ASSESSMENT OF INTERMEDIATE (PROCESS) OUTCOMES IN THE BARI 2D CLINICAL TRIAL

by

Linxi Liu

BS in Preventive Medicine, Sichuan University, China, 2013

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This thesis was presented

by

Linxi Liu

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and approved by

Thesis Advisor:
Robert M Boudreau, PhD
Assistant Professor, Epidemiology, Graduate School of Public Health, University of Pittsburgh

Committee Members:
Maria Mori Brooks, PhD
Professor, Epidemiology, Graduate School of Public Health, University of Pittsburgh

Oscar C. Marroquin, MD, FACC, PhD
Assistant Professor of Medicine, Epidemiology and Clinical and Translational Sciences, School of Medicine, University of Pittsburgh

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Robert M Boudreau, PhD

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ABSTRACT

BARI 2D is a 2-by-2 factorial clinical trial identifying optimal therapies for patients with documented stable coronary artery disease and Type 2 Diabetes. Previous results of the BARI 2D study indicated that there was a non-significant association between the therapies and 5-year survival outcomes. Our study hypothesizes that several intermediate variables may exist whose trajectories of improving or worsening in response to treatments act against each other leading to the previous non-significant associations. Before randomization, the participants were stratified to two types of revascularization - PCI or CABG. Then each participant was randomized to receive one cardiac therapy (prompt revascularization plus intensive medicine or intensive medicine alone), and also one glycemic therapy (insulin-sensitization or insulin-provision). Five intermediate outcomes BMI, SBP, HDL, LDL and Hba1c were studied. Linear regression was conducted to assess the difference of each intermediate outcome between therapies at Year 1 and at Year 3. Also conducted was a comparison of the trajectories over time by therapies using longitudinal repeated measures mixed models. In 2368 patients (mean age 62.4 years), the improvement of the intermediate outcomes was generally notable over the first year, and then slowly diminished over time. At both Year 1 and 3, insulin-provision resulted in higher BMI and Hba1c, and lower HDL than insulin-sensitization, irrespective of the assigned cardiac therapy

and revascularization stratum. Longitudinally, insulin-provision resulted in higher Hba1c, irrespective of the assigned cardiac therapy and revascularization stratum; and an interaction effect of the cardiac and glycemic therapies on BMI was found in CABG stratum. These results suggested that insulin-sensitization therapy is superior to insulin-provision therapy generally. In CABG stratum, the effect of cardiac therapy on BMI depends on the assignment of glycemic therapy. The public health significance of this study is that, though the cancelling-out hypotheses for these five intermediate variables may be overly optimistic, it involves a potentially illuminating perspective to explain the mechanisms through which the BARI 2D treatment therapies affect multiple intermediate outcomes. This in turn could also help inform and enhance the targeted adjuvant therapies, thus resulting in improved survival outcomes by better focusing on controlling the harmful intermediate variables.

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

LIST OF ABBREVIATIONS

BMI = Body Mass Index

CABG = Coronary Artery Bypass-Grafting

CAD = Coronary Artery Disease (also called CHD)

CHD = Coronary Heart Disease

CKD = Chronic Kidney Disease

DBP = Diastolic Blood Pressure

HbA1c = Hemoglobin A1C

HDL = High-Density Lipoprotein cholesterol

JNC = Hypertension guidelines from the Joint National Committee

LDL = Low-Density Lipoprotein cholesterol

NCEP = the National Cholesterol Education Program

OR = Odds Ratio

PCI = Percutaneous Coronary Intervention (also called PTCA)

PTCA = Percutaneous Trans-luminal Coronary Angioplasty

SBP = Systolic Blood Pressure

TZDs = Thiazolidinediones

PREFACE

ACKNOWLEDGEMENT

I would first like to express my sincere gratitude to my thesis advisor Prof. Boudreau of the Graduate School of Public Health at University of Pittsburgh for his strong support and rigorous training. The experience we work together has been one of my most precious memories in my life. I would also like to thank my thesis committee member Prof. Brooks and Prof. Marroquin, for your insightful comments and guidance, but also for the hard question which incented me to widen my research from various perspectives. My sincere thanks also goes to Ms. Joanne Pegher, who spend great effort and time for me during my final thesis submission. At last, I would like to say thank you to my family: thanks Yubo for your company in this journey; thanks my parents Mr. Liu and Ms. Meng for your critical support financially and spiritually. Thank you for all what you have done, true honor belongs to you.

1.0 LITERATURE REVIEW

1.1 TYPE II DIABETES

1.1.1 DEFINITION, EPIDEMIOLOGY, AND RISK FACTORS

Diabetes is a chronic disease characterized by raised blood glucose. Globally, 10% of diabetes is Type 1 Diabetes, and 90% is Type 2 Diabetes. The main focus of the thesis is on Type 2 Diabetes. The metabolic reason for Type 2 Diabetes is either due to the body's lack of insulin production or due to its inefficient use of insulin. Type 2 Diabetes over time can result in serious complications such as neuropathy, nephropathy, blindness, heart attack, stroke, and amputation [1, 2]. Since the 1990s, the prevalence of Type 2 Diabetes has increased remarkably worldwide [3]. The most recent data show that in 2014, nearly 8% of adults globally lived with Type 2 Diabetes; in 2012, about 1.5 million deaths worldwide were directly due to diabetes, which placed diabetes No. 8 in the worldwide leading causes of deaths list. Residents of low- and middle- income countries accounted for 80% of all diabetes-specific deaths. World Health Organization projected that the prevalence and mortality of diabetes will continue to rise such that, by the year 2030, diabetes will become the 7th leading cause of death throughout the world [3]. In the United States, 29.1 million people have diabetes, which comprises to 9.3% of the population. Among those, 8.1 million (27.8%) are undiagnosed [4].

According to the Centers for Disease Control and Prevention (CDC) and the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK), the risk factors for Type 2 Diabetes include older age; being overweight or obese; having an individual history of impaired glucose tolerance, gestational diabetes or giving birth to at least one baby more than 9 pounds; having a family history of diabetes; races or ethnicities; lack of physical activity; high blood pressure, abnormal cholesterol levels, having polycystic ovary syndrome (PCOS), having acanthosis nigricans, or having blood vessel problems [2, 5]. The Centers for Disease Control and Prevention have a National Diabetes Prevention Program for people who have pre-diabetes or are at high risk for type 2 Diabetes. The aim of this structured lifestyle change program program is to prevent Type 2 Diabetes. People can participate in person or online [6]. The National Institute of Diabetes and Digestive and Kidney Diseases suggested a number of ways to prevent Type 2 Diabetes, which can be categorized by the following 5 aspects - meal portion size reduction, physical activity habit development, healthy food choices, emotional adjustment, and keeping a record of everyday food intake and physical activities [7].

1.1.2 RISK FACTOR CONTROL GUIDELINES

1.1.2.1 BMI

According to the CDC, BMI between 18.5 and 24.9 (kg/m^2) is normal weight. Below this level ($<18.5\ kg/m^2$) is underweight. Above this range are overweight (25-29.9 kg/m^2) and obesity (30 kg/m^2 and above). [8] The American Diabetes Association recommends that for people who have diabetes, losing a few pounds weight through lifestyle change such as physical activity and healthy eating can help with diabetes control and decrease the risk of complications. [9] In the

BARI 2D study, all patients received counseling regarding smoking cessation, weight loss, and regular exercise, which were monitored regularly [10].

1.1.2.2 BLOOD PRESSURE

For general population, 120/80 mmHg or lower is normal blood pressure; 140/90 mmHg or higher is defined as high blood pressure; levels in between are prehypertension [11]. According to JNC8 (2014), for the general population with hypertension, blood pressure goals differ by age, with 150/90 mmHg for people aged 60 years and older, and 140/90 mmHg for people aged below 60 years. For those with both hypertension and diabetes (but no CKD), the target goal is below 140/90 mmHg for all ages. This guideline was driven by a systematic review of clinical trial evidence [12, 13]. In contrast, according to JNC7 (2003) and JNC6 (1997), the blood pressure control goals for patients with both hypertension and diabetes were below 130/80 mmHg and below 130/85 mmHg, respectively [14, 15]. The BARI 2D trial used the blood pressure ≤130/80 mm/Hg as the blood pressure control target [16].

1.1.2.3 LIPIDS

According to the NCEP guideline (2001), for the general population, the recommended optimal lipids profile is LDL < 100 mg/dL, HDL between 40 and 60 mg/dL, and total cholesterol less than 200 mg/dL. For patients with coronary heart disease or diabetes, LDL control goal is LDL <100 mg/dL [17]. The LDL target from the NCEP guideline (2001) was the same as in the 1994 NECP guideline [18, 19]. BARI 2D used LDL<100 mg/dL as the lipids control target [10].

1.1.2.4 HBA1C

For the general population, A1C equal to 6.5% is the clinical threshold. Equal or above this cut-point indicates a diabetes diagnosis [20]. For non-pregnant patients who already diagnosed with diabetes, current guideline suggests A1C <7.0% is a proper blood glucose target [20]. BARI2D used Hba1c <7.0% as the blood glucose control target [21].

