Repeat revascularization and death following percutaneous coronary intervention in patients with Type 2 Diabetes: risk factors, biological mechanisms and prognostic models

by

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Submitted to the Graduate Faculty of the Department of Epidemiology

Graduate School of Public Health in partial fulfillment

of the requirements for the degree of

Doctor of Philosophy

University of Pittsburgh

2020

UNIVERSITY OF PITTSBURGH

GRADUATE SCHOOL OF PUBLIC HEALTH

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November 24, 2020

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Abstract

Patients with Type 2 Diabetes (T2D) have higher rates of repeat revascularization following percutaneous coronary intervention (PCI) compared to patients without diabetes. We identified risk factors that are associated with repeat revascularization following PCI in this patient population and developed risk prediction models.

Aim 1 used Cox regression to assess the association of lipid, hemostasis, adipokine, and kidney function biomarkers with target vessel revascularization and any repeat revascularization (ARR), adjusting for non-biomarker risk factors identified in the Bypass Angioplasty Revascularization Investigation 2 Diabetes (BARI 2D) trial. Non-biomarker risk factors associated with the outcomes included age, prior revascularization, insulin, number of lesions with thrombus, hypercholesterolemia, insulin use and left circumflex artery stenosis. No biomarkers at baseline were associated with the outcomes. Time-varying fibrinopeptide A was associated with an increased risk for ARR.

Aim 2 identified potential biological mechanisms associated with repeat revascularization in the BARI 2D trial by leveraging time-varying survival Classification and Regression Tree (CART) analysis to identify high risk biomarker profiles. Biological mechanisms potentially associated with the outcome included hemostasis, endothelial dysfunction, hyperlipidemia, monocyte recruitment, and increased inflammation relative to baseline.

Aim 3 used University of Pittsburgh Medical Center registry data and CART methodology to identify profiles of patients with T2D associated with repeat revascularization and death following PCI. Risk flow charts with patient risk factor profiles for both repeat revascularization and death were created to aid physicians and patients in clinical settings. The 1-year risk flow chart for repeat revascularization included multivessel disease, age, prior peripheral arterial disease, prior PCI and number of lesions attempted for treatment. The 2-year risk flow chart for death included prior heart failure, age, and pre-procedure creatinine and hemoglobin.

Public health relevance: The rate of repeat revascularization after PCI in patients with T2D is higher than in patients without diabetes and the rate of repeat revascularization after PCI is also higher compared to coronary artery bypass grafting. Nevertheless, the use of PCI in patients with T2D is increasing. Given the rising global incidence of T2D, it is becoming increasingly important to understand factors that lead to repeat revascularization after PCI in this population.

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Acknowledgments

I would like to express my sincere gratitude to my advisor, Dr. Bertolet. Your support throughout my dissertation boosted my confidence in statistical methodology and coding, guided me to refine my research topic, and was a calming presence.

I would also like to thank the members of my dissertation committee, Dr. Brooks, Dr. Costacou and Dr. Mulukutla, for extending their time and expertise to me. Your questions prompted me to gain a deeper understanding of my research topic, and your guidance helped me to enhance the clinical applicability of my research.

My family has been phenomenally supportive in my PhD journey and I dedicate this dissertation to them. Mom and Dad, thank you for always inspiring me to aim higher. To my brothers, Kassim and Juma, and my sisters-in-law, Camilia and Iman, your encouragement helped to push me through when the task ahead seemed impossible.

Last, but not least, I would like to thank God because none of this would have been possible without His blessing.

1.0 Introduction

The overall objective of this dissertation is to use characteristics of patients with Type 2 Diabetes (such as demographics, medical history, biomarkers) to predict those individuals with diabetes who may be at higher risk for repeat revascularization following percutaneous coronary intervention (PCI). The central hypothesis is that among individuals with Type 2 Diabetes who have undergone PCI, there is an association between patient characteristics and repeat revascularization.

Atherosclerosis is the leading cause of coronary heart disease (CHD) and it is known to occur at an accelerated pace in patients with diabetes. The proportional use of PCI in patients with diabetes is increasing. However, when compared to coronary artery bypass grafting (CABG), patients who undergo PCI have higher rates of repeat revascularization. While the rate of repeat revascularization in patients with diabetes is significantly higher than in patients without diabetes, comparatively less research on risk factors in this population has been conducted. Furthermore, risk prediction scores for adverse events following PCI (including repeat revascularization) have not been developed for this population. This is despite the recognition that there is a heterogeneity in cardiovascular risk in the diabetes population. Risk prediction scores would enable clinicians to take this heterogeneity into account when weighing the decision to treat patients using PCI.

In this chapter, we will review the pathophysiology of atherosclerosis and diabetes. We will also explore the interplay between diabetes pathophysiology and atherosclerosis. We will demonstrate that there is a need for risk scores that predict the risk for repeat revascularization after PCI in patients with Type 2 Diabetes by discussing the limitations of existing PCI outcome

risk scores and providing an overview of the incidence of repeat revascularization in this population.

1.1 Atherosclerosis

1.1.1 Epidemiology

Cardiovascular disease (CVD), the leading cause of death in the United States[1], encompasses diseases of the heart (CHD, congenital heart disease and rheumatic heart disease), diseases of blood vessels (hypertension) and vascular diseases of the brain (cerebrovascular disease)[2]. The prevalence of CVD in the US in 2017 was approximately 7,200 per 100,000 people. 44% of CVD deaths are attributable to CHD and the prevalence of CHD in adults 20 years or older is 6.3%[2]. Atherosclerosis is the leading cause of CHD.

1.1.2 Pathogenesis

Atherosclerosis is an inflammatory disease and is caused by the formation of plaques along arterial walls. It is a complex process that arises from an interplay of several factors including lipid levels (low density lipoprotein cholesterol- LDL-C; triglycerides), genetics (e.g. mutations) and lifestyle factors (e.g. smoking, sedentary lifestyle) to name a few.

High cholesterol, fatty diet, hypertension, sedentary lifestyle, smoking and diabetes mellitus have all been associated with atherosclerosis[3]. Endothelial dysfunction due to these cardiovascular risk factors leads to increased permeability of the vascular endothelium (via

loosening of tight gap junctions), allowing accumulation of LDL-C in the subendothelial space of the coronary artery[4]. Once in the sub-endothelial space, LDL-C is oxidized. The entry of LDL-C into the sub-endothelial space triggers a proinflammatory response which attracts innate immune cells, including monocytes, into the intima. Monocytes gain entry either through the permeable endothelial wall or via adhesion molecules whose expression on endothelial cells is enhanced due to endothelial dysfunction. Monocytes differentiate into macrophage cells which engulf the oxidized LDL-C to form foam cells. These foam cells release a variety of growth factors and cytokines which stimulate the migration of vascular smooth muscle cells (VSMCs) into the sub-endothelial space. Foam cells and VSMCs undergo apoptosis and accumulate to form a necrotic core (also known as plaque). VSMCs also form a fibrous cap over the plaque through the generation of extracellular matrix.

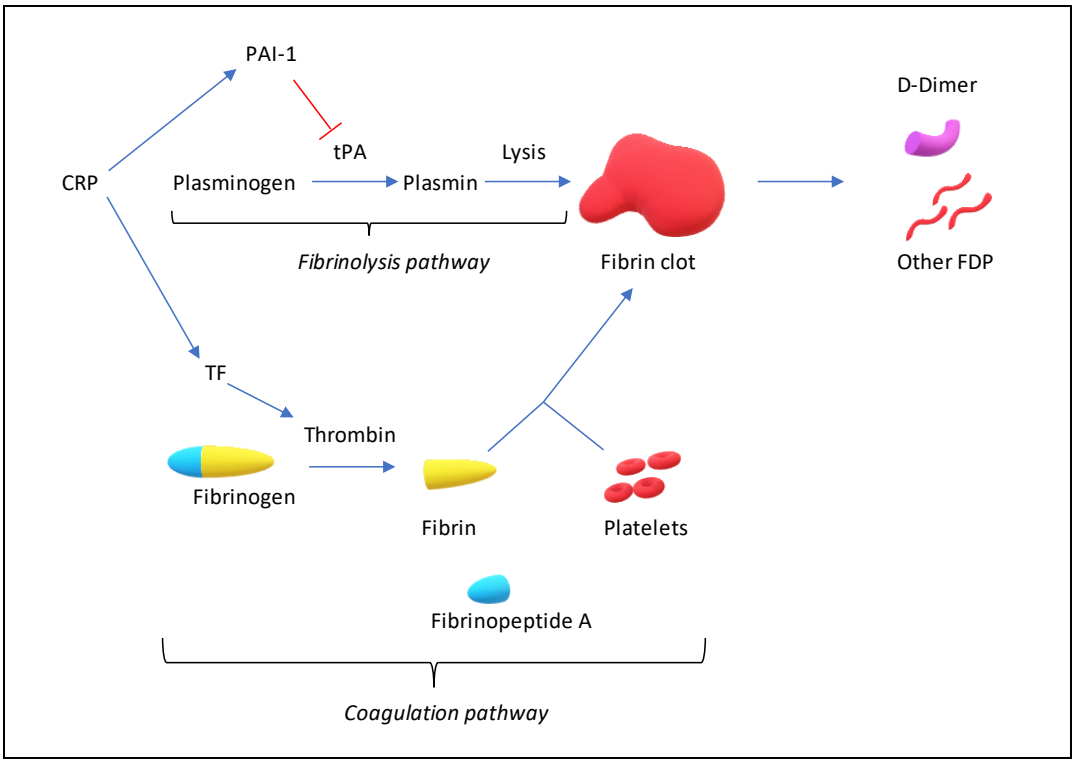
Apoptosis of VSMCs and foam cells leads to the release of metalloproteases that degrade the fibrous cap, leading to plaque vulnerability[4]. The stability of plaques is dependent on the concentration of lipids, macrophages and collagen in the plaque as well as on the thickness of the fibrous cap. Stable plaques contain a small lipid pool, have low macrophage density (an indicator of low inflammatory activity), high collagen content and a thick fibrous cap[3]. Unstable plaques, which are prone to rupture, contain a high lipid pool, have high macrophage density, low collagen content and a thin fibrous cap[3].

1.1.3 Sequelae

Stable plaques may cause narrowing of the artery, restricted blood flow to the myocardium and subsequently stable angina (chest pain) when there is increased demand for oxygen (such as with exercise or stress)[2]. Plaque rupture or erosion of unstable plaques exposes contents of the

plaque, such as tissue factor, to the lumen. Tissue factor triggers the coagulation cascade by activating thrombin which degrades fibrinogen to fibrin and fibrinopeptide A[4]. The presence of fibrin recruits platelets to the rupture site and a platelet rich thrombus forms with the fibrin. In a process known as fibrinolysis[5 6] (Figure 1), fibrin also leads to plasminogen release from the liver and the plasminogen is converted to plasmin by tissue plasminogen activator (tPA). Plasmin degrades the fibrin in the thrombus and lyses the clot into D-dimer and other fibrin degradation products. Fibrinolysis can be inhibited by the presence of plasminogen activator inhibitor-1 (PAI-1) which prevents tPA from converting plasminogen to plasmin. C-reactive protein (CRP), a biomarker associated with enhanced expression of tissue factor[7] and PAI-1[8], may lead to increased thrombus formation. Tissue factor triggers the coagulation cascade but with the increase in PAI-1 expression, fibrinolysis is impaired and thrombus lysis is limited. CRP is also associated with increased fibrin deposition[8], a state which may lead to the formation of strong fibrin bonds in the thrombi thus protecting the thrombi from degradation[4].

The thrombus resulting from plaque rupture or erosion leads to acute coronary syndrome (ACS). ACS includes unstable angina (UA), non-ST elevation myocardial infarction (NSTEMI) and ST elevation myocardial infarction (STEMI). STEMI occurs when a thrombus completely occludes an artery and blocks blood flow in the artery. NSTEMI and UA are caused by partial occlusion of an artery by a thrombus. NSTEMI and UA are differentiated by the severity of damage to the myocardium; damage caused by NSTEMI is severe enough to lead to elevated cardiac troponin levels (regulatory proteins released into the circulation when myocyte injury has occurred), while UA is less severe and does not lead to elevated cardiac troponin levels[4].



Abbreviations: CRP (C-reactive protein); TF (tissue factor); PAI-1 (plasminogen activator inhibitor-1); tPA (tissue plasminogen activator); FDP (fibrin degradation products)

Figure 1 Pathways and biomarkers in thrombus formation and lysis

1.1.4 Treatment: Percutaneous Coronary Intervention

Atherosclerosis and its sequalae (stable angina and ACS) can be treated using medication, invasive surgery (CABG) or a minimally invasive procedure known as PCI. Medical therapy for atherosclerosis includes an array of drugs for controlling lipoprotein levels, such as statins for lowering LDL-C[9] or anti-platelet therapy for lowering the risk of atherothrombosis[10]. PCI and CABG are revascularization procedures that seek to restore adequate blood flow in coronary arteries. In CABG, which is performed under general anesthesia, the diseased coronary artery is accessed via a 6-inch or longer vertical incision on the chest (traditional or off-pump CABG) or via incisions that are 3-inches or shorter (minimally invasive direct CABG). Artery or vein grafts

from other parts of the body, such as a mammary artery or saphenous vein, are used to bypass the region of the coronary artery that has a plaque (lesion). PCI does not require access via incisions; rather, the lesion is accessed via a femoral or radial artery using a catheter to support delivery of the stent to the lesion. We will focus on PCI in this dissertation.

1.1.4.1 PCI procedure overview and outcomes

PCI is a multi-step revascularization procedure that begins with assessment of the suspect lesion. Physical characteristics of the plaque such as vessel size, lesion length and lesion composition can be examined using various methods including intravascular ultrasound (IVUS) or optical coherence tomography (higher resolution but less depth than IVUS)[11]. If the lesion is found to be calcific, it can be modified using techniques such as cutting balloons or rotational atherectomy[12]. Once the lesion has been assessed and prepared as necessary, a guide catheter is inserted via femoral (more common) or radial access. A guide wire, which is passed through this catheter and past the lesion, is used to advance a balloon-tipped catheter. Once at the lesion site, the vessel is dilated by inflating the balloon to press the plaque and thrombus (if present) against the vessel wall. The deflated balloon is withdrawn and, in its place, a stent deployment balloon that is enclosed by a stent is advanced to the lesion. The pressure from the inflation of this balloon presses the stent into the vessel walls at the lesion site, after which a post-dilation balloon may be advanced to the stent site to ensure stent expansion. The deployed stent is typically assessed, e.g. with IVUS, after the guidewire and catheter are withdrawn to check for proper stent expansion and adherence to the vessel wall, and to determine if the stent edges extended beyond the lesion causing a tear in the vessel wall (edge dissection).

Procedural complications that may occur during and immediately after stent placement include coronary dissection or perforation, air embolization, loss of stents (stent is displaced from

the balloon at a location other than the intended lesion) and side branch occlusion (reduced blood flow in a side branch after an adjacent main vessel is stented)[13]. Post-procedure adverse events include stent thrombosis (ST) whereby a blood clot forms within the stent, and in-stent restenosis (ISR) where the vessel re-narrows at the stent location due to neointimal growth. Both adverse events may lead to target lesion revascularization (TLR), a sub-category of repeat revascularization. Al Muradi et al.[14] found that from 2004 through 2006 in the National Heart Lung and Blood Institute Dynamic Registry, an observational registry of patients undergoing PCI, 86.6% and 13.4% of TLR were due to restenosis and stent thrombosis, respectively.

1.1.4.2 Stent technology (stent types)

PCI has undergone several iterations, with each iterative method intended to improve upon the prior method. Percutaneous transluminal coronary angioplasty (PTCA), also known as balloon angioplasty, was the first type of coronary angioplasty[15]. It involved inserting a balloon tipped catheter into the vasculature and inflating the balloon at the coronary lesion to press the plaque against the vessel wall, and then withdrawing the balloon and catheter. The rate of restenosis was high with this method, ranging from 30% to 50%, and abrupt closure of the vessel once the balloon was withdrawn was a common adverse event[15]. Bare metal stents (BMS) were introduced to address the acute vessel closure and restenosis rates that were seen with PTCA[15,16]. While there was a reduction in acute vessel closure, the incidence of other adverse events was higher than rates in PTCA. These included stent thrombosis, myocardial infarction and death[15]. Through the results of various clinical trials, these adverse events were minimized through improved stenting procedures. In addition, dual anti-platelet therapy replaced anticoagulation therapy as the treatment of choice, and this helped in reducing thrombosis from as high as 24% incidence to 1.2% incidence[15]. However, restenosis remained a significant adverse event with rates between 20%-

25% within the first 6 months after stent placement[15]. The introduction of drug eluting stents (DES) further improved upon restenosis rates[16]. DES are bare metal stents that have been coated with a polymer containing anti-proliferative drugs to prevent neointimal growth of the artery wall. The first generation of DES used one of two antiproliferative drugs on the stent, paclitaxel eluting stent (PES) or sirolimus eluting stent (SES)[17]. Restenosis rates were lowered to less than 5% with the use of these first-generation DES, a sizeable reduction from what was seen with BMS. However, stent thrombosis rates were significantly higher when compared to rates in BMS, possibly due to delayed vessel wall healing caused by the anti-proliferative drugs coating the stent[15]. In addition, stent thrombosis occurred later than what was observed with BMS (greater than 1 year after stent implantation compared to within 1 year for BMS)[18]. While the overall risk of stent thrombosis is low ($\leq 3\%$), it is associated with high fatality and myocardial infarction rates (up to 75% and 65%, respectively)[15]. This increased risk of stent thrombosis requires a longer duration of dual antiplatelet therapy following DES placement compared to BMS placement (3-6 months for DES vs one month for BMS)[18]. Second-generation drug eluting stents incorporate sirolimus-derivative drugs (zotarolimus eluting stent- ZES; everolimus eluting stent- EES) coated on thinner stents (a positive correlation had been found between stent thickness and the reactive inflammatory process)[16], and are associated with lower stent thrombosis rates than first-generation stents[18]. Further developments in stent technology include DES made of biodegradable polymers which allow the stent to degrade over time, thus minimizing the risk for inflammation caused by long term interaction of the stent with the vessel wall[18].

1.1.4.3 PCI use in the United States

Epstein et al.[19] analyzed the annual volume of coronary revascularization between 2001 and 2008 using the Agency for Healthcare Research and Quality Healthcare Cost and Utilization

Project–Nationwide Inpatient Sample (NIS), supplemented by Medicare outpatient hospital claims. The NIS included data from 42 states and 1,000 hospitals using a stratified 20% random sample of all non-federal US hospitals. Patient-level data was weighted, allowing for estimation of the entire US population of hospitalized patients. Epstein et al. observed a 15% decrease in annual rate of coronary revascularizations, 38% decrease in annual CABG (steady decline) and 4% decrease (non-significant) in annual PCI. They also compared the burden of DES use to BMS use and found that 90% of all PCI used DES between 2003 (when FDA first approved DES) and 2005. During this same period, BMS use and the use of angioplasty without stenting decreased. Between 2006 and the first quarter of 2008, DES use decreased and accounted for 61% of all PCI but by the fourth quarter of 2008, DES use accounted for 68% of all PCI.

1.1.4.4 Repeat revascularization overview

PCI has been associated with higher rates of repeat revascularization compared to CABG.[20] Repeat revascularization includes TLR, target vessel revascularization (TVR) or any subsequent non-staged revascularization that occurs after initial PCI or CABG. TLR is defined as any repeat PCI or CABG which is performed in a previously stented segment or within 5mm distal or proximal of the stent due to restenosis or other complication related to the previously treated segment[21]. TLR is further classified as either being clinically indicated or non-clinically indicated whereby the criteria for clinically indicated have been defined by the Academic Research Consortium (Table 1). TLR caused by greater than 50% stenosis and at least one of the criteria listed in Table 1 is deemed as being clinically indicated. All other TLR are non-clinically indicated. TVR is repeat PCI or CABG that occurs in any segment of a previously stented vessel (entire major coronary vessel proximal or distal of the lesion)[21], therefore TLR falls within the definition of TVR.

Table 1 Definition of clinically indicated Target Lesion Revascularization

Stenosis ≥50% and one of the following:
(1) a positive history of recurrent angina pectoris, presumably related to the target vessel;
(2) objective signs of ischemia at rest (ECG changes) or during exercise test (or equivalent), presumably related to the target vessel;
(3) abnormal results of any invasive functional diagnostic test (e.g., Doppler flow velocity reserve, fractional flow reserve);
(4) A TLR or TVR with a diameter stenosis ≥70% even in the absence of the above-mentioned ischemic signs or symptoms

**Adapted from the Academic Research Consortium recommendations*[21]

TLR rates after approximately 1 year of follow-up range from less than 5% to greater than 10% of patients in clinical trials and registries. In a post-hoc analysis of the Synergy Between Percutaneous Coronary Intervention With TAXUS and Cardiac Surgery (SYNTAX) trial, Parasca et al.[22] found 26% and 19% cumulative incidence of TVR and TLR after 5 years of follow-up, respectively, in the 903 patients who had been randomized to undergo PCI. In the Endeavor Zotarolimus-Eluting Stent for Treatment of Native Coronary Artery Disease clinical trials (ENDEAVOR I, II, II Continued Access Registry, III), Mehta et al.[23] observed that 4.9% of the 1,306 patients experienced TLR after 9 months of follow-up. After 12 months of follow-up, Stolker et al.[24] observed 8.9% incidence of repeat revascularization in the Evaluation of Drug-Eluting Stents and Ischemic Events (EVENT) registry, a prospective observational registry for PCI use at 55 US centers (PES and SES). In an all-comer registry for Coroflex Please™ paclitaxel-eluting stent use in 16 European and 13 Asian sites, Leschke et al.[25] observed that 7.8% of 1142 patients experienced TLR after 10 months of follow-up.

1.1.4.5 Risk factors for repeat revascularization

Several studies have explored risk factors that are associated with repeat revascularization. Risk factors can be classified into patient-related (including biomarkers), lesion-related, and procedure-related characteristics.

History of PCI or CABG[24], diabetes, hemodialysis, peripheral vascular disease, multivessel disease and hyperlipidemia are patient-related factors that have been associated with repeat revascularization following PCI. Younger age and higher (worse) SYNTAX score, a score to determine optimal revascularization strategy based on coronary lesion complexity, have also been associated with higher odds for TLR. Conflicting results have been observed regarding the association of gender and of prior myocardial infarction with repeat revascularization. While Stolker et al.[24] found that male sex was associated with lower hazard ratio for TLR (HR 0.65, 95% CI [0.53-0.81]; n=10,144), Nakagawa et al.[26] and Kimura et al.[27] found an opposite trend (Nakagawa- OR=1.25, p=0.02, n=12,824; Kimura- HR=1.21, p=0.03, n=12,812). In a study conducted by Yanagi et al.[28], prior MI was associated with higher odds of TLR (OR=3.5, p<0.01, n=325) while Stolker et al.[24] and Iakovou et al.[29] had contradictory results (Stolker- HR 0.76, 95% CI [0.61-0.95]; n=10,144; Iakovou- OR=0.58, p=0.01, n=423).

Several studies have explored the association of biomarkers with restenosis or in-stent restenosis (ISR), conditions which may lead to repeat revascularization. For example, levels of fibrinolysis biomarkers such as fibrinogen may be used as an indicator for impaired fibrinolysis and subsequent predisposition for thrombosis. Elevated levels of inflammation biomarkers may indicate enhanced risk for endothelial dysfunction and subsequent restenosis. In a study of patients with stable angina who underwent PCI with first and second generation drug eluting stents, Lee et al.[30] observed that post-procedure creatinine kinase MB form (CK-MB; measured 6 to 9 hours

after PCI) that was more than two times the upper normal limit was significantly associated with TLR (OR 1.45; p=0.02). Enzyme markers such as CK-MB are elevated in up to 20% of patients undergoing PCI[31]. CK-MB is an enzyme marker of cardiac injury and is associated with increased mortality following PCI.[32] Although the pathophysiologic association between CK-MB and PCI is not well understood, it has been hypothesized that CK-MB is an indicator of high atherosclerotic burden.[31] A higher atherosclerotic burden may increase the likelihood of restenosis due to the pro-atherogenic state of the patient. The association of C-reactive protein (CRP), an inflammatory biomarker, with in-stent restenosis is equivocal with some studies finding elevated levels associated with ISR while other studies found no association. Xu et al.[33] compared ISR incidence in patients who underwent PCI (BMS and DES) relative to their pre-procedural CRP levels. CRP levels greater than 2 mg/L were significantly associated with ISR incidence after 7 months of follow-up (OR 1.89; $p<0.05$). They also observed that the pre-procedure CRP levels were higher in patients who developed ISR compared to those who did not develop ISR (OR 1.095; p=0.037). Walter et al.[34] had similar findings in their assessment of ISR in patients who had PCI with BMS. They found a direct relationship between pre-procedural CRP tertile and ISR whereby the ISR rate in the lowest tertile was 19% and increased to 45% in the third tertile ($p<0.005$) at the 6-month follow-up angiography. In contrast, Rittersma et al.[35] found no correlation between ISR and pre-procedure CRP quartiles or between TLR and pre-procedure CRP quartiles in patients who underwent PCI with BMS.

Some studies have shown that adverse outcomes are experienced when PAI-1 levels are relatively low. Katsaros et al.[36] assessed ISR incidence after 6-8 months of follow-up in patients who underwent PCI with drug eluting stents (PES, SES). They observed that patients with incident ISR had significantly lower plasma levels of pre-procedure PAI-1 active antigen compared to

patients who did not experience TLR. They further observed that patients in the lowest tertile of PAI-1 active antigen plasma levels had 9.5-fold higher risk of ISR compared to patients in the third tertile. Strauss et al.[37] observed a similar association, albeit in patients who underwent PTCA only or PCI with BMS. The restenosis rate in the lowest PAI-1 tertile was 40% whereas the rate in the 3rd tertile was 25% (p=0.0580). Prisco et al.[38] did not observe any significant difference in pre-procedural PAI-1 in patients who had restenosis at follow-up compared to patients with no restenosis (8.1 IU/ml and 5.5 IU/ml respectively). The study had a low sample size (n=48) and may have been underpowered to detect any differences in pre-procedural PAI-1. However, post-procedural PAI-1 levels were significantly different in those with restenosis at follow-up compared to those with no restenosis (12.0 IU/ml and 3.8 IU/ml respectively; $p<0.05$).

Fibrinogen is involved in the coagulation-fibrinolysis cascade and associates with platelets via the tissue factor activated pathway. Lupi et al.[39] observed that STEMI patients who underwent PCI with BMS and developed ISR at 6-months follow-up had significantly higher baseline and post-procedure (up to 72 hours after PCI) fibrinogen compared to similar patients who did not experience ISR. Jaster et al.[40] measured post-procedure fibrinogen-positive platelets following PCI with BMS in patients with acute myocardial infarction. After 5 months of follow-up, they found that patients who developed ISR had significantly higher amounts of fibrinogen-positive platelets than those who did not develop ISR. Further analysis showed that a ROC cutoff of 4% fibrinogen-positive platelets was predictive of ISR. In a study of patients with coronary artery disease who underwent PCI (stent type not specified), Otsuka et al.[41] assessed the 6-12 month incidence of TLR. They observed that the frequency of TLR significantly increased with increasing tertiles of pre-procedural fibrinogen levels (from 14.1% in the lowest tertile to 30.6% in the 3rd tertile;

p=0.0005). Fibrinogen levels higher than 100 mg/dl were significantly predictive of ISR (OR 1.82; p<0.0001).

Lipid levels have also been associated with ISR incidence. Li et al.[42] assessed ISR incidence in patients who underwent PCI with second generation DES for treatment of chronic total occlusion lesions. They found that higher LDL-C levels were predictive of ISR (OR 1.043; p=0.011). In a meta-analysis of 8 studies, He et al.[43] concluded that there was no significant association between baseline HDL-cholesterol (HDL-C) levels and ISR in patients who had PCI with either BMS or DES. In contrast, Kundi et al.[44] observed that in patients with stable angina who underwent PCI (BMS or DES), the hazard ratio for ISR increased as the quartile for pre-procedural triglyceride/HDL-C ratio increased. The HR for the lowest quartile was 1.2 while the HR for the fourth quartile was 4.7. An ROC cut-off of 3.8 for the triglyceride/HDL-C ratio was predictive of ISR (sensitivity 71%, specificity 68%). Furthermore, the ratio was independently associated with ISR (HR 1.2; p<0.001).

Lesion characteristics also play a role in TLR incidence with long lesions and small vessels being associated with higher odds of TLR. The location of the lesion has also been identified as an important factor in TLR risk. Lesions that are in saphenous vein grafts or in the left main coronary artery are strongly associated with higher TLR likelihood (OR ranging from 2.28 to 7.65)[14,45,46]. Similarly, ostial lesions, those occurring within 3mm of the vessel origin, are also associated with increased risk for TLR (OR ranging from 1.85 to 2.82)[26,28,45]. Complex lesions, such as those classified as ACC/AHA type B2 or C, lead to increased odds of TLR (OR 1.5)[26]. Treatment of chronic total occlusion (CTO) lesions and in-stent restenotic lesions have also been found to result in higher likelihood of TLR incidence (OR 1.75 to 5.96) [26,45,46].

Procedure-related characteristics that have been associated with increased risk of TLR include use of BMS (RR 3.8)[47], first-generation DES (OR 5.1)[48] and use of multiple stents to treat a lesion (OR 3.01)[49]. In addition, longer stents were found to lead to higher hazard rate of TLR (HR 1.08 to 1.65) [27 50] while lower hazard rates were found with smaller stent diameter (HR 0.52) [50]. Stent fracture is associated with high odds for TLR incidence (OR 27.24)[51].

1.2 Atherosclerosis in patients with diabetes

1.2.1 Diabetes classification

In 1980, the World Health Organization Expert Committee adopted the terms insulin-dependent diabetes mellitus (IDDM) or Type 1 and non-insulin-dependent diabetes mellitus (NIDDM) or Type 2 which were introduced by the National Diabetes Data Group. The terms IDDM and NIDDM are no longer used because it is now recognized that insulin dependence can occur in both types of diabetes. The currently used terms are Type 1 Diabetes (T1D), Type 2 Diabetes (T2D) and Gestational Diabetes. There are also other types of diabetes due to specific causes such as maturity-onset diabetes of the young (MODY) or chemical-induced diabetes (e.g. due to treatment for HIV/AIDS)[52].

T1D includes diabetes cases that have an autoimmune component, as well as cases that have β-cell destruction with no known etiology or pathogenesis (idiopathic). Excluding the idiopathic cases, T1D is characterized by the presence of autoimmune markers such as islet cell antibodies, anti-glutamic acid decarboxylase antibodies, islet antigen 2, and insulin autoantibodies[53]. The autoimmunity leads to the destruction of β-cells, with a higher destruction

rate observed in children when compared to adults, and leads to a dependence on insulin treatment[53]. In addition to the immune system's contribution to T1D pathophysiology, defects in bone marrow, thymus and β-cell function also play a role in T1D[54]. Environmental factors such as birth month (increased chance of T1D if born in spring), viruses, diets and vitamin D are also thought to be associated with T1D incidence[54]. While T1D affects both children and adults, peak incidence is observed at 5 to 7 years of age and at puberty[54].

T2D is the most common form of diabetes and it involves insulin secretion impairment and insulin resistance; both can coexist in a case. At the initial stages of T2D, insulin treatment is not required for survival. In most cases of T2D, this independence from insulin treatment lasts throughout the lifetime. However, in some cases, insulin is required in later stages due to loss of function of β-cells. T2D is asymptomatic in its early stages; however, individuals are still at risk for microvascular and macrovascular complications during the early stage[53]. Individuals with T2D have been observed to have both reduced β-cell mass and function. It is thought that this reduced volume is due to an increase in β-cell apoptosis and in other cell death mechanisms[53]. Islet amyloid polypeptide deposition in the pancreas has been linked to apoptosis and reduced β-cell volume[53].

Diabetes is characterized by hyperglycemia; therefore, diagnosis methods are focused on measurement of blood glucose. Diagnostic tests include random plasma glucose if the patient has hypoglycemia symptoms or crisis (cutoff >=200 mg/dL), fasting glucose test (cutoff >=126 mg/dL), oral glucose tolerance test (2-hour plasma glucose with cutoff >=200 mg/dL) and measurement of glycated hemoglobin (HbA1c; cutoff >=6.5%.). HbA1c is a glucose-hemoglobin complex that is found in the presence of hyperglycemia. It is a relatively new test and has several advantages over the other testing methods[53]. Patients are not required to fast prior to sample collection. Once collected, the HbA1c in the blood sample is more stable than glucose. There is

less day-to-day variation in HbA1c plasma levels and HbA1c is more reflective of glycemia over a three to four-month period. This contrasts with glucose whose levels may vary in response to short-term lifestyle interventions. A disadvantage of the HbA1c test is that non-glycemic conditions may interfere with test (e.g. kidney failure, blood loss, pregnancy)[53].

1.2.2 Epidemiology of diabetes and of atherosclerosis in diabetes

The International Diabetes Federation (IDF) estimates that the global prevalence of diabetes has tripled since the year 2000[55] and the global all-cause mortality attributable to diabetes is estimated to be 10.7%[55]. 8.8% of adults worldwide were estimated to have diabetes in 2017 and this prevalence is projected to increase 48% by 2045[55]. The IDF further estimates that the yearly global cost for diabetes-related healthcare is US$ 727 billion[55]. In the US, this cost is estimated to be $348 billion where an estimated 30.2 million adults in 2017 had diabetes (13% prevalence)[55]. Diabetes is projected to increase by 54% between 2015 and 2030 to affect nearly 55 million Americans[56]. A cost model using data from 1999 to 2015 estimates that the direct medical cost for treating diabetes complications is nearly $58 million per 10,000 US adults with diabetes over a 5-year treatment period[57]. The rising trend of diabetes in adults has also been observed among youth (0 to 19 years of age). In the SEARCH for Diabetes Youth Study carried out in five US clinical centers, Mayer-Davis et al.[58] observed a 1.4% annual increase in T1D incidence in youth (0-19 years old) between 2002 and 2012. The incidence between 2011 and 2012 was 21.7 per 100,000 youths[58]. Mayer-Davis et al. also observed a 7.1% annual increase in T2D incidence in youth (10-19 years old) between 2002 and 2012. The incidence of T2D in this population between 2011-2012 was 12.5 per 100,000 youths.

Einarson et al.[59] carried out a systematic review of the prevalence of CVD in T2D using original research across the world that was conducted between 2007 and 2017. They found that the prevalence of any CVD among 4.5 million patients with T2D was 32.2% while the prevalence of atherosclerosis was 29.1%. They also found that the mortality due to CVD among 3.2 million patients with T2D was 9.9%. The odds for death among patients with both T2D and CVD was significantly higher than the odds in persons with neither T2D or CVD (OR 4.56, 95% CI [3.53-5.89]).

The rising prevalence of diabetes, the high prevalence of atherosclerosis among patients with diabetes, the mortality risk associated with diabetes, and the high medical costs make it imperative to target patients with diabetes to minimize the public health impact of diabetes and its complications.

