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COMPARATIVE EFFECTIVENESS OF ENDOVASCULAR AND PHARMACOLOGIC TREATMENT PATHWAYS IN NON-DIABETIC PERIPHERAL ARTERIAL DISEASE PATIENTS USING ADMINISTRATIVE CLAIMS DATA

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By

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B.S., Pennsylvania State University, 2007

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An abstract of
A Thesis submitted to the Faculty of the
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ABSTRACT

COMPARATIVE EFFECTIVENESS OF ENDOVASCULAR AND PHARMACOLOGIC TREATMENT PATHWAYS IN NON-DIABETIC PERIPHERAL ARTERIAL DISEASE PATIENTS USING ADMINISTRATIVE CLAIMS DATA

By Ajit A. Londhe

BACKGROUND: Peripheral Arterial Disease (PAD) is a chronic disease affecting 12 million Americans in which plaque accumulates in the femoral, popliteal, tibial, or peroneal arteries, causing claudication, leg weakness, and conditions threatening limb viability like gangrene. Recent trends suggest increased usage of endovascular interventions as second-line therapy over pharmacologic treatments. As surgical procedures introduce safety risks, a comparative effectiveness study of second-line endovascular interventions against second-line pharmacologic treatment was performed to determine the risk of requiring lower limb amputation or peripheral arterial bypass (primary endpoint) and the risk of cardiovascular, ischemic, and mortality-related events (safety endpoint).

METHODS: Patients with PAD who had undergone first-line pharmacologic therapy (statins, clopidogrel, or aspirin) but required second-line therapy of either cilostazol, percutaneous transluminal angioplasty (PTA) with stent, or PTA with atherectomy between January 1, 2011 and December 31, 2016 were selected from three administrative claims data sets ("OPTUM," "MDCR," "CCAE"). Analyses were restricted to non-diabetic patients, due to confounding of outcomes and treatment patterns by diabetes status. Pairwise comparisons of two PTA-based treatment pathways were conducted against one cilostazol treatment pathway. Propensity score matching was implemented to adjust for all known confounders. Cox proportional hazards models were generated to assess risk. Empirical calibration of traditional *p*-values adjusted for the data sets' inherent systemic error.

RESULTS: The PTA-based treatment pathways consistently produced effect estimates suggesting elevated risk of requiring amputation or bypass compared to the cilostazol treatment pathway. In two of the three data sets, PTA with stent had statistically significant effects (OPTUM, HR 1.92, 95% CI [1.07, 3.47], traditional $p = 0.03$, calibrated $p = 0.049$; MDCR, HR 2.37, 95% CI [1.33, 4.31], traditional $p = 0.004$, calibrated $p = 0.001$). MDCR produced a statistically significant effect for PTA with atherectomy (HR 1.90, 95% CI [1.01, 3.75], traditional $p = 0.054$, calibrated $p = 0.024$). No statistically significant effects were observed for the safety endpoint.

CONCLUSIONS: A potential two-fold increase in lower limb amputation or peripheral arterial bypass was observed in patients receiving PTA with stent compared to those treated with cilostazol. No meaningful difference in risk was evident for the safety endpoint.

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LIST OF ABBREVIATIONS

Abbreviation	Description
ABI	Ankle-brachial index
AFS	Amputation-free survival
ALI	Acute limb ischemia
ATC	Anatomical Therapeutic Chemical Classification System
CCAE	Truven Health MarketScan® Commercial Claims and Encounters
CHADS2	Clinical prediction rule based on patient history of Congestive Heart Failure, Hypertension, Age, Diabetes, and Stroke
CLI	Critical limb ischemia
CPT4	Current Procedural Terminology, 4th Edition
CVD	Cardiovascular disease
DCSI	Diabetes Complications Severity Index
IC	Intermittent claudication
ICD	International Classification of Diseases; can be version 9 or version 10
IS	Ischemic stroke
LLA	Lower limb amputation
MACE	Major Adverse Cardiovascular Events (e.g. myocardial infarction, stroke, cardiovascular death)
MDCR	Truven Health MarketScan® Medicare Supplemental
MI	Myocardial infarction

OHDSI	Observational Health Data Sciences and Informatics
OMOP CDM	Observational Medical Outcomes Partnership Common Data Model
OPTUM	Optum Clinformatics™ Extended Data Mart, Date of Death Version
PAB	Peripheral arterial bypass
PAD	Peripheral arterial disease
PPV	Positive predictive value
PTA	Percutaneous transluminal angioplasty
SMD	Standardized mean difference

CHAPTER 1: BACKGROUND

Introduction

Peripheral Arterial Disease (PAD) is an undertreated chronic disease that affects over 12 million Americans every year, with associated outcomes as serious as lower limb amputation, heart attack, stroke, and death. PAD is treated with a variety of first- and second-line therapies that are both pharmacologic and endovascular. This thesis explores PAD's risk factors and characteristics as context for a comparative effectiveness study of multiple treatment pathways.

Arteriosclerosis and Atherosclerosis

Arteriosclerosis is a general cardiovascular condition in which arteries become thickened or hardened. The arteries, which are crucial in the migration of oxygenated, nutrient-rich blood to organs and tissues throughout the body, normally have a "flexible and elastic" nature, capable of supporting unencumbered blood flow [1]. Arteries that are not operating optimally are usually partially obstructed or fully occluded due to the excessive collection of "fat, cholesterol, calcium, fibrous tissue, and other substances" [2]. The hardening of the arteries due to this buildup is known as atherosclerosis.

The forming of thick plaque along the arterial wall can result in many serious chronic diseases and associated outcomes [2]. The types of chronic diseases are dependent upon the location of the plaque buildup. If the plaque forms in arteries near the heart, coronary heart disease (CHD) results, with angina and myocardial infarction as common outcomes [3]. If the plaque forms in arteries in the neck, carotid artery disease

can develop and lead to ischemic stroke. If the arteries near the kidneys are restricted, the resultant chronic kidney disease can hinder critical waste removal operations. If atherosclerotic plaque develops in the arteries of the limbs, peripheral arterial disease can result, increasing the risk for both ischemic events [4] and major adverse cardiovascular events (MACE), such as myocardial infarction, stroke, or cardiovascular death [3].

Peripheral Arterial Disease

Patients with peripheral arterial disease (PAD; also referred to in clinical literature as “peripheral vascular disease” or “PVD”) experience an accumulation of hardened plaque in their femoral, popliteal, tibial, or peroneal arteries, causing a loss of circulation to the legs [2]. PAD, a chronic disease that has been described as “undertreated” and “poorly understood” [5], follows a slow-developing trajectory that can be hastened by the presence and severity of other comorbidities. The American College of Cardiology and American Heart Association Practice Guidelines categorize this progression into four severity levels: “asymptomatic,” “claudication,” “acute limb ischemia” (ALI), and “critical limb ischemia” (CLI) [6].

In the asymptomatic stage, an estimated 50% of PAD patients experience no symptoms, despite of the multitude of potential debilitating effects of untreated PAD [5]. This lack of tangible limb pain contributes to the underreporting and underdiagnosing of PAD, but also may point to more adverse patient trajectories. A cross-sectional study of PAD patients indicated that compared to those with intermittent claudication, asymptomatic patients may have worse calf muscle conditions and slower walk performance, and thus may have more degraded lower limb nerves [7]. The authors do

posit, however, this may be a result of asymptomatic patients voluntarily avoiding more intensive exercise that would cause classic claudication symptoms [7].

Among patients early in the claudication stage of PAD, the primary symptoms include frequent limb fatigue and pain. This pain can manifest in the calves, particularly after elevated physical exertion [6]. More visible symptoms include sores or wounds that do not heal, pale or discolored skin, stunted nail and hair growth, and "weak or absent pulses in the legs or feet," causing decreases in skin temperature in those areas [8]. These symptoms can be debilitating for PAD patients' day-to-day activity, as their limb functionality becomes significantly weakened. The loss of personal autonomy through impaired motor ability degrades quality of life and has been linked to psychological disorders. Recent cross-sectional and longitudinal studies have found the prevalence of depression in PAD patients can be comparable to patients with cardiovascular disease (which has an established association with depression) [9]. Additionally, male patients, particularly those with pre-existing diabetes, can experience erectile dysfunction (ED) because of the reduced blood flow; ED has been characterized as a predictive indicator for developing coronary artery disease [10].

ALI or CLI can develop if the claudication is left untreated; in these stages of PAD, the tissue in the affected limbs dies, which can result in gangrene to develop, particularly in the feet. In ALI and CLI, limb blood flow rapidly reaches a critically low level [11]. Symptoms of ALI include pain, pale appearance, low pulse, cold temperature, paralysis, or burning sensations in the legs or feet [12], presenting for up to two weeks' time [6]. CLI patients additionally experience significant pain even at rest as well as a

propensity to develop wounds or sores [12], with episodes lasting for more than two weeks [6]. Studies have shown that PAD patients, particularly those with CLI, are associated with elevated risks for myocardial infarction (MI), ischemic stroke (IS), cardiovascular disease (CVD), renal artery stenosis, and death [13, 14]. With renal artery stenosis, the limited blood flow can result in the body's overall blood pressure to rise, causing strain on the kidneys, thus limiting waste filtration capability [15].

PAD Classification Systems

Beyond this set of four PAD categories, several classification systems that more granularly characterize PAD severity exist, each utilizing different strategies for describing the disease's trajectory: Fontaine, Rutherford, Bollinger, and Graziani. The Fontaine classification system, published in 1954, relies upon symptoms and patient viability, but no screening or diagnostic tests [6]. Stages in the Fontaine system include: Stage I, asymptomatic; Stage II, intermittent claudication (IC); Stage III, pain at rest; and Stage IV, ulcers or gangrene [6].

The Rutherford classification system, developed in 1986, attempts to characterize the progression of CLI through the usage of diagnostic tests, many of them based on patients' responses to exercise [6]. The system utilizes grades and categories to capture the clinical symptoms and the exercise diagnostics. Grade 0 reflects no symptoms or IC, and corresponds to completion of exercise activity with normal ankle pressure or slightly low ankle pressure [6]. Grade I patients have "moderate" to "severe" claudication, and have either slightly low ankle pressure post-exercise, or could not complete the exercise activity [6]. Grade II patients suffer from pain at rest and have moderately low ankle

pressure at rest, while grade III patients have lost limb or foot tissue due to gangrene and present severely low ankle pressure at rest [6].

Rather than utilize symptoms and diagnostic responses, the Bollinger Angiographic system instead examines the occlusive patterns in the patient's arteries and the extent to which plaque has accrued and stenosis has occurred [6]. Angiogram results showing whether lesions have formed in the aorta, iliac, profundal, femoral, popliteal, tibial, or peroneal arteries, combined with the number of lesions and the severity of the blockage are the key components of the score [6].

Lastly, as patients with diabetes present with conditions differently than patients without diabetes, Graziani's Morphologic Categorization system delineates seven anatomic classifications of PAD severity in diabetic PAD patients [6]. The classes include: class 1, a single obstruction in the tibial or peroneal artery; classes 2a and 2b, in which the patient has a single obstruction in their femoral or popliteal artery or two obstructions below the knee; class 3, a single occlusion and a narrowing of multiple arteries; class 4, two occlusions and narrowing of multiple arteries; class 5, in which the tibial and peroneal arteries are occluded; class 6, three occlusions and multiple arteries narrowed; and class 7, several blockages in the femoral or popliteal arteries [6].

PAD Outcomes

Several serious outcomes are associated with PAD, ranging from the need for highly invasive surgical procedures to limb amputation to MACE events and death. These outcomes were utilized as endpoints in the comparative effectiveness study.

Outcome: Peripheral Arterial Bypass

When pharmacologic or endovascular treatment pathways fail to restore healthy blood flow through arteries in the legs, PAD patients with "lifestyle-limiting claudication symptoms" may need to undergo peripheral arterial bypass (PAB) [16]. PAB, historically considered the "gold standard revascularization method" [17] can restore blood flow to the lower extremities by re-routing blood away from the blocked arteries and instead distribute it towards different paths around the blockage. As PAB is associated with elevated risks of myocardial infarction, blood clots, post-operative infections, and death [18], bypass of the affected arteries is not considered a desirable treatment for PAD, but rather a last resort procedure to salvage the affected limb. PAB usage among PAD patients decreased by 42% between the years of 1996 and 2006, as competing treatments, such as endovascular interventions, have significantly supplanted it [19].

Outcome: Lower Limb Amputation

CLI can make lower limb amputation (LLA) necessary to prevent further complications [20]. The National Institute for Health and Care Excellence estimates that 30% of patients with PAD and CLI are estimated to require LLA one year post-diagnosis; half of PAD patients with CLI will die largely due to associated cardiovascular disease [21]. An analysis of the 2008 US Medicare population estimated the incidence of lower extremity amputation procedures, inclusive of LLA, to be 5,790 per 100,000 PAD patients [22]. In this study population, a higher proportion of PAD patients with diabetes (60.3%) required an amputation than non-diabetic patients (35.7%) [22]. Amputation rates among PAD patients decreased by approximately 20% during the eight-year study

window, possibly in part due to earlier detection of CVD, coupled with advances in pharmacologic therapies and an increased usage of revascularization techniques like angioplasty and bypass surgery [22].

Outcome: Myocardial Infarction and Ischemic Stroke

Aside from LLA, other serious outcomes associated with PAD include myocardial infarction and ischemic stroke. The Rossi et al. prospective cohort study investigated revascularization patients with PAD symptoms in Fontaine stages II to IV in order to study the risk of myocardial infarction and other cardiac events [23]. The study found a 34% incidence of MIs during a two-year window [23]. A meta-analysis of seven studies examining the association between PAD and heart failure (HF) yielded statistically significant elevated relative risks of HF among PAD patients across all studies, with relative risks ranging from 1.35 to 3.09 [24].

PAD patients, regardless of symptoms, have been observed to have a higher risk of stroke than non-PAD patients [25]. Carotid stenosis, a condition in which the carotid arteries located in the neck become narrowed [26], is a significant risk factor for stroke. A study of Chinese patients with PAD, coronary arterial disease, and a history of abdominal aortic aneurism by Cheng et al. explored the relative risks of carotid stenosis between these groups, and found that PAD patients had the highest risk of carotid stenosis [27].

Outcome: Death

Death, regardless of cause, has been linked to PAD in several studies. A survival analysis of nearly 17,000 subjects, diagnosed with PAD between 1985 and 1995 in Saskatchewan, Canada found that nearly half of participants died within six years of follow-up, with an annual death rate of 8% [28]. The proportion of death within five years post-diagnosis in PAD patients with diminished blood flow to their limbs has been estimated at 25% [5].

PAD Prevalence and Incidence

In the United States, PAD is estimated to affect 12 million Americans [4], with increased prevalence associated with advanced age for both males and females. The number of cases is expected to rise, with the projected prevalence estimated to double by 2050 [12]. From a global perspective, countries with lower socio-economic status have been observed to have a lower incidence of PAD compared to countries with higher socio-economic status [29].

PAD Risk Factors

The Cleveland Clinic's medical guidelines indicate that common risk factors for PAD include smoking, age, race, diabetes, hypertension, and hyperlipidemia [13]. Additionally, the National Institute of Health advises that patients with metabolic diseases such as coronary heart disease (CHD) are also at risk for PAD [30]. No gender-specific differences have been observed in either developing PAD [31] or in the primary outcomes associated with PAD [32], though females may have a decreased risk of

undergoing amputation or bypass surgery than males [32]. The consensus risk factors are described in the next few sections for context, however, due to limitations in the data sets, the comparative effectiveness study could not adjust for race or ethnicity, but did utilize covariates related to the other risk factors.

Risk Factor: Age

PAD is not considered common among younger populations [29], but the risk increases substantially by age group, as there is "a 1.5- to twofold increase in risk for every 10-year increase in age" [12]. The Cleveland Clinic estimates that "12% to 20% of Americans age 65 and older," or approximately 4.5 to 7.6 million people, suffer from PAD [12]. PAD is present in 29% of people older than 70 years who have no conventional risk factors [12].

Risk Factor: Race and Ethnicity

Race and ethnicity play important roles in the risk of developing PAD. Non-Hispanic whites and Indian Americans tend to have low odds, but African Americans, Hispanics, and Asian Americans all have comparatively higher odds. Controlling for other established risk factors, African Americans have double the risk of developing PAD compared to Caucasians or Asians [13]. The National Heart, Lung, and Blood Institute's (NHLBI) Genetic Epidemiology Network of Arteriopathy (GENOA) study investigated differences in PAD prevalence in African American subjects against non-Hispanic white subjects [33]. Stratified by gender and adjusted for age and other conventional risk factors, higher odds of PAD were observed among African Americans (in men: OR 4.7, 95% CI [1.4, 16.0], $p = 0.012$; in women: OR 2.2, 95% CI [1.2, 4.2], $p = 0.014$) [33].

Few studies on Asian American cohorts and PAD are available, but several global studies have been published to characterize and compare Asian populations and prevalence of PAD. Although not specifically about American-based populations, these studies can provide context for the potential of confounding by race and/or ethnicity among these global populations' counterparts in the United States. A multi-country PAD study demonstrated that among diabetic southeastern and eastern Asians above the age of 50 years old, PAD can present as a "common complication" in that cohort, with nearly 18% being diagnosed for PAD through ABI measurements [34]. A comparative cohort study between at-risk Indian men and at-risk European men found that the former group had lower prevalence of PAD than the latter group, controlling for severity of coronary disease [35].

The CDC reports that Hispanics and non-Hispanics have similar risks for PAD [36]. Further analysis of various Hispanic ethnicities in the US found that Cuban Americans had odds ratios higher than other Hispanic ethnicities: compared to Mexican Americans, OR 2.9, 95% CI (1.9, 4.4); compared to Hispanics of Dominican, Puerto Rican, mixed/other, and two broad categories for Central and South America, the odds ratios ranged from 1.2 to 1.8 [37].

Risk Factor: Smoking

Smoking has been shown to be a major risk factor for PAD. In a prospective cohort study among CVD-free females, the researchers observed a "strong dose-response relationship between lifelong smoking exposure defined by pack years of smoking and risk of symptomatic PAD" [38]. This relationship was evident when the data was

stratified by cigarettes smoked per day, with increasingly larger adjusted hazard ratio estimates compared to non-smokers: former smokers, HR 3.14, 95% CI (2.01, 4.90); light smokers (fewer than 15 cigarettes per day), HR 8.93, 95% CI (5.02, 15.89); heavy smokers (at least 15 cigarettes per day), HR 16.95, 95% CI (10.77, 26.67) [38]. Consequently, the researchers concluded that smoking cessation was associated with diminished risks of PAD, while "active smoking and longer smoking abstinence was associated with an additional reduction of this risk" [38]. Similarly, in males aged 40 to 75, the researchers found an estimated hazard ratio of 12.89 (95% CI [8.59, 19.34]) when comparing heavy smokers against non-smokers [14].

Risk Factor: Diabetes

Diabetes has a strong association with PAD, as the proportion of PAD patients with diabetes has been estimated to be 20% [39] or as high as 30% [4], although these estimates are confounded by the difficulty in diagnosing PAD (further detailed in the "PAD Diagnosis" section). Diabetic PAD patients are more likely to exhibit symptoms earlier than non-diabetic patients. The severity and control of diabetes modifies the risk of PAD, as a dose-response effect has been observed in glycosylated hemoglobin levels: "with every 1% increase in glycosylated hemoglobin, the risk of PAD has been shown to increase by 28%" [4].

The risk of outcomes associated with diabetic PAD patients differs substantially from non-diabetic PAD patients. In a study from Jude et al., PAD patients were pre-identified via lower extremity angiograms, and then verified using the Bollinger classification system [40]. PAD outcomes were then compared between diabetic patients

and non-diabetic patients. The researchers found that diabetic patients had a significantly higher risk of LLA (OR 5.4, 95% CI [2.3, 12.9], $p < 0.001$) and of death (OR 3.1, 95% CI [1.5, 6.4], $p < 0.001$) [40]. Additionally, among diabetic PAD patients, a disparity in outcome risks between genders has been observed [12]. Results from the Framingham study estimate that diabetic PAD patients have a higher risk of claudication (in men, 3.5 times higher; in women, 8.6 times higher) and LLA (15 times higher).

PAD Diagnosis

Diagnosing PAD is challenging, as the bulk of patients begin asymptomatic, or do not know the criticality of their symptoms, resulting in severe underreporting. Additionally, peripheral neuropathy (in which nerve damage diminishes feeling in the hands or feet), could be present due to other comorbidities such as diabetes, and could prevent pain symptoms from being fully realized [39].

Consequently, PAD has been described as “underdiagnosed and undertreated” [14], in spite of its prevalence and the serious outcomes associated with it. The Cleveland Clinic’s PARTNERS (Peripheral Arterial Disease Awareness, Risk, and Treatment) program studied 7000 patients with a high risk for PAD. 44% of PAD diagnoses occurred shortly after enrollment, with 17% unaware of their condition and 51% of their physicians similarly unaware in spite of medical records indicating PAD presence [12]. A 2012 report from the American Heart Association concurs with those findings through analysis of the National Health and Nutrition Examination Survey (NHANES), estimating that only “one in four knew that PAD is associated with increased risk of heart attack and stroke,” and that “only 14% were aware that PAD could lead to amputation”

[41]. Early diagnosis of PAD is also challenging, as most patients are asymptomatic when the disease first presents. Premature PAD, defined as onset prior to 50 years of age, has an estimated prevalence of only 1% of the population, while PAD occurring before 25 years of age is even more rare [42].

Screening for PAD can entail noninvasive steps such as investigation of family history or a physical examination of the legs and feet [43]. Treadmill functional testing, in which the patient runs uphill on a treadmill and ankle blood pressure is measured, can test blood flow efficacy in the legs and feet [39]. As relying upon the main symptoms of PAD, such as intermittent claudication, can result in a 90% chance of misdiagnosis [12], diagnostic tests such as the Ankle-Brachial Index (ABI), Doppler ultrasound, treadmill test, Magnetic Resonance Angiogram (MRA), arteriogram, and blood tests can also be utilized to more accurately diagnose PAD [43].

With the ABI test, blood pressure levels from the ankle and arm are compared to demonstrate the efficacy of blood flow; the ratio of the two levels produces a score that can designate the likelihood of PAD being present. An ABI below 1.4 suggests PAD could be present; an ABI below 0.9 is considered a very strong indicator of the presence of PAD; and an ABI below 0.4 represents severe PAD, with CLI conditions likely to develop [16]. The ABI test has been characterized as well-perceived among clinicians, as 89% of surveyed physicians believe it can be accurate in detecting asymptomatic PAD and 96% trust its viability in symptomatic PAD [4]. The Cleveland Clinic's physician guidelines recommend that all patients with claudication or other limb disorders be administered an ABI test, particularly among those age 70 years and older, those age 50

to 69 years with diabetes or smoking history, or patients younger than 50 years but with diabetes and hypertension, hyperlipidemia, or smoking history [12]. Once a PAD diagnosis is obtained via ABI screening, lab tests such as vascular evaluation through segmental pressures and pulse volume recording, or imaging techniques like MRA, computed tomographic angiography (CTA), and Doppler ultrasound to confirm and characterize the PAD diagnosis.

PAD Treatments

First-Line Therapies

The leg weakness and pain experienced by PAD patients is initially managed through exercise- or smoking cessation-based programs aimed at relieving symptoms and preventing atherosclerosis from developing elsewhere in the body [16, 44]. If these lifestyle changes do not reduce symptoms, first-line medications are prescribed to mitigate the effects of the patient's cardiovascular and diabetic comorbidities. Statins and antiplatelet agents, along with drugs that lower systolic blood pressure (such as diuretics, beta blockers, calcium channel blockers, ACE inhibitors, angiotensin receptor blockers, and alpha blockers [45]), are crucial in lowering the risk of MACE and stroke outcomes.

Each of the first-line drug classes can be leveraged to treat PAD symptoms through different therapeutic strategies. Statins like atorvastatin, simvastatin, and rosuvastatin are designed to curtail the production of bad cholesterol (low-density lipoprotein, or LDL) in the liver, with higher doses prescribed for those with elevated risks of heart attack and stroke. The American Heart Association has found that PAD patients on high dose LDL-lowering statins have "a 33 percent lower risk of amputation

and 29 percent lower risk of death" [46]. Additionally, in the landmark Heart Protection Study (HPS, 2002), a subgroup analysis of PAD patients in the randomized placebo-controlled trial in the effects of simvastatin on cholesterol levels demonstrated that "aggressive LDL cholesterol-lowering therapy" could help reduce the risk of MACE events in PAD patients [31].

Antiplatelet agents, also known as blood thinners, limit "platelet activation and subsequent risk of an atherothrombotic event" [47]. Clopidogrel, a P_2Y_{12} platelet inhibitor, has an explicit label indication for patients with "established peripheral arterial disease" [48]. Clopidogrel, which has been shown to be more effective than aspirin in "preventing ischemic events" [47], is often prescribed concurrently with aspirin as a dual antiplatelet therapy.

Second-Line Therapies

If lifestyle changes and first-line therapies fail to reduce symptoms, second-line therapies may be utilized to prevent claudication and more serious symptoms from developing via ALI and CLI. Vasodilators like cilostazol and pentoxifylline increase the width of the affected arteries by "preventing the muscles from tightening and the walls from narrowing," which in turn promotes more efficient blood flow [49]. Some researchers have posited that even with their efficacy, vasodilators are still "underused agent[s] for amputation-free survival" [50].

Endovascular interventions can be utilized as a secondary approach to mitigating the presence of plaque in the peripheral arteries without invasive surgery. Patients without diabetes or untreated CVD are ideal candidates for PTA-based procedures,

particularly if they have arterial stenosis, experience recurrent claudication, but still have functioning kidneys [51]. The use of percutaneous transluminal angioplasty (PTA) to facilitate treatments has become popular for chronic PAD patients. In 1996, PTA-based procedures were largely performed by interventional radiologists, but in the 10 years following, cardiologists and vascular surgeons were estimated to have performed 80% of all endovascular interventions [19]. PTA procedures are designed to provide structural relief to the affected arteries; however, one potential consequence is traumatic plaque fracture, in which the arterial walls are weakened and clotting risks become elevated [52]. Still, studies comparing endovascular procedures against PAB indicate that the former may have superior patency and re-intervention rates [17].

Two applications of PTA procedures include stenting and atherectomy. In both cases, a catheter is inserted through the skin to facilitate the treatment. A PTA with stent entails the insertion and inflation of a balloon within the artery. A mesh stent can then be fit into the widened artery, with the stent ensuring that the artery remains open, restoring long-term circulation. While stenting can promote increased circulation, the rate of restenosis (restriction of a widened artery) are estimated to be "as high as 10-40% at six to 24 months," mainly as a consequence of "excessive movement and flexion" [53]. Another endovascular technique that uses PTA, atherectomy, involves the use of a small cutting device inside of the affected peripheral artery to "shave or cut off plaque" so that blood can pass naturally with less obstruction [54]. PTA with atherectomy has been demonstrated to maintain effective blood flow in PAD patients' affected limbs and significantly reduce the risk of amputation over the first year post-treatment [53]. PTA with atherectomy does carry a risk of embolization (in which loose plaque pieces can

become shifted and form a blockage) and a risk of perforation of the affected artery [55]. medical management and endovascular procedures are preferred primary treatments.

Study Objectives

For PAD patients in the symptomatic, ALI, or CLI stages, the second-line of treatment (pharmacologic therapies and endovascular interventions) not only present safety risks but also introduce varying levels of economic impact on patients and payers. Recent trends indicate that many PAD patients are receiving endovascular procedures in an outpatient setting [56]. From 2005 to 2013, while Medicare billing for coronary blockage procedures decreased by 30 percent, procedures aimed at relieving peripheral arterial blockages increased by 70 percent [56]. Though endovascular interventions are less risky than PAB, they are often more expensive than PAD prescription drugs and inherently carry additional safety risk as a surgical procedure.

The increased usage of endovascular interventions, such as PTA with stent or atherectomy, has led to significant discussion about the merits of early utilization in PAD patients. Few observational studies have made this comparison due to the inherent heterogeneity of covariates that could be correlated with the two types of interventions. Additionally, no studies comparing pharmacologic and endovascular procedures as second-line PAD treatments are known to have been conducted.

Primary Objective

The primary objective of this study was to compare the effectiveness of pharmacologic and outpatient endovascular second-line therapies, in a pairwise fashion, by comparing the risks of developing outcomes associated with PAD.

Secondary Objective

The secondary objective of this study was to compare the safety of pharmacologic and outpatient endovascular second-line therapies, in a pairwise fashion, by comparing the risks of experiencing serious MACE and mortality events.

CHAPTER 2: METHODS

Exposures of Interest

Treatment pathways that started with prior exposure to a statin or antiplatelet agents, and resulted in either cilostazol, PTA with stent, or PTA with atherectomy as second-line therapies were selected as exposures in this study.

Primary Endpoint

This study investigated the time to developing the need for last resort surgical procedures – LLA or PAB – as a primary endpoint. Both outcomes represented failure to effectively treat PAD.

Safety Endpoint

This study investigated the safety of the treatments by examining MACE outcomes known to be associated with PAD: myocardial infarction (STEMI and non-STEMI) and ischemic stroke, both defined as being incident events if they required a hospital admission during the risk window. To mitigate the risk of death being a competing risk for these serious cardiovascular outcomes, all-cause death was also included in this endpoint.

Study Inclusion Criteria and Setting

Three cohorts were designed using the following inclusion criteria, study window, and treatment settings.

- Patients with an index exposure of interest (cilostazol, PTA with stent, or PTA with atherectomy)
    - The PTA with stent and PTA with atherectomy exposures must have been administered in an outpatient setting.
    - Index exposures must be the first in the patient's known history.
    - Index exposures must have occurred between January 1, 2011 and December 31, 2016 (inclusive).
    - The patient must have continuous observation of at least 180 days prior up to and including the index date. This meant removing patients who had gaps in their insurance enrollment prior to the index date.
- Prior to the index date, patients must have:
    - No prior history of any of the three study exposures
    - No history of diabetes (both types 1 and 2)
    - At least 1 first-line drug exposure of a statin, clopidogrel, or aspirin
        - At least one diagnosis of PAD prior to this first-line treatment

All patients needed at least six months of continuous observation prior to the treatment index. This helped in establishing that the cohort index as the first occurrence of that treatment in the patient's available history. The treatment pathways recommended by the Mayo Clinic [44] and supported by preliminary inspection of PAD treatment pathways in the study data sets consisted of comorbidity mitigation and management as a first-line therapy, with the second-line aiming to curtail claudication and other ALI- or CLI-related symptoms. To ensure the three exposures were administered as a second-line treatment, the targeted treatment in each cohort required a diagnosis of PAD and

exposure to either a statin (simvastatin, rosuvastatin, pravastatin, pitavastatin, lovastatin, fluvastatin, or atorvastatin) or an antiplatelet agent (clopidogrel or aspirin) prior to index.

Preliminary diagnostics executed against the study data indicated that propensity score matching would not achieve suitable balance between cohort comparisons if both diabetics and non-diabetics were included in the cohorts. Due to the confounding of treatment options and outcomes by diabetes, and the clinical guidelines suggesting non-diabetics as ideal candidates for PTA-based procedures, all patients were required to not have a history of diabetes prior to index. Within each endpoint, patients also could not have a history of the endpoint's outcomes prior to index. For the cilostazol cohort, patients who underwent either of the two PTA procedures pre-index were excluded.

As CPT4 procedure codes for PTA with stent and PTA with atherectomy became valid in May 2011, cilostazol was first approved for use by the FDA in 1999, and the study data sets have coverage until the end of 2016, the study window was established to require the treatment index to have occurred between June 1, 2011 and December 31, 2016. This ensured that all treatments of interest were available therapies for the study population. The risk window for each patient was limited to a maximum of two years of observation post-index. This censoring point was selected as it was consistent with other observational PAD studies that utilized Cox proportional hazards analyses, and was clinically relevant based on the known risk of LLA, MI, and death within two years of PAD diagnosis.

Initial analysis of patients who receive PTA with stent or PTA with atherectomy procedures indicated that the majority were handled in the outpatient or inpatient settings.

Table A below shows the distribution of patient settings using the OPTUM database (detailed in the "Data Sets" section).

Table A: Breakdown of Patient Setting among Percutaneous Transluminal Angioplasty (stent and atherectomy) procedures in OPTUM

Patient Setting	Number of Patients
Outpatient Visit	14,432
Inpatient Visit	5,431
Emergency Room Visit	62
Long Term Care Visit	3

As recent publications have indicated a growing trend in PTA procedures being conducted in the outpatient setting [56], both PTA-based treatments were required to have occurred there. This allowed for an investigation on endovascular techniques that were ostensibly "routine": scheduled PAD treatments rather than those that occurred due to emergency or were serious enough to require hospitalization.

Study Design

This study followed a retrospective, observational, comparative cohort design. "Retrospective" is defined as a study conducted using data already collected prior to the start of the study. "Observational" is defined as having no intervention or treatment assignment imposed by the study. "Cohort" is defined as having set of patients satisfying one or more inclusion criteria for a duration of time. "Comparative cohort design" is defined as the formal comparison between two cohorts, a target cohort and comparator cohort, for the risk of a set of outcomes during a defined time window after cohort entry.

Using this framework, PTA with stent and PTA with atherectomy were chosen as target cohorts, with cilostazol serving as the comparator cohort to each. The pairwise comparisons are summarized in Table B; all treatments mentioned were the second-line therapies following exposure to at least one first-line therapy.