The current Hba1c target level was based on several fundamental trials. The UKPDS study indicated that intensive blood glucose control (Hba1c<7.0%) was better than less intensive control (Hba1c<7.9%) in terms of the risk of diabetic complications, especially microvascular complications [22]. The ACCORD trial found that targeting an A1C level of 7-7.9% was better than near normal levels (<6.0%) with respective to mortality and CVD risk [23]. The ADVANCE trial showcased that targeting HbA1c<6.5% was similar as targeting at 7-7.5% in terms of mortality and macrovascular risk [24]. The VA diabetes Trial showed that intensive therapy (Hba1c<7%) was superior to standard therapy (Hba1c 8-9%) in terms of modest effects on cardiovascular and microvascular outcomes [25].

1.1.3 MEDICATIONS FOR TYPE 2 DIABETES

The medication therapies for Type 2 Diabetes can be categorized into insulin provision therapy and insulin sensitization therapy according to their mechanisms. The mechanism of insulin provision is increasing the insulin levels in the body. The mechanism of insulin sensitivity is improving the body's response and the use of insulin [26].

1.1.3.1 INSULIN PROVISION

Two typical insulin provision medications are insulin and sulfonylureas, which are also the majority types of insulin provision medications administered in the BARI 2D study [27].

There are several types of insulin depending on the onset-time, peak-time, and the duration it works in the blood. They are rapid-acting insulin, regular (also called short-acting insulin), intermediate-acting insulin, and long-acting insulin. The reacting time ranges from 15 minutes to several hours. The peak hours range from 15 minutes to 10 or more hours. The duration of the insulin lowering blood glucose ranges from 2 to 24 hours. The most commonly used insulin is U-100 [28].

Sulfonylureas can stimulate the pancreas to release more insulin. Sulfonylureas can only be effective when there still are some beta cells remaining [29, 30].

1.1.3.2 INSULIN SENSITIZATION

Two typical insulin sensitization medications are metformin and thiazolidinediones (TZDs).

Metformin is the most commonly prescribed diabetic drug all over the world. It belongs to biguanides, a class of organic compounds. The American Diabetes Association (ADA) recommends metformin as the first-line oral treatment for people with newly diagnosed type 2 Diabetes, unless they have some contraindications or other reasons that keep them from taking it [31].

Thiazolidinediones (TZDs) is another type of insulin-sensitization drugs, which works as an insulin sensitizer, by binding to the PPAR receptors in fat cells and making the cells more responsive to insulin [32]. Prescription of TZDs should be with caution, since the FDA (2002)

approved the changes to strengthen the labeling for TZDs regarding the cardiovascular risks that associated with TZDs [33].

1.1.3.3 RISK FACTOR CONTROL COMPARISON OF MEDICATIONS FOR TYPE 2 DIABETES

Insulin, sulfonylureas, and TZDs use may lead to weight gain [34-36]. Metformin use may lead to weight loss [37, 38]. Insulin has beneficial effects on serum lipid profiles [39]. Sulfonylureas can slightly lower the levels of LDL and HDL, but the effect is small. [50]. Metformin decreases the blood lipids levels [40, 41]. The effects of TZDs on lipids profiles differ by the agent used [42]. Insulin use elevated blood pressure [43]. Sulfonylurea initiation was related with an elevated SBP compared to metformin, and BMI may be functioning as the potential mediator [44]. Metformin may decrease the blood pressure. The evidence was inconsistent [45]. TZDs may decrease both SBP and DBP, but the change is in a small scale [46]. Insulin use leads to a decrease in HbA1c by 1.5-2.5% [47]. Sulfonylureas use leads to a decrease in HbA1c by 1.5% [47]. Metformin was expected to decrease HbA1C by 1.5-2.0% [45]. TZDs were expected to lead a decrease in HbA1C by 0.5-1.4% [47]. Insulin and sulfonylureas are associated with more frequent episodes of hypoglycemia than metformin or TZDs [48]. A combination therapy of sulfonylurea plus insulin is being used less frequently [49]. There was a lack of longitudinal evidence for comparing effects of insulin-provision therapy vs. insulin-sensitization therapy on changes and control of BMI, lipids status, blood pressure, and glycemic profiles over time.

1.2 CORONARY ARTERY DISEASE

1.2.1 DEFINITION, EPIDEMIOLOGY, AND RISK FACTORS

Cardiovascular disease (CVD), also known as heart disease, is a class of heart and blood vessel diseases. There are several types of CVD including coronary artery diseases (CAD), heart valve diseases, heart failure, and arrhythmia [51]. Cardiovascular disease usually caused by narrowed blood vessels that could lead to chest pain (angina), or even blood block that could lead to heart attack, or stroke [52]. As the top one cause of death due to disease, CVDs showed high prevalence and high severity. In 2012, there were 17.5 million people that died from CVDs in the world, which represented a third of the total deaths during that year. Among those 17.5 million deaths, 42% were caused by coronary heart disease and 38% were caused by stroke. More than 75% of CVD deaths occur in low- and middle-income countries. CVD is also a major cause of death (37%) among people who died under the age of 70 due to non-communicable diseases [50].

Coronary artery disease (CAD), also known as coronary heart disease (CHD), is related with impaired coronary arteries, which lowers the blood flow that carries the oxygen and nutrients to the heart. The development of CAD is related with the formation of cholesterol-containing deposits (plaque) in the arteries and or inflammation. This process can progress over many years, and is known as atherosclerosis [53].

With the plaque building up, the blood vessels become narrower over time, and the severity of symptoms increases. Angina occurs when the blood flow to heart through arteries is decreased. It is represented as chest pain or discomfort in the surrounding area, and a shortness of breath. Myocardial infarction (MI), commonly known as heart attack, occurs when the blood flow is blocked. A sudden rupture of the plaque can cause a block. Without a quick treatment, a

heart attack can result in severe medical problems even death. CHD over time can impair the heart muscle and could cause heart failure and arrhythmias [54].

1.2.2 REVASCULARIZATIONS FOR CORONARY ARTERY DISEASE

1.2.2.1 PERCUTANEOUS CORONARY INTERVENTION (PCI)

Percutaneous coronary intervention (PCI or PTCA) is a non-surgical type of revascularization treating coronary artery disease. The procedure is to use a balloon catheter to broaden a blocked coronary artery from within. After the procedure, there will be more room for blood to go through, and transport the oxygen and nutrients to the heart muscle [55].

1.2.2.2 CORONARY ARTERY BYPASS GRAFTING (CABG)

Coronary artery bypass grafting (CABG) is a surgical type of revascularization treating serious coronary artery disease. The surgery is to use a healthy artery or vein from the patient he/herself to graft and bypass the blocked section of the coronary artery. This new vessel will serve as the new path for blood flow to the heart muscle [56].

1.2.2.3 COMPARISONS BETWEEN REVASCULARIZATION AND INTENSIVE MEDICAL THERAPY ALONE IN CONTROL OF RISK FACTORS

There was comparatively limited evidence comparing the effect of revascularization with PCI or CABG overall vs. intensive antianginal medical therapy alone on changes and control of BMI, lipids status, blood pressure, and glycemic profiles.

1.3 SUMMARY OF LITERATURE REVIEW

For Type 2 Diabetes, the major risk factors include overweight or obesity, unhealthy diet, physical inactivity, family history, ethnicity, older age, high blood pressure, and abnormal lipid profiles. The current guidelines for patients with both T2D and CAD suggested that the target levels of risk factors are: Hba1<7.0%, BP<140/90 mmHg, LDL<100 mg/dL, and losing a few pounds weight. Two common types of drugs treating Type 2 Diabetes are insulin-provision drugs and insulin-sensitization drugs. Insulin, sulfonylureas, metformin and TZDs were different in mechanisms and in their abilities of controlling risk factors. There exists evidence of insulin-provision therapy verses insulin-sensitization therapy on risk factor controls at baseline and at Year 3, but not longitudinally.

For CAD, the major risk factors include unhealthy diet and obesity, lack of physical activity, smoking, and excessive use of alcohol, elevated blood pressure, increased blood lipids, and elevated glucose. Two common types of revascularization are PCI and CABG. A gap remains in comparing the effectiveness of risk factors control between prompt revascularization with intensive medical therapy verses intensive medical therapy alone.