1.2.3 Role of insulin in diabetes

Atherosclerosis in individuals with diabetes is accelerated, manifests at a younger age, and is more diffuse with the involvement of smaller coronary arteries. Insulin resistance is a hallmark of T2D and it contributes to the formation of atherosclerotic plaques.[53]

1.2.3.1 Normal insulin function

Insulin is a pancreatic hormone that plays an important role in glucose homeostasis, a process whereby glucose levels in the blood are maintained within 4-6 mM[60]. The pancreas gland secretes digestive enzymes, via the exocrine component, and hormones, via the endocrine component. The endocrine component is organized into islets of Langerhans which have five hormone secreting cell types[53]. β-cells, one of these cell types, produce insulin and islet amyloid

polypeptide[53]. Upon ingestion of glucose, the glucose mediates insulin production in the β-cell through regulating insulin gene transcription factors[53]. In addition, glucose stabilizes preproinsulin mRNA in the β-cells, therefore an increase in blood glucose levels leads to increased preproinsulin mRNA in the pancreas. Glucose also induces proinsulin biosynthesis at the translational level and regulates the transcription of endopeptidase genes that are involved in proinsulin conversion to insulin. Insulin is then secreted from the pancreas in a biphasic manner, a process that sees the majority of insulin secreted in the first phase and the remaining insulin released slowly in the second phase[60]. The secreted insulin binds its receptors on liver, gut and peripheral cells (e.g. muscle cells) and stimulates glucose uptake by these tissues. Insulin also suppresses endogenous glucose production by the liver. Thus the overall effect of the secreted insulin is to lower blood glucose levels[53]. Glucagon, a hormone secreted by the α-cells of the islets of Langerhans, acts in opposition to insulin[60 53]. Its secretion is inhibited by hyperinsulinemia, such as that which occurs after glucose ingestion. Glucagon acts on the liver to stimulate endogenous glucose production, thus its suppression during hyperinsulinemia contributes to lowering of blood glucose levels[53]. As blood glucose levels decrease there is a slow decline in preproinsulin mRNA, and thus slowed production of insulin[53].

1.2.3.2 Insulin resistance

Insulin resistance, a cause of β-cell failure, occurs when the body has an abnormal response to insulin and the insulin is unable to properly reverse hyperglycemia. Ectopic and visceral fat are important factors in the development of insulin resistance[53]. An increase in adiposity causes fat cells to enlarge and become insulin resistant. Insulin is therefore unable to carry out its function of suppressing the release of free fatty acid (FFA) from the adipose tissue since the tissue no longer responds to insulin levels. The FFA leads to a state of hyperlipidemia whereby there is

accumulation of fat in the liver, elevated triglycerides and accumulation of fat in muscle tissue. Hepatic fat impairs glucose storage in the liver and promotes glucose production. Furthermore, the excess fat impairs glucose uptake by affected tissues. These conditions lead to a state of hyperglycemia and the pancreas increases insulin production to counteract this hyperglycemia. Over time, the pancreas becomes "exhausted" leading to β-cell failure and the loss of ability to produce enough insulin. Insulin resistance also leads to elevated triglyceride levels, low HDL-C levels, elevated apolipoprotein B (ApoB) levels and to an increased presence of small dense LDL particles. Chronic hyperglycemia and hyperlipidemia are thought to impair insulin gene expression, further exacerbating the pancreas' inability to produce enough insulin. Other factors leading to β-cell failure include age, genes, lipotoxicity (deposition of lipids in β-cells and chronically elevated plasma FFA), glucotoxicity (chronically elevated plasma glucose), excess islet amyloid polypeptide (and subsequent amyloid deposition on the pancreas), and resistance to the incretin hormones glucagon-like peptide-1 and glucose-dependent insulinotropic polypeptide (incretins stimulate glucose-dependent insulin secretion[61])[53].

1.2.4 Role of insulin resistance in atherosclerosis

Insulin resistance leads to low HDL-C levels, higher FFA, higher apoB and increased LDL-C. In the presence of high apoB levels, LDL-C is more prone to oxidation and thus forms oxidized LDL-C, a component of foam cells found in atherosclerotic plaques. Insulin resistance promotes fibrous cap formation through proliferation and migration of VSMCs into the subintimal arterial space. Apoptosis of VSMCs is also enhanced which leads to thinning of the fibrous cap. In the presence of insulin resistance, the MAP-K pathway is activated. This activation leads to stimulation of cellular growth and migration. It also causes a disruption in hemostasis through

production of prothrombotic and profibrotic factors. Increased levels of coagulation factors such as Factor VII (converts prothrombin to thrombin) and fibrinogen are favorable for thrombosis. Furthermore, elevated levels of coagulation factors have been associated with denser, more tightly packed fibrin structures, and hence to formation of thrombi that are more resistant to lysis. Insulin resistance is also associated with elevated levels of PAI-1 and decreased tPA, a state which impairs fibrinolysis. Hyperreactivity of platelets due to insulin resistance further acts to promote thrombus formation.

Hyperglycemia also plays a role in the promotion of atherosclerosis[53]. Hyperglycemia affects endothelial function, enhances oxidative stress (leading to vascular dysfunction), leads to increased VSMC proliferation (due to oxidative stress) and macrophage adhesion, enhances platelet activation, and causes increased production of oxidized LDL-C in the vessel wall. Hyperglycemia also leads to activation of protein kinase-C which enhances vascular permeability, promotes extracellular matrix synthesis and activates cytokines. Furthermore, it promotes gene transcription of PAI-1. Hyperglycemia leads to glycation (addition of sugar) to proteins, eventually leading to advanced glycation end products (AGE). Interaction of AGE with its receptor (RAGE) leads to enhanced leukocyte recruitment, release of pro-inflammatory and adhesion molecules, and induction of procoagulant factors in endothelial cells, thus stimulating prothrombotic pathways. In addition, hyperglycemia activates NF-kB, causing increased expression of endothelial adhesion molecule.

1.2.5 Revascularization in patients with diabetes

1.2.5.1 Current practice

Pandey et al.[62] used the National Cardiovascular Data Registry Acute Coronary Treatment and Intervention Outcomes Network Registry- Get with the Guidelines (NCDR ACTION Registry-GWTG) to study revascularization utilization in the diabetes population between 2008 and 2014. The focus of their study was NSTEMI patients with T2D who had multi-vessel coronary artery disease (CAD). Their study population was approximately 29,000 patients across 539 hospitals. They observed that 36.4% of these patients were treated with CABG, 46.2% with PCI and 17.3% had no revascularization procedure. Among those treated with PCI, 77.2% were treated with at least one DES. PCI use increased from 45.0% in 2008 to 48.9% in 2014 (p=0.0002) while there was no significant change in CABG use (36.1% in 2008 to 34.7% in 2014; p=0.8800). There was hospital-level variability in the choice of revascularization method; CABG use ranged from 0-78.0% across hospitals while PCI use ranged from 22.0-100.0%. Pandey et al. also found that the use of CABG decreased with decreasing complexity of CAD, and conversely that the use of PCI increased with decreasing complexity of CAD. It should be noted that even in the era of DES, BMS are still used in some patients (e.g. in those with large vessel and simple lesion, or in patients who cannot tolerate the longer duration of dual antiplatelet therapy that is required with DES use)[63].

1.2.5.2 Repeat revascularization in patients with diabetes

Individuals with diabetes have higher rates of repeat revascularization compared to those without diabetes. Several studies have assessed outcomes in patients with diabetes after PCI with

BMS, first-generation DES and second-generation DES, in comparison to patients with no diabetes.

In analysis of the Taiwanese Cardiovascular Atherosclerosis and Percutaneous TrAns-luminal INterventions (CAPTAIN) registry, Lu et al.[63] compared outcomes in patients with diabetes and patients with no diabetes who had undergone PCI with BMS. The CAPTAIN registry was a single center registry composed of patients who received either elective or emergency PCI. Lu et al. enrolled 2,300 patients from this registry who had received PCI between 1995 and 2004. They observed that during a 6-month follow-up angiography, patients with diabetes had higher restenosis rates compared to patients with no diabetes (26.0% vs 18.0%, $p<0.001$). Patients with diabetes were subsequently found to have a higher TLR rate than patients with no diabetes after a mean follow-up of 12 years (152+/-53 months). Jensen et al.[64] compared BMS to DES outcomes in the Danish National Health Service healthcare database of Western Denmark's entire population (55.0% of the Danish population) and found that DES conferred a lower risk for TLR relative to BMS (RR 0.63; 95% CI [0.47–0.85]). Daemen et al.[65] had a similar observation in their study of patients with diabetes in the Dutch RESEARCH and T-SEARCH registries where they observed that PES had a lower rate of TLR compared to BMS (5.3% vs. 15.6%; $p=0.0004$).

Study results regarding the effect of first-generation DES on TLR incidence in patients with diabetes are equivocal. In the Dutch RESEARCH and T-SEARCH registries analysis, Daemen et al.[65] found that TLR incidence with PES was lower than with SES (5.3% vs 13.2%, $p=0.0037$) after 2 years of follow-up. In contrast, analysis of the Korean DES-DIABETES (Drug-Eluting Stent in patients with DIABETES mellitus) Trial by Lee et al.[66] showed that the incidence of TLR after 2-year follow-up was higher with PES compared to SES (11.0% vs. 3.5%, $p<0.01$). This superiority of SES was attenuated after 4-years of follow-up. Daemen et al.[65] noted that their

analysis was underpowered to detect differences in TLR. Conflicting results are also seen when comparing first-generation to second-generation DES. In a meta-analysis of 18 randomized controlled trials, Bavishi et al.[67] analyzed data of 8000 patients with diabetes with a weighted mean follow-up of 27 months. They found that EES had lower TLR compared to first-generation DES (5.5% vs 6.7%; RR 0.71, p=0.05) and that ZES had higher TLR compared to first-generation DES (9.4% vs 5.4%; RR 1.89 p=0.02). The authors observed high heterogeneity in most analyses of ZES (few studies included ZES) and wide confidence intervals were seen in the ZES results. When Kereikas et al.[68] compared EES performance to PES performance in patients with and without diabetes in the SPIRIT IV (Clinical Evaluation of the XIENCE V Everolimus Eluting Coronary Stent System) trial, their results showed that there was no significant difference in TLR incidence after 1 year of follow-up in patients with diabetes (4.2% vs 4.7%, p=0.65). Sub-group analysis showed no difference in TLR incidence between EES and PES in non-insulin treated patients with diabetes, and no difference in TLR incidence in insulin-treated patients with diabetes. They did, however, find that TLR rate with EES was lower than with PES in patients with no diabetes (1.8% vs 4.5%, p<0.0001).

In a comparison of second-generation DES (EES, ZES), Park et al.[69] observed no significant difference in TLR incidence in patients with diabetes in the EXCELLENT [Efficacy of Xience/Promus Versus Cypher in Reducing Late Loss After Stenting] registry and RESOLUTE-Korea [Registry to Evaluate the Efficacy of Zotarolimus-Eluting Stent]) after 1 year of follow-up (1.7% vs 1.8%). Silbur et al.[70] compared ZES performance in patients with diabetes and patients with no diabetes in the RESOLUTE Global Clinical Trial Program which included 5 randomized clinical trials. After 2 years of follow-up, they found no significant difference in TLR incidence between patients with and without diabetes (4.8% vs 3.4%, p=0.1100).

While several studies have supported the observation that TLR incidence is higher in patients with diabetes when compared to patients with no diabetes (Jensen et al[64], RR 1.28 p<0.0001; and Jiang et al[71], RR 1.53, 95% CI 1.33-1.76), and that TLR rates are higher with BMS, it is not clear which DES is most beneficial for patients with diabetes in reducing TLR incidence. More nuanced studies may be required to parse out the benefits of each stent type. For example, Sawai et al.[72] assessed SES performance in patients with T2D and patients with impaired glucose tolerance in Japan based on their pre-PCI HbA1c levels. They observed a significantly higher incidence of TLR in patients with HbA1c greater than or equal to 7% compared to patients with HbA1c incidence lower than 7%. Furthermore, pre-procedural HbA1c greater than or equal to 7% was predictive of restenosis in SES (OR 3.61, p=0.03) in multivariate regression. In contrast, HbA1c was not found to be a predictor of restenosis in PES.

1.2.5.3 Other complications of diabetes

Complications of diabetes, grouped into microvascular and macrovascular complications, arise due to the hyperglycemic state that is characteristic of diabetes[73]. Microvascular complications affect small blood vessels (arterioles, capillaries, venules) and include diabetic nephropathy, neuropathy and retinopathy[73]. Diabetic retinopathy manifests within 20 years of being diagnosed with T1D and as early as 7 years after T2D diagnosis[73]. It affects one third of patients with diabetes and leads to reversible visual loss[53]. Diabetic nephropathy accounts for 50% of end-stage renal disease burden and nearly all diabetes-related end-stage renal disease cases are in patients with T2D[53]. Diabetic neuropathy involves peripheral nerve dysfunction resulting from demyelination and axonal degeneration[53]. It exists in several forms including sensory, focal and autonomic neuropathies[73].

Macrovascular complications affect large blood vessels (arteries, veins) and include coronary heart disease, peripheral arterial disease and cerebrovascular disease[73]. The underlying pathology in these complications is atherosclerosis[73]. Patients with diabetes account for approximately 30% of the peripheral arterial disease burden in the US[53]. Peripheral arterial disease can lead to intermittent claudication (cramping pain typically experienced in the legs) and critical limb ischemia[53]. Patients with diabetes are at an increased risk for cerebrovascular disease[73] and it is the leading long-term cause of morbidity and mortality in patients with T1D and in those with T2D. Among patients who have had T1D for greater than 40 years, the mortality rate due to coronary heart disease is 30%[53]. The prevalence of fatal and nonfatal coronary heart disease events among patients with diabetes who are older than 65 years is 20%[53].

1.3 Risk prediction models

1.3.1 Public health impact

Risk prediction models use various factors related to a patient's state of health to determine the probability that a particular outcome will occur in the future. These factors, which may include the patient's prior health history and current clinical measures, are typically used to calculate a score which is indicative of the magnitude of risk for development of the particular outcome. Risk scores provide opportunities for informed decision making when determining the optimal revascularization strategy. For example, it has been established that BMS result in significantly higher rates of TLR when compared with DES and that late stent thrombosis (>30 days to 1 year after stent placement) occurs almost exclusively in DES treated lesions. If a TLR risk score

indicates that a patient has a low risk of developing TLR, a physician may opt to use a BMS in the patient because the risk of TLR following BMS placement is low. The patient will then have been spared from the higher stent thrombosis risk that occurs with DES placement. Similarly, if a patient has a high likelihood of non-adherence to the dual anti-platelet therapy (DAPT) that is necessary following DES placement, and the risk score indicates low TLR risk, the physician may opt for BMS placement. The risk score may also be useful in determining optimal treatment following DES placement. If a patient is treated with a DES and the risk score indicates a high risk of TLR, extra care may be taken to ensure that the patient is adherent to DAPT. Finally, the risk prediction score stands to enhance shared decision-making between the patient and physician because the physician will be better informed about the patient's risk for certain outcomes.

1.3.2 Existing risk scores for outcomes following PCI

Several risk prediction scores for outcomes following PCI are currently used in clinical practice[74] (Table 2). Some of the scores are based on purely anatomical factors, some are based on purely clinical factors, and others are based on a combination of anatomical and clinical factors. Scores that are based on purely anatomical factors require that a patient undergo diagnostic catheterization before a decision on stent type can be made, whereas scores based on purely clinical factors allow for a comprehensive discussion on PCI risks before diagnostic catheterization occurs[50].

Table 2 PCI risk scores used in clinical practice

Risk score	Purpose of score	Predictor type	Predictors
SYNTAX Risk Score (SRS)[75]	Determine optimal revascularization strategy based on coronary lesion complexity	Anatomical	Various lesion characteristics
SYNTAX score II[76]	Improve decision making on optimal revascularization strategy based on coronary lesion complexity and important clinical variables	Anatomical and clinical	age, creatinine clearance, LVEF, left main disease, gender, COPD, peripheral vascular disease
Clinical SYNTAX (CSS)[77]	Predict mortality in patients with complex coronary artery disease undergoing PCI	Anatomical and clinical	age, LVEF, creatinine clearance
ACEF[78]	Predict mortality in patients undergoing cardiac surgery in elective PCI procedures	Clinical	age, LVEF, serum creatinine
NCDR[79]	Predict mortality in patients undergoing elective and primary PCI	Clinical	age, cardiogenic shock, prior CHF, peripheral vascular disease, chronic lung disease, GFR, NYHA functional class IV, PCI status (reason)
NY State Risk Score (NYSRS)[80]	Predict in-hospital mortality following PCI	Anatomical and clinical	age, gender, hemodynamic state, ejection fraction, pre-procedural MI, peripheral arterial disease, CHF, renal failure, left main CAD
EuroSCORE II[81] [82]	Predict risk for complications in patients undergoing cardiac surgery	Anatomical and clinical	age, gender, renal impairment, extracardiac arteriopathy, poor mobility, prior cardiac surgery, chronic lung disease, active endocarditis, critical preoperative state, diabetes on insulin, NYHA class, CCS class 4 angina, LV function, recent MI, pulmonary hypertension, PCI reason, intervention, surgery on thoracic aorta
Global Risk Classification score[83]	Predict cardiac mortality following PCI in patients with left main coronary artery disease	Anatomical and clinical	Combination of SYNTAX score and EuroSCORE strata

Abbreviations: SYNTAX (SYNergy between PCI with TAXUS™ and Cardiac Surgery); ACEF (Age, Creatinine, left ventricular Ejection Fraction); NCDR (National Cardiovascular Data Registry), NYHA (New York Heart Association), GFR (glomerular filtration rate), CHF (congestive heart failure), CAD (coronary artery disease), CCS (Canadian Cardiovascular Society)

Kovacic et al[74] observed that current risk scores for PCI outcome poorly predicted important outcomes such as myocardial infarction and TLR. Kovacic compared the predictive and discriminatory ability of these risk scores in the prediction of major adverse cardiac events (MACE; composite of death, myocardial infarction, TLR) following PCI with either DES or BMS. The comparison was conducted in a stable all-comer population of patients with three-vessel and/ or left main coronary artery disease undergoing PCI between 2007 and 2010, who had 12-months of follow-up data. All models were predictive of mortality. SYNTAX Risk Score (SRS), Clinical SYNTAX Score (CSS), NY State Risk Score (NYSRS) and ACEF (Age, Creatinine, left

ventricular Ejection Fraction) were predictive of MACE but had poor discriminatory ability. The SRS and CSS were the only scores that were significantly associated with MI. The SRS was the only score that was associated with TLR, but the association was not statistically significant (p=0.075). Paradoxically, the National Cardiovascular Data Registry (NCDR) score negatively predicted TLR; lower tertiles of the score predicted TLR incidence (p=0.045). This suggests that there is a need for risk scores that predict specific outcomes rather than composite or mortality outcomes. However, there do not appear to be any specific risk scores that are currently used to predict repeat revascularization in clinical practice. A few studies have assessed risk prediction for TLR, TVR and ISR following PCI. Stolker et al.[50] used the EVENT registry to identify clinical and angiographic predictors of TLR. The resulting prediction model from the selected predictors (younger age, female sex, diabetes, prior PCI, prior CABG, saphenous vein graft lesion location, in-stent restenosis lesion, smaller minimum stent diameter and longer stent length) was a marginally good model (c-statistic=0.68). Quadros et al.[84] developed a prediction model for TVR following BMS placement. The final model (with predictors diabetes, reference vessel diameter and lesion length) was also a marginally good model with a c-statistic of 0.60. Kurtul et al.[85] assessed the feasibility of using the CHA2DS2-VASc score (congestive heart failure [CHF]; hypertension; age greater than equal to 75 years [doubled]; Type 2 Diabetes; previous stroke or transient ischemic attack [doubled]; vascular disease; age 65-74 years; and sex [female] category) to predict the risk of ISR. The CHA2DS2-VASc score, ranging from 1 to 7, is used to predict thromboembolic risk in patients with atrial fibrillation and the risk of adverse events in various cardiovascular diseases. ROC analysis showed that a score of 4 or higher was predictive of ISR (AUC=0.714 95% CI 0.66 - 0.77; sensitivity 74%, specificity 69%).

1.3.3 Need for repeat revascularization risk scores in the diabetes population

The need for specific outcome risk scores is perhaps even more crucial in patients with diabetes given the higher rate of adverse cardiovascular outcomes in this population. Until recently, presence of diabetes was treated as a homogenous risk for poor cardiovascular outcomes. It is now recognized that there is heterogeneity in cardiovascular risk among patients with diabetes and several treatment guidelines now recommend that patients with diabetes should be stratified into risk categories[86]. This stratification can be based on risk scores, such as the Atherosclerotic Cardiovascular Disease score (ASCVD), or on age, history of prior cardiovascular events or presence of other risk factors. However, there is a paucity of risk prediction scores that were created specifically to be used in the diabetes population. While there are 110 risk scoring methods that can potentially be used in clinical practice, van Dieren et al.[87] found that there are only 45 risk scoring methods that are applicable to the diabetes population, of which 12 were developed from diabetes populations and 33 included diabetes as a predictor. The study conducted by Esper et al[88] on using the SYNTAX score in patients with diabetes illustrates that predictions from risk scores developed in a general population may not be wholly suitable for patients with diabetes. Esper assessed the utility of the SYNTAX score in predicting major adverse cardiac and cerebrovascular events (MACCE; death, nonfatal MI, nonfatal stroke, repeat revascularization) following either PCI or CABG in patients with both diabetes and multivessel CAD. In those who were randomized to CABG, there was no significant difference in MACCE between the SYNTAX score categories (low, intermediate, high) while in the PCI group, there was a significant difference in MACCE dependent on the SYNTAX score category (low SYNTAX score had lowest incidence of MACCE). The authors concluded that in contrast with the results from the SYNTAX trial (all-

comers design), the SYNTAX score should not be used to determine optimal revascularization strategy in patients with diabetes and multivessel CAD.

Several organizations also recognize the importance of actively identifying risk scores that are suitable for patients with diabetes. For example, five well known organizations with a focus on patients with diabetes recommend calculating CVD risk in patients with T2D using models that can be applied to the diabetes population[87] (Table 3). Of these models, the UKPDS is the most popular[86].

Table 3 Cardiovascular Disease prediction models recommended for use in patients with diabetes

Prediction model	Organizations that recommend use	Model development population	Outcome	Predicted years	Number of predictors	Externally validated in diabetes population?
Kothari 2002 (UKPDS risk engine)	International Diabetes Federation, National Institute for Health and Care Excellence (UK), Canadian Diabetes Association, Australian National Vascular Disease Prevention Alliance	Newly diagnosed NIDDM from UK	Stroke	Variable	7	Yes
Stevens 2001 (UKPDS risk engine)	International Diabetes Federation, National Institute for Health and Care Excellence (UK), Canadian Diabetes Association, Australian National Vascular Disease Prevention Alliance	Newly diagnosed NIDDM from UK	CHD	Variable	7	Yes
Assmann 2002 (PROCAM)	Canadian Diabetes Association	German men	CHD	10	8	Yes
Assmann 2007 (PROCAM)	Canadian Diabetes Association	German GP	CHD, stroke	10	8, 5	No
Lee 2006 (Strong Heart Study)	Canadian Diabetes Association	American Indian GP	CHD	10	9	No
Anderson 1991 (Framingham)	European Association for the Study of Diabetes, Australian National Vascular Disease Prevention Alliance, JBS2	US GP	CHD, stroke, CVD, CVD mortality	Variable	7	Yes
Anderson 1991 (2) (Framingham)	European Association for the Study of Diabetes, Australian National Vascular Disease Prevention Alliance, JBS2	US GP	CHD	5, 10	8	No
DECODE study Group 2004	European Association for the Study of Diabetes	European GP	CVD, death	5, 10	6	Yes

Abbreviations: UKPDS (UK Prospective Diabetes Study); PROCAM (Prospective Cardiovascular Munster); DECODE (Diabetes Epidemiology: Collaborative analysis Of Diagnostic criteria in Europe); JBS2 (Joint British Society); GP (General Population); NIDDM (Non-Insulin Dependent Diabetes Mellitus); CHD (Coronary Heart Disease); CVD (Cardiovascular Disease)

While the models in Table 3 are useful for predicting CVD risk, there do not appear to be any risk prediction tools for adverse PCI outcomes that were specifically developed for use by patients with diabetes. Similarly, it appears that there are no risk tools for repeat revascularization prediction that were developed for use by the diabetes population. This is despite several studies

showing that TLR and TVR are among the most frequently occurring adverse outcomes in patients with diabetes who have undergone PCI (Table 4). In 22 out of 23 studies, TVR ranked as the outcome with either the highest or second-highest incidence among an average of 4 outcomes per study (highest in 15 studies; second highest to mortality or myocardial infarction in 7 studies). Similarly, in 22 out of 23 studies, TLR ranked as the outcome with either the highest or second highest incidence among an average of 4 outcomes per study (highest in 11 studies; second highest to mortality in 11 studies).

Table 4 Incidence of adverse outcomes following PCI in patients with diabetes

				Incidence							
Author	**Stent type**	**Follow-up time**	**N**	**TLR**	**TVR**	**MI**	**All-cause mortality**	**Definite ST**	**Outcomes (n)**	**TLR rank**	**TVR rank**
Daemen 2007[65]	BMS	2 years	252	15.6%	19.5%	-	9.8%	0.8%	3	1	1
Jiang 2017[71]	DES	2 years	200	12.0%	7.5%	9.0%	5.0%	2.5%	4	1	2
Lee 2011[66]	DES	4 years	400	9.8%	11.8%	1.3%	4.0%	2.8%	4	1	1
Lee 2011[66]	DES	2 years	400	7.3%	9.8%	0.8%	0.8%	0.5%	4	1	1
Kereiakes 2010[68]	DES	1 year	1140	6.6%	3.6%	3.0%	1.0%	1.0%	4	1	1
Maeng 2011[89]	DES	1.5 years	337	7.0%	8.6%	3.0%	7.0%	1.0%	4	1	1
Jeong 2013[90]	DES	2 years	1095	4.9%	6.1%	0.1%	1.4%	2.5%	4	1	1
Kufner 2013~ [91]	DES	3 years	377	15.6%	15.6%	4.8%	1.3%	2.1%	4	1	1
Vardi 2013[92]	DES	5 years	605	11.4%	18.2%	2.8%	10.7%	0.8%	4	1	1
D'Amico 2014[93]	DES	2 years	816	7.2%	10.3%	4.4%	5.9%	0.9%	4	1	1
Stone 2011[94]	DES	2 years	1869	5.4%	8.9%	4.3%	3.4%	1.2%	4	1	1
Lu 2017~ [63]	BMS	12 years	579	13.0%	13.0%	6.0%	28.0%	0.0%	4	2	2
Jensen 2010* [64]	BMS	2 years	982	10.0%	10.0%	6.5%	13.3%	0.6%	4	2	2
Daemen 2007[65]	DES	2 years	456	9.0%	12.1%	-	12.0%	3.0%	3	2	1
Silber 2013[70]	DES	2 years	861	4.8%	7.9%	2.3%	4.9%	0.3%	4	2	1
Park 2014[69]	DES	1 year	1855	1.8%	2.9%	0.7%	2.9%	-	3	2	2
Maeng 2015[95]	DES	4 years	213	8.0%	14.1%	5.0%	11.0%	0.9%	4	2	1
Simsek 2013[96]	DES	3 years	1963	8.0%	13.1%	5.0%	15.0%	3.0%	4	2	2
Jensen 2012[97]	DES	1.5 years	390	5.4%	8.7%	2.1%	5.9%	1.0%	4	2	1
Kaul 2015[98]	DES	1 year	1830	2.3%	2.3%	1.9%	2.4%	0.9%	4	2	2
Jang 2013[99]	DES	2 years	760	4.9%	5.4%	6.6%	2.4%	0.8%	4	2	2
Laynez 2013[100]	DES	1 year	968	5.4%	8.3%	3.0%	7.6%	0.9%	4	2	1
Jensen 2010* [64]	DES	2 years	593	6.5%	6.5%	7.4%	11.0%	1.0%	4	3	3

~Data shown is for TLR (TVR was not assessed).

**Data shown is for TLR (TVR was not assessed). Data is based on % of lesions (not % of patients)- DES N=978 lesions, BMS N=1323 lesions.*

Abbreviations: TLR (Target Lesion Revascularization); MI (Myocardial Infarction); ST (Stent Thrombosis)

A lack of TLR or TVR-specific risk tools for use in patients with diabetes presents a missed opportunity to improve PCI outcomes in the diabetes population. This dissertation seeks to close the gap in predictive risk modeling for repeat revascularization following PCI in patients with diabetes by leveraging the extensive research that has been conducted to identify risk factors for repeat revascularization. The methodologies employed by other researchers who have created risk prediction tools will also be leveraged.

2.0 Specific Aims

The preceding Introduction section (Section 1.0) has illustrated the importance of determining risk factors for repeat revascularization in individuals with Type 2 Diabetes who have undergone PCI. In order to achieve the objectives of this dissertation, research will be conducted to address two main goals, namely:

Goal 1: We will use biomarker data to identify potential biological pathways that are associated with the repeat revascularization following PCI. This goal will be addressed in Aims 1 and 2 and will use data from patients from the PCI stratum of the Bypass Angioplasty Revascularization Investigation 2 Diabetes (BARI 2D) trial (n=741).

Goal 2: We will use a real-world data set to develop a model that will be internally validated for potential use in a clinical setting to predict repeat revascularization following PCI. This goal will be addressed in Aim 3 and will use data from patients with Type 2 Diabetes (n=5,160) who underwent PCI in the University of Pittsburgh Medical Center hospital system.

2.1 Aim 1

We will identify biomarkers that are independently associated with repeat revascularization following PCI in the BARI 2D PCI stratum.

Hypotheses:

(i) Elevated lipid, coagulation and fibrinolysis biomarkers at baseline are associated with increased risk for the outcome.

(ii) Increase in coagulation biomarkers & decrease in fibrinolysis biomarkers over time is associated with increased risk for the outcome.

2.2 Aim 2

We will identify biomarker profiles that are associated with repeat revascularization following PCI in the BARI 2D PCI stratum.

Hypotheses:

(i) Elevated coagulation and inflammation biomarkers combined with low fibrinolysis biomarkers at baseline will present the greatest risk for repeat revascularization in a baseline only model.

(ii) Change in lipid, coagulation, inflammation and fibrinolysis biomarkers will be associated with risk for repeat revascularization.

2.3 Aim 3

We will develop and internally test a risk prediction model for repeat revascularization and death following PCI using real-world data from patients with Type 2 Diabetes who have undergone PCI in the University of Pittsburgh Medical Center hospital system.

Hypothesis:

(i) Within a real-world population of patients with diabetes who have undergone PCI there will be heterogeneity in risk of repeat revascularization and death, with one or more sub-groups having significantly higher risk for repeat revascularization and death than other sub-groups in the population.

3.0 Biomarkers associated with repeat revascularization after PCI: secondary analysis of the Bypass Angioplasty Revascularization Investigation 2 Diabetes (BARI 2D) trial

3.1 Abstract

Background: Patients with diabetes have higher rates of subsequent revascularization after PCI compared to patients without diabetes. However, it is recognized that there is heterogeneity in risk in patients with Type 2 Diabetes. We will explore and quantify this heterogeneity by identifying patient characteristics and key combinations of biomarkers that are associated with higher risk for any repeat revascularization (ARR) or target vessel revascularization (TVR). In addition, determining associations between biomarkers and ARR or TVR may provide insights into the underlying biological mechanisms that contribute to the need for subsequent revascularization.

Methods: Participants (n=741) from the Bypass Angioplasty Revascularization Investigation 2 Diabetes (BARI 2D) trial were eligible for this analysis if they were selected for and received PCI and were randomized to the prompt revascularization arm. Participants were followed for up to 7 years after the index PCI and the outcomes of interest were TVR or ARR. Participant characteristics (biomarker and non-biomarker) were measured at baseline (prior to the index PCI). Lipid biomarkers were measured annually while non-lipid biomarkers were measured at baseline and up to two additional time points (year 1 and potentially a last measure between year 1 and year 7). Baseline characteristics including demographic factors (e.g. age, race), medical history, lesion characteristics, and insulin therapy during the trial, as well as biomarkers (lipid, fibrinolytic, inflammation, adipokine, kidney function) were compared in participants who did

versus who did not develop the outcomes of interest during the trial. Continuous variables were compared using t-tests, ANOVA, or Wilcoxon tests as appropriate while categorical variables were compared using the chi-square test. Cox regression was used to assess the associations between baseline and change from baseline biomarkers with the outcomes of interest.

Results: Younger age, prior revascularization (PCI or CABG), insulin-providing therapy during the trial, and baseline number of lesions with thrombus were associated with TVR. Prior PCI, hypercholesterolemia requiring treatment at baseline, insulin use at baseline, insulin-providing therapy during the trial, number of lesions with thrombus and 50-89% diameter stenosis in the left circumflex artery (LCX) were associated with ARR. The effects of log baseline biomarkers and annualized change from log baseline were also assessed, with annualized change being calculated as area under the curve from baseline to the time point of interest and dividing by the number of years elapsed in that time frame. After adjusting for non-biomarker risk factors, each 1-unit difference in annualized change from log baseline fibrinopeptide A (FPA) was associated with a 27% increased risk for ARR (HR 1.27, p=0.0127). No significant associations between biomarkers and TVR were observed.

Conclusion: The direction of the statistically significant associations between the assessed biomarkers and subsequent revascularization in any vessel suggest that a pro-thrombotic state resulting from elevated levels of FPA may convey an increased risk for ARR after an initial PCI in patients with Type 2 Diabetes.

3.2 Introduction

Diabetes is associated with higher risk for cardiovascular disease and patients with diabetes are often considered a homogenous risk group for poor cardiovascular outcomes.[86] However, it is becoming increasingly recognized that different phenotypes of Type 2 Diabetes have different cardiovascular risk and that there is a need to define and account for these phenotypes. Treatment options for coronary artery disease include coronary artery bypass graft (CABG) and percutaneous coronary intervention (PCI). There are higher rates of subsequent revascularization (any repeat revascularization- ARR, or target vessel revascularization- TVR) following PCI in patients with diabetes compared to patients without diabetes.[63,64,71] In addition, in patients with diabetes, PCI results in lower survival rates and in higher risk for subsequent revascularization when compared to CABG.[101,102,103] Nevertheless, the utilization of PCI in patients with Type 2 Diabetes has been increasing as shown in a study of revascularization utilization in the diabetes population between 2008 and 2014.[62] In line with several treatment guidelines that recommend identifying subsets of patients with diabetes who may be at higher risk for particular outcomes[86], our study seeks to determine whether biomarkers can be used to quantify risk factor combinations associated with higher risk for subsequent revascularization after PCI in this population. We will assess the associations of inflammation, lipid, metabolic, fibrinolysis and renal function biomarkers with TVR and with ARR. We will also utilize the risk information provided by these biomarkers to gain an understanding about potential biological pathways that may be important predictors of subsequent revascularization. This assessment utilizes data from the Bypass Angioplasty Revascularization Investigation 2 Diabetes (BARI 2D) trial, a study of optimal treatment strategy for participants with both Type 2 Diabetes and stable coronary artery disease.

3.3 Methods

3.3.1 Study population: BARI 2D Trial

The BARI 2D trial was a 2 x 2 factorial design clinical trial which enrolled participants with both Type 2 Diabetes and stable coronary artery disease suitable for elective revascularization.[104,105] Recruitment occurred between January 1, 2001 and March 31, 2005. The responsible physician for each participant selected an appropriate revascularization method for the participant, either CABG or PCI, prior to randomization. Within each revascularization stratum, participants were randomized to immediate revascularization with the selected revascularization method (revascularization within 4 weeks after randomization), or to medical therapy (with revascularization during follow-up only if clinically indicated). All participants in the trial were also randomized to receive either primarily Insulin Providing (IP) or primarily Insulin Sensitizing (IS) drugs. Our study included only those participants who were randomized to immediate revascularization within the PCI stratum and who received an initial PCI. Demographic, clinical (medical history, physical measurements, ECG, angiographic characteristics) and medication information was collected for each participant at baseline (prior to the index PCI). Participant follow-up ranged from 3.5 to 7 years. Any PCI or CABG procedures that occurred after the first protocolized PCI were documented.