Table B: Pairwise comparisons in the comparative effectiveness study

Target Treatment Pathway	Comparator Treatment Pathway	Domains Compared
PTA with stent	cilostazol	Procedure vs Drug
PTA with atherectomy	cilostazol	Procedure vs Drug

For each pairwise comparison, patients were excluded from consideration if they qualified for both the target cohort and comparator cohort at any time in their medical claims history. The time-to-event of the outcome in consideration among patients in the target and comparator cohorts was determined by calculating the number of days from the start of the time-at-risk window (1 day after index) until the earliest event among the following exit criteria:

(1) The end of the time-at-risk window.

Patients were censored two years after the treatment index date.

(2) The first occurrence of the outcome before the end of the time-at-risk window.

The index date was the incident occurrence of the targeted treatment, and the risk window begun one day after.

(3) The end of the available observation period that spans the time-at-risk start.

The observation periods in this study were obtained from insurance enrollment data.

Data Sets

The datasets utilized in this study were sourced from commercially available administrative insurance claims databases that were collected in an observational fashion. They capture all adjudicated claims for diagnoses, procedures, and outpatient drugs well, but cannot represent clinical events in which the patient did not seek medical care, and underrepresent lab tests, measurements, and death. These datasets included: (1) Optum Clinformatics™ Extended Data Mart, Date of Death ("OPTUM"); (2) Truven Health MarketScan® Commercial Claims and Encounters ("CCAE"); and (3) Truven Health MarketScan® Medicare Supplemental ("MDCR").

OPTUM data includes de-identified adjudicated claims sourced from a selection of large national payers, representing insurance plan enrollees with both medical and pharmacy benefits. Most payers in OPTUM operate commercial health plans covering populations across the entire United States. OPTUM covers 77,410,154 patients, spanning from May 2000 to December 2016. It includes conditions obtained from medical claims' diagnoses (International Classification of Diseases version 9 [ICD9CM] or version 10 [ICD10CM]) and procedure codes (version 9 [ICD9Proc] or version 10 [ICD10PCS]). Drug exposures (through National Drug Codes [NDC]) are available for patients, but are limited to the outpatient setting. Procedure occurrences originate from medical claims via Current Procedural Terminology, 4th Edition (CPT4) codes, Healthcare Common Procedure Coding System (HCPCS), ICD9Proc and ICD10PCS

procedural codes, ICD9CM and ICD10CM diagnoses codes, and lab results (Logical Observation Identifiers Names and Codes [LOINC]; CPT4, ICD9Proc, and ICD10PCS).

This version of OPTUM, "Date of Death," provides death data sourced from the United States Social Security Administration (SSA) and through the National Death Index (NDI) from the Centers for Disease Control (CDC). However, as the SSA stopped providing death data sourced from states in November 2011, this information has become limited to just records from the NDI. Consequently, death information can be considered incomplete for most patients in this study. Prior to November 2011, death records had an incidence of approximately 1.6 records per 1000 patients, but from then until the end of 2016, the incidence dropped to approximately 0.4 records per 1000 patients.

The Truven Health MarketScan® Research Databases contain individual-level, de-identified, healthcare claims information from employers, health plans, hospitals, Medicare, and Medicaid programs. These databases reflect the real world of treatment patterns and costs by tracking millions of patients as they travel through the healthcare system offering detailed information about all aspects of care. Data from individual patients are integrated from all providers of care, maintaining all healthcare utilization and cost record connections at the patient level.

Both CCAE and MDCR consist of enrollees in employer-sponsored insurance plans. Enrollees can be active employees, early retirees, or beneficiaries of the Consolidated Omnibus Budget Reconciliation Act (COBRA) from the United States with primary or Medicare supplemental coverage through privately insured fee-for-service, point-of-service, or capitated health plans. CCAE claims data spans across the continuum

of care (e.g. inpatient, outpatient, outpatient pharmacy, carve-out behavioral healthcare) as well as enrollment data from large employers and health plans across the United States, covering 133,649,076 patients up until age 65. A subset of patients then can be found in MDCR, which includes only Medicare-eligible active and retired employees and their dependents for 9,757,544 patient lives. Both include data for enrollees from January 2000 to December 2016.

CCAE and MDCR utilize codes originating from multiple source vocabularies: ICD9CM and ICD10CM codes for diagnoses; NDC codes for drug exposures; CPT4, HCPCS, and ICD9Proc for procedures. Without a primary source for death data, patient mortality records in CCAE and MDCR are inferred where possible by ICD9CM and ICD10CM codes (brain and cardiac death, infant mortality, severe brain injury, or legal execution) and discharge codes (any discharge status of "expired") [57]. As such, death information is sparse, with an incidence of approximately 0.05 records per 1000 patients.

Modelling and Tools

This study employed the usage of several open source data modelling and statistical analysis applications from the Observational Medical Outcomes Partnership (OMOP) [58] and the Observational Health Data Sciences and Informatics (OHDSI) initiative [59].

OMOP Common Data Model and OHDSI Analytic Packages

The OMOP Common Data Model (CDM), version 5.0.1 [60] is a framework to model observational data into a "comprehensive view of the clinical data a patient

accumulates while receiving healthcare" [61] that can allow for "a network-based approach to observational research across multiple, disparate observational health databases" [62]. The process to convert data into the CDM requires designating observational data events, such as insurance claim codes, towards a finite list of domains: condition, drug, procedure, measurement, observation, device, and specimen. All events must occur during a patient's known observation period to be considered valid, research-quality data; in the case of the databases used in this study, the observation period was derived from insurance enrollment records. Additionally, all source codes were translated to the OMOP Vocabulary, which utilizes standard terminologies from SNOMED, MedDra, LOINC, RxNorm, CPT4, and UCUM to provide "transparent and consistent content across disparate observational databases" [63] by mapping diagnosis, procedure, drug, and lab source code vocabularies into one comprehensive standardized vocabulary.

Once source terminologies are mapped to standard terminologies, the concepts per patient are then linked and aggregated to provide clinically relevant time durations that a disease or exposure is present in a patient's history. The concept of creating an "era" is a modelling technique in the OMOP CDM to link together chronological occurrences of coded events from a particular domain for a patient. Condition eras are defined as a span of time when the patient is assumed to have a given condition (such as a chronic disease), while drug eras are defined as a span of time when the patient is assumed to be taking a given drug.

Concept sets were designed using the OHDSI web application Atlas [64], which leverages the OMOP Vocabulary to provide a collection of source code and standard

vocabularies. “Concept set” refers to the selection of code concepts (e.g. conditions, drugs, procedures, measurements, observations, devices) that can define the elements of a disease- or exposure-based cohort. For this study, concept sets for the three treatment pathways, the two outcomes, the first-line therapy, and the historical diagnoses of PAD and diabetes were all constructs necessary to define the study cohorts (see “Concept Sets” supplemental section). The cohort definitions for each of the treatments and the outcomes were also built using Atlas, and leveraged these concept sets to build logical criteria for patient inclusion into the cohort. Condition eras for PAD, along with drug eras for cilostazol, statins, clopidogrel, and aspirin, established criteria such as treatment-naïve history or the targeted treatment itself.

Statistical analyses were completed using several open-source R packages published by stakeholders and community collaborators within OHDSI. All R packages were executed using R Version 3.4.0 (“You Stupid Darkness”) [65] to conduct cohort and covariate extraction, feature generation, propensity-score matching, large-scale regularized regression, and empirical calibration. The FeatureExtraction R package extracted all enabled covariates available for the subjects in the treatment, comparator, and outcome cohorts from the databases to act as features for use in propensity-score matching and outcome modelling [66]. The OHDSI R package CohortMethod [67] was utilized to generate one-to-one propensity scores between each intervention comparison via regularized logistic regression. Using propensity-score matched cohorts, the Cyclops R package [68] provided the regularized regression of the study cohort comparisons. Cyclops (“Cyclic Coordinate Descent for Logistic, Poisson and Survival Analysis”) is designed to model large-scale claims data like those used in this study, as millions of

covariates are possible. The EmpiricalCalibration R package [69] calibrated the outcome model *p*-values through the use of negative controls.

CHAPTER 3: STATISTICAL ANALYSIS

Feature Extraction

Table 6 shows the suite of covariate settings used in the FeatureExtraction package execution. Along with demographic categories, the covariate settings defined the allowable set of CDM domains from which covariates could be generated and the derived risk scores that were computed for each patient.

Covariate Settings

The covariate settings in FeatureExtraction also afforded the ability to establish time window categories for each domain. In this study, as the minimum observation period for entry into the targeted cohorts was 180 days, these categories were designated to fall within this range; “short-term” was set to 30 days, “medium-term” was set to 90 days, and “long-term” was set to 180 days. Computed covariates were also selected as features: the Charlson Comorbidity Index, which weights 19 comorbidities to create a risk score for mortality [70]; the $CHADS_2$ score, which provides a risk estimate for stroke in patients with atrial fibrillation based on diabetic- and cardiac-related comorbidities [71]; the CHA_2DS_2-VASc score, which provides a more granular risk estimate than $CHADS_2$ by adding factors of vascular disease, age, and sex [71]; and the Diabetes Complications Severity Index (DCSI), which provides a risk score for diabetic complications [72]. The interaction of each covariate with the year of the covariate’s occurrence was also captured to address potential bias of a covariate’s (such as a drug) availability and application given the year of occurrence. The minimum cell size for each

covariate was set to 100 to restrict infrequent covariates from hindering the propensity score matching.

Covariate Selection

While a wide array of covariates allowed in the propensity-score matching was theoretically useful in achieving strong balance between target and comparator cohorts, the sensitivity resulted in selecting covariates that were highly correlated with the exposures. Using such covariates diminished the number of patients viable for matching as the propensity model easily predicted which of the two exposures would be administered for patients who have those highly correlated covariates in their patient history.

One strategy to accommodate for these covariates was to simply remove them from consideration; that is, from the set of available covariates, the included concepts used to construct the cohorts were removed from the set of features extracted. Additionally, other concepts that were removed for being part of the treatment pathways included PAD conditions, statins, clopidogrel, and aspirin. However, as the study compares a drug against two different procedures, a variety of indirectly associated covariates needed to be excluded. For the PTA-based cohorts, special care to exclude pre- and post-operative covariates that are associated with procedures was taken. Among these excluded covariates: local and intravenous anesthetics for the PTA procedure, catheter usage, antiemetic drugs for postoperative nausea, and outpatient visit-related concepts. Additionally, due to the use of heparin-based drugs pre- and post-PTA [73], heparin-based treatments (including low molecular weight heparin [LMWH]) were excluded as

covariates in the propensity-score matching process; protamine sulfate, which is often used to reverse the effects of heparin, was also excluded.

Propensity-Score Matching

Propensity scores were used as an analytic strategy to reduce potential confounding due to imbalance between the target and comparator cohorts in baseline covariates. The propensity score refers to the probability of a patient being classified in the target cohort versus the comparator cohort, given a set of observed covariates. In each sub-study, the propensity score was estimated for each patient, using the predicted probability from a regularized logistic regression model, and was fit with a Laplace prior (LASSO); the regularization hyper-parameter was selected by optimizing the likelihood in a 10-fold cross validation, using a starting variance of 0.01 and a tolerance of 2e-7. Cohorts were determined to be well balanced if their covariates had a standardized mean difference (SMD) below 0.1. This threshold has been identified as a benchmark in propensity-score matching that indicates “a negligible difference in the mean or prevalence of a covariate between treatment groups” [74].

Outcome Modelling

Conditional Cox proportional hazards models were generated for each cohort comparison after propensity-score matching and were summarized by providing the hazards ratio and associated 95% confidence interval. The number of patients, amount of time-at-risk, and number of outcomes in each cohort were also reported. The statistical tests executed to support outcome modelling were two-sided; all *p*-values were interpreted to be significant if below 0.05.

Negative Controls

Negative control outcomes were used to evaluate the potential impact of residual systematic error in the study design and facilitated empirical calibration of the *p*-value for the outcomes of interest. The negative control outcomes selected were concepts known not to be associated with either the target or comparator group, such that it would be reasonable to assume the true relative risk should equal 1. The Largescale Adverse Effects Related to Treatment Evidence Standardization (LAERTES) system [75, 76] was utilized to identify these concepts. LAERTES culls known drug-outcome associations through: the US Food and Drug Administration (FDA) Adverse Event Reporting System (FAERS); the Structured Produce Labelling (SPL) system; the Summary of Product Characteristics (SPC); the First Databank™ Electronic Health Record; the National Drug File Reference Terminology (NDF-RT); and the Comparative Toxicogenomics Database (CTD). A clinically curated subset of negative controls was selected from the outcomes with no known associations across these sources and then utilized as outcomes for the 4 sub-studies.

For each negative control outcome, the study design described above was implemented and the effect estimate was recorded. The distribution of effect estimates across all negative control outcomes was used to fit an empirical null distribution which modeled the observed residual systematic error. The empirical null distribution was then applied to the target outcome of interest to calibrate the *p*-value. Empirical calibration served as an important diagnostic tool to evaluate if the residual systematic error was sufficient to cast doubt on the accuracy of the unknown effect estimate. A calibration

effect plot and calibration probability plots were generated and reviewed. Consequently, the results from this study report both the traditional *p*-value and empirically calibrated p-value for each negative control, as well as the unknown outcomes of interest.

The final list of negative control candidates (Table 8) was designed by selecting the intersection of the LAERTES-generated candidates for the drug exposures in the study: statins, clopidogrel, aspirin, and cilostazol. This list was then curated via clinical review to ensure that, even with the absence of known literature in LAERTES, the negative controls could not plausibly be associated with the exposures of interest. The curated list of negative controls was utilized for each intervention comparison as part of a new study endpoint, whose purpose was to model the distribution of non-null effect estimates. The distribution was then the basis for the empirical calibration of the outcome models' *p*-values.

CHAPTER 4: RESULTS

Cohort Characterization

Tables 1a and 1b summarize the cohorts pre- and post-propensity score matching from OPTUM. In a data set with patients covering all age ranges, the median age at index was between 69 and 72 years across the treatment pathways pre-matching, with initial diagnosis for PAD approximately two years prior. Based on $CHADS_2$ (median score of 2) and CHA_2DS_2Vasc (median score of 4) scores, subjects had an adjusted stroke risk of 4% per year at baseline [71]. Hypertension and hyperlipidemia were extremely prevalent comorbidities (over 90%); statin usage was approximately 85%, while about 45% of subjects had exposure to clopidogrel.

Table 1a: OPTUM, First-line to PTA with Stent vs First-line to Cilostazol

("OPTUM" = Optum Clinformatics™ Extended Data Mart, Date of Death version; "First-line" = first line treatment of statins, clopidogrel, or aspirin; "PTA" = percutaneous transluminal angioplasty; "N" = number of patients; "SD" = standard deviation; "LLA" = lower limb amputation; "PAB" = peripheral arterial bypass; "MI" = myocardial infarction; "Dx" = diagnosis; "PAD" = peripheral arterial disease)

Baseline Characteristic	Before Matching				After Matching: LLA/PAB				After Matching: MI/Stroke/Death			
	Stent		Cilostazol		Stent		Cilostazol		Stent		Cilostazol	
	N=2804	%	N=3779	%	N=1720	%	N=1720	%	N=1536	%	N=1536	%
Age at Index												
mean	68.81		71.74		70.45		70.13		70.38		69.74	
sd	10.12		10.27		10.33		10.00		10.29		10.09	
median	69		72		71		71		71		70	
min	22		15		22		32		22		15	
max	89		89		89		89		89		89	
Age groups												
15-19	0	0	1	0.03	0	0	0	0.00	0	0	1	0.05
20-24	1	0.02	1	0.03	1	0.04	0	0.00	1	0.05	0	0
25-29	0	0.00	1	0.03	0	0	0	0.00	0	0	0	0
30-34	1	0.02	2	0.05	1	0.04	2	0.09	1	0.05	2	0.1
35-39	6	0.12	5	0.13	3	0.14	3	0.14	4	0.2	4	0.20
40-44	31	0.65	24	0.64	20	0.91	14	0.64	15	0.76	12	0.61

45-49	113	2.35	59	1.56	37	1.68	37	1.68	34	1.72	32	1.62
50-54	256	5.33	134	3.55	96	4.37	93	4.23	90	4.56	95	4.82
55-59	493	10.27	272	7.20	201	9.14	192	8.73	175	8.87	178	9.03
60-64	682	14.21	350	9.26	225	10.23	269	12.23	202	10.24	246	12.47
65-69	919	19.14	635	16.80	377	17.14	401	18.24	340	17.24	379	19.22
70-74	906	18.87	702	18.58	423	19.24	428	19.46	393	19.93	369	18.71
75-79	577	12.02	608	16.09	327	14.87	335	15.23	286	14.50	289	14.65
80-84	518	10.79	596	15.77	308	14.01	274	12.46	275	13.95	237	12.02
85-89	298	6.21	389	10.29	180	8.19	151	6.87	156	7.91	128	6.49
$CHADS_2$												
Mean	1.99		2.13		2.08		2.06		1.95		1.9	
Sd	1.28		1.29		1.33		1.29		1.26		1.22	
median	2.00		2.00		2.00		2.00		2.00		2.00	
Min	0		0		0		0		0		0	
Max	6		6		6		6		6		6	
CHA_2DS_2Vasc												
mean	4.20		4.23		4.26		4.20		4.16		4.03	
sd	1.60		1.59		1.63		1.63		1.55		1.57	
median	4		4		4		4		4		4	
min	1		1		1		1		1		1	
max	9		9		9		9		9		9	
Days from First PAD Dx												
mean	1051.36		1106.68		1039.26		1081.33		1031.18		1061.89	
sd	1081.58		1053.18		1076.53		1046.20		1073.27		1044.74	
median	677.00		779.00		658.00		755.00		642.00		724.00	
min	1		1		1		1		1		1	
max	5908		5943		5908		5810		5908		5810	
Comorbidities												
Smoking	2680	55.82	1582	41.86	1101	50.07	1000	45.48	954	48.38	891	45.18
Hypertension	4378	91.19	3460	91.56	1997	90.81	2010	91.41	1783	90.42	1782	90.36
Hyperlipidemia	4360	90.81	3390	89.71	1996	90.77	1998	90.86	1767	89.60	1774	89.96
Medications												
Statins	4124	85.90	3263	86.35	1887	85.81	1902	86.49	1651	83.72	1676	84.99
Clopidogrel	2788	58.07	1659	43.90	1231	55.98	979	44.52	1070	54.26	832	42.19
Aspirin	142	2.96	139	3.68	70	3.18	79	3.59	51	2.59	54	2.74

Table 1b: OPTUM, First-line to PTA with Atherectomy vs First-line to Cilostazol

("OPTUM" = Optum Clinformatics™ Extended Data Mart, Date of Death version; "First-line" = first line treatment of statins, clopidogrel, or aspirin; "PTA" = percutaneous transluminal angioplasty; "N" = number of patients; "SD" = standard deviation; "LLA" = lower limb amputation; "PAB" = peripheral arterial bypass; "MI" = myocardial infarction; "Dx" = diagnosis; "PAD" = peripheral arterial disease)

Baseline Characteristic	Before Matching				After Matching: LLA/PAB				After Matching: MI/Stroke/Death			
	Atherectomy		Cilostazol		Atherectomy		Cilostazol		Atherectomy		Cilostazol	
	N=2804	%	N=3779	%	N=1720	%	N=1720	%	N=1536	%	N=1536	%
Age at Index												
mean	70.98		71.74		70.98		71.46		70.87		71.13	
sd	10.00		10.27		10.04		10.02		10.01		9.96	
median	71		72		71		72		71		72	
min	25		15		30		39		30		39	
max	89		89		89		89		89		89	
Age groups												
15-19	0	0	1	0.03	0	0	0	0.00	0	0	0	0
20-24	0	0	1	0.03	0	0	0	0.00	0	0	0	0
25-29	1	0.04	1	0.03	0	0	0	0.00	0	0	0	0
30-34	2	0.07	2	0.05	2	0.12	0	0.00	2	0.13	0	0
35-39	3	0.11	5	0.13	2	0.12	1	0.06	2	0.13	1	0.06
40-44	7	0.25	24	0.64	5	0.29	10	0.58	5	0.33	10	0.65
45-49	36	1.28	59	1.56	21	1.22	20	1.16	21	1.37	16	1.04
50-54	97	3.46	134	3.55	66	3.84	57	3.31	59	3.84	54	3.52
55-59	260	9.27	272	7.20	153	8.89	149	8.66	129	8.40	139	9.05
60-64	313	11.16	350	9.26	191	11.11	182	10.58	169	11.00	164	10.68
65-69	496	17.69	635	16.80	302	17.56	292	16.98	288	18.75	274	17.84
70-74	516	18.40	702	18.58	304	17.67	301	17.50	272	17.71	268	17.45
75-79	427	15.23	608	16.09	263	15.29	280	16.28	232	15.10	248	16.15
80-84	391	13.94	596	15.77	258	15.00	274	15.93	227	14.78	229	14.91
85-89	255	9.09	389	10.29	153	8.89	154	8.95	130	8.46	133	8.66
$CHADS_2$												
mean	2.19		2.13		2.13		2.29		2.02		2.11	
sd	1.32		1.29		1.31		1.34		1.26		1.26	
median	2.00		2.00		2.00		2.00		2.00		2.00	
min	0		0		0		0		0		0	
max	6		6		6		6		6		6	
CHA_2DS_2Vasc												
mean	4.41		4.23		4.33		4.42		4.23		4.24	
sd	1.62		1.59		1.58		1.64		1.52		1.58	
median	4		4		4		4		4		4	

min	1		1		1		1		1		1	
max	9		9		9		9		9		9	
Days from First PAD Dx												
mean	1064.86		1106.68		988.97		1162.49		955.94		1134.57	
sd	1074.96		1053.18		1014.90		1110.71		977.16		1097.63	
median	696.50		779.00		627.50		789.50		605.00		758.50	
min	2		1		2		2		2		2	
max	5487		5943		5375		5943		5155		5943	
Comorbidities												
Smoking	1352	48.22	1582	41.86	796	46.28	771	44.83	696	45.31	694	45.18
Hypertension	2625	93.62	3460	91.56	1600	93.02	1608	93.49	1417	92.25	1423	92.64
Hyperlipidemia	2580	92.01	3390	89.71	1580	91.86	1568	91.16	1393	90.69	1390	90.50
Medications												
Statins	2365	84.34	3263	86.35	1459	84.83	1503	87.38	1275	83.01	1309	85.22
Clopidogrel	1837	65.51	1659	43.90	1111	64.59	804	46.74	982	63.93	684	44.53
Aspirin	93	3.32	139	3.68	64	3.72	74	4.30	44	2.87	54	3.52

In MDCR (Tables 1c and 1d), which has a population largely 65 years of age and above, the median age at index for all treatment pathways was 76 to 78 years. Initial diagnosis for PAD was nearly three years prior to index for most subjects. Based on $CHADS_2$ (median score of 2) and CHA_2DS_2Vasc (median score of 5) scores, subjects had an adjusted stroke risk of between 4% and 6.7% per year at baseline [71]. Hypertension was an extremely prevalent comorbidity, with over 90% of subjects having a diagnosis prior to index. Hyperlipidemia was also very prevalent, with over 83% across both comparisons. Statin usage was similar to OPTUM, with approximately 85% of subjects. Approximately 60% to 67% of PTA subjects had prior clopidogrel usage pre-matching, but this proportion dropped to 40% to 45% post-matching.

Table 1c: MDCR, First-line to PTA with Stent vs First-line to Cilostazol

("MDCR" = Truven Health MarketScan® Medicare Supplemental; "First-line" = first line treatment of statins, clopidogrel, or aspirin; "PTA" = percutaneous transluminal angioplasty; "N" = number of patients; "SD" = standard deviation; "LLA" = lower limb amputation; "PAB" = peripheral arterial bypass; "MI" = myocardial infarction; "Dx" = diagnosis; "PAD" = peripheral arterial disease)

Baseline Characteristic	Before Matching				After Matching: LLA/PAB				After Matching: MI/Stroke/Death			
	Stent		Cilostazol		Stent		Cilostazol		Stent		Cilostazol	
	N=4214	%	N=3697	%	N=2400	%	N=2400	%	N=2087	%	N=2087	%
Age at Index												
mean	76.28		78.19		77.08		77.00		76.87		76.69	
sd	7.26		7.79		7.42		7.53		7.39		7.50	
median	76		78		77		77		76		76	
min	53		53		53		53		53		53	
max	102		100		102		100		102		100	
Age groups												
50-54	3	0.07	2	0.05	3	0.12	2	0.08	1	0.05	2	0.1
55-59	17	0.40	11	0.30	11	0.46	5	0.21	9	0.43	4	0.19
60-64	51	1.21	29	0.78	31	1.29	15	0.62	30	1.44	12	0.57
65-69	780	18.51	512	13.85	369	15.38	419	17.46	335	16.1	394	18.88
70-74	1018	24.16	761	20.58	533	22.21	560	23.33	476	22.81	502	24.05
75-79	971	23.04	791	21.40	547	22.79	534	22.25	482	23.09	452	21.66
80-84	742	17.61	744	20.12	470	19.58	458	19.08	385	18.45	387	18.54
85-89	456	10.82	540	14.61	308	12.83	281	11.71	267	12.79	229	10.97
90-94	142	3.37	245	6.63	111	4.62	86	3.58	90	4.31	77	3.69
95-99	33	0.78	58	1.57	16	0.67	38	1.58	11	0.53	26	1.25
100+	1	0.02	4	0.11	1	0.04	2	0.08	1	0.05	2	0.10
$CHADS_2$												
mean	2.42		2.53		2.45		2.44		2.28		2.2	
sd	1.35		1.34		1.36		1.34		1.29		1.24	
median	2.00		2.00		2.00		2.00		2.00		2.00	
min	0		0		0		0		0		0	
max	6		6		6		6		6		6	
CHA_2DS_2Vasc												
mean	4.95		4.83		4.86		4.82		4.70		4.61	
sd	1.50		1.50		1.49		1.51		1.43		1.45	
median	5		5		5		5		5		4	
min	1		1		1		1		1		1	
max	9		9		9		9		9		9	
Days from First PAD Dx												
mean	1420.03		1435.82		1373.58		1375.79		1329.35		1318.46	

sd	1197.03		1213.55		1206.56		1195.30		1186.84		1156.01	
median	1096.00		1083.00		1040.50		997.00		972.00		962.00	
min	1		1		1		1		1		1	
max	5728		5619		5728		5619		5728		5619	
Comorbidities												
Smoking	1122	26.63	735	19.88	552	23.00	519	21.62	460	22.04	437	20.94
Hypertension	3897	92.48	3401	91.99	2195	91.46	2195	91.46	1889	90.51	1887	90.42
Hyperlipidemia	3520	83.53	3052	82.55	1973	82.21	1995	83.12	1714	82.13	1733	83.04
Medications												
Statins	3691	87.59	3185	86.15	2095	87.29	2079	86.62	1805	86.49	1801	86.30
Clopidogrel	2590	61.46	1661	44.93	1430	59.58	1087	45.29	1200	57.50	874	41.88
Aspirin	193	4.58	195	5.28	104	4.33	117	4.88	64	3.07	79	3.79

Table 1d: MDCR, First-line to PTA with Atherectomy vs First-line to Cilostazol

("MDCR" = Truven Health MarketScan® Medicare Supplemental; "First-line" = first line treatment of statins, clopidogrel, or aspirin; "PTA" = percutaneous transluminal angioplasty; "N" = number of patients; "SD" = standard deviation; "LLA" = lower limb amputation; "PAB" = peripheral arterial bypass; "MI" = myocardial infarction; "Dx" = diagnosis; "PAD" = peripheral arterial disease)

Baseline Characteristic	**Before Matching**				**After Matching: LLA/PAB**				**After Matching: MI/Stroke/Death**			
	Atherectomy N=2906	**%**	**Cilostazol N=3697**	**%**	**Atherectomy N=1920**	**%**	**Cilostazol N=1920**	**%**	**Atherectomy N=1715**	**%**	**Cilostazol N=1715**	**%**
Age at Index												
mean	77.53		78.19		77.28		78.17		77.10		77.65	
sd	7.52		7.79		7.58		7.75		7.63		7.69	
median	78		78		77		78		77		77	
min	45		53		45		53		45		53	
max	101		100		97		100		101		100	
Age groups												
45-49	1	0.03	0	0.00	1	0.05	0	0.00	1	0.06	0	0
50-54	1	0.03	2	0.05	1	0.05	1	0.05	1	0.06	1	0.06
55-59	14	0.48	11	0.30	11	0.57	3	0.16	11	0.64	3	0.18
60-64	31	1.07	29	0.78	24	1.25	18	0.94	17	0.99	16	0.93
65-69	435	14.97	512	13.85	299	15.57	284	14.79	285	16.6	281	16.39
70-74	597	20.54	761	20.58	407	21.20	370	19.27	375	21.87	353	20.58
75-79	636	21.89	791	21.40	407	21.20	404	21.04	356	20.76	358	20.88
80-84	628	21.61	744	20.12	404	21.04	409	21.30	355	20.70	353	20.58
85-89	394	13.56	540	14.61	260	13.54	292	15.21	216	12.60	238	13.88
90-94	156	5.37	245	6.63	100	5.21	102	5.31	90	5.25	87	5.07
95-99	12	0.41	58	1.57	6	0.31	36	1.88	7	0.41	24	1.40
100+	1	0.03	4	0.11	0	0.00	1	0.05	1	0.06	1	0.06
$CHADS_2$												

mean	2.61		2.53		2.49		2.63		2.31		2.37	
sd	1.36		1.34		1.33		1.35		1.27		1.27	
median	2.00		2.00		2.00		2.00		2.00		2.00	
min	0		0		0		0		0		0	
max	6		6		6		6		6		6	
CHA_2DS_2Vasc												
mean	5.06		4.83		4.93		4.99		4.76		4.76	
sd	1.46		1.50		1.43		1.49		1.38		1.42	
median	5		5		5		5		5		5	
min	1		1		1		1		1		1	
max	9		9		9		9		9		9	
Days from First PAD Dx												
mean	1492.54		1435.82		1391.72		1518.77		1328.25		1431.40	
sd	1243.06		1213.55		1218.79		1251.13		1189.66		1215.39	
median	1166.50		1083.00		1028.00		1175.00		935.00		1098.00	
min	4		1		5		1		4		1	
max	6075		5619		6075		5357		6075		5318	
Comorbidities												
Smoking	668	22.99	735	19.88	408	21.25	398	20.73	355	20.70	354	20.64
Hypertension	2709	93.22	3401	91.99	1772	92.29	1776	92.50	1569	91.49	1568	91.43
Hyperlipidemia	2483	85.44	3052	82.55	1629	84.84	1625	84.64	1433	83.56	1436	83.73
Medications												
Statins	2488	85.62	3185	86.15	1641	85.47	1661	86.51	1445	84.26	1476	86.06
Clopidogrel	1950	67.10	1661	44.93	1281	66.72	878	45.73	1113	64.90	735	42.86
Aspirin	152	5.23	195	5.28	90	4.69	103	5.37	71	4.14	70	4.08

Lastly, in CCAE (Tables 1e and 1f), which has a population mainly below age 65, the median age at index for all treatment pathways was 59 years. Initial diagnosis for PAD was much closer to index than in OPTUM or MDCR; most subjects had their first PAD diagnosis within 1.5 years prior to index. Based on $CHADS_2$ (median score of 1) and CHA_2DS_2Vasc (median scores of 2 and 3) scores, subjects had an adjusted stroke risk of between 2.8% and 3.2% per year at baseline [71]. Hypertension was less prevalent than in the other data sets, with 80 to 85% of subjects having a prior diagnosis, while hyperlipidemia prevalence was similar to MDCR, with approximately 80 to 83% across

all treatment pathways. Statin and clopidogrel history was similar to OPTUM and MDCR, but aspirin usage slightly higher with 6% to 7% usage observed.