1.4 BARI 2D CLINICAL TRIAL

1.4.1.1 DESIGN OF THE BARI 2D CLINICAL TRIAL

The BARI 2D study implemented a 2-by-2 factorial design, with two cardiac therapies: either prompt revascularization with intensive medical therapy or intensive medical therapy alone; and two glycemic therapies: either insulin-sensitization therapy or insulin-provision therapy. The intensive medical therapy for management of coronary risk factors included the following medications: adrenergic blockers, angiotensin converting enzyme inhibitors, and aspirin for all patients unless contraindicated. Insulin-providing strategy included medications as follows: sulfonylurea drugs, repaglinide, nateglinide, or insulin itself. Insulin-sensitizing strategy included medications as follows: thiazolidinediones (TZDs) or metformin. All patients had targets of Hba1c<7.0% and uniform control of hypertension (BP<130/80 mmHg), dyslipidemia (LDL<100 mg/dL), and obesity following recommended medical guidelines. Before randomization, the participants were stratified to percutaneous coronary intervention (PCI) or coronary-artery bypass grafting (CABG) stratum according to the prior choice of revascularization recommended by the cardiologist as the more appropriate intervention. BARI 2D recruited 2368 eligible and enrolled patients with both type 2 diabetes and stable ischemic heart disease at 49 clinical centers in North America, South America, and Europe. Patients were followed for an average of 5.3 years. The primary outcome was 5-year mortality. The secondary outcome was major cardiovascular events, which was represented by a composite of death, myocardial infarction, or stroke [10].

1.4.2 MAIN RESULTS OF THE BARI 2D TRIAL

A core paper regarding the primary outcomes by the BARI 2D Study Group (2009) evaluated and compared the effect of two cardiac therapies and two glycemic therapies on patients' 5-year survival rate and major cardiovascular events. During the average follow-up of 5 years, no statistically significant difference was found in the rates of death and major cardiovascular events between the two cardiac therapy groups, or between glycemic therapy groups. In PCI stratum, no significant difference was found between the cardiac therapy and glycemic therapy groups. In CABG stratum, revascularization was better than medical therapy alone in terms of the rate of major cardiovascular events (P=0.002 for interaction between CABG stratum and cardiac treatment groups) [10].

Bittner V et al (2015) based on the BARI 2D clinical trial data and analyzed the feasibility and effects of controlling multiple risk factors (RFs) in their target levels of the protocol guidelines through intensive medical therapy on cardiovascular events and mortality. A non-randomized analysis of 2,265 patients' mortality/cardiovascular events and control of 6 RFs (no smoking, low density lipoprotein cholesterol <130 mg/dl, triglycerides <150 mg/dl, blood pressure [systolic <130 mm Hg; diastolic <80 mm Hg], glycosylated hemoglobin <7%) in the BARI 2D trial was conducted. The number of RFs at 5 years had shown been improved a lot from baseline (4.2 ± 1.3 vs. 3.5 ± 1.4, $p < 0.0001$). Cox models were conducted with the following covariates: time-varying number of RFs in control, baseline number of RFs in control, other clinical characteristics, and group assignments. The RFs control status during the trial was highly associated with the survival outcome (global $p = 0.0010$) and composite endpoint (global $p = 0.0035$). Specifically, patients with less than 2 RFs in control during the five years follow-up had an approximately 2-fold higher risk of death (HR=2.0, 95% CI=1.3-3.3, p=0.0031) and of

the composite endpoint (HR=1.7, 95% CI=1.2-2.5; p=0.0043), compared with the patients with all six RFs under control. Their findings supported the feasibility and effectiveness of simultaneous control of multiple RFs through protocol-guided intensive medical therapy on reducing the rate of cardiovascular morbidity and mortality in patients with coronary disease and Type 2 Diabetes [57].

1.5 AIMS AND HYPOTHESIS

Based on the literature review, I will assess the trajectories of most important/well known modifiable risk factors for both T2D and CAD in the BARI 2D clinical trial. The selected intermediate variables were HDL, LDL, SBP, Hba1c, and BMI.

Aim 1: To assess differences between insulin-provision therapy and insulin-sensitization therapy in their control of the intermediate risk factors at Year 1 and at Year 3 and longitudinally

> **Hypothesis 1** Insulin-provision therapy will be associated with higher BMI and SBP, and lower HDL and Hba1c, and a similar LDL, as compared to insulin-sensitization therapy, at both Year 1 and Year 3 and longitudinally.

Aim 2: (exploratory) To assess the strength of association of revascularization with control of the intermediate risk factors at both Year 1 and Year 3 and longitudinally.

2.0 ANALYSIS PLAN

2.1 STUDY DESIGN AND PARTICIPANTS

The BARI 2D dataset we used in the analyses was a public use “deidentified” dataset available at BioLINCC including 2368 patients with both type 2 diabetes and stable documented coronary artery disease. The average follow-up time was 5.3 years. Before randomization, the participants were stratified to a percutaneous coronary intervention (PCI) or coronary-artery bypass-grafting (CABG) stratum according to the prior choice of revascularization as the more appropriate intervention. Each participant received either prompt revascularization with intensive cardiac medical therapy or intensive cardiac medical therapy alone. Each participant was then randomly assigned to one of two glycemic therapies: either insulin-sensitization therapy or insulin-provision therapy. This resulted in four arms per revascularization strata (Figure 1). The primary outcome was 5-year mortality. The secondary outcome was major cardiovascular events, which was represented as a composite of death, myocardial infarction, or stroke. Previous results of the BARI 2D trial indicated there was a non-significant association between the assigned treatments and 5-year survival outcomes.

2.2. INTERMEDIATE VARIABLES

BMI, SBP, HDL, LDL, and Hba1c were selected as intermediate variables (also called process outcomes). Each of these risk factors was measured at baseline and annually for a maximum of 5 years of follow-up period. BMI was calculated by the equation weight (in kilograms) over height squared (in meters). One-minute resting blood pressure was measured with participants in the seated position. The systolic and diastolic blood pressures were based on an average of two sitting blood pressures. LDL-cholesterol, HDL-cholesterol, and HbA1c levels were measured from blood samples collected at baseline and annually, and were analyzed at the BARI 2D core Biochemistry Laboratory.

2.3 STATISTICAL ANALYSIS

Linear regression analyses were conducted to assess whether there were differences in the intermediate outcomes between treatment groups at Year 1 (short term) and at Year 3 (longer term) after the baseline. Also conducted was a comparison of the trajectories over time by treatment group using a longitudinal repeated measures mixed model that included all five years of follow-up with an AIC-selected best fitting heterogeneous autoregressive covariance structure plus random subject-level intercept.

All models were adjusted for baseline, age and sex. Analyses were conducted separately within each revascularization stratum. Revascularization and insulin provision were entered as

separate terms in all models. Their interaction term was also entered and tested for presence of potential synergistic or antagonistic effects. If a significant interaction was found, the four intervention arms within that stratum were modeled as separate groups. The interaction of time and treatments were also tested.

2.4 RESULTS

The BARI 2D dataset used in the analyses was a public use "deidentified" dataset available at BioLINCC. The total sample size was 2368 patients, with 1605 patients in the PCI stratum and 763 patients in the CABG stratum, respectively (Figure 1). The mean age (SD) of the total population was 62.4 (8.9) years, with a range of 40 to 80 years. At baseline, the PCI revascularization stratum was younger, with a higher proportion of females and non-whites. The PCI stratum also generally had higher BMI, lower SBP and HbA1c than patients in the CABG stratum. Mean HDL and LDL were similar. There was no major imbalance by randomized treatment assignment (Table 1).

Graphically, it was revealed that the risk factors generally and notably improved over the first year after baseline, after which the benefit for most of the risk factors slowly diminished over time (Figure 2).

The linear regression models, focusing on Year 1 or Year 3 adjusted for baseline, showed that revascularization (either PCI or CABG) when combined with either type of diabetic medical therapy generally did not further improve control of the risk factors (all $p > 0.061$). Table 2 also showed that insulin provision resulted in higher BMI and Hba1c, and lower HDL in the PCI and CABG strata at both Year 1 and Year 3. Adjusted for baseline levels, generally across all

intervention arms, females showed statistically significant less improvement than males in their LDL and SBP in the short term (Year 1) and longer term (Year 3). Females showed better improvement than males in HDL at both of these time points. For each model, the interactions of time and treatments were also tested and none were found to be significant (Table 2).

Longitudinal analyses showed that several risk-factor trajectories differed depending on the revascularization procedure recommended by the cardiologist. Revascularization with PCI (vs. medication therapy) was not statistically different for BMI, HDL, LDL, SBP, and Hba1c in terms of their mean trajectories ($p > 0.386$), which indicated longitudinally that revascularization with PCI when combined with diabetic medical therapy generally did not further improve control of the risk factors. The effect of revascularization with CABG (vs. intensive medical therapy alone) on BMI depends on the glycemic therapy that the revascularization with CABG was combined with (interaction term $p=0.032$). The combination of revascularization with CABG plus insulin-sensitization therapy was associated with a lower BMI (-1.16 kg/m^2, $p=0.021$) as compared to the combination of intensive medical therapy alone plus insulin-sensitization therapy. The risk-factor trajectories also differed depending on the type of glycemic therapy. In the PCI stratum, participants randomized to insulin provision had a higher mean level of BMI (1.03 kg/m^2, $p= 0.014$) and a higher mean level of Hba1c (0.22%, $p=0.006$) across all 5 years than those randomized to insulin-sensitization therapy. In the CABG strata, participants randomized to insulin provision had a higher mean level of Hba1c (0.43%, $p < .0001$) across all 5 years than those randomized to insulin-sensitization therapy. The effect of insulin provision (vs. insulin sensitization) on BMI depends on the cardiac randomization group (revascularization with CABG vs. intensive medical alone) (interaction term $p=0.032$). For each model, the interaction of time and treatment was also tested and none were found to be significant (Table 3).