3.3.2 Biomarker assessment

Biomarker levels were measured at baseline (prior to the index PCI in the trial) and included inflammation (C-reactive protein [CRP], interleukin-6 [IL-6], monocyte chemoattractant

protein-1 [MCP-1], tumor necrosis factor-α [TNF-α], soluble cluster of differentiation 14 [sCD14]), lipids (low density lipoprotein [LDL], high density lipoprotein [HDL], triglycerides, total cholesterol), metabolic (leptin, insulin, adiponectin), renal function (serum creatinine, analyzed as estimated glomerular filtration rate [eGFR]) and hemostasis biomarkers (plasminogen activator inhibitor-1 [PAI-1] antigen, PAI-1 activity, tissue plasminogen activator [tPA], fibrinogen, fibrinopeptide A [FPA], D-dimer). The lipid and kidney function biomarkers were then measured annually for up to 7 years. The remaining biomarkers were measured at up to two additional time points (year 1 and potentially a last measure which occurred at the last available stored blood sample between year 1 and year 7). Lipid biomarker values were obtained from frozen serum samples that were analyzed at the Biochemistry Central Laboratory at the University of Minnesota.[104] The assay and analysis methods for the lipid biomarkers have been described by Pambianco et al.[106] Serum creatinine was measured from blood samples at each study site and eGFR was calculated using the abbreviated Chronic Kidney Disease Epidemiology Collaboration Equation.[107] The inflammation, metabolic and hemostasis biomarker values were obtained from plasma samples analyzed at the Fibrinolysis and Coagulation Core Laboratory at the University of Vermont.[104] The assays used by the Fibrinolysis and Coagulation Core Laboratory for measuring IL-6, leptin, TNF-α, MCP-1, insulin, adiponectin and CRP have been described by Wolk et al.[108] The methods used for measuring tPA, fibrinogen, PAI-1 activity, PAI-1 antigen, D-dimer and FPA have been described by Sobel et al.[109] and Schneider et al.[110]

3.3.3 Outcome assessment

Our outcomes of interest were occurrence of the first clinically indicated PCI in the same vessel for TVR and the first clinically indicated repeat revascularization (either PCI or CABG) of

any vessel for ARR following the initial planned PCI in our study population. We excluded any revascularization that was a subsequent stage of a previous PCI. All revascularizations were systematically documented through the study, including the segment location of the lesions that were intended for intervention, where the segment referred to sections within either the Right Coronary Artery (RCA) or within the Left Coronary Artery (LCA). We used this information to determine which participants had undergone TVR or ARR. For example, an unplanned PCI in the proximal RCA that occurred after a prior PCI in the distal RCA would be categorized as TVR while a revascularization in the proximal RCA that occurred after a prior revascularization in the proximal LAD would be categorized as ARR.

3.3.4 Statistical analysis

Baseline characteristics of study participants were compared by the two outcomes of interest (TVR and ARR during the trial). Continuous variables were assessed as mean (SD) and skewed continuous variables were assessed as median (Q1, Q3). Continuous variables for each outcome were compared using t-tests, ANOVA, or Wilcoxon tests as appropriate. Categorical variables were assessed by number and percent, and the chi-square test was used to compare the outcome groups.

Stepwise Cox regression, with $p=0.25$ to enter the model and $p=0.10$ to stay in the model, was used to identify non-biomarker risk factors that were associated with TVR and with ARR. The patient characteristics listed in Table 5 as well as insulin therapy randomization group (IP versus IS) were included in a stepwise Cox regression. Risk factors identified via the stepwise process were retained in the final model if $p<0.05$ or if $0.05 \leq p < 0.10$ and there was evidence from prior literature of an association with future revascularization.

Table 5 Non-biomarker risk factors in BARI 2D assessed for association with subsequent revascularization

Demographics and Medical History	Lesion characteristics
Age at baseline	LAD, LCX, RCA disease severity (% diameter stenosis)*
Sex	Number of lesions* in RCA, LAD, LCX
Race	Number of significant lesions (≥50% diameter stenosis)* in RCA, LAD, proximal LAD, LCX
Family history of CAD	Number of lesions with ≥70% diameter stenosis* in RCA, LAD, proximal LAD, LCX
History of CABG, PCI, MI, CHF, hypertension	Number of overall significant lesions (≥50% diameter stenosis)~
Hypercholesterolemia requiring treatment	Number of significant lesions (≥50% diameter stenosis) in left main
Chronic renal dysfunction	Number of totally occluded lesions (≥99% diameter stenosis)
History of smoking (ever smoked)	Number of class C lesions
Currently taking insulin at baseline	Number of nondiscrete C lesions
BMI category at baseline	Number of ostial lesions
Duration of diabetes mellitus	Number of side branch lesions
Myocardial jeopardy index	Number of calcified lesions
Albuminuria category	Number of lesions with thrombus
	Presence of significant lesions in proximal LAD (yes/no)
	Presence of totally occluded lesion (yes/no)
	Presence of in-stent lesion (yes/no)

*vessels assessed separately
~sum of such lesions in RCA, LAD, proximal LAD, LCX

Linear interpolation using adjacent non-missing values was used to impute missing biomarker values, including biomarker values that were missing due to different protocolized timepoints of lipid and adipokine biomarker measures. If the time between two interpolated values was greater than 457 days, the later interpolated time was set to missing. Dates assigned to the interpolated values were either the date of blood draw or the date of visit if no blood draw date was available. The last interpolated value was then carried forward for any missing values up to three annual visits to maximize the number of visits used for the Cox regression.

Biomarker values were natural log-transformed due to skewness. Correlations between biomarkers (log scale) was assessed using Pearson's correlation coefficient. The annualized change from baseline for the log transformed biomarker values at each time point was calculated by summing the area under the curve between time points up to the time point of interest and then dividing by the years elapsed since baseline and deducting the baseline value. The biomarkers (CRP, IL-6, MCP-1, TNF-α, sCD14, LDL, HDL, triglycerides, total cholesterol, leptin, insulin,

adiponectin, eGFR, PAI-1 antigen, PAI-1 activity, tPA, fibrinogen, FPA, and D-dimer) were assessed as time-varying covariates in Cox regressions. Associations of log baseline and change from log baseline biomarkers were assessed one at a time in unadjusted Cox regressions and subsequently in Cox regressions adjusted for the variables in Table 5 that were found to be significantly associated with the given outcome (either TVR or ARR). Stepwise Cox regression, adjusted for risk factors identified from Table 5, was used to select a set of biomarkers that were associated with each outcome (p=0.25 to enter the model and p=0.05 to stay in the model). Hazard ratios (HR) of biomarkers were interpreted as per unit of the log transformed biomarker value. For example, a HR of 1.50 for log baseline CRP association with TVR would be interpreted as a 50% increase in the risk for TVR per 1-unit difference in the annualized log transformed CRP biomarker value.

Data analysis was conducted using SAS software, version 9.4 (SAS Institute Inc.; Cary, NC).

3.4 Results

3.4.1 Comparison of baseline data between the outcome groups

Figure 2 outlines the selection criteria to determine participants from the BARI 2D trial who were eligible for this study. Among the 741 PCI patients included in this analysis, 129 participants underwent TVR and 182 underwent ARR. Those who subsequently experienced TVR were younger (60.2 years of age vs. 62.3, p=0.0129), were more likely to have had prior CABG (13.4% vs. 6.9%, p=0.0153) or PCI (34.1% vs. 21.2%, p=0.0017), and were more likely to be

taking insulin at baseline (38.0% vs. 28.9%, p=0.0422), when compared to those who did not experience TVR at baseline (prior to the index PCI in the trial) (Table 6). The distribution of race in the two outcome groups was different (p=0.0160) with White race being 57.4% vs. 70.1%, Black/African American race being 25.6% vs. 19.1%, and Other race being 17.1% vs. 10.8% of the group that experienced TVR vs. that did not experience TVR, respectively. The group who experienced TVR also had a higher proportion of participants who had been randomized to receive IP instead of IS therapy (61.2% vs. 38.8%, p=0.0096) (Table 6). Participants in the subsequent TVR group also had more lesions in the LCX (1.3 vs. 1.1, p=0.0488), more significant lesions (≥50% diameter stenosis) in the LCX (0.8 vs. 0.6, p=0.0354) and overall more lesions with greater than 50% stenosis (2.5 vs. 2.2, p=0.0430) when compared to those who did not experience TVR (Table 7). There were no significant differences in baseline biomarker levels between those with subsequent TVR and those who did not undergo TVR (Table 8).

Similarly, participants who subsequently underwent ARR were younger (60.4 years of age vs. 62.3, p=0.0215), more likely to have had prior PCI (34.6% vs. 19.9%, p<0.0001), and were more likely to be taking insulin at baseline (36.8% vs. 28.4%, p=0.0332) (Table 6). The group who had ARR also had a higher proportion of participants who had been randomized to receive IP instead of IS therapy (57.7% vs. 36.8%, p=0.0342) (Table 6). They also had more lesions in the LCX (1.3 vs. 1.0, p=0.0040) when compared to those who did not experience ARR (Table 7). Those with ARR also had higher baseline levels of tPA (10.0 vs. 9.1 ng/ml, p=0.0114) and insulin (10.0 vs. 9.3 IU/ml, p=0.0433) compared to those who did not undergo ARR (Table 8).

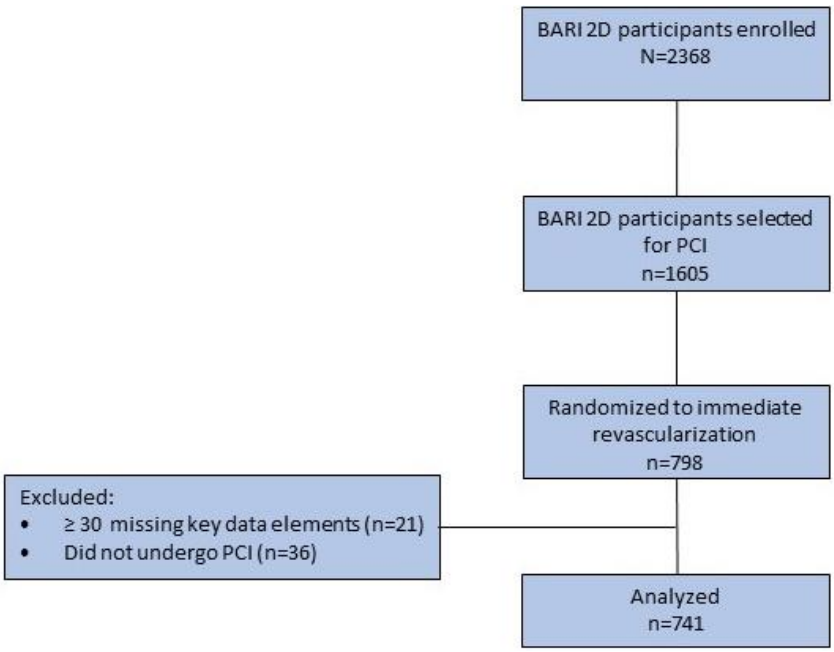


Figure 2 Selection of study population

Table 6 Comparison of baseline characteristics in outcome groups

	Total (N=741)	Target Vessel Revascularization			Any Repeat Revascularization		
		No (n=612)	Yes (n=129)	p*	No (n=559)	Yes (n=182)	p*
Age at study entry, mean (SD)	61.9 (8.9)	62.3 (8.8)	60.2 (9.5)	**0.0129**	62.3 (8.8)	60.4 (9.5)	**0.0215**
Male, n (%)	509 (68.7)	419 (68.5)	90 (69.8)	0.7717	382 (68.3)	127 (69.8)	0.7152
Race, n (%)				**0.0160**			0.1040
Black/African American	150 (20.2)	117 (19.1)	33 (25.6)		105 (18.8)	45 (24.7)	
White	503 (67.9)	429 (70.1)	74 (57.4)		391 (69.9)	112 (61.5)	
Other	88 (11.9)	66 (10.8)	22 (17.1)		63 (11.3)	25 (13.7)	
Prior revascularization							
CABG, n (%)	59 (8.1)	42 (6.9)	17 (13.4)	**0.0153**	40 (7.2)	19 (10.6)	0.1486
PCI, n (%)	174 (23.5)	130 (21.2)	44 (34.1)	**0.0017**	111 (19.9)	63 (34.6)	**<.0001**
Family history of coronary artery disease, n (%)	343 (48.2)	282 (48.0)	61 (49.2)	0.8155	256 (47.9)	87 (49.4)	0.7157
Hypertension requiring treatment, n (%)	595 (81.3)	499 (82.3)	96 (76.2)	0.1072	458 (82.7)	137 (77.0)	0.0896
Hypercholesterolemia requiring treatment, n (%)	608 (83.3)	505 (83.9)	103 (80.5)	0.3465	464 (84.5)	144 (79.6)	0.1209
Chronic renal dysfunction, n (%)	25 (3.4)	20 (3.3)	5 (3.9)	0.7262	18 (3.2)	7 (3.9)	0.6873
Ever smoked cigarettes or other tobacco product, n (%)	498 (67.2)	409 (66.8)	89 (69.0)	0.6345	373 (66.7)	125 (68.7)	0.6256
Currently taking insulin, n (%)	226 (30.5)	177 (28.9)	49 (38.0)	**0.0422**	159 (28.4)	67 (36.8)	**0.0332**
Duration of diabetes mellitus at baseline, n (%)							
< 0.5 yrs	66 (9.0)	53 (8.7)	13 (10.2)	0.7931	50 (9.0)	16 (8.8)	0.8171
< 5 years	192 (26.1)	156 (25.6)	36 (28.1)		147 (26.4)	45 (24.9)	
5 - <10 yrs	159 (21.6)	132 (21.7)	27 (21.1)		114 (20.5)	45 (24.9)	
10 - <20 yrs	209 (28.4)	172 (28.2)	37 (28.9)		160 (28.8)	49 (27.1)	
>= 20 yrs	111 (15.1)	96 (15.8)	15 (11.7)		85 (15.3)	26 (14.4)	
Insulin Therapy (during trial), n (%)							
Insulin-Providing	377 (50.9)	298 (48.7)	79 (61.2)	**0.0096**	272 (48.7)	105 (57.7)	**0.0342**
Insulin-Sensitizing	364 (49.1)	314 (51.3)	50 (38.8)		287 (51.3)	77 (42.3)	
BMI categories, n (%)							
Low, < 20	2 (0.3)	1 (0.2)	1 (0.8)	0.3746	1 (0.2)	1 (0.6)	0.2951
Normal, 20 to < 25	58 (7.9)	51 (8.4)	7 (5.5)		46 (8.3)	12 (6.6)	
Overweight, 25 to < 30	248 (33.8)	204 (33.7)	44 (34.4)		184 (33.3)	64 (35.4)	
Class 1 obesity, 30 to < 35	229 (31.2)	194 (32.0)	35 (27.3)		182 (32.9)	47 (26.0)	
Class 2 obesity, 35 to < 40	109 (14.9)	88 (14.5)	21 (16.4)		80 (14.5)	29 (16.0)	
Class 3/4 obesity, >= 40	88 (12.0)	68 (11.2)	20 (15.6)		60 (10.8)	28 (15.5)	

*nominal p
Note: Except for Insulin Therapy, all characteristics were measured at baseline (prior to first PCI in the trial).

Table 7 Comparison of baseline lesion characteristics in outcome groups

		Target Vessel Revascularization			Any Repeat Revascularization		
	Total (N=741)	No (n=612)	Yes (n=129)	p*	No (n=559)	Yes (n=182)	p*
LAD disease severity, n (%)							
No LAD disease	104 (14.0)	85 (13.9)	19 (14.7)	0.9111	79 (14.1)	25 (13.7)	0.8542
Stenosis: <50%	128 (17.3)	102 (16.7)	26 (20.2)		91 (16.3)	37 (20.3)	
Stenosis: 50-69%	143 (19.3)	120 (19.6)	23 (17.8)		110 (19.7)	33 (18.1)	
Stenosis: 70-89%	216 (29.1)	180 (29.4)	36 (27.9)		163 (29.2)	53 (29.1)	
Stenosis: 90-99%	106 (14.3)	87 (14.2)	19 (14.7)		83 (14.8)	23 (12.6)	
Stenosis: 100%	44 (5.9)	38 (6.2)	6 (4.7)		33 (5.9)	11 (6.0)	
LCX disease severity, n (%)							
No LCX disease	175 (23.6)	152 (24.9)	23 (17.8)	0.2802	145 (26.0)	30 (16.5)	0.0589
Stenosis: <50%	143 (19.3)	120 (19.6)	23 (17.8)		111 (19.9)	32 (17.6)	
Stenosis: 50-69%	92 (12.4)	71 (11.6)	21 (16.3)		63 (11.3)	29 (15.9)	
Stenosis: 70-89%	168 (22.7)	138 (22.6)	30 (23.3)		119 (21.3)	49 (26.9)	
Stenosis: 90-99%	108 (14.6)	84 (13.7)	24 (18.6)		78 (14.0)	30 (16.5)	
Stenosis: 100%	54 (7.3)	46 (7.5)	8 (6.2)		42 (7.5)	12 (6.6)	
RCA disease severity, n (%)							
No RCA disease	157 (21.2)	130 (21.2)	27 (20.9)	0.8981	127 (22.7)	30 (16.5)	0.2894
Stenosis: <50%	122 (16.5)	102 (16.7)	20 (15.5)		91 (16.3)	31 (17.0)	
Stenosis: 50-69%	91 (12.3)	74 (12.1)	17 (13.2)		63 (11.3)	28 (15.4)	
Stenosis: 70-89%	186 (25.1)	152 (24.8)	34 (26.4)		138 (24.7)	48 (26.4)	
Stenosis: 90-99%	96 (13.0)	77 (12.6)	19 (14.7)		69 (12.3)	27 (14.8)	
Stenosis: 100%	89 (12.0)	77 (12.6)	12 (9.3)		71 (12.7)	18 (9.9)	
Number of lesions in LAD, mean (SD)	1.7 (1.2)	1.7 (1.2)	1.8 (1.1)	0.4710	1.6 (1.2)	1.8 (1.1)	0.0684
Number of lesions in LCX, mean (SD)	1.1 (1.0)	1.1 (1.0)	1.3 (1.1)	**0.0488**	1.0 (1.0)	1.3 (1.0)	**0.0040**
Number of lesions in RCA, mean (SD)	1.5 (1.1)	1.5 (1.1)	1.6 (1.3)	0.2774	1.4 (1.1)	1.6 (1.2)	0.0642
Number of significant lesions in LAD, mean (SD)	0.8 (0.9)	0.8 (0.9)	0.9 (0.8)	0.4781	0.8 (0.9)	0.9 (0.9)	0.5890
Number of significant lesions in LCX, mean (SD)	0.6 (0.8)	0.6 (0.8)	0.8 (0.9)	**0.0354**	0.6 (0.8)	0.7 (0.9)	0.0549
Number of significant lesions in RCA, mean (SD)	0.7 (0.8)	0.7 (0.8)	0.8 (0.9)	0.4085	0.7 (0.8)	0.8 (0.8)	0.3598
Lesions >= 50% stenosis, mean (SD)	2.3 (1.7)	2.2 (1.7)	2.5 (1.6)	**0.0430**	2.2 (1.8)	2.4 (1.6)	0.0855

*nominal p

Abbreviations: LAD (Left Anterior Descending), LCX (Left Coronary Circumflex), RCA (Right Coronary Artery)

Note: (i) Lesion characteristics were measured at baseline (prior to first PCI in the trial).
(ii) Significant lesions are lesions with greater than or equal to 50% diameter stenosis.

Table 8 Comparison of baseline biomarkers in outcome groups

Biomarker [median (Q1, Q3)]	Total (N=741)	Target Vessel Revascularization			Any Repeat Revascularization		
		No (n=612)	Yes (n=129)	p*	No (n=559)	Yes (n=182)	p*
CRP ug/ml	2.3 (1.0, 6.2)	2.2 (1.0, 6.0)	3.0 (1.0, 6.9)	0.2005	2.2 (1.0, 6.2)	2.6 (1.0, 6.0)	0.7437
IL-6 pg/ml	2.3 (1.3, 4.0)	2.3 (1.3, 4.1)	2.4 (1.4, 3.8)	0.8497	2.2 (1.2, 4.1)	2.5 (1.5, 3.8)	0.3657
Leptin pg/ml	18721.0 (9282.0, 37534.0)	17729.1 (9297.2, 36742.5)	23360.7 (8708.4, 44239.8)	0.1500	17602.6 (9281.8, 36558.0)	22515.4 (9180.4, 43228.3)	0.1321
MCP-1 pg/ml	198.0 (152.0, 244.0)	196.1 (151.3, 246.6)	203.6 (158.3, 237.9)	0.7524	194.7 (150.5, 246.3)	208.5 (160.7, 242.7)	0.3909
TNFa pg/ml	4.8 (3.6, 6.7)	4.8 (3.6, 6.6)	5.0 (3.8, 7.1)	0.2256	4.8 (3.6, 6.5)	5.0 (3.7, 7.3)	0.1128
PAI-1 activity au/ml	16.0 (9.8, 27.0)	16.0 (9.5, 26.0)	19.0 (11.0, 29.0)	0.2427	16.0 (9.3, 26.0)	19.0 (11.0, 29.0)	0.0523
PAI-1 antigen ng/ml	22.0 (14.0, 34.0)	22.0 (14.0, 34.0)	23.0 (13.0, 34.0)	0.8587	22.0 (14.0, 34.0)	23.0 (14.0, 35.0)	0.4414
tissue Plasminogen Activator ng/ml	9.3 (7.1, 12.0)	9.2 (7.0, 12.0)	9.7 (7.4, 13.0)	0.1239	9.1 (6.9, 12.0)	10.0 (7.4, 13.0)	**0.0114**
Insulin micro IU/ml	9.5 (5.7, 17.0)	9.3 (5.5, 17.0)	11.0 (6.9, 18.0)	0.0785	9.3 (5.4, 16.0)	10.0 (6.4, 19.0)	**0.0433**
Adiponectin ng/ml	4615.0 (2904.0, 8011.0)	4813.8 (2952.8, 8010.5)	4322.2 (2503.6, 8097.4)	0.1368	4834.9 (2987.1, 8207.3)	4316.0 (2770.1, 7739.8)	0.1015
sCD14 ng/ml	1261.0 (1071.0, 1473.0)	1255.7 (1071.1, 1471.2)	1262.4 (1084.4, 1489.0)	0.7052	1252.0 (1067.8, 1465.9)	1262.9 (1099.8, 1520.4)	0.2357
Fibrinogen mg/dl	361.0 (294.0, 423.0)	361.0 (292.5, 423.0)	365.0 (299.0, 424.0)	0.4891	362.0 (293.5, 423.0)	359.0 (294.0, 424.0)	0.9292
Fibrinopeptide A ng/ml	10.0 (5.0, 30.0)	10.0 (5.0, 30.0)	10.0 (5.4, 38.0)	0.5803	10.0 (5.0, 32.0)	9.8 (5.2, 24.0)	0.7873
D-dimer ug/ml	0.3 (0.2, 0.6)	0.3 (0.2, 0.6)	0.3 (0.2, 0.6)	0.8418	0.3 (0.2, 0.6)	0.3 (0.2, 0.6)	0.7077
Serum creatinine mg/dl	1.0 (0.9, 1.2)	1.0 (0.9, 1.2)	1.0 (0.9, 1.2)	0.8652	1.0 (0.9, 1.2)	1.0 (0.8, 1.2)	0.6698
HbA1c %	7.2 (6.4, 8.4)	7.2 (6.4, 8.4)	7.4 (6.6, 8.5)	0.2111	7.1 (6.4, 8.3)	7.4 (6.6, 8.5)	0.1176
Total cholesterol mg/dl	161.0 (139.0, 187.0)	161.0 (139.0, 187.0)	162.0 (137.0, 185.0)	0.7872	161.0 (139.0, 187.0)	162.5 (139.0, 186.0)	0.9192
HDL mg/dl	36.0 (31.0, 43.0)	37.0 (31.0, 43.0)	35.0 (30.0, 43.0)	0.4605	37.0 (32.0, 43.0)	35.0 (30.0, 42.0)	0.1922
LDL mg/dl	90.0 (73.0, 114.0)	90.0 (74.0, 113.0)	89.0 (70.0, 118.0)	0.8353	90.0 (74.0, 112.0)	88.5 (71.0, 118.0)	0.8974
Triglyceride mg/dl	137.0 (90.0, 209.0)	138.0 (92.0, 212.0)	129.0 (84.0, 195.0)	0.3936	138.0 (90.0, 209.0)	133.5 (89.0, 209.0)	0.9023

*nominal p

3.4.2 Non-biomarker risk factors for subsequent revascularization

The demographic and clinical variables selected for the final prediction model for TVR are shown in Table 9. Each one-year difference in age was associated with a lower hazard ratio for TVR (HR 0.98, p=0.0134). Prior PCI and prior CABG were associated with 67% and 75% higher risk for TVR, respectively (HR 1.67, p=0.0077 and HR 1.75, p=0.0383 respectively). Each one-unit difference in the number of lesions with thrombus was associated with a three-fold increase

in the hazard ratio for TVR (HR 3.22, p=0.0119). Participants who were receiving IP therapy during the trial were at 54% higher risk for TVR compared to participants using IS treatment (HR 1.54, p=0.0187).

Non-biomarker risk factors associated with ARR are shown in Table 9. Prior PCI (HR=1.87, p<0.0001) and IP therapy during the trial (HR=1.36, p=0.0461) were associated with an increased risk for ARR. Those taking insulin at baseline had a nearly 40% increased hazard ratio for ARR (HR 1.36, p=0.0489) while hypercholesterolemia requiring treatment at baseline was associated with a lower risk (HR=0.66, p=0.0283). Lesion characteristics were also associated with higher risk for ARR. Each one-unit difference in the number of lesions with thrombus more than doubled the hazard ratio for ARR (HR 2.78, p=0.0268). LCX disease severity, classified by percent diameter stenosis, was also associated with an increased risk. Stenosis greater than or equal to 50% nearly doubled the risk for each category of stenosis up to 89% diameter stenosis. 90-99% stenosis was associated with ARR at the p<0.1 level. There was no association between totally occluded lesions (100% stenosis) and ARR, possibly due to the small sample size (n=12) (Table 9). Even though age was not significantly associated with the risk for ARR (HR 0.99, p=0.0704), we opted to keep it in the final model because numerous studies have found an association between age and subsequent revascularization.[111,112,113]

All the covariates retained in the final model for TVR associations and for ARR associations (Table 9) were included as covariates in subsequent models that sought to determine associations of biomarkers with TVR and with ARR.

Table 9 Risk factors associated with subsequent revascularization

	TVR		Any repeat revascularization	
	HR	p	HR	p
Age at study entry	0.98	0.0134	0.99	0.0704
Prior PCI	1.67	0.0077	1.87	<.0001
Prior CABG	1.75	0.0383	-	-
Insulin treatment				
Insulin Sensitizing	1.00	reference	1.00	reference
Insulin Providing	1.54	0.0187	1.36	0.0461
Number of lesions with thrombus	3.22	0.0119	2.78	0.0268
Hypercholesterolemia requiring treatment at baseline	-	-	0.66	0.0283
Currently taking insulin at baseline	-	-	1.36	0.0489
LCX disease severity	-	-		0.1143
No LCX disease	-	-	1.00	reference
Stenosis <50%	-	-	1.23	0.4250
Stenosis 50-69%	-	-	1.83	0.0217
Stenosis 70-89%	-	-	1.77	0.0151
Stenosis 90-99%	-	-	1.66	0.0503
Stenosis 100%	-	-	1.41	0.3199

3.4.3 One-at-a-time biomarker associations with subsequent revascularization

Separate Cox regression models (unadjusted and adjusted for the demographic, clinical and angiographic risk factors shown in Table 9) were used to assess associations of log baseline biomarker measures alone, and log baseline and annualized change from log baseline measures with TVR and with ARR. Each 1-unit increase in annualized change in FPA was associated with approximately 30% increased risk for TVR in unadjusted (HR 1.32, p=0.0170) and adjusted (HR 1.27, p=0.0441) models (Table 10). Each 1-unit difference in baseline insulin (HR 1.20, p=0.0280) and tPA (HR 1.71, p=0.0055), and in annualized change in FPA (HR 1.34, p=0.0022) were all associated with increased risk for ARR in an unadjusted model (Table 11). Each 1-unit difference

in baseline insulin (HR 1.18, p=0.0490) and tPA (HR 1.61, p=0.0145), and in annualized change in FPA (HR 1.30, p=0.0070) were associated with increased risk for ARR in the adjusted models (Table 11).

Table 10 One-at-a-time biomarker association with TVR

	Unadjusted Cox regression				Adjusted Cox regression			
	Log baseline		Annualized change from log baseline*		Log baseline		Annualized change from log baseline*	
Biomarker	HR	p	HR	p	HR	p	HR	p
Insulin	1.19	0.0756	0.99	0.9422	1.17	0.1095	0.94	0.6320
TNF-α	1.23	0.2464	1.28	0.3279	1.41	0.0720	1.27	0.3372
sCD14	1.22	0.5808	1.06	0.4697	1.13	0.7407	1.06	0.4389
CRP	1.10	0.1716	1.28	0.1318	1.05	0.4672	1.14	0.4239
IL-6	1.03	0.7409	1.12	0.4735	1.01	0.9208	1.08	0.6082
Leptin	1.11	0.2314	1.07	0.2786	1.14	0.1213	1.07	0.2829
Adiponectin	0.83	0.1215	1.02	0.7359	0.81	0.0985	1.04	0.5197
MCP-1	1.19	0.3817	1.08	0.4743	1.23	0.2965	1.09	0.4369
Fibrinogen	1.34	0.3613	1.16	0.1611	1.14	0.6851	1.18	0.1341
FPA	1.06	0.4865	1.32	**0.0170**	1.04	0.6492	1.27	**0.0441**
D-dimer	0.95	0.6019	1.10	0.6243	0.98	0.8201	1.12	0.5819
tPA	1.51	0.0688	1.34	0.2056	1.37	0.1580	1.24	0.3006
PAI-1 antigen	1.03	0.8398	1.16	0.3435	0.97	0.7930	1.11	0.5014
PAI-1 activity	1.13	0.3173	1.18	0.2986	1.06	0.6384	1.11	0.5065
LDL	0.89	0.6736	1.10	0.3485	0.86	0.5876	1.11	0.3300
HDL	0.82	0.5789	1.15	0.2820	0.84	0.6332	1.19	0.1874
Triglycerides	0.99	0.9447	1.12	0.2380	0.93	0.5907	1.14	0.1762
Total cholesterol	0.89	0.7606	1.10	0.3018	0.68	0.3324	1.12	0.2295
eGFR	1.17	0.5873	1.05	0.5939	1.00	0.9924	1.11	0.2937

Models adjusted for the risk factors listed in Table 9.
*These models also included log baseline biomarker.

Table 11 One-at-a-time biomarker association with ARR

	Unadjusted Cox regression				Adjusted Cox regression			
	Log baseline only		Annualized change from log baseline*		Log baseline only		Annualized change from log baseline*	
Biomarker	HR	p	HR	p	HR	p	HR	p
Insulin	1.20	**0.0280**	0.94	0.5765	1.18	**0.0490**	0.89	0.2786
TNF-α	1.28	0.0942	1.20	0.3619	1.23	0.1835	1.14	0.5147
sCD14	1.51	0.1712	1.02	0.7990	1.36	0.3223	1.00	0.9580
CRP	1.03	0.6228	1.25	0.0981	0.97	0.6071	1.19	0.2151
IL-6	1.04	0.5130	1.14	0.3266	1.01	0.8479	1.10	0.4703
Leptin	1.10	0.1931	1.03	0.4591	1.09	0.2340	1.02	0.6282
Adiponectin	0.84	0.0959	1.01	0.9164	0.84	0.0942	1.00	0.9358
MCP-1	1.24	0.1965	1.04	0.6149	1.15	0.4151	1.03	0.7030
Fibrinogen	1.12	0.6724	1.04	0.5437	0.96	0.8845	1.03	0.6449
FPA	0.98	0.8020	1.34	**0.0022**	0.93	0.2738	1.30	**0.0070**
D-dimer	0.97	0.7083	1.18	0.3257	0.98	0.7862	1.22	0.2435
tPA	1.71	**0.0055**	1.10	0.5634	1.61	**0.0145**	1.03	0.8660
PAI-1 antigen	1.08	0.5285	1.09	0.4913	1.04	0.7217	1.04	0.7631
PAI-1 activity	1.19	0.0864	1.04	0.7179	1.18	0.1150	0.99	0.9327
LDL	0.94	0.7986	1.12	0.2037	0.85	0.5140	1.12	0.2074
HDL	0.77	0.3834	1.12	0.2783	0.77	0.4031	1.13	0.2532
Triglycerides	1.08	0.4979	1.07	0.3277	1.07	0.5642	1.08	0.3022
Total cholesterol	1.03	0.9386	1.07	0.3374	0.88	0.7031	1.08	0.3173
eGFR	1.10	0.7126	1.06	0.4976	1.04	0.8770	1.06	0.4733

Models adjusted for the risk factors listed in Table 9.
*These models also included log baseline biomarker.

3.4.4 Joint biomarker associations with subsequent revascularization

Baseline and annualized change from baseline biomarkers that were independently associated with TVR and ARR, adjusting for demographic, clinical and angiographic factors, were identified using stepwise Cox regression ($p<0.10$ to stay in the model). No biomarker variables met the $p<0.05$ significance level in a final Cox regression model for TVR.

Change from baseline FPA was associated with a 27% increased risk for ARR (HR 1.27, p=0.0127) (Table 12). TNF-α was selected as statistically significant in stepwise regression but was not significant in the final Cox regression model (HR 1.26, p=0.1324; data not shown).

Table 12 Combined biomarkers association with subsequent revascularization

	Any repeat revascularization*			
	Log baseline only		Annualized change from log baseline	
	HR	p	HR	p
FPA	1.00	0.9468	1.27	**0.0127**

*Models adjusted for the risk factors listed in Table 9. All biomarkers were included in the baseline-only and baseline plus change from baseline models for each outcome.

3.5 Discussion

The overall purpose of this study was to assess the relationship of lipid biomarkers and biomarkers of renal, inflammation and hemostasis function with the risk for subsequent revascularization after PCI in participants with both Type 2 Diabetes and stable coronary artery disease, and in doing so, identify pathways that may be important in understanding factors that lead to subsequent revascularization. Our results suggest that the hemostasis pathway may be important indicators for the risk of subsequent revascularization following PCI.

Our finding that younger age, prior revascularization and IP therapy are associated with increased risk for subsequent revascularization is in line with several studies that assessed risk factors for subsequent revascularization.[114] IP and IS therapy were found to have differential effects on adipokine and hemostasis biomarker levels.[108,115] In analysis of the BARI 2D trial, Sobel et al[115] observed that the change in biomarker levels seen with IS therapy was pro-fibrinolytic and anti-inflammatory while Wolk et al[108] found that IP therapy was pro-inflammatory when compared to IS therapy. The results of these two studies suggest that IP therapy may lead to a pro-thrombotic

state that could necessitate revascularization treatment. Our finding that IP therapy is associated with an increased risk for subsequent revascularization is also in agreement with several studies that identified insulin treated diabetes as a risk factor for target lesion revascularization (TLR).[45,48,51] The number of lesions with thrombus may be an indicator of a pro-thrombotic state, hence this may explain why an increase in the number of such lesions is associated with an increase in risk for subsequent revascularization. It should be noted that the number of participants in our study with one or more lesions with thrombus was low (n=7; 0.9% of the study population), therefore the observed association between number of lesions with thrombus and subsequent revascularization following PCI should be further assessed in a study population with a higher proportion of participants who have lesions with thrombus.

The risk for ARR rose by 30% for each one-unit difference in annualized change from baseline FPA. Thrombin degrades fibrinogen into fibrin and FPA as part of the coagulation cascade. Increased levels of FPA suggest that levels of fibrin are also likely increased, an indication that the body may be in a pro-thrombotic state since fibrin recruits platelets to form a fibrin clot (thrombus).

