model included our variable of interest (exposure to ACEI/ ARB), the variables with a significant effect, as well as any variables that were found to confound the results. We tested for different interactions between the use of ACEI/ARB and race, age as well as gender. However, none of these interactions had any significant effects. The multivariable model is presented in table 4.44 below.

Table 4.44: Multivariable model using the ATP definition for the metabolic syndrome

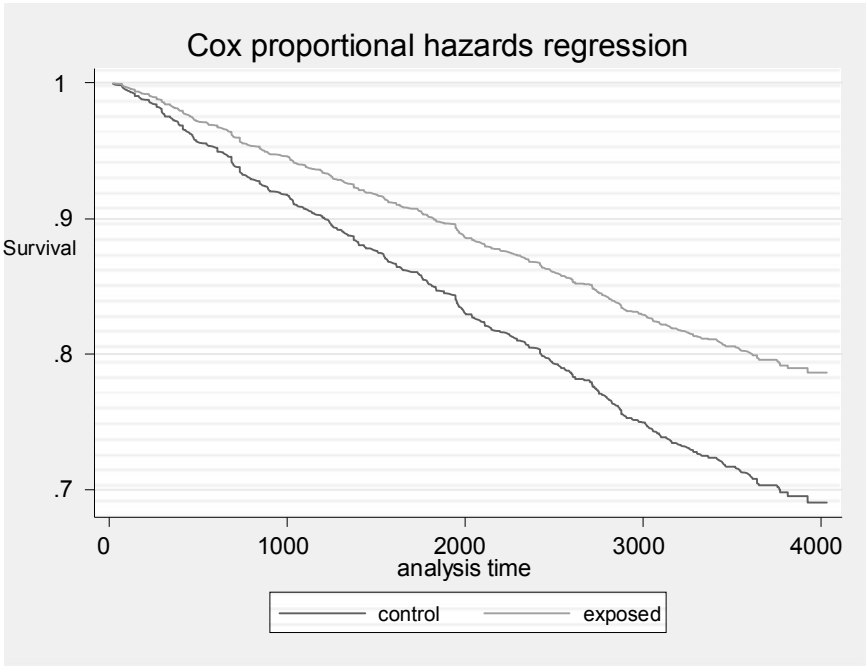
Parameter	DF	Parameter Estimate	Standard Error	Chi-Square	p-value	Hazard Ratio (HR)	95% HR Confidence Limits	
Use of ACEI/ARB	1	-0.41856	0.20996	3.9743	0.0462	0.658	0.436	0.993
Development of CHF	1	2.02361	0.18044	125.7765	<.0001	7.566	5.312	10.775
SBP	1	0.00729	0.00300	5.9084	0.0151	1.007	1.001	1.013
Development of diabetes	1	0.34978	0.42389	0.6809	0.4093	1.419	0.618	3.256
Age	1	0.03441	0.01264	7.4108	0.0065	1.035	1.010	1.061
Gender (male vs. female)	1	0.76092	0.13494	31.7965	<.0001	2.140	1.643	2.788
Former smoker vs. never	1	0.19716	0.14391	1.8768	0.1707	1.218	0.919	1.615
Current smoker vs. never	1	0.76167	0.18661	16.6595	<.0001	2.142	1.486	3.088
Race (black vs. other)	1	-0.21260	0.25750	0.6817	0.4090	0.808	0.488	1.339
Triglycerides	1	0.00272	0.0009689	7.8946	0.0050	1.003	1.001	1.005
LDL	1	0.00445	0.00183	5.8774	0.0153	1.004	1.001	1.008

After adjusting for the different confounding variables, the use of ACEI or ARB was found to reduce the hazard to develop any incident cardiovascular event when using the ATP definition. The hazard ratio associated with the use of either ACEI or ARB was found to be equal to 0.66 with a 95 % confidence interval (0.43, 0.99). This result suggests that the hazard to develop CVD with the use of ACEI/ARB is only 66% of the hazard for those who were not exposed to ACEI/ARB.

D) Survival Plot

Cox regression survival plot for the multivariable model is presented in figure 4.10 below. Survival estimates for the exposed group (exposed to ACEI/ARB) were significantly higher than the control group, suggesting that the exposure to ACEI/ARB in hypertensive non-diabetic subjects with the metabolic syndrome defined by the ATP criteria, has significant protective effect against the development of CVD.

Figure 4.10: Cox regression survival plot using the ATP definition for the metabolic syndrome



E) Testing the Proportional Hazard Assumption

1) We added interactions of each main effect with log (time) to the model to evaluate the proportional hazard assumption. Table 4.45 below presents the estimated

coefficients, standard errors, Wald statistics and p-values for the Wald statistics for the interactions with log-time. Wald test for each interaction with time was not statistically significant suggesting that the proportional hazard is most likely met.

Table 4.45: Testing the proportional hazard assumption by including interactions of independent variables with time using the ATP definition for the metabolic syndrome

Variable	DF	Parameter Estimates	Standard Error	Chi-Square	p-value	Hazard Ratio (HR)	95% Confidence Interval	
Use of ACEI/ARB * log(t)	1	-0.37253	0.20160	3.415	0.065	0.689	0.464	1.023
Age *log(t)	1	-0.00997	0.01281	0.605	0.437	0.990	0.966	1.015
Gender * log(t)	1	-0.15045	0.14846	1.027	0.311	0.860	0.643	1.151
Never Smoking vs. current *log(t)	1	-0.03530	0.20768	0.029	0.865	0.965	0.643	1.450
Former smoking vs. current*log(t)	1	-0.08442	0.19994	0.178	0.673	0.919	0.621	1.360
Race *log(t)	1	0.07825	0.29487	0.070	0.791	1.081	0.607	1.927
LDL *log(t)	1	0.0003081	0.00198	0.024	0.876	1.000	0.996	1.004
Triglycerides * log(t)	1	-0.00154	0.00096 17	2.564	0.109	0.998	0.997	1.000
Development of CHF *log(t)	1	-0.19671	0.20197	0.949	0.331	0.821	0.553	1.220
Development of diabetes *log(t)	1	1.19552	1.80094	0.441	0.507	3.305	0.097	112.7 64
SBP *log(t)	1	-0.00221	0.00329	0.452	0.502	0.998	0.991	1.004

2) The proportional hazard assumption was also tested by examining a plot of the scaled Schoenfeld residuals from the model without the interactions terms with. time. Each subplot has a slope essentially equal to zero suggesting that the proportional hazard assumption is met for all the variables (see appendix B for details).

3) The proportional hazard assumption was tested using the rank test as shown in table 4.46 below. All of the variables seem to satisfy the proportional hazard assumption except for "the use of ACEI/ARB" variable (p value = 0.045).

Table 4.46: Testing the proportional hazard assumption by the rank test using the ATP definition for the metabolic syndrome

Variable	rho	Chi	DF	p-value
Use of ACEI/ARB	-0.12	4.01	1	0.045
CHF	-0.032	0.29	1	0.588
Diabetes	0.024	0.15	1	0.6978
SBP	-0.046	0.54	1	0.462
Age	-0.042	0.48	1	0.489
Gender	-0.096	2.28	1	0.1314
Former smoking vs. never	-0.031	0.25	1	0.62
Current smoking vs. never	0.018	0.08	1	0.7799
Race	-0.0182	0.09	1	0.771
Triglycerides	-0.114	3.34	1	0.0675
LDL	0.024	0.16	1	0.6892
Global test		12.76	11	0.3095

As can be seen from table 4.46 above, the variable "use of ACEI and/or ARB" might not satisfy the proportional hazard assumption. Therefore, another possible model that might be fitted is the model where this variable is treated as time-varying covariate; which means that besides allowing the value of that variable to change over time, the effect of that variable is allowed to interact with the follow-up time. The final multivariable model in this case is presented in table 4.47 below.

Table 4.47: Alternative multivariable model using the ATP definition for the metabolic syndrome

Parameter	DF	Parameter Estimate	Standard Error	Chi-Square	p-value	Hazard Ratio	95% HR Confidence Limits	
Use of ACEI/ARB	1	2.21262	1.43032	2.3930	0.1219	9.140	0.554	150.805
Development of CHF	1	2.05242	0.18083	128.8252	<.0001	7.787	5.463	11.099
SBP	1	0.00732	0.00300	5.9545	0.0147	1.007	1.001	1.013
Development of diabetes	1	0.38538	0.42423	0.8252	0.3637	1.470	0.640	3.377
Age category	1	0.03409	0.01263	7.2834	0.0070	1.035	1.009	1.061
Gender	1	0.75911	0.13499	31.6241	<.0001	2.136	1.640	2.783
Never smoker	1	0.19044	0.14409	1.7469	0.1863	1.210	0.912	1.605
Former smoker	1	0.75705	0.18666	16.4495	<.0001	2.132	1.479	3.074
Race (black vs. other)	1	-0.21965	0.25780	0.7260	0.3942	0.803	0.484	1.331
Triglycerides	1	0.00272	0.0009718	7.8072	0.0052	1.003	1.001	1.005
LDL	1	0.00452	0.00183	6.0913	0.0136	1.005	1.001	1.008
Use of ACEI/ARB*log(t)	1	-0.35952	0.19679	3.3377	0.0677	0.698	0.475	1.027

In this final model, we found that the interaction between the use of ACEI/ARB and time was not significant. Therefore, the final multivariable model that was adopted was the model presented in table 4.44 above.

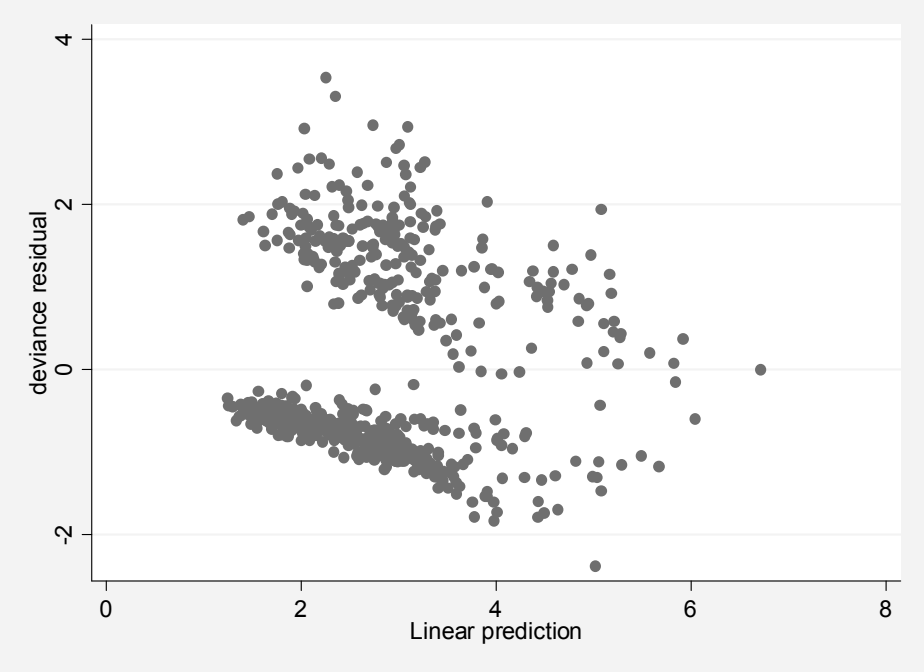
F) Influence Diagnostics

F.1 Deviance residuals:

Deviance residual plot is shown in figure 4.11 below. We notice the 2 clusters that are due to censoring; the upper portion represents the uncensored subjects and the lower portion represents the censored subjects. None of the observations seem to be of a

striking distance between the other points indicating that there do not appear to be any outliers.

Figure 4.11: Deviance residuals plot using the ATP definition for the metabolic syndrome



F.2 DFBETA statistic

DFBETA was calculated for each variable and none of the variables had exceptionally large values for any of the DFBETAs; DFBETAs were less than 2. DFBETA for the use of ACEI/ARB ranged from -0.0199 to 0.0415; -0.023 to 0.0279 for CHF; -0.063 to 0.177 for diabetes, -0.0004 to 0.0006 for SBP; -0.147 to 0.147 for age; 0.0137 to 0.015 for gender; -0.015 to 0.017 for former smoking, -0.022 to 0.027 for current smoking; -0.0128 to 0.071 for race; -0.0003 to 0.0004 for LDL; -0.000097 to 0.00018 for triglycerides. Thus, we may conclude that there were no unusually influential observations.

Study Number 4: The metabolic syndrome was defined based on the AACE criteria

A) Consideration of Age as an Independent Variable

The difference in -2 log likelihood between the model with age as a categorical variable and the model where age was treated as a continuous variable was equal to 18.025 which is less than $\chi^2_{11,\ 0.05} = 19.68$, suggesting no trend for non-linearity of the age variable. Thus age was included in the analysis as a continuous variable. Sensitivity analysis using age as a categorical variable was also performed (see Appendix A for details).

B) Univariate Analysis of the Independent Variables

The results of the univariate analyses of all the independent variables are shown in table 4.48 below. The variables that were found to have a significant effect on the time to incidence of CVD include: age, gender, smoking, race, HDL, BMI and income level. Among the time dependent variables, SBP, development of CHF were significantly associated with the outcome.

Table 4.48: Univariate analyses using the AACE definition for the metabolic syndrome

Variable	DF	Parameter Estimate	Standard Error	Chi-Square	p-value	Hazard Ratio
Age	1	0.06014	0.00987	37.1412	<.0001	1.062
Gender (male vs. female)	1	0.57561	0.10200	31.8425	<.0001	1.778
Smoking(former vs. never)	1	0.25874	0.11080	5.4536	0.0195	1.295
Smoking(current vs. never)	1	0.71888	0.15131	22.5721	<.0001	2.052
Race (black vs. other)	1	-0.29623	0.19724	2.2558	0.1331	0.744
# alcohol beverages	1	0.00385	0.00719	0.2860	0.5928	1.004
Aspirin use	1	0.02942	0.11131	0.0698	0.7916	1.030
Exercise intensity level	1	-0.01387	0.06751	0.0422	0.8372	0.986
BMI	1	-0.02341	0.01377	2.8928	0.0890	0.977
Income level	1	-0.03353	0.02618	1.6401	0.2003	0.967
Family hx of MI	1	-0.03167	0.11159	0.0806	0.7765	0.969
Triglycerides	1	0.0006736	0.0008584	0.6157	0.4327	1.001
HDL	1	-0.00800	0.00386	4.2934	0.0383	0.992
LDL	1	0.0008524	0.00151	0.3172	0.5733	1.001
Time dependent covariates						
Use of ACEI/ARB	1	-0.06731	0.15676	0.1844	0.6677	0.935
SBP	1	0.00812	0.00244	11.0387	0.0009	1.008
Development of CHF	1	2.04171	0.13971	213.5536	<.0001	7.704
Development of diabetes	1	0.22754	0.41488	0.3008	0.5834	1.256
Number of HTN medications	1	-0.04488	0.04860	0.8527	0.3558	0.956

C) The Multivariable Model

We included the variables that were statistically significant in the univariate analysis. We then tested the variables that lost their significant effect upon inclusion in the multivariable model as well as the variables that were not significant in the univariate analysis for any confounding effect. Tests for interactions between the exposure variable and age, race, gender were also conducted (see model building technique section in chapter 3 for details). However, none of these interactions were

found to be statistically significant. The final multivariable model is shown in table 4.49 below.

Table 4.49: Multivariable model for the model using the AACE definition for the metabolic syndrome

Parameter	DF	Parameter Estimate	Standard Error	Chi-Square	p-value	Hazard Ratio (HR)	95% HR Confidence Limits	
Use of ACEI/ARB	1	-0.29815	0.16106	3.4268	0.0641	0.742	0.541	1.018
SBP	1	0.00593	0.00250	5.6366	0.0176	1.006	1.001	1.011
Development of CHF	1	1.89384	0.14535	169.7619	<.0001	6.645	4.998	8.835
Development of diabetes	1	0.23912	0.34468	0.4813	0.4878	1.270	0.646	2.496
Age	1	0.04538	0.01017	19.8924	<.0001	1.046	1.026	1.067
Gender (males vs. females)	1	0.58454	0.10956	28.4678	<.0001	1.794	1.447	2.224
Former smoker vs. never	1	0.23236	0.11628	3.9928	0.0457	1.262	1.004	1.584
Current smoker vs. never	1	0.75686	0.15629	23.4523	<.0001	2.132	1.569	2.896
Race (black vs. other)	1	-0.38979	0.20482	3.6216	0.0570	0.677	0.453	1.012
Income level	1	-0.05666	0.02775	4.1699	0.0411	0.945	0.895	0.998

The hazard ratio for the incidence of any cardiovascular event in the exposed group was found to be equal to 0.74 compared to the control group with a 95% C.I. (0.541, 1.018) suggesting that the hazard for cardiovascular events for those exposed to the drug of interest was only about 74% of the hazard for those who were not exposed to ACEI or ARB but was not statistically significant.

D) Testing the Proportional Hazard Assumption

1) We included interactions between each variable and log (time) to test for the proportional hazard assumption (table 4.50). We notice that the age variable may violate

the proportional hazard assumption as its interaction with log (time) was significant (p-value = 0.015).

Table 4.50: Testing the proportional hazard assumption by including interactions of independent variables with time using the AACE definition for the metabolic syndrome

Covariate	Hazard Ratio	Standard Error	z	p-value	95% Conf. Interval	
Use of ACEI/ARB *log (time)	.9999774	.0001525	-0.15	0.882	.9996785	1.000276
Development of CHF *log(time)	.9999753	.0001479	-0.17	0.867	.9996855	1.000265
Development of diabetes *log (time)	.9998096	.0004842	-0.39	0.694	.9988611	1.000759
SBP *log (time)	.9999987	2.36e-06	-0.53	0.594	.9999941	1.000003
Age *log (time)	.9999768	9.55e-06	-2.43	0.015	.9999581	.9999955
Gender*log (time)	.9998254	.0001028	-1.70	0.089	.9996239	1.000027
Smoking*log (time)	.9999639	.0000715	-0.51	0.613	.9998238	1.000104
Race *log (time)	.9999688	.0002186	-0.14	0.887	.9995405	1.000397
Income level*log (time)	1.000028	.0000259	1.07	0.286	.9999769	1.000079

2) The proportional hazard assumption was also tested by examining a plot of the scaled Schoenfeld residuals from the model without the interactions terms with time. Each subplot has a slope essentially equal to zero suggesting that the proportional hazard assumption is met for all the variables except for the age variable (see appendix B for details).