Table 1e: CCAE, First-line to PTA with Stent vs First-line to Cilostazol

("CCAE" = Truven Health MarketScan® Commercial Claims and Encounters; "First-line" = first line treatment of statins, clopidogrel, or aspirin; "PTA" = percutaneous transluminal angioplasty; "N" = number of patients; "SD" = standard deviation; "LLA" = lower limb amputation; "PAB" = peripheral arterial bypass; "MI" = myocardial infarction; "Dx" = diagnosis; "PAD" = peripheral arterial disease)

Baseline Characteristic	Before Matching				After Matching: LLA/PAB				After Matching: MI/Stroke/Death			
	Stent		Cilostazol		Stent		Cilostazol		Stent		Cilostazol	
	N=3883	%	N=2340	%	N=1555	%	N=1555	%	N=1420	%	N=1420	%
Age at Index												
mean	57.76		57.56		57.68		57.79		57.72		57.81	
sd	5.53		6.38		5.79		5.86		5.81		5.77	
median	59		59		59		59		59		59	
min	26		15		26		23		26		23	
max	65		65		65		65		65		65	
Age groups												
15-19	0	0	3	0.13	0	0	0	0.00	0	0	0	0
20-24	0	0	4	0.17	0	0	1	0.06	0	0	1	0.07
25-29	2	0.05	1	0.04	2	0.13	0	0.00	2	0.14	0	0
30-34	4	0.10	12	0.51	3	0.19	5	0.32	3	0.21	4	0.28
35-39	16	0.41	21	0.90	6	0.39	12	0.77	6	0.42	7	0.49
40-44	68	1.75	59	2.52	35	2.25	34	2.19	35	2.46	27	1.90
45-49	240	6.18	132	5.64	103	6.62	80	5.14	90	6.34	81	5.70
50-54	636	16.38	356	15.21	249	16.01	245	15.76	211	14.86	230	16.20
55-59	1127	29.02	639	27.31	423	27.20	434	27.91	396	27.89	390	27.46
60-64	1631	42.00	1006	42.99	667	42.89	668	42.96	621	43.73	610	42.96
65-69	159	4.09	107	4.57	67	4.31	76	4.89	56	3.94	70	4.93
$CHADS_2$												
mean	1.3		1.3		1.27		1.31		1.17		1.17	
sd	0.97		0.99		0.97		0.99		0.91		0.89	
median	1.00		1.00		1.00		1.00		1.00		1.00	
min	0		0		0		0		0		0	
max	5		4		5		4		5		4	
CHA_2DS_2Vasc												
mean	2.95		2.76		2.74		2.80		2.67		2.67	
sd	1.24		1.21		1.14		1.24		1.11		1.19	
median	3		3		2		3		2		2	

min	1		1		1		1		1		1	
max	7		7		7		7		7		7	
Days from First PAD Dx												
mean	808.46		871.66		754.96		871.46		759.71		829.70	
sd	982.64		981.39		947.36		987.04		951.66		936.29	
median	408.00		490.50		357.00		493.00		366.50		483.00	
min	1		1		1		1		1		1	
max	5836		5709		5836		5709		5836		5709	
Comorbidities												
Smoking	2245	57.82	1135	48.50	850	54.66	779	50.10	761	53.59	703	49.51
Hypertension	3152	81.17	1898	81.11	1244	80.00	1275	81.99	1116	78.59	1136	80.00
Hyperlipidemia	3219	82.90	1948	83.25	1273	81.86	1330	85.53	1153	81.20	1202	84.65
Medications												
Statins	3346	86.17	1938	82.82	1326	85.27	1330	85.53	1194	84.08	1192	83.94
Clopidogrel	2248	57.89	1015	43.38	855	54.98	683	43.92	756	53.24	602	42.39
Aspirin	249	6.41	149	6.37	111	7.14	95	6.11	83	5.84	80	5.63

Table 1f: CCAE, First-line to PTA with Atherectomy vs First-line to Cilostazol

("CCAE" = Truven Health MarketScan® Commercial Claims and Encounters; "First-line" = first line treatment of statins, clopidogrel, or aspirin; "PTA" = percutaneous transluminal angioplasty; "N" = number of patients; "SD" = standard deviation; "LLA" = lower limb amputation; "PAB" = peripheral arterial bypass; "MI" = myocardial infarction; "Dx" = diagnosis; "PAD" = peripheral arterial disease)

Baseline Characteristic	**Before Matching**				**After Matching: LLA/PAB**				**After Matching: MI/Stroke/Death**			
	Atherectomy		**Cilostazol**		**Atherectomy**		**Cilostazol**		**Atherectomy**		**Cilostazol**	
	N=1542	**%**	**N=2340**	**%**	**N=1125**	**%**	**N=1125**	**%**	**N=1039**	**%**	**N=1039**	**%**
Age at Index												
mean	58.35		57.56		58.13		58.07		58.15		58.23	
sd	5.17		6.38		5.34		5.70		5.34		5.58	
median	59		59		59		59		59		59	
min	30		15		30		22		30		22	
max	65		65		65		65		65		65	
Age groups												
15-19	0	0	3	0.13	0	0	0	0.00	0	0	0	0
20-24	0	0	4	0.17	0	0	1	0.09	0	0	1	0.1
25-29	0	0.00	1	0.04	0	0	0	0.00	0	0	0	0
30-34	4	0.26	12	0.51	3	0.27	3	0.27	3	0.29	3	0.29
35-39	5	0.32	21	0.90	5	0.44	8	0.71	4	0.38	5	0.48
40-44	22	1.43	59	2.52	18	1.60	25	2.22	18	1.73	20	1.92
45-49	65	4.21	132	5.64	52	4.62	54	4.80	44	4.24	48	4.62

50-54	204	13.23	356	15.21	165	14.67	148	13.16	156	15.01	135	12.99
55-59	477	30.93	639	27.31	342	30.40	337	29.96	313	30.12	308	29.64
60-64	691	44.81	1006	42.99	487	43.29	495	44.00	450	43.31	466	44.85
65-69	74	4.80	107	4.57	53	4.71	54	4.80	51	4.91	53	5.10
$CHADS_2$												
mean	1.34		1.3		1.27		1.37		1.15		1.23	
sd	0.97		0.99		0.94		1.02		0.83		0.94	
median	1.00		1.00		1.00		1.00		1.00		1.00	
min	0		0		0		0		0		0	
max	5		4		5		4		4		4	
CHA_2DS_2Vasc												
mean	2.84		2.76		2.78		2.80		2.65		2.67	
sd	1.20		1.21		1.18		1.24		1.09		1.20	
median	3		3		2		3		2		2	
min	1		1		1		1		1		1	
max	8		7		8		7		6		7	
Days from First PAD Dx												
mean	792.53		871.66		739.66		874.79		708.10		829.90	
sd	954.95		981.39		929.80		976.15		893.95		921.74	
median	421.00		490.50		378.00		492.00		365.00		484.00	
min	2		1		2		1		2		1	
max	5342		5709		5342		5413		5204		5413	
Comorbidities												
Smoking	851	55.19	1135	48.50	598	53.16	591	52.53	545	52.45	544	52.36
Hypertension	1315	85.28	1898	81.11	941	83.64	924	82.13	856	82.39	828	79.69
Hyperlipidemia	1281	83.07	1948	83.25	919	81.69	958	85.16	835	80.37	870	83.73
Medications												
Statins	1278	82.88	1938	82.82	934	83.02	971	86.31	843	81.14	879	84.60
Clopidogrel	1069	69.33	1015	43.38	777	69.07	534	47.47	707	68.05	482	46.39
Aspirin	108	7.00	149	6.37	69	6.13	80	7.11	54	5.20	70	6.74

Propensity Score Matching

Propensity score matching was largely successful in achieving balance between the cohort comparisons, as the SMD was below 0.1 (visualized in Figures 1-6). Excluding correlated covariates from the propensity score matching helped in balancing the cohorts being compared, although, a minority of covariates had an SMD above 0.1. The number

of covariates and the proportion relative to all covariates is summarized below in Table 2. No imbalance proportion was larger than 0.55% of the matched covariates.

Table 2: Proportion of Unbalanced Covariates across OPTUM, MDCR, and CCAE

("OPTUM" = Optum Clinformatics™ Extended Data Mart, Date of Death version; "MDCR" = Truven Health MarketScan® Medicare Supplemental; "CCAE" = Truven Health MarketScan® Commercial Claims and Encounters; "T" = Target; "C" = Comparator; "First-line" = first line treatment of statins, clopidogrel, or aspirin; "Stent" = First-line to PTA with stent; "Ath" = "First-line to PTA with atherectomy"; "Cilo" = First-line to cilostazol; "LLA" = lower limb amputation; "PAB" = peripheral arterial bypass; "MI" = myocardial infarction)

Database	T vs C	Outcome	Total Covariates	Unbalanced Covariates	Proportion Imbalance
OPTUM	Ath vs Cilo	LLA/PAB	2324	3	0.13%
OPTUM	Stent vs Cilo	LLA/PAB	2725	0	0.00%
OPTUM	Ath vs Cilo	MI/Stroke/ Death	2324	3	0.13%
OPTUM	Stent vs Cilo	MI/Stroke/ Death	2725	0	0.00%
MDCR	Ath vs Cilo	LLA/PAB	1583	5	0.32%
MDCR	Stent vs Cilo	LLA/PAB	1838	0	0.00%
MDCR	Ath vs Cilo	MI/Stroke/ Death	1583	4	0.25%
MDCR	Stent vs Cilo	MI/Stroke/ Death	1838	1	0.05%
CCAE	Ath vs Cilo	LLA/PAB	731	4	0.55%
CCAE	Stent vs Cilo	LLA/PAB	1137	0	0.00%
CCAE	Ath vs Cilo	MI/Stroke/ Death	731	2	0.27%
CCAE	Stent vs Cilo	MI/Stroke/ Death	1137	0	0.00%

Examining further, no after matching SMD exceeded an absolute value of 0.147 (Table 7). 10 of the 22 total unbalanced covariates were related to the computed risk scores of $CHADS_2$, Charlson Comorbidity Index, and DCSI. Before matching, all three

scores were higher on average for the patients undergoing PTA with atherectomy than the cilostazol patients, but after matching, the scores skewed higher among the cilostazol patients.

The eight unbalanced covariates consisted of prior drug eras of tramadol (an opioid), ramapril (an ACE inhibitor), labetalol (a calcium channel blocker), allopurinol (an antigout agent), atropine (an antimuscarinic agent), cyclobenzaprine (a muscle relaxant), and ibuprofen. The specificity in drug exposures was determined to be a byproduct of the covariate setting in FeatureExtraction disabling drug concept grouping into higher level ATC codes and ingredients (Table 6). Two of the unbalanced covariates were related to the number of observations recorded in the 180 days prior to index. Additionally, as temporal covariates related to the index were allowed in the propensity modelling, one covariate related to the month of April with the PTA with atherectomy vs cilostazol safety endpoint in CCAE could not be matched suitably. The low number of total unbalanced covariates, the limited deviation of the SMD absolute value from the 0.1 threshold, and the lack of clinical significance associated with the unbalance covariates factored into the decision to proceed with outcome modelling despite technically failing to achieve full balance.

The attrition from removing subjects in both target and comparator, subjects with prior outcomes, subjects without at least one day at risk, and subjects not matched on propensity score resulted in study cohorts with at least 1,039 patients (visualized in Figures 13-24). Initial cohort sizes were smaller in CCAE due to the age range of the data

set being limited to those younger than 65 years and the majority of PAD patients skewing towards ages 60 and above [36].

Survival Time

Median survival time, measured in days, is summarized in the table below (visualized in Figures 25-30). In the OPTUM and MDCR data sets, half of the patients in both target and comparator have at least 523 days of survival time. In CCAE, partly due to the enrollment switching of patients at age 65 to MDCR, the distribution of follow-up time skews more left, as half of the target and comparator cohorts each survived at least 422 days.

Table 3: Survival Time Summary, in Days ("T" = Target, "C" = Comparator)

("OPTUM" = Optum Clinformatics™ Extended Data Mart, Date of Death version; "MDCR" = Truven Health MarketScan® Medicare Supplemental; "CCAE" = Truven Health MarketScan® Commercial Claims and Encounters; "T" = Target; "C" = Comparator; "First-line" = first line treatment of statins, clopidogrel, or aspirin; "Stent" = First-line to PTA with stent; "Ath" = "First-line to PTA with atherectomy"; "Cilo" = First-line to cilostazol; "LLA" = lower limb amputation; "PAB" = peripheral arterial bypass; "MI" = myocardial infarction)

Database	Target	Comparator	Outcome	T Median Survival Time	C Median Survival Time
OPTUM	Ath	Cilo	LLA/PAB	552	523.5
OPTUM	Stent	Cilo	LLA/PAB	572	578
MDCR	Ath	Cilo	LLA/PAB	619	588
MDCR	Stent	Cilo	LLA/PAB	628	610
CCAE	Ath	Cilo	LLA/PAB	428	427
CCAE	Stent	Cilo	LLA/PAB	476	442
OPTUM	Ath	Cilo	MI/Stroke/Death	549	529
OPTUM	Stent	Cilo	MI/Stroke/Death	591.5	572.5
MDCR	Ath	Cilo	MI/Stroke/Death	629	595
MDCR	Stent	Cilo	MI/Stroke/Death	627	615
CCAE	Ath	Cilo	MI/Stroke/Death	422	432
CCAE	Stent	Cilo	MI/Stroke/Death	477	437.5

Outcome Models (Uncalibrated)

The outcome models across the three data sets detailed in Table 4 below (and visualized in Figures 37-39), show the effect estimates, confidence intervals with uncalibrated *p*-values, incidence rate per 100 person-years (IR), and event counts.

Table 4: Uncalibrated Primary Outcome Models across OPTUM, MDCR, and CCAE

("OPTUM" = Optum Clinformatics™ Extended Data Mart, Date of Death version; "MDCR" = Truven Health MarketScan® Medicare Supplemental; "CCAE" = Truven Health MarketScan® Commercial Claims and Encounters; "T" = Target; "C" = Comparator; "First-line" = first line treatment of statins, clopidogrel, or aspirin; "Stent" = First-line to PTA with stent; "Ath" = "First-line to PTA with atherectomy"; "Cilo" = First-line to cilostazol; "LLA" = lower limb amputation; "PAB" = peripheral arterial bypass; "MI" = myocardial infarction; "+" and red font = statistically significant; "IR" = Incidence Rate per 100 person-years)

Database	T vs C	Outcome	HR	95% CI	*p*-value	IR (T)	IR (C)	Events (T)	Events (C)
OPTUM	Stent vs Cilo	LLA, PAB	1.92	1.07, 3.47	0.030+	3.51	2.04	140	84
OPTUM	Stent vs Cilo	MI, Stroke, Death	1.05	0.64, 1.76	0.848	5.38	4.98	200	181
OPTUM	Ath vs Cilo	LLA, PAB	1.53	0.85, 2.89	0.175	3.17	2.13	96	64
OPTUM	Ath vs Cilo	MI, Stroke, Death	1.05	0.62, 1.88	0.877	4.57	5.47	125	144
MDCR	Stent vs Cilo	LLA, PAB	2.37	1.33, 4.31	0.004+	3.38	1.87	159	88
MDCR	Stent vs Cilo	MI, Stroke, Death	1.10	0.72, 1.68	0.673	6.41	6.33	259	252
MDCR	Ath vs Cilo	LLA, PAB	1.90	1.01, 3.75	0.054	3.00	1.78	113	65
MDCR	Ath vs Cilo	MI, Stroke, Death	0.59	0.35, 0.98	0.045	4.99	6.52	168	207
CCAE	Stent vs Cilo	LLA, PAB	1.05	0.56, 1.90	0.878	3.23	2.97	80	71
CCAE	Stent vs Cilo	MI, Stroke, Death	0.53	0.24, 1.11	0.102	2.48	2.67	58	59
CCAE	Ath vs Cilo	LLA, PAB	1.47	0.80, 2.79	0.224	4.86	3.52	78	59
CCAE	Ath vs Cilo	MI, Stroke, Death	0.79	0.34, 1.81	0.582	2.55	2.84	39	45

For the PTA with stent vs cilostazol treatment pathway comparisons, the PTA with stent treatment pathway was estimated to have a statically significant elevated risk of LLA or PAB than cilostazol in OPTUM: (HR 1.92, 95% CI [1.07, 3.47], $p = 0.03$) and MDCR (HR 2.37, 95% CI [1.33, 4.31], $p = 0.00$); this effect was non-significant in CCAE (HR 1.05, 95% CI [0.56, 1.90], $p = 0.88$). A slightly elevated and non-significant risk of MI, stroke, or all-cause death was estimated in OPTUM (HR 1.05, 95% CI [0.64, 1.76], $p = 0.85$) and MDCR (HR 1.10, 95% CI [0.72, 1.68], $p = 0.67$). The CCAE data set shows the PTA with stent treatment pathway has a non-significant protective effect against MI, stroke, or death (HR 0.53, 95% CI [0.24, 1.11], $p = 0.10$).

Among the PTA Atherectomy vs cilostazol treatment pathway comparisons, the PTA Atherectomy treatment pathway was estimated to have a non-significant elevated risk of LLA or PAB than the cilostazol treatment pathway in OPTUM (HR 1.53, 95% CI [0.85, 2.89], $p = 0.17$), MDCR (HR 1.90, 95% CI [1.01, 3.75], $p = 0.05$), and CCAE (HR 1.47, 95% CI [0.80, 2.79], $p = 0.22$). A non-significant elevated risk of MI, stroke, or death was present in the OPTUM comparison (HR 1.05, 95% CI [0.62, 1.88], $p = 0.88$), while a significant protective effect was seen in MDCR (HR 0.59, 95% CI [0.35, 0.98], $p = 0.045$) and a non-significant effect in CCAE (HR 0.79, 95% CI [0.34, 1.81], $p = 0.58$).

Negative Controls

131 negative control outcomes were utilized in this study to empirically calibrate the outcome model *p*-values (detailed in Table 8). These negative control candidate outcomes were presumed to have a null effect in each of the three study data sets, based

on the multiple evidence reporting systems that LAERTES sources, along with the clinical opinion of the research team.

Outcome Models (Empirically Calibrated)

The empirical calibration using negative controls yielded varying results between the three study data sets. Figures 40-45 show the distribution of negative control effect estimates (represented by blue dots) and the outcomes of interest (denoted by yellow diamonds). These plots were mapped against the uncalibrated *p*-values (gray shaded areas with dashed lines) and calibrated *p*-values (orange shaded areas with solid lines) to visualize the impact of residual systematic bias in the 3 data sets on the treatment pathway comparisons. Effect estimates falling within those respective areas were considered statistically significant relative to their context, using $\alpha < 0.05$. Table 5 below summarizes the primary outcome models with empirically calibrated *p*-values.

Table 5: Calibrated Primary Outcome Models across OPTUM, MDCR, and CCAE

("OPTUM" = Optum Clinformatics™ Extended Data Mart, Date of Death version; "MDCR" = Truven Health MarketScan® Medicare Supplemental; "CCAE" = Truven Health MarketScan® Commercial Claims and Encounters; "T" = Target; "C" = Comparator; "First-line" = first line treatment of statins, clopidogrel, or aspirin; "Stent" = First-line to PTA with stent; "Ath" = "First-line to PTA with atherectomy"; "Cilo" = First-line to cilostazol; "LLA" = lower limb amputation; "PAB" = peripheral arterial bypass; "MI" = myocardial infarction; "+" and red font = statistically significant; "IR" = Incidence Rate per 100 person-years)

Database	T vs C	Outcome	HR	95% CI	*p*-value	IR (T)	IR (C)	Events (T)	Events (C)
OPTUM	Stent vs Cilo	LLA, PAB	1.92	1.07, 3.47	0.049+	3.51	2.04	140	84
OPTUM	Stent vs Cilo	MI, Stroke, Death	1.05	0.64, 1.76	0.906	5.38	4.98	200	181
OPTUM	Ath vs Cilo	LLA, PAB	1.53	0.85, 2.89	0.275	3.17	2.13	96	64

OPTUM	Ath vs Cilo	MI, Stroke, Death	1.05	0.62, 1.88	0.887	4.57	5.47	125	144
MDCR	Stent vs Cilo	LLA, PAB	2.37	1.33, 4.31	0.001+	3.38	1.87	159	88
MDCR	Stent vs Cilo	MI, Stroke, Death	1.10	0.72, 1.68	0.293	6.41	6.33	259	252
MDCR	Ath vs Cilo	LLA, PAB	1.90	1.01, 3.75	0.024+	3.00	1.78	113	65
MDCR	Ath vs Cilo	MI, Stroke, Death	0.59	0.35, 0.98	0.136	4.99	6.52	168	207
CCAE	Stent vs Cilo	LLA, PAB	1.05	0.56, 1.90	0.459	3.23	2.97	80	71
CCAE	Stent vs Cilo	MI, Stroke, Death	0.53	0.24, 1.11	0.251	2.48	2.67	58	59
CCAE	Ath vs Cilo	LLA, PAB	1.47	0.80, 2.79	0.225	4.86	3.52	78	59
CCAE	Ath vs Cilo	MI, Stroke, Death	0.79	0.34, 1.81	0.607	2.55	2.84	39	45

OPTUM

OPTUM appeared to introduce little systematic bias, as the shaded areas for the uncalibrated and calibrated *p*-values were nearly identical, and most of the negative controls had effect estimates clustered around the null (Figures 40-41). Additionally, for the negative controls and the treatment patterns of interest, no changes in statistical significance status was observed.

In the PTA with stent vs cilostazol treatment pathway comparison, 75.6% of the negative controls had a non-significant effect estimate between 0.5 and 2 (referred to as the "null effect window" hereafter), and only 6.9% of the negative controls outside of the null effect window were statistically significant using the traditional *p*-value (Figure 40).

Of the two outcomes of interest, only LLA or PAB had an effect estimate that was statistically significant traditional *p*-value, which held consistent under the lens of empirical calibration; this suggested that its null hypothesis could be rejected.

In the PTA with atherectomy vs cilostazol treatment pathway, 77.4% of the negative controls were within the null effect window and non-significant, and only 8% of the negative controls outside of the null effect window were statistically significant using traditional *p*-values. Additionally, as the outcomes of interest were nearly indistinguishable from the negative controls, the null hypothesis could not be rejected for either the negative controls or the treatment pathways of interest (Figure 41).

MDCR

For both treatment pathways of interest executed against MDCR, the boundaries of the calibrated *p*-value area appeared to be shifted to the left of the corresponding uncalibrated *p*-value area (Figures 42-43), which suggested that there was systemic error that biased the effect estimates to skew high.

In the PTA with stent vs cilostazol treatment pathway, 87.7% of negative control outcomes were within the null effect window and non-significant; only 7.7% of effect estimates not within the null effect window were statistically significant using the traditional *p*-value. Despite the systemic error in MDCR, there was no impact on the statistical significance of the negative controls. The one outcome of interest with a statistically significant traditional *p*-value, LLA or PAB, remained statistically significant with empirical calibration; for this outcome, the null hypothesis could be rejected.

In the PTA with atherectomy vs cilostazol treatment pathway, 74.3% of negative control outcomes were within the null effect window and non-significant, with only 3.7% of negative controls outside of the null effect window having a statistically significant traditional *p*-value. The systemic error in MDCR affected the LLA or PAB outcome, as the calibrated *p*-value was statistically significant in contrast to its non-significant traditional *p*-value. Empirical calibration in this case resulted in the null hypothesis not being rejected.

CCAE

In CCAE, systemic error was observed in the PTA with stent vs cilostazol treatment pathway comparison. The boundaries of the calibrated *p*-value appeared to shift the traditional *p*-value area to the left. Still, this shifting of presumably null effects did not alter the statistical significance of the outcomes tested. Neither the negative controls nor the outcomes of interest were statistically significant under the lenses of the traditional and empirically calibrated *p*-values (Figure 44). Additionally, as 79.5% of negative controls had effect estimates in the null effect window, the null hypothesis could not be rejected for the negative controls or the treatment pathways of interest.

In the PTA with atherectomy vs cilostazol treatment pathway comparison, the traditional and empirically calibrated *p*-value areas were nearly identical, with the outcomes of interest having effect estimates clustered among the negative controls around the null (Figure 45). No systemic error from CCAE was observed when studying these this treatment pathway's outcomes of interest, so the null hypothesis was not rejected.

CHAPTER 5: DISCUSSION

Summary

PAD is an undertreated and underreported chronic disease affecting millions of Americans every year with major implications on patient quality of life and mortality. The risks of psychological disorders, cardiovascular and ischemic events, and all-cause death underscore the seriousness of the disease and the need for effective therapy. Due to the trajectory of the disease, a variety of treatments are available, each designed to provide therapy in different ways: enacting lifestyle changes to improve overall health, mitigating cardiovascular or diabetic comorbidities, limiting platelet activation, widening arteries, trimming plaque build-up, or re-channeling blood flow. This retrospective cohort study compared the effectiveness of three treatment pathways in order to characterize the risk of requiring an undesirable procedure: LLA or PAB, both of which indicate a failure in treatment; and, in doing so, the study also captured the risk of experiencing known complications from PAD: MI, ischemic stroke, or all-cause death.

Across three large administrative claims data sets with varying age ranges, the primary endpoint outcome models indicated there could be an elevated risk of LLA or PAB for both PTA-based treatment pathways. Among PTA with stent comparisons, multiple statistically significant (and empirically calibrated) results were observed in two of three data sets: in OPTUM, HR 1.92, 95% CI (1.07, 3.47), traditional $p = 0.03$, calibrated $p = 0.049$; and, in MDCR, HR 2.37, 95% CI (1.33, 4.31), traditional $p = 0.004$, calibrated $p = 0.001$. However, in CCAE, no effect was observed (HR 1.05, 95% CI [0.56, 1.90], traditional $p = 0.878$, calibrated $p = 0.459$). Compared to OPTUM and

MDCR, the age distribution of CCAE is unique in that it is constrained from birth to age 65, which could account for this disparity. As the PAD patient population skews towards ages 60 and above, CCAE produced small sample sizes and event counts in both endpoints across the pairwise comparisons. When examining PAD populations that include adequate representation of ages 60 and above, patients undergoing PTA with stent as a second-line therapy have a hazard rate that is approximately twice that of patients starting cilostazol as a second-line therapy, with similar median survival times observed in both treatment pathways.

Among PTA with atherectomy comparisons, the MDCR effect estimate (HR 1.90, 95% CI [1.01, 3.75], traditional $p = 0.054$, calibrated $p = 0.024$) concurs with the two-fold elevated risk of LLA or PAB seen in the PTA with stent comparisons, although this was not reproducible in OPTUM or CCAE. While the effect estimates from OPTUM and CCAE were not statistically significant post-calibration, they were consistent in producing effect estimates that suggested an elevated risk of LLA or PAB. As no statistically significant effects were observed in the safety endpoint outcome models, the risk of MI, ischemic stroke, or all-cause death does not appear to be different between the PTA-based treatment pathways and the cilostazol treatment pathway.

Strengths and Study Limitations

This study's strengths included the availability to three large administrative claims data sets that included a substantial number of diverse covariates from two to three years of longitudinal data prior to index, and approximately one to two years of follow-up time post-index. CCAE is among the largest claims data sets publicly available for

patients under 65 years of age, while MDCR provides a considerably large representation of the elderly. OPTUM, even with the drop-off in SSA death information post-2011, can still be a viable source of verified death data from the NDI in subsequent years. Requiring that each subject be on a specific treatment pathway ensured that inappropriate comparisons of treatments were not conducted. The OMOP Common Data Model allowed for the robust re-use of concept sets, cohort designs, and analysis code. The usage of propensity score matching and empirical calibration also aided in mitigating the risks of confounding and systemic error.

However, there were some data set and design limitations that should be considered to contextualize the results. Administrative claims data sets, while highly comprehensive of the patient's continuum of care, can only represent clinical events submitted for insurance reimbursement. This means granular conditions experienced by the patient are abstracted to ICD9CM and ICD10CM diagnosis codes, which do not fully convey PAD severity. This also means some degree of missing data is possible, although the outcomes in both endpoints (excluding death) should have accurate representation as they are serious procedural or emergency events that would most likely be submitted for reimbursement. The lack of patient race or ethnicity attributes in the data sets limited the study's ability to control for all clinically known confounders of PAD outcomes. The usage of missing and sparse death data to construct a key component of the safety endpoint likely yielded underrepresented mortality events across the study populations, which could have played a role in the failure to reject the safety endpoint's null hypothesis.

Death also represents a design limitation in the study. Death is often a competing risk in survival analyses, particularly when studying cardiovascular conditions [77]. In this study, the primary endpoint did not account for death as a competing risk, which meant patients who were known to have died were censored before any LLA or PAB event could have occurred, yet contributed time-at-risk to the outcome models. Utilization of the cumulative incidence function (CIF) would help in evaluating the bias from death as a competing risk [77]. Additionally, the design's utilization of treatment pathways and the restriction of diabetic patients resulted in low sensitivity of subjects in the cohorts relative to the PAD population, which could hinder study reproducibility. Lastly, in utilizing the 0.1 SMD benchmark for evaluating covariate balance, the study failed to reach complete covariate balance across all pairwise comparisons. The minority of unbalanced covariates suggests the slight potential for biased effect estimates.

Further research, supported by stronger death data and evaluated for competing risk bias, along with representation of race and ethnicity information, could provide more clarity on the differential safety risks between the PTA and cilostazol treatment pathways. Larger sample sizes could also yield better covariate balance.

Conclusion

PTA with stent and PTA with atherectomy procedures have gained popularity in recent years as alternatives to pharmacologic and surgical interventions for symptomatic PAD patients who continue to experience claudication and worsening blood flow in spite attempts to mitigate comorbidities. However, the primary endpoint results from this study

do not support their usage over cilostazol, due to the elevated risk of lower limb amputation or peripheral arterial bypass.

SUPPLEMENTARY TABLES AND FIGURES

Project Code

The R package designed to execute this study can be found in the following GitHub repository: https://github.com/alondhe/MPHThesisPAD.

Concept Sets

Cilostazol

Concept Id	Concept Name	Domain	Vocabulary	Excluded	Descendants
1350310	cilostazol	Drug	RxNorm	NO	YES

PTA with Stent

Concept Id	Concept Name	Domain	Vocabulary	Excluded	Descendants
40757050	Revascularization, endovascular, open or percutaneous, femoral, popliteal artery(s), unilateral; with transluminal stent placement(s), includes angioplasty within the same vessel, when performed	Procedure	CPT4	NO	YES
40756927	Revascularization, endovascular, open or percutaneous, iliac artery, unilateral, initial vessel; with transluminal stent placement(s), includes angioplasty within the same vessel, when performed	Procedure	CPT4	NO	YES
40757135	Revascularization, endovascular, open or	Procedure	CPT4	NO	YES

	percutaneous, tibial, peroneal artery, unilateral, initial vessel; with transluminal stent placement(s), includes angioplasty within the same vessel, when performed				

PTA with Atherectomy

Concept Id	Concept Name	Domain	Vocab	Excluded	Descendants
4284964	Atherectomy	Procedure	SNOMED	NO	YES
4081578	Coronary artery atherectomy	Procedure	SNOMED	YES	YES
4106556	Coronary atherectomy by laser	Procedure	SNOMED	YES	YES
4194238	Endarterectomy	Procedure	SNOMED	YES	YES
42872521	Endarterectomy of axillary artery	Procedure	SNOMED	YES	YES
44512093	Endarterectomy of subclavian artery NEC	Procedure	OPCS4	YES	YES
2731055	Extirpation of Matter from Left Anterior Tibial Artery, Percutaneous Approach	Procedure	ICD10PCS	NO	NO
2731043	Extirpation of Matter from Left Femoral Artery, Percutaneous Approach	Procedure	ICD10PCS	NO	NO
2735010	Extirpation of Matter from Left Femoral Vein, Percutaneous Approach	Procedure	ICD10PCS	NO	NO

2731067	Extirpation of Matter from Left Peroneal Artery, Percutaneous Approach	Procedure	ICD10PCS	NO	YES
2731049	Extirpation of Matter from Left Popliteal Artery, Percutaneous Approach	Procedure	ICD10PCS	NO	YES
2731061	Extirpation of Matter from Left Posterior Tibial Artery, Percutaneous Approach	Procedure	ICD10PCS	NO	YES
2731052	Extirpation of Matter from Right Anterior Tibial Artery, Percutaneous Approach	Procedure	ICD10PCS	NO	YES
2731040	Extirpation of Matter from Right Femoral Artery, Percutaneous Approach	Procedure	ICD10PCS	NO	YES
2735007	Extirpation of Matter from Right Femoral Vein, Percutaneous Approach	Procedure	ICD10PCS	NO	YES
2731064	Extirpation of Matter from Right Peroneal Artery, Percutaneous Approach	Procedure	ICD10PCS	NO	YES
2731046	Extirpation of Matter from Right Popliteal Artery, Percutaneous Approach	Procedure	ICD10PCS	NO	YES

2731058	Extirpation of Matter from Right Posterior Tibial Artery, Percutaneous Approach	Procedure	ICD10PCS	NO	YES
46271741	Fluoroscopy guided coronary artery atherectomy	Procedure	SNOMED	YES	YES
4119874	Mechanical endarterectomy	Procedure	SNOMED	YES	YES
40756811	Percutaneous atherectomy of extracranial vessel(s)	Procedure	ICD9Proc	YES	YES
4337739	Percutaneous directional coronary atherectomy	Procedure	SNOMED	YES	YES
4336469	Percutaneous high speed rotational coronary atherectomy	Procedure	SNOMED	YES	YES
4337740	Percutaneous low speed rotational coronary atherectomy	Procedure	SNOMED	YES	YES
44511138	Percutaneous transluminal atherectomy of coronary artery	Procedure	OPCS4	YES	YES
43527997	Percutaneous transluminal coronary atherectomy, with coronary angioplasty when performed; each additional branch of a major coronary artery (List separately in addition to code for primary procedure)	Procedure	CPT4	YES	YES

43527996	Percutaneous transluminal coronary atherectomy, with coronary angioplasty when performed; single major coronary artery or branch	Procedure	CPT4	YES	YES
43533353	Percutaneous transluminal coronary atherectomy, with drug eluting intracoronary stent, with coronary angioplasty when performed; single major coronary artery or branch	Procedure	HCPCS	YES	YES
43533248	Percutaneous transluminal coronary atherectomy, with drug-eluting intracoronary stent, with coronary angioplasty when performed; each additional branch of a major coronary artery (list separately in addition to code for primary procedure)	Procedure	HCPCS	YES	YES
44511135	Percutaneous transluminal laser coronary angioplasty	Procedure	OPCS4	YES	YES
4106321	Radiofrequency endarterectomy	Procedure	SNOMED	YES	YES
4244381	Thromboendarterecto my of abdominal artery	Procedure	SNOMED	YES	YES
40756789	Transluminal coronary atherectomy	Procedure	ICD9Proc	YES	YES
4121743	Ultrasonic endarterectomy	Procedure	SNOMED	YES	YES