This study has two main limitations. First, lipid biomarkers were measured yearly with follow-up extending up to 7 years for some participants while the remaining biomarkers were measured at up to three timepoints during the follow-up period. This resulted in non-measured data for the non-lipid biomarkers. To maximally utilize the data that was collected, we used linear interpolation and last observation carried forward (LOCF) to fill in the non-measured non-lipid data. This may have resulted in an over-representation of high non-lipid biomarker values that may have been carried forward. However, the associations that we found between non-lipid biomarkers and the events of interest in our study are biologically plausible. The second limitation involves

our use of stepwise regression to select biomarkers for the Cox regression models. Stepwise regression excluded participants with missing values. This led to a difference between number of observations used in stepwise regression vs. the final Cox regression model, and subsequently to differences in biomarker statistical significance. Both limitations can be addressed by repeating similar analysis in a study population that had lipid and non-lipid biomarkers measured at equivalent time points.

While our study found underlying risk factors that were similar to those found in studies conducted in participants with and without diabetes (e.g. younger age, prior revascularization), the inclusion of biomarkers in our risk models provides additional information that may be used to identify patients who may be at higher risk for subsequent revascularization following PCI. This information may be used to identify patients with Type 2 Diabetes who may be at higher risk for subsequent revascularization following PCI and who may benefit from increased health monitoring, or for whom PCI may not be an optimal treatment option. For example, our study found that increase in FPA level from baseline were associated with increased risk for ARR.

Individuals with diabetes are at higher risk for CVD, including atherosclerosis. The global prevalence of Type 2 Diabetes is rising[116] and prevalence in children and young adults is also increasing[117]. There is evidence that Type 2 Diabetes in young adults is more aggressive and leads to earlier onset of complications, including CVD. This underscores the importance of determining the optimal therapies for complications such as atherosclerosis. Assessing factors for success of these therapies, such as PCI, will continue to be important. Further, with the rising prevalence of Type 2 Diabetes, it is likely that this younger patient population will account for most cases of CVD and its complications. In an assessment of 23 studies that determined the incidence of PCI outcomes in individuals with diabetes we found that subsequent revascularization following PCI

was higher in incidence than myocardial infarction (MI) and all-cause mortality across the studies. This highlights the importance of understanding risk factors for subsequent revascularization following PCI in this population alongside the more serious MI and mortality outcomes. Our study identified risk factors that are generally in agreement with other studies that were conducted in all-comer and diabetes populations. In addition, we were able to leverage biomarker data from the BARI 2D trial to gain insight into possible biological pathways that are important when determining risk factors for subsequent revascularization following PCI. The biomarker that we identified as potentially important are not currently measured as part of routine clinical care. Further studies are warranted to assess the clinical utility of adding this biomarker to existing risk prediction models or as part of routine clinical measures for both patients with and without diabetes.

4.0 Biological mechanisms underlying risk for repeat revascularization after PCI: time-varying survival tree-based analysis of biomarker data in BARI 2D

4.1 Abstract

Background: Patients with diabetes have higher rates of repeat revascularization following percutaneous coronary intervention (PCI) than patients without diabetes. The pathophysiology of diabetes leads to accelerated and more severe atherosclerosis and diabetes is known to alter normal physiological levels of several biomarkers. Understanding the association of these biomarkers with repeat revascularization may enable us to gain insight into the biological mechanisms that lead to higher rates of repeat revascularization in patients with diabetes.

Methods: This study used biomarker information from participants (n=741) in the Bypass Angioplasty Revascularization Investigation 2 Diabetes (BARI 2D) trial who were selected for and received PCI and were randomized to the prompt revascularization arm. Categorical baseline characteristics of participants who did and who did not undergo repeat revascularization were compared using the chi-square test. Continuous variables were compared using t-tests, ANOVA, or Wilcoxon tests as appropriate. Biomarkers (lipid, fibrinolytic, inflammation, adipokine, kidney function) were measured at baseline (prior to index PCI) and annually (lipid biomarkers), or at year 1 and potentially a last measure between year 1 and year 7 (all other biomarkers). Biomarker values were log transformed due to skewness and change from the log baseline value was calculated at each time point. We constructed two classification trees using Classification and Regression Tree analysis- one using baseline biomarker values, and the other using time-varying (change from baseline) biomarker values- to identify biomarker combinations that were associated

with repeat revascularization. We adjusted for age, history of PCI, current insulin use at baseline, hypercholesterolemia requiring treatment at baseline, insulin therapy during the trial (insulin providing or insulin sensitizing), left circumflex artery diameter stenosis and number of lesions with thrombus when determining splits at each node.

Results: Our pruned tree for baseline biomarkers had 12 terminal nodes and 6 of these terminal nodes were statistically different from all other terminal nodes. Participants with high baseline tissue plasminogen activator (tPA), low D-dimer, and high leptin (HR 3.23, p<.0001), participants with high tPA, low fibrinogen, high D-dimer, and high leptin (HR 4.08, p<.0001), participants with high tPA, high fibrinogen, high D-dimer, high leptin, and high total cholesterol (HR 2.49, p=0.0224), participants with high tPA, low leptin, and high monocyte chemoattractant protein-1 (MCP-1) (HR 2.33, p=0.0007), participants with low tPA, low fibrinopeptide A (FPA), high D-dimer, and high insulin (HR 5.28, p<.0001), and participants with low tPA, low FPA, low D-dimer, and high insulin (HR 2.08, p=0.0402) had the highest risk for repeat revascularization relative to participants who did not have these combinations of baseline biomarker levels.

The pruned time-varying biomarker tree had 9 terminal nodes with 4 of these terminal nodes being significantly different from all other terminal nodes. Participants with visits where change from baseline plasminogen activator inhibitor 1 (PAI-1) activity was below the mean change and C-reactive protein (CRP) change was at/above the mean change (HR 3.77, p<.0001), participants with visits where PAI-1 activity, CRP and low density lipoprotein (LDL) change was below the mean and FPA change was at/ above the mean (HR 8.22, p<.0001), participants with visits where PAI-1 activity, tumor necrosis factor-α (TNF-α) and estimated glomerular filtration rate (eGFR) change were at/ above the mean (HR 3.51, p<.0001), and participants with visits where PAI-1 activity and FPA change were at/ above the mean and TNF-α and CRP change was below

the mean (HR 3.30, p=0.0014) had higher risk for repeat revascularization relative to participants who did not have visits with these biomarker combinations.

Conclusion: The baseline biomarker levels and change from baseline biomarker levels in profiles that were found to be significant suggest that hemostasis, endothelial dysfunction, hyperlipidemia, monocyte recruitment and increased inflammation may lead to higher risk for repeat revascularization.

4.2 Introduction

The rate of repeat revascularization following percutaneous coronary intervention (PCI) in patients with Type 2 Diabetes has decreased with advancements in drug eluting stent technology. However, the rate continues to be higher in patients with diabetes than in patients without diabetes[63,64,71]. The increasing use of PCI in this patient population necessitates a good understanding of factors that may be associated with the risk for repeat revascularization[62,118]. In addition to diabetes, several other risk factors that are independently associated with repeat revascularization have been identified such as prior PCI[14,24,112], age[111], peripheral arterial disease[27,119], lesion complexity[120], and insulin providing therapy[45,48,51]. While knowledge of independent risk factors is useful, it does not give insight into the biological complexity that may lead to the need for repeat revascularization. Assessing the association of biomarker levels with repeat revascularization may provide this insight. Specifically, biomarker combinations can be leveraged to identify biological mechanisms that may underlie atherosclerotic progression leading up to repeat revascularization.

Our study seeks to identify biomarker profiles that may provide insight into the biological mechanisms that underlie the risk for repeat revascularization following PCI in patients with Type 2 Diabetes. We will use Classification and Regression Tree (CART) analysis to create the biomarker profiles. We will assess biomarker levels at baseline (prior to the index PCI procedure) as well as the change relative to biomarker levels at baseline. Biomarkers that will be included in our study are markers of inflammation, fibrinolysis, coagulation, and renal function, as well as lipid biomarkers. The assessment will use data from the PCI treatment stratum of the Bypass Angioplasty Revascularization Investigation 2 Diabetes (BARI 2D) trial.

4.3 Methods

4.3.1 Study population: BARI 2D Trial

The BARI 2D trial was a 2 x 2 factorial design clinical trial which enrolled participants with both T2D and stable coronary artery disease suitable for elective revascularization. Recruitment occurred between January 1, 2001 and March 31, 2005. The responsible physician for each participant selected an appropriate revascularization method for the participant, either CABG or PCI, prior to randomization. Within each revascularization stratum, participants were randomized to immediate revascularization with the selected revascularization method (revascularization within 4 weeks after randomization), or to medical therapy (with revascularization during follow-up only if clinically indicated). All participants in the trial were also randomized to receive either Insulin Providing (IP) or Insulin Sensitizing (IS) drugs. Our

study included only those participants who were randomized to immediate revascularization within the PCI stratum and who received an initial PCI. Demographic, clinical (medical history, physical measurements, ECG, angiographic characteristics) and medication information was collected for each participant at baseline (prior to the index PCI). Participant follow-up ranged from 3.5 to 7 years. Any PCI or CABG procedures that occurred after the first protocolized PCI were documented.

4.3.2 Biomarker assessment

Biomarker levels were measured at baseline (prior to the index PCI in the trial) and included inflammation (C-reactive protein [CRP], interleukin-6 [IL-6], monocyte chemoattractant protein-1 [MCP-1], tumor necrosis factor- α [TNF-α], soluble cluster of differentiation 14 [sCD14]), lipids (low density lipoprotein [LDL], high density lipoprotein [HDL], triglycerides, total cholesterol), metabolic (leptin, insulin, adiponectin), renal function (serum creatinine; analyzed as estimated glomerular filtration rate [eGFR]) and hemostasis biomarkers (plasminogen activator inhibitor-1 [PAI-1] antigen, PAI-1 activity, tissue plasminogen activator [tPA], fibrinogen, fibrinopeptide A [FPA], D-dimer). The lipid and kidney function biomarkers were then measured annually for up to 7 years. The remaining biomarkers were measured at up to two additional time points (year 1 and potentially a last measure which occurred at the last available stored blood sample between year 1 and year 7). Lipid biomarker values were obtained from frozen serum samples that were analyzed at the Biochemistry Central Laboratory at the University of Minnesota.[104] The assay and analysis methods for the lipid biomarkers have been described by Pambianco et al.[106] Serum creatinine was measured from blood samples at each study site and eGFR was calculated using the abbreviated Chronic Kidney Disease Epidemiology Collaboration

Equation.[107] The inflammation, metabolic and hemostasis biomarker values were obtained from plasma samples analyzed at the Fibrinolysis and Coagulation Core Laboratory at the University of Vermont.[104] The assays used by the Fibrinolysis and Coagulation Core Laboratory for measuring IL-6, leptin, TNF-α, MCP-1, insulin, adiponectin and CRP have been described by Wolk et al.[108] The methods used for measuring tPA, fibrinogen, PAI-1 activity, PAI-1 antigen D-dimer and FPA have been described by Sobel et al.[109] and Schneider et al.[110]

4.3.3 Outcome assessment

Our outcome of interest was occurrence of the first clinically indicated subsequent revascularization (either PCI or CABG) of any vessel (any repeat revascularization- ARR) following the initial planned PCI in our study population. We excluded any revascularization that was a subsequent stage of a previous PCI. All revascularizations were systematically documented through the study, including the segment location of the lesions that were intended for intervention, where the segment referred to sections within either the Right Coronary Artery (RCA) or within the Left Coronary Artery (LCA). We used this information to determine which participants had undergone ARR. For example, a revascularization in the proximal RCA that occurred after a prior revascularization in the proximal LAD would be categorized as ARR.

4.3.4 Statistical analysis

4.3.4.1 Baseline characteristics

Baseline characteristics of study participants were compared by the outcome of interest (ARR during the trial). Continuous variables were assessed as mean (SD) and skewed continuous

variables were assessed as median (Q1, Q3). Continuous variables for each outcome were compared using t-tests, ANOVA, or Wilcoxon tests as appropriate. Categorical variables were assessed by number and percent, and the chi-square test was used to compare the outcome groups.

4.3.4.2 Determining non-biomarker risk factors for repeat revascularization

Non-biomarker risk factors that were associated with ARR were identified in Chapter 3.0 (age, history of PCI, current insulin use at baseline, hypercholesterolemia requiring treatment at baseline, insulin therapy during the trial (insulin providing or insulin sensitizing), presence of LCX diameter stenosis greater than 50% and number of lesions with thrombus). Briefly, stepwise Cox regression, with $p=0.25$ to enter the model and $p=0.10$ to stay in the model, was used to identify non-biomarker risk factors that were associated with ARR from a set of 13 demographic and medical history factors, and 26 lesion characteristic variables. Risk factors identified via the stepwise process were retained in the final model if $p<0.05$ or if $0.05 \leq p < 0.10$ and there was evidence from prior literature of an association with future revascularization.

4.3.4.3 Preparing biomarker data for analysis

Biomarker values were natural log-transformed due to skewness. The annualized change from baseline for the log transformed biomarker values at each time point was calculated by determining the area under the curve between time points up to the time point of interest and then dividing by the years elapsed since baseline and deducting the baseline value. Correlations between baseline biomarker values (log scale) and their corresponding change from baseline biomarker value (log scale) were assessed using Pearson's correlation coefficient.

4.3.4.4 Classification and Regression Tree Analysis: Baseline biomarker tree

Classification and Regression Tree Analysis (CART), based on the method described by Bertolet et al.[121], was used to identify log baseline biomarker profiles that were associated with ARR. To create the first split, we calculated the mean log baseline biomarker values using baseline data from all participants, and then classified each participant as being below (<) or at/ above the mean (≥) for each biomarker. We then ran separate Cox regression models for each biomarker (each model adjusted for the non-biomarker risk factors identified in Chapter 3.0), comparing participants who were at/ above the mean to those who were below the mean, to determine the baseline biomarker that created the largest separation between all participants with regards to ARR. We selected the biomarker model with the largest χ^2 value for the null hypothesis that participants with values below the mean were not equivalent to participants with values at/ above the mean for the outcome. Participants were then assigned to either of the two resulting child nodes, depending on whether the participant's log biomarker value of the selected biomarker was less than or at/ above the mean log biomarker of all participants. Participants could only be in one of the two resulting child nodes.

Within each child node, we calculated the mean biomarker values using only the data from participants within the child node of interest; participants in that node were then reclassified as being less than or at/ above the mean of the biomarker values within that child node. We split each child node using Cox regression models as described above using the below and at/ above mean designations for that node. These steps were repeated recursively to create more child nodes until the predefined stopping criteria was met (no χ^2 value greater than 2.0, or the child node had less than 50 participants).

Once all nodes met the stopping criteria, we pruned the tree, from the bottom up, by eliminating any child nodes that were created from a split with a χ^2 value less than 3.0. To further reduce complexity of the tree, we determined whether any of the nodes could be collapsed by using the Wald test for joint hypotheses to identify nodes that were equal. Each terminal node of the final tree was designated as a "biomarker profile". Biomarker profiles were compared to the reference profile in a Cox regression model adjusted for the non-biomarker risk factors identified in Chapter 3. Those profiles that were found to be significantly different ($p<0.05$) from the reference profile were then compared to all other profiles in a second Cox regression model.

4.3.4.5 Classification and Regression Tree Analysis: Time-varying tree

To assess the biomarkers as time-varying covariates, we used an approach similar to that described for the baseline tree (Section 4.3.4.4) with a few modifications. First, we used the mean change from log baseline biomarker when determining the best biomarker for a split. The change from log baseline biomarker was calculated for each participant at each visit during the follow-up period. We then determined the mean change from log baseline across all visits for all participants who met the node criteria. At each split, participants were assigned to a child node for all visits that met the node criteria. Thus, it was possible for a participant to occupy different nodes at different visits, depending on their biomarker values at each visit. Second, we included all log baseline biomarkers as adjustment variables in addition to the non-biomarker risk factors. Finally, when determining the biomarker split that would create the largest separation in nodes, the model for the potential split included all participants and nodes. This differs from the baseline biomarker tree where the model for the potential split only included the participants in the node being split. As in Section 4.3.4.4, the χ^2 value was used to determine the best split and as a pruning criteria, the Wald test was used to identify nodes that could be collapsed, and all terminal nodes were first

compared to the lowest risk group (rightmost terminal node) and significant ($p<0.05$) terminal nodes were then compared to all other participants.

4.3.4.6 Missing data

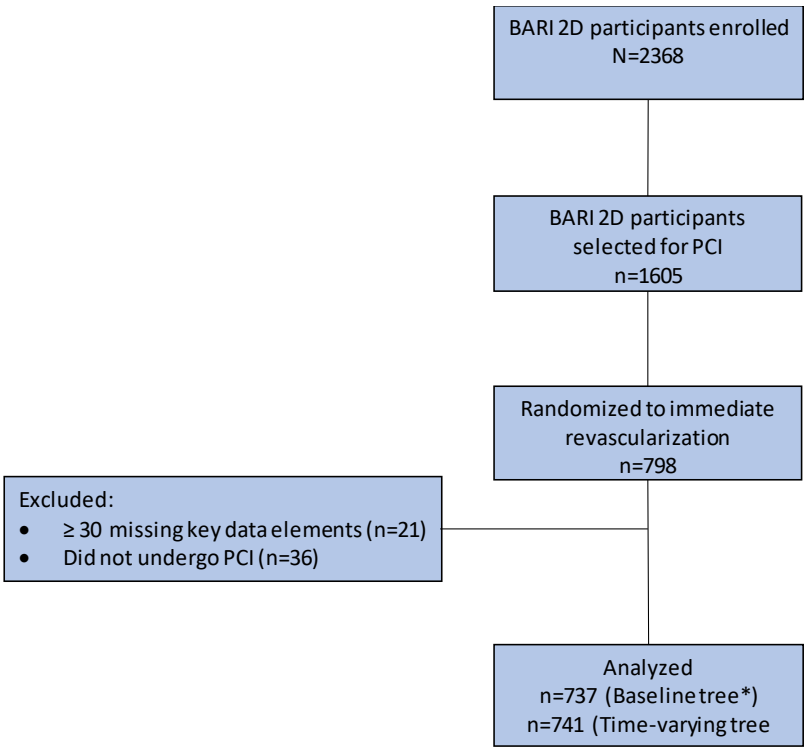
Prior to CART, we modeled missing non-biomarker risk factors from Chapter 3 by creating two new variables, one that indicated whether a participant was missing data on the risk factor and one to indicate whether a participant was not missing data on the risk factor. These two new variables for each non-biomarker risk factor were used as adjustment variables at each split in both the baseline and time-varying CART analysis. Missing biomarker values, including biomarker values that were missing due to different protocolized timepoints of lipid and adipokine biomarker measures, were imputed as described in Chapter 3 and then were log transformed as described in Section 4.3.4.3. In summary, linear interpolation using adjacent non-missing values was used to impute missing biomarker values and the final value was then carried forward for any missing values up to three annual visits to maximize the number of visits used for the Cox regression. These two new variables for each biomarker were also used as adjustment variables in the time-varying CART analysis.

Data analysis was conducted using SAS software, version 9.4 (SAS Institute Inc.; Cary, NC).

4.4 Results

4.4.1 Comparison of baseline data between the outcome groups

Figure 3 outlines the selection criteria to determine participants from the BARI 2D trial who were eligible for participation in these CART analyses. Among the 741 participants included in the CART analyses, participants who subsequently underwent repeat revascularization were younger (60.4 years of age vs. 62.3, p=0.0215), more likely to have had prior PCI (34.6% vs. 19.9%, p<0.0001), and were more likely to be taking insulin at baseline (36.8% vs. 28.4%, p=0.0332) (Table 13). This group also had a higher proportion who had been randomized to receive primarily IP therapy when compared to the proportion randomized to receive primarily IP therapy in the group of participants who did not undergo repeat revascularization (57.7% vs. 48.7%, overall p=0.0342) (Table 13). Participants in this group also had higher baseline levels of tPA (10.0 vs. 9.1 ng/ml, p=0.0114) and insulin (10.0 vs. 9.3 IU/ml, p=0.0433) compared to those who did not undergo repeat revascularization (Table 13).



*4 participants were missing baseline tPA data which was selected as the top split for the Baseline tree.

Figure 3 CART: Selection of study population

Table 13 CART: Comparison of baseline data between the outcome groups

		Any Repeat Revascularization		
	Total (N=741)	**No (n=559)**	**Yes (n=182)**	**p***
Age at study entry, mean (SD)	61.9 (8.9)	62.3 (8.8)	60.4 (9.5)	**0.0215**
Male, n (%)	509 (68.7)	382 (68.3)	127 (69.8)	0.7152
Race, n (%)				0.1040
Black/African American	150 (20.2)	105 (18.8)	45 (24.7)	
White	503 (67.9)	391 (69.9)	112 (61.5)	
Other	88 (11.9)	63 (11.3)	25 (13.7)	
Prior revascularization				
CABG, n (%)	59 (8.1)	40 (7.2)	19 (10.6)	0.1486
PCI, n (%)	174 (23.5)	111 (19.9)	63 (34.6)	**<.0001**
Hypercholesterolemia requiring treatment, n (%)	608 (83.3)	464 (84.5)	144 (79.6)	0.1209
Currently taking insulin, n (%)	226 (30.5)	159 (28.4)	67 (36.8)	**0.0332**

	Total (N=741)	Any Repeat Revascularization		
		No (n=559)	Yes (n=182)	p*
Insulin Therapy (during trial), n (%)				
Insulin-Providing	377 (50.9)	272 (48.7)	105 (57.7)	**0.0342**
Insulin-Sensitizing	364 (49.1)	287 (51.3)	77 (42.3)	
LCX disease severity, n (%)				
No LCX disease	175 (23.6)	145 (26.0)	30 (16.5)	0.0589
Stenosis: <50%	143 (19.3)	111 (19.9)	32 (17.6)	
Stenosis: 50-69%	92 (12.4)	63 (11.3)	29 (15.9)	
Stenosis: 70-89%	168 (22.7)	119 (21.3)	49 (26.9)	
Stenosis: 90-99%	108 (14.6)	78 (14.0)	30 (16.5)	
Stenosis: 100%	54 (7.3)	42 (7.5)	12 (6.6)	
Number of lesions with thrombus, mean (SD)	0.0 (0.1)	0.0 (0.1)	0.0 (0.2)	0.2867
Biomarker [median (Q1, Q3)]				
CRP ug/ml	2.3 (1.0, 6.2)	2.2 (1.0, 6.2)	2.6 (1.0, 6.0)	0.7437
IL-6 pg/ml	2.3 (1.3, 4.0)	2.2 (1.2, 4.1)	2.5 (1.5, 3.8)	0.3657
Leptin pg/ml	18721.0 (9282.0, 37534.0)	17602.6 (9281.8, 36558.0)	22515.4 (9180.4, 43228.3)	0.1321
MCP-1 pg/ml	198.0 (152.0, 244.0)	194.7 (150.5, 246.3)	208.5 (160.7, 242.7)	0.3909
TNF-α pg/ml	4.8 (3.6, 6.7)	4.8 (3.6, 6.5)	5.0 (3.7, 7.3)	0.1128
PAI-1 activity au/ml	16.0 (9.8, 27.0)	16.0 (9.3, 26.0)	19.0 (11.0, 29.0)	0.0523
PAI-1 antigen ng/ml	22.0 (14.0, 34.0)	22.0 (14.0, 34.0)	23.0 (14.0, 35.0)	0.4414
tissue Plasminogen Activator ng/ml	9.3 (7.1, 12.0)	9.1 (6.9, 12.0)	10.0 (7.4, 13.0)	**0.0114**
Insulin micro IU/ml	9.5 (5.7, 17.0)	9.3 (5.4, 16.0)	10.0 (6.4, 19.0)	**0.0433**
Adiponectin ng/ml	4615.0 (2904.0, 8011.0)	4834.9 (2987.1, 8207.3)	4316.0 (2770.1, 7739.8)	0.1015
sCD14 ng/ml	1261.0 (1071.0, 1473.0)	1252.0 (1067.8, 1465.9)	1262.9 (1099.8, 1520.4)	0.2357
Fibrinogen mg/dl	361.0 (294.0, 423.0)	362.0 (293.5, 423.0)	359.0 (294.0, 424.0)	0.9292
Fibrinopeptide A ng/ml	10.0 (5.0, 30.0)	10.0 (5.0, 32.0)	9.8 (5.2, 24.0)	0.7873
D-dimer ug/ml	0.3 (0.2, 0.6)	0.3 (0.2, 0.6)	0.3 (0.2, 0.6)	0.7077
Serum creatinine mg/dl	1.0 (0.9, 1.2)	1.0 (0.9, 1.2)	1.0 (0.8, 1.2)	0.6698
Total cholesterol mg/dl	161.0 (139.0, 187.0)	161.0 (139.0, 187.0)	162.5 (139.0, 186.0)	0.9192
HDL mg/dl	36.0 (31.0, 43.0)	37.0 (32.0, 43.0)	35.0 (30.0, 42.0)	0.1922
LDL mg/dl	90.0 (73.0, 114.0)	90.0 (74.0, 112.0)	88.5 (71.0, 118.0)	0.8974
Triglyceride mg/dl	137.0 (90.0, 209.0)	138.0 (90.0, 209.0)	133.5 (89.0, 209.0)	0.9023

*nominal p

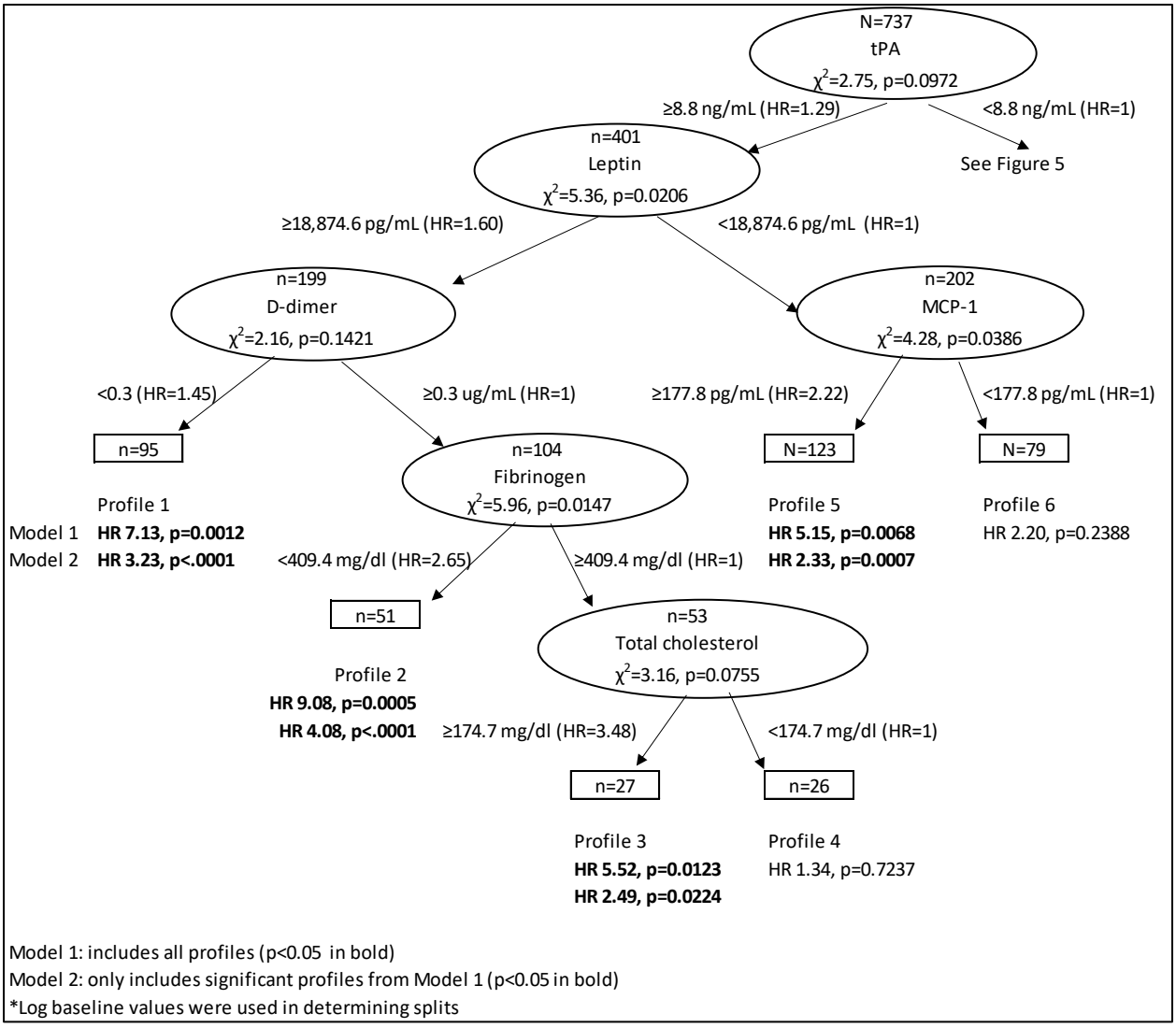
Note: Except for Insulin Therapy, all characteristics were measured at baseline (prior to first PCI in the trial).

4.4.2 Baseline biomarker CART profiles associated with ARR

After growing the tree until the stopping criteria were met, 18 terminal nodes were generated from the CART analysis (tree not shown). Pruning reduced the number of terminal nodes to 15 and we were able to further reduce the number of nodes to 12 by combining nodes that were not statistically different. Leptin was selected as a splitting biomarker in two branches of our baseline biomarker tree albeit with differing mean values in each branch (based on the mean leptin measure of participants who met the splitting criteria of all nodes along the branch preceding the leptin split).

We assigned each one of our participants into one of the 12 profiles, whereby participants in each profile met all the biomarker criteria along the branch leading up to the terminal node (Figure 4 and Figure 5, Table 14). For example, a participant in Profile 1 must have had baseline tPA at or above 8.8 ng/mL, baseline D-dimer less than 0.3 µg/ml and baseline leptin at or above 18,874.6 pg/mL. We compared these profiles in Cox regression analysis (Model 1), with Profile 12 designated as the reference group (Table 14). 8 out of the 12 profiles were significantly different from the reference node (Profile 1- HR 7.13, p=0.0012; Profile 2- HR 9.08, p=0.0005; Profile 3- HR 5.52, p=0.0123; Profile 5- HR 5.15, p=0.0068; Profile 7- HR 11.63, p=0.0001; Profile 8- HR 4.58, p=0.0201; Profile 10- HR 3.75, p=0.0366; Profile 11- HR 3.83, p=0.0446) (Table 14, Figure 4 and Figure 5). These 8 profiles were tested in a second model (Model 2) where the reference was all participants other than participants in these 8 profiles. Of the 8 profiles tested in Model 2, 6 retained their significant association with ARR (Profile 1- HR 3.23, p<.0001; Profile 2- HR 4.08, p<.0001; Profile 3- HR 2.49, p=0.0224; Profile 5- HR 2.33, p=0.0007; Profile 7- HR 5.28, p<.0001; Profile 8- HR 2.08, p=0.0402) (Table 14, Figure 4 and Figure 5).

Table 15 shows the mean biomarker values for participants in each of the terminal nodes that were found to be statistically significant in Model 2.



Model 1: includes all profiles (p<0.05 in bold)
Model 2: only includes significant profiles from Model 1 (p<0.05 in bold)
*Log baseline values were used in determining splits

Figure 4 CART Baseline biomarker tree (left branch)

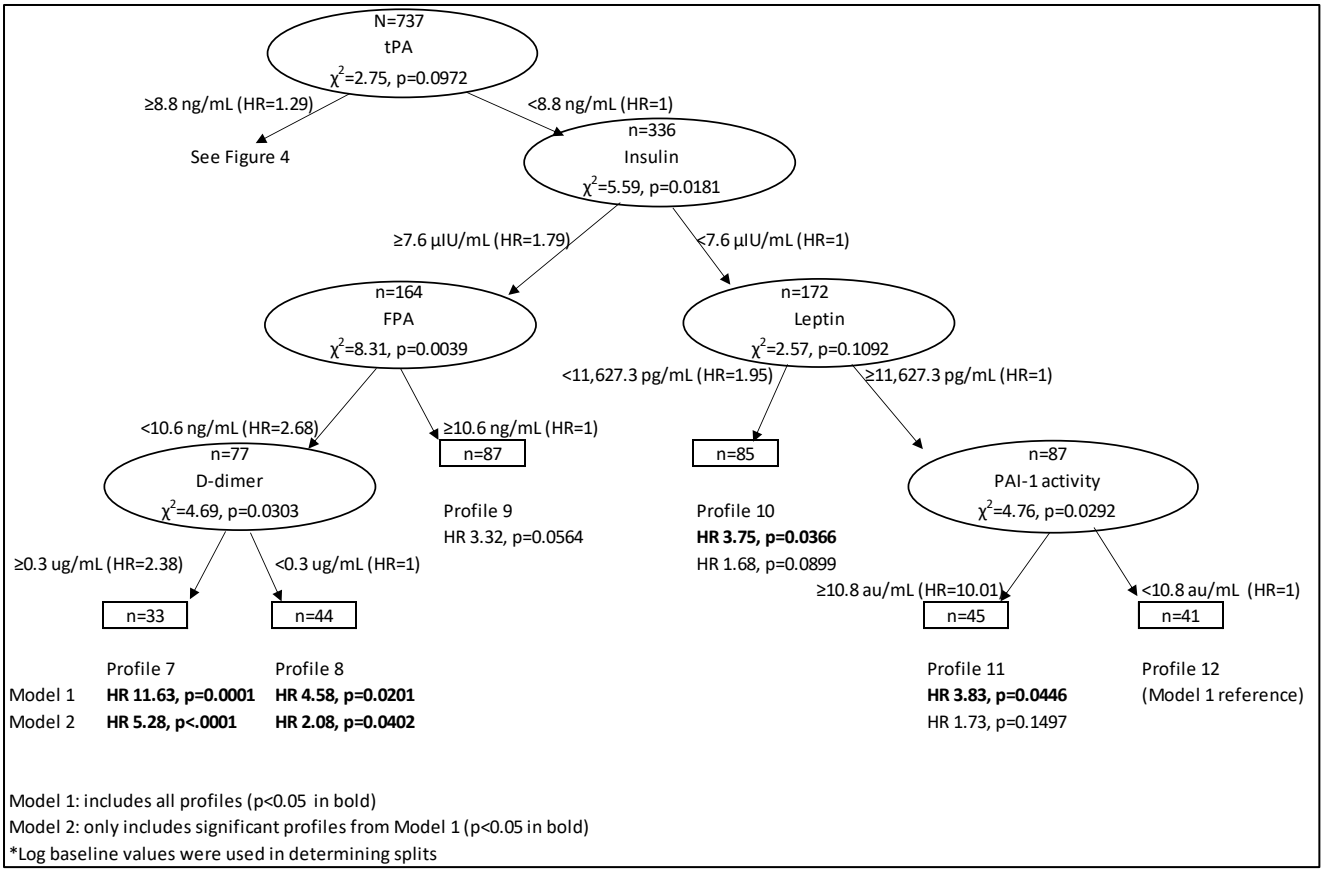


Figure 5 CART Baseline biomarker tree (right branch)

Table 14 CART Baseline biomarker tree: Testing terminal nodes

		Model 1*		Model 2*	
Profile	**Biomarker combinations**	**HR**	**p**	**HR**	**p**
1	**tPA+, D-dimer-, Leptin+**	**7.13**	**0.0012**	**3.23**	**<.0001**
2	**tPA+, Fibrinogen-, D-dimer+, Leptin+**	**9.08**	**0.0005**	**4.08**	**<.0001**
3	**tPA+, Fibrinogen+, D-dimer+, Leptin+, Total cholesterol+**	**5.52**	**0.0123**	**2.49**	**0.0224**
4	tPA+, Fibrinogen+, D-dimer+, Leptin+, Total cholesterol-	1.34	0.7237	-	-
5	**tPA+, Leptin-, MCP-1+**	**5.15**	**0.0068**	**2.33**	**0.0007**
6	tPA+, Leptin-, MCP-1-	2.20	0.2388	-	-
7	**tPA-, FPA-, D-dimer+, Insulin+**	**11.63**	**0.0001**	**5.28**	**<.0001**
8	**tPA-, FPA-, D-dimer-, Insulin+**	**4.58**	**0.0201**	**2.08**	**0.0402**
9	tPA-, FPA+, Insulin+	3.32	0.0564	-	-
10	tPA-, Leptin-, Insulin-	3.75	0.0366	1.68	0.0899
11	tPA-, PAI-1 activity+, Leptin+, Insulin-	3.83	0.0446	1.73	0.1497
12 (reference)	tPA-, PAI-1 activity-, Leptin+, Insulin-	1.00	reference	-	-

+ indicates that participants in the node have biomarker values at or above the mean log biomarker value of the parent node.