3) The proportional hazard assumption was examined using the rank test .We notice that the age variable might violate the proportional hazard assumption as shown in table 4.51 below.

Table 4.51: Testing the proportional hazard assumption by the rank test using the AACE definition for the metabolic syndrome

Variable	rho	Chi	DF	p-value
Use of ACEI/ARB	-0.0096	0.04	1	0.849
Development of CHF	-0.008	0.02	1	0.875
Development of diabetes	-0.014	0.08	1	0.777
SBP	-0.026	0.26	1	0.613
Age	-0.123	6.02	1	0.0142
Gender	-0.073	2.04	1	0.154
Former smoking vs. never	-0.072	2.0	1	0.1573
Current smoking vs. never	-0.001	0.0	1	0.983
Race	0.0006	0.0	1	0.983
Income	0.061	1.46	1	0.23
Global test		14.05	10	0.171

E) The Modified Multivariable Model

We notice that the age variable may violate the proportional hazard assumption. Thus, the final modified model included the interaction between the age and time as shown in table 4.52 below. Similar results were generated when age was included as a 3-level categorical variable. The detailed model is presented in Appendix A.

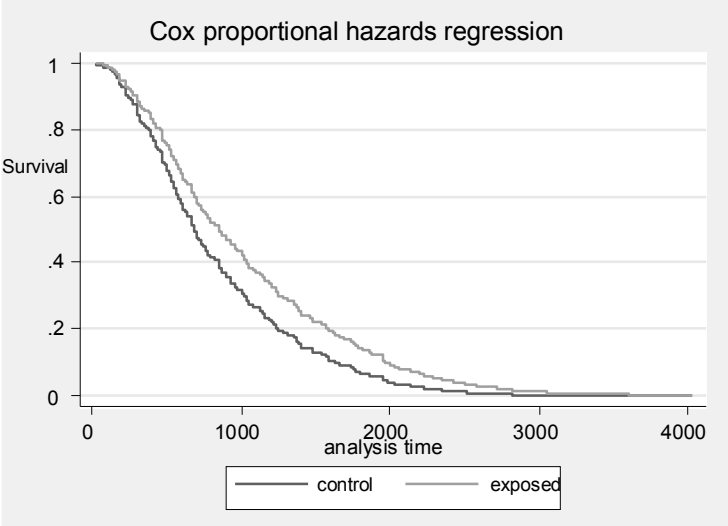
Table 4.52: Modified multivariable model using the AACE definition for the metabolic syndrome

Parameter	DF	Parameter Estimate	Standard Error	Chi-Square	p-value	Hazard Ratio (HR)	95% HR Confidence Limits	
Use of ACEI/ARB	1	-0.30676	0.16128	3.6176	0.0572	0.736	0.536	1.009
SBP	1	0.00580	0.00250	5.3571	0.0206	1.006	1.001	1.011
Development of CHF	1	1.92191	0.14480	176.1644	<.0001	6.834	5.145	9.077
Development of diabetes	1	0.19104	0.34478	0.3070	0.5795	1.211	0.616	2.379
Age	1	0.25336	0.06808	13.8497	0.0002	1.288	1.127	1.472
Gender (male vs. female)	1	0.57147	0.10999	26.9970	<.0001	1.771	1.427	2.197
Former smoker vs. never	1	0.22036	0.11633	3.5881	0.0582	1.247	0.992	1.566
Current smoker vs. never	1	0.75682	0.15628	23.4507	<.0001	2.131	1.569	2.895
Race (black vs. other)	1	-0.38179	0.20490	3.4720	0.0624	0.683	0.457	1.020
Income level at baseline	1	-0.05270	0.02772	3.6135	0.0573	0.949	0.898	1.002
Age *log (time)	1	-0.02929	0.00953	9.4377	0.0021	0.971	0.953	0.989

F) Survival Plot

Cox regression survival plot for the multivariable model is presented in figure 4.12 below. Survival estimates for the exposed group (exposed to ACEI/ARB) are marginally higher than the control group.

Figure 4.12: Cox regression survival plot using the AACE definition for the metabolic syndrome

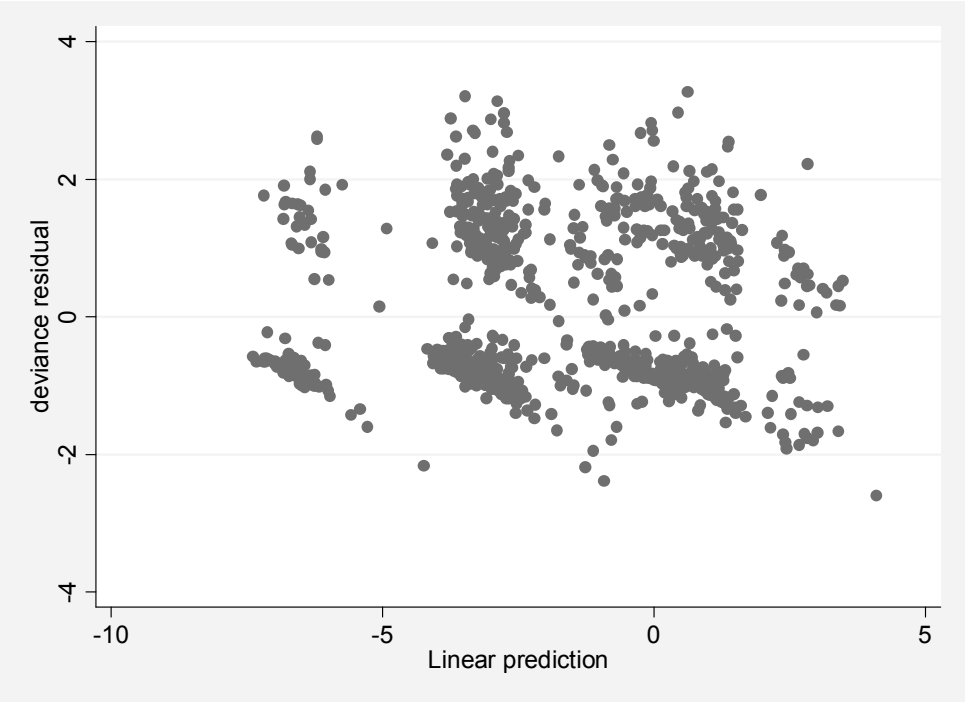


G) Influence Diagnostics

G.1 Deviance residuals

Deviance residuals are presented in figure 4.13 below. None of the observations seem to be of a striking distance between the other points indicating that there do not appear to be any outliers.

Figure 4.13: Deviance residuals plot using the AACE definition for the metabolic syndrome



G.2 DFBETA statistic

DFBETA was calculated for each variable and none of the variables had exceptionally large values for any of the DFBETAs; all DFBETAs were less than 2. DFBETA for the use of ACEI/ARB ranged from -0.017 to 0.025; -0.017 to 0.021 for CHF; -0.045 to 0.12 for diabetes; -0.0003 to 0.0004 for SBP; -0.14 to 0.082 for age; -0.011 to 0.01 for gender; -0.0098 to 0.0094 for former smoking; -0.02 to 0.021 for current smoking; -0.014 to 0.04 for race; -0.0035 to 0.0032 for income; -0.014 to 0.023 for the interaction between age and time. Thus, we may conclude that there were no unusually influential observations.

Specific Aim 2: Identify the effect of ACEI/ARB on the long term development of cardiovascular events in elderly non-diabetic hypertensive patients with insulin resistance.

A) Consideration of Age as Independent Variable

Age was tested for its linear relationship with the hazard to incident cardiovascular event. The -2 log likelihood was compared between the model with age as a linear continuous variable (-2 log likelihood = 5432.072) and the model where age was treated as a 13-level categorical variable (-2 log likelihood = 5415.161). The difference in -2 log likelihood was equal to 16.91 which was less than $\chi^2_{11,\ 0.05} = 19.68$ suggesting no trend for non-linearity. Therefore, age was included in the analysis as a continuous variable. Sensitivity analysis using age as a categorical variable was also performed (for details see Appendix A).

B) Univariate Analysis of the Independent Variables

The following table 4.53 presents the results of the univariate Cox regression analyses. The variables that were found to have a statistically significant effect on the time to incidence of cardiovascular event included: age, gender, current smokers vs. never, race, HDL level, triglycerides, use of aspirin at baseline, BMI at baseline, and family history of MI at baseline. Among the time dependent variables, SBP, the total

number of antihypertensive medications used and the development of CHF were significantly associated with the outcome.

Table 4.53: Univariate analyses for specific aim 2 using the upper quartile of HOMA to define insulin resistance

Variable	DF	Parameter Estimate	Standard Error	Chi-Square	p-value	Hazard Ratio
Age	1	0.058	0.0097	35.58	<0.0001	1.06
Gender (male vs. female)	1	0.558	0.0998	31.289	< 0.0001	1.748
Smoking(former vs. never)	1	0.20226	0.10835	3.4846	0.0619	1.224
Smoking(current vs. never)	1	0.64079	0.14915	18.4578	<.0001	1.898
Race (black vs. other)	1	-0.28901	0.18033	2.5687	0.1090	0.749
# alcohol beverages	1	0.00487	0.00718	0.4606	0.4974	1.005
Aspirin use	1	0.16493	0.10585	2.4280	0.1192	1.179
Exercise Intensity level	1	0.06582	0.06402	1.0571	0.3039	1.068
BMI	1	-0.01833	0.01279	2.0540	0.1518	0.982
Income level	1	-0.00924	0.02561	0.1302	0.7183	0.991
Family hx of MI	1	0.13231	0.10756	1.5130	0.2187	1.141
Triglycerides	1	0.00100	0.0008296	1.4568	0.2274	1.001
HDL	1	-0.01176	0.00381	9.5133	0.0020	0.988
LDL	1	0.00105	0.00147	0.5104	0.4750	1.001
Time dependent covariates						
Use of ACEI/ARB	1	-0.06190	0.15761	0.1542	0.6945	0.940
SBP	1	0.00722	0.00244	8.7461	0.0031	1.007
Development of diabetes	1	0.34268	0.32309	1.1249	0.2889	1.409
Development of CHF	1	1.73429	0.14487	143.3086	<.0001	5.665
Number of HTN medications	1	-0.05733	0.04800	1.4264	0.2323	0.944

C) The Multivariable Model

After adjusting for the other variables, the following variables (level of HDL, triglycerides level, BMI, race, use of aspirin, and family history of MI at baseline) lost their significant effect. However, LDL level at baseline was found to be significantly associated with the time to develop any cardiovascular event after adjusting for other

variables. The total number of anti-hypertensives was found to have a confounding effect in the model. The final model included our variable of interest, the variables with a significant effect, as well as any variables that were found to confound the results. We tested for different interactions between exposure to ACEI/ ARB with race, age and gender. However, none of these interactions had any significant effects. The final model is presented in table 4.54 below.

Table 4.54: Multivariable model for specific aim 2 using the upper quartile of HOMA to define insulin resistance

Parameter	DF	Parameter Estimate	Standard Error	Chi-Square	p-value	Hazard Ratio (HR)	95% HR Confidence Limits	
Use of ACEI/ARB	1	-0.20914	0.17000	1.5135	0.2186	0.811	0.581	1.132
SBP	1	0.00630	0.00247	6.4828	0.0109	1.006	1.001	1.011
Development of CHF	1	1.62256	0.14965	117.5510	<.0001	5.066	3.778	6.793
Development of diabetes	1	0.50339	0.32709	2.3685	0.1238	1.654	0.871	3.141
Number of HTN medications	1	-0.05656	0.05146	1.2078	0.2718	0.945	0.854	1.045
Age	1	0.04919	0.00987	24.8525	<.0001	1.050	1.030	1.071
Gender (male vs. female)	1	0.55373	0.10690	26.8311	<.0001	1.740	1.411	2.145
Former smoker vs. never	1	0.09733	0.11339	0.7368	0.3907	1.102	0.883	1.377
Current smoker vs. never	1	0.58948	0.15148	15.1442	<.0001	1.803	1.340	2.426
Race (black vs. other)	1	-0.29170	0.18273	2.5485	0.1104	0.747	0.522	1.069
LDL	1	0.00397	0.00155	6.5592	0.0104	1.004	1.001	1.007

The multivariable Cox model shows that the hazard ratio for the incidence of any cardiovascular event in the exposed group was found to be equal to 0.81 compared to the control group with a 95% C.I. (0.58, 1.13); suggesting that the hazard for cardiovascular events for those exposed to the drug of interest was only about 81 % of

the hazard for those who were not exposed to ACEI or ARB. However, that association was not statistically significant.

D) Testing the Proportional Hazard Assumption:

1) We tested for the proportional hazard assumption by including interactions between each variable and log (time). Table 4.55 shows the interactions without the main effect as well as the estimated coefficients, standard errors, Wald statistics and p-values for the Wald statistics. Wald test for each interaction with time was not statistically significant except for gender and the total number of antihypertensive medications used. Therefore, it seems that these 2 variables need to be incorporated in the model along with their interactions with log (time).

Table 4.55: Testing the proportional hazard assumption by including the interactions of independent variables with time for specific aim 2

Parameter	DF	Parameter Estimate	Standard Error	Chi-Square	p-value	Hazard Ratio (HR)	95% HR Confidence Limits	
Use of ACEI/ARB *log(time)	1	-0.21688	0.19755	1.2052	0.2723	0.805	0.547	1.186
SBP*log(time)	1	-0.00175	0.00274	0.4048	0.5246	0.998	0.993	1.004
Development of CHF*log(time)	1	-0.11317	0.19887	0.3238	0.5693	0.893	0.605	1.319
Development of diabetes*log(time)	1	0.14597	1.07086	0.0186	0.8916	1.157	0.142	9.439
Gender*log(time)	1	-0.27543	0.12730	4.6815	0.0305	0.759	0.592	0.974
Never Smoking*log(time)	1	0.18752	0.17057	1.2086	0.2716	1.206	0.863	1.685
Former Smoking*log(time)	1	0.00344	0.16218	0.0004	0.9831	1.003	0.730	1.379
Race*log(time)	1	-0.02112	0.20920	0.0102	0.9196	0.979	0.650	1.475
LDL*log(time)	1	-0.0006868	0.00173	0.1581	0.6910	0.999	0.996	1.003
Number of HTN medications *log(time)	1	0.13791	0.06296	4.7978	0.0285	1.148	1.015	1.299

2) The proportional hazard assumption was also tested by examining a plot of the scaled Schoenfeld residuals from the model without the interactions terms with time. Each subplot has a slope essentially equal to zero except for 2 variables (gender and number of antihypertensive medications) suggesting that the proportional hazard assumption was met for all the variables except for these 2 variables.(see appendix B for details).

3) The proportional hazard assumption was examined using the rank test as shown in table 4.56 below. Similarly, we find that gender and total number of antihypertensive medications used may violate the proportional hazard assumption.

Table 4.56: Testing the proportional hazard assumption using the rank test for specific aim 2

Variable	rho	Chi	DF	p-value
Use of ACEI/ARB	-0.044	0.85	1	0.357
Development of CHF	0.0099	0.04	1	0.84
Development of diabetes	0.0024	0.0	1	0.96
SBP	-0.021	0.18	1	0.6672
Age	-0.093	3.39	1	0.066
Number of HTN medications	0.104	4.69	1	0.0304
Gender	-0.095	3.66	1	0.056
Former smoker vs. never smoker	-0.099	3.93	1	0.0473
Current smoker vs. never smoker	-0.046	0.85	1	0.36
Race	-0.041	0.69	1	0.41
LDL	-0.026	0.3	1	0.58
Global test		18.97	11	0.062

E) The Modified Multivariable Model

Gender and total number of antihypertensive medications used may violate the proportional hazard assumption and thus their interactions with time need to be included to the model as shown in table 4.57 below. Exposure to either ACEI/ARB had no statistically significant effect on the incidence of cardiovascular events using the HOMA definition for insulin resistance. The hazard ratio for the incidence of any cardiovascular event in the exposed group was found to be equal to 0.78 compared to the control group with a 95% C.I. (0.56, 1.09) suggesting that the hazard for cardiovascular events for those exposed to the drug of interest was not statistically

different from the hazard for those who were not exposed to ACEI or ARB for the subjects in the upper quartile of HOMA.

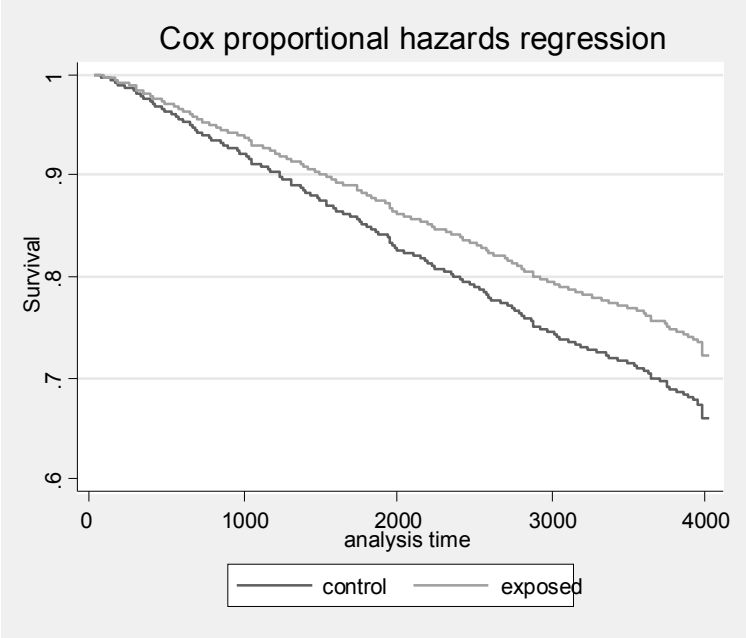
Table 4.57: Interactions of the gender and total number of antihypertensive medications with log (time) added to the model for specific aim 2

Parameter	DF	Parameter Estimate	Standard Error	Chi-Square	p-value	Hazard Ratio (HR)	95% HR Confidence Limits	
Use of ACEI/ARB	1	-0.24721	0.17173	2.0722	0.1500	0.781	0.558	1.093
SBP	1	0.00626	0.00247	6.4341	0.0112	1.006	1.001	1.011
Development of CHF	1	1.63010	0.14998	118.1242	<.0001	5.104	3.804	6.849
Development of diabetes	1	0.48882	0.32750	2.2278	0.1355	1.630	0.858	3.098
Number of HTN medications	1	-0.87803	0.43259	4.1197	0.0424	0.416	0.178	0.970
Age	1	0.04936	0.00986	25.0553	<.0001	1.051	1.030	1.071
Gender	1	2.77431	0.86782	10.2201	0.0014	16.028	2.925	87.812
Former smoking	1	-0.59222	0.15147	15.2865	<.0001	0.553	0.411	0.744
Current smoking	1	-0.49552	0.15182	10.6528	0.0011	0.609	0.452	0.820
Race (black vs. other)	1	-0.26712	0.18283	2.1346	0.1440	0.766	0.535	1.096
LDL	1	0.00406	0.00155	6.8504	0.0089	1.004	1.001	1.007
Gender*log(time)	1	-0.30742	0.11888	6.6871	0.0097	0.735	0.583	0.928
Number of HTN medications*log(time)	1	0.11360	0.05894	3.7140	0.0540	1.120	0.998	1.257

F) Survival Plot

Cox regression survival plot for the multivariable model is presented in figure 4.14 below. Survival estimates for the exposed group (exposed to ACEI/ARB) were not significantly higher than the control group.