The significant revascularization by insulin provision interaction term in Table 3 for the BMI outcome in the CABG stratum (p=0.032) suggests a further analysis. Table 4 focused on trajectories of the BMI among the four arms of the CABG stratum with MedIS as the referent group. The combination of revascularization with CABG and insulin-sensitization therapy (RevIS) was associated with a significant lower BMI (-1.16 kg/m^2) as compared to the combination of intensive medical and insulin-sensitization therapy (i.e. MedIS, set as the referent group) (p=0.020). The combination of revascularization with CABG and insulin provision (RevIP), and the combination of intensive medical therapy alone plus insulin provision (MedIP), were not statistically different from the combination of intensive medical alone and insulin-sensitization therapy (MedIS) in terms of the longitudinal BMI (p=0.833 and p=0.346, respectively). Table 5 similarly focuses on the differences of the trajectories of BMI among the four arms in the CABG stratum with RevIP as the referent group. The combination of revascularization with CABG and insulin-sensitization therapy (RevIS) was associated with a significant lower BMI (-1.05 kg/m^2) as compared to the combination of revascularization with CABG and insulin-provision therapy (RevIP). The combination of intensive medical therapy alone plus insulin-sensitization therapy (MedIS), and the combination of intensive medical therapy alone plus insulin-provision therapy (MedIP), were not statistically different from the combination of revascularization with CABG and insulin-provision therapy (RevIP, set as the referent group) in terms of the longitudinal BMI (p=0.833 and p=0.468, respectively).

2.5 DISCUSSIONS AND CONCLUSIONS

Our study suggested that different glycemic therapies (insulin-provisioning vs. insulin-sensitizing) were associated with significantly different levels of BMI, HDL, and Hba1c at both short-term (Year 1) and longer-term (Year 3). Insulin-sensitizing therapy was superior in terms of controlling BMI, HDL, and Hba1c. In other words, with insulin-sensitizing therapy, the blood glucose and weight control targets were achieved more efficiently than with insulin-provisioning therapy. The reason Year 3 was chosen as the longer-term time-window, instead of Year 5, is that at Year 5 the sample size was relatively small (for most intermediate outcomes, the remaining sample size was about 50% in Year 5 vs. 70% in Year 3).

Longitudinally, the linear mixed model is a relatively robust model, so we included all five years of follow-up data irrespective of the retention rate at later time-points. It was revealed that the superior effects of insulin-sensitizing therapy in controlling risk factors still existed in Hba1c levels irrespective of the revascularization strata. The uniformly superior risk-factor control ability of insulin-sensitizing (vs. insulin-provisioning) for the BMI outcome existed only in the PCI stratum. In contrast, in the CABG stratum, the effect of glycemic therapy (insulin-provisioning vs. insulin-sensitizing) on BMI control depended on the assigned cardiac therapy (either prompt revascularization or intensive medical only). This may due to the fact that linear mixed model provided more statistically power and can detect smaller differences than linear regression model at one time point. To further address this issue, instead of using two separate (cardiac and glycemic therapy) terms and their interaction term, we compared the four therapy-arms (RevIP, RevIS, MedIP, MedIS) in the CABG stratum.

A more interpretable version of the effect of insulin-provisioning therapy (vs. insulin-sensitizing therapy) on BMI over time showed that the revascularization with CABG plus

insulin-sensitization therapy (RevIS) had a significantly lower BMI, as compared to the intensive medical therapy alone plus insulin-sensitization therapy (MedIS, the referent group). The other two therapy groups were not statistically significant from this referent group. The revascularization with CABG plus insulin-sensitizing therapy group (RevIS) had a significantly lower BMI, as compared to the revascularization with CABG plus insulin-provisioning therapy (RevIP, the referent group). The other two therapy groups were not statistically significant from this referent group.

It was also suggested that the interaction effect between time and therapies might exist since the longitudinal trajectories figures showed a “fan-shape” over time generally for all risk factors. However, the interaction terms of time, treated as categorical variable, and therapies were assessed, and they were not statistically significant. Therefore time interaction terms were not included in the models. Future studies may try a “random slope” in addition to the current “random intercept” to assess if the new model fits better and if the interaction of continuous time and treatment was significant. By including therapy arm specific time-slopes, this modeling approach has the potential to reveal increasingly better rates of control over time for certain risk factors by some of the cardiac-glycemic control therapy combinations.

It is interesting that, although the Bittner et al. study suggested that the number of risk factors under control has a significant effect on the survival outcome and major cardiovascular outcome [57], and that our study suggested the treatment therapies have significantly different effect on some of those risk factors, none of the survival outcomes or cardiovascular clinical outcomes differed by treatment groups according to the core paper of the BARI 2D study by Frye et al. [10]. A potential explanation is that the risk factors were functioning as the mediators

between the treatments and outcomes, but the survival analyses were not statistically powered enough to detect mediation effects based on the number of events.

The main strength of this study is that a gap in the literature was partially filled by the longitudinal analyses of the effect of revascularization with PCI or CABG (vs. intensive medical therapy alone) and the effect of insulin-sensitization therapy (vs. insulin-provision therapy) on control of risk factors including BMI, HDL, LDL, SBP, and Hba1c over 5 years. Insulin-sensitizing therapy was shown to be superior vs insulin-provisioning therapy longitudinally in terms of controlling BMI and Hba1c even when factoring in that all patients in all therapy arms were monitored and had goals of Hba1c <7.0% and uniform control of hypertension, dyslipidemia and obesity following recommended medical guidelines. Another strength is that the hypotheses are innovative. The hypotheses involve a potentially illuminating perspective to explain the mechanisms through which the BARI 2D treatment therapies affect multiple intermediate outcomes, which in turn could also help enhance the targeted adjuvant therapies resulting in improved survival outcomes by focusing on treating or controlling the harmful intermediate variables. Although the assessed intermediate variables in this study did not show the compensating effects against one another, it is still a good example for other researchers to refer when further analyzing other potential intermediate variables.

The limitations include the following points. Firstly, the categorical form of the time variable limited the power of time interaction assessments. Secondly, other potential intermediate variables could be assessed regarding my hypotheses.

The conclusion for this study is that the original hypothesis of a cancellation of effects between the five risk factors (BMI, HDL, LDL, SBP, and Hba1c) was not supported. Insulin-sensitization therapy showed generally superior risk-factor control ability than insulin-

provisioning therapy. Further analyses can include more risk factors (i.e. renal risk factors, CRP) in the analyses to assess the effect of the treatments on control of those.