- indicates that participants in the node have biomarker values below the mean log biomarker value of the parent node.

*Model 1 included all terminal nodes (i.e. all profiles) while Model 2 included only those profiles that were found to be significant in Model 1. The reference group for Model 2 is all study participants in profiles 4, 6, 9, 12). Profiles in bold font had p<0.05 in the final model (Model 2).All models adjusted for age, history of PCI, current insulin use at baseline, hypercholesterolemia requiring treatment at baseline, insulin therapy during the trial (insulin providing or insulin sensitizing), presence of LCX diameter stenosis greater than 50% and number of lesions with thrombus.

Table 15 Baseline tree: Mean biomarker values of participants in terminal nodes

	Biomarker values						
Biomarker (reference values)	Profile 7 (HR 5.28)*	Profile 2 (HR 4.08)	Profile 1 (HR 3.23)	Profile 3 (HR 2.49)	Profile 5 (HR 2.33)	Profile 8 (HR 2.08)	Mean biomarker value in all other profiles
tPA (<10 ng/ml)[122]	7.1	***12.2***	***11.9***	***11.9***	***12.0***	6.6	7.6
Insulin (2-20 µIU/ml)[123]	17.0	14.8	13.6	11.4	9.7	14.3	7.3
FPA (<2 ng/ml)[124,125]	***4.3***	***14.3***	***15.3***	***12.0***	***9.8***	***4.0***	***14.8***
D-dimer (<0.5 ug/ml)[126,127]	***0.7***	***0.6***	0.2	***0.7***	0.3	0.2	0.4
Leptin (9-24k pg/ml)[128]	23,565.3	***42,192.0***	***38,454.3***	***41,191.9***	8,718.7	21,108.3	13,455.4
Fibrinogen (200-400mg/dl)[129]	368.1	331.3	371.3	***500.1***	341.0	297.5	351.8
MCP-1 (<160pg/ml)[130]	***177.5***	***218.0***	***205.5***	***180.8***	***237.8***	***175.3***	***169.2***
Total cholesterol (<175 mg/dl)[131,132]	156.8	161.5	172.5	***209.4***	166.1	156.3	155.5

Shaded values indicate the biomarkers that were selected for splitting in the nodes along the CART branch leading up to the terminal node of the profile. Values in ***bold italic*** indicate values that are above the normal reference values (reference values in a healthy population).
*Model 2 hazard ratios (all 6 profiles were statistically significant).

Abbreviations: tPA (tissue Plasminogen Activator), FPA (fibrinopeptide A), MCP-1 (monocyte chemoattractant protein-1)

4.4.3 Time-varying biomarker CART profiles associated with ARR

After growing the tree until the stopping criteria were met, 15 terminal nodes were generated from the CART analysis (tree not shown). Pruning reduced the number of terminal nodes to 13 and we were able to further reduce the number of nodes to 9 by combining nodes that were not statistically different.

We assigned each of our participants into one of the 9 profiles, whereby participant visits in each profile met all the biomarker criteria along the branch leading up to the terminal node

(Figure 6 and Figure 7, Table 16). For example, a participant in Profile 1 must have had at least one visit where their change from log baseline PAI-activity at the visit less was than -0.07 and change from log baseline CRP was at or above -0.43. We compared these profiles in Cox regression analysis (Model 1; Table 16), with Profile 9 designated as the reference group (Table 16). 4 out of the 9 profiles were significantly different from the reference node (Profile 1- HR 6.28, p=0.0002; Profile 2- HR 13.90, p<.0001; Profile 5- HR 5.86, p=0.0007; Profile 7- HR 5.51, p=0.0023) (Table 16, Figure 6 and Figure 7). These 4 profiles were tested in a second model (Model 2) where the reference was all participants other than participants in these 4 profiles. All 4 profiles retained their significant association with ARR when tested in Model 2 (Profile 1- HR 3.77, p<.0001; Profile 2- HR 8.22, p<.0001; Profile 5- HR 3.51, p<.0001; Profile 7, HR 3.30, p=0.0014) (Table 16, Figure 6 and Figure 7).

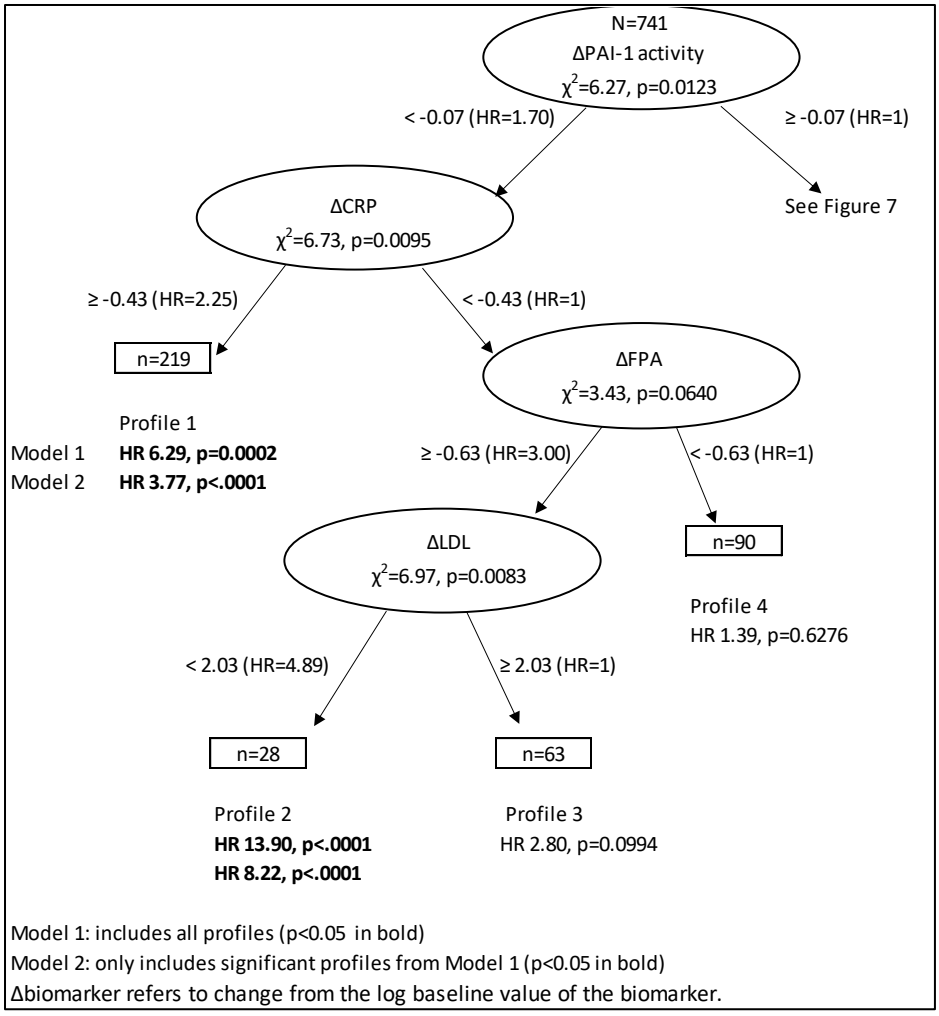


Figure 6 CART Time-varying tree (left branch)

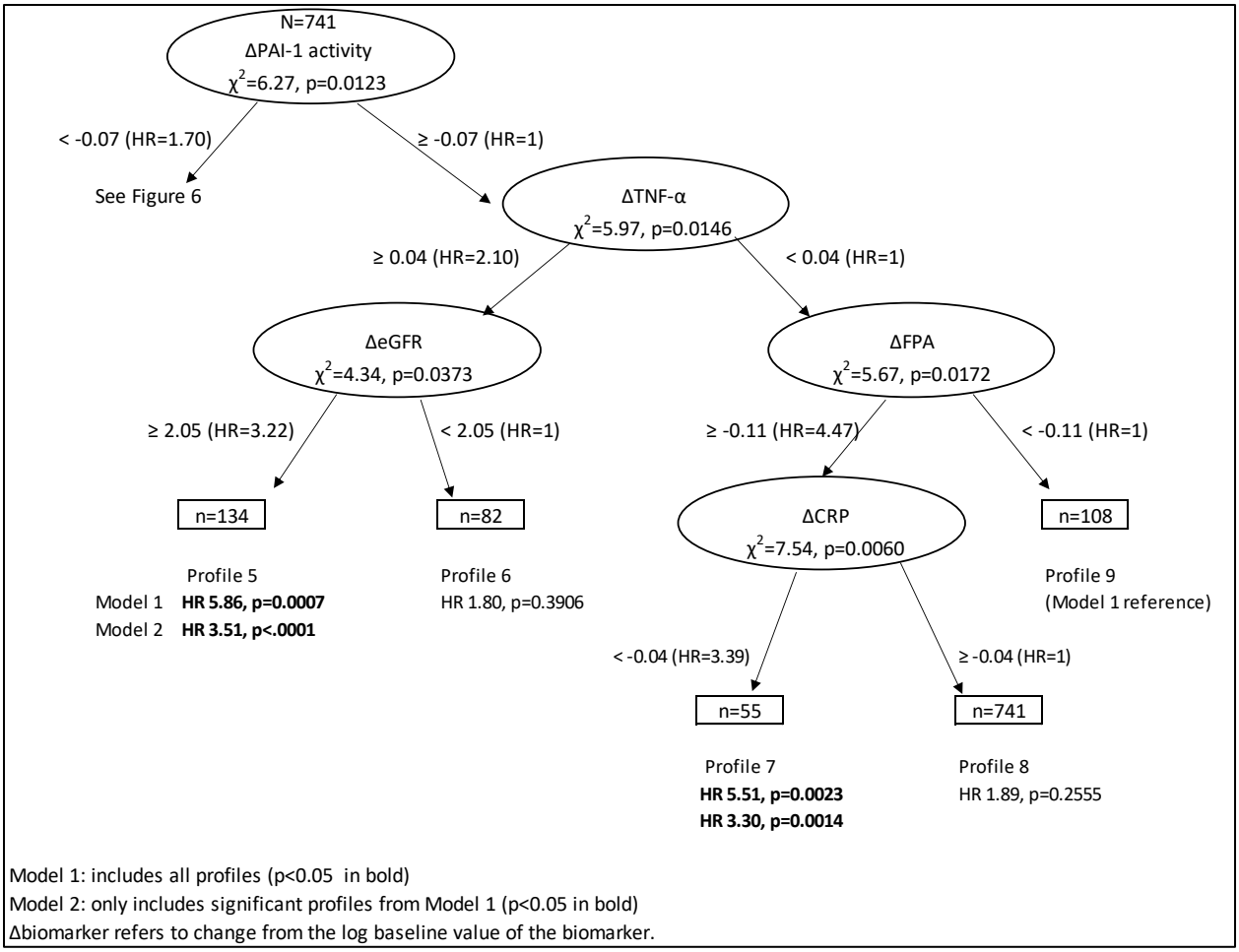


Figure 7 CART Time-varying tree (right branch)

Table 16 CART Time-varying biomarker tree: Testing terminal nodes

		Model 1*		Model 2*	
Profile	**Biomarker combinations**	**HR**	**p**	**HR**	**p**
1	ΔPAI-1 activity-, ΔCRP+	6.28	0.0002	**3.77**	**<.0001**
2	ΔPAI-1 activity-, ΔCRP-, ΔFPA+, ΔLDL-	13.90	<.0001	**8.22**	**<.0001**
3	ΔPAI-1 activity-, ΔCRP-, ΔFPA+, ΔLDL+	2.80	0.0994	-	-
4	ΔPAI-1 activity-, ΔCRP-, ΔFPA-	1.39	0.6276	**-**	**-**
5	ΔPAI-1 activity+, ΔTNF-α+, ΔeGFR+	5.86	0.0007	**3.51**	**<.0001**
6	ΔPAI-1 activity+, ΔTNF-α+, ΔeGFR-	1.80	0.3906	-	-
7	ΔPAI-1 activity+, ΔTNF-α-, ΔFPA+, ΔCRP-	5.51	0.0023	**3.30**	**0.0014**
8	ΔPAI-1 activity+, ΔTNF-α-, ΔFPA+, ΔCRP+	1.89	0.2555	-	-
9	ΔPAI-1 activity+, ΔTNF-α-, ΔFPA-	1.00	reference	-	-

+ indicates that the change from log baseline biomarker value of participants in the node was at or above the mean change from log baseline for that biomarker.

- indicates that the change from log baseline biomarker value of participants in the node was below the mean change from log baseline for that biomarker.

*Model 1 included all terminal nodes (i.e. all profiles) while Model 2 included only those profiles that were found to be significant in Model 1. The reference group for Model 2 is all study participants in profiles 3, 4, 6, 8 and 9). Profiles in bold font had p<0.05 in the final model (Model 2).All models adjusted for age, history of PCI, current insulin use at baseline, hypercholesterolemia requiring treatment at baseline, insulin therapy during the trial (insulin providing or insulin sensitizing), presence of LCX diameter stenosis greater than 50% and number of lesions with thrombus.

Table 17 CART Time-varying biomarker tree: Mean biomarker values of participants in terminal nodes

		Change from log baseline biomarker values				
Biomarker (normal reference range [log scale])	Mean log baseline value (n=741)	Profile 2 (HR 8.22)*	Profile 1 (HR 3.77)	Profile 5 (HR 3.51)	Profile 7 (HR 3.30)	Mean log baseline change in all other profiles
PAI-1 activity (1.61-3.61)[133,134]	2.77	-0.56	-0.57	0.42	0.31	-0.05
CRP (<1.10)[135]	0.83	-1.09	0.14	-0.02	-0.60	-0.57
FPA (<0.69)[124,125]	***2.30***	0.17	-0.44	-0.03	0.91	-0.62
LDL (3.91-4.25)[136]	***4.50***	1.35	1.92	2.08	2.01	1.86
TNF-α (<3.00)[137]	1.57	-0.11	-0.01	0.31	-0.18	-0.11
eGFR (>4.09)[138]	4.32	1.73	1.82	2.20	2.08	1.81

Shaded values indicate the biomarkers that were selected for splitting in the nodes along the CART branch leading up to the terminal node of the profile. Values in ***bold italic*** indicate values that are outside the normal reference range (reference range in a healthy population).

*Model 2 hazard ratios (all 4 profiles were statistically significant).

4.5 Discussion

Patients with diabetes who undergo PCI have higher rates of repeat revascularization compared to patients with diabetes who undergo CABG and compared to patients without diabetes who undergo PCI. This patient population also has accelerated atherosclerosis, as well as more severe and diffuse atherosclerosis compared to patients without diabetes. This implies that the initiation and progression of atherosclerosis may be a factor in the higher repeat revascularization rate.

Lesion formation in an artery occurs in the presence of endothelial dysfunction and increased endothelial membrane permeability. The entry of LDL into the intima as a result of increased permeability triggers a pro-inflammatory response that attracts monocytes into the intima. LDL is oxidized in the intima and monocytes differentiate into macrophages that engulf the oxidized LDL to form foam cells. The foam cells stimulate the recruitment of more LDL and monocytes leading to the formation of a fatty streak. The foam cells eventually stimulate vascular smooth muscle cell (VSMC) migration into the intima. VSMCs generate extracellular matrix to form a fibrous cap over the foam cell, thus forming a lesion. Over time, VSMC apoptosis and extracellular matrix degradation lead to thinning of the fibrous cap and subsequent plaque erosion or rupture[139]. Revascularization is used to remediate stenosis in stable plaques and to remediate plaque rupture or erosion.

Our classification tree using baseline biomarkers revealed that coagulation, fibrinolysis, lipid, insulin and chemoattractant biomarkers were associated with risk for repeat revascularization. Fibrinogen, FPA, D-dimer and tPA are hemostasis biomarkers that maintain the balance between coagulation and fibrinolysis. Fibrinogen is cleaved by thrombin to form fibrin and FPA. Fibrin molecules polymerize and interact with platelets and other components to form a

fibrin clot. tPA production is stimulated by thrombin and converts plasminogen clots to plasmin. Plasmin degrades the fibrin into D-dimer and other fibrin degradation products. MCP-1 is a chemoattractant that facilitates the recruitment and migration of monocytes into the intima.

In our decision tree based on baseline (prior to index PCI) biomarker levels, participants in Profiles 1, 2, 3 and 5 had mean tPA values that were above the normal range. In addition to its role in fibrinolysis, tPA enhances endothelial dysfunction[140] and is thought to facilitate VSMC migration into the intima by activating plasmin which degrades the extracellular matrix around VSMCs[141]. All profiles had mean FPA values above the normal range, an indication of a hypercoagulable state. However, profiles 1, 5 and 8 had D-dimer values within the normal range which may suggest that fibrinolysis is impaired in participants in these profiles. Profiles 1, 2 and 3 had elevated leptin levels. Leptin stimulates VSMC migration, enhances endothelial dysfunction and enhances expression of MCP-1[142]. The mean value of MCP-1 in all profiles was above the normal range, and Profile 3 had mean values of fibrinogen and total cholesterol above the normal range.

Participants with relatively low baseline tPA, low FPA, high D-dimer, and high insulin had the highest risk for repeat revascularization relative to participants who did not have this combination of biomarker levels at baseline. Though the mean FPA level for this group of participants was above normal, it was among the lowest compared to participants not in this group. This implies that the presence of "low" FPA and elevated D-dimer is the reason why these participants had the highest risk for repeat revascularization. A possible explanation is that the rate of fibrin lysis exceeds that of fibrin deposition (i.e. there is an imbalance between fibrinolysis and coagulation, with fibrinolysis being favored). It is not clear why this imbalance would lead to the highest risk for repeat revascularization but given that fibrin is a major component of

atherosclerotic plaques, the presence of elevated D-dimer may be an indication of plaque instability that would lead to subsequent revascularization.

Participants with high baseline tPA, low fibrinogen, high D-dimer, and high leptin may have coexistence of hypercoagulability, enhanced endothelial dysfunction, enhanced VSMC migration, and elevated monocyte recruitment at baseline which may have led to a high risk for repeat revascularization in our study. Participants with a combination of high baseline tPA, low D-dimer, and high leptin may have impaired fibrinolysis, enhanced endothelial dysfunction, enhanced VSMC migration, and elevated monocyte recruitment, factors which may have led to the high rate of repeat revascularization in these participants. Participants with high baseline tPA, high fibrinogen, high D-dimer, high leptin, and high total cholesterol may have hypercoagulability, hyperlipidemia, and enhanced endothelial dysfunction which may explain the high risk for repeat revascularization in this group. In participants with high tPA, low leptin, and high MCP-1, it appears that the main driver for high risk of repeat revascularization may be the coexistence of endothelial dysfunction and elevated monocyte recruitment. The combination of low baseline tPA, low FPA, low D-dimer, and high insulin suggest that impaired fibrinolysis leads to high risk for repeat revascularization.

In our time-varying biomarker tree, the direction of change from baseline of biomarkers suggests that increase in coagulation (FPA increase), worsened hyperlipidemia (LDL increase), increase in inflammation (CRP and TNF-α increase) and impaired fibrinolysis (PAI-1 increase) lead to a high risk for repeat revascularization.

Our study had two limitations. First, in order to isolate the association of biomarkers with repeat revascularization, we adjusted for non-biomarker patient characteristics that we found to be independently associated with repeat revascularization in a prior study. In that prior study, we also

assessed the independent association of biomarkers with repeat revascularization. We found that no baseline biomarkers were independently associated with the outcome and only time varying FPA was associated with the outcome. However, as shown in this current study, several biomarkers are associated with repeat revascularization when they are assessed in the context of biomarker combinations. It is therefore possible that, had we assessed the association of non-biomarker patient characteristics using CART methodology, we may have uncovered additional non-biomarker associations that are associated with the outcome. This implies that there may be unmeasured confounding in our biomarker CART analysis which may impact some of the biomarker associations that we observed in this study. Second, by categorizing our biomarker measures as at/ above or below the mean, we were not able take full advantage of the CART methodology's ability to identify optimal cut-points for continuous variables. This may have led to not identifying more significant cut points and thus may have missed a better tree.

By identifying combinations of biomarkers that are associated with repeat revascularization, we have gained insight into biological mechanism that may underlie the risk for repeat revascularization. Our study suggests that hemostasis, endothelial dysfunction, hyperlipidemia and monocyte recruitment are important biological mechanisms when considering the risk for repeat revascularization. In addition, our study suggests that a shift to impaired fibrinolysis, and increased inflammation and coagulation relative to baseline may lead to a higher risk for repeat revascularization.

5.0 Prognostic models for repeat revascularization and death following PCI in patients with Type 2 Diabetes

5.1 Abstract

Background: Patients with Type 2 Diabetes are at higher risk for repeat revascularization and death after percutaneous coronary intervention (PCI) when compared to patients without Type 2 Diabetes. While coronary artery bypass grafting (CABG) presents a lower risk for these outcomes in this patient population, there is an increasing trend in the use of PCI in patients with Type 2 Diabetes. It is therefore important to understand the risk for poor outcomes following PCI in this patient population. We will leverage the heterogeneity in risk for cardiovascular outcomes in this population to identify prognostic combinations of risk factors and will quantify the risk for repeat revascularization and death in these prognostic risk factor groups.

Methods: Patients with diabetes (n=5,160) who underwent PCI in the University of Pittsburgh Medical Center hospital system between 2010 and 2016 were eligible for this study. The outcomes of interest were post-discharge repeat revascularization and death following PCI. Pre-procedure patient characteristics were compared in patients who did versus who did not experience the outcomes of interest. Patient characteristics were also compared in the Training and Test data sets (80/20 split). Continuous variables were compared using t-tests while categorical variables were compared using the chi-square test. Classification and Regression Tree survival analysis of the Training data was used to identify combinations of patient characteristics (risk groups) that were associated with repeat revascularization and death. Absolute Cox risk estimates at 0.5 and 1-7 years after PCI were assigned to each risk group by comparing the terminal nodes

of the trees to a reference terminal node. Discrimination was assessed using inverse probability of censoring weighting to generate receiver operator characteristic curves for estimating overall concordance (Uno's concordance statistic) and time-dependent concordance statistics (area under the curve, AUC). Calibration was visually assessed using calibration plots. The Test data set was used to internally validate the risk model by assessing discrimination and calibration of the risk model in the Test set. The trees were then used to construct risk flow charts for illustrating risk for the outcomes.

Results: The mean time to repeat revascularization and death was 1.5 years and 2.7 years, respectively. Multivessel disease and prior heart failure were the strongest discriminators for predicting risk of repeat revascularization and death, respectively. Patients with 3 or more arteries with 70% or higher stenosis, were less than 70 years old, had 1 or more high complexity lesions and had stable angina had the highest risk for repeat revascularization relative to patients who did not have this combination of risk factors (HR 5.64, p<.0001; absolute risk ranging from 27% to 75% at 0.5 and 1-7 years after PCI). Patients with both prior heart failure and pre-procedure creatinine at 1.70 mg/dL or greater (HR 20.81, p<.0001; absolute risk ranging from 17% to 93%) had the highest risk for death compared to patients who did not have this combination of risk factors. Uno's concordance statistic for the repeat revascularization model was 0.62 and time-dependent AUC ranged from 0.62 to 0.67. In the risk model for death Uno's concordance statistic was 0.71 and time-dependent AUC ranged from 0.75 to 0.77. Both risk models (repeat revascularization and death) showed good calibration across all time points, with slight overestimation of risk seen with the risk models. We constructed risk flow charts for 1-year risk of repeat revascularization and 2-year risk of death based on the patient characteristics that were selected in our classification trees.

Conclusion: We created risk flow charts with potential clinical utility for quickly determining risk for post-discharge repeat revascularization and death following PCI in patients with Type 2 Diabetes.

5.2 Introduction

Patients with Type 2 Diabetes are at higher risk for repeat revascularization and death following percutaneous coronary intervention (PCI) compared to patients who do not have diabetes. Nevertheless, a recent study using data from the National Cardiovascular Data Registry Acute Coronary Treatment and Intervention Outcomes Network Registry- Get with the Guidelines (NCDR ACTION Registry-GWTG), the use of PCI was found to have increased from 45% in 2008 to 49% in 2014 in patients with diabetes who had non-ST elevation myocardial infarction and multi-vessel coronary artery disease[62].

Given the increase in PCI utilization in patients with Type 2 Diabetes and the higher risk for repeat revascularization and death following PCI compared to patients without diabetes, there is a need to quantify the level of risk associated with PCI in this patient population to allow for informed patient-clinician communication. It is recognized that there is heterogeneity in cardiovascular risk in patients with diabetes and several treatment guidelines recommend stratifying risk levels in this patient population[86]. For example, studies have shown that insulin treated diabetes[45,48,51], presence of renal impairment[143] or peripheral arterial disease[144] are associated with poorer cardiovascular outcomes, including repeat revascularization and death, in patients with diabetes who have these conditions compared to patients with diabetes who do not.

We will use Classification and Regression Tree (CART) analysis to classify patients with diabetes who underwent PCI in the University of Pittsburgh (UPMC) hospital system into risk groups for risk of repeat revascularization and risk of death. These risk group classifications will be used to construct a prognostic tool with the potential for use in a clinical setting.

5.3 Methods

5.3.1 Study population: University of Pittsburgh Medical Center (UPMC)

Deidentified patient information was provided by the UPMC Heart and Vascular Institute (HVI). The data was obtained from UPMC's CathPCI® registry (Diagnostic Catheterization and Percutaneous Coronary Intervention Registry). The CathPCI® registry is a hospital registry included in the American College of Cardiology's National Cardiovascular Data Registry (NCDR®). Participating hospitals use a standard data collection form to record information for each incidence of PCI that occurs at the hospital. The form includes information on demographics, medical history and risk factors, catheterization lab evaluation, diagnostic catheterization, coronary anatomy, PCI procedure, lesions, devices used, procedure medication, lab measures, intra- and post-procedure events, discharge medications, and discharge details.

The data set comprised 5,311 adult patients (18 years of age or greater) with Type 2 Diabetes who underwent PCI in the UPMC hospital system between 2010 and 2016. The patients were distributed across five hospitals within the UPMC hospital system, namely UPMC Shadyside, UPMC East, UPMC Hamot, UPMC Jameson and UPMC Presbyterian. Prior to providing us with the data set, UPMC HVI substituted patient identifiers with a sequential ID

number (starting from 1 to 5,311). As part of the deidentification, UPMC HVI converted dates in the dataset to number of days (e.g when indicating date of index PCI, a new variable indicating number of days since arrival was provided in lieu of providing the date that the PCI was performed). Arrival, procedure and discharge dates were treated in this manner. Supplemental to the information collected on the CathPCI® data forms, UPMC HVI also created new variables to sum the total number of lesions, the number of lesions in different segments of the coronary artery vasculature (e.g. number of lesions in left main coronary artery), and to indicate whether a patient had PCI or CABG after discharge along with the number of days from discharge to the subsequent revascularization.

Our study was conducted under an existing Quality Improvement project approved by the UPMC institutional review board (STUDY18120143: Clinical Outcomes in HVI patients).

5.3.2 Data preparation and outcome assessment

Of the 5,311 patients in the data set provided by UPMC HVI, we excluded 151 patients who died in hospital prior to discharge (final study population of 5,160 patients). We created the following additional variables: body mass index (using height and weight information from the data set), summation of the total number of coronary arteries with 50% or greater stenosis, summation of the total number of coronary arteries with 70% or greater stenosis, and outcome indicators.

We had two outcomes of interest: occurrence of the first subsequent revascularization of any vessel (either PCI or CABG) within the UPMC health system after discharge following the index PCI (defined as the first PCI performed at UPMC), and death after discharge following index PCI. Time to subsequent revascularization was defined as the time between discharge and the first

occurring subsequent revascularization (PCI or CABG). Time to death was defined as the time between discharge and death. For the outcome of repeat revascularization, patients were censored if no subsequent revascularization occurred at UPMC in the period between discharge and the last date that the patient had contact with the UPMC hospital system (up to 2020). For the outcome of death, patients were censored if they were alive at the last date that mortality data was available for the patient (via hospital data or the Social Security Death Index, assessed in 2020).

5.3.3 Statistical analysis

5.3.3.1 Baseline characteristics

We used simple random sampling to split our population of 5,160 patients 80/20 into training and test data sets. Baseline characteristics of the 5,160 patients were compared by the outcomes of interest. Continuous variables were assessed as mean (SD) and were compared using t-tests. Categorical variables were assessed by number and percent, and the chi-square test was used to compare the outcome groups. We also compared baseline characteristics between our training and test data sets. The magnitude of the differences between outcome groups was assessed via effect sizes which were reported as Cohen's d for continuous variables and as Relative Risk for categorical variables (proportion in patients with repeat revascularization ÷ proportion in patients with no repeat revascularization)[145].

5.3.3.2 Classification and Regression Tree Analysis: Training data set

Classification and Regression Tree Analysis (CART) on the Training data set, based on the method described by Bertolet et al.[121], was used to identify combinations of patient characteristics that were associated with repeat revascularization and death following PCI in patients with Type

2 Diabetes. We selected 40 patient characteristics to include in our CART analysis (Table 18). Potential splits of continuous variables were based on the mean value of all patients in the node while potential splits of categorical variables were based on their categories. To create the first split, we calculated the mean of each continuous variable using data from all patients, and then classified each patient as being below or at/ above the mean. We then ran separate Cox regression models for each categorical variable level and each dichotomized continuous variable (comparing patients who were at/ above the mean to those who were below the mean) to determine the variable that created the largest separation between all patients. We selected the model with the largest χ^2 value for the null hypothesis that participants with values below the mean were not equivalent to participants with values at/ above the mean for the outcome. Patients were then assigned to either of the two resulting child nodes, depending on whether the patient's value of the selected variable was less than or at/ above the mean of all patients (if a continuous variable was selected as the best split), or whether the patient was/ was not in a category found to be the highest risk among the categories of the selected variable (if a categorical variable was selected as the best split). Within each child node, we calculated the mean values of each continuous variable using only the data from patients within the child node of interest; patients in that node were then reclassified as being less than or at/ above the mean for each continuous variable within that child node. We split each child node using Cox regression models as described above using the below and at/ above mean designations for that node and the categorical variables. These steps were repeated recursively to create more child nodes until the predefined stopping criteria was met (no χ^2 value greater than 2.0, or the child node had less than 150 participants).

Once all nodes met the stopping criteria, we pruned the tree, from the bottom up, by eliminating any child nodes that were created from a split with a χ^2 value less than 3.0. To further

reduce complexity of the tree, we determined whether any of the nodes could be collapsed by using the Wald test for joint hypotheses to identify nodes that were equal. Participants in the terminal nodes were compared to participants in the reference node in a Cox regression model to generate log hazard ratios (β). Similarly, participants in the reference node were compared to participants who were not in the reference node in a Cox regression model to generate a log hazard ratio for the reference node. Two trees were created in this manner, one for each outcome (repeat revascularization and death).

The log hazard ratios of each terminal node, along with Kaplan Meier survival estimates at 0.5 and 1 to 7 years and the proportion of the study population in each terminal node, were used to estimate that node's risk for repeat revascularization or death (dependent on the risk profile that the patient was classified into) using the following equation[146]:

$$\hat{p}(t) = 1 - S_0(t)^{\exp\left(\sum_{i=1}^{p} \beta_i X_i - \sum_{i=1}^{p} \beta_i \bar{X}_i\right)}$$

where $S_0(t)$ is the baseline survival curve for the training set at time *t*, β_i is the Cox regression parameter estimate for risk profile *i*, X_i is an indicator variable for risk profile *i* (0 if patient is not in the risk profile, 1 if patient is in the risk profile), and $\bar{X}_i$ is the proportion of the training set in risk profile *i* (number of patients in the risk profile ÷ number of patients in the training set). Therefore $\sum_{i=1}^{p} \beta_i X_i$ represents the risk for an individual patient dependent on risk profiles *i…p*, while $\sum_{i=1}^{p} \beta_i \bar{X}_i$ represents the population risk (sum of proportional risk for risk profiles *i…p*).

Table 18 Patient characteristics included in CART analysis

Age	Pre-procedure creatinine
Sex	Pre-procedure hemoglobin
Race	Number of arteries with 50% stenosis or higher
BMI	Number of arteries with 70% stenosis or higher
Current/ recent smoker (<1 year)	Total number of lesions attempted to be treated
Hypertension	Number of lesions in LMCA segment
Dyslipidemia	Number of lesions in proximal LAD segment
Family history of premature CAD	Number of lesions in proximal LCx segment
Prior MI	Number of lesions in proximal RCA segment
Prior heart failure	Number of lesions in the rest of LAD segment
Heart failure within 2 weeks prior to index PCI	Number of lesions in the rest of LCx segment
Prior valve surgery/ procedure	Number of lesions in the rest of RCA segment
Prior PCI	Number of lesions in Ramus Intermedius segment
Prior CABG	Number of lesions with low complexity
Current dialysis	Number of lesions with high complexity
Prior cerebrovascular disease	Number of lesions that are bifurcated
Prior peripheral arterial disease	Number of lesions with thrombus
Chronic lung disease	Number of lesions with chronic total occlusion
Diabetes therapy	Mean length of all lesions
CAD presentation prior to index PCI	
Dominance	

Abbreviations: CAD, coronary artery disease; LMCA, left main coronary artery; LAD, left anterior descending artery; LCx, left circumflex artery; RCA, right coronary artery

5.3.3.3 Assessment of the training data risk model: discrimination and calibration

We assessed discrimination of the absolute risk estimates (i.e. how well the risk estimate differentiated patients who had the outcome from those who did not) at select time points (0.5 year, 1, 2, 3, 4, 5, 6 and 7 years) by generating time-dependent receiver operator characteristic (ROC) curves for the risk estimates at each time point[147]. Inverse probability of censoring weighting (IPCW) was used to estimate the ROC curve. Overall concordance was assessed using Uno's concordance statistic while discrimination at each time point was assessed using the time-dependent area under the curve (AUC). Calibration was assessed visually in a calibration curve

using a scatterplot of observed event rate (Kaplan-Meier estimate) against estimated probability (Cox regression absolute risk estimate). The data was fit using locally estimated scatterplot smoothing (LOESS) method with the smoothing parameter that minimized the corrected Akaike Information Criterion (AIC_C). The proximity of the smoothed line to a line of slope=1 indicated how well the risk estimate predicted the outcome at the given time point.

5.3.3.4 Internal validation of the training data risk model

The test data set was used to internally validate the risk model that was generated from the training data set. Patients in the test data set were assigned to a risk group based on the training data risk model, and their estimated absolute risk for each outcome equaled the training data risk estimate for the risk group to which they were assigned. Discrimination and calibration in the test data set were then assessed as described for the training data (see section 5.3.3.3).

5.3.3.5 Prognostic tool development

We used the classification trees (see section 5.3.3.2) as the basis of our prognostic tool. The trees were converted into risk flow charts by using the nodes along a branch leading up to a terminal node as decision points. Movement from one decision point (i.e. node) to the next decision point was determined by "Yes" or "No" responses to the criteria within the decision point. The risk flow terminated in the Cox absolute risk estimate for the terminal node (see section 5.3.3.2). For example, following the decision points along the branch for Profile 1 would result in a risk estimate equivalent to the Cox absolute risk estimate for Profile 1. We designated risk level as being Low, Moderate or Elevated by dividing the range of risk estimates into tertiles. Where the risk levels downstream of a decision point were the same (e.g. if all downstream risk levels were

"Low"), we terminated the decision point and indicated the range of risk estimates that were possible beyond the decision point.