Figure 4.14: Cox regression survival plot for specific aim 2

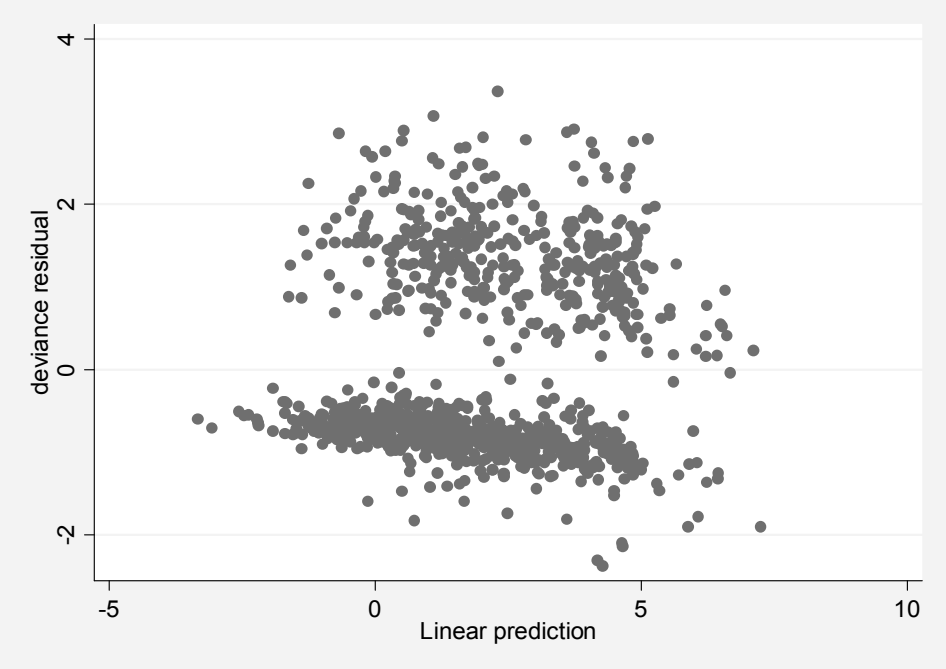


G) Influence Diagnostics

G.1 Deviance residuals

Deviance residuals are presented in figure 4.15 below. None of the observations seem to be of a striking distance from the other points indicating that there do not appear to be any outliers.

Figure 4.15: Deviance residuals plot for specific aim 2



G.2 DFBETA statistic

DFBETA was calculated for each variable and none of the variables had exceptionally large values for any of the DFBETAs; all DFBETAs were less than 2. DFBETA for the use of ACEI/ARB ranged from -0.017 to 0.028; -0.01 to 0.022 for CHF; -0.041 to 0.11 for diabetes; 0.0035 to 0.0004 for SBP; -0.064 to 0.11 for the number of anti-hypertensives; -0.031 to 0.018 for age; -0.33 to 0.083 for gender; -0.009 to 0.0096 for former smoking; -0.0095 to 0.019 for current smoking, -0.01 to 0.033 for race; -0.0002 to 0.0003 for LDL; -0.011 to 0.044 for the interaction between gender and time; -0.015 to 0.01 for the interaction between the number of anti-hypertensives and time. Thus, we may conclude that there were no unusually influential observations.

Summary of the Results for the Primary Outcome of Interest

Table 4.58 below shows a summary for the effect of ACEI/ARB on the primary outcome: the development of the first incident cardiovascular event including MI, claudication, stroke, TIA, angina, angioplasty, CABG, ECG MI or death due to CHD in elderly hypertensive non-diabetic individuals using different criteria for the definition of metabolic syndrome or insulin resistance.

Table 4.58: Summary of the results for the primary outcome of interest

Criteria	Sample Size	Hazard ratio (HR) for using ACEI/ARB	95 % HR Confidence Limits	p value
WHO	990	0.682	(0.48, 0.966)	0.0311
EGIR	749	0.899	(0.605, 1.335)	0.598
ATP III	777	0.652	(0.433, 0.984)	0.04
AACE	1102	0.742	(0.541, 1.017)	0.0635
Upper quartile of HOMA	1216	0.779	(0.557, 1.09)	0.1464

Results for the Effect of Using ACEI/ARB on the Secondary Outcomes of Interest

Results for the different secondary outcomes according to the different definitions of the metabolic syndrome and according to the insulin resistance definition measured by being in the upper quartile of HOMA after adjusting for the different covariates, possible confounders and interactions are shown in table 4.59 below. The secondary outcomes included development of each of the following definite incident events separately: MI, claudication, stroke, TIA, angina, angioplasty, CABG, ECG MI

(silent MI), CHD (development of MI, or angina, or ECG MI, or CHD death), CVA (development of stroke, or TIA).

Different results were observed according to the criteria used to define the insulin resistance. Exposure to ACEI/ARB was found to have a protective effect against the development of MI in elderly hypertensive subjects with evidence of insulin resistance by being in the upper quartile of HOMA, but not in subjects who satisfied the different definitions for the metabolic syndrome. The exposure to ACEI/ARB was found to have a non-significant effect on the development of stroke, CVA, CABG, ECG MI but a significant hazardous effect on the development of TIA in subjects with metabolic syndrome according to WHO and AACE criteria. ACE/ARB had a significant protective effect against having an angioplasty in subjects in the upper quartile of HOMA, and in subjects with metabolic syndrome defined by all criteria except for the EGIR criteria. A hazardous effect on the development of claudication associated with the use of ACEI/ARB was observed in subjects in the upper quartile of HOMA. All the criteria showed a significant protective effect for the use of ACEI/ARB against the development of CHD.

Table 4.59: Summary of the results for the effect of ACEI/ARB on the secondary outcomes of interest in elderly hypertensive non-diabetic subjects using different criteria for the definition of the metabolicsyndrome or insulin resistance

Metabolic syndrome / Insulin resistance definition	Hazard ratio (HR)	95 % C.I.	p value
MI			
WHO	0.527	(0.276, 1.008)	0.0529
EGIR	0.725	(0.332, 1.59)	0.4206
ATP	0.795	(0.365, 1.73)	0.56
AACE	0.541	(0.285, 1.028)	0.0606
HOMA	0.477	(0.23, 0.98)	0.0453
Stroke			
WHO	0.644	(0.327, 1.27)	0.2038
EGIR	0.998	(0.492, 2.02)	0.996
ATP	0.69	(0.299, 1.63)	0.406
AACE	0.488	(0.235, 1.014)	0.0546
HOMA	0.824	(0.439, 1.55)	0.5452
TIA			
WHO	2.2	(1.003, 4.87)	0.0492
EGIR	1.61	(0.615, 4.22)	0.332
ATP	1.93	(0.76, 4.89)	0.165
AACE	2.158	(1.071, 4.34)	0.0314
HOMA	1.77	(0.796, 3.94)	0.1613
CVA (stroke/TIA)			
WHO	1.083	(0.655, 1.79)	0.755
EGIR	1.24	(0.697, 2.19)	0.4701
ATP	1.17	(0.62, 2.2)	0.623
AACE	0.97	(0.592, 1.589)	0.903
HOMA	1.149	(0.703, 1.877)	0.5801

Table 4.61 continued

Metabolic syndrome / insulin resistance definition	Hazard ratio (HR)	95 % C.I.	p value
Angioplasty			
WHO	0.113	(0.015, 0.84)	0.0334
EGIR	0.17	(0.022, 1.31)	0.0886
ATP	0.129	(0.017, 0.952)	0.045
AACE	0.106	(0.014, 0.774)	0.0269
HOMA	0.101	(0.014, 0.752)	0.0252
CABG			
WHO	0.55	(0.22, 1.3)	0.189
EGIR	1.79	(0.68, 4.7)	0.238
ATP	0.352	(0.107, 1.16)	0.086
AACE	0.658	(0.292, 1.48)	0.3141
HOMA	0.863	(0.386, 1.932)	0.7203
Claudication			
WHO	2.3	(0.991, 5.4)	0.0524
EGIR	2.35	(0.79, 6.98)	0.123
ATP	1.97	(0.71, 5.43)	0.19
AACE	1.36	(0.546, 3.398)	0.5078
HOMA	3.12	(1.38, 7.09)	0.0065
ECG MI			
WHO	1.06	(0.22, 5.09)	0.9434
EGIR	1.51	(0.165, 13.8)	0.7144
ATP	0.6	(0.075, 4.8)	0.63
AACE	1.19	(0.341, 4.169)	0.7835
HOMA	1.16	(0.246, 5.5)	0.8488
CHD (MI, angina, ECG MI and CHD death)			
WHO	0.49	(0.32, 0.76)	0.0013
EGIR	0.598	(0.35, 1.008)	0.054
ATP	0.56	(0.339, 0.93)	0.0264
AACE	0.61	(0.411, 0.907)	0.0145
HOMA	0.52	(0.33, 0.798)	0.003

Chapter V
Discussion

Introduction

Identification of subjects with the metabolic syndrome or insulin resistance may provide opportunities to intervene earlier in the development of disease pathways that predispose the individuals to both CVD and diabetes. In this observational study we assessed the effect of ACEI and/ or ARB on the incidence of CVD as an aggregate in hypertensive non-diabetic subjects with the metabolic syndrome or insulin resistance. The use of these medications was found to have a significant protective effect against the incidence of any CVD when the metabolic syndrome was defined according to the ATP and WHO criteria and had only marginally significant protective effect with the use of the AACE criteria for the metabolic syndrome. On the other hand, using the EGIR criteria and the upper quartile of HOMA, the use of ACEI/ARB had a protective trend against the development of CVD but that trend was not statistically significant.

The effect of ACEI/ARB on the separate cardiovascular endpoints was also assessed in elderly hypertensive non-diabetic subjects with evidence of metabolic syndrome or insulin resistance. The results differ according to the criteria used to define the insulin resistance. However, all of the criteria showed a significant protective effect with the use of ACEI/ARB on the incidence of CHD after adjusting for the different

possible confounding factors. This suggests that the effect might be different between the coronary and non-coronary cardiovascular events.

Possible Hazardous Effect of ACEI, But Not ARB, On Cerebrovascular Accidents

The use of ACEI/ARB was associated with a trend for a protective effect against the incidence of different cardiovascular endpoints except for the transient ischemic attacks, cerebrovascular accidents and claudication. The hazardous effect of using either ACEI/ARB in the results section was prominent in the time to incident TIA, especially when the metabolic syndrome was defined according to the AACE and the WHO criteria. The effect of using ACEI or ARB on the time to develop TIA was investigated and the results are shown in tables 5.1 and 5.2 below. As can be seen, the use of ACEI, but not ARB, resulted in a higher hazard to develop TIA when the metabolic syndrome was defined according to the WHO and AACE criteria. The high value of the standard error for the "use of ARB" and the insignificant p value might be explained by the small sample size of ARB users and thus the lack of power to detect a protective or hazardous effect of using ARB on the incidence of TIA. The number of subjects on ACEI and ARB are presented in tables 5.3 and 5.4 below.

Table 5.1: Effect of using ACEI or ARB on the time to incidence of TIA event for patients with the metabolic syndrome defined by the WHO criteria

Parameter	DF	Parameter Estimate	Standard Error	Chi-Square	p-value	Hazard Ratio (HR)
Use of ACEI	1	0.81919	0.40221	4.1482	0.0417	2.269
Use of ARB	1	-13.13705	1949	0.0000	0.9946	0.000

Table 5.2: Effect of using ACEI or ARB on the time to incidence of TIA event for patients with the metabolic syndrome defined by the AACE criteria

Parameter	DF	Parameter Estimate	Standard Error	Chi-Square	p-value	Hazard Ratio (HR)
Use of ACEI	1	0.79574	0.35197	5.1113	0.0238	2.216
Use of ARB	1	-11.01465	803.75573	0.0002	0.9891	0.000

Table 5.3: Number of subjects using ACEI with the metabolic syndrome defined by WHO and AACE criteria

	ACEI baseline	ACEI year 1	ACEI year 2	ACEI year 3	ACEI year4	ACEI year 5	ACEI year 6	ACEI year 7	ACEI year 8	ACEI year 9	ACEI year 10	ACEI year 11
WHO Criteria												
Sample size (percent %)	109 (11%)	108 (10.9%)	108 (10.9%)	128 (12.9%)	139 (14%)	156 (15.8%)	159 (16.1%)	171 (17.3%)	202 (20.4%)	211 (21.3%)	231 (23.3%)	237 (23.9%)
AACE Criteria												
Sample size (percent %)	95 (8.6%)	94 (8.5%)	95 (8.6%)	118 (10.7%)	134 (12.2%	150 (13.6%)	156 (14.2%)	173 (15.7%)	199 (18.1%	210 (19.1%)	226 (20.5%)	236 (21.4%)

Table 5.4: Number of subjects using ARB with the metabolic syndrome defined by WHO and AACE criteria

	ARB baseline	ARB year 1	ARB year 2	ARB year 3	ARB year4	ARB year 5	ARB year 6	ARB year 7	ARB year 8	ARB year 9	ARB year 10	ARB year 11
WHO Criteria												
Sample size (percent %)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (0.1%)	2 (0.2%)	5 (0.5%)	6 (0.6%)	14 (1.4%)	27 (2.7%)	33 (3.3%)
AACE Criteria												
Sample size (percent %)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	3 (0.27%)	6 (0.54%)	8 (0.73%)	13 (1.2%)	24 (2.2%)	28 (2.5%)

The hazardous effect of using ACEI on cerebrovascular events is in agreement with similar findings that were reported in the literature where patients treated with ACEI were found to have more strokes (123-126). It has been suggested that there is an apparent reduction of strokes associated with ARB but not ACEI (127;128). One possible reason is that ACEIs, but not ARBs, increase the systemic bradykinin level that causes vasodilation in both the ischemic and non-ischemic areas of the brain and thus might induce a "cerebral steal syndrome" that might exacerbate the cerebral ischemia. ARBs prevent the action of angiotensin 2 but ACEI prevent the formation of angiotensin 2. It is hypothesized that ARBs selectively block angiotensin 2 subtype 1 (AT1) and is associated with a reflexive increase in angiotensin 2 and unopposed activation of angiotensin 2 subtype 2 receptors. Angiotensin 2 subtype 2 receptors which are up-regulated under ischemic conditions induce vasodilation in the collateral circulation and thus improve cerebral blood flow. Thus, the result would be reduction in the cerebral ischemia without causing the "cerebral steal syndrome".

Metabolic Syndrome vs. Insulin Resistance

It has been suggested that some criteria for the metabolic syndrome such as the ATP criteria might be highly specific but not a sensitive approach to detect insulin resistant subjects (121). This suggests that a substantial number of patients who are insulin resistant would not be labeled as "metabolic syndrome patients". However, a large proportion of non-insulin resistant subjects would not satisfy the "metabolic

syndrome" criteria. Thus, some of the proposed "metabolic syndrome" criteria might not serve as a good screening method to detect insulin resistance.

What makes the subjects at higher risk for CVD is still unknown: is it the underlying insulin resistance or the clustering of different cardiovascular risk factors for the metabolic syndrome? Taking that into consideration, we chose to study the effect of inhibiting the renin-angiotensin system on 2 different populations: subjects who had a clustering of risk factors by satisfying different criteria for the metabolic syndrome, and insulin resistant subjects according to the HOMA level as well. We found a significant protective effect for the use of ACEI/ARB on the incidence of CVD in elderly hypertensive non-diabetic subjects who satisfied the metabolic syndrome definition according to the ATP and WHO criteria. However, that association was not significant in those who were insulin resistant according to the HOMA level and those who satisfied the other definitions of metabolic syndrome. These results might suggest that the ATP and WHO criteria might be the best criteria available to identify elderly subjects at high CVD risk as suggested by other studies (129). Insulin resistance by being in the upper quartile of HOMA might not be the best method to identify elderly patients at risk for CVD (130;131). There is still a need for more studies to find the criteria that best identify the elderly subjects who are at high risk to develop CVD.

The Metabolic Syndrome Criteria and Prediction of CVD

The literature has many conflicting results concerning the performance of the different available metabolic syndrome definitions in the prediction of cardiovascular

events. Some of the proposed criteria might have limited ability to detect subjects at high CVD risk; a substantial number of subjects will still be undetected (129). In particular, the criteria adopted by AACE and EGIR were found to have a much lower discriminatory power among the other criteria including the WHO, and ATP criteria for the metabolic syndrome (129). That finding might explain the insignificant results for the effect of ACEI/ARB on the CVD when the metabolic syndrome was defined according to AACE or EGIR criteria.

Discrepancy between the Middle Aged and the Elderly Population

It has been well established that the metabolic syndrome is associated with increased CVD in the middle age population. However, our study involved elderly subjects 65 years and older. In the elderly population, some studies have suggested the limited predictive utility of the metabolic syndrome to predict total or CVD mortality compared with the assessment of only the fasting glucose and blood pressure among the other risk factors (132). In other words, the higher risk of cardiovascular mortality associated with metabolic syndrome in the elderly was confined to individuals who had hypertension or altered glucose metabolism as one of the criteria, suggesting a lower impact of the other risk factors such as HDL, triglycerides and waist circumference levels.