PAD

Concept Id	Concept Name	Domain	Vocabulary	Excluded	Descendants
318443	Arteriosclerotic vascular disease	Condition	SNOMED	NO	YES
312934	Atherosclerosis of aorta	Condition	SNOMED	YES	YES
195834	Atherosclerosis of renal artery	Condition	SNOMED	YES	YES
316437	Cerebral atherosclerosis	Condition	SNOMED	YES	YES
317576	Coronary arteriosclerosis	Condition	SNOMED	YES	YES
40481919	Coronary atherosclerosis	Condition	SNOMED	YES	YES
321882	Generalized atherosclerosis	Condition	SNOMED	YES	YES
317309	Peripheral arterial occlusive disease	Condition	SNOMED	NO	YES
321052	Peripheral vascular disease	Condition	SNOMED	NO	YES

Aspirin

Concept Id	Concept Name	Domain	Vocabulary	Excluded	Descendants
1112807	Aspirin	Drug	RxNorm	NO	YES

Diabetes

Concept Id	Concept Name	Domain	Vocabulary	Excluded	Descendants
35506609	Diabetes mellitus	Condition	MedDRA	NO	YES

Statins

Concept Id	Concept Name	Domain	Vocabulary	Excluded	Descendants
21601860	atorvastatin	Drug	ATC	NO	YES
21601859	fluvastatin	Drug	ATC	NO	YES
21601857	lovastatin	Drug	ATC	NO	YES
21601863	pitavastatin	Drug	ATC	NO	YES
21601858	pravastatin	Drug	ATC	NO	YES
21601862	rosuvastatin	Drug	ATC	NO	YES
21601856	simvastatin	Drug	ATC	NO	YES

Clopidogrel

Concept Id	Concept Name	Domain	Vocabulary	Excluded	Descendants
1322184	clopidogrel	Drug	RxNorm	NO	YES

Covariate Settings and Exclusions

Table 6: Covariate Settings

Covariate Setting for Feature Extraction	Enabled
Gender	Yes
Race	Yes
Ethnicity	Yes
Age	Yes
Calendar year	Yes
Calendar month	Yes
Condition occurrences during the 180 days, pre-index	Yes
Condition occurrences during the 30 days, pre-index	Yes
Condition occurrences during the 90 days, pre-index	Yes
All condition eras pre-index	Yes
Condition eras overlapping with the index	Yes
Group conditions by MedDra vocabulary	Yes
Group conditions by SNOMED vocabulary	Yes
Drug exposures during the 180 days, pre-index	Yes
Drug exposures during the 30 days, pre-index	Yes
Drug eras during the 180 days, pre-index	Yes
Drug eras during the 30 days, pre-index	Yes
Drug eras overlapping with the index	Yes
All drug eras pre-index	Yes
Group drugs by higher level vocabularies such as ATC or SNOMED	No
Procedure occurrences during the 180 days, pre-index	Yes
Procedure occurrences during the 30 days, pre-index	Yes
Group procedures by higher level concepts	No
Observations during the 180 days, pre-index	Yes
Observations during the 30 days, pre-index	Yes
Counts of observations during the 180 days, pre-index	Yes
Measurements during the 180 days, pre-index	Yes
Measurements during the 30 days, pre-index	Yes
Counts of measurements during the 180 days, pre-index	Yes
Indicator of measurement results below normal range	Yes
Indicator of measurement results above normal range	Yes
Counts of all concepts per domain pre-index	No
Charlson Comorbidity Index	Yes
DCSI risk score	Yes
$CHADS_2$ risk score	Yes
CHA_2DS_2Vasc risk score	Yes

Interaction term of year and the covariate	Yes
Interaction term of month and the covariate	No

Covariate Imbalance

Table 7: Unbalanced covariates ("T" = Target, "C" = Comparator, "Stent" = First-line to PTA with stent, "Ath" = "First-line to PTA with atherectomy", "Cilo" = First-line to cilostazol, "Abs" = Absolute Value)

Database	T vs C	Outcome	Covariate Name	Before SMD (Abs)	After SMD (Abs)
OPTUM	Ath vs Cilo	LLA, PAB	CHADS2	0.047	0.120
OPTUM	Ath vs Cilo	LLA, PAB	Charlson	0.061	0.106
OPTUM	Ath vs Cilo	LLA, PAB	DCSI	0.290	0.142
OPTUM	Ath vs Cilo	MI, Stroke, Death	Charlson	0.061	0.109
OPTUM	Ath vs Cilo	MI, Stroke, Death	DCSI	0.290	0.117
OPTUM	Ath vs Cilo	MI, Stroke, Death	30 days, Immature granulocytes [#/volume] in Blood	0.219	0.101
CCAE	Ath vs Cilo	LLA, PAB	Drug era of Ibuprofen * 2015	0.013	0.101
CCAE	Ath vs Cilo	LLA, PAB	Drug era of Atropine	0.044	0.109
CCAE	Ath vs Cilo	LLA, PAB	180 days, Drug era, cyclobenzaprine	0.012	0.103
CCAE	Ath vs Cilo	LLA, PAB	180 days, Number of observations, Past history of procedure	0.021	0.102
CCAE	Ath vs Cilo	MI, Stroke, Death	180 days, Drug era, cyclobenzaprine	0.012	0.104
CCAE	Ath vs Cilo	MI, Stroke, Death	Index month: 4	0.003	0.110
MDCR	Ath vs Cilo	LLA, PAB	CHADS2	0.057	0.107
MDCR	Ath vs Cilo	LLA, PAB	Charlson	0.121	0.147
MDCR	Ath vs Cilo	LLA, PAB	DCSI	0.323	0.139

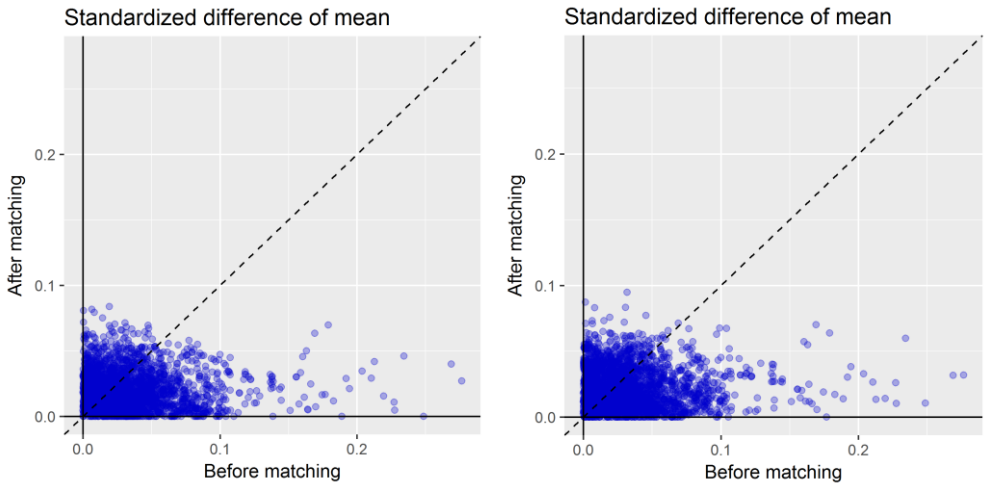
MDCR	Ath vs Cilo	LLA, PAB	Drug era, Labetalol	0.034	0.111
MDCR	Ath vs Cilo	LLA, PAB	180 days, Drug era, Tramadol * 2012	0.026	0.101
MDCR	Ath vs Cilo	MI, Stroke, Death	Charlson	0.121	0.107
MDCR	Ath vs Cilo	MI, Stroke, Death	DCSI	0.323	0.112
MDCR	Stent vs Cilo	MI, Stroke, Death	Drug era, 1334456-Ramipril	0.003	0.102
MDCR	Ath vs Cilo	MI, Stroke, Death	Drug era, Allopurinol	0.030	0.109
MDCR	Ath vs Cilo	MI, Stroke, Death	180 days, Number of observations, Hospital outpatient clinic visit for assessment and management of a patient	0.031	0.102

Covariate Balance Plots

OPTUM

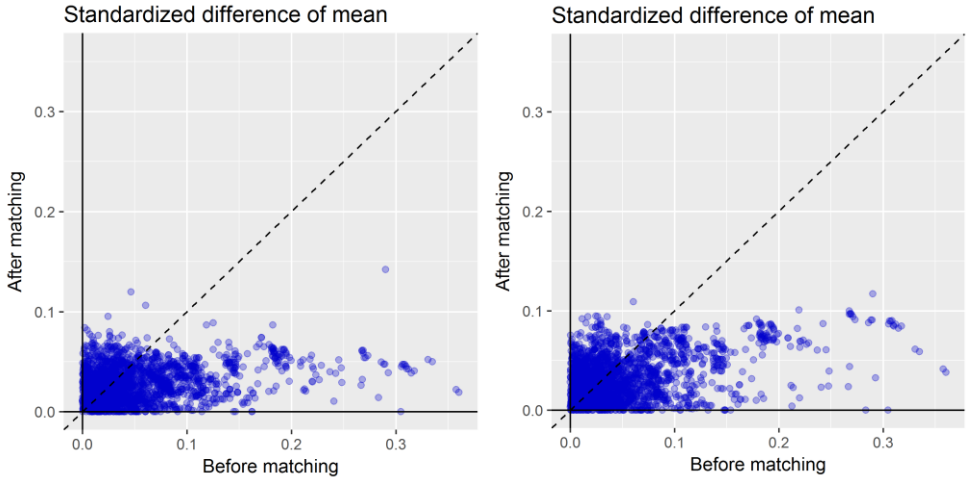
PTA with Stent vs Cilostazol

Figure 1: Covariate Balance Plots: Lower Limb Amputation (LLA) or Peripheral Arterial Bypass (PAB) and Myocardial Infarction (MI) or Ischemic Stroke or All-Cause Death. Absolute values of the SMD for each covariate before and after propensity-score matching are plotted.



PTA with Atherectomy vs Cilostazol

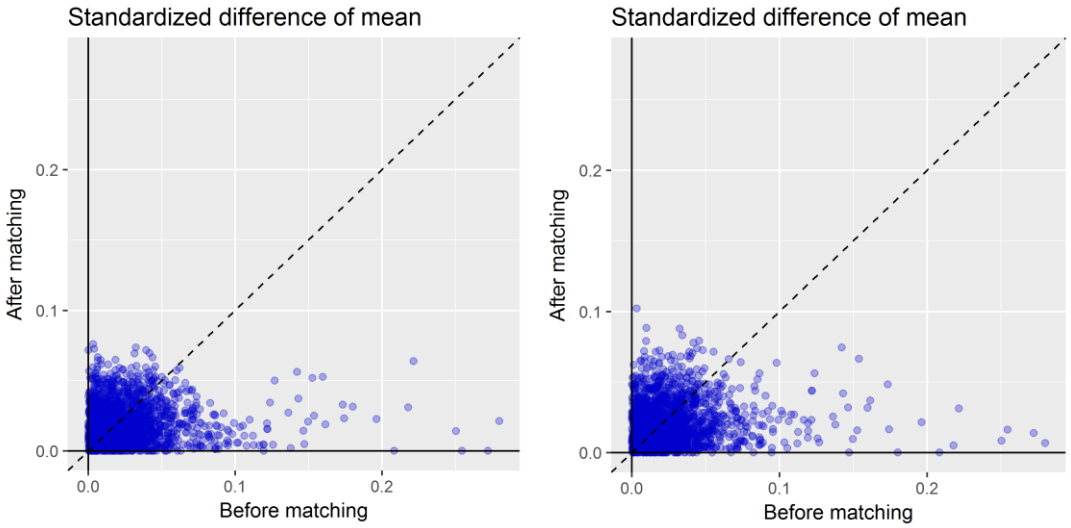
Figure 2: Covariate Balance Plots: Lower Limb Amputation (LLA) or Peripheral Arterial Bypass (PAB) and Myocardial Infarction (MI) or Ischemic Stroke or All-Cause Death. Absolute values of the SMD for each covariate before and after propensity-score matching are plotted.



MDCR

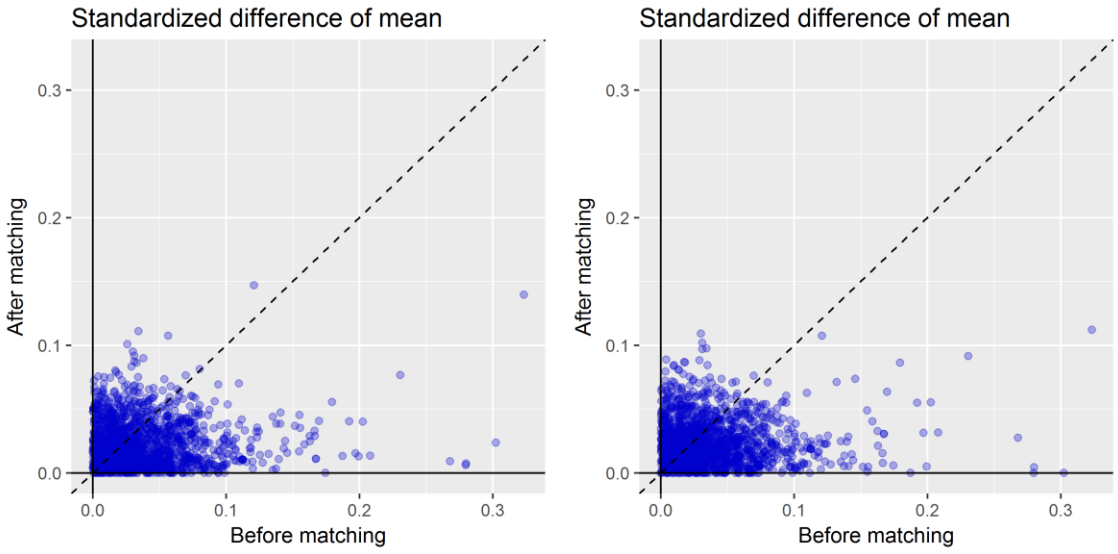
PTA with Stent vs Cilostazol

Figure 3: Covariate Balance Plots: Lower Limb Amputation (LLA) or Peripheral Arterial Bypass (PAB) and Myocardial Infarction (MI) or Ischemic Stroke or All-Cause Death. Absolute values of the SMD for each covariate before and after propensity-score matching are plotted.



PTA with Atherectomy vs Cilostazol

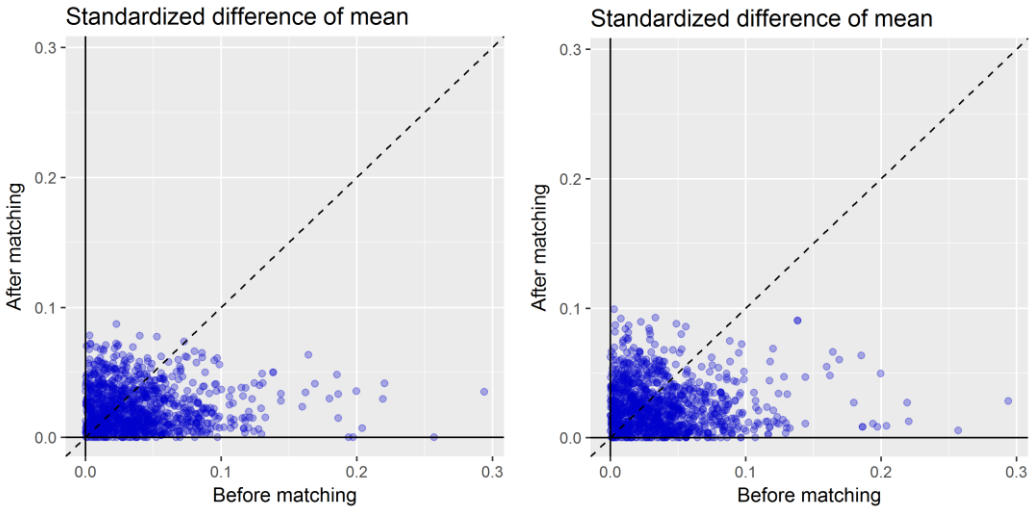
Figure 4: Covariate Balance Plots: Lower Limb Amputation (LLA) or Peripheral Arterial Bypass (PAB) and Myocardial Infarction (MI) or Ischemic Stroke or All-Cause Death. Absolute values of the SMD for each covariate before and after propensity-score matching are plotted.



CCAE

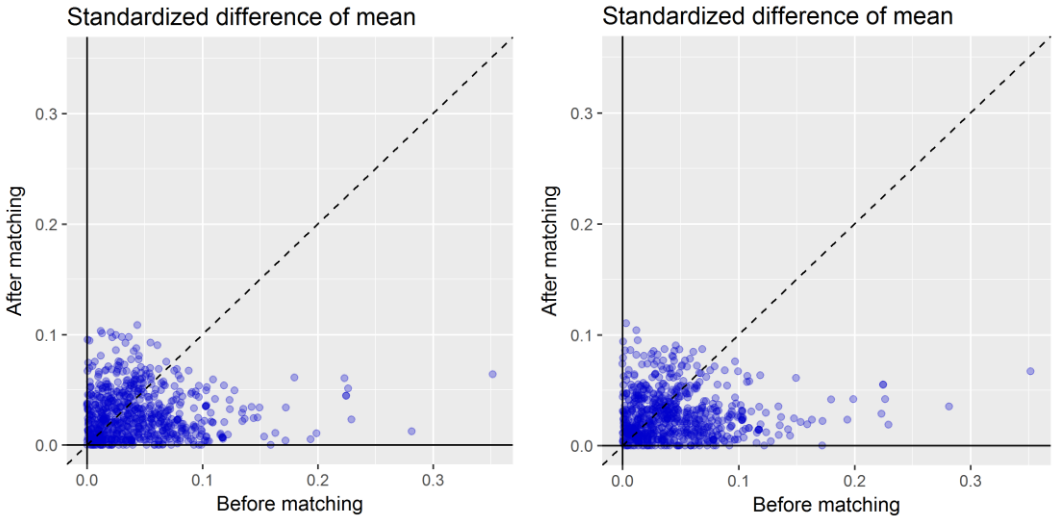
PTA with Stent vs Cilostazol

Figure 5: Covariate Balance Plots: Lower Limb Amputation (LLA) or Peripheral Arterial Bypass (PAB) and Myocardial Infarction (MI) or Ischemic Stroke or All-Cause Death. Absolute values of the SMD for each covariate before and after propensity-score matching are plotted.



PTA with Atherectomy vs Cilostazol

Figure 6: Covariate Balance Plots: Lower Limb Amputation (LLA) or Peripheral Arterial Bypass (PAB) and Myocardial Infarction (MI) or Ischemic Stroke or All-Cause Death. Absolute values of the SMD for each covariate before and after propensity-score matching are plotted.



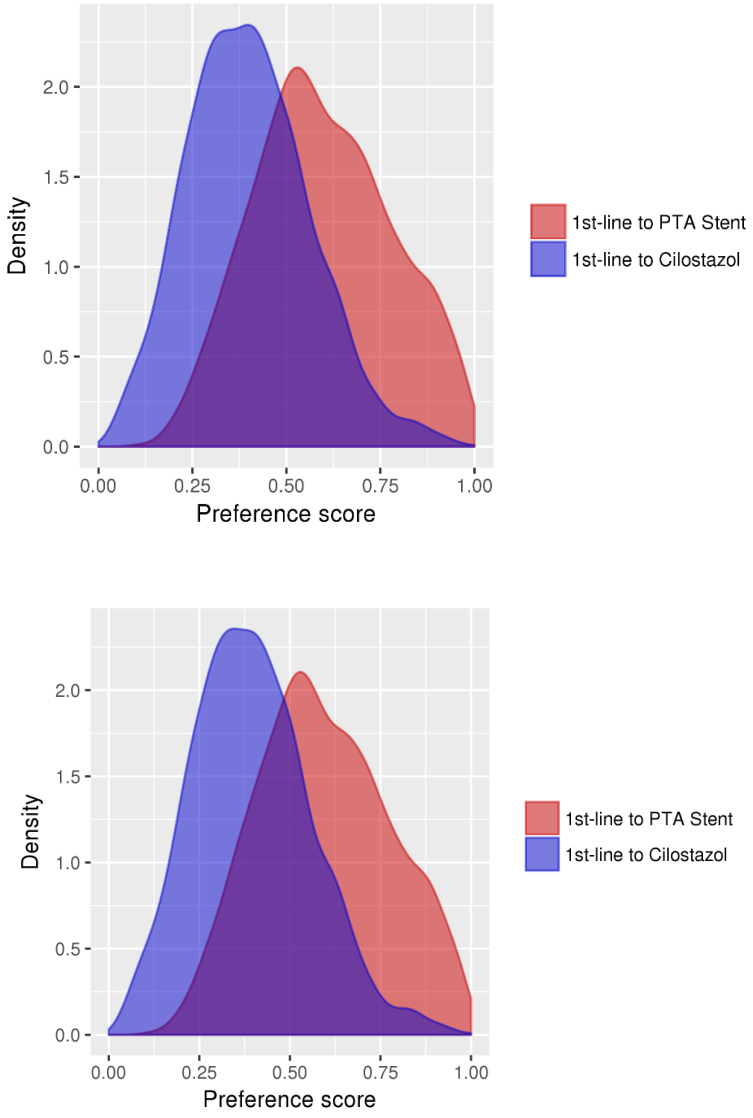
Preference Plots

OPTUM

PTA with Stent vs Cilostazol

Figure 7: Preference Plots: (1) Lower Limb Amputation or Peripheral Arterial Bypass and (2) Myocardial Infarction or Ischemic Stroke or All-Cause Death

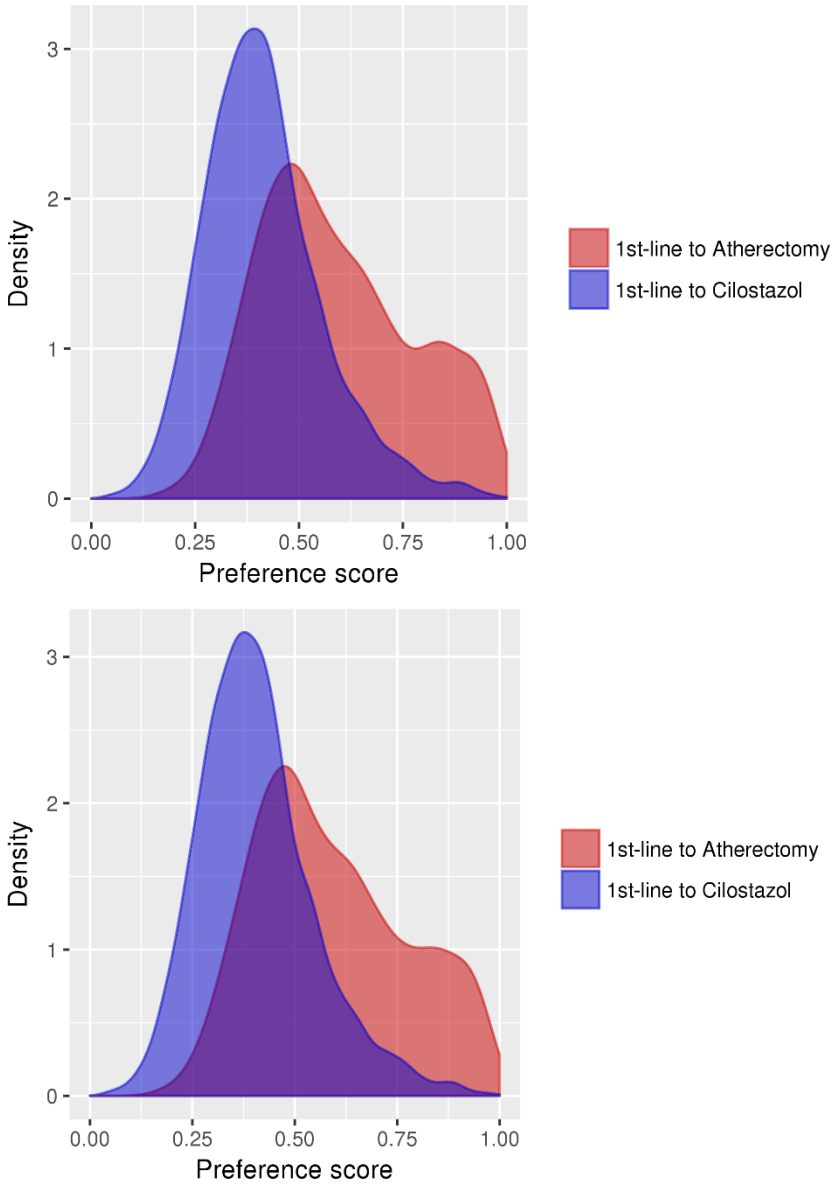
("First-line" = first line treatment of statins, clopidogrel, or aspirin; "PTA" = percutaneous transluminal angioplasty)



PTA with Atherectomy vs Cilostazol

Figure 8: Preference Plots: (1) Lower Limb Amputation or Peripheral Arterial Bypass and (2) Myocardial Infarction or Ischemic Stroke or All-Cause Death

("First-line" = first line treatment of statins, clopidogrel, or aspirin; "PTA" = percutaneous transluminal angioplasty)

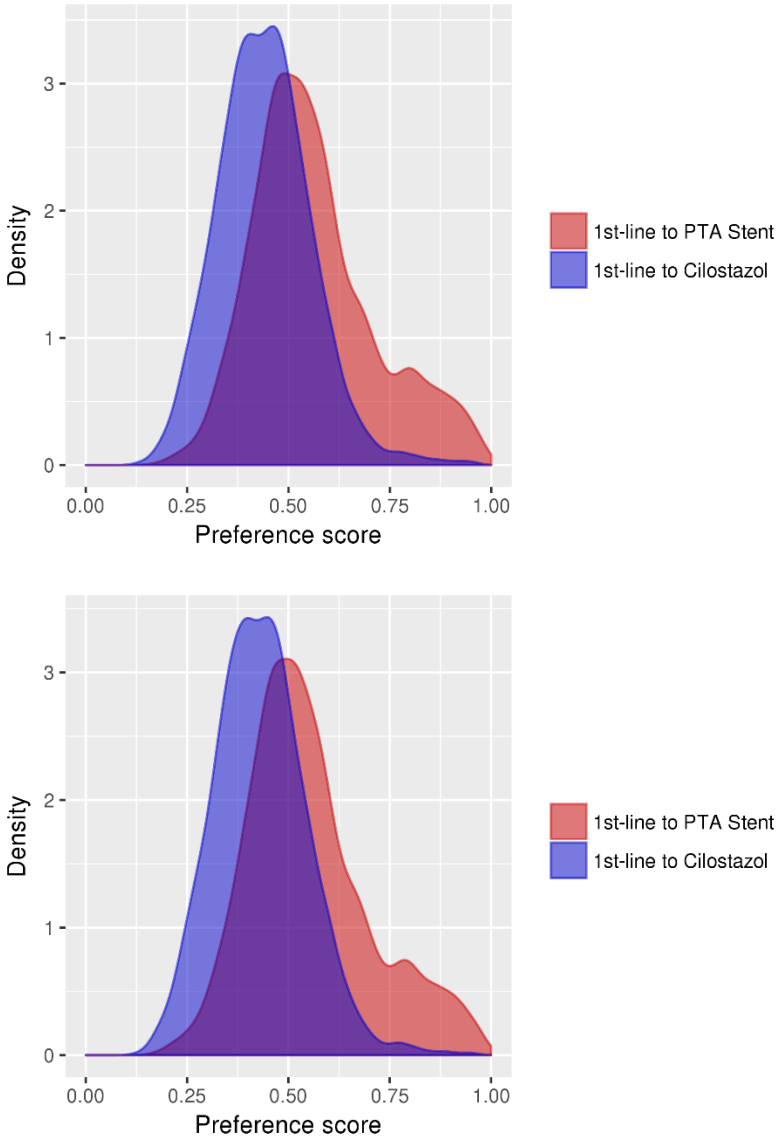


MDCR

PTA with Stent vs Cilostazol

Figure 9: Preference Plots: (1) Lower Limb Amputation or Peripheral Arterial Bypass and (2) Myocardial Infarction or Ischemic Stroke or All-Cause Death

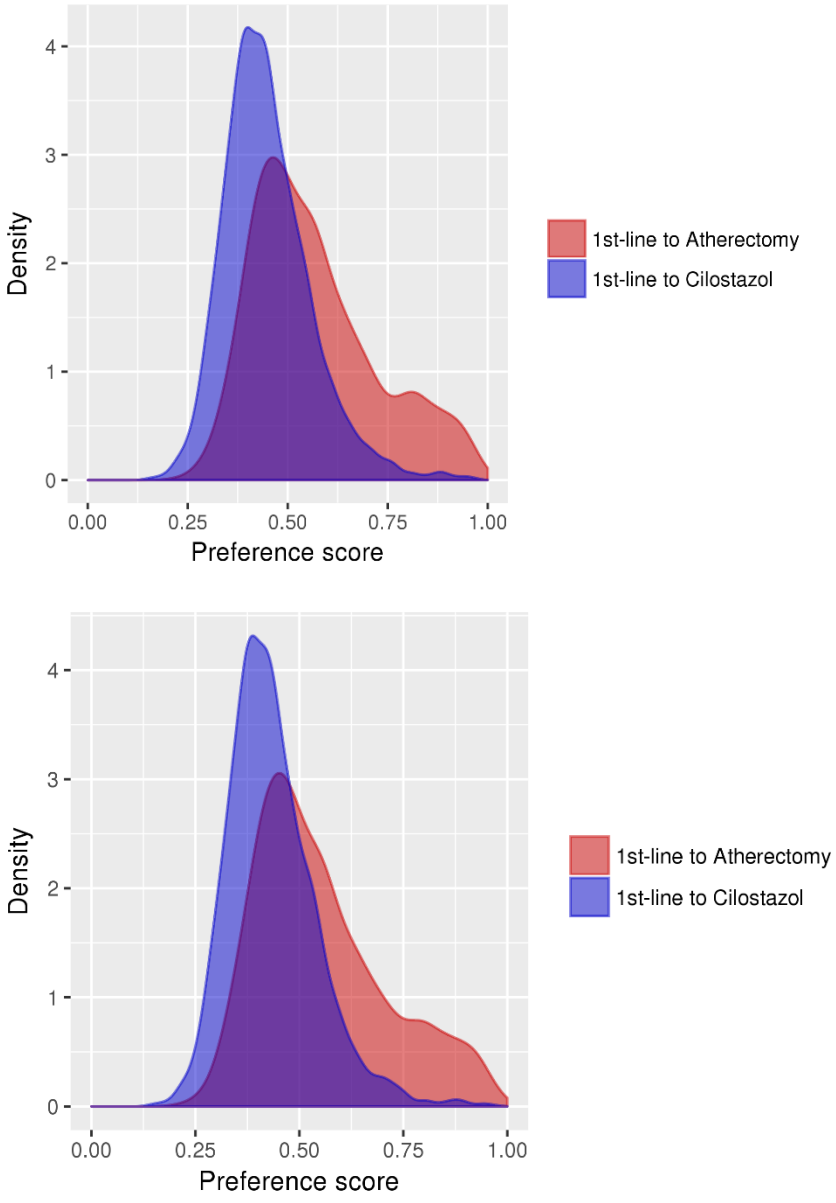
("First-line" = first line treatment of statins, clopidogrel, or aspirin; "PTA" = percutaneous transluminal angioplasty)



PTA with Atherectomy vs Cilostazol

Figure 10: Preference Plots: (1) Lower Limb Amputation or Peripheral Arterial Bypass and (2) Myocardial Infarction or Ischemic Stroke or All-Cause Death

("First-line" = first line treatment of statins, clopidogrel, or aspirin; "PTA" = percutaneous transluminal angioplasty)

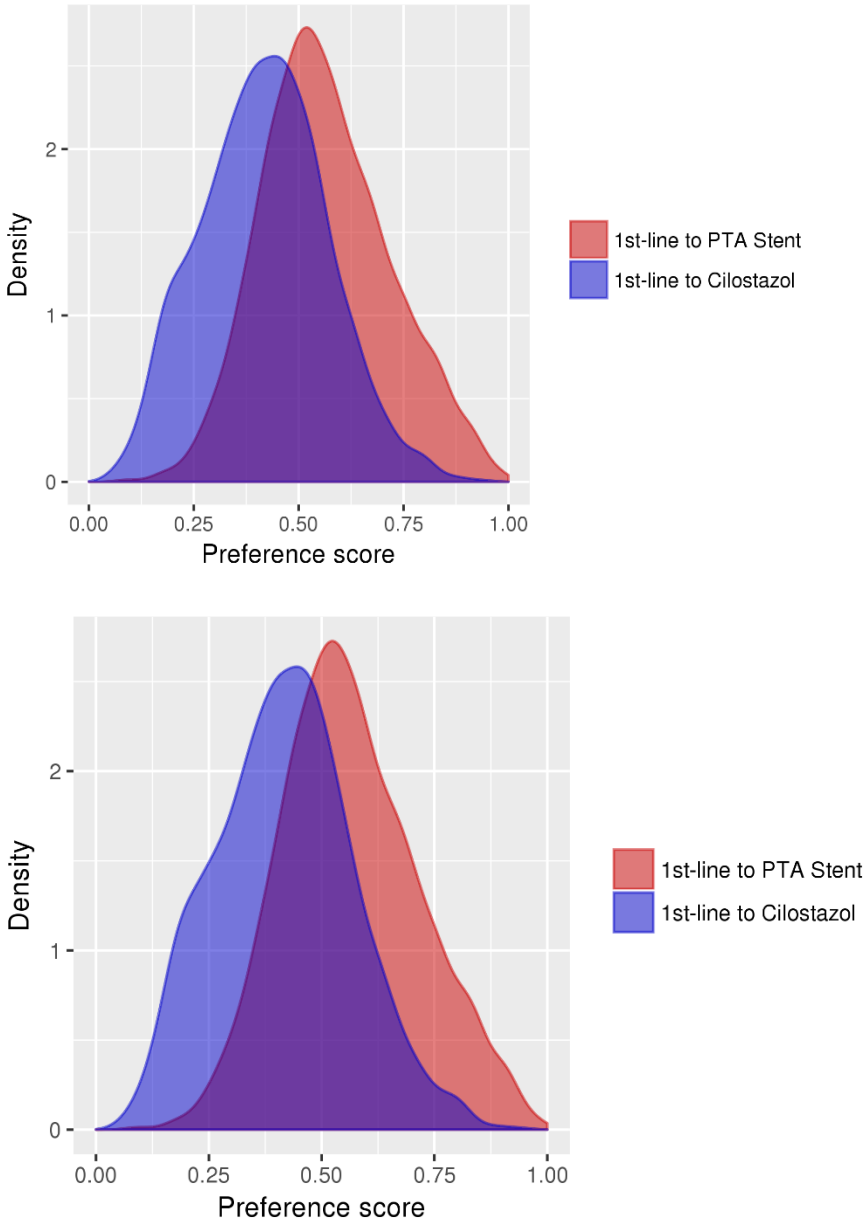


CCAE

PTA with Stent vs Cilostazol

Figure 11: Preference Plots: (1) Lower Limb Amputation or Peripheral Arterial Bypass and (2) Myocardial Infarction or Ischemic Stroke or All-Cause Death