APPENDIX: FIGURES

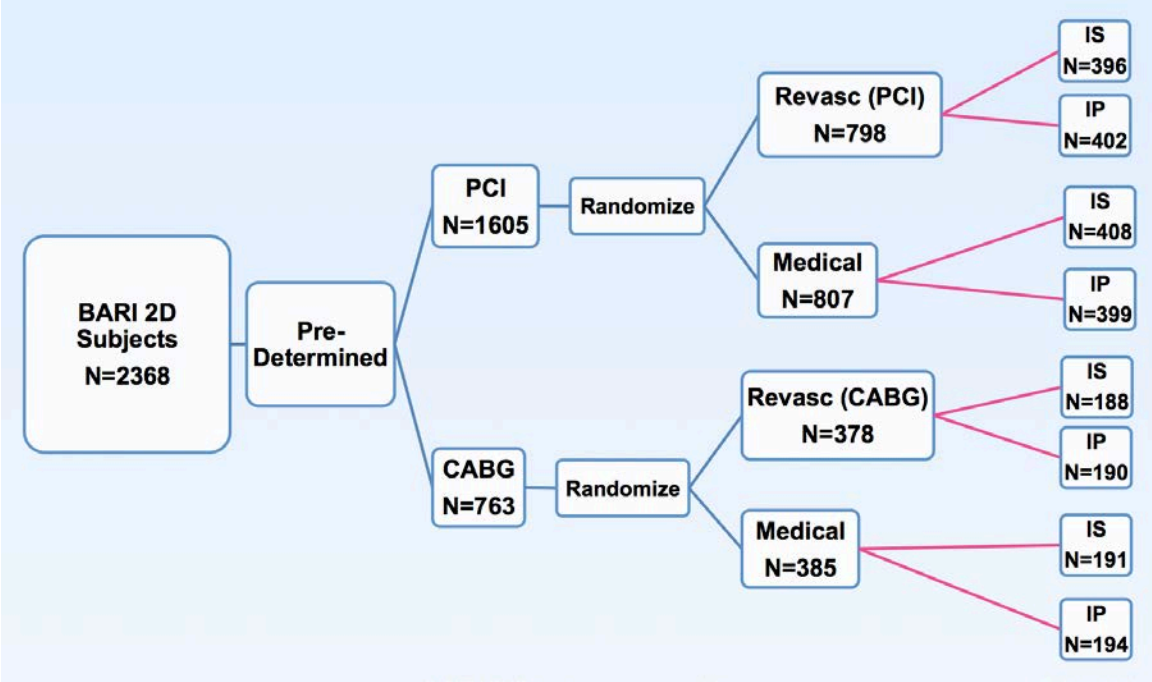

Figure 1. Enrollment Flow Chart, BARI 2D

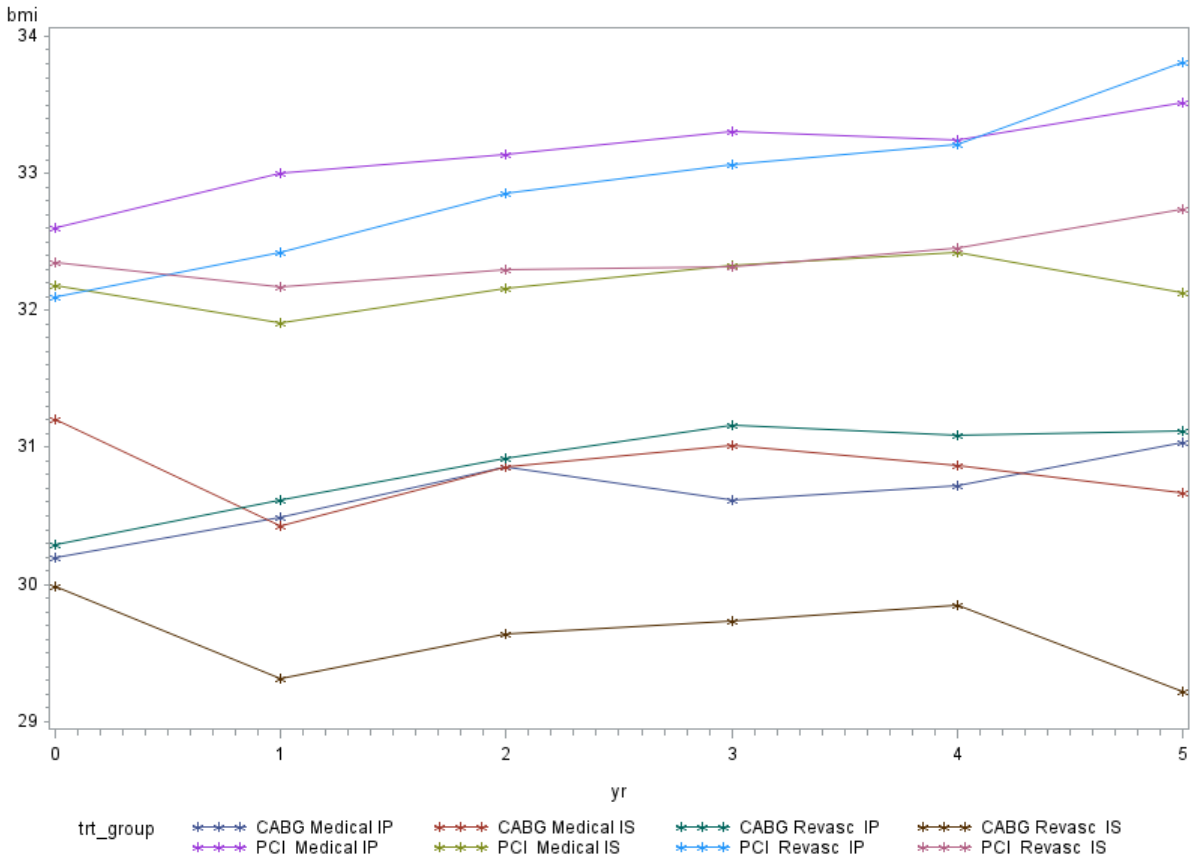

Figure 2. Longitudinal Trajectories of BMI Over 5 Years of Follow-up Time

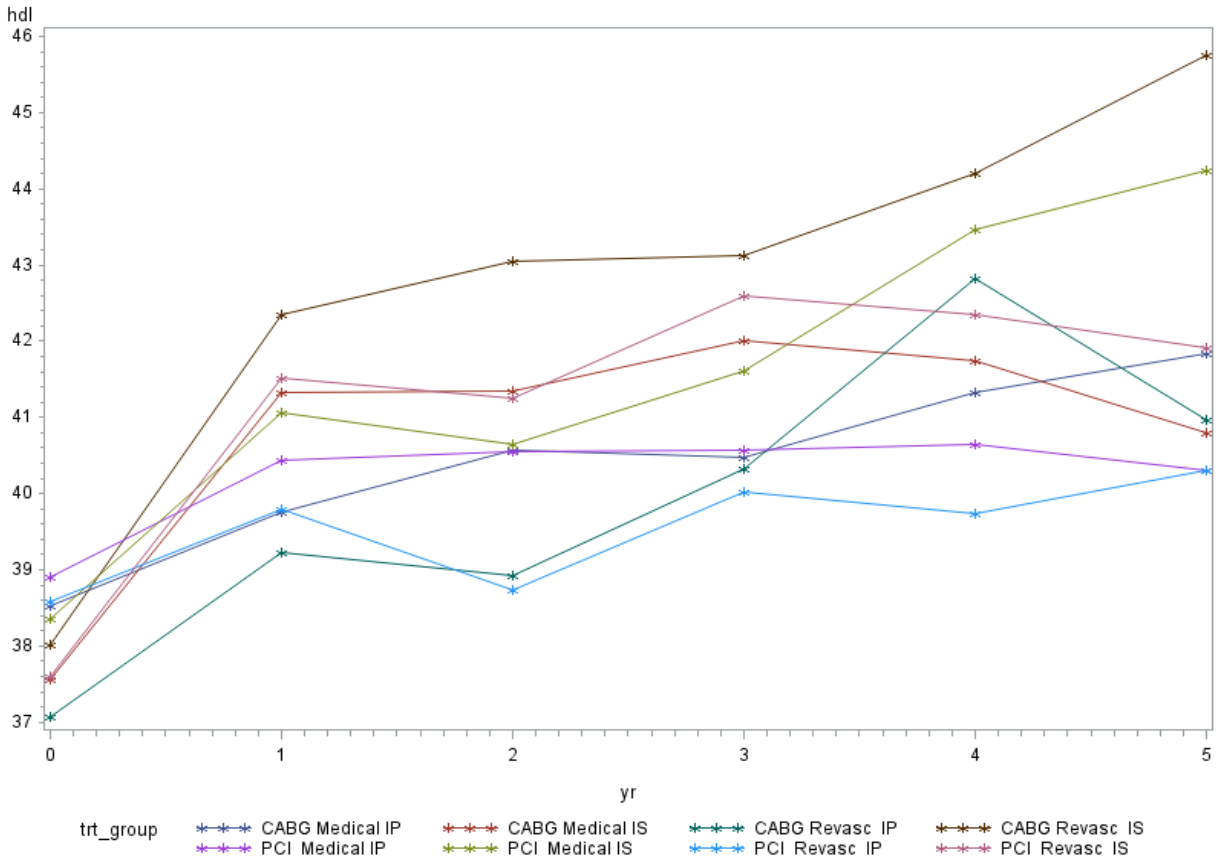

Figure 3. Longitudinal Trajectories of HDL Over 5 Years of Follow-up Time

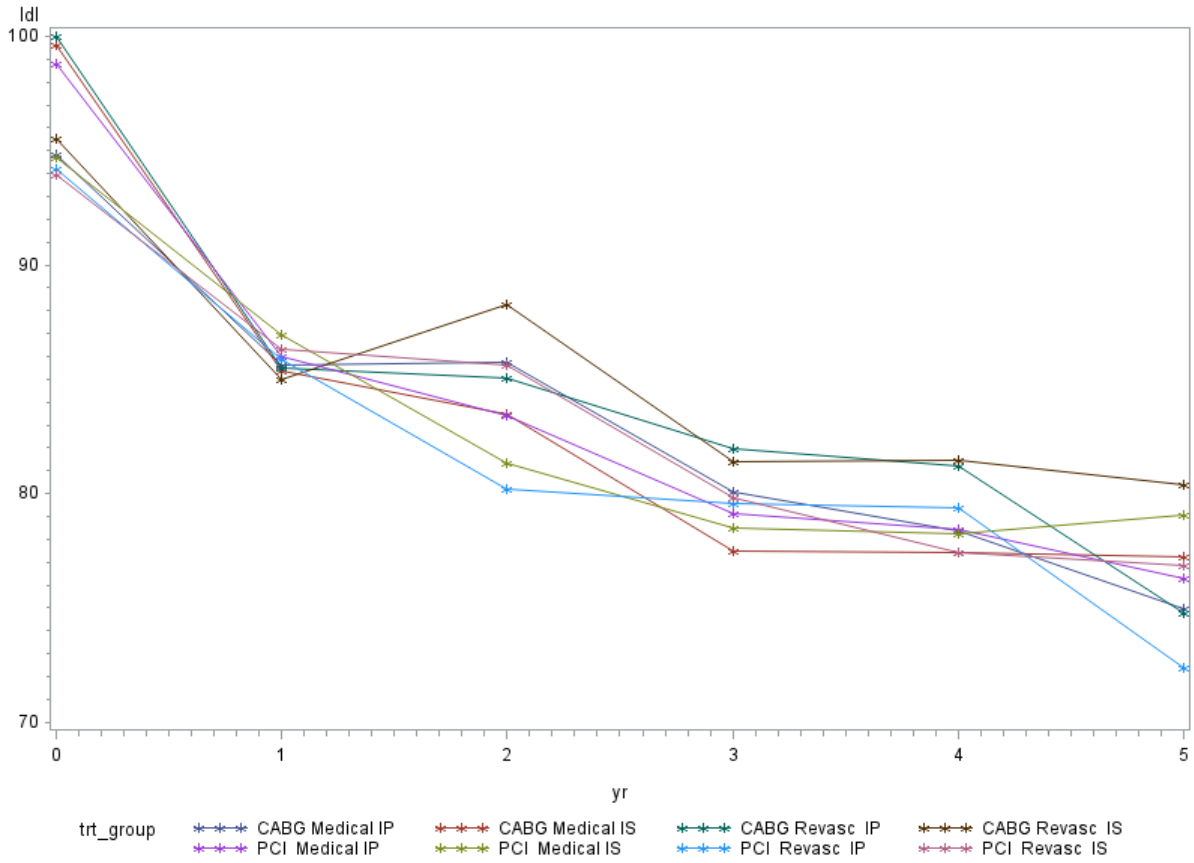

Figure 4. Longitudinal Trajectories of LDL Over 5 Years of Follow-up Time

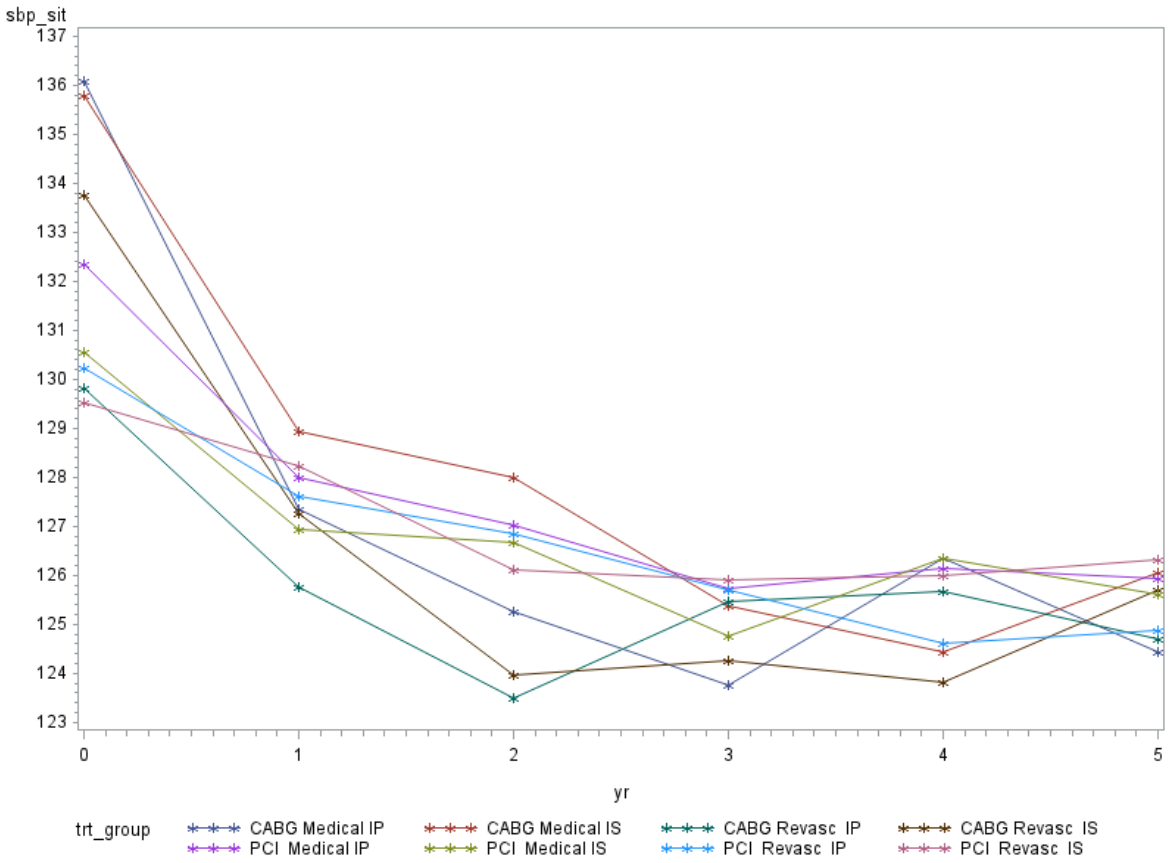

Figure 5. Longitudinal Trajectories of SBP Over 5 Years of Follow-up Time

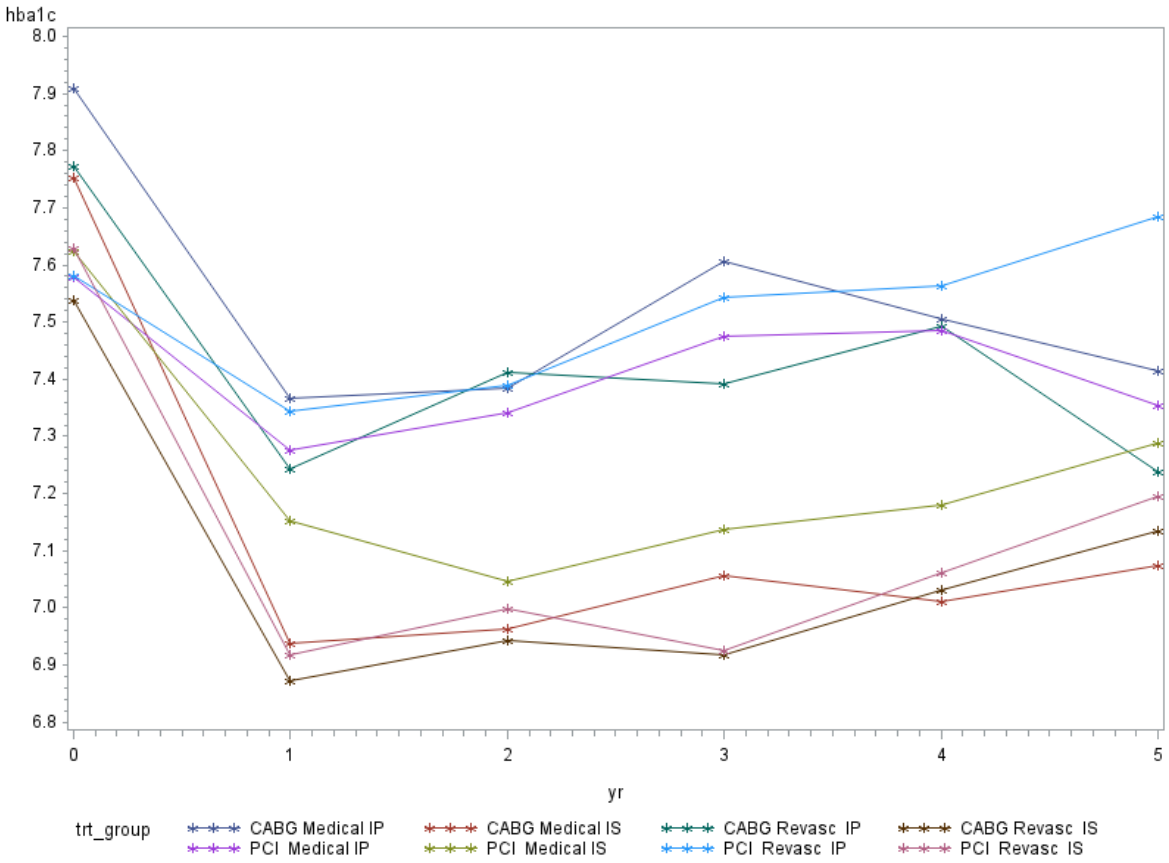

Figure 6. Longitudinal Trajectories of Hba1c Over 5 Years of Follow-up Time

APPENDIX: TABLES

Table 1. Demographic Characteristic and Intermediate Variables Levels at Baseline by Stratum

	PCI N=1605	CABG N=763	P
Age, mean (SD)	61.5 (9.0)	62.8 (8.3)	**0.0003**
Female, N (%)	517 (32.2)	185 (24.3)	**<. 0001**
Non-White, N (%)	510 (31.8)	192 (25.2)	**0.001**
BMI, mean (SD)	32.3 (6.1)	30.4 (4.9)	**<. 0001**
HDL, mean (SD)	38.4 (10.6)	37.8 (9.4)	0.1970
LDL, mean (SD)	95.4 (32.8)	97.5 (34.7)	0.1791
SBP, mean (SD)	130.7 (19.7)	133.9 (20.6)	**0.0003**
HbA1c (%), mean (SD)	7.6 (1.6)	7.7 (1.7)	**0.0478**