It has also been suggested that for the elderly population, many metabolic parameters increase with age and thus the threshold of many of these variables need to be increased adjusting for these physiological changes. Therefore, in the definition of

the metabolic syndrome, higher cut points for the risk factors might be more appropriate for risk prediction (120). There is a need for future studies designed specifically to define the best criteria with the best cut-points that might predict cardiovascular risk and mortality in the elderly population.

Despite the unavailability of the best criteria to define the metabolic syndrome that are predictive of the CVD risk in the elderly population as mentioned above, we found a significant protective effect for the use of ACEI/ARB against the development of CVD in elderly hypertensive non-diabetic subjects with the metabolic syndrome according to the WHO and the ATP criteria. In addition, we found a significant protective effect for the use of ACEI/ARB against the development of CHD in the elderly hypertensive non-diabetic subjects with the metabolic syndrome according to all the available criteria for the metabolic syndrome.

Validation of the Final Multivariable Models

All of the final multivariable Cox models that assessed the effect of using ACEI/ARB, in hypertensive non-diabetic subjects with a diagnosis of the metabolic syndrome or evidence of insulin resistance, showed the effects of the other well-established cardiovascular risk factors as expected. These models showed an increased risk of CVD with increased age, male gender, higher SBP, CHF diagnosis, smoking, and higher LDL, triglycerides levels and lower income level as expected.

To validate the conclusions obtained from the multivariable models, we tested the effect of using ACEI/ARB on the first incident CVD after adjusting for the use of

the other antihypertensive classes of medications by including them as time dependent variables in the models (see appendix C for details of the models). In addition, these models allowed us to evaluate the effect of each of the following classes of anti-hypertensives: beta blockers, alpha blockers, calcium channel blockers, diuretics and vasodilators on the outcome. None of the new variables had any confounding effect on the results. In addition, we found that the use of ACEI/ARB, but not any other antihypertensive class of drugs, was associated with a significant protective effect against the development of CVD in hypertensive non-diabetic subjects with the metabolic syndrome according to the ATP and the AACE criteria. In study 1 (Aim 1) which used the WHO definition as criteria for the metabolic syndrome, all the other anti-hypertensives were not significantly associated with the outcome. However, ACE/ARB use had a protective hazard ratio of 0.68 with a marginally significant p-value (0.063). These findings strengthen our conclusion that the use of ACEI/ARB specifically, among all the antihypertensive medications, might reduce the risk of CVD in elderly hypertensive non-diabetic subjects with the metabolic syndrome after adjusting for the use of other anti-hypertensives.

Limitations and Potential Pitfalls

There are certainly some limitations in our study. The obvious primary limitation, as any other epidemiological study, is the lack of random assignment of subjects to the exposed group. Thus, unmeasured systematic differences between patients prescribed ACEI/ARB and those who were not might be potentially present.

However, many possible confounding variables were controlled for in the analysis. It is also possible that the healthcare providers chose ACEI or ARB for patients who were at increased risk of developing CVD such as diabetic and CHF patients. Therefore, the development of diabetes and CHF were adjusted for in the model as time dependent variables in order to control for possible confounding by indication bias.

The use of ACEI/ARB might need a relatively long period of time to exert their cardiovascular protective effect. The duration of exposure to ACEI/ARB for some subjects in this study was less than the full follow-up time of the study because they were not prescribed these medications at baseline. However, we were able to show that the use of ACEI/ARB was associated with lower CVD despite the inconsistent duration of exposure which strengthened our conclusion. Another possible limitation is that the use of medication was determined using an annual medication inventory. Therefore, it is possible that drug exposure might have changed during the interval between assessment and any cardiovascular event.

CVD is known to develop over a long time period. Therefore, it is possible that some subjects might have cardiovascular abnormalities that might not be clinically evident at baseline, which led to the early development of CVD few years after participating in the study. Events prevented in the early years of follow-up may indicate that ACEI/ARB not only reduces the incidence of CVD but also might modulate the progression of preclinical CVD. Cox regression survival plots using the WHO and the ATP criteria to define the metabolic syndrome as shown in figures 4.6

and 4.10 show that the survival curves for subjects who had been exposed to ACEI/ARB and those using other anti-hypertensives start to separate 1-2 years after the start of the follow-up.

The WHO definition of the metabolic syndrome included the level of microalbuminuria as one of the risk criteria. However, it was ignored in our analysis as microalbuminuria was not assessed at baseline in the CHS data. Similarly the WHO criteria uses the euglycemic clamp as an insulin resistance measure; however we were not able to use the euglycemic clamp as the measure of insulin resistance since such labor-intensive measures were not available from this large epidemiology dataset. HOMA level measurements were used instead.

Starting from year 12 on, the follow-up data for the subjects were retrieved from patients' self report through phone follow-up interviews. There were no reliable measurements of blood pressure, fasting plasma glucose and glucose tolerance test. Therefore, the use of the time dependent variables (SBP, development of diabetes and CHF) and follow-up event data were limited to the first 11 years of the study.

Moreover, the results of this study might not be generalizable to patients younger than 65 years old as only elderly subjects were included in the database. Similarly, volunteer bias cannot be ruled out; as there is a possibility that the cohort of 5888 subjects who agreed to participate in the CHS study might be different than those who did not participate in the study.

Conclusion

The effect of ACEI/ARB differs between metabolic syndrome patients and patients in the upper quartile of HOMA. In addition, the effect of ACEI/ARB differs according to the metabolic syndrome criteria used. Different definitions of the metabolic syndrome represent different views regarding the etiology and pathophysiology basis of the syndrome. Overall, in elderly hypertensive non-diabetic subjects, ACEI/ARB might be protective against the development of CVD in subjects who satisfied the WHO and ATP criteria for the metabolic syndrome. There is a significant beneficial effect for the use of ACEI/ARB on the CHD specifically in all the study subsets. On the other hand, a possible hazardous effect for the development of TIA might be associated with the use of ACEI but not ARB. However, there is still a need for future studies to establish the criteria that best identify elderly subjects who are at increased risk for CVD.

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Appendix A
"Presentation of Different Multivariable Models Using the Age Variable According to the Classical Geriatric Classification"

The age variable was included in the multivariable models above as a linear continuous variable if the formal test of linearity was satisfied. Age is usually grouped in the elderly according to the classical geriatric classification: (65-74 years), (75-84) and (85 years and older). Therefore, the analyses were repeated using age as a categorical variable according to the three previously mentioned categories to account for any differences between these age groups. Similar results and conclusions regarding the multivariable models, testing the proportional hazard assumption and influential diagnostics were generated when age was treated as continuous and as categorical. Detailed multivariable models using age as a categorical variable are presented below.

Table 1: Multivariable model for the EGIR criteria using age as a categorical variable

Parameter	DF	Parameter Estimate	Standard Error	Chi-Square	P-value	Hazard Ratio (HR)	95% HR Confidence Limits	
Use of ACEI/ARB	1	-0.10450	0.20217	0.2672	0.6052	0.901	0.606	1.339
SBP	1	0.00752	0.00309	5.9245	0.0149	1.008	1.001	1.014
Development of CHF	1	1.56172	0.19166	66.3952	<.0001	4.767	3.274	6.940
Development of diabetes	1	0.61650	0.46121	1.7868	0.1813	1.852	0.750	4.574
Number of HTN medications	1	-1.15407	0.54696	4.4520	0.0349	0.315	0.108	0.921
Age level (65-74)	1	-1.00999	0.46857	4.6461	0.0311	0.364	0.145	0.912
Age level (75-84)	1	-0.66394	0.47654	1.9411	0.1635	0.515	0.202	1.310
Gender (male vs. female)	1	0.32870	0.13523	5.9086	0.0151	1.389	1.066	1.811
Former smoking vs. never	1	0.06818	0.14667	0.2161	0.6421	1.071	0.803	1.427
Current smoking vs. never	1	0.74407	0.19134	15.1229	0.0001	2.104	1.446	3.062
Race (black vs. other)	1	-0.34051	0.22103	2.3733	0.1234	0.711	0.461	1.097
Number of HTN medications *log(time)	1	0.14605	0.07417	3.8774	0.0489	1.157	1.001	1.338

Table 2: Multivariable model for the ATP criteria using age as a categorical variable

Parameter	DF	Parameter Estimate	Standard Error	Chi-Square	P-value	Hazard Ratio (HR)	95% HR Confidence Limits	
Use of ACEI/ARB	1	-0.42014	0.21049	3.9842	0.0459	0.657	0.435	0.992
Development of CHF	1	2.02094	0.18261	122.4766	<.0001	7.545	5.275	10.79
Development of SBP	1	0.00793	0.00301	6.9343	0.0085	1.008	1.002	1.014
Development of diabetes	1	0.31719	0.42321	0.5617	0.4536	1.373	0.599	3.148
Age level (65-74)	1	-0.77645	0.34064	5.1957	0.0226	0.460	0.236	0.897
Age level (75-84)	1	-0.49789	0.34918	2.0331	0.1539	0.608	0.307	1.205
Gender (male vs. female)	1	0.77303	0.13466	32.9542	<.0001	2.166	1.664	2.821
Former smoker vs. never	1	0.19373	0.14387	1.8132	0.1781	1.214	0.916	1.609
Current Smoker vs. never	1	0.76674	0.18745	16.7311	<.0001	2.153	1.491	3.108
Race (black vs. others)	1	-0.21540	0.25791	0.6975	0.4036	0.806	0.486	1.337
Triglycerides	1	0.00263	0.0009776	7.2140	0.0072	1.003	1.001	1.005
LDL	1	0.00448	0.00184	5.9031	0.0151	1.004	1.001	1.008

Table 3: Multivariable model for the AACE criteria using age as a categorical variable

Parameter	DF	Parameter Estimate	Standard Error	Chi-Square	P-value	Hazard Ratio (HR)	95% HR Confidence Limits	
Use of ACEI/ARB	1	-0.30674	0.16139	3.6123	0.0574	0.736	0.536	1.010
SBP	1	0.00634	0.00252	6.3519	0.0117	1.006	1.001	1.011
Development of CHF	1	1.92640	0.14519	176.0388	<.0001	6.865	5.165	9.125
Development of diabetes	1	0.16731	0.34417	0.2363	0.6269	1.182	0.602	2.321
Age level (65-74)	1	-5.43315	1.41542	14.7345	0.0001	0.004	0.000	0.070
Age level (75-84)	1	-3.03716	1.39622	4.7318	0.0296	0.048	0.003	0.740
Gender (male vs. female)	1	0.57877	0.11012	27.6263	<.0001	1.784	1.438	2.214
Former smoking vs. never	1	0.21891	0.11646	3.5331	0.0602	1.245	0.991	1.564
Current smoking vs. never	1	0.74885	0.15663	22.8572	<.0001	2.115	1.556	2.874
Race (black vs. other)	1	-0.39548	0.20501	3.7213	0.0537	0.673	0.451	1.006
Income level at baseline		-0.05234	0.02773	3.5622	0.0591	0.949	0.899	1.002
Age level (65-74) *log(time)	1	0.62059	0.21023	8.7140	0.0032	1.860	1.232	2.808
Age level (75-84)*log(time)	1	0.33475	0.20878	2.5708	0.1089	1.398	0.928	2.104

Table 4: Multivariable model for specific aim 2 using age as a categorical variable

Parameter	DF	Parameter Estimate	Standard Error	Chi-Square	p-value	Hazard Ratio (HR)	95% HR Confidence Limits	
Use of ACEI/ARB	1	-0.25493	0.17192	2.1987	0.1381	0.775	0.553	1.085
SBP	1	0.00688	0.00247	7.7862	0.0053	1.007	1.002	1.012
Development of CHF	1	1.64171	0.15032	119.284	<.0001	5.164	3.846	6.933
Development of diabetes	1	0.43283	0.32711	1.7508	0.1858	1.542	0.812	2.927
Number of HTN medications	1	-0.82859	0.43026	3.7088	0.0541	0.437	0.188	1.015
Age level (65-74)	1	-0.82488	0.31367	6.9156	0.0085	0.438	0.237	0.811
Age level (75-84)	1	-0.42610	0.31954	1.7781	0.1824	0.653	0.349	1.222
Gender	1	2.79502	0.86797	10.3696	0.0013	16.363	2.986	89.677
Former smoking	1	0.09633	0.11368	0.7181	0.3968	1.101	0.881	1.376
Current smoking	1	0.60474	0.15236	15.7541	<.0001	1.831	1.358	2.468
Race (black vs. other)	1	-0.28830	0.18298	2.4824	0.1151	0.750	0.524	1.073
LDL	1	0.00390	0.00156	6.2432	0.0125	1.004	1.001	1.007
Gender*log(time)	1	-0.30872	0.11891	6.7403	0.0094	0.734	0.582	0.927
Number of HTN medications*log(time)	1	0.10683	0.05865	3.3173	0.0686	1.113	0.992	1.248

Appendix B
"Assessment of the Proportional Hazard Assumption Using the Scaled Schoenfeld Residuals"

List of Abbreviations

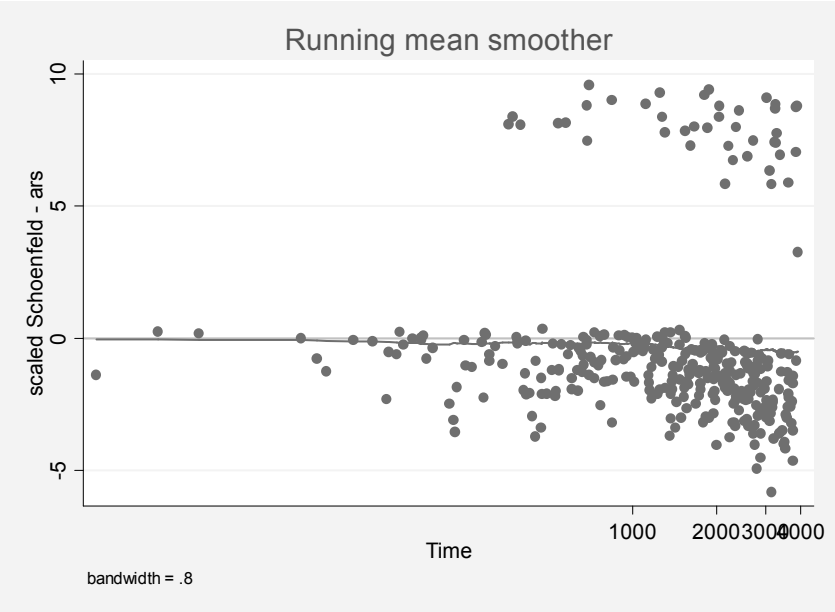
Table 5 below presents the list of abbreviations used in the residuals plots.

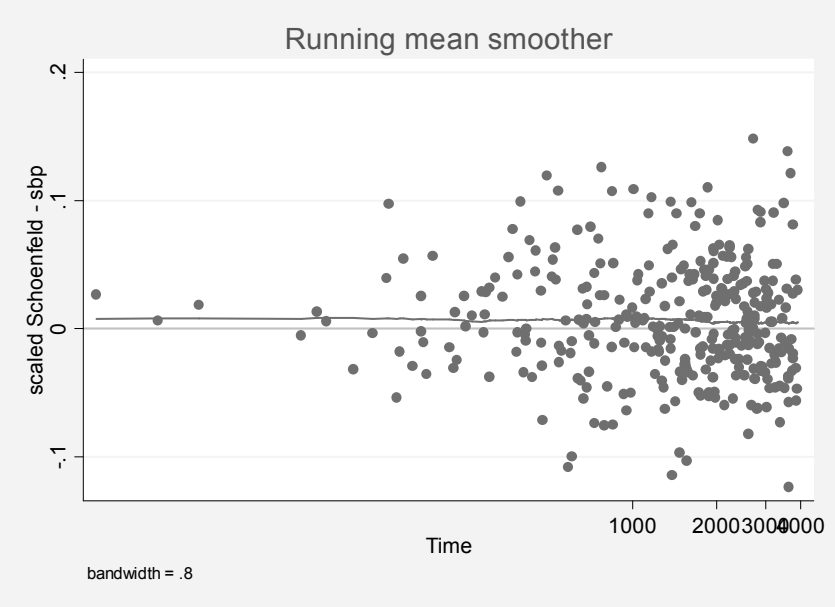
Table 5: List of abbreviations

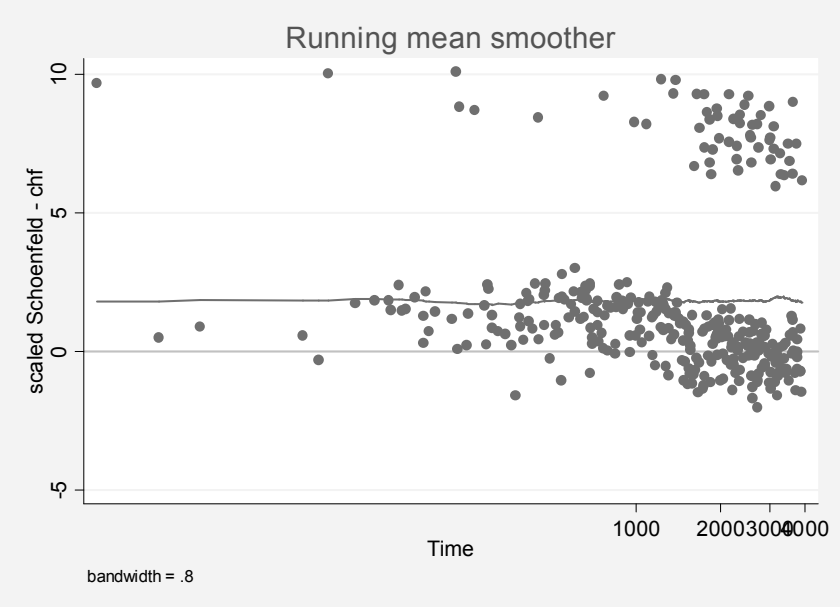
Abbreviation	Label
ars	Use of ACE/ARB
htnmd	Number of HTN medications
Agecatbl, newagecat, z	Age variable
gendbl	Gender
ldlbl	LDL at baseline
smokebl	Smoking at baseline
trigbl	Triglycerides at baseline
incomebl	Income level at baseline

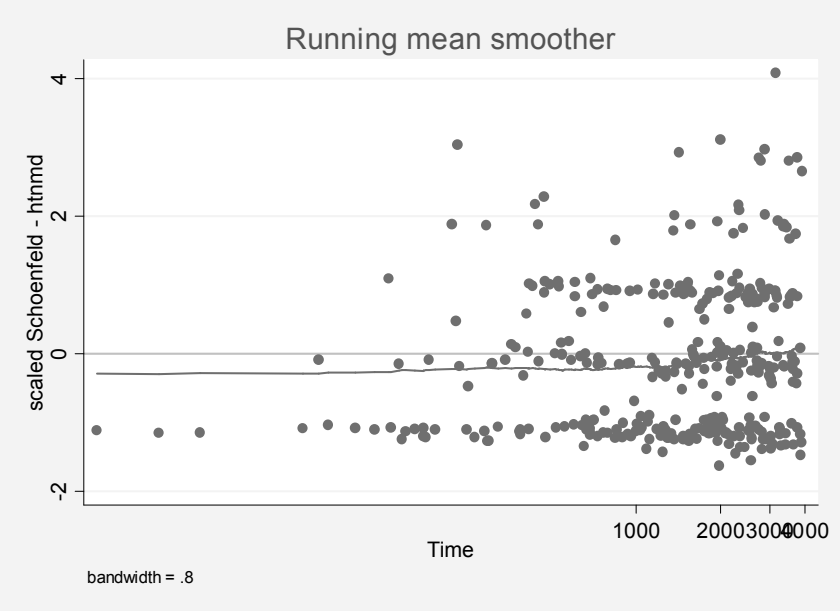
Specific Aim 1: Identify the effect of ACEI/ARB on the long term development of cardiovascular events in elderly non-diabetic hypertensive patients with metabolic syndrome.