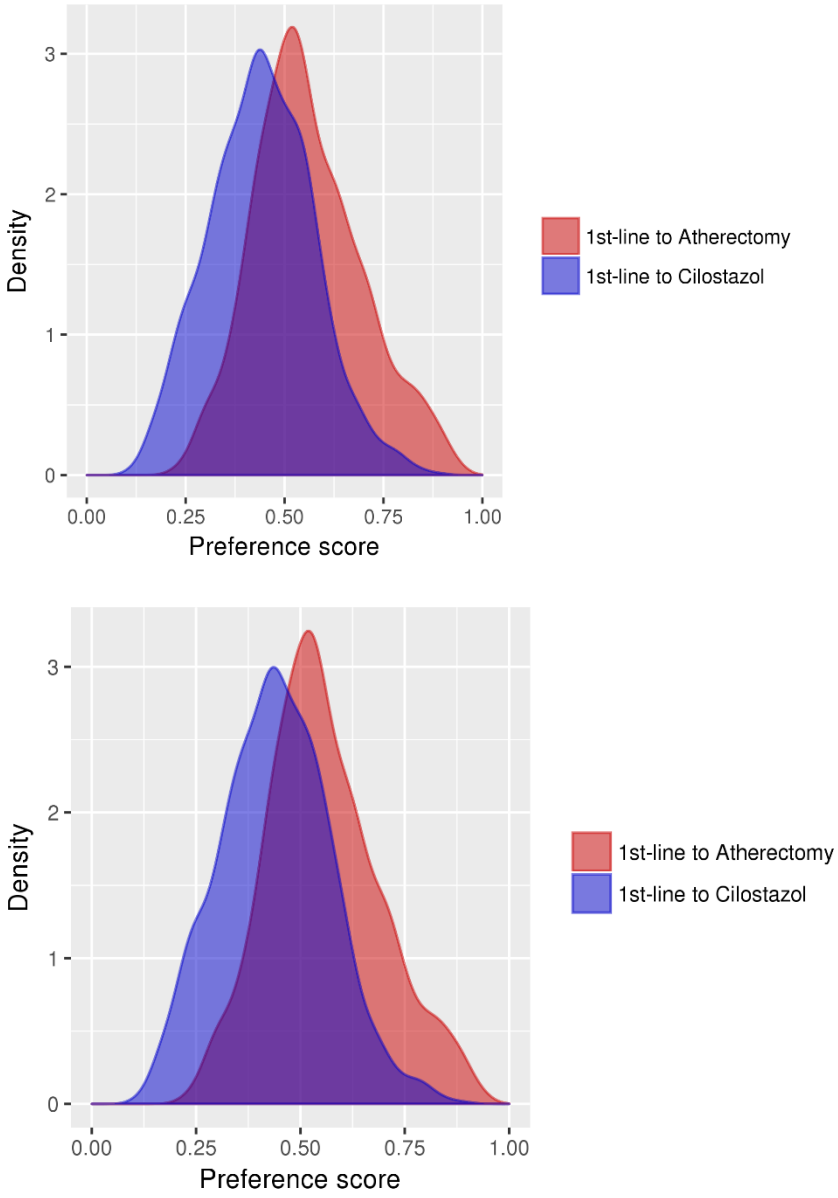
("First-line" = first line treatment of statins, clopidogrel, or aspirin; "PTA" = percutaneous transluminal angioplasty)



PTA with Atherectomy vs Cilostazol

Figure 12: Preference Plots: (1) Lower Limb Amputation or Peripheral Arterial Bypass and (2) Myocardial Infarction or Ischemic Stroke or All-Cause Death

("First-line" = first line treatment of statins, clopidogrel, or aspirin; "PTA" = percutaneous transluminal angioplasty)



Attrition Diagrams

OPTUM

PTA with Stent vs Cilostazol

Figure 13: Attrition Diagram: Lower Limb Amputation or Peripheral Arterial Bypass

("First-line" = first line treatment of statins, clopidogrel, or aspirin; "subs" = cohort subjects)

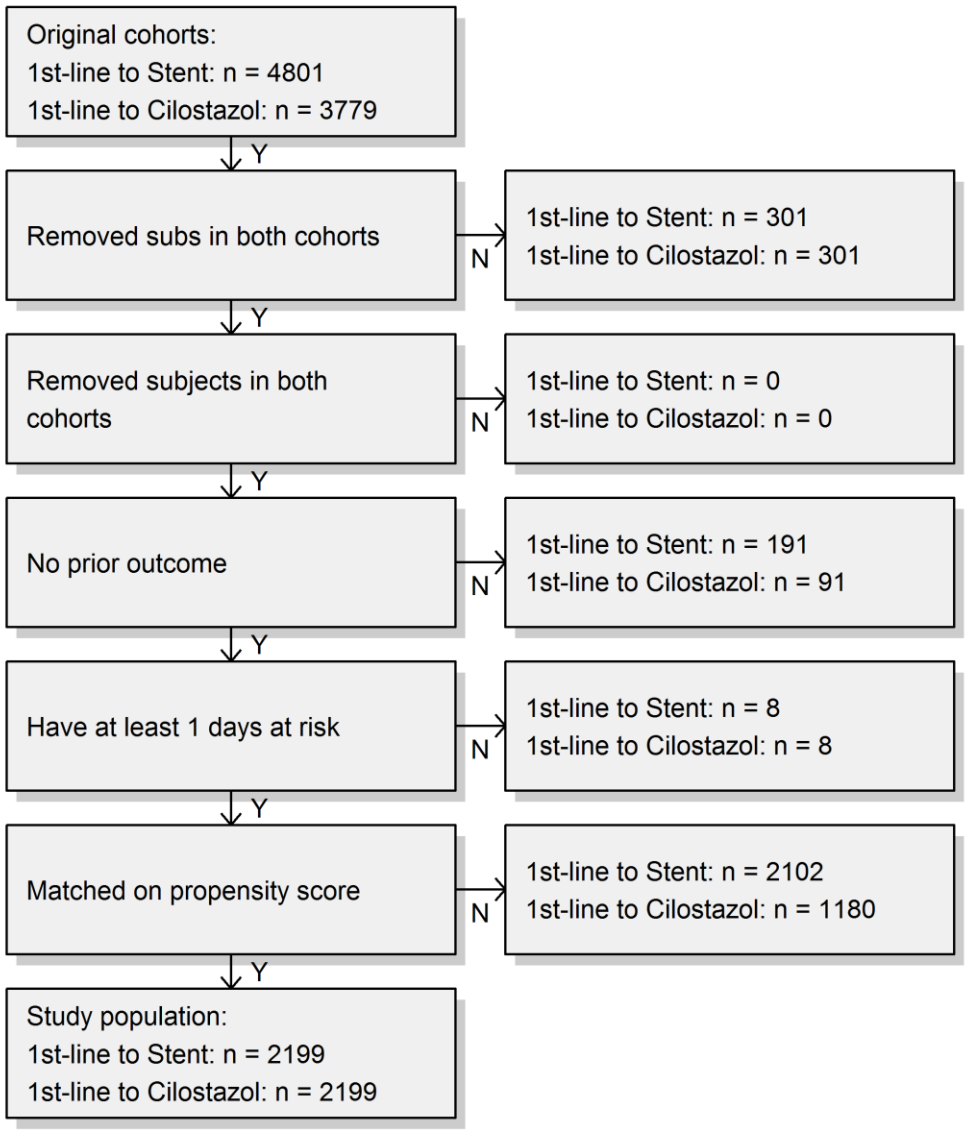
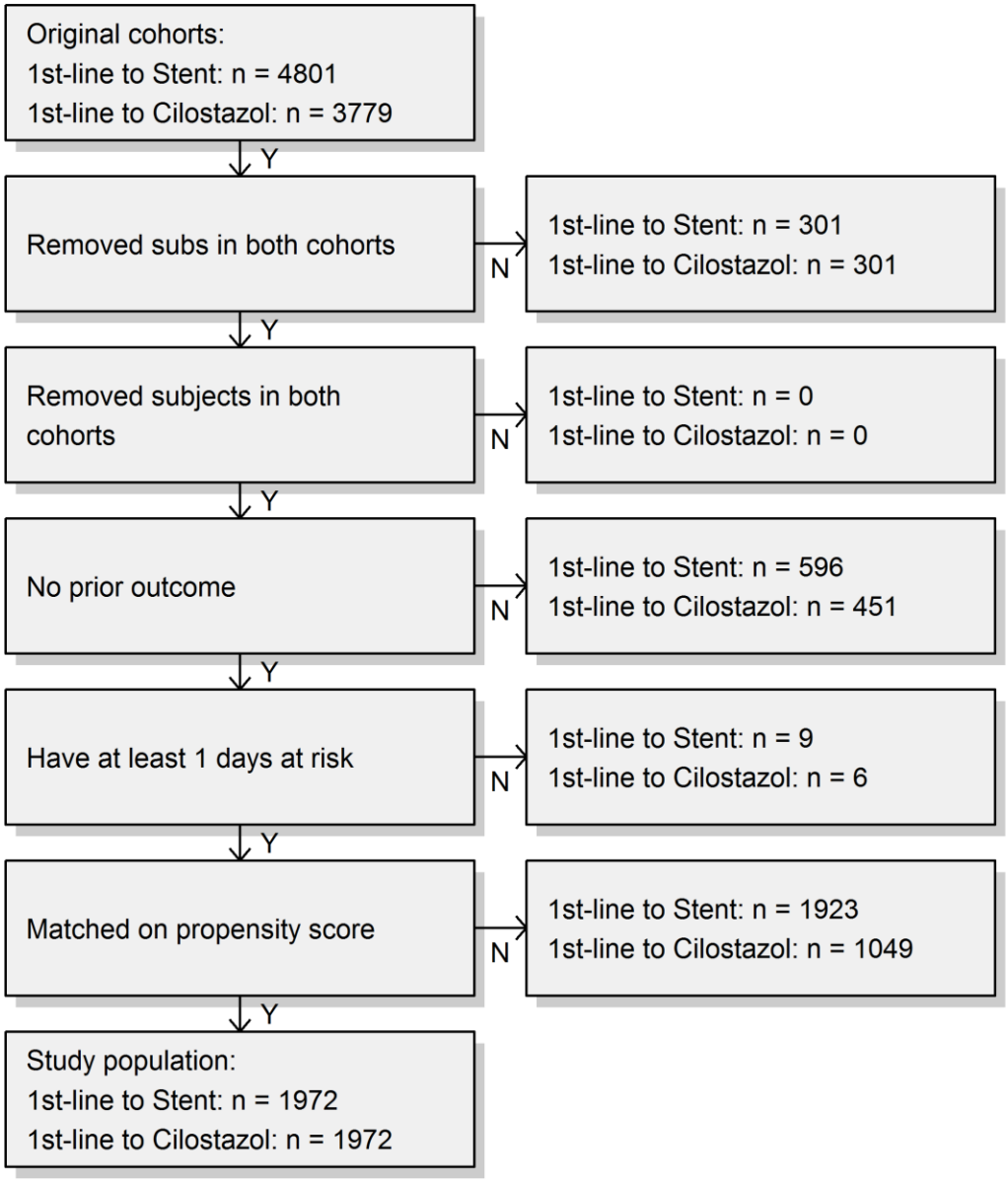


Figure 14: Attrition Diagram: Myocardial Infarction or Ischemic Stroke or All-Cause Death

("First-line" = first line treatment of statins, clopidogrel, or aspirin; "subs" = cohort subjects)



PTA with Atherectomy vs Cilostazol

Figure 15: Attrition Diagram: Lower Limb Amputation or Peripheral Arterial Bypass

("First-line" = first line treatment of statins, clopidogrel, or aspirin; "subs" = cohort subjects)

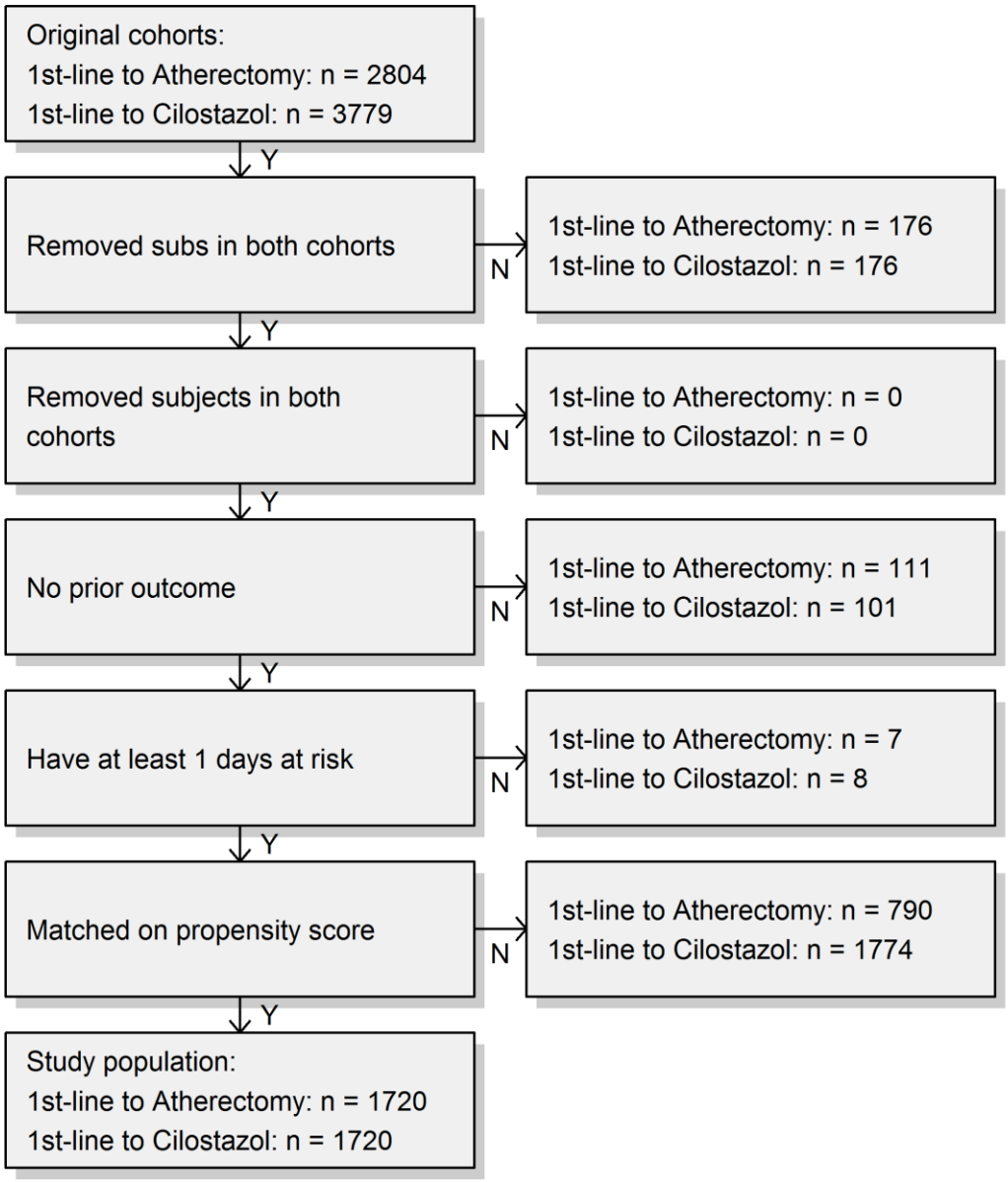
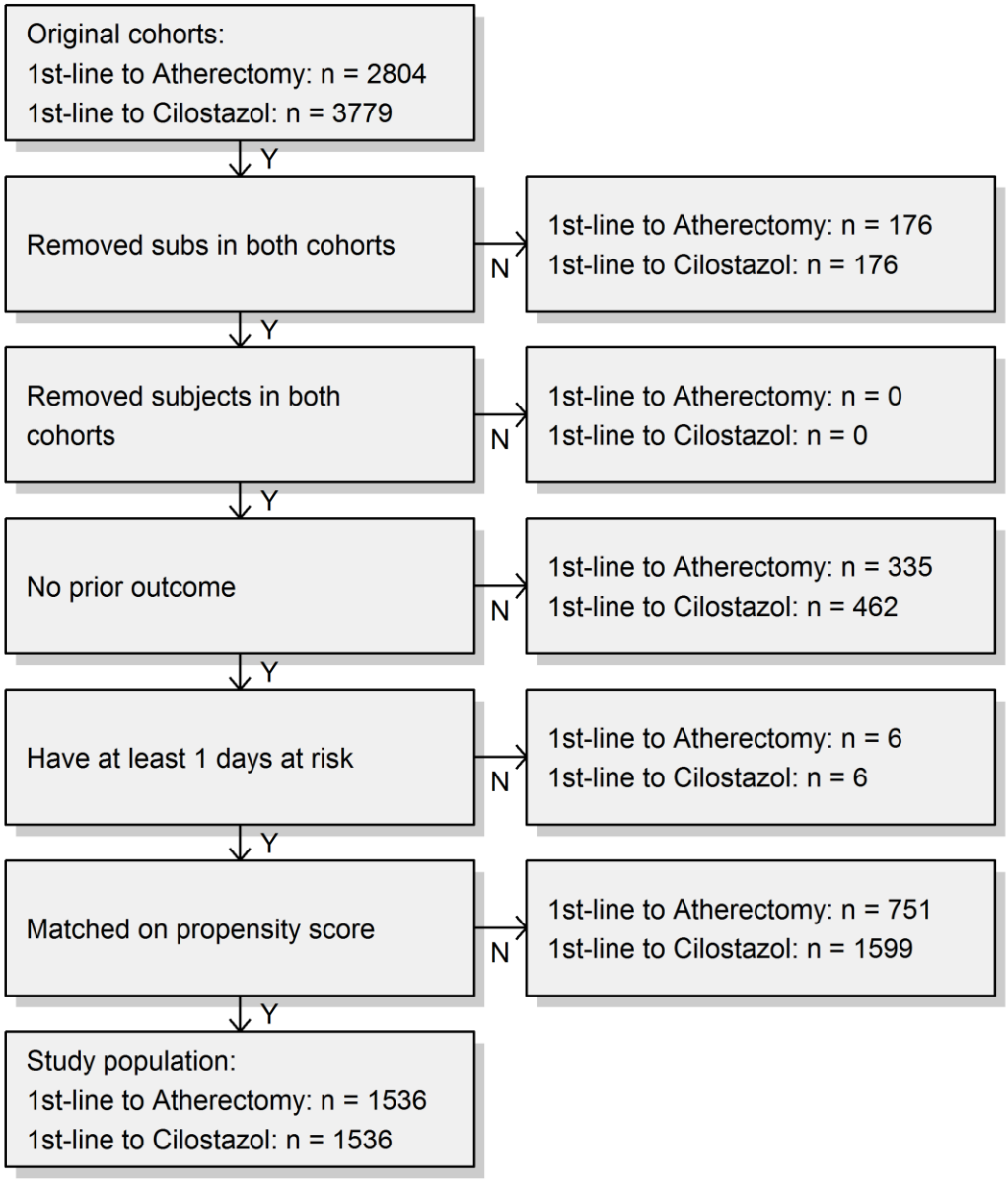


Figure 16: Attrition Diagram: Myocardial Infarction or Ischemic Stroke or All-Cause Death

("First-line" = first line treatment of statins, clopidogrel, or aspirin; "subs" = cohort subjects)



MDCR

PTA with Stent vs Cilostazol

Figure 17: Attrition Diagram: Lower Limb Amputation or Peripheral Arterial Bypass

("First-line" = first line treatment of statins, clopidogrel, or aspirin; "subs" = cohort subjects)

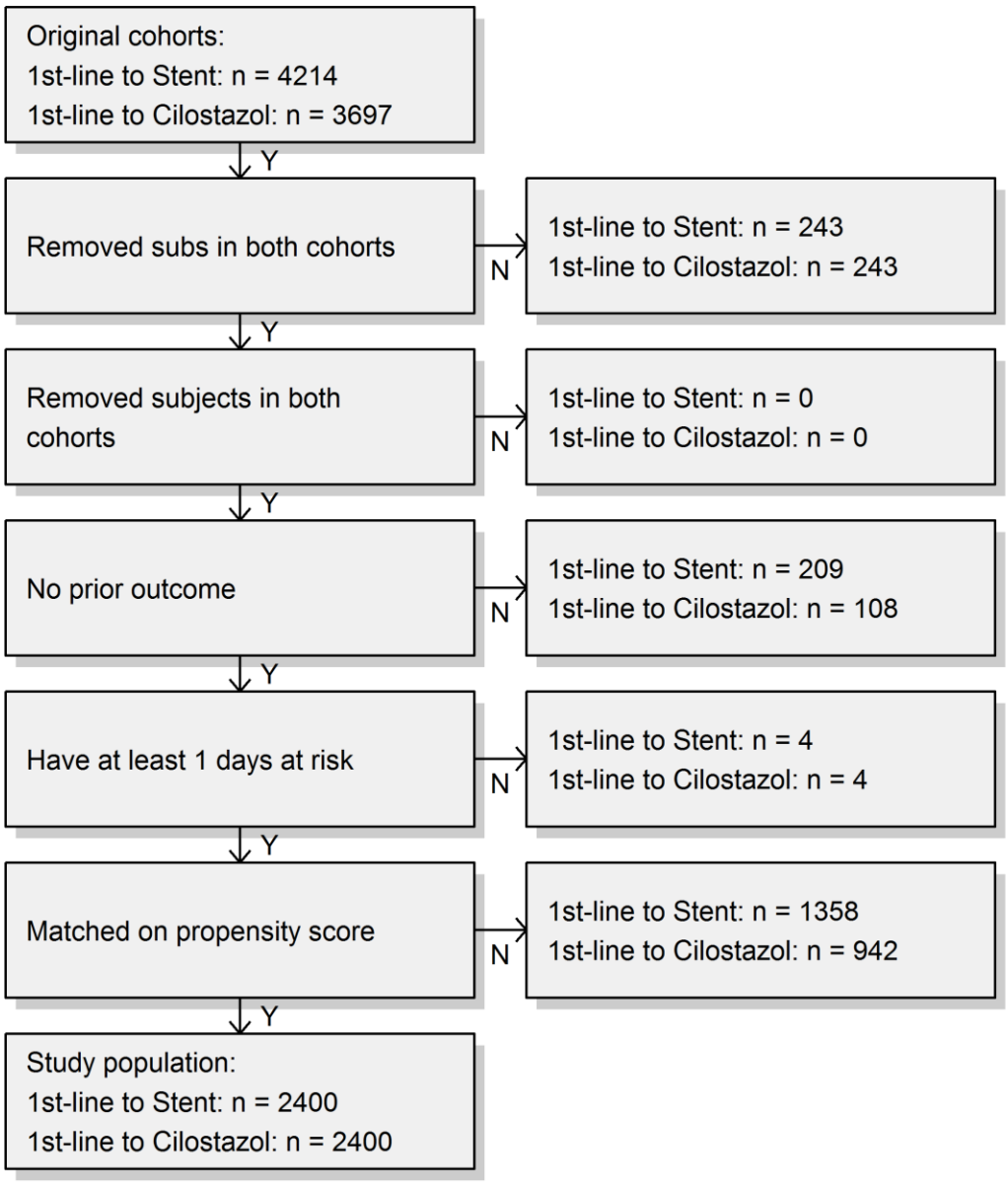
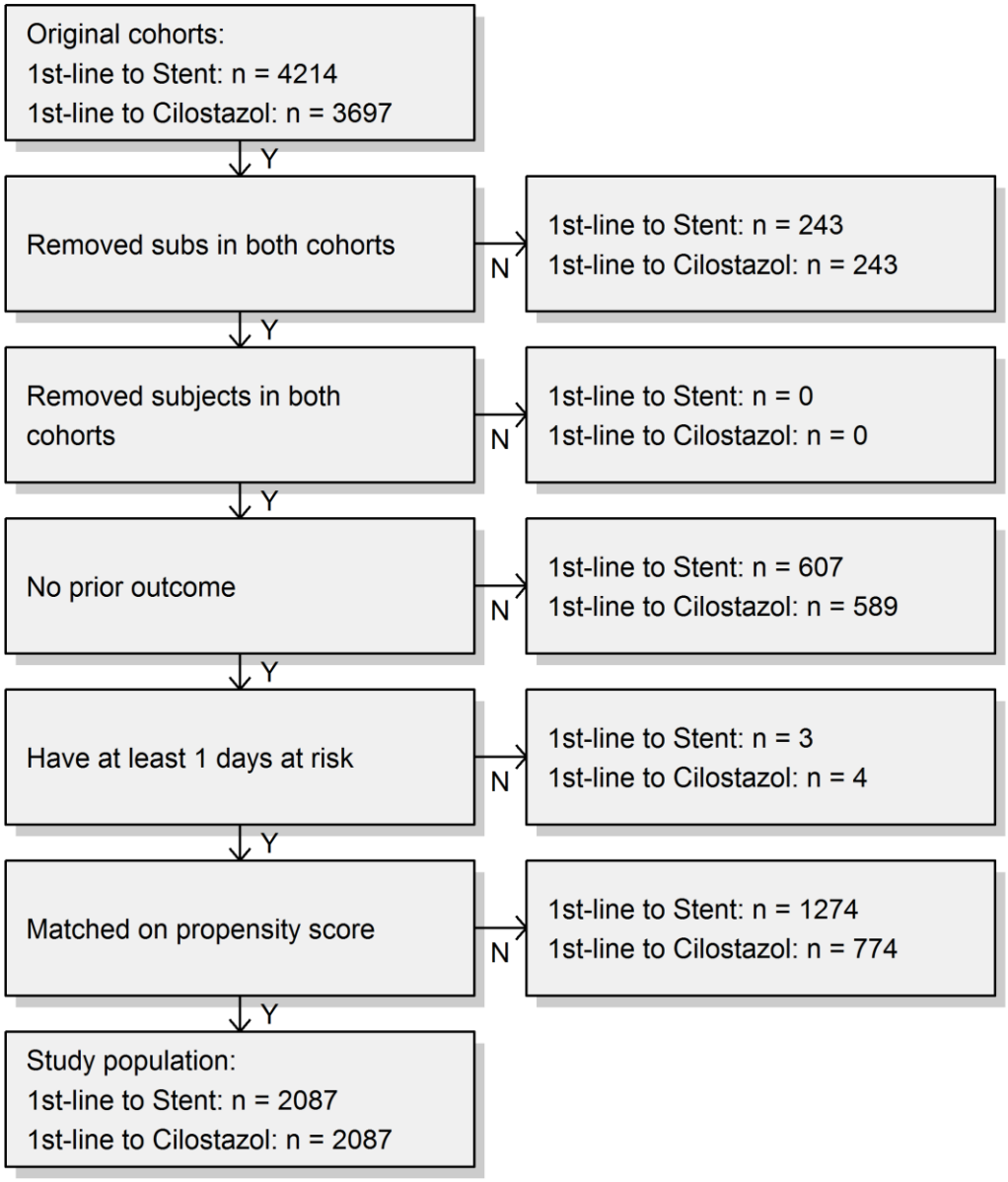


Figure 18: Attrition Diagram: Myocardial Infarction or Ischemic Stroke or All-Cause Death

("First-line" = first line treatment of statins, clopidogrel, or aspirin; "subs" = cohort subjects)



PTA with Atherectomy vs Cilostazol

Figure 19: Attrition Diagram: Lower Limb Amputation or Peripheral Arterial Bypass

("First-line" = first line treatment of statins, clopidogrel, or aspirin; "subs" = cohort subjects)

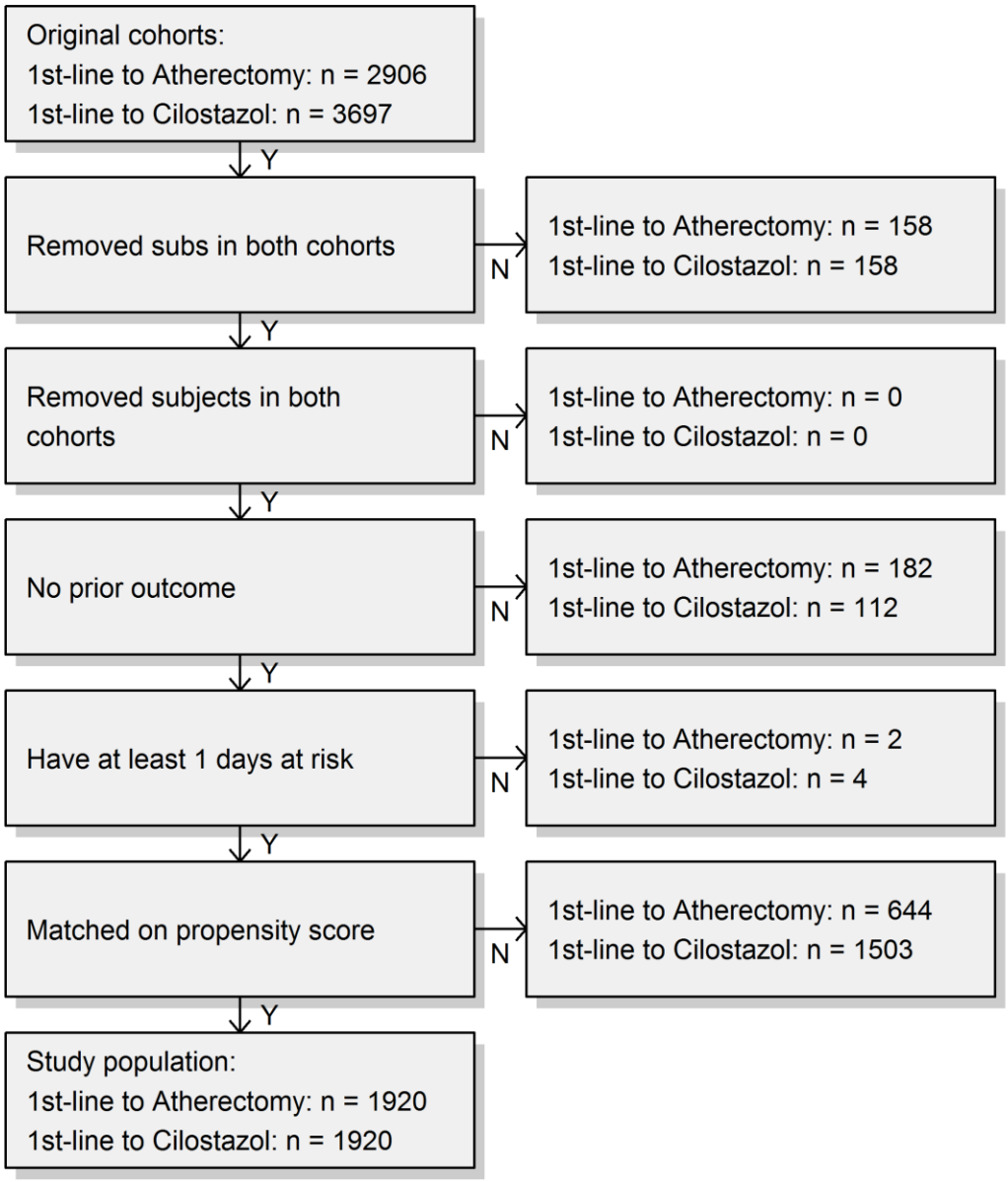
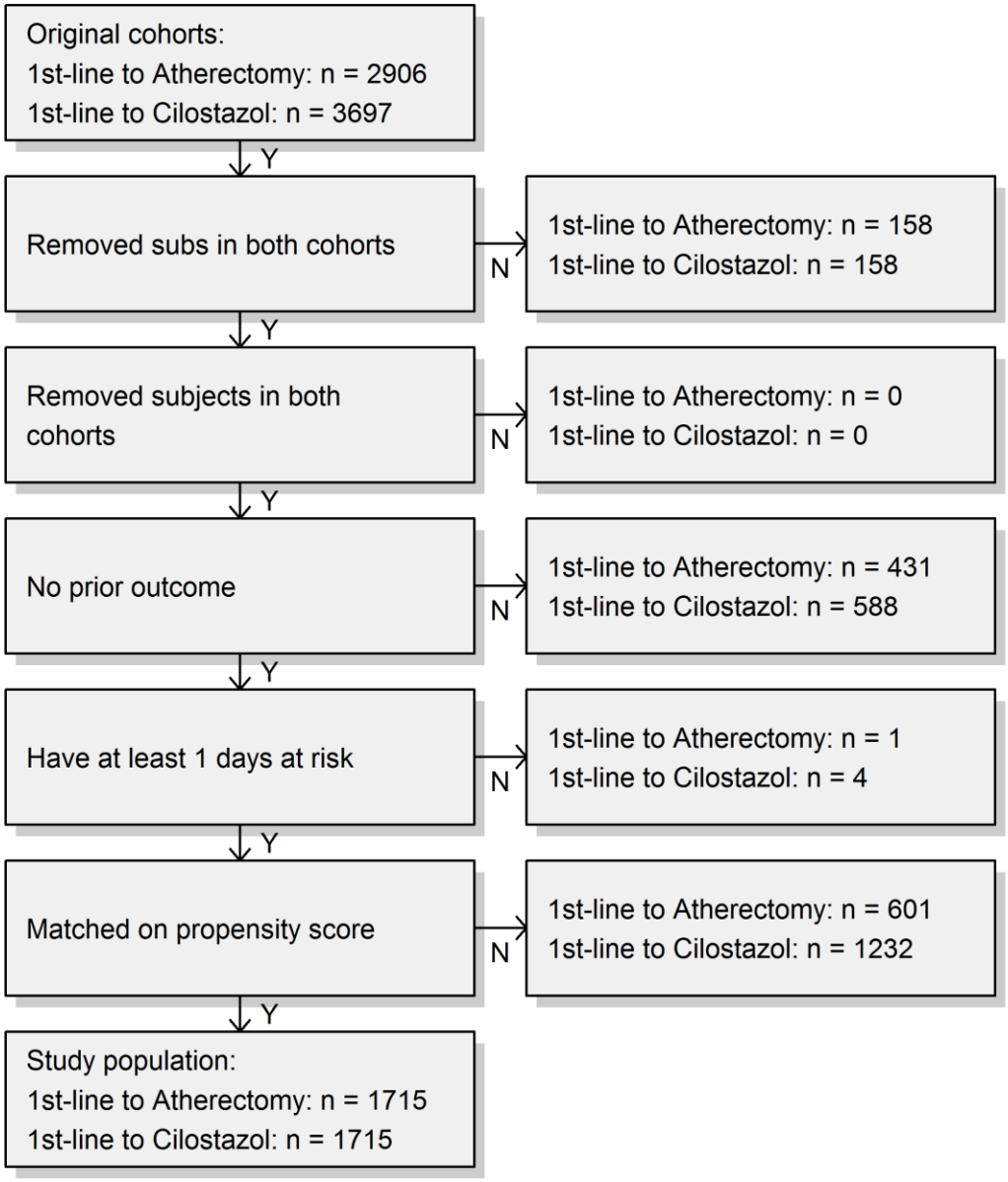