Data analysis was conducted using SAS software, version 9.4 (SAS Institute Inc.; Cary, NC).

5.4 Results

5.4.1 Comparison of baseline data between the outcome groups

Of the 5,160 patients included in our study, 1,594 patients had repeat revascularization with mean time to repeat revascularization of 1.5 years (Table 19). More than half of our study population (58.9%) had at least 3 years of contact time (based on the last date of contact with the UPMC hospital system). A higher proportion of patients with repeat revascularization had at least 3 years of contact time compared to the proportion of patients without repeat revascularization who had at least 3 years of contact time (72.2% vs. 53.0%, $p<.0001$). Further analysis based on mortality status showed that among those who did not die, those who did not undergo repeat revascularization had shorter follow-up (4.6±1.8 vs. 5.4±1.9 years, data not shown) and contact time (3.9±2.0 vs. 4.9±2.0 years, data not shown) than those who had repeat revascularization. This further analysis also found that among those who died, those who did not undergo repeat revascularization had shorter follow-up (2.5±1.9 vs. 3.4±2.0 years, data not shown) and contact time (2.3±1.9 vs. 3.2±2.0 years, data not shown) than those who had repeat revascularization.

At baseline (prior to index PCI) the group of patients with repeat revascularization was younger (65.9 years old vs. 67.8 years, p<.0001) and had higher proportions of patients with hypertension (93.7% vs. 91.8%, p=0.0223, small effect size), dyslipidemia (89.6% vs. 85.9%, p=0.0002, small effect size), family history of premature coronary artery disease (29.5% vs. 26.1%, p=0.0096), prior myocardial infarction (39.1% vs. 30.7%, p<.0001), prior PCI (48.2% vs. 36.7%, p<.0001), prior CABG (31.0% vs. 22.7%, p<.0001), prior cerebrovascular disease (20.3% vs. 17.6%, p=0.0215) and prior peripheral arterial disease (18.9% vs. 14.8%, p=0.0001) when compared to the group of patients who did not undergo repeat revascularization. Diabetes therapy and coronary artery disease presentation prior to PCI differed between the group of patients with repeat revascularization and those with no repeat revascularization (p=0.0033 and p<.0001, respectively). A higher proportion of patients who did not undergo repeat revascularization had heart failure within the 2 weeks preceding the index PCI compared to the proportion in patients who underwent repeat revascularization (18.8% vs. 14.7%, p=0.0004). Further analysis found that among those who died, the proportion of patients with prior heart failure was higher in those who did not versus who did undergo repeat revascularization (31.3% vs. 21.9%, data not shown). Patients with repeat revascularization also had more arteries with 70% or higher stenosis (mean 2.7 vs. 2.3, p<.0001), more lesions in the RCA segment (excluding proximal RCA; mean 0.4 vs. 0.3, p=0.0074) and a greater proportion of patients with 50% or higher stenosis in the left main (3.2% vs. 2.2%, p=0.0419) when compared to the group of patients with no repeat revascularization. The differences between the outcome groups in number of lesions in the left main coronary artery segment and in the rest of the LAD segment, and in the levels of pre-procedure creatinine were statistically significant but the effect sizes were small. There was no difference in the proportion of patients who died post-discharge in the group who did not versus

the group that did have repeat revascularization (26.8% vs 25.8% respectively, p=0.4287) (Table 19).

Table 19 Repeat revascularization outcome: comparing baseline data by outcome

		Repeat revascularization			
Characteristic	Total (N=5160)	No (n=3566)	Yes (n=1594)	p-value (nominal)	Effect size*
DEMOGRAPHIC VARIABLES ----------					
Age, mean (SD)	67.2 (10.9)	67.8 (11.1)	65.9 (10.5)	**<.0001**	*0.2*
Male, n (%)	3387 (65.6)	2315 (64.9)	1072 (67.3)	0.1029	1.0
Race, n (%)				0.3943	
White	4686 (90.8)	3253 (91.2)	1433 (90.0)		1.0
Black	427 (8.3)	280 (7.9)	147 (9.2)		1.2
Other	45 (0.9)	32 (0.9)	13 (0.8)		0.9
Hypertension, n (%)	4768 (92.4)	3275 (91.8)	1493 (93.7)	**0.0223**	1.0
Dyslipidemia, n (%)	4491 (87.0)	3062 (85.9)	1429 (89.6)	**0.0002**	1.0
Family History of Premature CAD, n (%)	1401 (27.2)	930 (26.1)	471 (29.5)	**0.0096**	1.1
Prior MI, n (%)	1717 (33.3)	1093 (30.7)	624 (39.1)	**<.0001**	1.3
Prior Heart Failure, n (%)	957 (18.6)	664 (18.6)	293 (18.4)	0.8349	1.0
Heart failure in 2 weeks prior to index PCI, n (%)	905 (17.5)	670 (18.8)	235 (14.7)	**0.0004**	0.8
Prior Valve Surgery/Procedure, n (%)	149 (2.9)	106 (3.0)	43 (2.7)	0.5859	0.9
Prior PCI, n (%)	2077 (40.3)	1309 (36.7)	768 (48.2)	**<.0001**	1.3
Prior CABG, n (%)	1304 (25.3)	810 (22.7)	494 (31.0)	**<.0001**	1.4
Prior Cerebrovascular Disease, n (%)	953 (18.5)	629 (17.6)	324 (20.3)	**0.0215**	1.2
Prior Peripheral Arterial Disease, n (%)	828 (16.0)	526 (14.8)	302 (18.9)	**0.0001**	1.3
Chronic Lung Disease, n (%)	1083 (21.0)	752 (21.1)	331 (20.8)	0.7926	1.0
Current/Recent Smoker (< 1 year), n (%)	1016 (19.7)	696 (19.5)	320 (20.1)	0.6416	1.0
Diabetes Therapy, n (%)				**0.0033**	
None	133 (2.6)	87 (2.4)	46 (2.9)		1.2
Diet	464 (9.0)	344 (9.7)	120 (7.5)		0.8
Oral agent	2585 (50.1)	1814 (50.9)	771 (48.4)		1.0
Insulin treatment	1941 (37.6)	1301 (36.5)	640 (40.2)		1.1
Other	34 (0.7)	18 (0.5)	16 (1.0)		2.0
Currently on Dialysis, n (%)	232 (4.5)	152 (4.3)	80 (5.0)	0.2257	1.2
CAD Presentation (prior to PCI), n (%)				**<.0001**	
No symptom, no angina	528 (10.2)	375 (10.5)	153 (9.6)		0.9
Symptom unlikely to be ischemic	173 (3.4)	138 (3.9)	35 (2.2)		0.6
Stable angina	1054 (20.4)	724 (20.3)	330 (20.7)		1.0
Unstable angina	1639 (31.8)	1064 (29.8)	575 (36.1)		1.2
Non-STEMI	1257 (24.4)	897 (25.2)	360 (22.6)		0.9
STEMI with thrombolytics (7 days prior up to index PCI)	23 (0.4)	15 (0.4)	8 (0.5)		1.3
STEMI with no thrombolytics	486 (9.4)	353 (9.9)	133 (8.3)		0.8
Dominance, n (%)				0.0624	

Characteristic	Total (N=5160)	Repeat revascularization			
		No (n=3566)	Yes (n=1594)	p-value (nominal)	Effect size*
Left	402 (7.8)	296 (8.3)	106 (6.6)		0.8
Right	4314 (83.6)	2954 (82.8)	1360 (85.3)		1.0
Co-dominant	444 (8.6)	316 (8.9)	128 (8.0)		0.9
BMI (kg/m^2), mean (SD)	32.3 (6.9)	32.2 (6.9)	32.5 (6.8)	0.2985	*0.0*
LAB VARIABLES ----------					
Pre-Procedure Creatinine (mg/dL), mean (SD)	1.3 (1.2)	1.3 (1.1)	1.4 (1.5)	**0.0099**	*0.1*
Pre-Procedure Hemoglobin (g/dL), mean (SD)	13.0 (2.1)	12.9 (2.1)	13.0 (2.1)	0.3551	*0.0*
Lesion characteristics, mean (SD) ----------					
Number of arteries >= 50% stenosis	0.4 (0.6)	0.4 (0.6)	0.4 (0.6)	0.0512	*0.0*
Number of arteries >= 70% stenosis	2.4 (1.5)	2.3 (1.5)	2.7 (1.5)	**<.0001**	*0.3*
Total number of lesions attempted to be treated	1.4 (0.6)	1.3 (0.6)	1.4 (0.6)	0.6783	*0.2*
Number of lesions in LMCA segment	0.0 (0.2)	0.0 (0.2)	0.0 (0.2)	**0.0458**	*0.0*
Number of lesions in Proximal LAD segment	0.2 (0.4)	0.2 (0.4)	0.2 (0.4)	0.1538	*0.0*
Number of lesions in Proximal LCx segment	0.1 (0.3)	0.1 (0.3)	0.1 (0.3)	0.4749	*0.0*
Number of lesions in Proximal RCA segment	0.1 (0.3)	0.1 (0.3)	0.1 (0.3)	0.4565	*0.0*
Number of lesions in the rest of LAD segment	0.3 (0.5)	0.3 (0.5)	0.3 (0.5)	**0.0250**	*0.0*
Number of lesions in the rest of LCx segment	0.3 (0.5)	0.3 (0.5)	0.3 (0.5)	0.0614	*0.0*
Number of lesions in the rest of RCA segment	0.3 (0.6)	0.3 (0.6)	0.4 (0.6)	**0.0074**	*0.2*
Number of lesions in Ramus Intermedius segment	0.0 (0.2)	0.0 (0.2)	0.0 (0.2)	0.2656	*0.0*
Number of lesions with low complexity	0.5 (0.7)	0.5 (0.7)	0.5 (0.7)	0.5849	*0.0*
Number of lesions with high complexity	0.8 (0.7)	0.8 (0.7)	0.8 (0.7)	0.3503	*0.0*
Number of lesions that are bifurcated	0.3 (0.6)	0.3 (0.5)	0.3 (0.6)	0.6613	*0.0*
Number of lesions with thrombus	0.2 (0.4)	0.2 (0.4)	0.2 (0.4)	0.8688	*0.0*
Number of lesions with Chronic Total Occlusion	0.0 (0.2)	0.0 (0.2)	0.0 (0.2)	0.3875	*0.0*
Mean length of all lesions	22.1 (14.9)	22.3 (14.9)	21.8 (15.0)	0.2584	*0.0*
Proportion with at least 1 year of follow-up, n (%)[§]	4611 (89.4)	3100 (86.9)	1511 (94.8)	**<.0001**	1.1
Proportion with at least 2 years of follow-up, n (%)[§]	4006 (77.6)	2638 (74.0)	1368 (85.8)	**<.0001**	1.2
Proportion with at least 3 years of follow-up, n (%)[§]	3041 (58.9)	1890 (53.0)	1151 (72.2)	**<.0001**	1.4
Proportion with at least 4 years of follow-up, n (%)[§]	2240 (43.4)	1342 (37.6)	898 (56.3)	**<.0001**	1.5
Proportion with at least 5 years of follow-up, n (%)[§]	1554 (30.1)	881 (24.7)	673 (42.2)	**<.0001**	1.7
Proportion with at least 6 years of follow-up, n (%)[§]	975 (18.9)	532 (14.9)	443 (27.8)	**<.0001**	1.9
Proportion with at least 7 years of follow-up, n (%)[§]	465 (9.0)	228 (6.4)	237 (14.9)	**<.0001**	2.3
Time to repeat revascularization (years), mean (SD)			1.5 (1.6)		
Post-discharge death, n (%)	1368 (26.5)	957 (26.8)	411 (25.8)	0.4287	1.0
Overall follow-up time (years), mean (SD)[‡]	4.3 (2.1)	4.0 (2.1)	4.9 (2.1)	**<.0001**	0.4

*Effect size for continuous variables is the absolute value of Cohen's d (*in italics*). Effect size for categorical variables is Relative Ratio (proportion in repeat revascularization group/ proportion in non-repeat revascularization group).

[§]Based on date of last contact with UPMC hospital system.

[‡]Censored at date of death index search

1,368 out of the 5,160 patients included in our study died within the mean follow-up period of 4.3 years after the index PCI, with a mean time to death of 2.7 years (Table 20). More than half of our study population (52.2%) had at least 4 years of follow-up data (based on the date of death index search in 2020). At baseline (prior to index PCI) the group of patients who died within the follow-up period was older (71.4 years old vs. 65.7 years, p<.0001), and had lower proportions of patients who were male (62.9% vs. 66.6%, p=0.0117), had a family history of premature coronary artery disease (23.5% vs. 28.5%, p=0.0003), and who were current or recent smokers within the past year (17.0% vs. 20.6%, p=0.0039) compared to patients who remained alive throughout the follow-up period. Those who died also had higher proportions of patients with hypertension (94.7% vs. 91.6%, p=0.0002, small effect size), prior myocardial infarction (41.2% vs. 30.4%, p<.0001), prior heart failure (34.5% vs. 12.8%, p<.0001), heart failure within the 2 weeks preceding the index PCI (28.5% vs. 13.6%, p<.0001), prior valve surgery or procedure (4.8% vs. 2.2%, p<.0001), prior PCI (45.1% vs. 38.5%, p<.0001), prior CABG (33.6% vs. 22.3%, p<.0001), prior cerebrovascular disease (26.2% vs. 15.7%, p<.0001), prior peripheral arterial disease (27.7% vs. 11.8%, p<.0001), chronic lung disease (29.8% vs. 17.8%, p<.0001), and patients currently on dialysis (9.8% vs. 2.6%, p<.0001). Diabetes therapy and coronary artery disease presentation prior to PCI differed between the two groups of patients (p<.0001). Mean BMI (32.7 kg/m^2 vs. 31.2 kg/m^2, p<.0001) was higher in patients who were alive at the end of follow-up. Pre-procedure creatinine (1.7 mg/dL vs. 1.2 mg/dL, p<.0001) was higher in the group of patients who died while pre-procedure hemoglobin was lower (12.0 g/dL vs. 13.3 g/dL, p<.0001) compared to those who did not die. Patients who died also had more arteries with 70% or higher stenosis (mean 2.8 vs. 2.2, p<.0001), more lesions in the proximal RCA segment (mean 0.2 vs. 0.1, p=0.0003), a greater proportion of patients with 50% or higher stenosis in the left main (4.2% vs. 1.9%, p<.0001), and

a greater proportion of patients with 70% or higher stenosis (10.0% vs. 5.4%, p<.0001) when compared to the group of patients who did not die. The differences between the outcome groups in number of lesions in the left main coronary artery segment and in the rest of the LAD and LCx segments, in the number of high complexity lesions and lesions with chronic total occlusion, and in the mean lesion length were statistically significant but the effect sizes were small (Table 20).

Table 20 Death outcome: baseline data

		Death			
Characteristic	Total (N=5160)	No (n=3792)	Yes (n=1368)	p-value (nominal)	Effect size*
DEMOGRAPHIC VARIABLES ----------					
Age, mean (SD)	67.2 (10.9)	65.7 (10.7)	71.4 (10.5)	**<.0001**	*0.5*
Male, n (%)	3387 (65.6)	2527 (66.6)	860 (62.9)	**0.0117**	0.9
Race, n (%)				0.1214	
White	4686 (90.8)	3435 (90.6)	1251 (91.5)		1.0
Black	427 (8.3)	317 (8.4)	110 (8.0)		1.0
Other	45 (0.9)	39 (1.0)	6 (0.4)		0.4
Hypertension, n (%)	4768 (92.4)	3473 (91.6)	1295 (94.7)	**0.0002**	1.0
Dyslipidemia, n (%)	4491 (87.0)	3300 (87.0)	1191 (87.1)	0.9728	1.0
Family History of Premature CAD, n (%)	1401 (27.2)	1080 (28.5)	321 (23.5)	**0.0003**	0.8
Prior MI, n (%)	1717 (33.3)	1153 (30.4)	564 (41.2)	**<.0001**	1.4
Prior Heart Failure, n (%)	957 (18.6)	486 (12.8)	471 (34.5)	**<.0001**	2.7
Heart failure within prior 2 weeks	905 (17.5)	515 (13.6)	390 (28.5)	**<.0001**	2.1
Prior Valve Surgery/Procedure, n (%)	149 (2.9)	84 (2.2)	65 (4.8)	**<.0001**	2.2
Prior PCI, n (%)	2077 (40.3)	1461 (38.5)	616 (45.1)	**<.0001**	1.2
Prior CABG, n (%)	1304 (25.3)	844 (22.3)	460 (33.6)	**<.0001**	1.5
Prior Cerebrovascular Disease, n (%)	953 (18.5)	595 (15.7)	358 (26.2)	**<.0001**	1.7
Prior Peripheral Arterial Disease, n (%)	828 (16.0)	449 (11.8)	379 (27.7)	**<.0001**	2.3
Chronic Lung Disease, n (%)	1083 (21.0)	675 (17.8)	408 (29.8)	**<.0001**	1.7
Current/Recent Smoker (< 1 year), n (%)	1016 (19.7)	783 (20.6)	233 (17.0)	**0.0039**	0.8
Diabetes Therapy, n (%)					
None	133 (2.6)	104 (2.7)	29 (2.1)	**<.0001**	0.8
Diet	464 (9.0)	360 (9.5)	104 (7.6)		0.8
Oral agent	2585 (50.1)	2040 (53.8)	545 (39.9)		0.7
Insulin treatment	1941 (37.6)	1269 (33.5)	672 (49.2)		1.5
Other	34 (0.7)	19 (0.5)	15 (1.1)		2.2
Currently on Dialysis, n (%)	232 (4.5)	98 (2.6)	134 (9.8)	**<.0001**	3.8
CAD Presentation (prior to PCI), n (%)					
No symptom, no angina	528 (10.2)	326 (8.6)	202 (14.8)	**<.0001**	1.7
Symptom unlikely to be ischemic	173 (3.4)	122 (3.2)	51 (3.7)		1.2

Characteristic	Total (N=5160)	Death			
		No (n=3792)	Yes (n=1368)	p-value (nominal)	Effect size*
Stable angina	1054 (20.4)	838 (22.1)	216 (15.8)		0.7
Unstable angina	1639 (31.8)	1204 (31.8)	435 (31.8)		1.0
Non-STEMI	1257 (24.4)	897 (23.7)	360 (26.3)		1.1
STEMI with thrombolytics (7 days prior up to index PCI)	23 (0.4)	20 (0.5)	3 (0.2)		0.4
STEMI with no thrombolytics	486 (9.4)	385 (10.2)	101 (7.4)		0.7
Dominance, n (%)					
Left	402 (7.8)	281 (7.4)	121 (8.8)	0.2098	1.2
Right	4314 (83.6)	3179 (83.8)	1135 (83)		1.0
Co-dominant	444 (8.6)	332 (8.8)	112 (8.2)		0.9
BMI (kg/m^2), mean (SD)	32.3 (6.9)	32.7 (6.8)	31.2 (7.0)	**<.0001**	*0.2*
LAB VARIABLES ----------					
Pre-Procedure Creatinine (mg/dL), mean (SD)	1.3 (1.2)	1.2 (1.0)	1.7 (1.6)	**<.0001**	*0.4*
Pre-Procedure Hemoglobin (g/dL), mean (SD)	13.0 (2.1)	13.3 (2.0)	12.0 (2.0)	**<.0001**	*0.6*
Lesion characteristics, mean (SD) ----------					
Number of arteries >= 50% stenosis	0.4 (0.6)	0.4 (0.6)	0.4 (0.6)	0.5171	*0.0*
Number of arteries >= 70% stenosis	2.4 (1.5)	2.2 (1.4)	2.8 (1.6)	**<.0001**	*0.4*
Total number of lesions attempted to be treated	1.4 (0.6)	1.3 (0.6)	1.4 (0.6)	0.1126	*0.2*
Number of lesions in LMCA segment	0.0 (0.2)	0.0 (0.2)	0.0 (0.2)	**0.0086**	*0.0*
Number of lesions in Proximal LAD segment	0.2 (0.4)	0.2 (0.4)	0.2 (0.4)	0.0848	*0.0*
Number of lesions in Proximal LCx segment	0.1 (0.3)	0.1 (0.3)	0.1 (0.3)	0.3155	*0.0*
Number of lesions in Proximal RCA segment	0.1 (0.3)	0.1 (0.3)	0.2 (0.4)	**0.0003**	*0.3*
Number of lesions in the rest of LAD segment	0.3 (0.5)	0.3 (0.5)	0.3 (0.5)	**0.0148**	*0.0*
Number of lesions in the rest of LCx segment	0.3 (0.5)	0.3 (0.5)	0.3 (0.5)	**0.0122**	*0.0*
Number of lesions in the rest of RCA segment	0.3 (0.6)	0.3 (0.6)	0.3 (0.6)	0.1242	*0.0*
Number of lesions in Ramus Intermedius segment	0.0 (0.2)	0.0 (0.2)	0.0 (0.2)	0.0878	*0.0*
Number of lesions with low complexity	0.5 (0.7)	0.5 (0.7)	0.5 (0.7)	0.2290	*0.0*
Number of lesions with high complexity	0.8 (0.7)	0.8 (0.7)	0.9 (0.7)	**0.0084**	*0.1*
Number of lesions that are bifurcated	0.3 (0.6)	0.3 (0.6)	0.3 (0.5)	0.3403	*0.0*
Number of lesions with thrombus	0.2 (0.4)	0.2 (0.4)	0.1 (0.4)	0.1828	*0.3*
Number of lesions with Chronic Total Occlusion	0.0 (0.2)	0.0 (0.2)	0.0 (0.2)	**0.0016**	*0.0*
Mean length of all lesions	22.1 (14.9)	22.5 (15.3)	20.9 (14.0)	**0.0005**	*0.1*
>= 50% stenosis in left main, n (%)	117 (2.5)	65 (1.9)	52 (4.2)	**<.0001**	2.2
>= 70% stenosis in left main, n (%)	313 (6.7)	188 (5.4)	125 (10.0)	**<.0001**	1.9
Follow-up time in years, mean (SD)	4.3 (2.1)	4.9 (1.9)	2.7 (1.9)	**<.0001**	*1.0*
Proportion with at least 1 year of follow-up, n (%)	4845 (93.9)	3792 (100.0)	1053 (77.0)	**<.0001**	0.8
Proportion with at least 2 years of follow-up, n (%)	4476 (86.7)	3686 (97.2)	790 (57.7)	**<.0001**	0.6
Proportion with at least 3 years of follow-up, n (%)	3519 (68.2)	2984 (78.7)	535 (39.1)	**<.0001**	0.5
Proportion with at least 4 years of follow-up, n (%)	2692 (52.2)	2325 (61.3)	367 (26.8)	**<.0001**	0.4

Characteristic	Total (N=5160)	Death			
		No (n=3792)	Yes (n=1368)	p-value (nominal)	Effect size*
Proportion with at least 5 years of follow-up, n (%)	1929 (37.4)	1717 (45.3)	212 (15.5)	**<.0001**	0.3
Proportion with at least 6 years of follow-up, n (%)	1285 (24.9)	1186 (31.3)	99 (7.2)	**<.0001**	0.2
Proportion with at least 7 years of follow-up, n (%)	652 (12.6)	619 (16.3)	33 (2.4)	**<.0001**	0.1
Time to death (years), mean (SD)			2.7 (1.9)		
Repeat revascularization, n (%)	1594 (30.9)	1183 (31.2)	411 (30.0)	0.4287	1.0

*Effect size for continuous variables is the absolute value of Cohen's d (*in italics*). Effect size for categorical variables is Relative Ratio (proportion in repeat revascularization group/ proportion in non-repeat revascularization group).

After splitting our study population 80/20 into Training and Test sets, there were 4,128 patients in the Training set and 1,032 patients in the Test set. The data sets were well balanced with no statistically significant differences in baseline characteristics or in outcomes (repeat revascularization and death) between the two data sets (Table 21).

Table 21 Comparison of baseline data between Training and Test data sets

Characteristic	Total (N=5160)	Training Set (n=4128)	Test Set (n=1032)	p-value (nominal)	Effect size*
DEMOGRAPHIC VARIABLES ----------					
Age, mean (SD)	67.2 (10.9)	67.3 (10.9)	67.1 (11.0)	0.7516	*0.0*
Male, n (%)	3387 (65.6)	2695 (65.3)	692 (67.1)	0.2847	1.0
Race, n (%)				0.4298	
White	4686 (90.8)	3755 (91.0)	931 (90.2)		1.0
Black	427 (8.3)	333 (8.1)	94 (9.1)		1.1
Other	45 (0.9)	38 (0.9)	7 (0.7)		0.8
Hypertension, n (%)	4768 (92.4)	3815 (92.4)	953 (92.3)	0.9372	1.0
Dyslipidemia, n (%)	4491 (87.0)	3590 (87.0)	901 (87.3)	0.7717	1.0
Family History of Premature CAD, n (%)	1401 (27.2)	1105 (26.8)	296 (28.7)	0.2163	1.1
Prior MI, n (%)	1717 (33.3)	1374 (33.3)	343 (33.2)	0.9764	1.0
Prior Heart Failure, n (%)	957 (18.6)	769 (18.6)	188 (18.2)	0.7583	1.0
Heart failure in 2 weeks prior to index PCI, n (%)	905 (17.5)	716 (17.3)	189 (18.3)	0.4641	1.1
Prior Valve Surgery/Procedure, n (%)	149 (2.9)	116 (2.8)	33 (3.2)	0.5060	1.1
Prior PCI, n (%)	2077 (40.3)	1679 (40.7)	398 (38.6)	0.2148	0.9
Prior CABG, n (%)	1304 (25.3)	1041 (25.2)	263 (25.5)	0.8601	1.0
Prior Cerebrovascular Disease, n (%)	953 (18.5)	763 (18.5)	190 (18.4)	0.9571	1.0
Prior Peripheral Arterial Disease, n (%)	828 (16.0)	656 (15.9)	172 (16.7)	0.5439	1.1

Characteristic	Total (N=5160)	Training Set (n=4128)	Test Set (n=1032)	p-value (nominal)	Effect size*
Chronic Lung Disease, n (%)	1083 (21.0)	867 (21.0)	216 (20.9)	0.9591	1.0
Current/Recent Smoker (< 1 year), n (%)	1016 (19.7)	805 (19.5)	211 (20.4)	0.4948	1.0
Diabetes Therapy, n (%)				0.7994	
None	133 (2.6)	105 (2.5)	28 (2.7)		1.1
Diet	464 (9.0)	369 (8.9)	95 (9.2)		1.0
Oral agent	2585 (50.1)	2065 (50.1)	520 (50.4)		1.0
Insulin treatment	1941 (37.6)	1556 (37.7)	385 (37.3)		1.0
Other	34 (0.7)	30 (0.7)	4 (0.4)		0.6
Currently on Dialysis, n (%)	232 (4.5)	190 (4.6)	42 (4.1)	0.4599	0.9
CAD Presentation (prior to PCI), n (%)				0.8746	
No symptom, no angina	528 (10.2)	434 (10.5)	94 (9.1)		0.9
Symptom unlikely to be ischemic	173 (3.4)	136 (3.3)	37 (3.6)		1.1
Stable angina	1054 (20.4)	834 (20.2)	220 (21.3)		1.1
Unstable angina	1639 (31.8)	1312 (31.8)	327 (31.7)		1.0
Non-STEMI	1257 (24.4)	1003 (24.3)	254 (24.6)		1.0
STEMI with thrombolytics (7 days prior up to index PCI)	23 (0.4)	18 (0.4)	5 (0.5)		1.3
STEMI with no thrombolytics	486 (9.4)	391 (9.5)	95 (9.2)		1.0
Dominance, n (%)				0.8104	
Left	402 (7.8)	319 (7.7)	83 (8.0)		1.0
Right	4314 (83.6)	3458 (83.8)	856 (82.9)		1.0
Co-dominant	444 (8.6)	351 (8.5)	93 (9.0)		1.1
BMI (kg/m^2), mean (SD)	32.3 (6.9)	32.3 (6.8)	32.4 (7.1)	0.4732	*0.0*
LAB VARIABLES ----------					
Pre-Procedure Creatinine (mg/dL), mean (SD)	1.3 (1.2)	1.3 (1.3)	1.3 (1.2)	0.6094	*0.0*
Pre-Procedure Hemoglobin (g/dL), mean (SD)	13.0 (2.1)	13.0 (2.1)	13.0 (2.0)	0.8846	*0.0*
Lesion characteristics, mean (SD) ----------					
Number of arteries >= 50% stenosis	0.4 (0.6)	0.4 (0.6)	0.4 (0.6)	0.4757	*0.0*
Number of arteries >= 70% stenosis	2.4 (1.5)	2.4 (1.5)	2.4 (1.5)	0.8644	*0.0*
Total number of lesions attempted to be treated	1.4 (0.6)	1.4 (0.6)	1.3 (0.6)	0.4767	*0.2*
Number of lesions in LMCA segment	0.0 (0.2)	0.0 (0.2)	0.0 (0.2)	0.6924	*0.0*
Number of lesions in Proximal LAD segment	0.2 (0.4)	0.2 (0.4)	0.2 (0.4)	0.1535	*0.0*
Number of lesions in Proximal LCx segment	0.1 (0.3)	0.1 (0.3)	0.1 (0.3)	0.4609	*0.0*
Number of lesions in Proximal RCA segment	0.1 (0.3)	0.1 (0.3)	0.1 (0.3)	0.7449	*0.0*
Number of lesions in the rest of LAD segment	0.3 (0.5)	0.3 (0.5)	0.3 (0.5)	0.5707	*0.0*
Number of lesions in the rest of LCx segment	0.3 (0.5)	0.3 (0.5)	0.3 (0.5)	0.6177	*0.0*
Number of lesions in the rest of RCA segment	0.3 (0.6)	0.3 (0.6)	0.3 (0.5)	0.9803	*0.0*
Number of lesions in Ramus Intermedius segment	0.0 (0.2)	0.0 (0.2)	0.0 (0.2)	0.8682	*0.0*
Number of lesions with low complexity	0.5 (0.7)	0.5 (0.7)	0.5 (0.7)	0.9836	*0.0*
Number of lesions with high complexity	0.8 (0.7)	0.8 (0.7)	0.8 (0.7)	0.5396	*0.0*
Number of lesions that are bifurcated	0.3 (0.6)	0.3 (0.6)	0.3 (0.5)	0.1443	*0.0*
Number of lesions with thrombus	0.2 (0.4)	0.2 (0.4)	0.2 (0.4)	0.7490	*0.0*
Number of lesions with Chronic Total Occlusion	0.0 (0.2)	0.0 (0.2)	0.1 (0.2)	0.1974	*0.5*

Characteristic	Total (N=5160)	Training Set (n=4128)	Test Set (n=1032)	p-value (nominal)	Effect size*
Mean length of all lesions	22.1 (14.9)	22.3 (15.1)	21.4 (14.5)	0.0990	*0.1*
Outcome: Repeat revascularization					
Follow-up time in years, mean (SD)	3.8 (2.2)	3.8 (2.2)	3.8 (2.1)	0.7436	*0.0*
Repeat revascularization, n (%)	1594 (30.9)	1273 (30.8)	321 (31.1)	0.8684	1.0
Time to repeat revascularization (years), mean (SD)	2.9 (2.2)	2.9 (2.2)	2.8 (2.1)	0.7982	*0.0*
Proportion with at least 1 year of follow-up, n (%)	4611 (89.4)	3682 (89.2)	929 (90.0)	0.4428	1.0
Proportion with at least 2 years of follow-up, n (%)	4006 (77.6)	3196 (77.4)	810 (78.5)	0.4623	1.0
Proportion with at least 3 years of follow-up, n (%)	3041 (58.9)	2434 (59.0)	607 (58.8)	0.9323	1.0
Proportion with at least 4 years of follow-up, n (%)	2240 (43.4)	1800 (43.6)	440 (42.6)	0.5743	1.0
Proportion with at least 5 years of follow-up, n (%)	1554 (30.1)	1256 (30.4)	298 (28.9)	0.3315	1.0
Proportion with at least 6 years of follow-up, n (%)	975 (18.9)	790 (19.1)	185 (17.9)	0.3740	0.9
Proportion with at least 7 years of follow-up, n (%)	465 (9.0)	372 (9.0)	93 (9.0)	1.0000	1.0
Outcome: Death					
Follow-up time in years, mean (SD)	4.3 (2.1)	4.3 (2.1)	4.3 (2.1)	0.9915	*0.0*
Death, n (%)	1368 (26.5)	1089 (26.4)	279 (27.0)	0.6703	1.0
Proportion with at least 1 year of follow-up, n (%)	4845 (93.9)	3873 (93.8)	972 (94.2)	0.6628	1.0
Proportion with at least 2 years of follow-up, n (%)	4476 (86.7)	3570 (86.5)	906 (87.8)	0.2677	1.0
Proportion with at least 3 years of follow-up, n (%)	3519 (68.2)	2824 (68.4)	695 (67.3)	0.5108	1.0
Proportion with at least 4 years of follow-up, n (%)	2692 (52.2)	2154 (52.2)	538 (52.1)	0.9778	1.0
Proportion with at least 5 years of follow-up, n (%)	1929 (37.4)	1549 (37.5)	380 (36.8)	0.6765	1.0
Proportion with at least 6 years of follow-up, n (%)	1285 (24.9)	1031 (25.0)	254 (24.6)	0.8092	1.0
Proportion with at least 7 years of follow-up, n (%)	652 (12.6)	522 (12.6)	130 (12.6)	0.9666	1.0

*Effect size for continuous variables is the absolute value of Cohen's d (*in italics*). Effect size for categorical variables is Relative Ratio (proportion in repeat revascularization group/ proportion in non-repeat revascularization group).

5.4.2 Repeat revascularization: Training data CART and risk estimation

We used our Training data set (n=4128) to build the classification tree for our outcome of repeat revascularization. The number of arteries with 70% or higher stenosis was selected as the top split. After growing the tree until the stopping criteria were met, 16 terminal nodes were generated from the CART analysis (Figure 8 and Figure 9). None of the nodes met the criteria for pruning. We assigned each patient into one of the 16 profiles, whereby patients in each profile met all the criteria along the branch leading up to the terminal node. For example, a patient in Profile

1 must have had 3 or more arteries with 70% or higher stenosis, must have been younger than 70 years old, must have had 1 or more class C lesions and must have had unstable angina at baseline (prior to index PCI). We compared these profiles in Cox regression analysis with Profile 16 designated as the reference group. All profiles, with the exception of Profile 15, had statistically higher hazard ratios than the reference Profile 16 (HR ranging from 1.72 to 5.64, Figure 8 and Figure 9). We also compared Profile 16 to all other profiles in a Cox regression (Profiles 1-15 were the reference; HR 0.35, p<.0001).