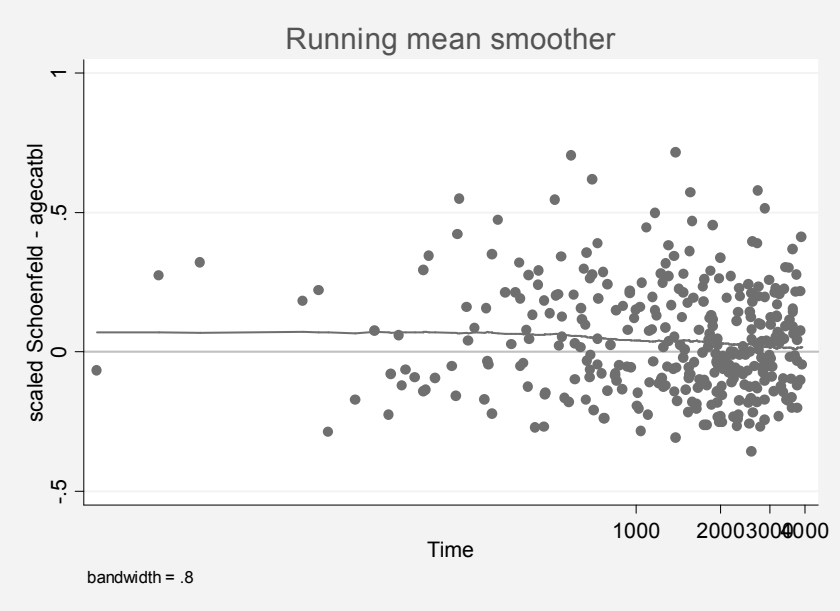
Study number 1: The metabolic syndrome defined using the WHO Criteria

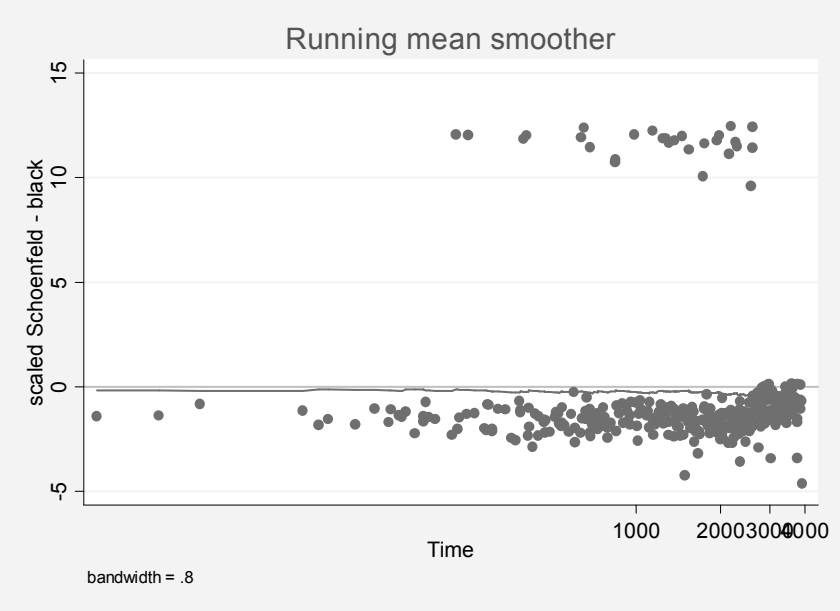


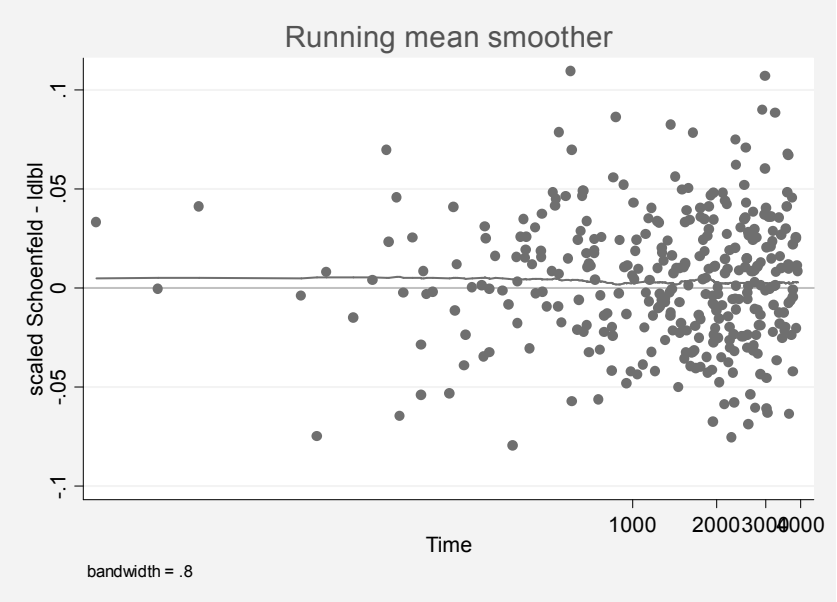




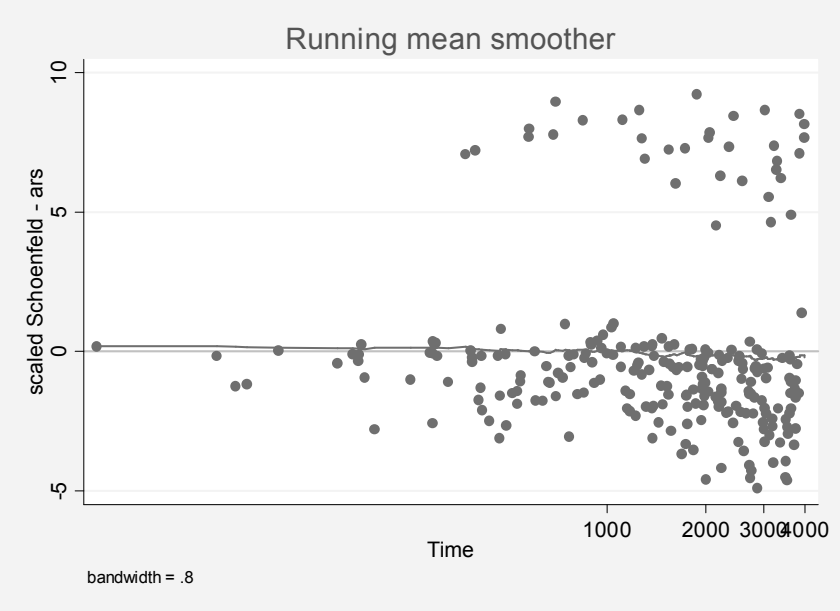


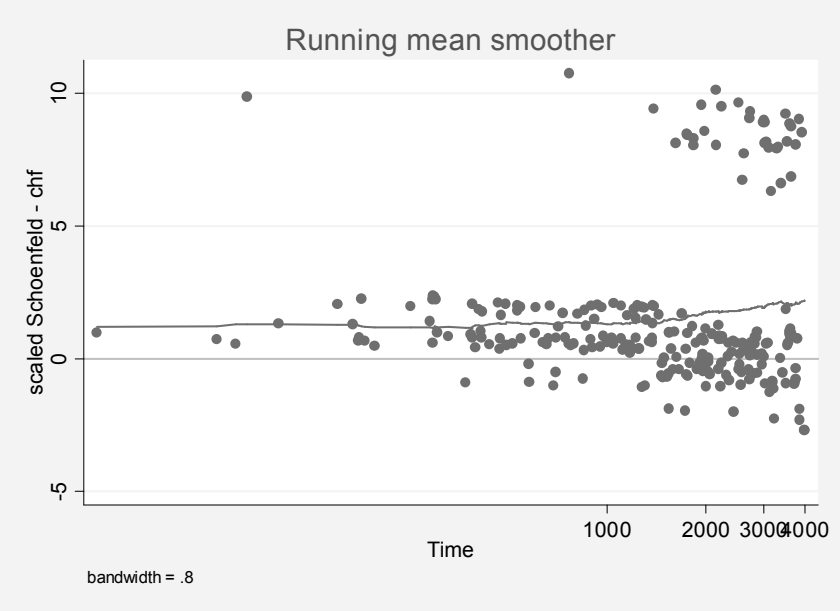


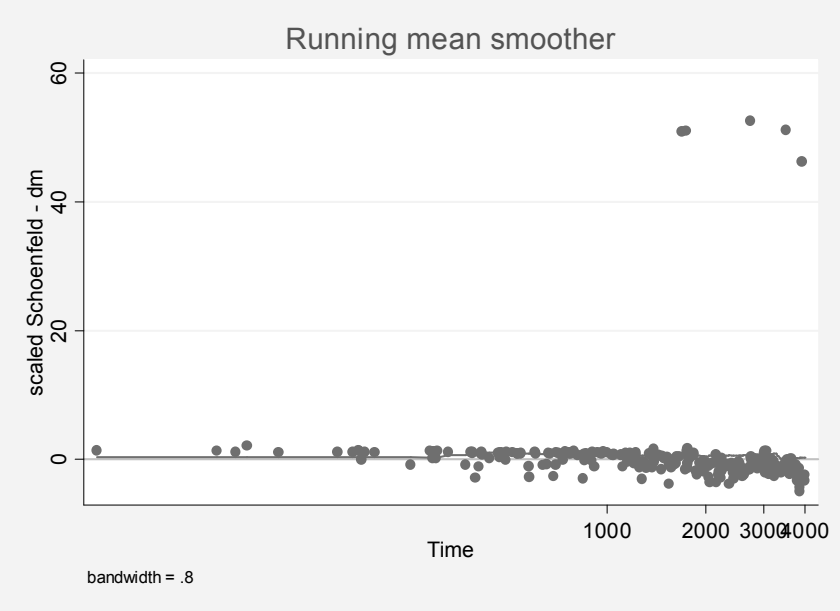


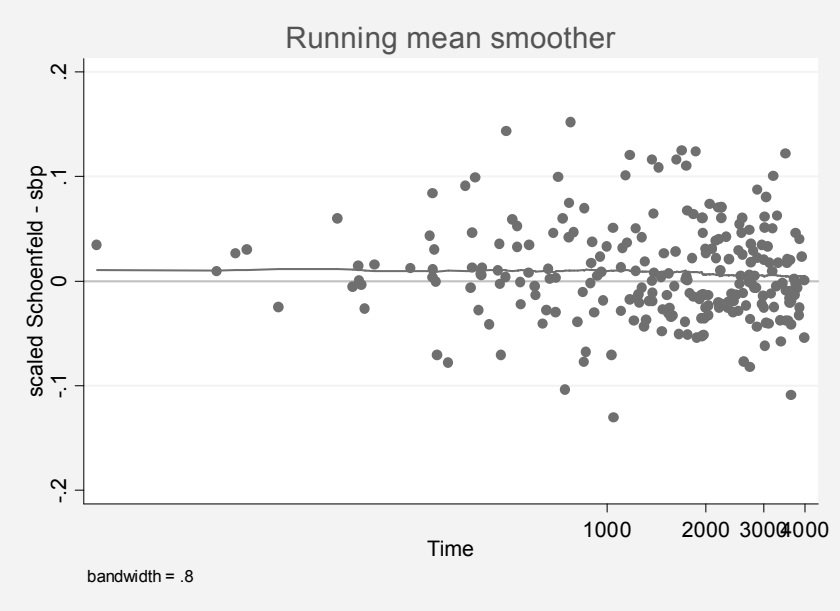


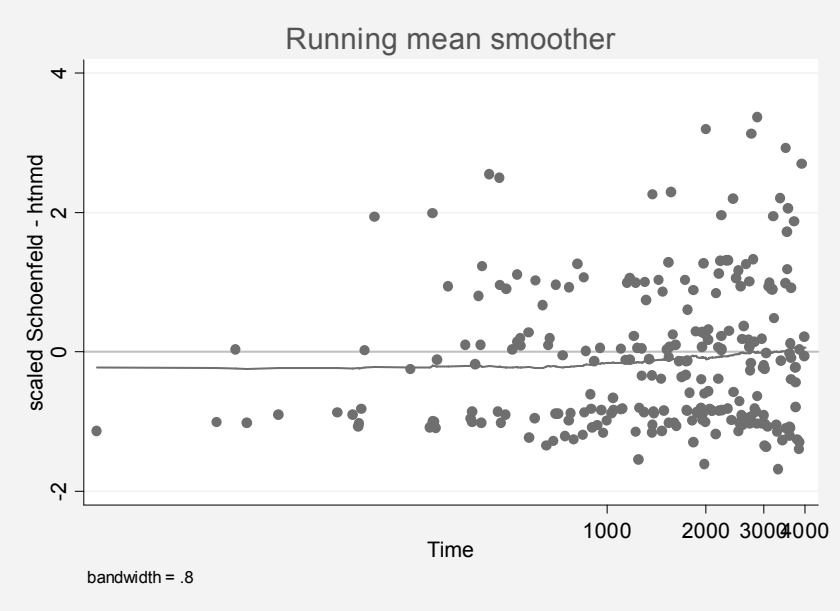
Study 2: The metabolic syndrome defined using the EGIR Criteria