SD standard deviation

Table 2. Linear Regression Models for Intermediate Outcomes at Year 1 (short term) and Year 3 (longer term) by Stratum

Intermediate Variables	Demogr char & basel lev	PCI						CABG					
		Year 1			Year 3			Year 1			Year 3		
		Coef	SE	P	Coef	SE	P	Coef	SE	P	Coef	SE	P
BMI	**Sex**	0.20	0.12	0.094	0.10	0.17	0.538	-0.01	0.18	0.946	0.01	0.24	0.956
	Age	-0.04	0.01	**<.0001**	-0.07	0.01	**<.0001**	-0.05	0.01	**<.0001**	-0.05	0.01	**0.000**
	Revasc	0.11	0.11	0.319	0.09	0.15	0.568	0.16	0.15	0.301	0.38	0.20	0.061
	Insul Prov.	0.58	0.11	**<.0001**	0.63	0.15	**<.0001**	0.81	0.15	**<.0001**	0.63	0.20	**0.002**
	Baseline Level	0.95	0.01	**<.0001**	0.92	0.01	**<.0001**	0.92	0.02	**<.0001**	0.93	0.02	**<.0001**
HDL	**Sex**	1.64	0.50	**0.001**	1.76	0.57	**0.002**	1.84	0.74	**0.014**	2.01	0.95	**0.034**
	Age	0.07	0.03	**0.008**	0.03	0.03	0.268	-0.06	0.04	0.113	-0.02	0.05	0.735
	Revasc	0.50	0.44	0.253	0.54	0.50	0.286	0.49	0.61	0.427	0.87	0.79	0.269
	Insul Prov.	-1.78	0.44	**<.0001**	-1.98	0.50	**<.0001**	-2.22	0.61	**0.000**	-2.44	0.79	**0.002**
	Baseline Level	0.72	0.02	**<.0001**	0.74	0.03	**<.0001**	0.68	0.03	**<.0001**	0.65	0.04	**<.0001**
LDL	**Sex**	7.03	1.66	**<.0001**	5.65	1.70	**0.001**	4.69	2.37	**0.049**	2.57	2.64	0.329
	Age	-0.35	0.09	**0.000**	-0.16	0.09	0.081	-0.30	0.13	**0.017**	-0.23	0.14	0.090
	Revasc	0.55	1.55	0.722	0.71	1.57	0.653	-1.27	2.03	0.531	3.03	2.23	0.174
	Insul Prov.	-0.07	1.54	0.963	-0.09	1.57	0.953	0.73	2.02	0.718	1.37	2.23	0.538
	Baseline Level	0.25	0.02	**<.0001**	0.18	0.02	**<.0001**	0.23	0.03	**<.0001**	0.21	0.03	**<.0001**
SBP	**Sex**	2.70	0.92	**0.004**	2.55	0.94	**0.007**	2.34	1.35	0.083	2.38	1.40	0.090
	Age	0.15	0.05	**0.002**	0.17	0.05	**0.001**	0.07	0.07	0.298	0.07	0.07	0.351
	Revasc	0.84	0.86	0.328	0.73	0.87	0.406	-0.52	1.13	0.644	1.07	1.18	0.367
	Insul Prov.	0.02	0.86	0.985	0.20	0.87	0.815	-1.13	1.12	0.312	-0.03	1.17	0.977
	Baseline Level	0.27	0.02	**<.0001**	0.20	0.02	**<.0001**	0.24	0.03	**<.0001**	0.17	0.03	**<.0001**
Hba1c	**Sex**	0.07	0.07	0.347	0.05	0.08	0.542	0.11	0.10	0.271	0.03	0.12	0.819
	Age	-0.01	0.00	0.130	-0.02	0.00	**<.0001**	-0.01	0.01	0.114	-0.02	0.01	**0.001**
	Revasc	-0.09	0.07	0.164	-0.04	0.07	0.595	-0.09	0.08	0.271	-0.15	0.10	0.133
	Insul Prov.	0.29	0.07	**<.0001**	0.49	0.07	**<.0001**	0.31	0.08	**0.000**	0.44	0.10	**<.0001**
	Baseline Level	0.46	0.02	**<.0001**	0.41	0.02	**<.0001**	0.38	0.03	**<.0001**	0.34	0.03	**<.0001**

Revasc Revascularization vs. Medicine Therapy (referent), **Insul Prov.** Insulin Provision (IP) vs. Insulin Sensitization (IS) (referent)

Table 3. Linear Mixed Models for Trajectories of Intermediate Outcomes Over All five Years of Follow-up Time by Stratum

Intermediate Variables	Treatment Groups and Other Covariates	PCI			CABG		
		Coef	SE	P	Coef	SE	P
BMI	sex	2.08	0.32	**<.0001**	-0.08	0.41	0.839
	age	-0.15	0.02	**<.0001**	-0.08	0.02	**0.000**
	Revasc	0.36	0.42	0.394	-1.16	0.50	**0.021**
	Insul Prov.	1.03	0.42	**0.014**	-0.47	0.50	0.346
	Revasc * Insul Prov.	-0.75	0.60	0.205	1.52	0.71	**0.032**
	Year	Annual terms	Annual terms	Annual terms	Annual terms	Annual terms	Annual terms
HDL	sex	7.09	0.51	**<.0001**	4.99	0.74	**<.0001**
	age	0.10	0.03	**0.000**	0.05	0.04	0.184
	Revasc	0.14	0.67	0.841	0.87	0.89	0.328
	Insul Prov.	-0.33	0.67	0.625	-0.66	0.89	0.458
	Revasc * Insul Prov.	-0.76	0.96	0.428	-1.55	1.26	0.220
	Year	Annual terms	Annual terms	Annual terms	Annual terms	Annual terms	Annual terms
LDL	sex	8.82	1.10	**<.0001**	7.37	1.73	**<.0001**
	age	-0.37	0.06	**<.0001**	-0.43	0.09	**<.0001**
	Revasc	0.77	1.44	0.595	1.08	2.09	0.606
	Insul Prov.	1.14	1.44	0.427	-0.67	2.07	0.748
	Revasc * Insul Prov.	-2.05	2.05	0.316	-0.26	2.96	0.930
	Year	Annual terms	Annual terms	Annual terms	Annual terms	Annual terms	Annual terms
SBP	sex	3.41	0.62	**<.0001**	4.50	0.90	**<.0001**
	age	0.19	0.03	**<.0001**	0.16	0.05	**0.001**
	Revasc	0.35	0.82	0.667	-1.85	1.09	0.089
	Insul Prov.	0.94	0.82	0.250	-1.35	1.07	0.209
	Revasc * Insul Prov.	-1.29	1.16	0.268	0.68	1.53	0.655
	Year	Annual terms	Annual terms	Annual terms	Annual terms	Annual terms	Annual terms
Hba1c	sex	0.30	0.06	**<.0001**	0.30	0.09	**0.001**
	age	-0.04	0.00	**<.0001**	-0.04	0.00	**<.0001**
	Revasc	-0.07	0.08	0.386	-0.12	0.11	0.276
	Insul Prov.	0.22	0.08	**0.006**	0.43	0.11	**<.0001**
	Revasc * Insul Prov.	0.14	0.12	0.219	-0.07	0.16	0.637
	Year	Annual terms	Annual terms	Annual terms	Annual terms	Annual terms	Annual terms

Revasc Revascularization vs. Medicine Therapy (referent), **Insul Prov.** Insulin Provision (IS) vs. Insulin Sensitization (referent)

Revasc * Diab Meds Therapy Interaction term

Table 4. Linear Mixed Model for Trajectories of BMI Control Over All Five Years of Follow-up Time by Specific Treatment Group (ref=MedIS)

Intermediate Outcomes	Treatment Groups and Other Covariates	CABG		
		Coef	SE	P
BMI	sex	-0.08	0.41	0.839
	age	-0.08	0.02	**0.000**
	MedIP	-0.47	0.49	0.346
	RevIP	-0.11	0.50	0.833
	RevIS	-1.16	0.50	**0.020**
	MedIS (ref)	ref	ref	ref
	Year	Annual terms	Annual terms	Annual terms

Table 5. Linear Mixed Model for Trajectories of BMI Control Over All Five Years of Follow-up Time by Specific Treatment Group (ref=RevIP)

Intermediate Outcomes	Treatment Groups and Other Covariates	CABG		
		Coef	SE	P
BMI	sex	-0.08	0.41	0.839
	age	-0.08	0.02	**0.000**
	MedIS	0.11	0.50	0.833
	MedIP	-0.36	0.50	0.468
	RevIS	-1.05	0.50	**0.037**
	RevIP (ref)	ref	ref	ref
	Year	Annual terms	Annual terms	Annual terms

BIBLIOGRAPHY

[1] Lisa M. Leontis and Amy Hess-Fischl. Endocrineweb. Endocrine Disorders, Diabetes, Type 2 Diabetes: Type 2 Diabetes Complications, 2016.

[2] Centers for Disease Control and Prevention, Diabetes Home, Basics, What is Diabetes? Basics about Diabetes, 2015.