Figure 20: Attrition Diagram: Myocardial Infarction or Ischemic Stroke or All-Cause Death

("First-line" = first line treatment of statins, clopidogrel, or aspirin; "subs" = cohort subjects)



CCAE

PTA with Stent vs Cilostazol

Figure 21: Attrition Diagram: Lower Limb Amputation or Peripheral Arterial Bypass

("First-line" = first line treatment of statins, clopidogrel, or aspirin; "subs" = cohort subjects)

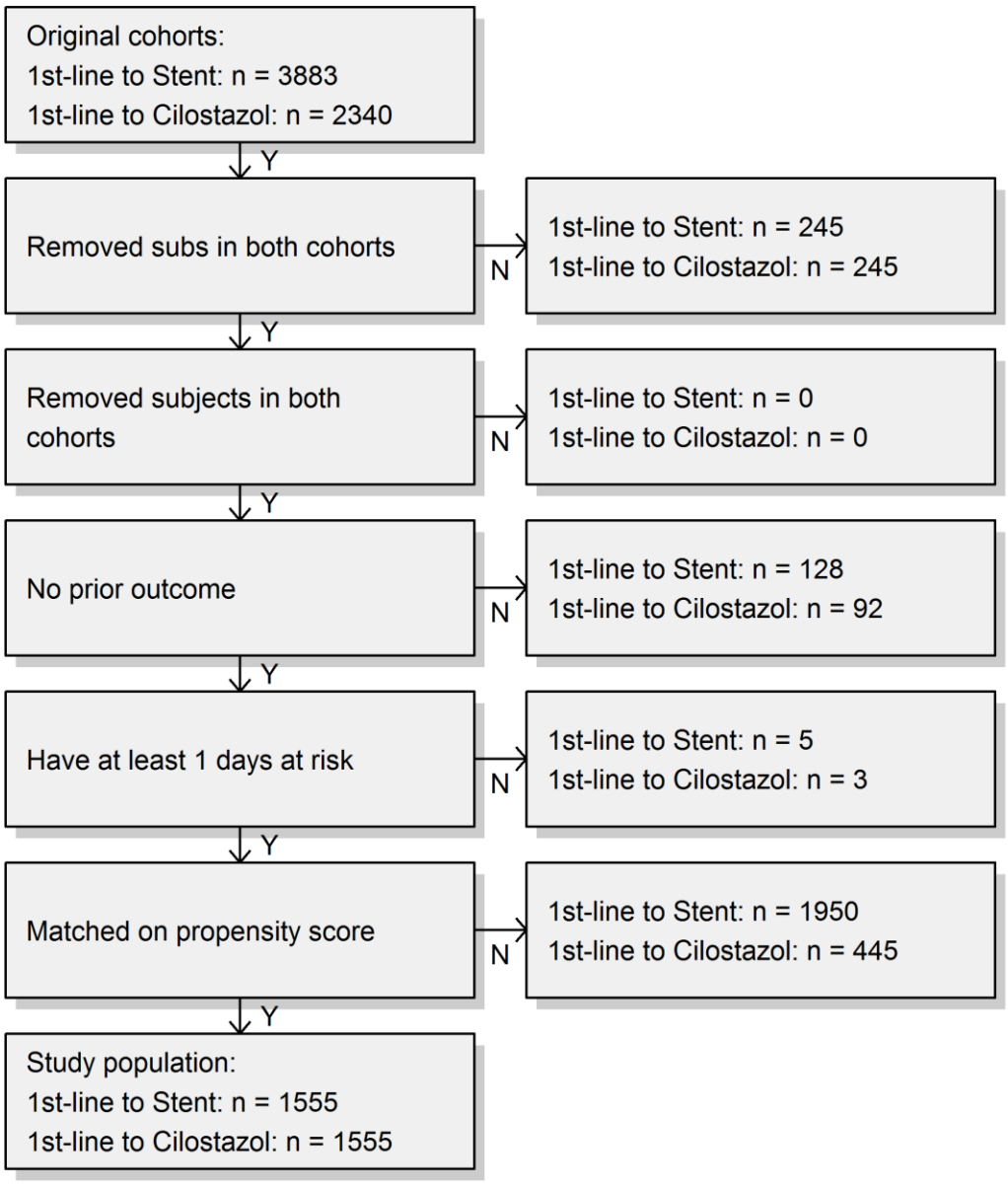
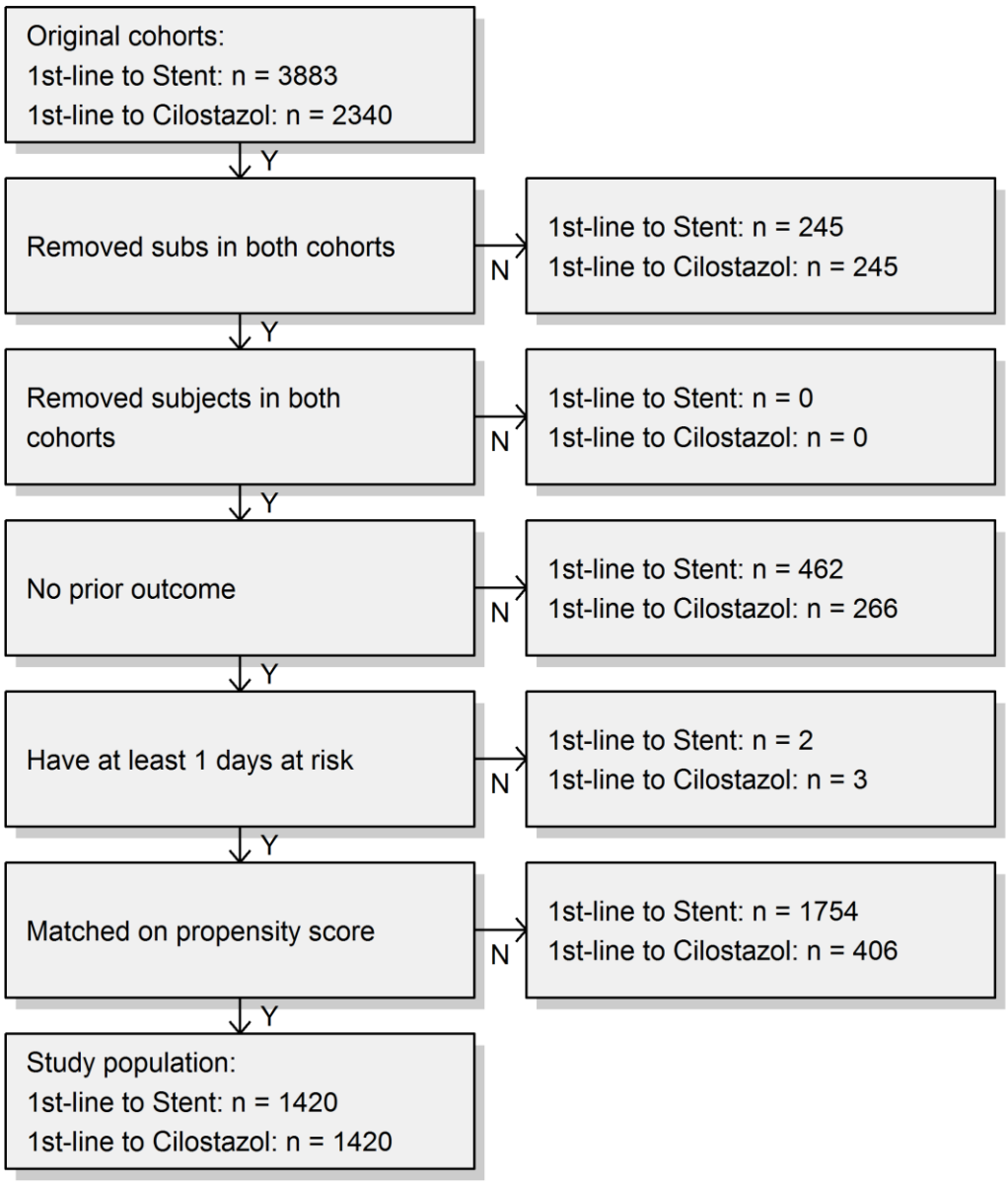


Figure 22: Attrition Diagram: Myocardial Infarction or Ischemic Stroke or All-Cause Death

("First-line" = first line treatment of statins, clopidogrel, or aspirin; "subs" = cohort subjects)



PTA with Atherectomy vs Cilostazol

Figure 23: Attrition Diagram: Lower Limb Amputation or Peripheral Arterial Bypass

("First-line" = first line treatment of statins, clopidogrel, or aspirin; "subs" = cohort subjects)

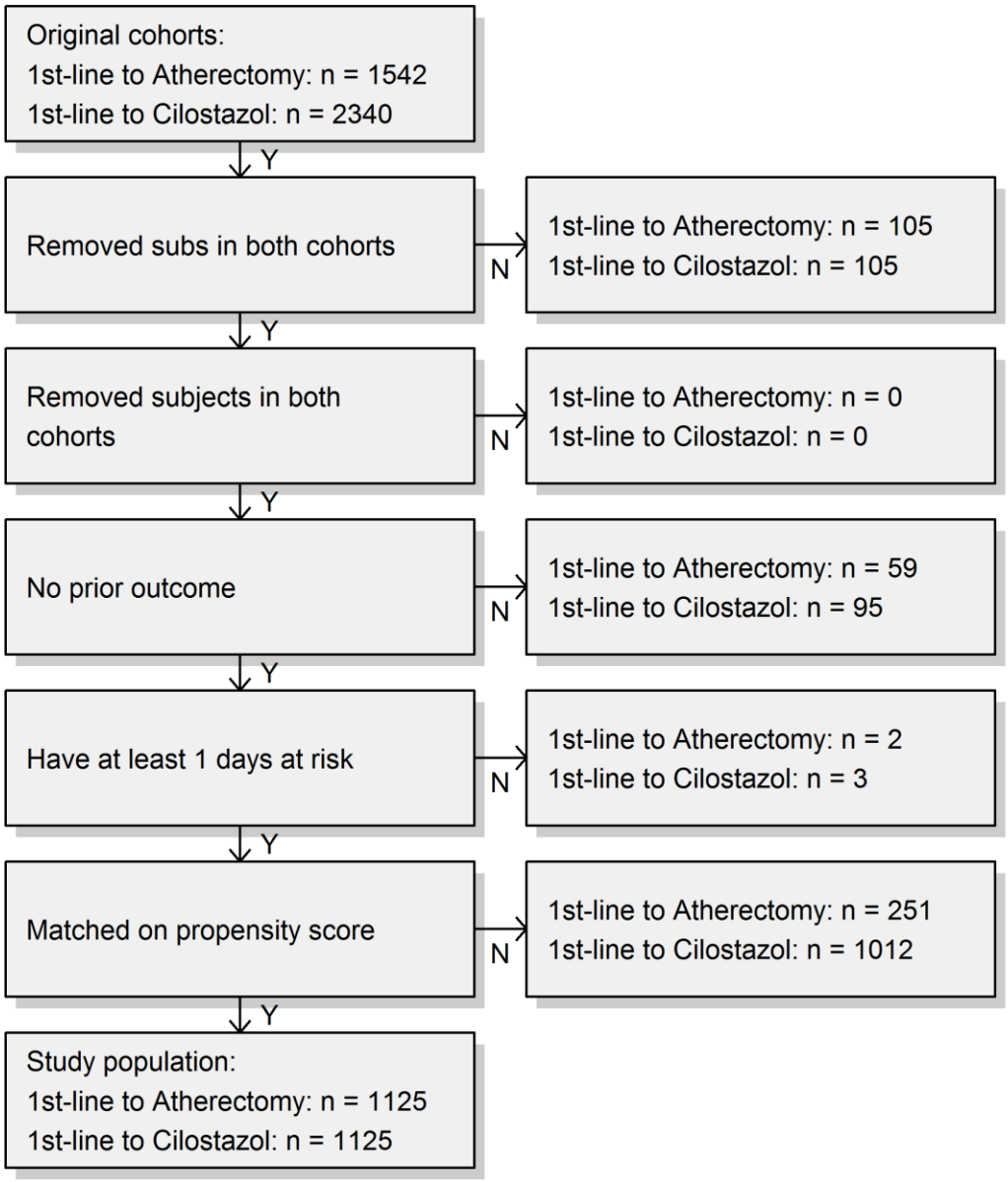
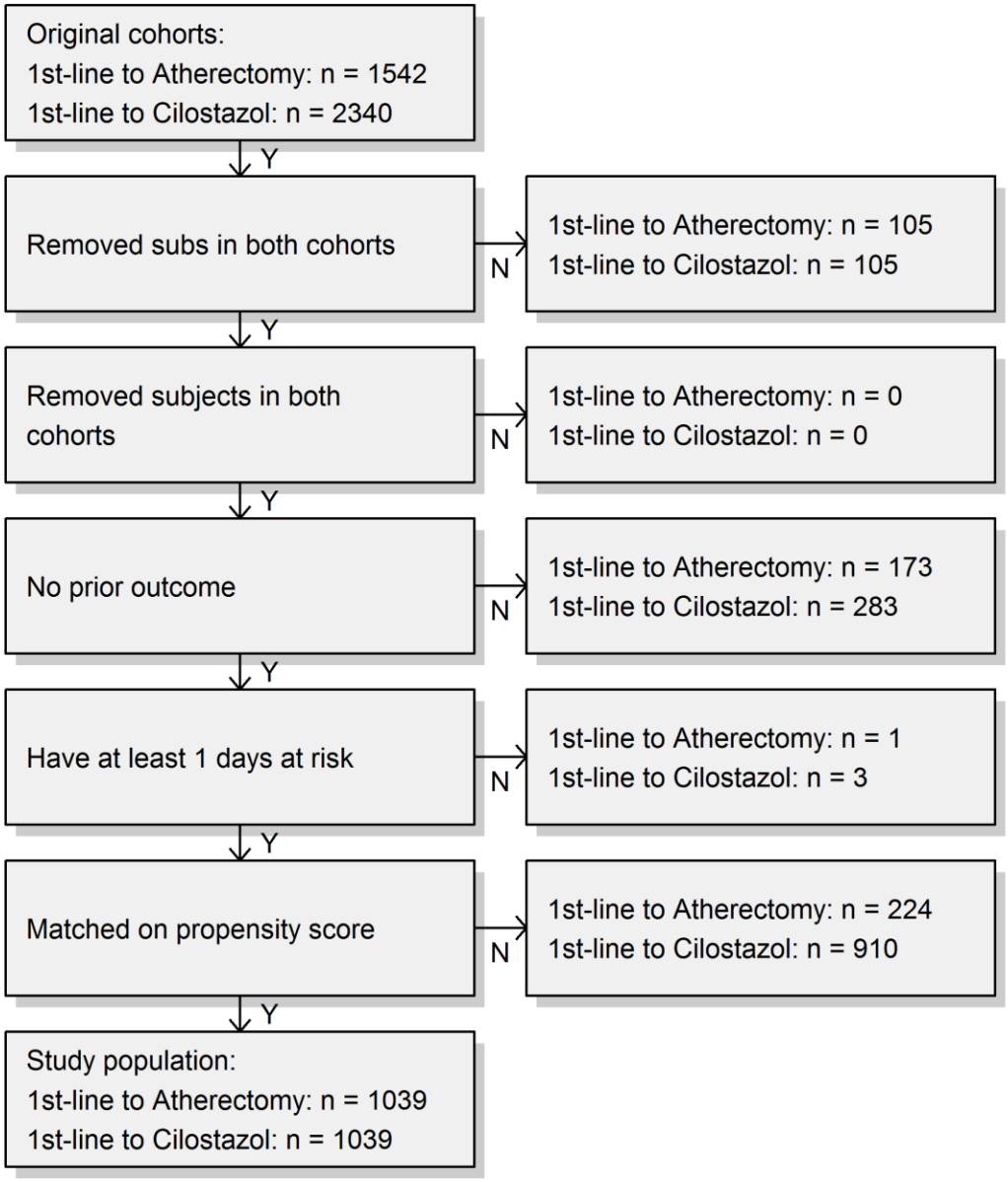


Figure 24: Attrition Diagram: Myocardial Infarction or Ischemic Stroke or All-Cause Death

("First-line" = first line treatment of statins, clopidogrel, or aspirin; "subs" = cohort subjects)



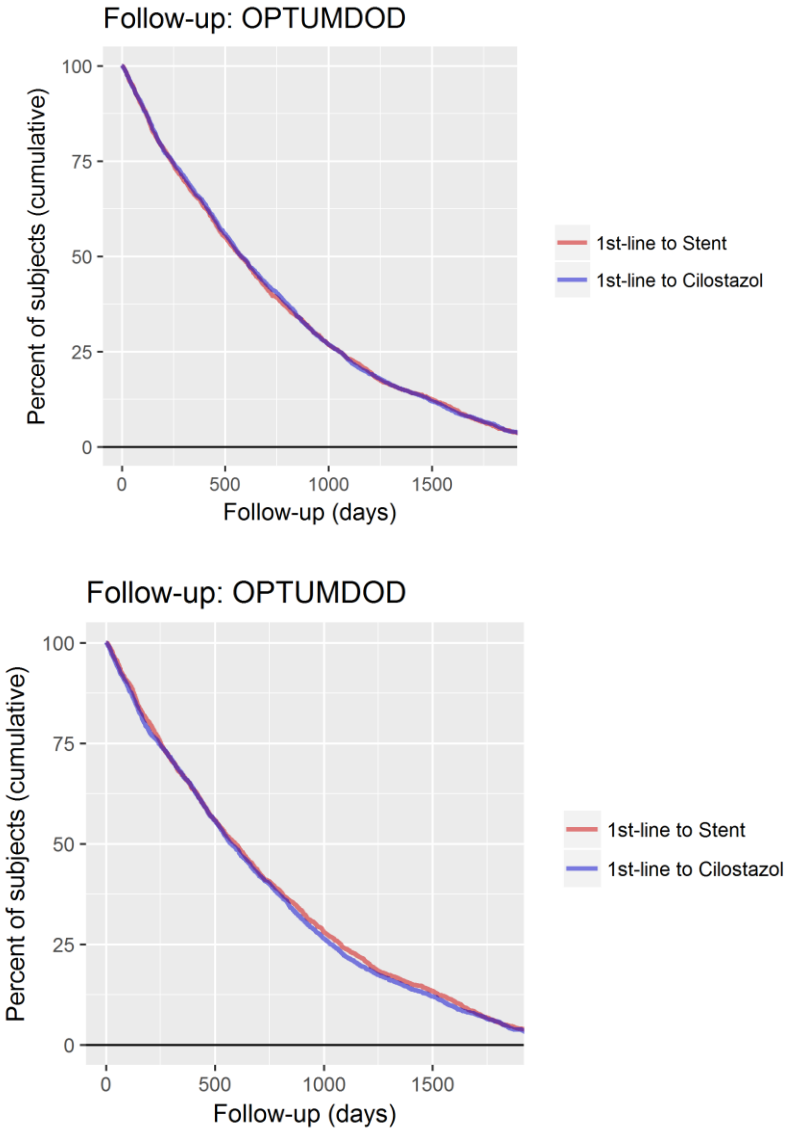
Survival Time

OPTUM

PTA with Stent vs Cilostazol

Figure 25: Survival Time Plots: (1) Lower Limb Amputation or Peripheral Arterial Bypass and (2) Myocardial Infarction or Ischemic Stroke or All-Cause Death

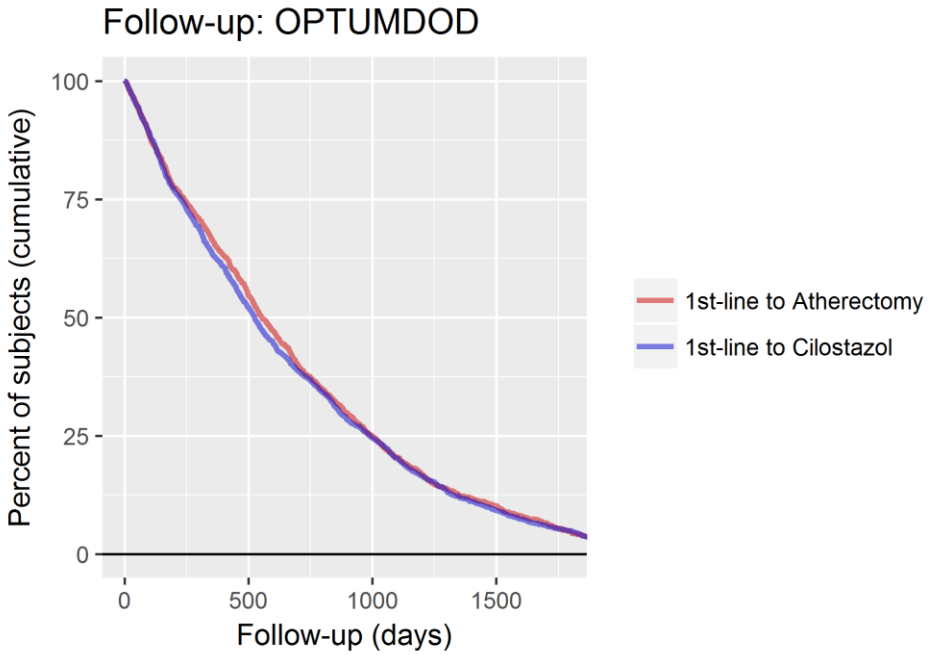
("First-line" = first line treatment of statins, clopidogrel, or aspirin)

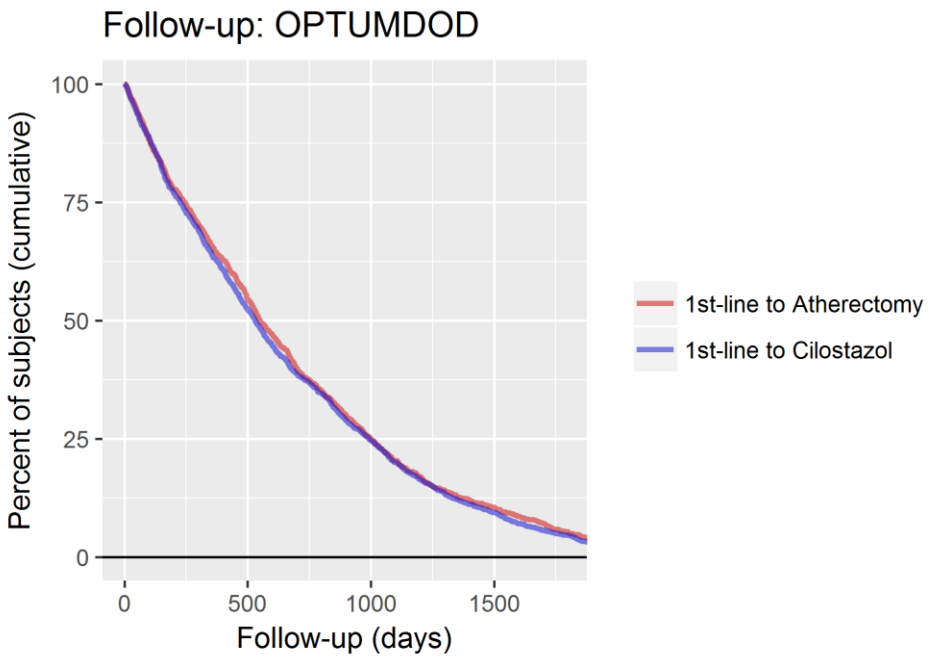


PTA with Atherectomy vs Cilostazol

Figure 26: Survival Time Plots: (1) Lower Limb Amputation or Peripheral Arterial Bypass and (2) Myocardial Infarction or Ischemic Stroke or All-Cause Death

("First-line" = first line treatment of statins, clopidogrel, or aspirin)



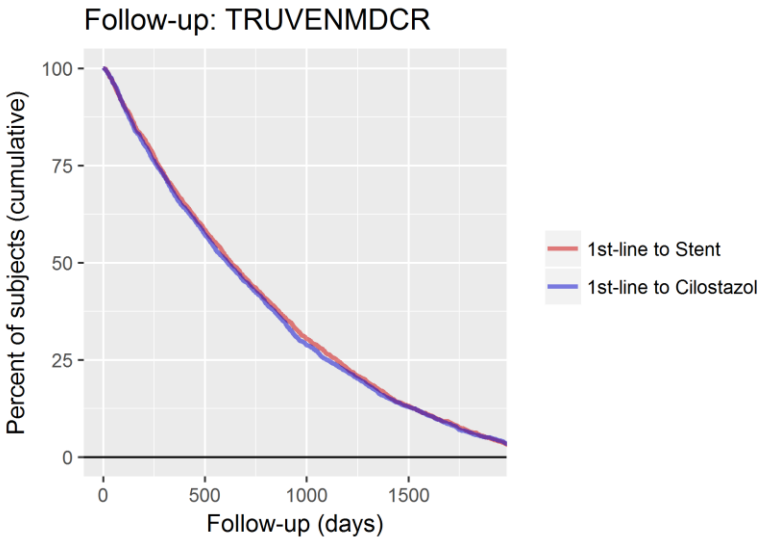


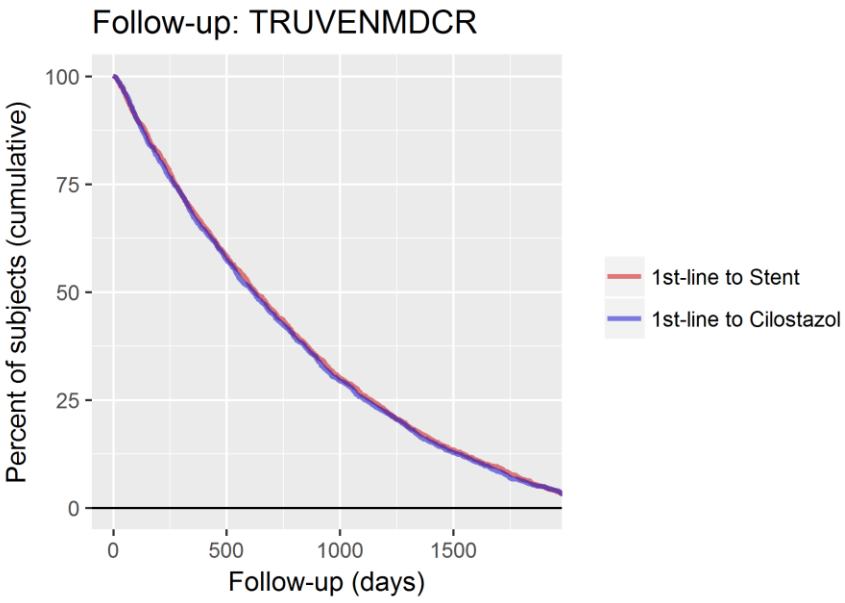
MDCR

PTA with Stent vs Cilostazol

Figure 27: Survival Time Plots: (1) Lower Limb Amputation or Peripheral Arterial Bypass and (2) Myocardial Infarction or Ischemic Stroke or All-Cause Death

("First-line" = first line treatment of statins, clopidogrel, or aspirin)

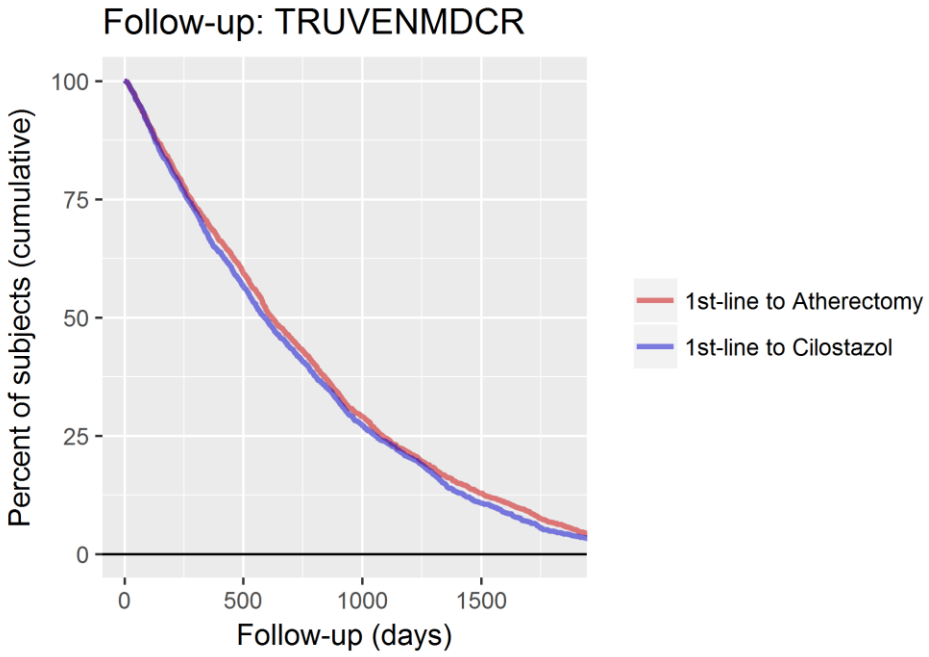


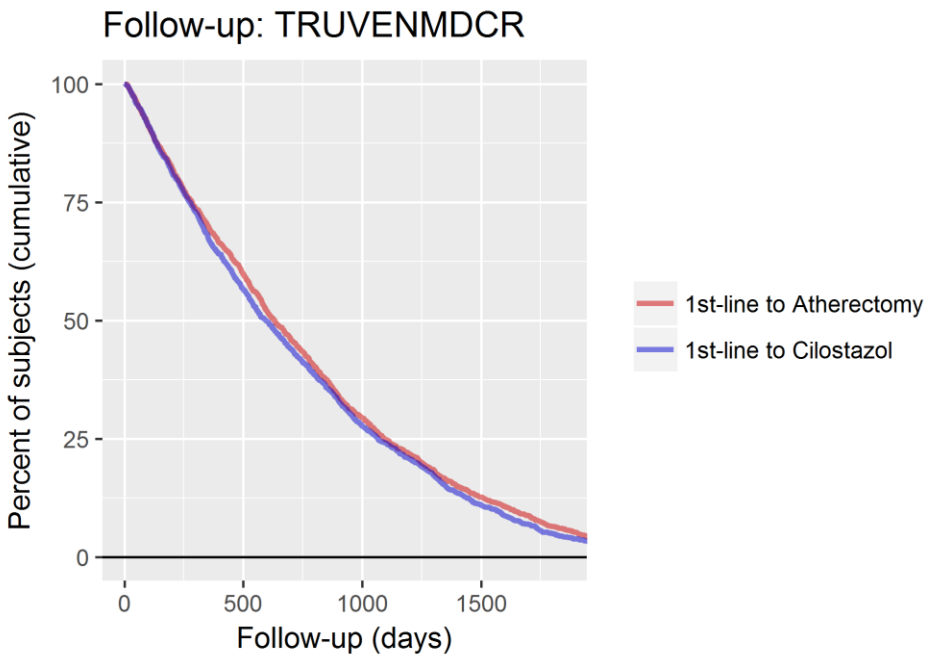


PTA with Atherectomy vs Cilostazol

Figure 28: Survival Time Plots: (1) Lower Limb Amputation or Peripheral Arterial Bypass and (2) Myocardial Infarction or Ischemic Stroke or All-Cause Death