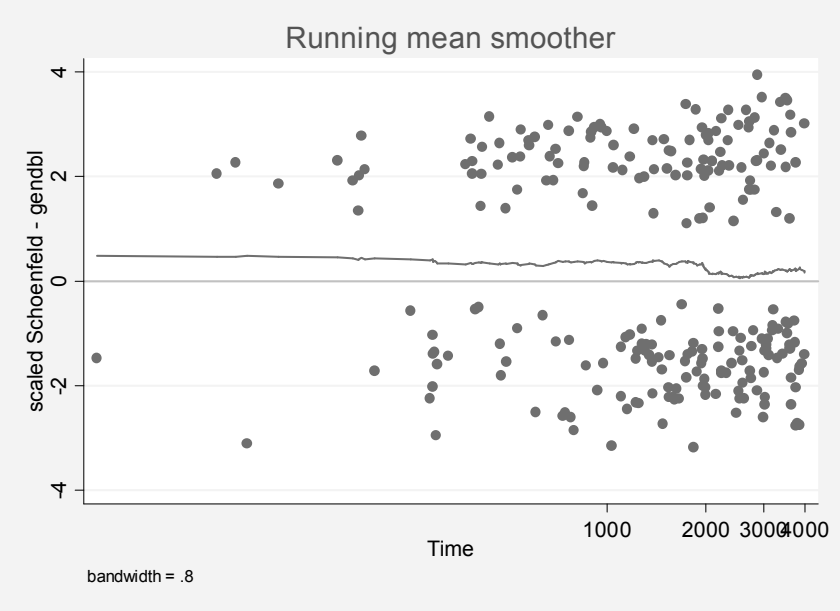


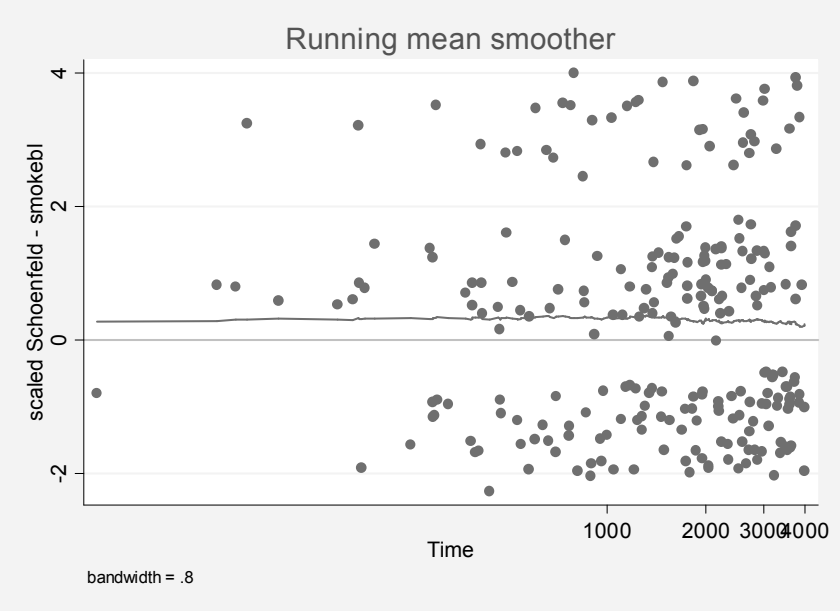




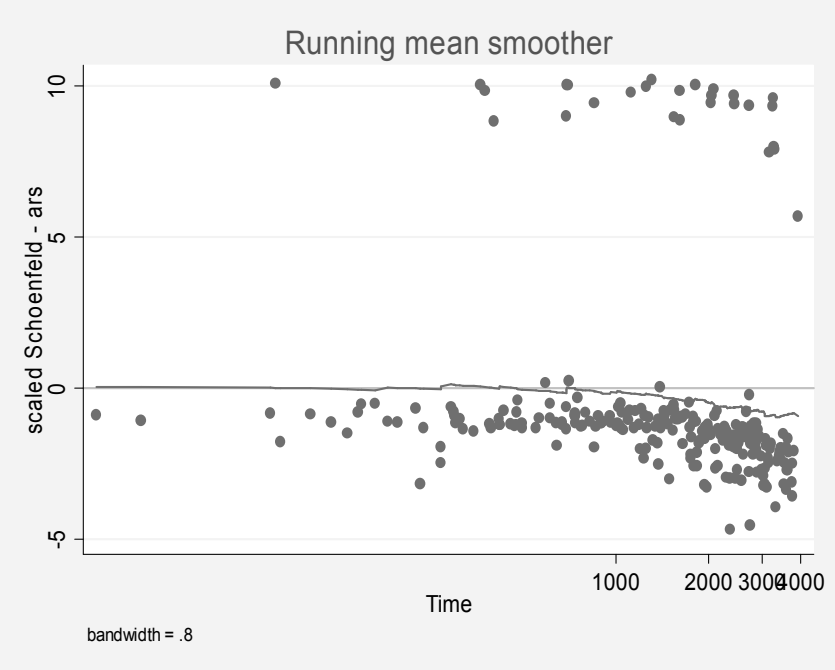


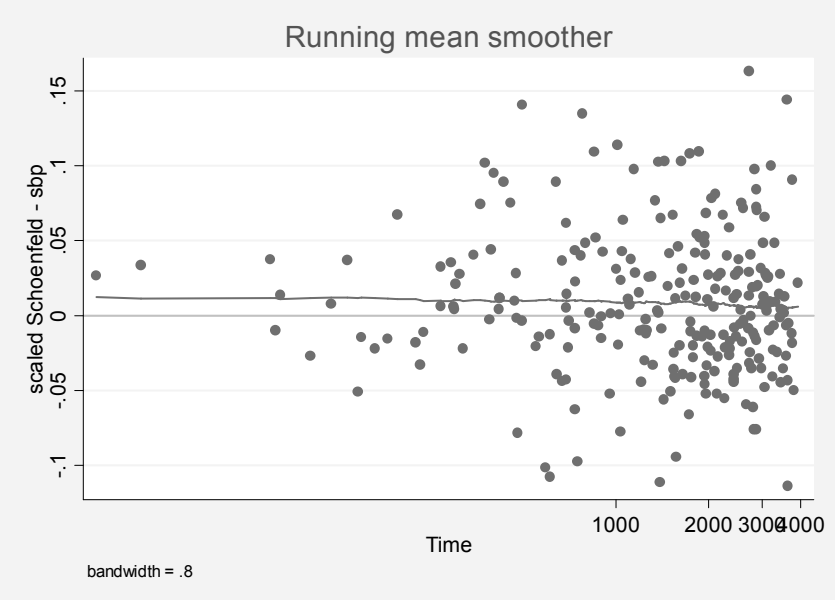


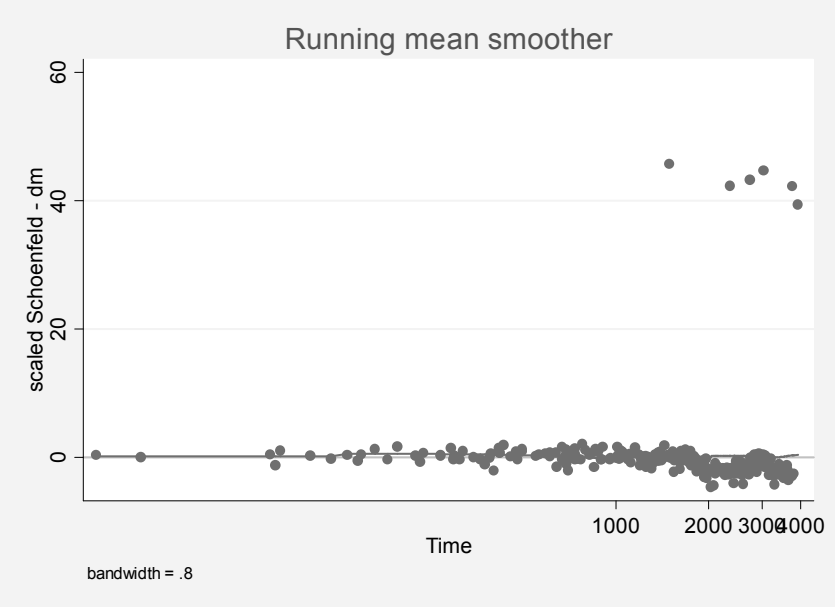


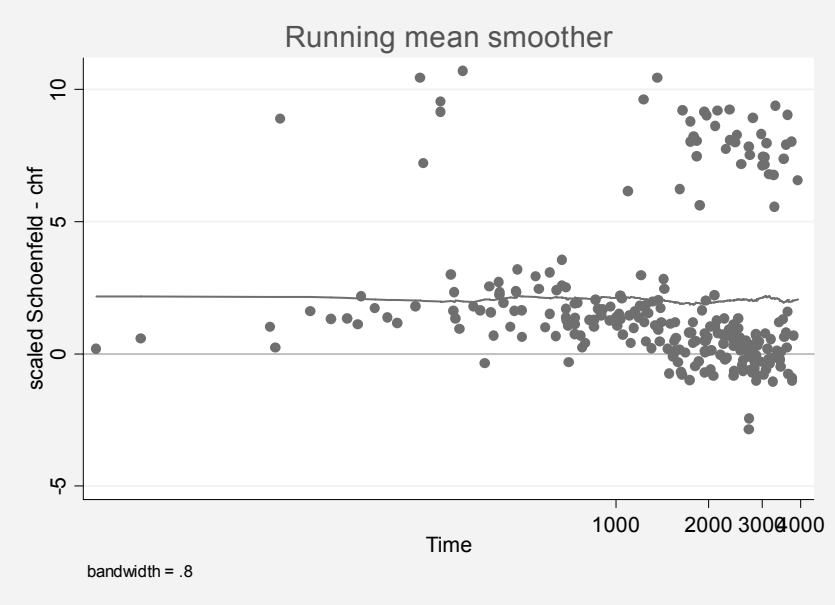


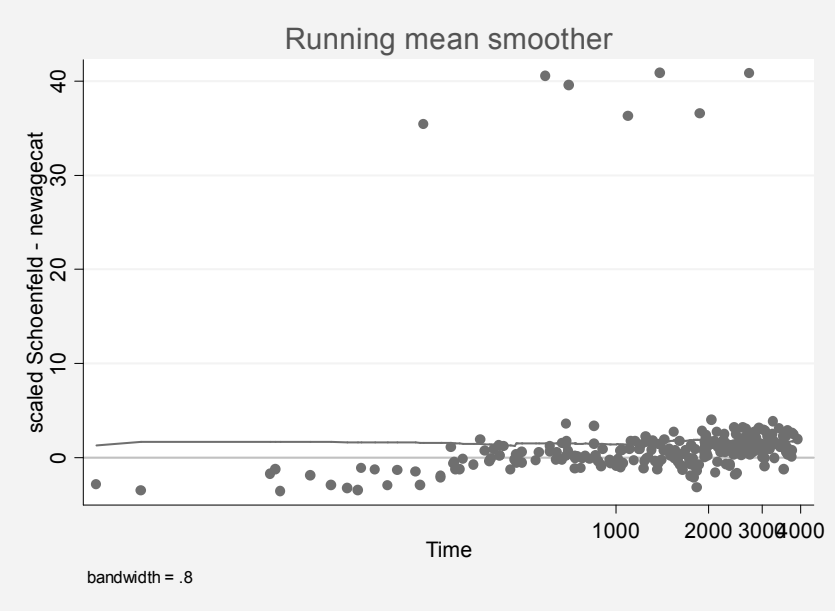
Study number 3:The metabolic syndrome defined using the ATP Criteria