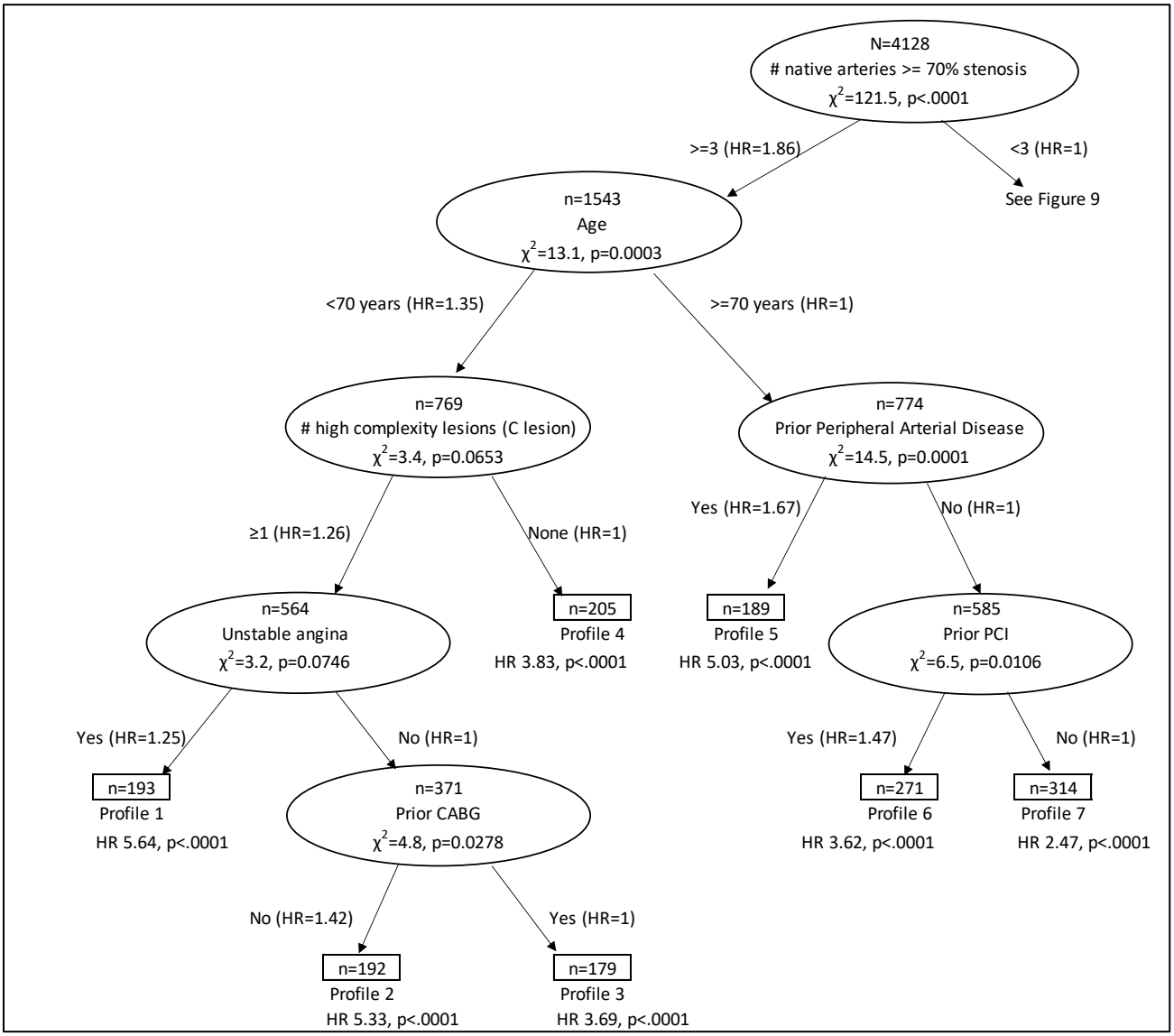


Figure 8 Repeat revascularization: Left branch of classification tree

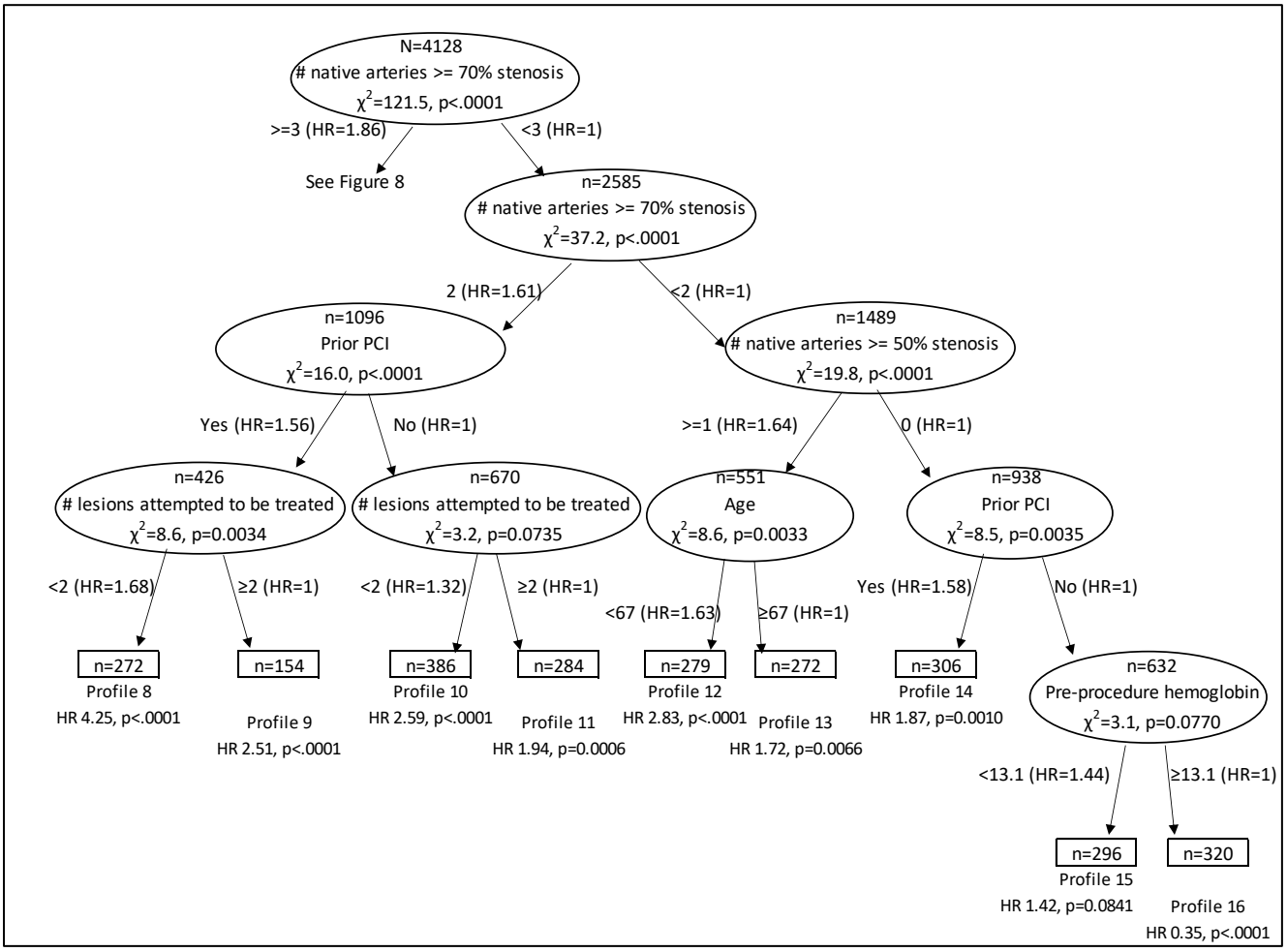


Figure 9 Repeat revascularization: Right branch of classification tree

Table 23 compares the repeat revascularization risk estimates for each profile, calculated at 0.5 to 7 years using parameter estimates from the Cox regressions of the classification tree terminal nodes and the survival estimates shown in Table 22, to the observed event rates from Kaplan Meier estimation. Both the risk estimates and event rates show that patients who met the criteria of Profile 1 had the highest risk estimates and event rates at each time point compared to

patients who fell under the other profiles, while patients under Profile 16 had the lowest risk estimates and event rates.

Table 22 Repeat revascularization: Kaplan Meier survival estimates for all patients in training set

Time point	Survival estimate
0.5 year	0.876
1 year	0.832
2 years	0.765
3 years	0.708
4 years	0.665
5 years	0.620
6 years	0.596
7 years	0.559

Table 23 Repeat revascularization: Risk estimate vs. event rate in profiles at specified time points

		0.5 year		1 year		2 year		3 year		4 year		5 year		6 year		7 year	
Profile	β (log hazard ratio)	Cox	K-M	Cox	K-M	Cox	K-M	Cox	K-M	Cox	K-M	Cox	K-M	Cox	K-M	Cox	K-M
1	1.730	27%	24%	35%	32%	47%	44%	56%	51%	62%	57%	68%	62%	71%	67%	75%	67%
2	1.674	26%	31%	34%	34%	45%	41%	54%	46%	60%	53%	66%	55%	69%	58%	73%	62%
3	1.307	19%	14%	25%	20%	34%	31%	41%	39%	47%	44%	52%	50%	55%	50%	59%	50%
4	1.343	19%	15%	26%	24%	35%	30%	43%	37%	48%	43%	54%	49%	56%	52%	61%	59%
5	1.616	24%	21%	32%	29%	43%	41%	52%	50%	58%	53%	64%	56%	66%	56%	71%	56%
6	1.286	18%	16%	24%	21%	33%	30%	41%	37%	46%	42%	52%	46%	54%	49%	59%	56%
7	0.902	13%	13%	17%	15%	24%	20%	30%	26%	34%	30%	39%	31%	41%	34%	45%	45%
8	1.447	21%	20%	28%	25%	38%	33%	46%	39%	52%	46%	57%	53%	60%	55%	64%	62%
9	0.922	13%	10%	18%	15%	25%	23%	30%	31%	35%	32%	40%	34%	42%	34%	46%	34%
10	0.951	13%	15%	18%	17%	25%	22%	31%	28%	36%	32%	40%	35%	43%	37%	47%	39%
11	0.663	10%	9%	14%	11%	20%	17%	24%	21%	28%	27%	32%	32%	34%	32%	38%	32%
12	1.041	15%	7%	20%	13%	27%	20%	34%	30%	38%	36%	43%	41%	46%	44%	50%	54%
13	0.541	9%	5%	12%	9%	18%	13%	22%	18%	25%	21%	29%	29%	31%	30%	34%	34%
14	0.626	10%	5%	13%	10%	19%	17%	24%	20%	27%	24%	31%	29%	33%	33%	37%	33%
15	0.353	8%	5%	10%	8%	15%	14%	19%	17%	22%	19%	25%	23%	27%	23%	29%	26%
16	-1.042	2%	5%	3%	7%	4%	9%	5%	11%	6%	13%	7%	16%	7%	20%	8%	22%

*β estimates for Profiles 1-15 were generated by comparing these profiles to the reference profile (Profile 16) in Cox regression. The β estimate for Profile 16 was generated by comparing this profile to all other profiles in Cox regression. "Cox" refers to the Cox regression risk estimate. "K-M" is the Kaplan Meier event rate.

5.4.3 Repeat revascularization: Training data risk model assessment

The discriminative ability of the Cox risk estimates for repeat revascularization in the Training data is shown in Table 24. The overall Uno's concordance statistic was 0.62 while the time-dependent AUC ranged from 0.67 at 0.5-year follow-up to 0.62 at 7 years of follow-up. The Cox risk estimates were generally well calibrated across all time points compared to the Kaplan Meier event rates, with slight underestimation of risk at the lower range of event rates and slight over-estimation of risk in the remaining range (Figure 10).

Table 24 Repeat revascularization: Discrimination in Training data

Year	Uno's concordance statistic	Standard error	AUC
0.5	0.62	0.0109	0.67
1	0.62	0.0081	0.66
2	0.62	0.0092	0.66
3	0.62	0.0097	0.66
4	0.62	0.0082	0.66
5	0.62	0.0086	0.65
6	0.62	0.0080	0.64
7	0.62	0.0113	0.62

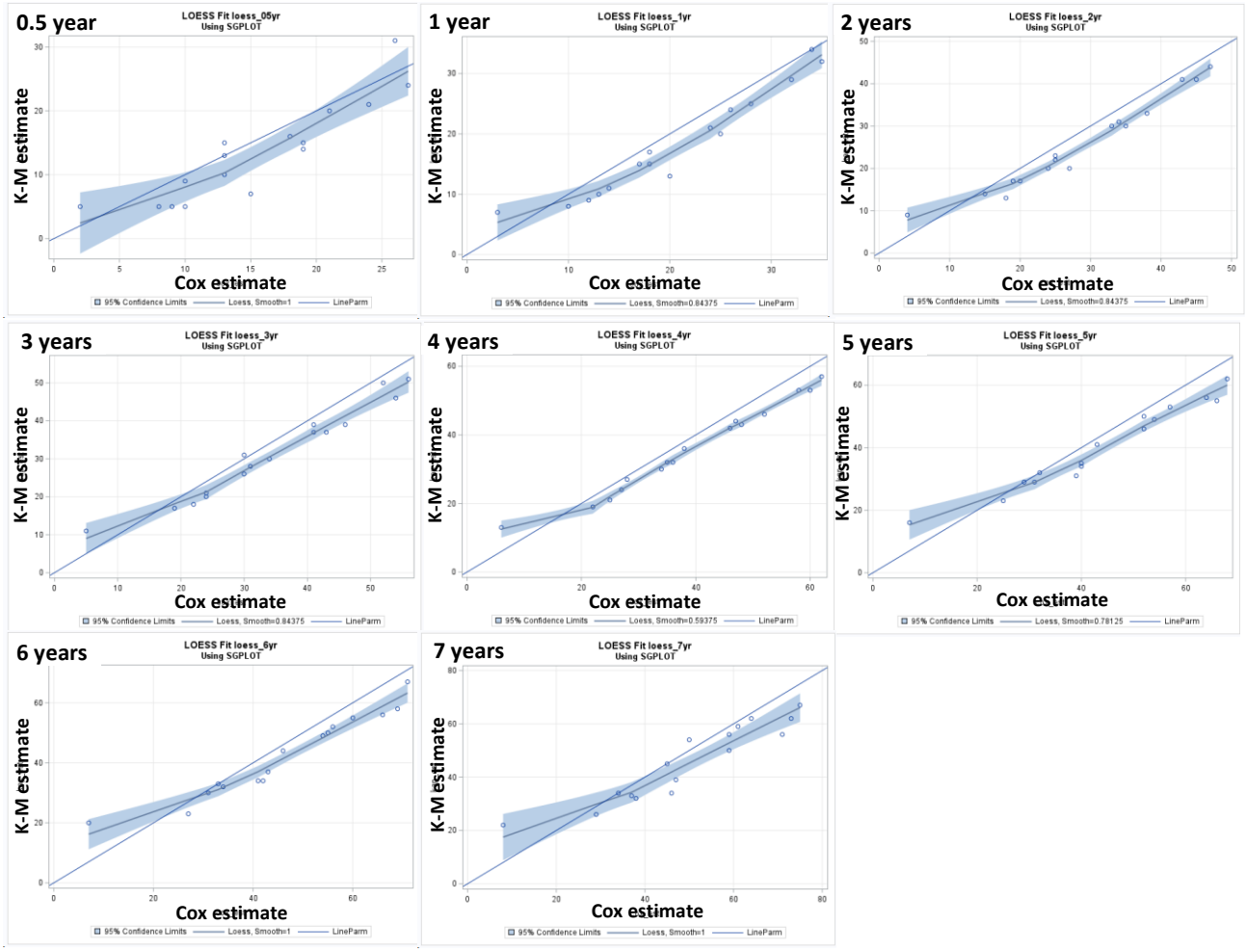


Figure 10 Repeat revascularization: Training data calibration plots

5.4.4 Repeat revascularization: Internal validation of risk model

Table 25 shows the discrimination of the absolute Cox risk estimates, as estimated in the Training data, when applied to the Test data set. The overall concordance statistic was similar to the overall statistic in the Training data (0.61 in Test data vs. 0.62 in Training data). However, the time-dependent AUC of the risk estimates when applied to the Test data set were lower at each time point than what was observed in the Training data (range 0.57 to 0.63 in Test data vs. 0.62 to 0.67 in Training data).

Table 25 Repeat revascularization: Discrimination in Test data

Year	Uno's concordance statistic	Standard error	AUC
0.5	0.61	0.0203	0.57
1	0.61	0.0223	0.60
2	0.61	0.0277	0.61
3	0.61	0.0200	0.62
4	0.61	0.0255	0.63
5	0.61	0.0220	0.62
6	0.61	0.0172	0.60
7	0.61	0.0197	0.61

Calibration of the absolute Cox risk estimates, as estimated in the Training data, is shown in Figure 11. The calibration plots in the Test data had wider confidence intervals than what was observed in the Training data, with tightening confidence intervals at incremental time points. As in the Training data, the calibration plots in the Test data show slight underestimation at the lower range of event rates and slight overestimation in the remaining range.

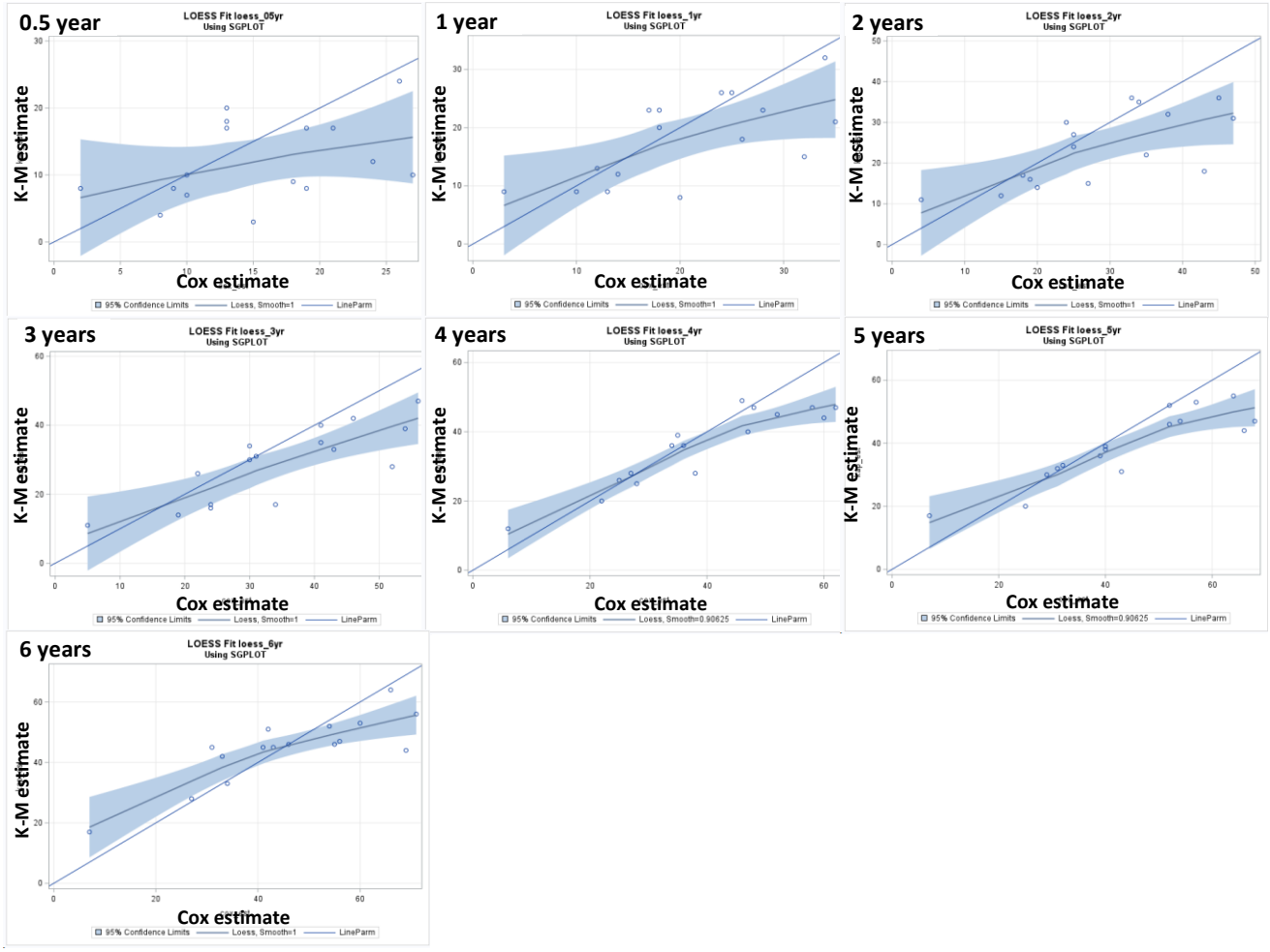


Figure 11 Repeat revascularization: Test data calibration plots

5.4.5 Repeat revascularization: prognostic tool development

The risk estimates showed similar discrimination and calibration across most time points. Therefore, we opted to construct our prognostic tool based on 1-year risk estimates for repeat revascularization (Figure 12 and Figure 13). Absolute risk estimates designated as "Low" risk level ranged from 0% to 12%, Moderate from 13 to 24% and High from 25 to 35%. We collapsed decision points following the "Yes" selection for decision point "Less than 70 years old", "No" for "Prior Peripheral Arterial Disease" and "No" for "Prior PCI" because they terminated in risk

estimates that fell within the same risk level. Due to the large number of decision points, we split our risk flow chart into 2 separate "sides", namely side A (Figure 12) and side B (Figure 13). Patients with elevated risk for repeat revascularization in the Training data set were (i) those with 3 or more arteries with 70% stenosis or higher and who were less than 70 years old (25-35% risk), (ii) those with 3 or more arteries with 70% stenosis or higher, and who were less than 70 years old and had prior peripheral arterial disease (32% risk), and (iii) those with 2 arteries with 70% or higher stenosis, and who had prior PCI and had 2 or less lesions that were being attempted for treatment (28% risk).

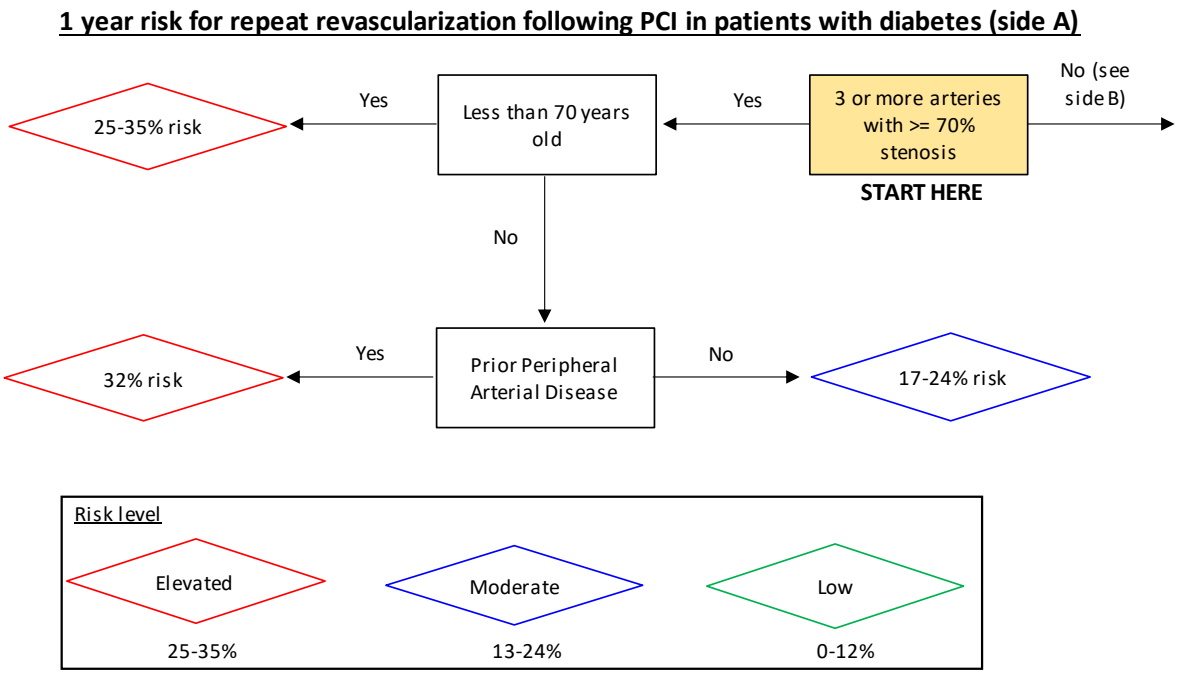


Figure 12 Risk flow chart showing 1 year risk for repeat revascularization following PCI in patients with diabetes (side A)

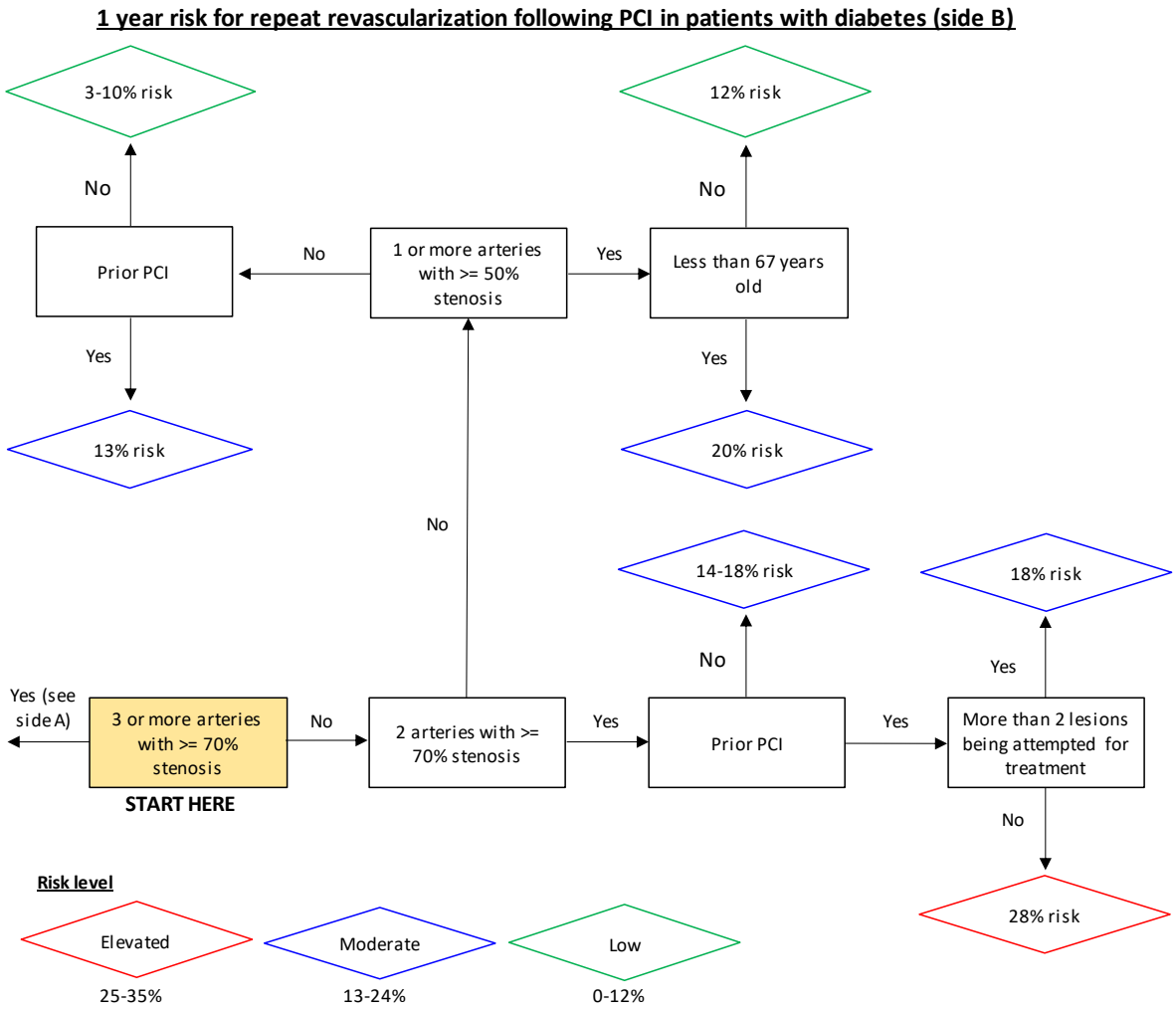


Figure 13 Risk flow chart showing 1 year risk for repeat revascularization following PCI in patients with diabetes (side B)

5.4.6 Death: Training data CART and risk estimation

We used our Training data set (n=4128) to build the classification tree for our outcome of death. Prior heart failure was selected as the top split and we excluded 1 patient who was missing information on prior heart failure. After growing the tree until the stopping criteria were met, 18 terminal nodes were generated from the CART analysis (data not shown). One node met the criteria for pruning, resulting in a final tree with 17 terminal nodes (Figure 14, Figure 15, Figure 16). We

assigned each patient into one of the 17 profiles, whereby patients in each profile met all the criteria along the branch leading up to the terminal node. For example, a patient in Profile 1 must have had prior heart failure and pre-procedure creatinine of 1.70 mg/dL or higher at baseline (prior to index PCI). We compared these profiles in Cox regression analysis with Profile 17 designated as the reference group. All profiles, with the exception of Profiles 10 and 14, had statistically higher hazard ratios than the reference Profile 17 (HR ranging from 1.84 to 20.81, Figure 14, Figure 15 and Figure 16). We also compared Profile 17 to all other profiles in a Cox regression (Profiles 1-16 were the reference; HR 0.13, p<.0001).

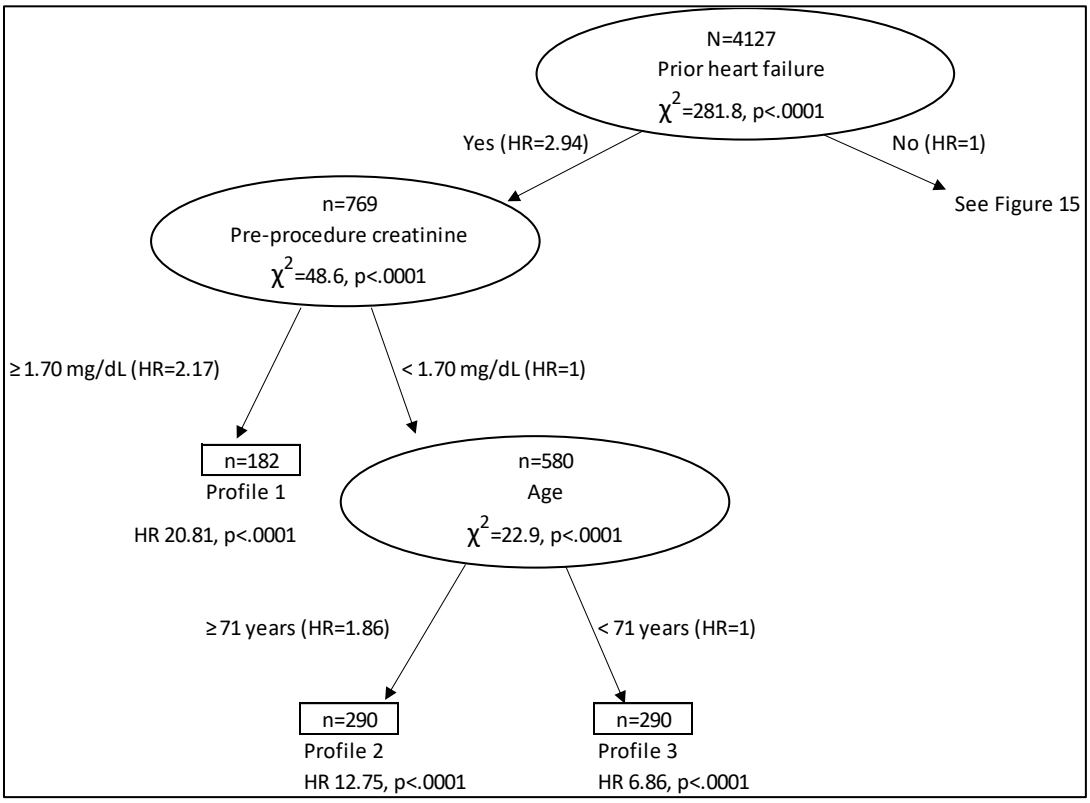


Figure 14 Death: Left branch of classification tree

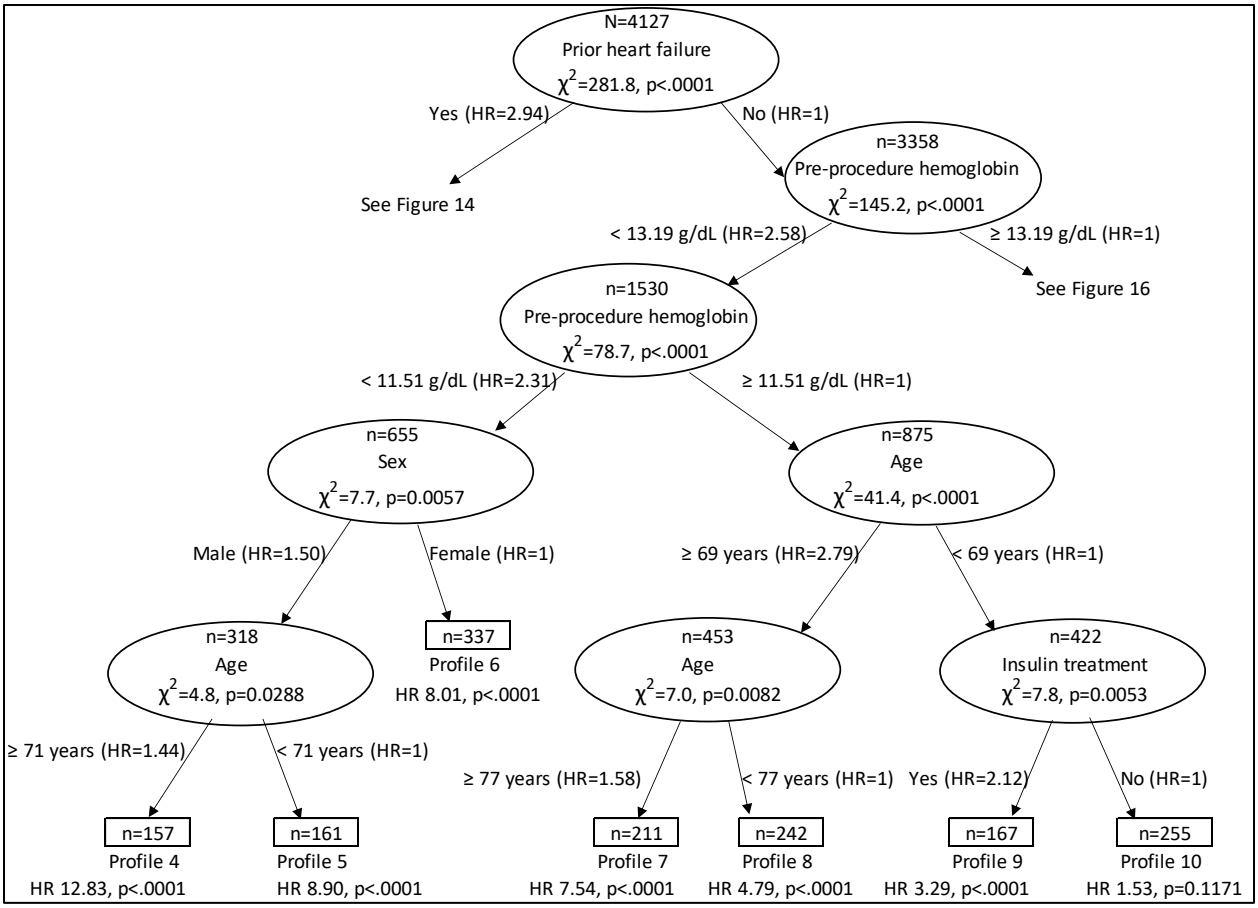


Figure 15 Death: Right branch (a) of classification tree

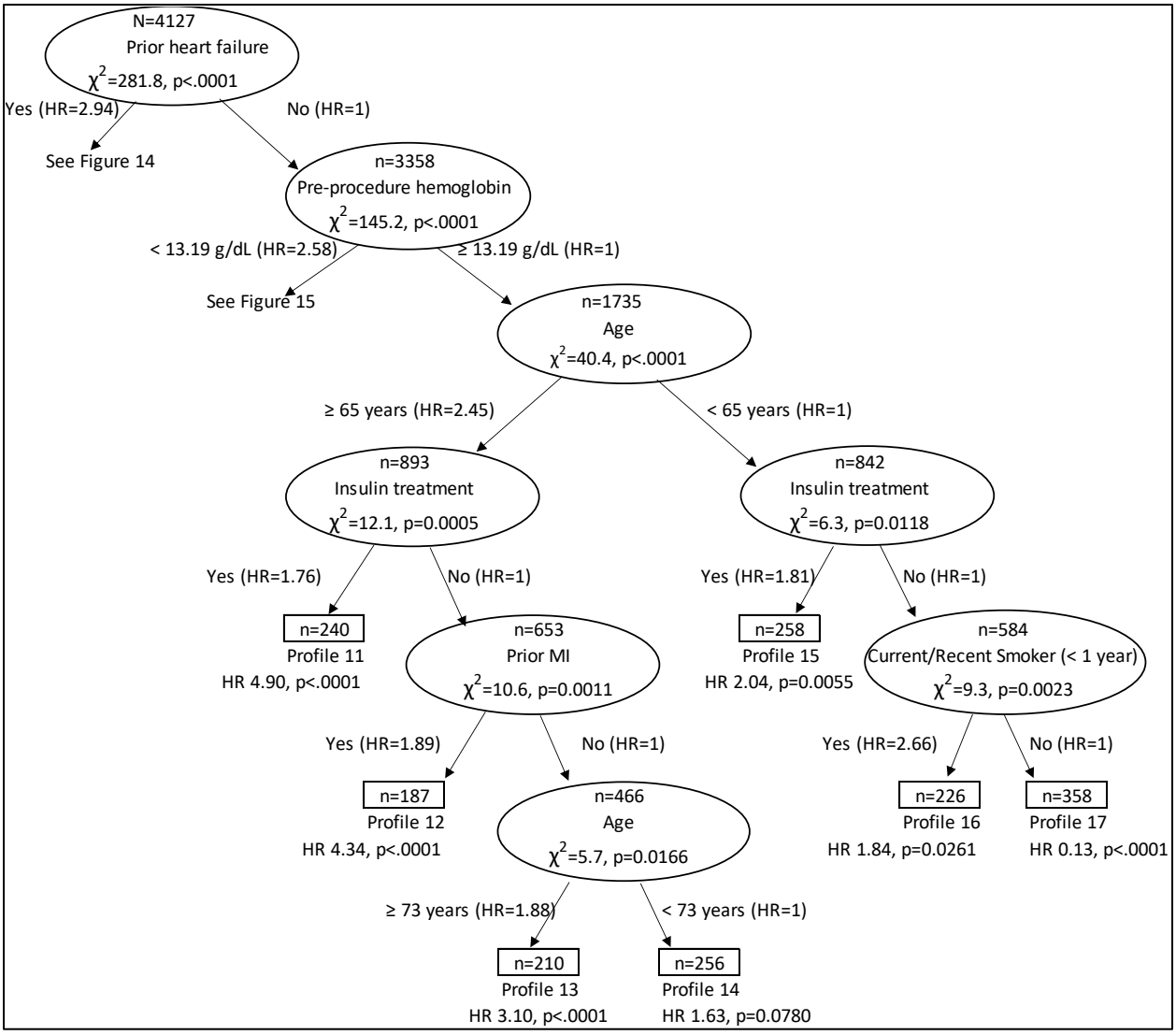


Figure 16 Right branch (b) of classification tree

Table 27 compares the death risk estimates for each profile, calculated at 0.5 to 7 years using parameter estimates from the Cox regressions of the classification tree terminal nodes and the survival estimates shown in Table 26, to the observed event rates from Kaplan Meier estimation. Both the risk estimates and event rates show that patients who met the criteria of Profile 1 had the highest risk estimates and event rates at each time point compared to patients who fell

under the other profiles, while patients in Profile 17 generally had the lowest risk estimates and event rates.