("First-line" = first line treatment of statins, clopidogrel, or aspirin)



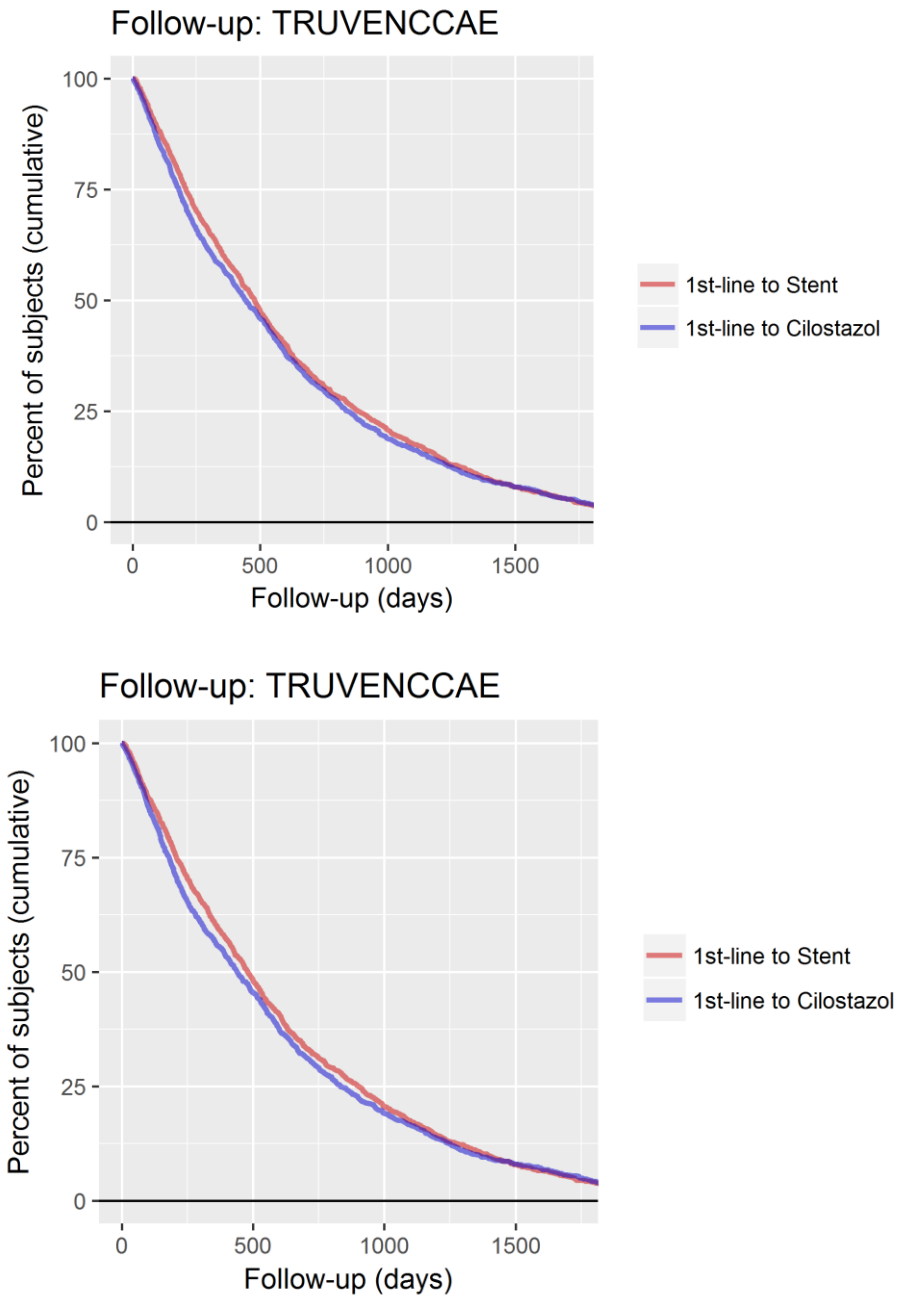


CCAE

PTA with Stent vs Cilostazol

Figure 29: Survival Time Plots: (1) Lower Limb Amputation or Peripheral Arterial Bypass and (2) Myocardial Infarction or Ischemic Stroke or All-Cause Death

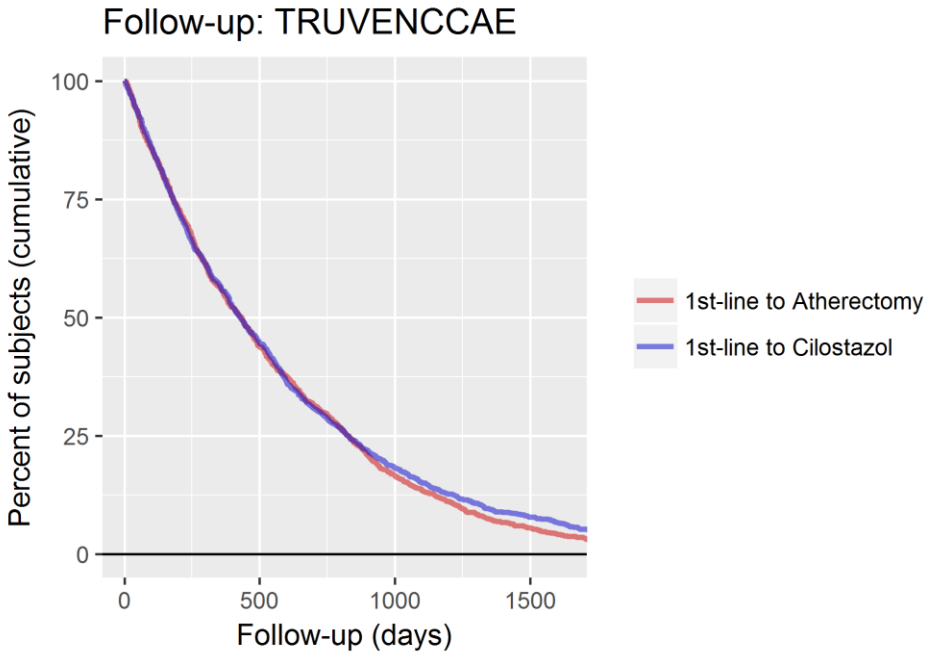
("First-line" = first line treatment of statins, clopidogrel, or aspirin)

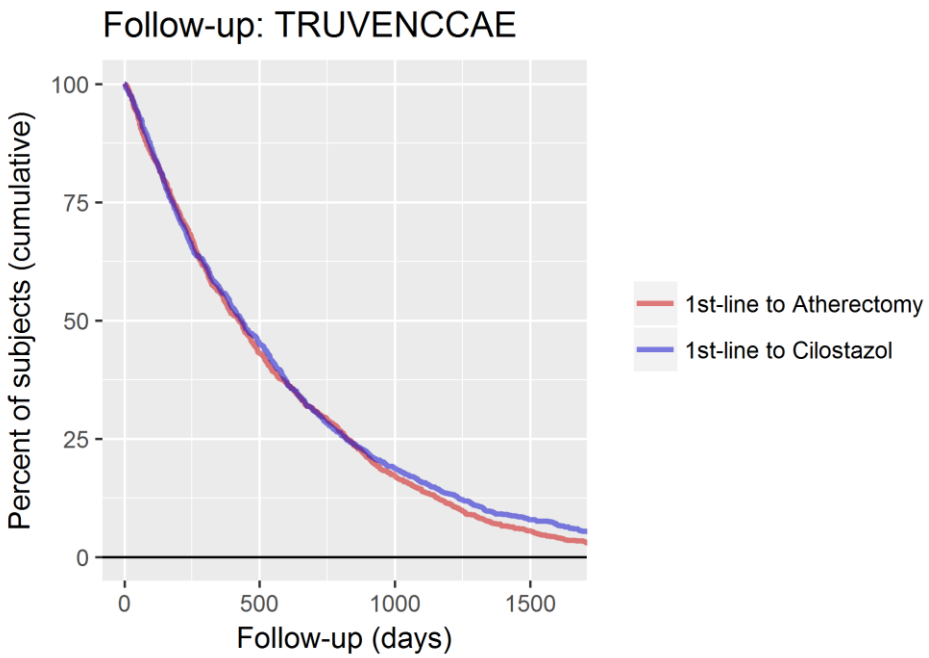


PTA with Atherectomy vs Cilostazol

Figure 30: Survival Time Plots: (1) Lower Limb Amputation or Peripheral Arterial Bypass and (2) Myocardial Infarction or Ischemic Stroke or All-Cause Death

("First-line" = first line treatment of statins, clopidogrel, or aspirin)





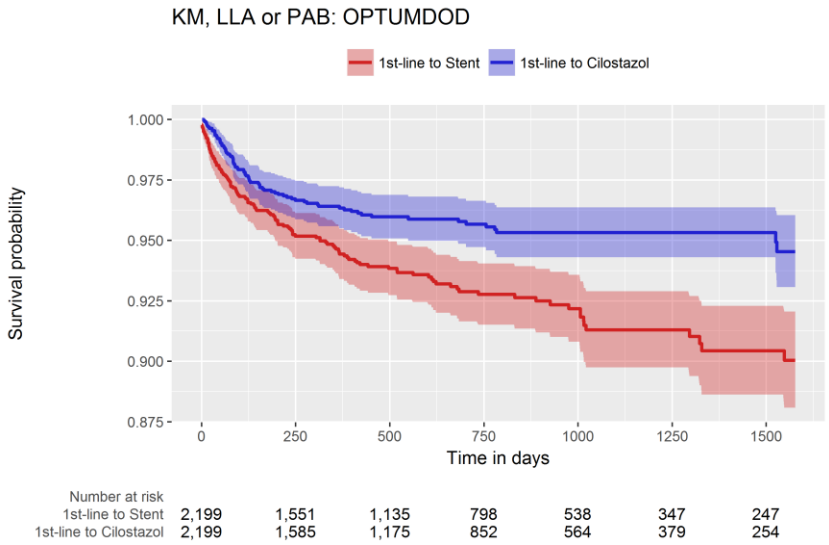
Kaplan-Meier Plots

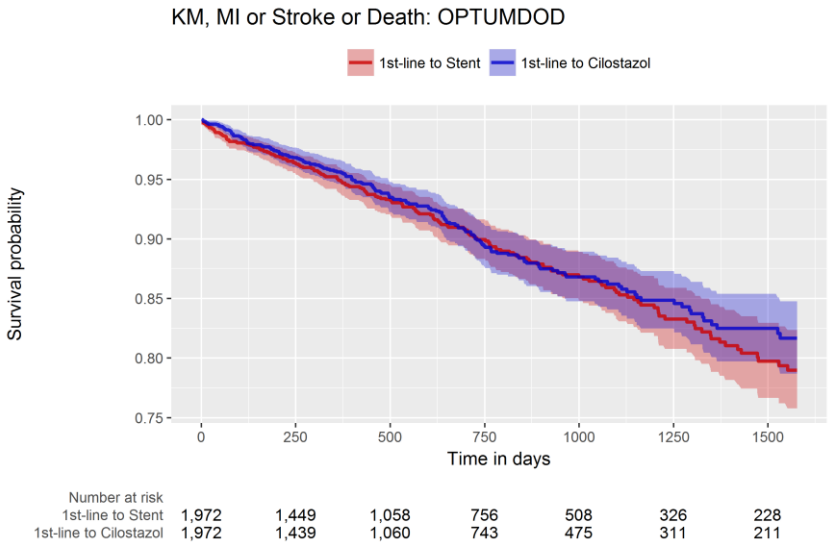
OPTUM

PTA with Stent vs Cilostazol

Figure 31: Kaplan-Meier Plots: (1) Lower Limb Amputation or Peripheral Arterial Bypass and (2) Myocardial Infarction or Ischemic Stroke or All-Cause Death

("First-line" = first line treatment of statins, clopidogrel, or aspirin)

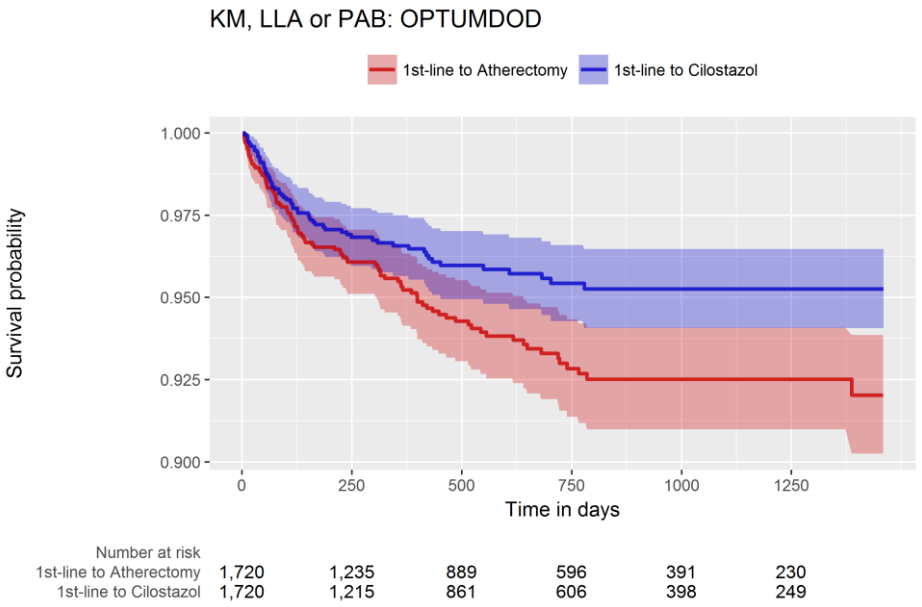


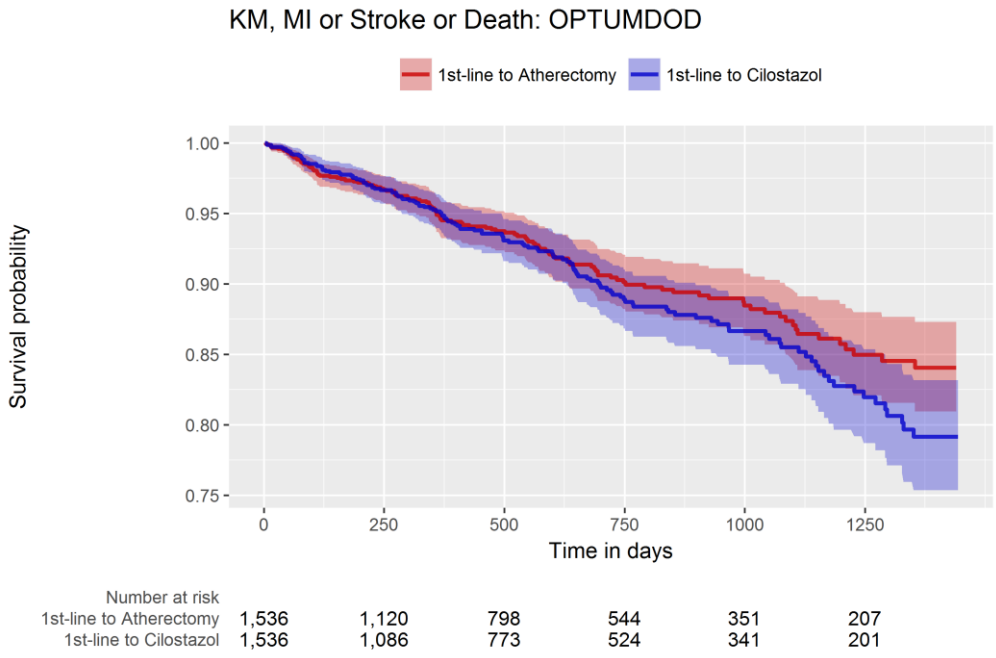


PTA with Atherectomy vs Cilostazol

Figure 32: Kaplan-Meier Plots: (1) Lower Limb Amputation or Peripheral Arterial Bypass and (2) Myocardial Infarction or Ischemic Stroke or All-Cause Death

("First-line" = first line treatment of statins, clopidogrel, or aspirin)



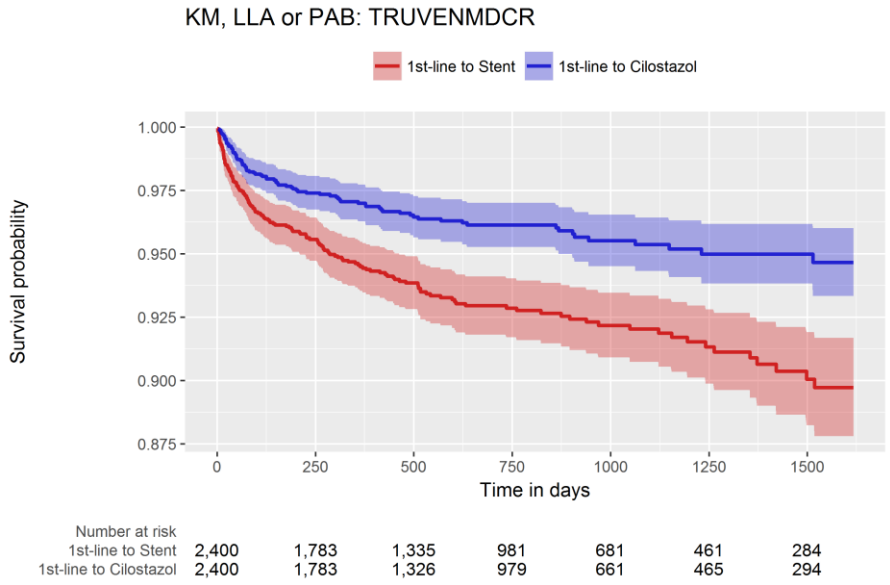


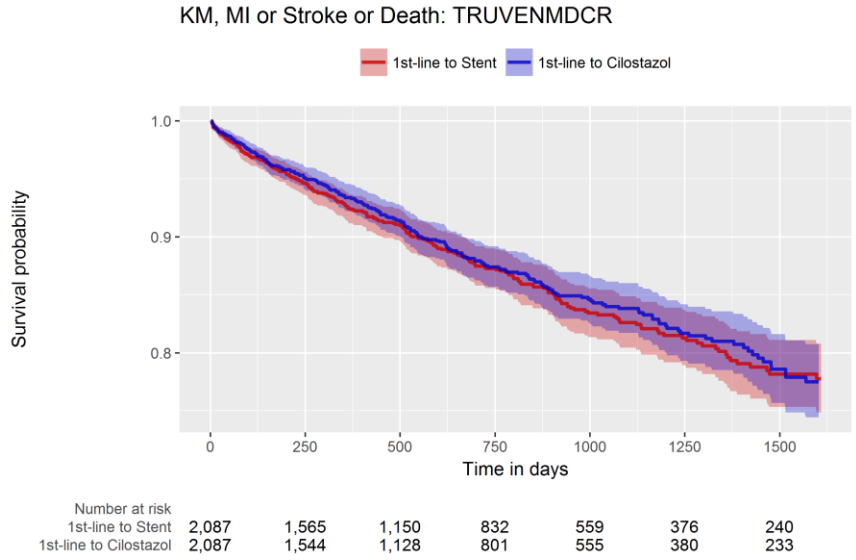
MDCR

PTA with Stent vs Cilostazol

Figure 33: Kaplan-Meier Plots: (1) Lower Limb Amputation or Peripheral Arterial Bypass and (2) Myocardial Infarction or Ischemic Stroke or All-Cause Death

("First-line" = first line treatment of statins, clopidogrel, or aspirin)

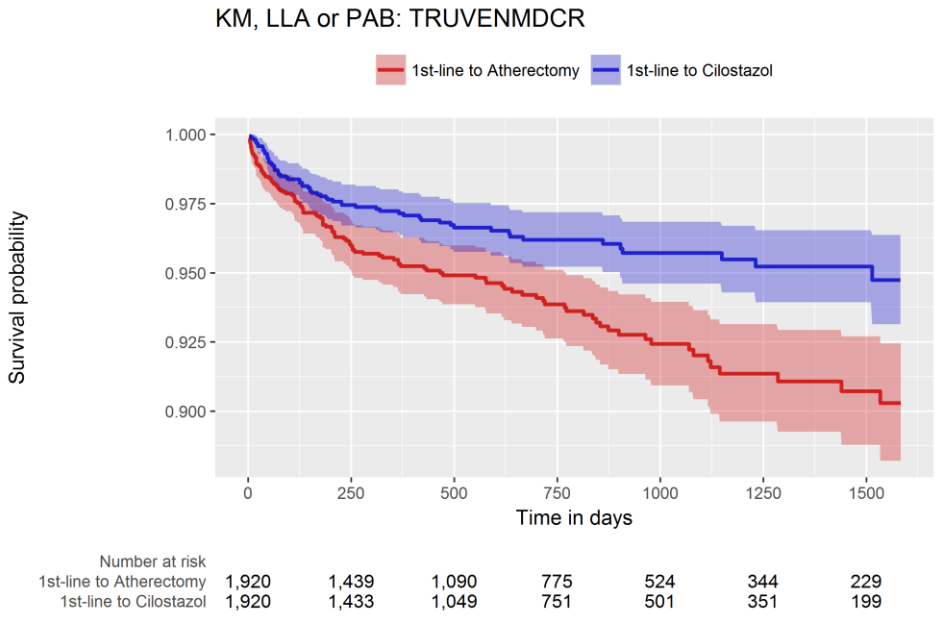


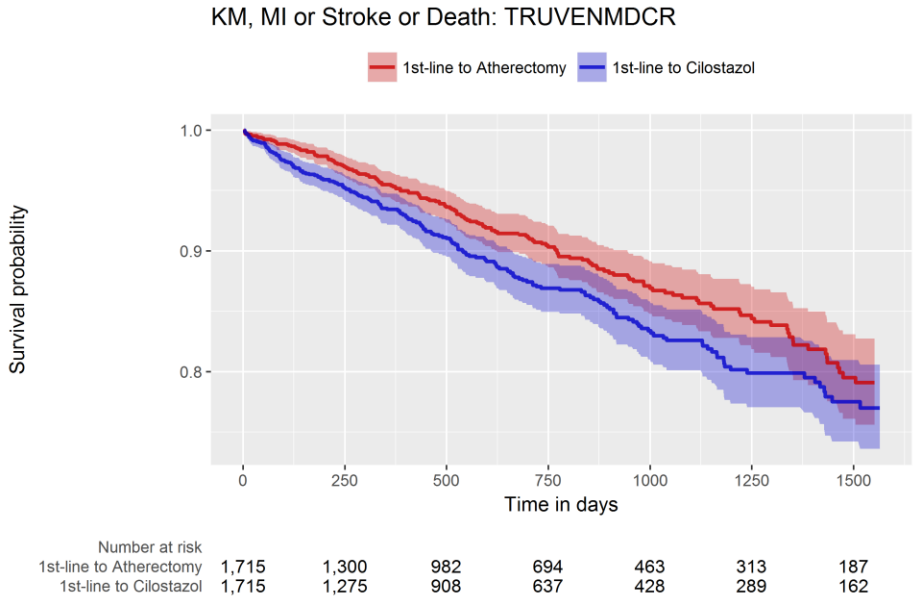


PTA with Atherectomy vs Cilostazol

Figure 34: Kaplan-Meier Plots: (1) Lower Limb Amputation or Peripheral Arterial Bypass and (2) Myocardial Infarction or Ischemic Stroke or All-Cause Death

("First-line" = first line treatment of statins, clopidogrel, or aspirin)



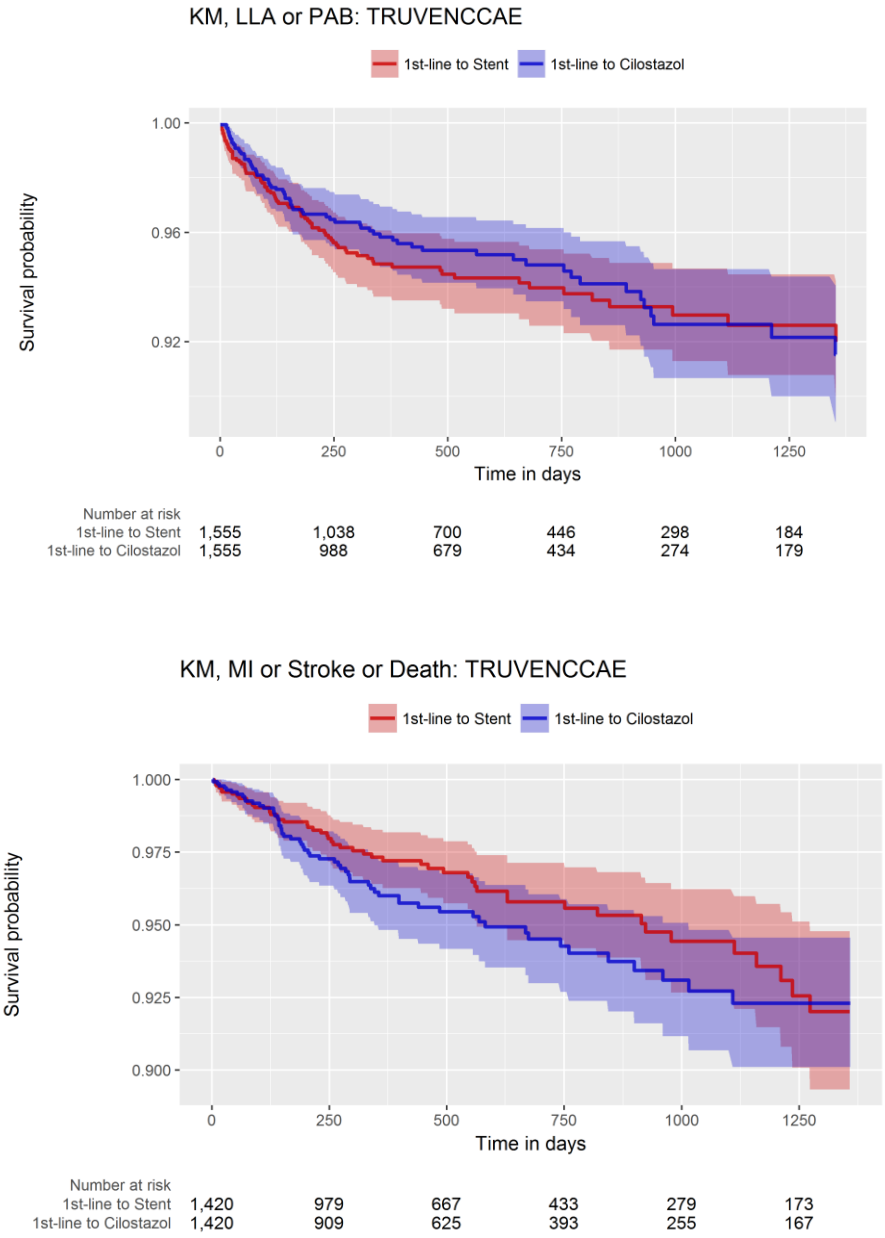


CCAE

PTA with Stent vs Cilostazol

Figure 35: Kaplan-Meier Plots: (1) Lower Limb Amputation or Peripheral Arterial Bypass and (2) Myocardial Infarction or Ischemic Stroke or All-Cause Death

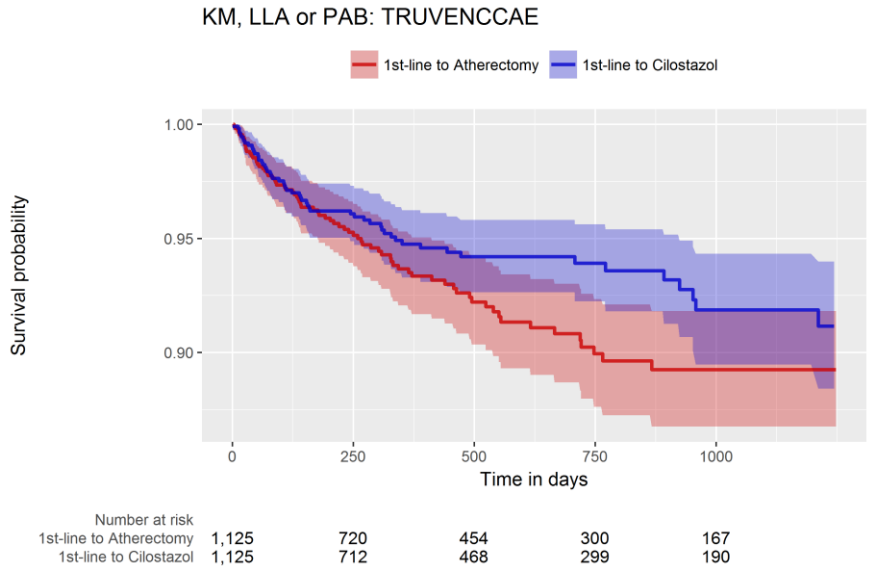
("First-line" = first line treatment of statins, clopidogrel, or aspirin)

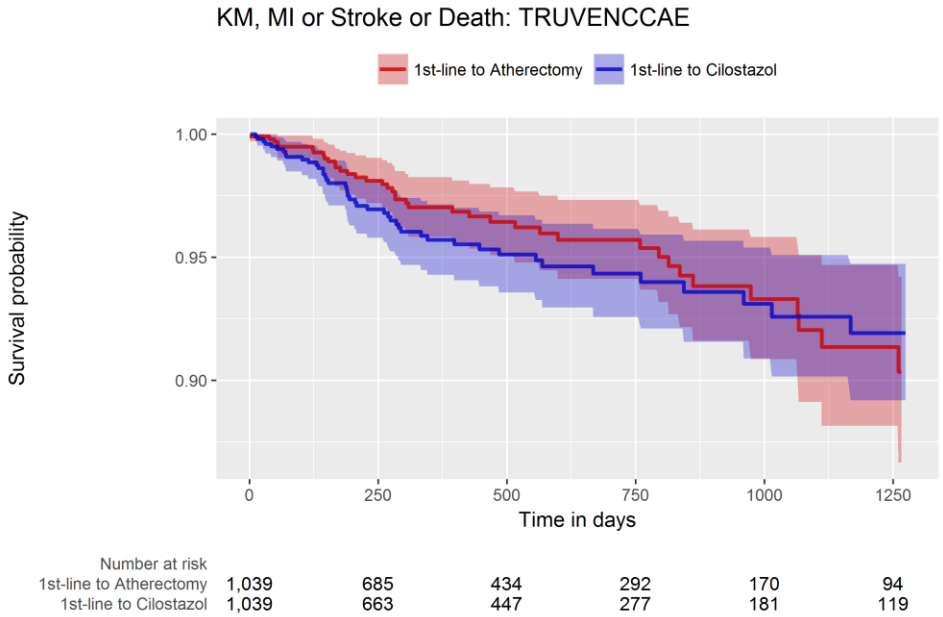


PTA with Atherectomy vs Cilostazol

Figure 36: Kaplan-Meier Plots: (1) Lower Limb Amputation or Peripheral Arterial Bypass and (2) Myocardial Infarction or Ischemic Stroke or All-Cause Death

("First-line" = first line treatment of statins, clopidogrel, or aspirin)



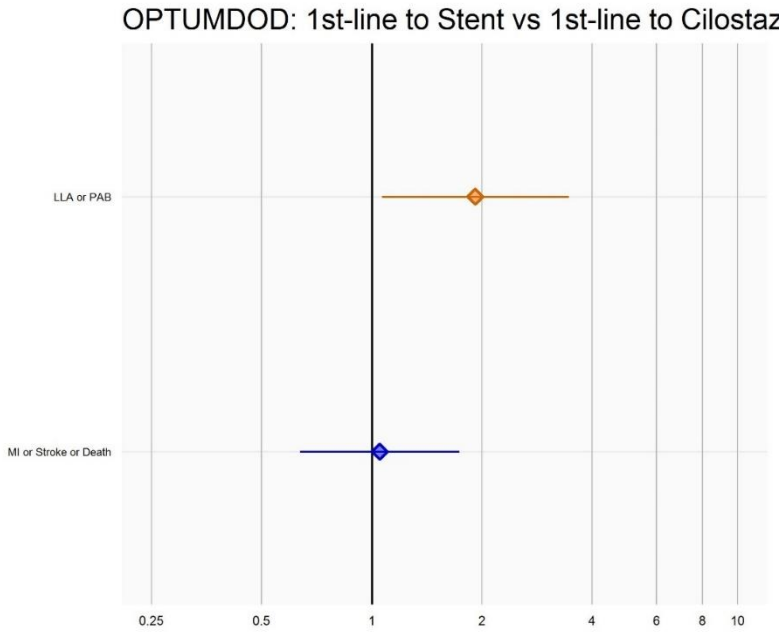


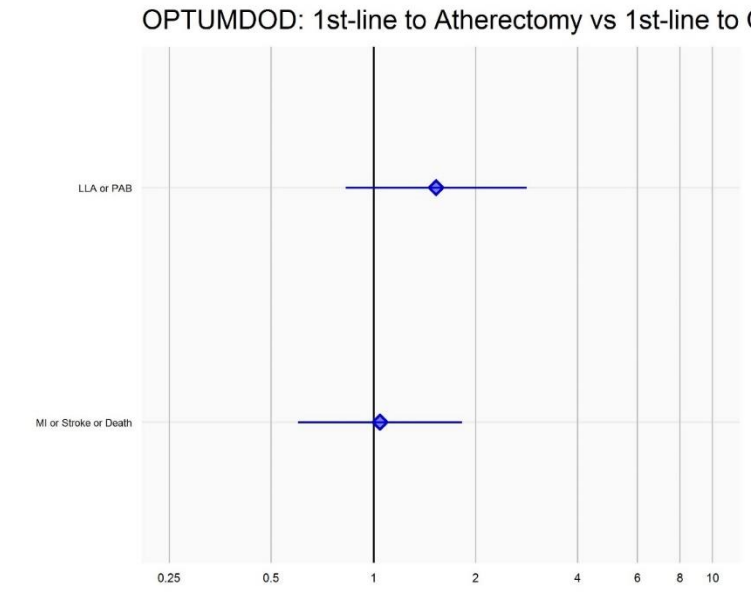
Forest Plots

OPTUM

Figure 37: Forest Plots of Hazard Ratios and 95% Confidence Intervals: diamonds represent effect estimates and the horizontal lines around them confidence interval bands.