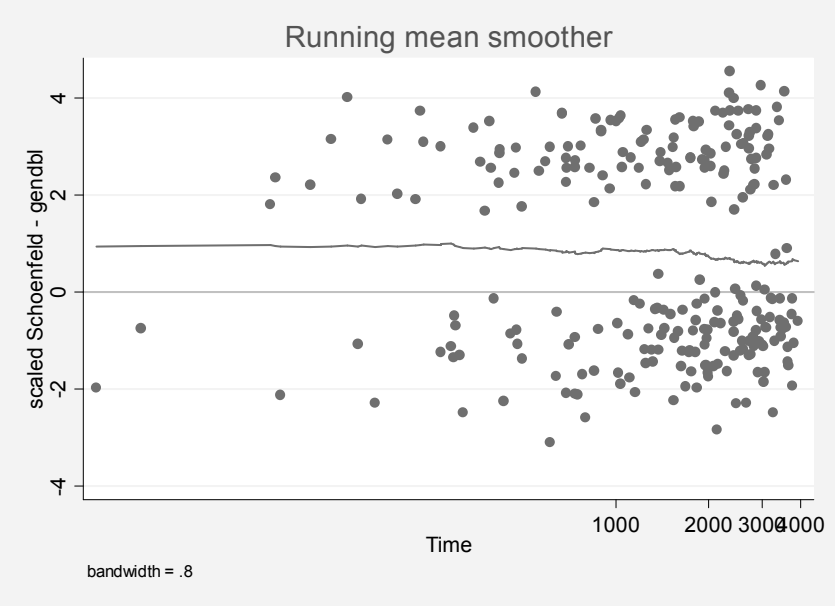


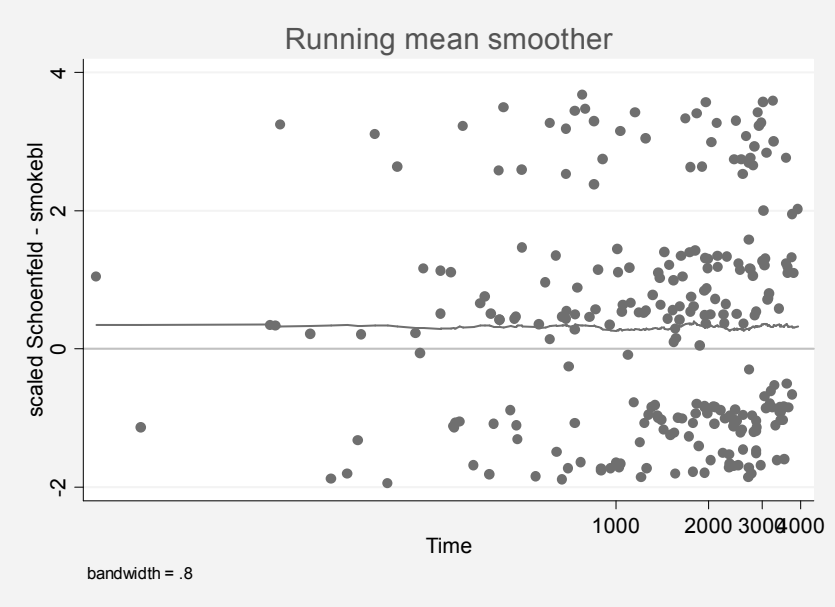


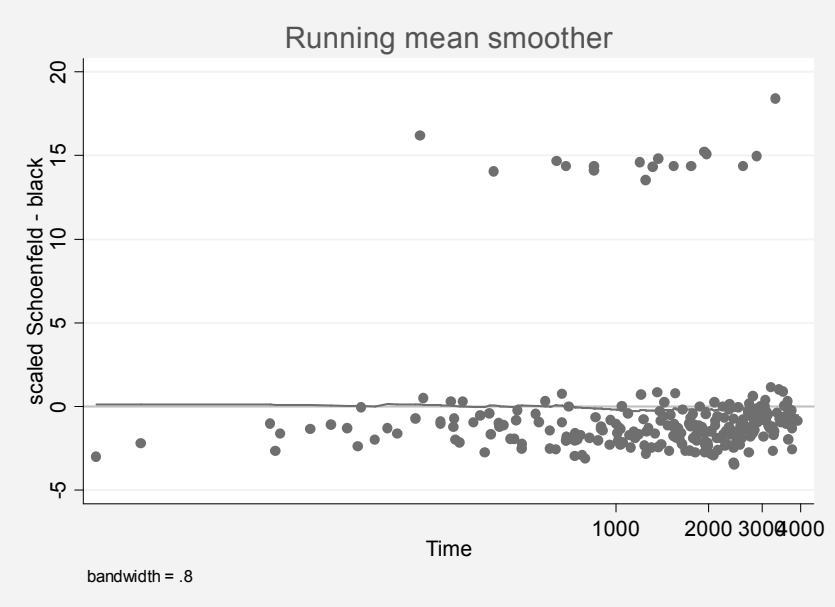


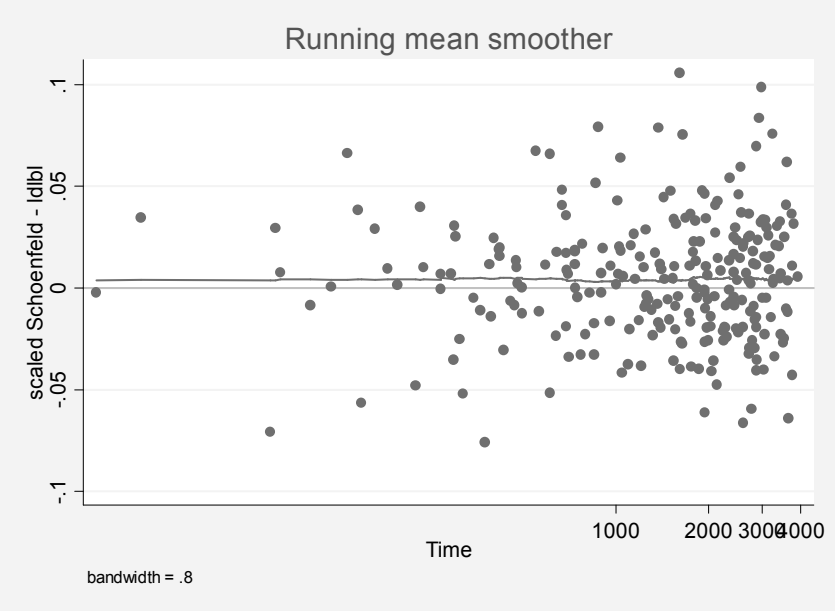


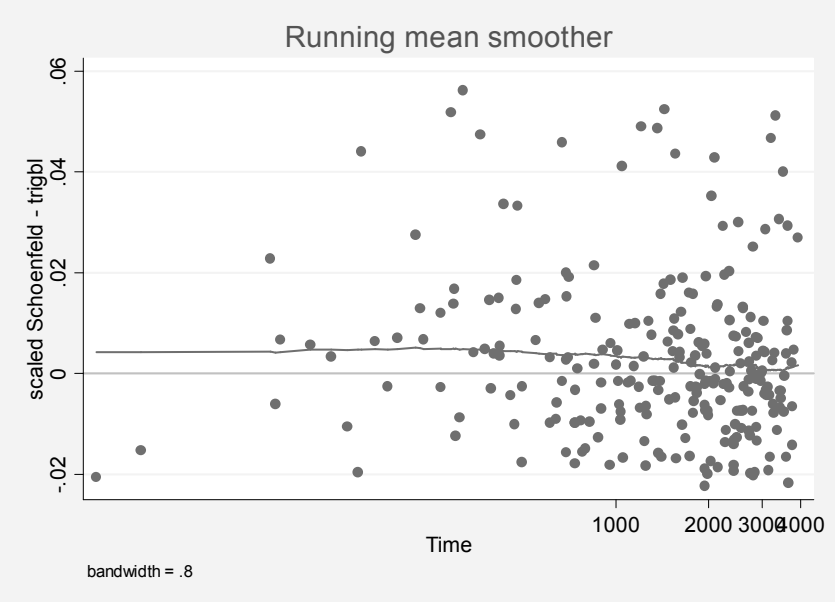




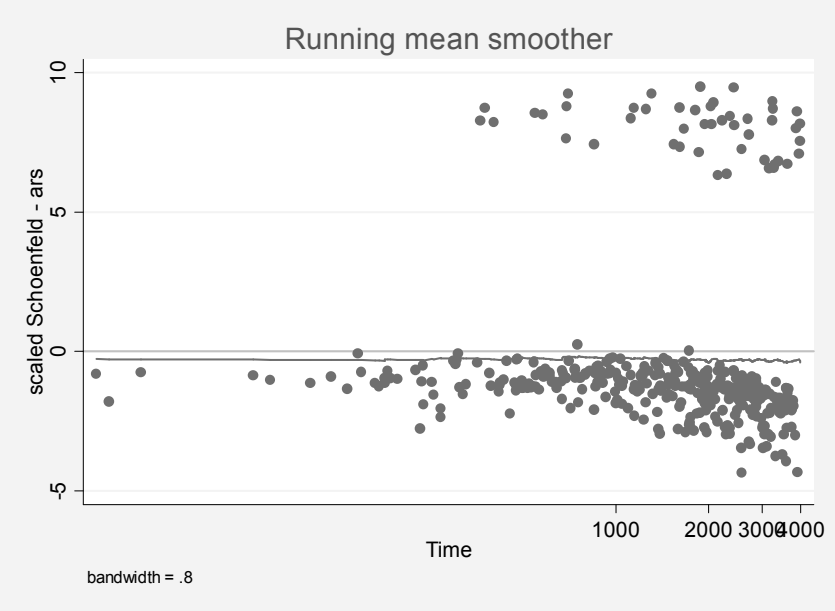


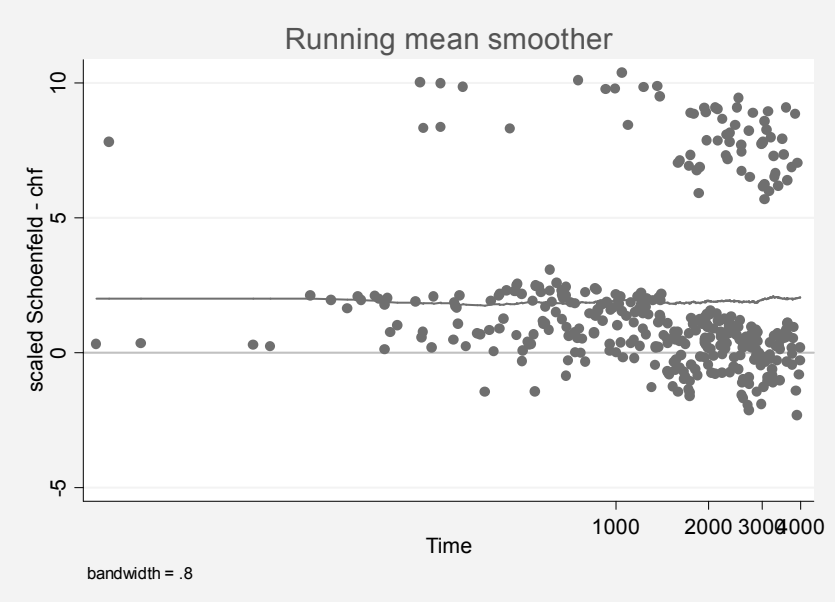


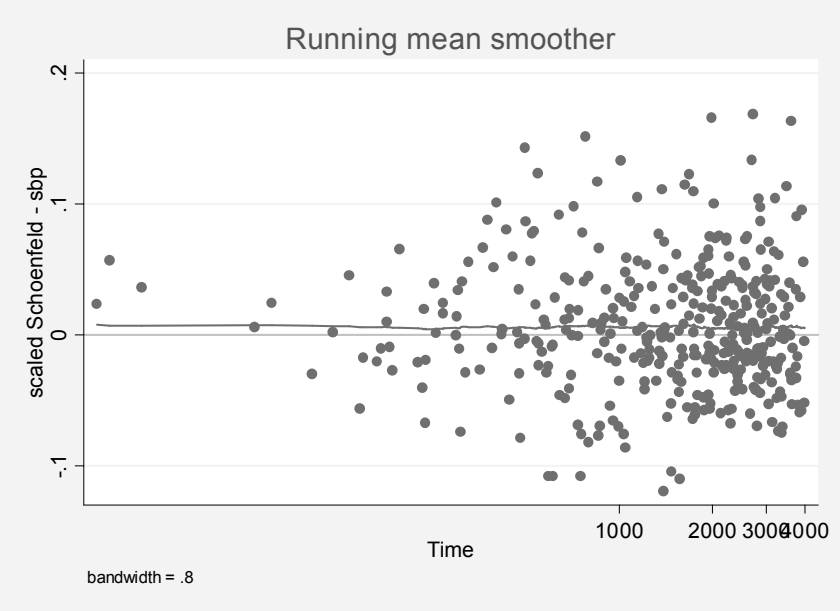


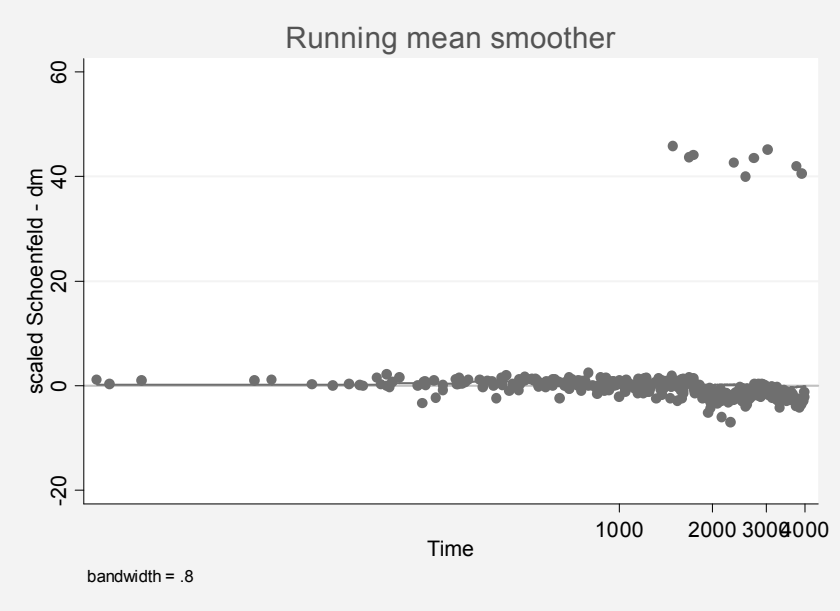


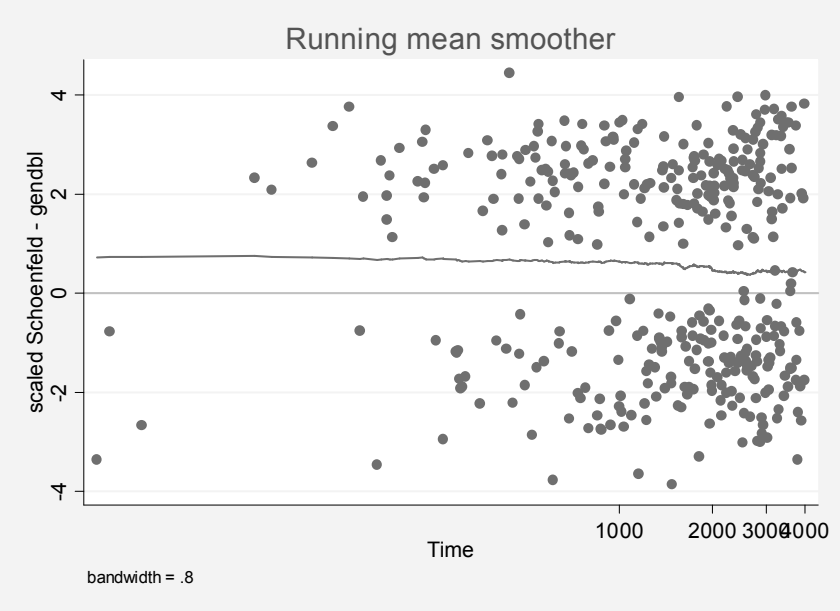
Study number 4: The metabolic syndrome defined using the AACE Criteria

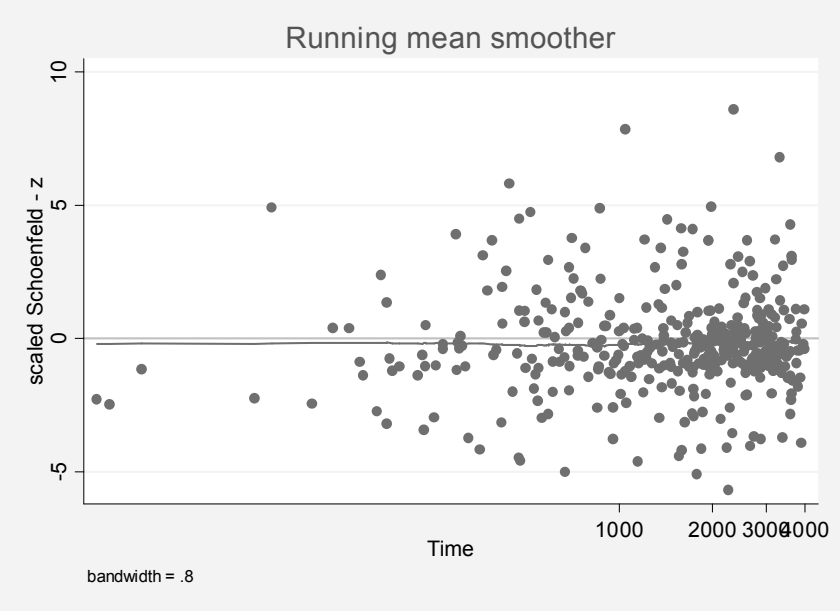


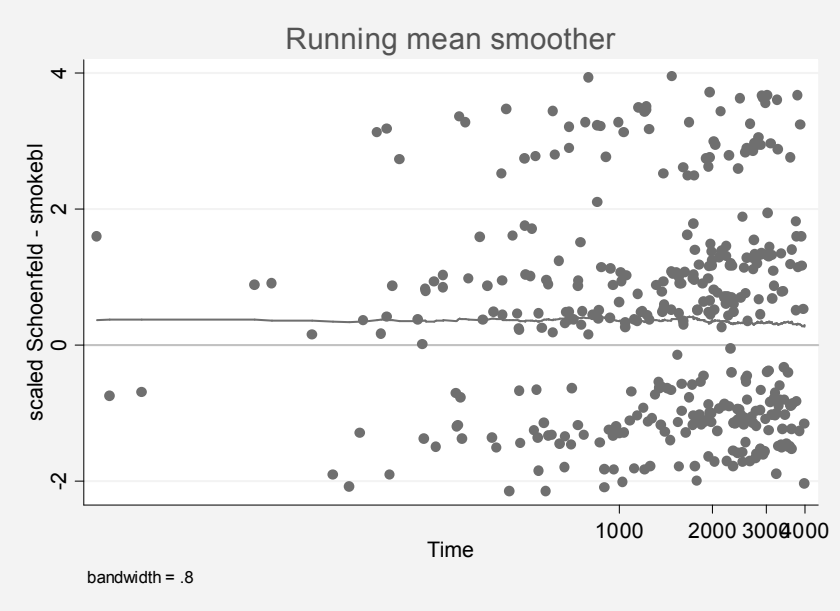


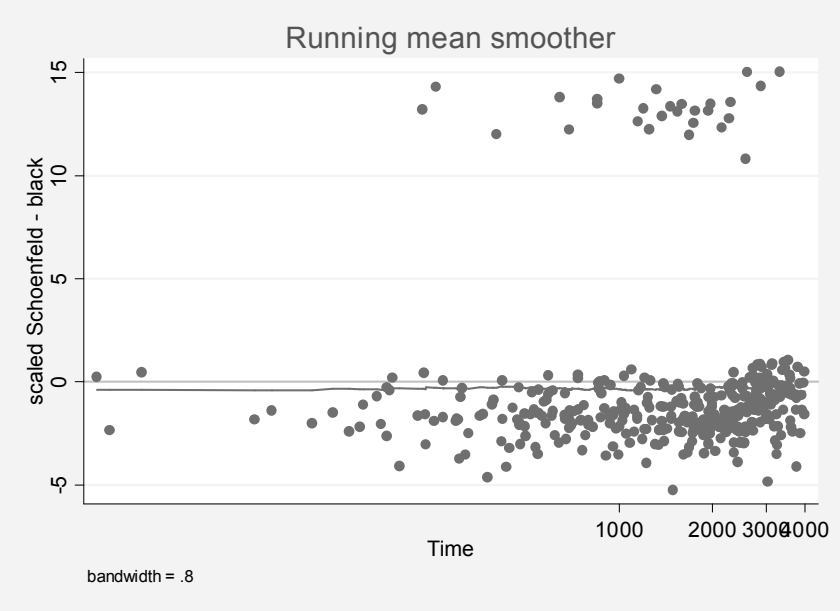


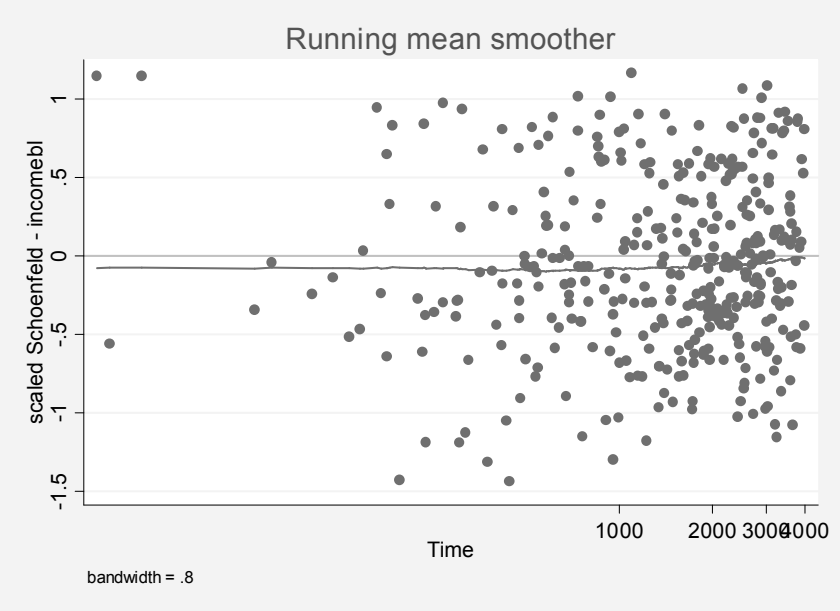




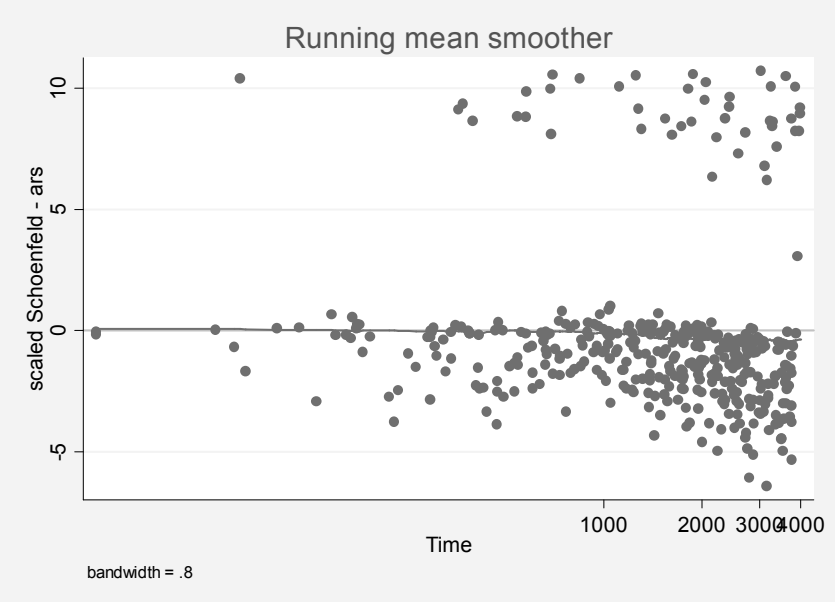


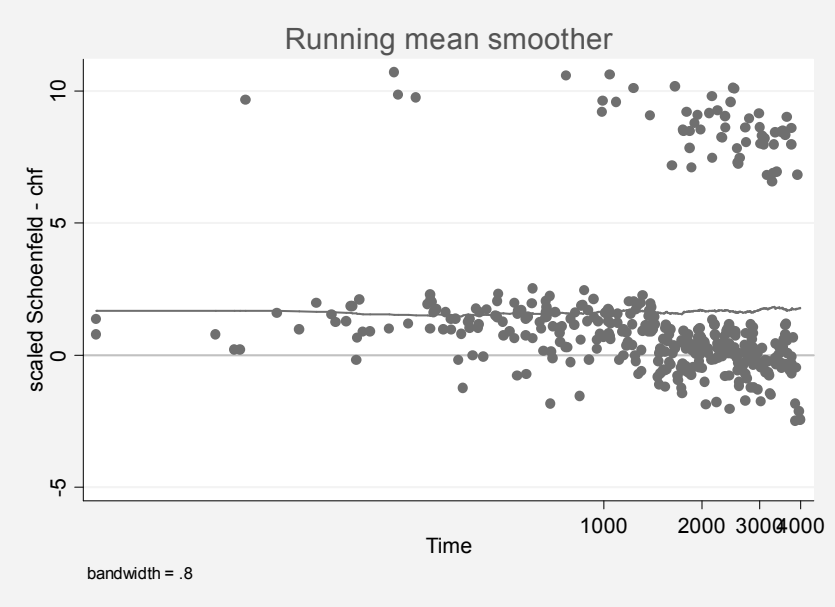


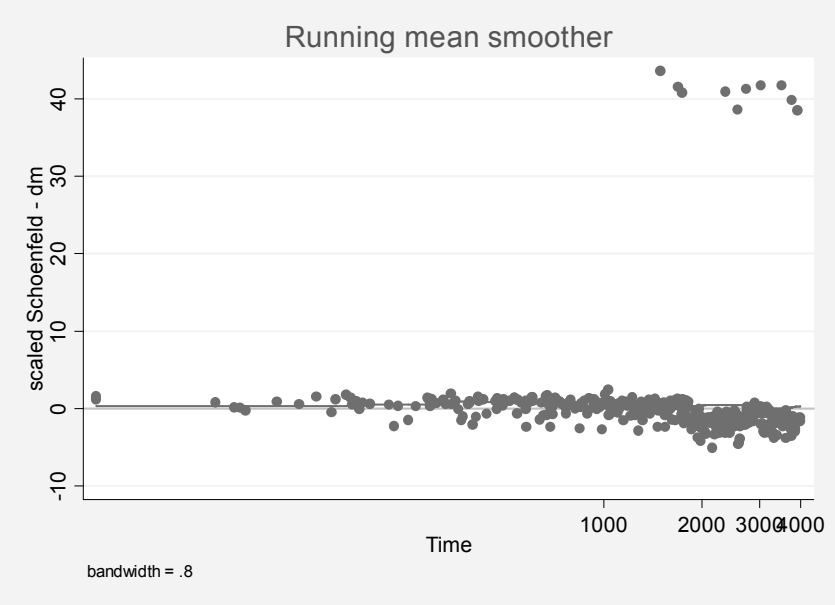


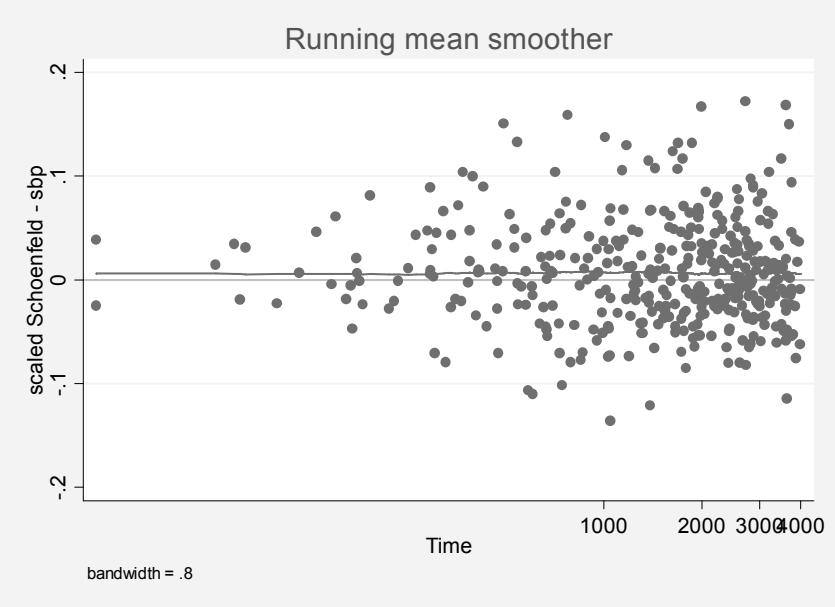


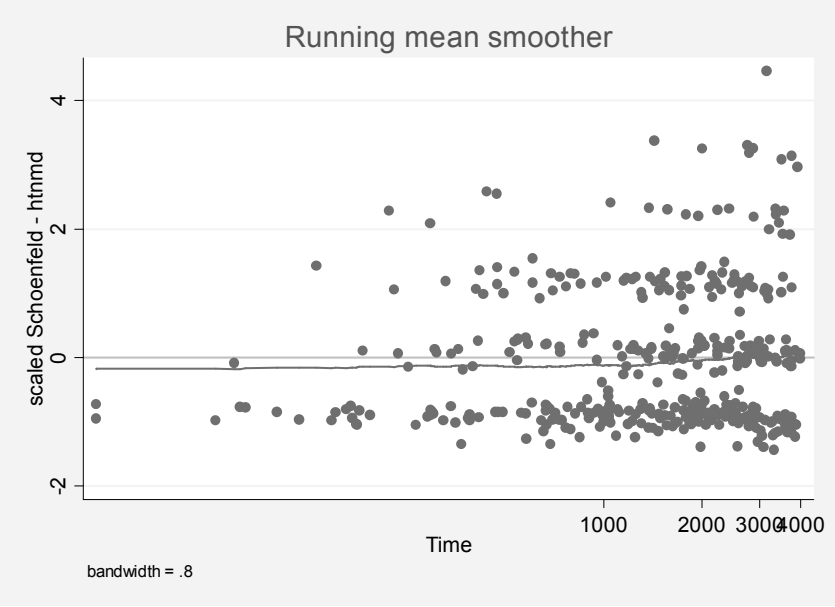
Specific Aim 2: Identify the effect of ACEI/ARB on the long term development of cardiovascular events in elderly non-diabetic hypertensive patients with insulin resistance.