[3] World Health Organization, Media Centre, Diabetes: Fact sheet, 2016.

[4] Centers for Disease Control and Prevention, Diabetes Home Data and Statistics, 2014. Statistics Report: 2014 National Center for Health Statistics, 2014.

[5] National Institute of Health, National Institute of Diabetes and Digestive and Kidney Disease, Health Information, Health Communication Programs, National Diabetes Education Program, Am I at Risk? Diabetes Risk Factors, 2016.

[6] The Centers for Disease Control and Prevention, Diabetes Home, National Diabetes Prevention Program, 2016.

[7] National Institute of Health, National Institute of Diabetes and Digestive and Kidney Disease, NIDDK, Health Information, Health Topics, Diabetes, Choose More than 50 Ways to Prevent Type 2 Diabetes, 2014.

[8] Centers for Disease Control and Prevention, Healthy Weight, Assessing Your Weight, Body Mass Index (BMI), 2015.

[9] American Diabetes Association, Food and Fitness, Weight Loss, 2016.

[10] Frye RL, August P, Brooks MM, et al. A randomized trial of therapies for type 2 diabetes and coronary artery disease. *N Engl J Med* 2009;360(24): 2503-2015

[11] ICD10Data.com, 2016 ICD-10-CM Diagnosis Code I10, Essential (primary) hypertension, 2016.

[12] James PA, Oparil S, Carter BL, et al. 2014 evidence-based guideline for the management of high blood pressure in adults: report from the panel members appointed to the Eighth Joint National Committee (JNC 8). *JAMA* 2014;311(5):507-520.

[13] The JAMA Network, Hypertention Guidelines, Evidence-Based Guideline for the Management of High Blood Pressure in Adults, 2015.

[14] Chobanian AV, Bakris GL, Black HR, et al. The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC 7). *Hypertension* 2003;42(6):1206-1252.

[15] Sheldon G. Sheps, Henry R. Black, Jerome D. Cohen, et al. The Sixth Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure. *Arch Intern Med* 1998;158(6):573.

[16] American Heart Association, Diabetes with Coronary Artery Disease: Putting BARI 2D into 3D Perspective, 2009.

[17] National Institution of Health, National Heart, Lung, and Blood Institute, ATP III At-A-Glance: Quick Desk Reference, 2001.

[18] NCEP. National Cholesterol Education Program: second report of the Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel II). *Circulation* 1994:89:1329-1445.

[19] Ansell BJ, Watson KE, Fogelman AM. An evidence-based assessment of the NCEP Adult Treatment Panel II guidelines. National Cholesterol Education Program. *JAMA* 1999;282(21):2051-2057.

[20] National Diabetes Education Initiative, ADA 2016 Diabetes Screening and Diagnosis, Diabetes Management Guidelines, 2016.

[21] Jeanine Albu, Sheldon H. Gottlieb, Phyllis August, et al. Modifications of Coronary Risk Factors. *Am J Cardiol* 2006; 97(12A): 41G–52G.

[22] University of Oxford, Diabetes Trials Unit, UK Prospective Diabetes Study (Completed), 2015.

[23] Gerstein HC, Miller ME, Byington RP, et al. Effects of intensive glucose lowering in type 2 diabetes. *N Engl J Med* 2008;358(24):2545-2559.

[24] International Diabetes Federation, Diabetes Voice, the Results and Implications of the Accord and Advance Trials, 2009.

[25] U.S. Department of Veterans Affairs, Office of Research & Development, The legacy and lessons of the VA Diabetes Trial, 2015.

[26] Wolk R, Bertolet M, Brooks MM, et al. Differential effects of insulin sensitization and insulin provision treatment strategies on concentrations of circulating adipokines in patients with diabetes and coronary artery disease in the BARI 2D trial. *Eur J Prev Cardiol* 2016;23(1): 50-58.

[27] Brooks MM, Kelley D, Orchard TJ, et al. Baseline characteristics of patients with diabetes and coronary artery disease enrolled in the Bypass Angioplasty Revascularization Investigation 2 Diabetes (BARI 2D) trial. *Am Heart J* 2008;156(3): 528-536.

[28] American Diabetes Association, Living With Diabetes, Treatment and Care, Medication, Insulin & Other Injectables: Insulin Basics, 2015.

[29] Inzucchi SE, Bergenstal RM, Buse JB, et al. (2012). Management of hyperglycemia in type 2 diabetes: A patient-centered approach. *Diabetes Care* 2012;35(6): 1364-1379.

[30] Proks P, Reimann F, Green N, et al. Sulfonylurea stimulation of insulin secretion. *Diabetes* 2002;51 Suppl 3:S368-376.

[31] Everyday Health, Drugs, Non-Sulfonylureas Metformin: What Is Metformin (Glucophage)? 2015.

[32] FDA, Safety, Rosiglitazone-containing Diabetes Medicines: Drug Safety Communication - FDA Eliminates the Risk Evaluation and Mitigation Strategy (REMS), 2015.

[33] FDA, Safety, Thiazolidinediones [Actos (pioglitazone HCl), Avandia (rosiglitazone)], 2002.

[34] Home P, Riddle M, Cefalu WT, et al. Insulin therapy in people with type 2 diabetes: opportunities and challenges? *Diabetes Care* 2014;37(6):1499-1508.

[35] Diabetes Self-Management, Diabetes Drugs: Sulfonylureas, 2009.

[36] Fonseca V. Effect of thiazolidinediones on body weight in patients with diabetes mellitus. *Am J Med* 2003;115 Suppl 8A:42S-48S.

[37] Diabetes.co.uk, Metformin (Glucophage) and Weight Loss, 2016.

[38] Myheart.net, Metformin Weight Loss – Does it Work? 2014.

[39] Chaudhuri A, Dandona P. Effects of insulin and other antihyperglycaemic agents on lipid profiles of patients with diabetes. *Diabetes Obes Metab* 2011;13(10):869-879.

[40] Hermann LS, Karlsson JE, Sjøstrand AI. Prospective com-parative study in NIDDM patients of metformin and giben-clamide with special reference to lipid profiles. *Eur J ClinPharmaco*l 1991;41:263-265.

[41] Elkeles RS. The effects of oral hypoglycemic drugs on serumlipids and lipoproteins in non-insulin-dependent diabetes (NIDDM). *Diabete Metab* 1991;17:197-200.

[42] Pankaj Madan. Effect of thiazolidinediones on lipid profile. *CMAJ*. 2005;173(4):344.

[43] Randeree HA, Omar MA, Motala AA, et al. Effect of insulin therapy on blood pressure in NIDDM patients with secondary failure. *Diabetes Care* 1992;15(10):1258-1263.

[44] Roumie CL, Liu X, Choma NN, et al. Initiation of sulfonylureas versus metformin is associated with higher blood pressure at one year. *Pharmacoepidemiol Drug Saf* 2012;21(5):515-523.

[45] Ben Keidan, Judith Hsia, Richard Katz. Plasma lipids and antidiabetic agents: a brief overview. *Br J Diabetes Vasc Dis* 2002;2:40-43.

[46] Qayyum R, Adomaityte J. A meta-analysis of the effect of thiazolidinediones on blood pressure. *J Clin Hypertens (Greenwich)* 2006;8(1):19-28.

[47] Pharmacist's Letter / Prescriber's Letter, American Diabetes Association Treatment Algorithm for Type 2 Diabetes, 2006.

[48] Zammitt NN, Frier BM. Hypoglycemia in type 2 diabetes: pathophysiology, frequency, and effects of different treatment modalities. *Diabetes Care* 2005;28(12):2948-2961.

[49] Mogensen UM, Andersson C, Fosbøl EL, et al. Sulfonylurea in combination with insulin is associated with increased mortality compared with a combination of insulin and metformin in a retrospective Danish nationwide study. *Diabetologia* 2015;58(1):50-58.

[50] Chen YH, Du L, Geng XY, et al. Effects of sulfonylureas on lipids in type 2 diabetes mellitus: a meta-analysis of randomized controlled trials. *J Evid Based Med* 2015;8(3):134-148.

[51] American Heart Association. Caregiver. What is Cardiovascular Disease? 2014.

[52] Mayo Clinic. Patient care and health info. Disease and Conditions. Heart Disease, 2014.

[53] Mayo Clinic. Patient Care & Health Information. Diseases & Conditions. Coronary artery disease: Overview, 2015.

[54] National Institute of Health, National Heart, Lung, and Blood Institute, Health Information for the Public, Health Topics, Coronary Heart Disease, What Is Coronary Heart Disease? 2015.

[55] Medscape, Drugs and Diseases, Percutaneous Coronary Intervention, 2015.

[56] National Health, Lung, and Blood Institute. Health Professionals for the Public, Health Topics, Coronary Artery Bypass Grafting: What Is Coronary Artery Bypass Grafting? 2012

[57] Bittner V, Bertolet M, Barraza Felix R, et al. Comprehensive Cardiovascular Risk Factor Control Improves Survival: The BARI 2D Trial. *J Am Coll Cardiol* 2015;66(7): 765-773.