Table 26 Death: Kaplan Meier survival estimates for all patients in training set

Time point	Survival estimate
0.5 year	0.970
1 year	0.938
2 years	0.886
3 years	0.833
4 years	0.789
5 years	0.738
6 years	0.689
7 years	0.647

Table 27 Death: Risk estimate vs. event rate in profiles at specified time points

		0.5 year		1 year		2 year		3 year		4 year		5 year		6 year		7 year	
Profile	β (log hazard ratio)	Cox	K-M	Cox	K-M	Cox	K-M	Cox	K-M	Cox	K-M	Cox	K-M	Cox	K-M	Cox	K-M
1	3.035	17%	14%	32%	27%	53%	42%	68%	53%	77%	62%	85%	68%	90%	73%	93%	79%
2	2.546	11%	7%	21%	11%	37%	23%	50%	37%	59%	44%	68%	53%	76%	64%	81%	67%
3	1.925	6%	2%	12%	6%	22%	12%	31%	22%	38%	28%	46%	34%	53%	40%	59%	46%
4	2.552	11%	8%	21%	16%	37%	24%	50%	36%	59%	45%	68%	55%	76%	61%	81%	68%
5	2.186	8%	8%	15%	14%	27%	25%	38%	29%	46%	36%	55%	40%	63%	43%	68%	43%
6	2.080	7%	3%	14%	7%	25%	16%	35%	25%	43%	31%	51%	40%	59%	47%	64%	50%
7	2.021	7%	3%	13%	8%	24%	16%	34%	21%	41%	27%	49%	39%	56%	43%	62%	53%
8	1.567	4%	2%	9%	6%	16%	11%	23%	15%	29%	18%	35%	24%	41%	28%	46%	42%
9	1.191	3%	1%	6%	4%	11%	8%	16%	11%	21%	15%	26%	16%	30%	24%	35%	26%
10	0.428	1%	1%	3%	2%	5%	3%	8%	4%	10%	7%	13%	10%	16%	11%	18%	13%
11	1.589	4%	2%	9%	5%	16%	8%	23%	14%	29%	20%	36%	28%	42%	31%	47%	35%
12	1.468	4%	2%	8%	4%	14%	7%	21%	11%	26%	15%	32%	18%	38%	29%	43%	39%
13	1.130	3%	0%	6%	0%	11%	5%	15%	9%	19%	13%	24%	18%	29%	19%	33%	23%
14	0.486	1%	0%	3%	2%	6%	3%	8%	4%	11%	7%	14%	10%	16%	11%	19%	15%
15	0.712	2%	2%	4%	3%	7%	4%	10%	6%	13%	8%	17%	11%	20%	16%	23%	17%
16	0.607	2%	1%	3%	2%	6%	3%	9%	5%	12%	7%	15%	11%	18%	17%	21%	17%
17	-2.032	0%	0%	0%	1%	0%	1%	1%	2%	1%	2%	1%	2%	1%	4%	2%	6%

*β estimates for Profiles 1-16 were generated by comparing these profiles to the reference profile (Profile 17). The β estimate for Profile 17 was generated by comparing this profile to all other profiles. Cox refers to the Cox regression risk estimate. K-M is the Kaplan Meier event rate.

5.4.7 Death: Training data risk model assessment

The discriminative ability of the Cox risk estimates for death in the Training data is shown in Table 28. The overall Uno's concordance statistic was 0.71 while the time-dependent AUC ranged from 0.75 to 0.77. Calibration of the Cox risk estimates revealed moderate over-estimation of risk across all time points when compared to Kaplan Meier event rates (Figure 17).

Table 28 Death: Discrimination in Training data

Year	Uno's concordance statistic	Standard error for Uno	AUC (IPCW)
0.5	0.71	0.0100	0.76
1	0.71	0.0122	0.75
2	0.71	0.0116	0.75
3	0.71	0.0094	0.76
4	0.71	0.0109	0.76
5	0.71	0.0096	0.76
6	0.71	0.0091	0.77
7	0.71	0.0079	0.76

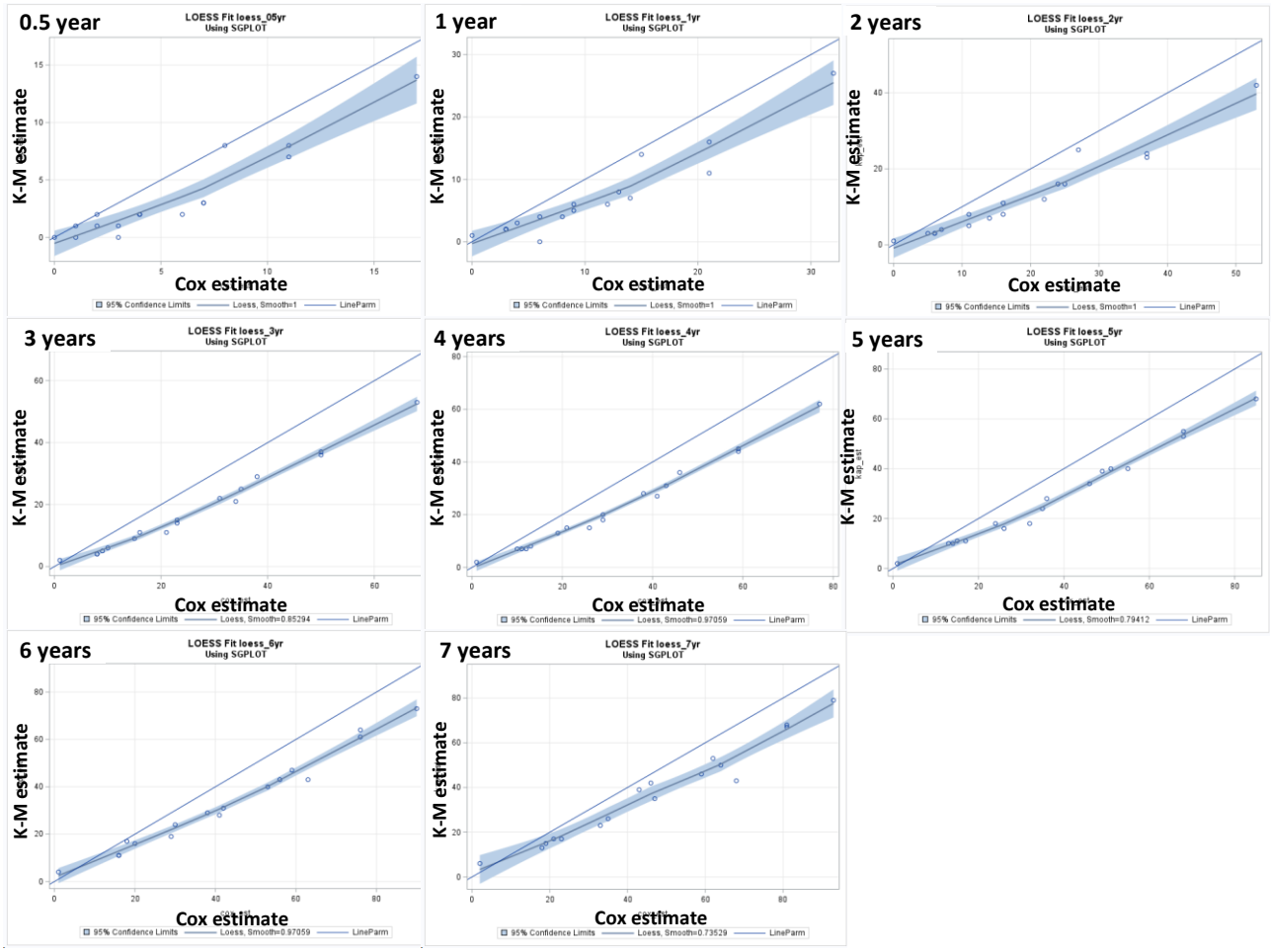


Figure 17 Death: Training data calibration plots

5.4.8 Death: Internal validation of risk model

Table 29 shows the discrimination of the absolute Cox risk estimates, as estimated in the Training data, when applied to the Test data set. The overall concordance statistic was the same as the overall statistic in the Training data (0.71). The time-dependent AUC of the risk estimates when applied to the Test data set was also similar to what was observed across all time points in the Training data (range 0.74 to 0.79 in Test data vs. 0.75 to 0.77 in Training data).

Table 29 Death: Discrimination in Test data

Year	Uno's concordance statistic	Standard error	AUC
0.5	0.71	0.0219	0.79
1	0.71	0.0261	0.78
2	0.71	0.0261	0.75
3	0.71	0.0200	0.75
4	0.71	0.0194	0.74
5	0.71	0.0231	0.75
6	0.71	0.0280	0.77
7	0.71	0.0214	0.74

Calibration of the absolute Cox risk estimates, as estimated in the Training data, is shown in Figure 18. The calibration plots in the Test data had wider confidence intervals than what was observed in the Training data, with tightening confidence intervals at incremental time points. Poor calibration was observed at the 0.5 year, 1 year and 3 year timepoints relative to the Training data calibration plots. The calibration plots across all other time points were similar to the Training data calibration plots, with slight over-estimation of risk across all estimates.

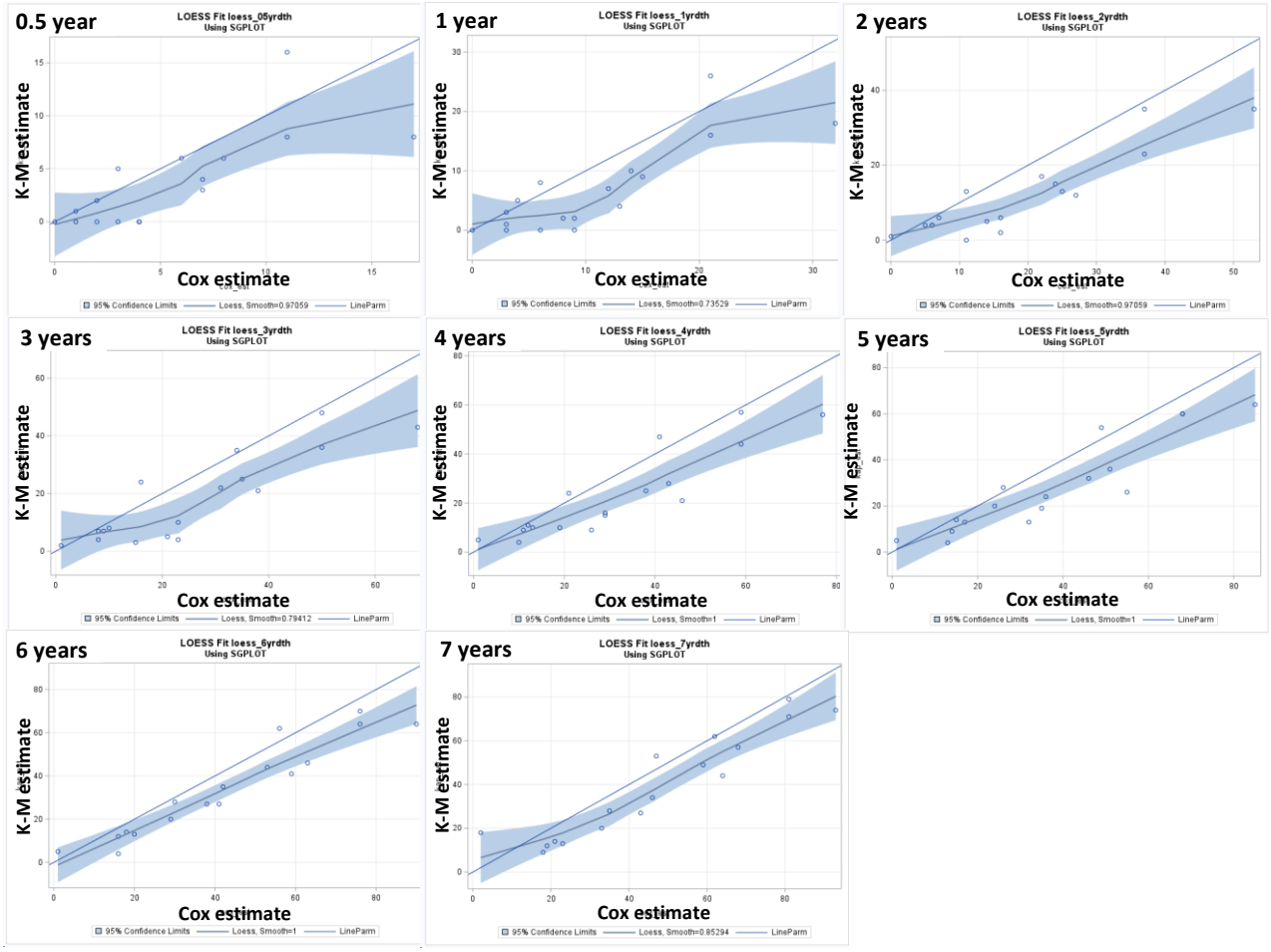


Figure 18 Death: Test data calibration plots

5.4.9 Death: prognostic tool development

The risk estimates across all time points showed similar calibration. While slightly better discrimination was observed at time points beyond the 2-year risk estimates, we opted to construct a risk flow chart based on 2-year risk estimates for death because the mean time to death in our study population was 2.7 years (Figure 19). Absolute risk estimates designated as "Low" level ranged from 0% to 18%, Moderate from 19 to 37% and High from 38 to 53%. We collapsed decision points following the "No" selection for decision point "Pre-procedure creatinine 1.70

mg/dL or higher", "No" for "Pre-procedure hemoglobin less than 13.19 g/dL", "Yes" for "Pre-procedure hemoglobin less than 11.51 g/dL", and "No" for "69 years old or greater" because they terminated in risk estimates that fell within the same risk level. Patients with elevated risk for death in the Training data were those who had prior heart failure and pre-procedure creatinine that was 1.70 mg/dL or higher (53% risk estimate).

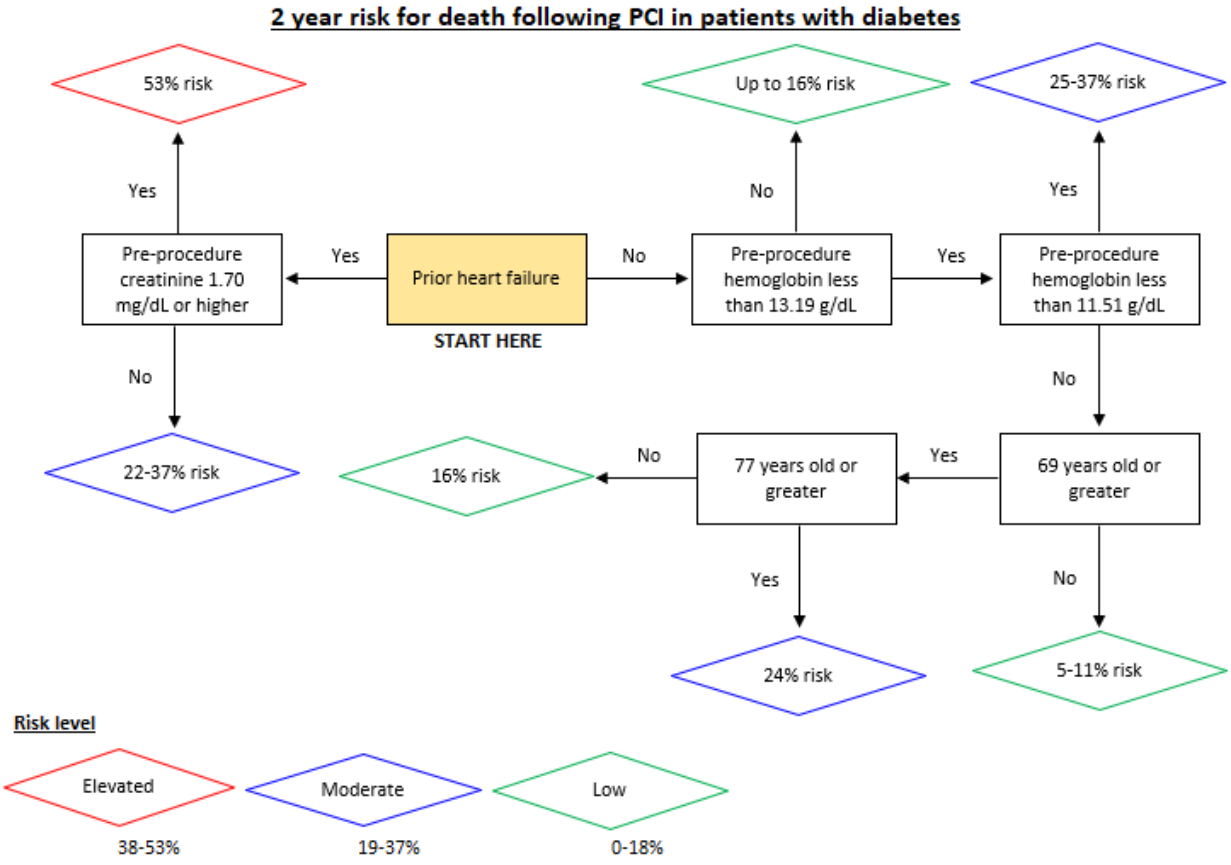


Figure 19 Risk flow chart showing 2 year risk for death following PCI in patients with diabetes

5.5 Discussion

We developed two risk flow charts for predicting risk of repeat revascularization and risk of death following PCI in patients with Type 2 Diabetes. We were able to leverage CART analysis to classify patients into distinct groups, to assign absolute risk estimates to each group, and to create user-friendly flow charts that can be used to quickly determine a patient's risk for repeat revascularization or death.

We found that presence of 3 or more vessels with 70% or greater stenosis was the strongest discriminating characteristic for risk of repeat revascularization. Multivessel disease, defined as having 2 or more vessels with 50% or higher stenosis[148], is prevalent in patients with diabetes and has been associated with poorer outcomes following PCI. The Future Revascularization Evaluation in Patients with Diabetes Mellitus: Optimal Management of Multivessel Disease (FREEDOM) trial found that repeat revascularization occurred in approximately 13% of patients with diabetes and multivessel disease in their study 1 year after undergoing PCI compared to approximately 5% incidence in patients with diabetes and multivessel disease who were treated with CABG[149]. Among the 37% of patients in our Training data set who had 3 or more vessels with 70% or higher stenosis, approximately 40% experienced repeat revascularization. The higher event rate seen in our population of patients with multivessel disease is likely due to the exclusion of risk factors for repeat revascularization from the FREEDOM trial (trial excluded patients with prior PCI, prior CABG, 50% or higher stenosis in the left main artery, 2 or more chronic total occlusions, among other exclusions)[150] whereas our study did not exclude these risk factors. Our additional finding that prior revascularization[14,24,112], high lesion complexity[120], peripheral arterial disease[27,119], younger age[111], and incomplete revascularization for multivessel disease (fewer than 2 lesions

attempted for treatment in patients with 2 arteries with 70% or higher stenosis)[151] are important in predicting risk for repeat revascularization is also in agreement with what other studies have found.

Prior heart failure was the strongest discriminating factor for predicting risk of death in our study population. This is consistent with Zareini et al.'s finding that patients with both Type 2 Diabetes and heart failure have 2 to 3 times higher 5-year risk for death, dependent on number of years since diabetes diagnosis, when compared to patients with Type 2 Diabetes who did not have heart failure[152]. Their study also found that heart failure in combination with chronic kidney disease resulted in one of the highest 5 -year risks for death when compared to other cardiovascular or renal diseases. This lends support to our finding that patients with both heart failure and pre-procedure creatinine of 1.70 mg/dL or higher (a probable indicator of poor renal function) had the highest risk for death in our study population. Low pre-procedure hemoglobin (less than 11.51 g/dL) also emerged as an important discriminator for risk of death in our study. Anemia, defined as less than 12 g/dL in females and less than 13 g/dL in males[153], is associated with higher 1-year risk for mortality following PCI when compared to non-anemic patients[154].

CART survival analysis has been used in the medical field for prognosis of outcomes such as breast cancer[155], tooth loss[156], endometrial carcinoma[157], and cardiovascular disease incidence in individuals with Type 1 Diabetes[158]. CART analysis has also been used to estimate the probability of the presence of diseases such as diabetes[159]. To the best of our knowledge, CART survival analysis has not been carried out for prognostication of repeat revascularization or death following PCI in patients with Type 2 Diabetes. We identified factors that have been shown to be independent risk factors for repeat revascularization and death in several studies. Identifying these in the context of classification trees enabled us to gain additional knowledge about the impact of interactions of these risk factors on risk for the outcomes. By reporting absolute risk, we are

creating a prognostic tool that acknowledges the higher risk of patients with Type 2 Diabetes compared to patients who do not have Type 2 Diabetes. In so doing, we are employing a personalized medicine approach that enables the identification of patients who are at lower or higher risk within this high-risk population.

Our study had several limitations. First, in assessing repeat revascularization we were unable to distinguish staged from unplanned revascularization as this information was not recorded in our data set. This may have an impact on our finding that having 3 or more arteries with 70% or greater stenosis led to an elevated risk estimate for repeat revascularization. Staged PCI procedures may take place in the context of multivessel disease when multiple procedures are required to complete the revascularization of all impacted vessels. Second, our study only documented repeat revascularizations that took place within the UPMC hospital system. This incomplete follow-up may explain the relatively weaker discrimination of the Cox risk estimates for repeat revascularization in the Training and Test data sets. Some patients who had high risk estimates for repeat revascularization may have had repeat revascularization outside the UPMC hospital system and were thus recorded as having had no repeat revascularization. In comparison, the Cox risk estimates for death likely showed good discrimination (better than repeat revascularization) because the Social Security Death Index was utilized in addition to hospital records to ascertain death (more complete follow-up). We found that those who did not undergo repeat revascularization had shorter follow-up and contact time compared to those with repeat revascularization. A higher proportion of patients who did not undergo repeat revascularization had prior heart failure compared to the proportion in those who underwent repeat revascularization. Our study showed that prior heart failure was a significant risk factor for death following PCI, therefore it is possible that the shorter follow-up and contact time seen in those who did not

undergo repeat revascularization was due to their higher likelihood for death. We also found that among those who did not die, the follow-up time was shorter in those who did not undergo repeat revascularization compared to those who underwent repeat revascularization. It is possible that this shorter follow-up time did not allow us to observe repeat revascularization that may have occurred in the group of patients who did not undergo repeat revascularization. Lastly, by categorizing continuous variables into at/ above or below the mean, we were unable to make full use of the CART methodology's ability to identify optimal cut-points. This may have led to not identifying more significant cut points and thus may have missed a better tree.

In order for a prognostic tool to have potential utility in a clinical setting, it should have the ability to differentiate patients who will and will not experience an outcome, it should be quick and simple to use, and it must be easily understood by both the clinician and patient. We developed two risk flow charts that do not require the clinician to perform any calculations or to input patient characteristics into a software algorithm. The charts that we developed can easily be printed and kept on hand by clinicians for discussions with their patients. The flow charts provide the clinician with a visual tool that can be used to articulate risk for repeat revascularization or death to a patient. In addition to the ease of use, we have shown that our models have reasonable discrimination and calibration. Though we have not yet externally validated our risk models, our risk flow charts may potentially have immediate utility for facilitating informed discussions between clinicians and patients with Type 2 Diabetes who are undergoing PCI.

6.0 Synthesis

6.1.1 Summary of Findings

The overall goal of this dissertation research was to identify risk factors associated with repeat revascularization following PCI in patients with Type 2 Diabetes, and to develop a risk prediction model for this outcome in patients with Type 2 Diabetes. The research was carried out across three Specific Aims. Aim 1 used Cox regression to identify patient characteristics and biomarkers that were independently associated with repeat revascularization following PCI. Aim 2 furthered this research by using survival CART and time-varying survival CART methodology to identify biomarker profiles that were associated with high risk for repeat revascularization. In Aim 3, the survival CART method that was developed in Aim 2 was used to identify patient profiles that were associated with high risk for repeat revascularization and death following PCI in a real-world population. These high-risk patient profiles were used to develop risk prediction flow charts for repeat revascularization and death.

Specific Aim 1: To identify biomarkers that are independently associated with repeat revascularization in the BARI 2D PCI stratum *(Hypotheses: (i) Elevated lipid, coagulation and fibrinolysis biomarkers at baseline are associated with increased risk for the outcome. (ii) Increase in coagulation biomarkers & decrease in fibrinolysis biomarkers over time is associated with increased risk for the outcome.)*

This Aim had two outcomes of interest, namely target vessel revascularization (TVR) and any repeat revascularization (ARR). We first identified non-biomarker risk factors that were

associated with each outcome using stepwise Cox regression. Younger age, prior PCI, prior CABG, insulin treatment during the trial (primarily Insulin-Providing), and number of lesions with thrombus were associated with increased risk for TVR. Prior PCI, insulin treatment during the trial (primarily Insulin-Providing), number of lesions with thrombus, insulin use at baseline and 50%-99% stenosis in the left circumflex artery were associated with increased risk for ARR while hypercholesterolemia requiring treatment at baseline was associated with decreased risk. After adjusting for non-biomarker risk factors, no biomarkers at baseline were independently associated with TVR or ARR. No time-varying biomarkers were associated with TVR and only time-varying fibrinopeptide A (a marker of the coagulation cascade) was associated with ARR.

Specific Aim 2: To identify biomarker profiles that are associated with repeat revascularization in the BARI 2D PCI stratum *(Hypotheses: (i) Elevated coagulation and inflammation biomarkers, combined with low fibrinolysis biomarkers at baseline will present the greatest risk for repeat revascularization in a baseline only model. (ii) Change in lipid, coagulation, inflammation and fibrinolysis biomarkers will be associated with risk for repeat revascularization.)*

We used survival Classification and Regression Tree (CART) analysis to identify baseline biomarker profiles that were associated with ARR, and time-varying survival CART to identify biomarker change from baseline profiles associated with ARR. After adjusting for non-biomarker risk factors identified in Aim 1, the profile with the highest risk for ARR in the baseline biomarker tree included high baseline level of D-dimer (a marker of active coagulation and fibrinolysis) which suggests that participants in this profile had hypercoagulability at baseline. tPA (fibrinolysis biomarker) levels were within a normal range. While insulin level was in the upper range of

normal, the level was higher than in all other profiles. Other high-risk profiles included various combinations of fibrinolysis biomarkers (tPA), coagulation biomarkers (D-dimer, fibrinogen, FPA), insulin, leptin, total cholesterol and MCP-1. In the time-varying survival tree, change in baseline lipid (LDL), coagulation (FPA), inflammation (CRP, TNF-α), fibrinolysis (PAI-1 activity), and kidney function (eGFR) biomarkers were associated with risk for repeat revascularization.

Specific Aim 3: To develop and internally test a risk prediction model for repeat revascularization and death using real-world data from patients with Type 2 Diabetes who have undergone PCI in the University of Pittsburgh Medical Center hospital system *(Hypothesis: Within a real-world population of patients with diabetes who have undergone PCI there will be heterogeneity in risk of repeat revascularization and death, with one or more sub-groups having significantly higher risk for repeat revascularization and death than other sub-groups in the population.)*

Using the survival CART methodology developed in Aim 2, we analyzed data from patients who underwent PCI in the UPMC health system to identify patient profiles that were associated with ARR and death following discharge (two separate trees). After building the classification trees using Training data (data was split 80/20 into Training and Test sets), we assigned risks to all profiles in the trees using absolute Cox risk estimation. We assessed the discrimination and calibration of the Cox risk estimates at 0.5 and 1-7 years in the Training set. The Cox risk estimates were applied to the Test set and discrimination and calibration was assessed in the Test set. Time-dependent AUC in the Training data ranged from 0.62 to 0.67 for repeat revascularization (0.57 to 0.63 in Test data) and from 0.75 to 0.77 for the death outcome (0.74 to

0.79 in Test data). Calibration plots across most time points for repeat revascularization and death showed good calibration in the Training and Test data sets. We developed a 1-year risk flow chart for repeat revascularization and a 2-year risk flow chart for death based on the profiles that were identified in the classification trees and using the absolute Cox risk estimates. Factors included in the 1-year risk flow chart for repeat revascularization were multivessel disease, age, prior peripheral arterial disease, prior PCI and number of lesions attempted for treatment. Factors in the 2-year risk flow chart for death included prior heart failure, age, and pre-procedure creatinine and hemoglobin.

6.1.2 Conclusion, Strengths and Limitations

Taken together, our results demonstrate that medical history (prior revascularization, hypercholesterolemia, prior peripheral arterial disease, insulin use), demographics (age), lesion characteristics (multivessel disease, left circumflex artery stenosis, number of lesions attempted for treatment), fibrinolysis, coagulation, inflammation, elevated baseline insulin, hyperleptinemia, and enhanced endothelial dysfunction are associated with risk for repeat revascularization following PCI in patients with Type 2 Diabetes. Medical history (prior heart failure), demographics (age), impaired kidney function and anemia are associated with mortality risk following PCI in this patient population.

Our research had several strengths. We were able to draw upon the extensive biomarker information collected in the BARI 2D trial to identify biological mechanisms that potentially lead to the higher risk of repeat revascularization in patients with Type 2 Diabetes. By using CART methodology, we identified a higher number of biomarkers associated with the outcome compared to stepwise Cox regression and were thus able to get more information from the biomarker data.

To the best of our knowledge, no other studies have assessed biomarker profiles that are associated with repeat revascularization in this population to the extent that our study did. Our use of time-varying survival CART to explore risk factors for repeat revascularization is innovative. Furthermore, we leveraged CART methodology to create an innovative risk prediction tool with potential clinical utility for assessing risk for death and repeat revascularization in patients with Type 2 Diabetes. By assessing discrimination and calibration in Training and Test data sets, we were able to demonstrate the accuracy of our prediction tool, an important criterion for determining clinical utility of a risk model.

There were also limitations in our research. We used the last-observation-carried-forward method to address biomarker values that were missing. Non-lipid biomarkers had a relatively higher number of missing values than lipid biomarkers due to protocolized differences in the time points at which the lipid and non-lipid biomarkers were measured. Whereas lipid biomarkers were measured at as many as 7 time points, non-lipid biomarkers were measured at a maximum of 3 time points. This may have resulted in high (or low) non-lipid biomarker levels being carried forward across several time points. This may have impacted Aim 1 and 2 results for time-varying biomarkers. In Aim 3, we did not determine the estimation error associated with predictions based on the Training data CART model. This is typically determined using k-fold validation whereby the Training data is split into k groups, k CART trees are built using k-1 data sets, and the estimation error rate is determined in each k-fold using the k^{th} group that was not used to build the tree. The estimation error is then averaged across all folds to obtain an overall estimation error. Though we did not perform this estimation, we remain confident that the CART model performed well, given the results of our assessment of discrimination and calibration in the Training and Test data sets.

6.1.3 Future Research

Our research has added important information to the knowledge base for adverse outcomes associated with PCI in patients with Type 2 Diabetes. However, more research is needed to support the conclusions that we reached in this dissertation and to build upon our work.

As discussed in the limitations, the use of last-observation-carried-forward to address missing biomarker data in Aims 1 and 2 may have impacted our time-varying biomarker analysis. This can be addressed in a future study using data with similar number of data collection points for all biomarkers assessed in this dissertation. As most of these biomarkers are not typically measured in a clinical setting, it is likely that this research would have to be addressed as part of a clinical trial. The risk prediction flow charts that we developed in Aim 3 should be externally validated to assess generalizability of the flow charts.

Our results from Aims 1 and 2 demonstrated that CART methodology is a useful method for understanding the complex association of risk factors when assessing their impact on outcome. Future research can focus on creating a classification tree using both biomarker and non-biomarker risk factors to determine risk factors for repeat revascularization and death. The addition of biomarkers to predictive models that use traditional risk factors (non-biomarker) often improves performance of the model. Combining traditional and biomarker risk factors in a CART model may provide more information about underlying mechanisms compared to using only traditional risk factors or only biomarkers.

6.1.4 Public Health Significance

Patients with Type 2 Diabetes experience higher rates of repeat revascularization after PCI compared to patients without diabetes. Rates of repeat revascularization are also higher in PCI when compared to rates in CABG. Nevertheless, the use of PCI in patients with diabetes is increasing. Therefore, with the rising global incidence of Type 2 Diabetes, it is increasingly important to understand the risk factors associated with adverse outcomes following PCI in this population.

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