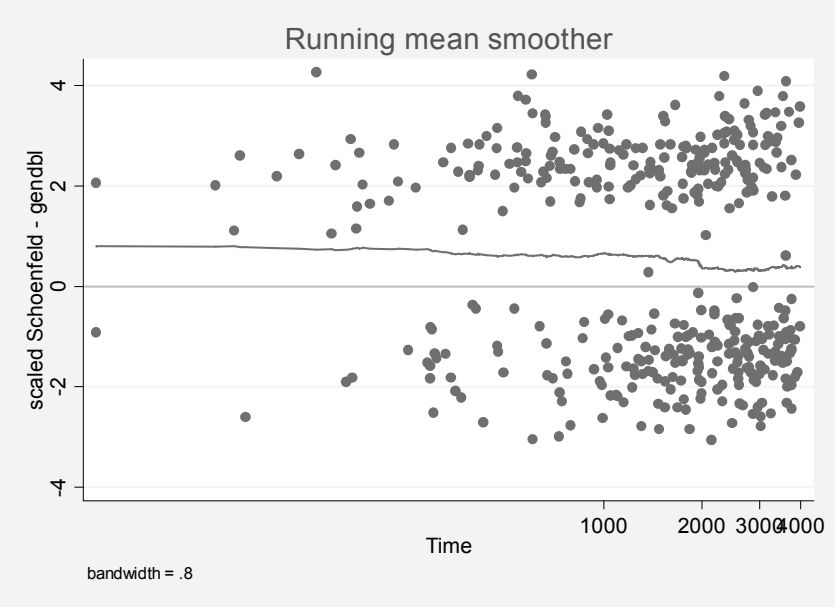


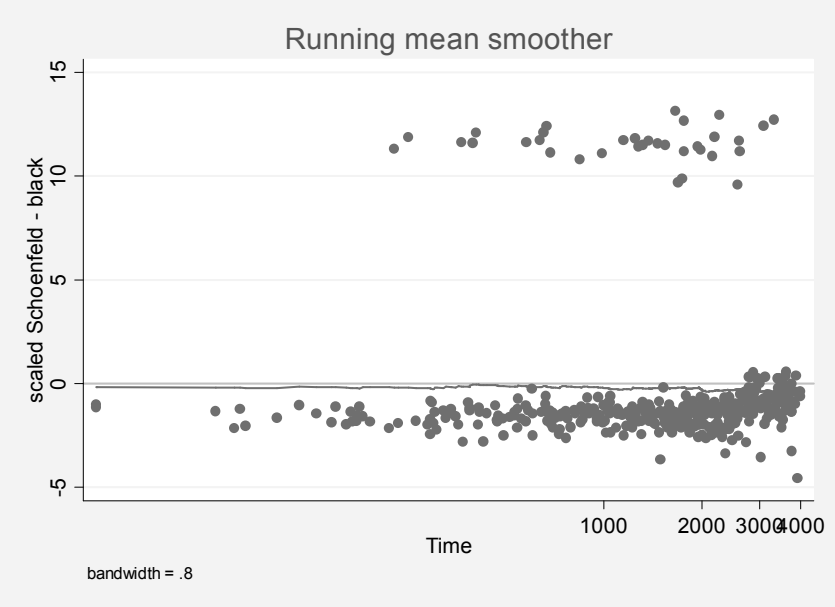


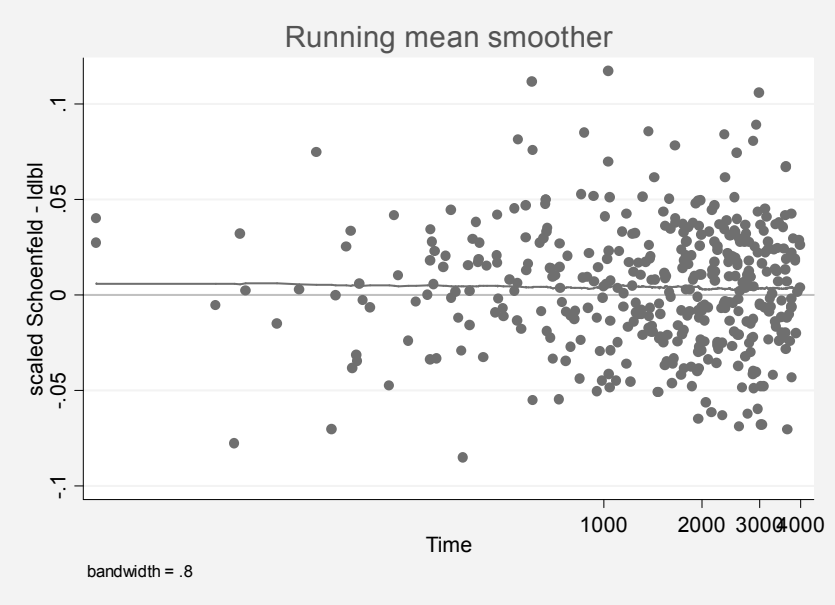












Appendix C
"Multivariable Models for the Effect of ACEI/ARB and the Other Anti-Hypertensives on CVD"

The following multivariable models show the effect of using ACEI/ARB adjusting for the use of the other antihypertensive medications on the CVD in elderly hypertensive non-diabetic subjects in the upper quartile of HOMA and in subjects satisfying the different metabolic syndrome criteria.

Specific Aim 1

Table 6: Effect of different anti-hypertensives on the CVD in patients with the metabolic syndrome defined by the WHO criteria

Parameter	DF	Parameter Estimate	Standard Error	Chi-Square	p value	Hazard Ratio	95% HR Confidence Limits	
Use of ACEI/ARB	1	-0.37947	0.20522	3.4190	0.0644	0.684	0.458	1.023
Use of beta blockers	1	0.00868	0.18717	0.0021	0.9630	1.009	0.699	1.456
Use of CCB	1	0.12135	0.18014	0.4538	0.5005	1.129	0.793	1.607
Use of vasodilators	1	-0.17256	0.30549	0.3191	0.5722	0.842	0.462	1.531
Use of diuretics	1	0.06333	0.18390	0.1186	0.7306	1.065	0.743	1.528
Use of alpha blockers	1	-0.06904	0.39816	0.0301	0.8623	0.933	0.428	2.037
SBP	1	0.00563	0.00259	4.7150	0.0299	1.006	1.001	1.011
Development of CHF	1	1.80639	0.15764	131.3105	<.0001	6.088	4.470	8.293
Development of diabetes	1	0.53280	0.36666	2.1115	0.1462	1.704	0.830	3.495
Number of HTN medications	1	-1.45235	0.46504	9.7533	0.0018	0.234	0.094	0.582
Age	1	0.04216	0.01074	14.77	0.0001	1.042	1.02	1.064
Gender (male vs. female)	1	0.54102	0.11648	21.5731	<.0001	1.718	1.367	2.158
Former smoker vs. never	1	0.20262	0.12385	2.6764	0.1018	1.225	0.961	1.561
Current smoker vs. never	1	0.69027	0.17051	16.3880	<.0001	1.994	1.428	2.786
Race (black vs. not)	1	-0.38386	0.20321	3.5683	0.0589	0.681	0.457	1.015
LDL	1	0.00353	0.00167	4.4739	0.0344	1.004	1.000	1.007
Number of HTN medications* log(time)	1	0.18724	0.06326	8.7597	0.0031	1.206	1.065	1.365

Table 7: Effect of different anti-hypertensives on the CVD in patients with the metabolic syndrome defined by the EGIR criteria

Parameter	DF	Parameter Estimate	Standard Error	Chi-Square	p value	Hazard Ratio	95% HR Confidence Limits	
Use of ACEI/ARB	1	0.03115	0.24470	0.0162	0.8987	1.032	0.639	1.667
Use of beta blockers	1	0.44477	0.25046	3.1535	0.0758	1.560	0.955	2.549
Use of CCB	1	0.34221	0.22611	2.2906	0.1302	1.408	0.904	2.193
Use of vasodilators	1	0.06439	0.37927	0.0288	0.8652	1.067	0.507	2.243
Use of diuretics	1	0.20174	0.23694	0.7249	0.3945	1.224	0.769	1.947
Use of alpha blockers	1	-0.35669	0.52978	0.4533	0.5008	0.700	0.248	1.977
SBP	1	0.00656	0.00315	4.3395	0.0372	1.007	1.000	1.013
Development of CHF	1	1.57737	0.19183	67.6150	<.0001	4.842	3.325	7.052
Development of diabetes	1	0.66936	0.46198	2.0993	0.1474	1.953	0.790	4.830
Number of HTN medications	1	-1.39362	0.57397	5.8954	0.0152	0.248	0.081	0.764
Age	1	0.05038	0.01276	15.58	<0.0001	1.052	1.026	1.078
Gender (male vs. female)	1	0.30166	0.13470	5.0155	0.0251	1.352	1.038	1.761
Former smoker vs. never	1	0.09449	0.14644	0.4164	0.5188	1.099	0.825	1.464
Current smoker vs. never	1	0.79649	0.19218	17.1762	<.0001	2.218	1.522	3.232
Race (black vs. not)	1	-0.35549	0.22278	2.5463	0.1106	0.701	0.453	1.085
Number of HTN medications* log(time)	1	0.15737	0.07742	4.1324	0.0421	1.170	1.006	1.362

Table 8: Effect of different anti-hypertensives on the CVD in patients with the metabolic syndrome defined by the ATP criteria

Parameter	DF	Parameter Estimate	Standard Error	Chi-Square	p-value	Hazard Ratio (HR)	95% HR Confidence Limits	
Use of ACEI/ARB	1	-0.43939	0.21167	4.3089	0.0379	0.644	0.426	0.976
Use of beta blockers	1	-0.14595	0.17829	0.6702	0.4130	0.864	0.609	1.226
Use of CCB	1	-0.08366	0.17483	0.2290	0.6323	0.920	0.653	1.296
Use of vasodilators	1	-0.15742	0.35214	0.1998	0.6548	0.854	0.428	1.704
Use of diuretics	1	-0.03537	0.13736	0.0663	0.7968	0.965	0.737	1.263
Use of alpha blockers	1	-0.12709	0.45738	0.0772	0.7811	0.881	0.359	2.158
Development of CHF	1	2.02121	0.18241	122.7766	<.0001	7.547	5.279	10.791
SBP	1	0.00786	0.00307	6.5742	0.0103	1.008	1.002	1.014
Development of diabetes	1	0.35732	0.42404	0.7101	0.3994	1.429	0.623	3.282
Age	1	0.0336	0.01281	6.0801	0.0087	1.034	1.009	1.06
Gender (male vs. female)	1	0.76182	0.13564	31.5469	<.0001	2.142	1.642	2.795
Former smoker vs. never	1	0.18977	0.14433	1.7288	0.1886	1.209	0.911	1.604
Current smoker vs. never	1	0.75328	0.18666	16.2863	<.0001	2.124	1.473	3.062
Race (black vs. other)	1	-0.19095	0.25904	0.5434	0.4610	0.826	0.497	1.373
Triglycerides	1	0.00276	0.0009732	8.0150	0.0046	1.003	1.001	1.005
LDL	1	0.00434	0.00184	5.5453	0.0185	1.004	1.001	1.008

Table 9: Effect of different anti-hypertensives on the CVD in patients with the metabolic syndrome defined by the AACE criteria

Parameter	DF	Parameter Estimate	Standard Error	Chi-Square	p value	Hazard Ratio (HR)	95% HR Confidence Limits	
Use of ACEI/ARB	1	-0.32097	0.16300	3.8774	0.0489	0.725	0.527	0.999
Use of diuretics	1	0.00200	0.11233	0.0003	0.9858	1.002	0.804	1.249
Use of CCB	1	0.11674	0.13849	0.7106	0.3992	1.124	0.857	1.474
Use of Beta blockers	1	-0.09575	0.15264	0.3935	0.5305	0.909	0.674	1.226
Use of vasodilators	1	-0.16291	0.27172	0.3595	0.5488	0.850	0.499	1.447
Use of alpha blockers	1	-0.16457	0.37766	0.1899	0.6630	0.848	0.405	1.778
SBP	1	0.00599	0.00256	5.4624	0.0194	1.006	1.001	1.011
Development of CHF	1	1.91875	0.14621	172.2144	<.0001	6.812	5.115	9.073
Development of diabetes	1	0.18039	0.34528	0.2730	0.6014	1.198	0.609	2.356
Age	1	0.25274	0.06813	13.763	0.0002	1.288	1.127	1.47
Gender (male vs. female)	1	0.57574	0.11062	27.0891	<.0001	1.778	1.432	2.209
Former smoker vs. never	1	0.21010	0.11711	3.2184	0.0728	1.234	0.981	1.552
Current smoker vs. never	1	0.74766	0.15660	22.7951	<.0001	2.112	1.554	2.871
Race (black vs. other)	1	-0.39597	0.20673	3.6688	0.0554	0.673	0.449	1.009
Income level at baseline	1	-0.05359	0.02783	3.7083	0.0541	0.948	0.898	1.001
Age *log(time)	1	-0.02934	0.00954	9.4679	0.0021	0.971	0.953	0.989

Specific aim 2

Table 10: Effect of different anti-hypertensives on the CVD in specific aim 2 study

Parameter	DF	Parameter Estimate	Standard Error	Chi-Square	p-value	Hazard Ratio (HR)	95% HR Confidence Limits	
Use of ACEI/ARB	1	-0.20123	0.19725	1.0407	0.3076	0.818	0.556	1.204
Use of beta blockers	1	0.03593	0.18884	0.0362	0.8491	1.037	0.716	1.501
Use of CCB	1	0.25517	0.17746	2.0676	0.1505	1.291	0.912	1.828
Use of vasodilators	1	0.03626	0.29586	0.0150	0.9025	1.037	0.581	1.852
Use of diuretics	1	0.22808	0.18033	1.5997	0.2059	1.256	0.882	1.789
Use of alpha blockers	1	-0.04678	0.39434	0.0141	0.9056	0.954	0.441	2.067
SBPI	1	0.00620	0.00255	5.9146	0.0150	1.006	1.001	1.011
Development of CHF	1	1.91116	0.14677	169.5563	<.0001	6.761	5.071	9.014
Development of diabetes	1	0.25473	0.34566	0.5431	0.4612	1.290	0.655	2.540
Number of HTN medications	1	-0.41254	0.41317	0.9969	0.3181	0.662	0.295	1.488
Age	1	0.0467	0.0101	21.11	<0.0001	1.048	1.027	1.069
Gender	1	1.70509	0.85084	4.0160	0.0451	5.502	1.038	29.157
Former smoking	1	0.20770	0.11662	3.1723	0.0749	1.231	0.979	1.547
Current smoking	1	0.77613	0.15601	24.7478	<.0001	2.173	1.601	2.950
Race (black vs. other)	1	-0.26310	0.20180	1.6998	0.1923	0.769	0.518	1.142
LDL	1	0.00331	0.00157	4.4558	0.0348	1.003	1.000	1.006
Gender*log(time)	1	-0.15632	0.11677	1.7922	0.1807	0.855	0.680	1.075
Number of HTN medications*log(time)	1	0.03578	0.05663	0.3992	0.5275	1.036	0.928	1.158

Vita

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Publications:

K.I. Cheang, Villanueva J, H.H. Zreikat, Nestler JE. "Relative importance of obesity, insulin resistance and metabolic syndrome in the elderly: risk of cardiovascular events". The Endocrine society's 90th Annual Meeting 2008; P3-467.

K. I. Cheang, H. H. Zreikat, J. Villanueva. "Relative importance of the metabolic syndrome vs. hypertension in the elderly: risk of cardiovascular disease" at the American Society of Clinical Pharmacology and Therapeutics Annual Meeting, Washington DC, March 19, 2009.