("First-line" = first line treatment of statins, clopidogrel, or aspirin; "LLA" = lower limb amputation; "PAB" = peripheral arterial bypass)

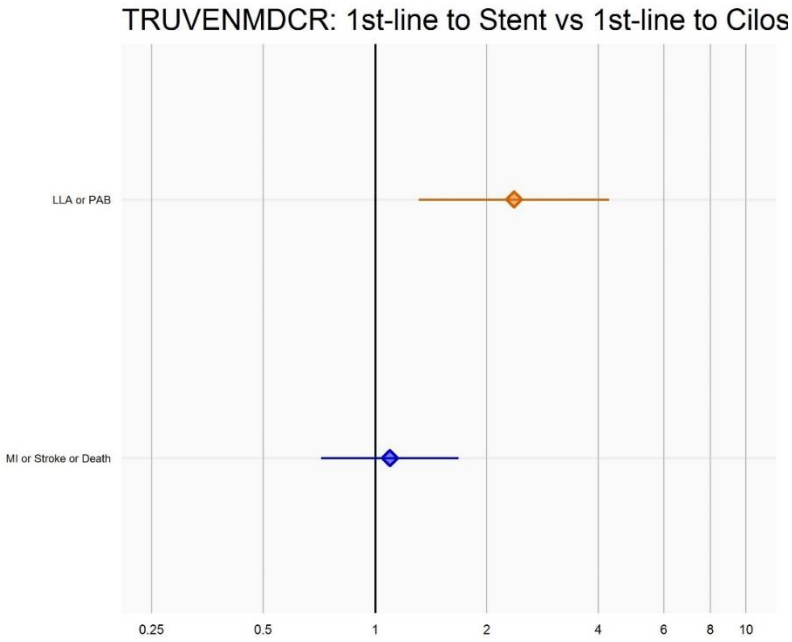


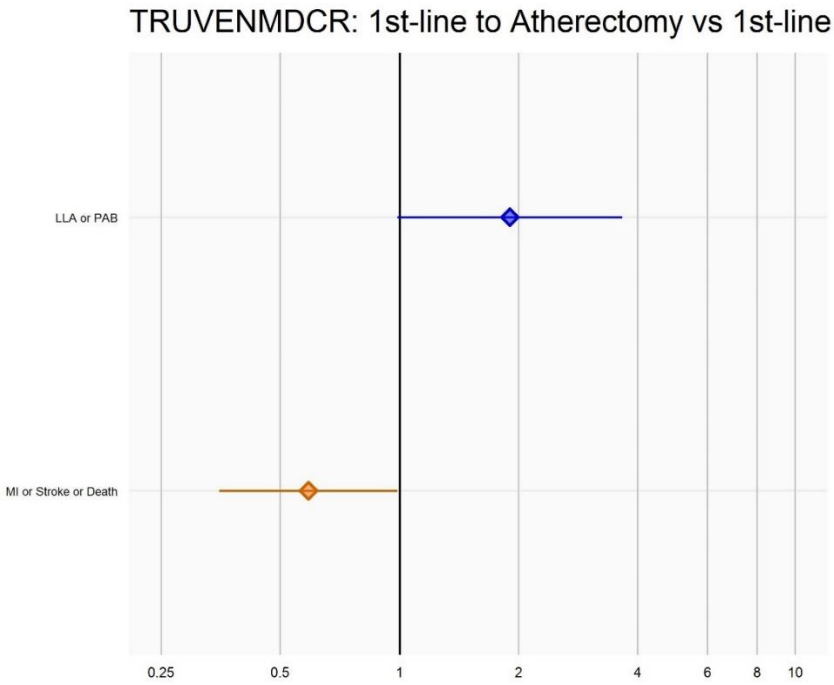


MDCR

Figure 38: Forest Plots of Hazard Ratios and 95% Confidence Intervals: diamonds represent effect estimates and the horizontal lines around them confidence interval bands.

("First-line" = first line treatment of statins, clopidogrel, or aspirin; "LLA" = lower limb amputation; "PAB" = peripheral arterial bypass)

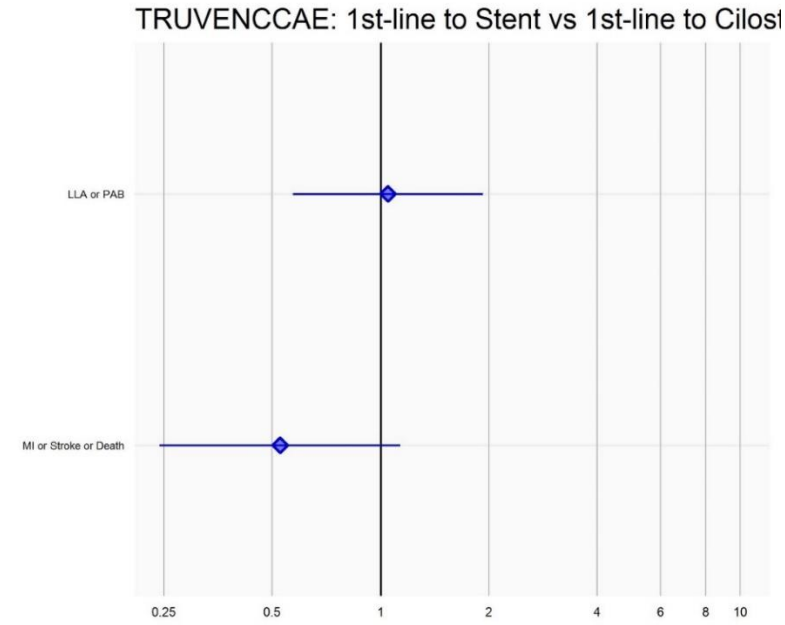


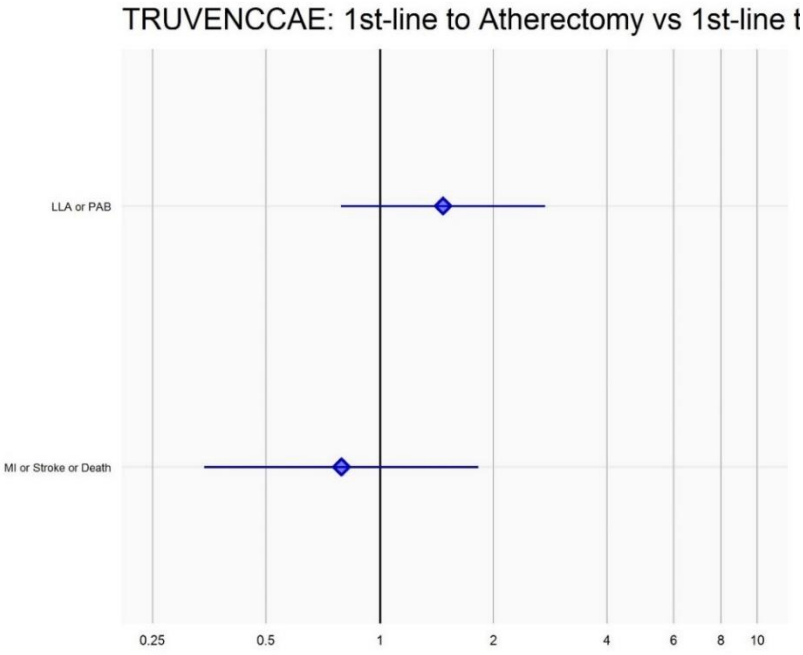


CCAE

Figure 39: Forest Plots of Hazard Ratios and 95% Confidence Intervals: diamonds represent effect estimates and the horizontal lines around them confidence interval bands.

("First-line" = first line treatment of statins, clopidogrel, or aspirin; "LLA" = lower limb amputation; "PAB" = peripheral arterial bypass)





Negative Controls

Table 8: Negative Control Candidates. Each candidate negative control was selected by LAERTES (Largescale Adverse Effects Related to Treatment Evidence Standardization) and clinically reviewed to ensure no associations with the exposures of interest are known or are plausible.

OMOP Concept Id	Concept Name
4171019	Abdominal visceral abscess
4102856	Abnormality of atrial septum
40490966	Abnormality of pulmonary valve
141095	Acne
4227594	Acne vulgaris
30133	Acute laryngitis
4173027	Acute laryngitis and/or tracheitis
4033294	Acute mucositis
4148204	Acute tracheobronchitis
436677	Adjustment disorder
375519	Alcohol withdrawal syndrome
376383	Alcohol-induced organic mental disorder
256439	Allergic rhinitis due to pollen
440424	Aphasia
44783158	Arthritis of pelvis
378424	Astigmatism
134118	Atrophic condition of skin
374923	Bell's palsy
4113639	Benign genital neoplasm
201817	Benign neoplasm of female genital organ
4242498	Benign neoplasm of pelvis
4114223	Benign tumor of head and neck
4182455	Body fat finding
80509	Bone cyst
4082039	Borreliosis
134765	Cachexia
4172458	Candidiasis of skin
81250	Carcinoma in situ of breast
381581	Chalazion
4189855	Chronic arthropathy
198075	Condyloma acuminatum
4161410	Cyst of breast
379822	Cyst of eyelid

201061	Diaphragmatic hernia
4198086	Diffuse spasm
134681	Diffuse spasm of esophagus
4311399	Dilatation of intestine
4253013	Disease due to Gram-negative cocci
4147672	Disease due to Papilloma virus
4248392	Disease due to Papillomaviridae
4190076	Disorder of oculomotor system
4266661	Disorder of perianal skin
4271029	Disorder of skin of upper limb
4090616	Disorder of soft tissue of upper limb
4288085	Disorder of umbilicus
4270571	Distribution of body fat loss - finding
441260	Drug withdrawal
433440	Dysthymia
4090401	Ear canal finding
437986	Failure to thrive
4116798	Finding of general observation of appearance
4095940	Finding of pattern of menstrual cycle
4302801	Finding of sacroiliac joint
4091208	Foreskin finding
4278447	General form of body - finding
4292391	Hand and/or foot eczema
4163735	Hemochromatosis
441788	Human papilloma virus infection
76737	Hydrocele
376415	Hypermetropia
40481970	Infection of bone of pelvic region and/or femur
444078	Inflammation of cervix
4082014	Inflammation of ear canal
4208390	Inflammation of sacroiliac joint
196162	Inflammatory disease of the uterus
139099	Ingrowing nail
4092885	Inguinal canal finding
4288544	Inguinal hernia
444191	Injury of face
44783028	Injury of shoulder and upper arm
4154163	Jaw injury
4100932	Knee joint finding
74052	Labyrinthitis
4199395	Lesion of bronchus

4204991	Lichen simplex chronicus
4086984	Loss of body fat - finding
4086687	Lump on extremities
440638	Lyme disease
4178979	Malignant tumor of neck
4079722	Mechanical joint disorder
439045	Mediastinitis
4186461	Medication-induced movement disorder
4087808	Meibomian gland finding
40483111	Mental disorder due to drug
4035007	Metritis
141216	Molluscum contagiosum infection
437233	Multiple myeloma
4130037	Neoplasm of cerebrum
4129880	Neoplasm of sigmoid colon
140357	Neoplasm of uncertain behavior of endocrine gland
4171549	Nodular goiter
42872416	Non-allergic rhinitis
4051476	Non-infective non-allergic rhinitis
136661	Non-toxic nodular goiter
134898	Non-toxic uninodular goiter
4215978	Onychomycosis
4134605	Optic disc disorder
380731	Otitis externa
372328	Otitis media
378160	Otorrhea
4304010	Phobic disorder
134870	Pityriasis versicolor
373478	Presbyopia
442131	Primary malignant neoplasm of head
194997	Prostatitis
200169	Pruritus ani
375504	Psychoactive substance-induced organic mental disorder
4001453	Sacroiliac disorder
4280726	Seasonal allergic rhinitis
141825	Simple goiter
4033781	Site-specific eczema
434630	Sleep-wake schedule disorder
4083779	Specific body function causing pain
200527	Splenomegaly
4268622	Stricture of esophagus

74396	Temporomandibular joint disorder
134461	Tietze's disease
440814	Torticollis
435140	Toxic effect of alcohol
4312497	Toxic effect of heavy metal
437754	Toxic effect of metal
373470	Toxic polyneuropathy
379801	Trigeminal neuralgia
4096860	Umbilicus finding
4030055	Uninodular goiter
4082798	Urinary tract pain
4305500	Vasomotor rhinitis
140641	Verruca vulgaris
133551	Vesicular eczema of hands and/or feet
4207187	Viral lower respiratory infection
261326	Viral pneumonia

Empirical Calibration Plots

OPTUM

Figure 40: Empirical Calibration Plot, Percutaneous Transluminal Angioplasty with Stent vs Cilostazol

(Blue dot = negative control effect estimate; yellow diamond = outcome of interest effect estimate; area under dashed line = traditional *p*-value; area under orange shading = empirically calibrated *p*-values; "First-line" = first line treatment of statins, clopidogrel, or aspirin)

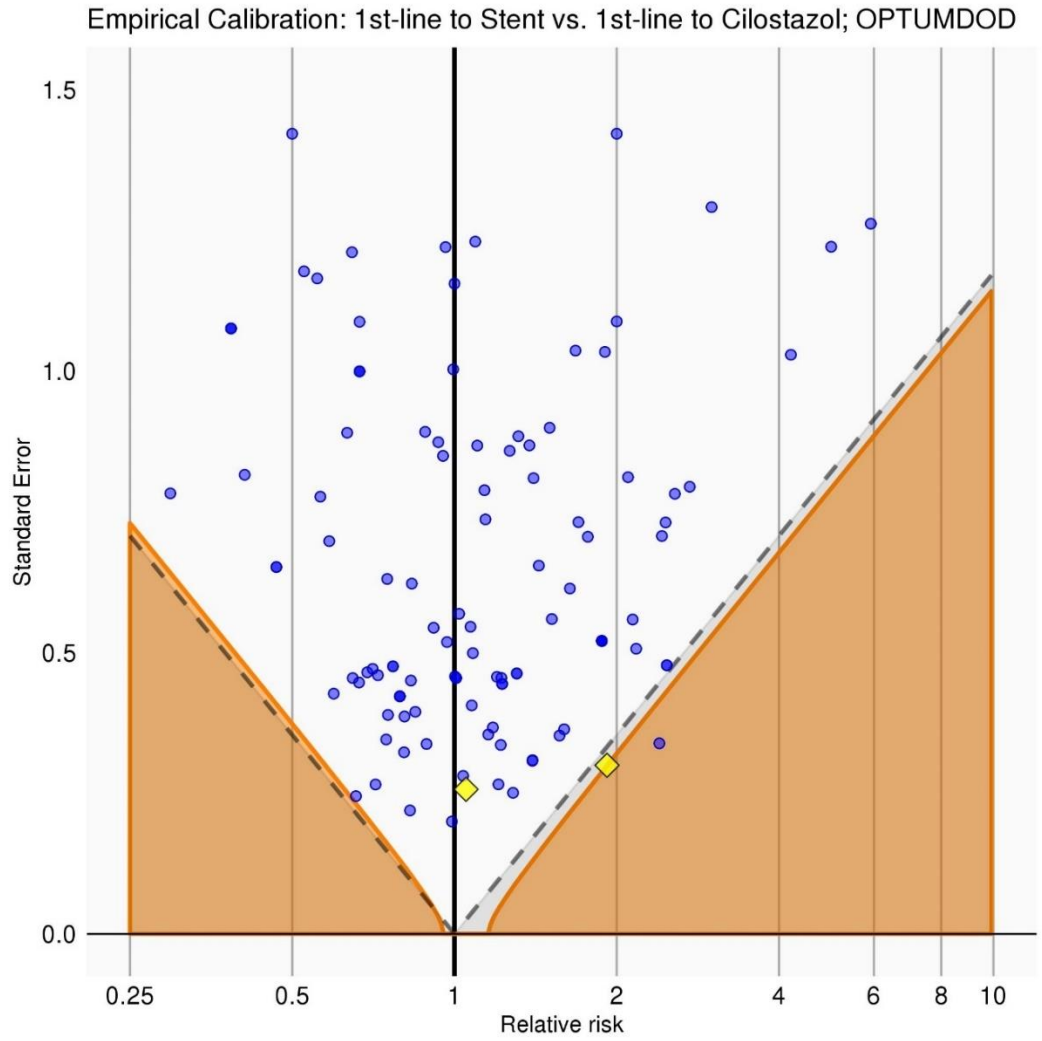


Figure 41: Empirical Calibration Plot, Percutaneous Transluminal Angioplasty with Stent vs Cilostazol

(Blue dot = negative control effect estimate; yellow diamond = outcome of interest effect estimate; area under dashed line = traditional *p*-value; area under orange shading = empirically calibrated *p*-values; "First-line" = first line treatment of statins, clopidogrel, or aspirin)

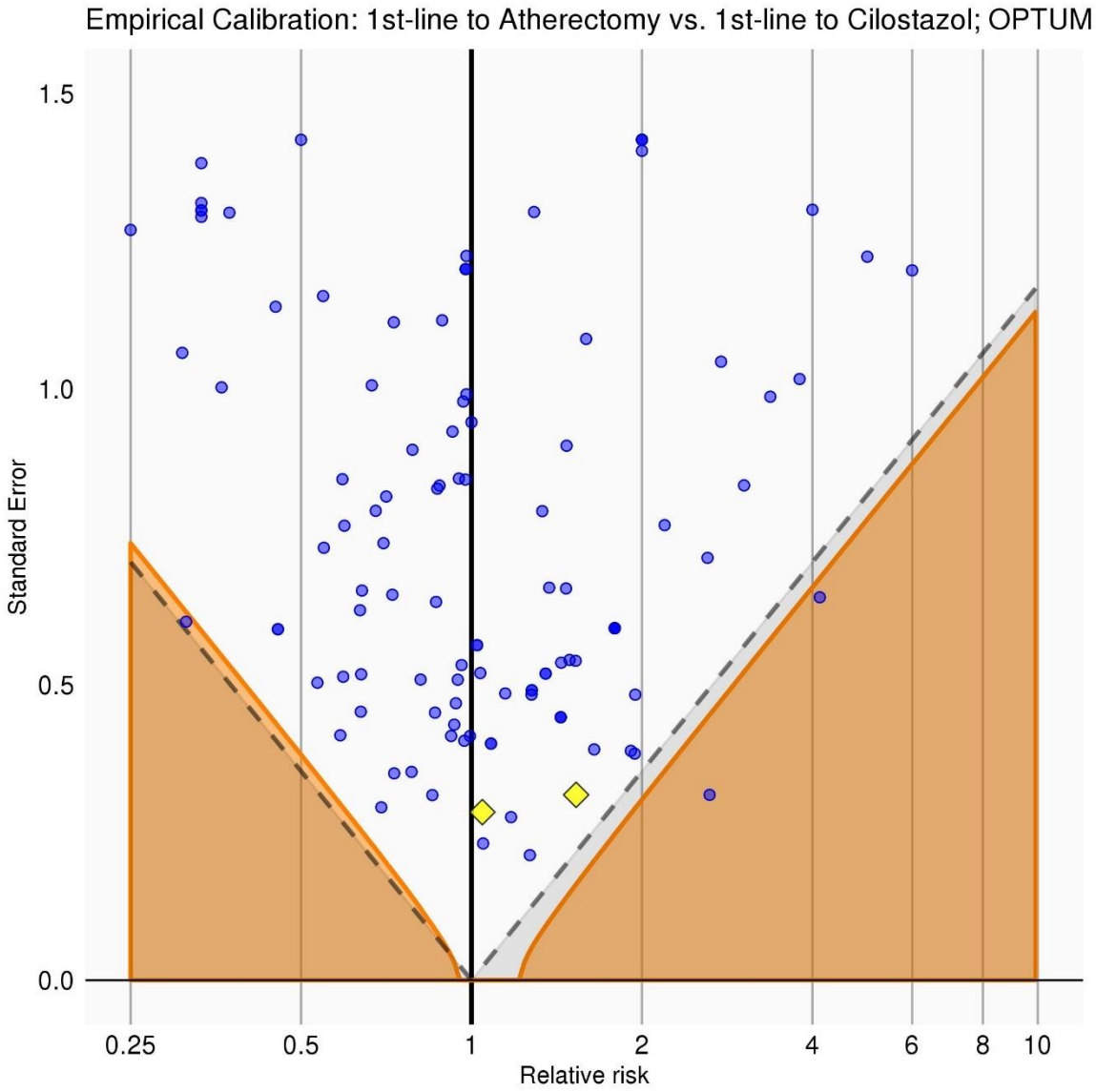


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Figure 42: Empirical Calibration Plot, Percutaneous Transluminal Angioplasty with Stent vs Cilostazol

(Blue dot = negative control effect estimate; yellow diamond = outcome of interest effect estimate; area under dashed line = traditional *p*-value; area under orange shading = empirically calibrated *p*-values; "First-line" = first line treatment of statins, clopidogrel, or aspirin)

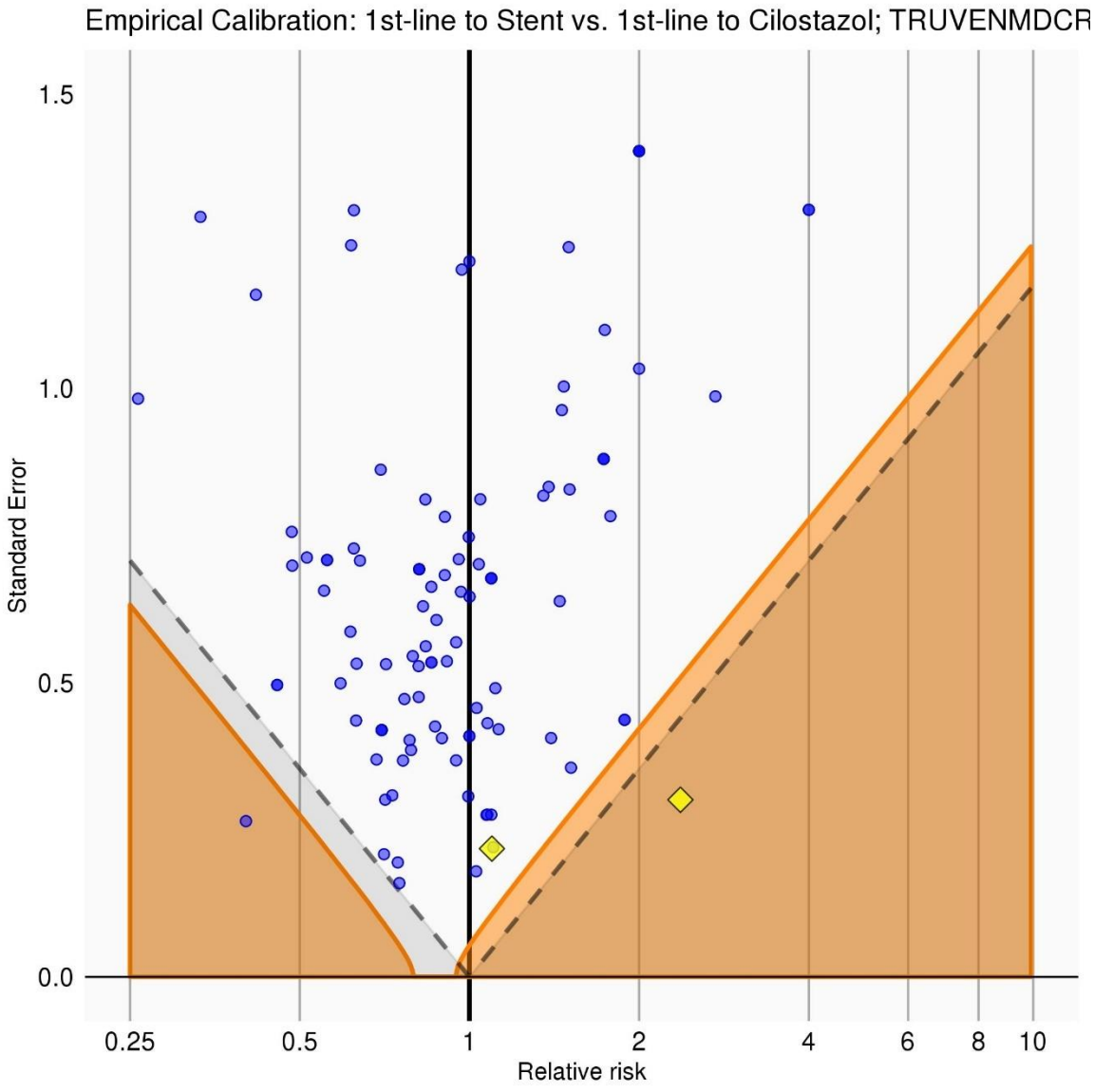
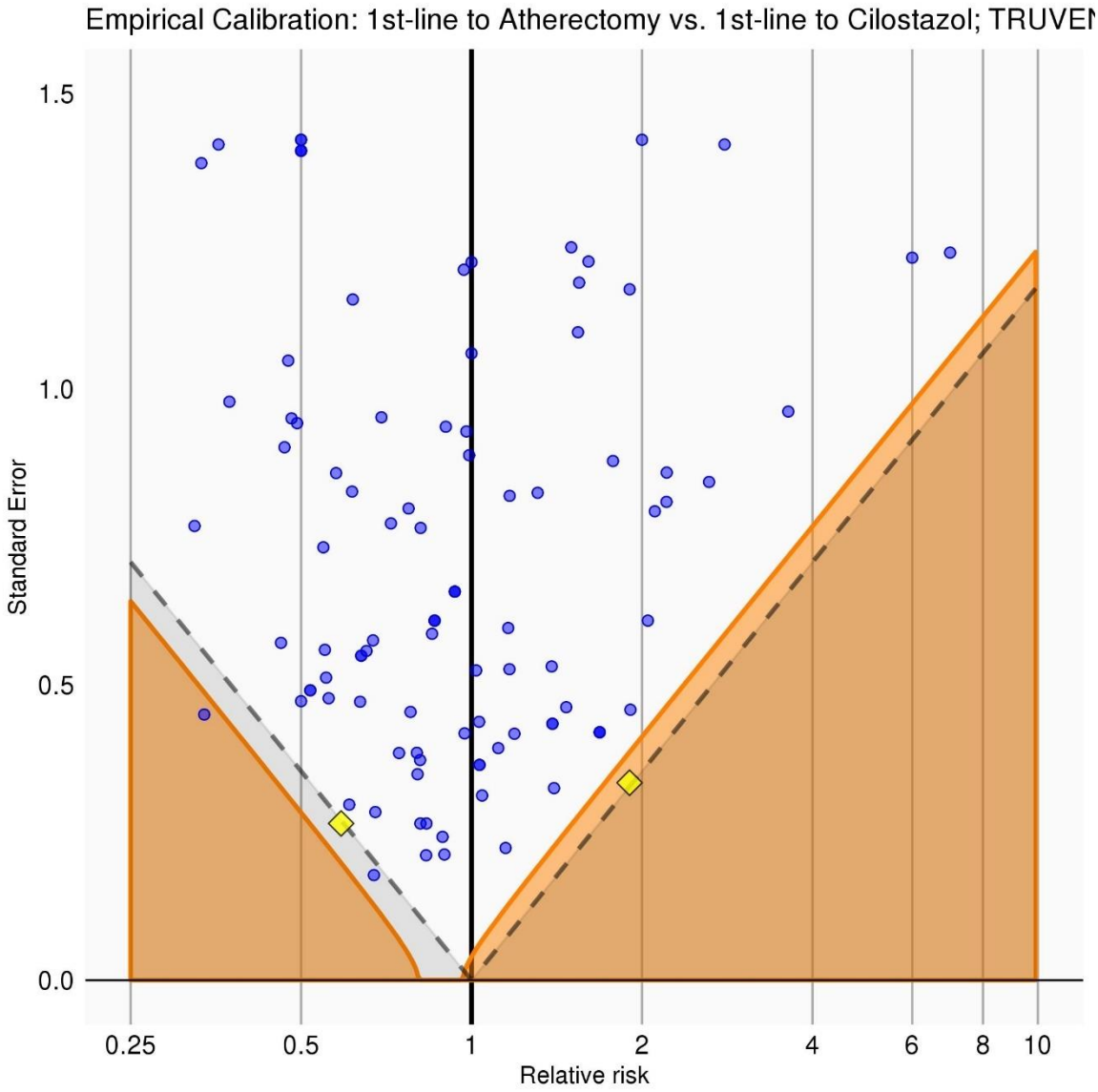


Figure 43: Empirical Calibration Plot, Percutaneous Transluminal Angioplasty with Stent vs Cilostazol

(Blue dot = negative control effect estimate; yellow diamond = outcome of interest effect estimate; area under dashed line = traditional *p*-value; area under orange shading = empirically calibrated *p*-values; "First-line" = first line treatment of statins, clopidogrel, or aspirin)



CCAE

Figure 44: Empirical Calibration Plot, Percutaneous Transluminal Angioplasty with Stent vs Cilostazol

(Blue dot = negative control effect estimate; yellow diamond = outcome of interest effect estimate; area under dashed line = traditional *p*-value; area under orange shading = empirically calibrated *p*-values; "First-line" = first line treatment of statins, clopidogrel, or aspirin)

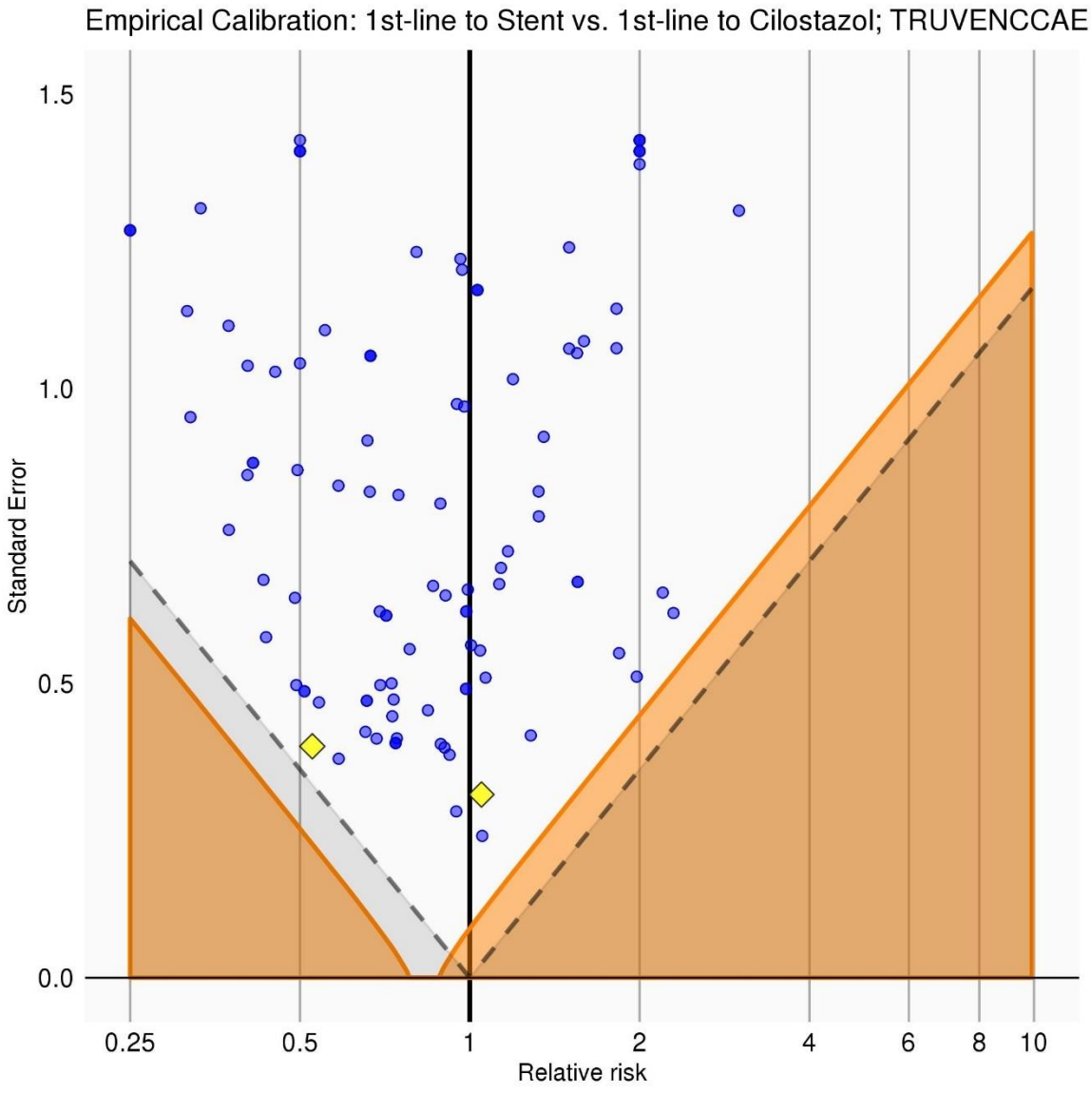
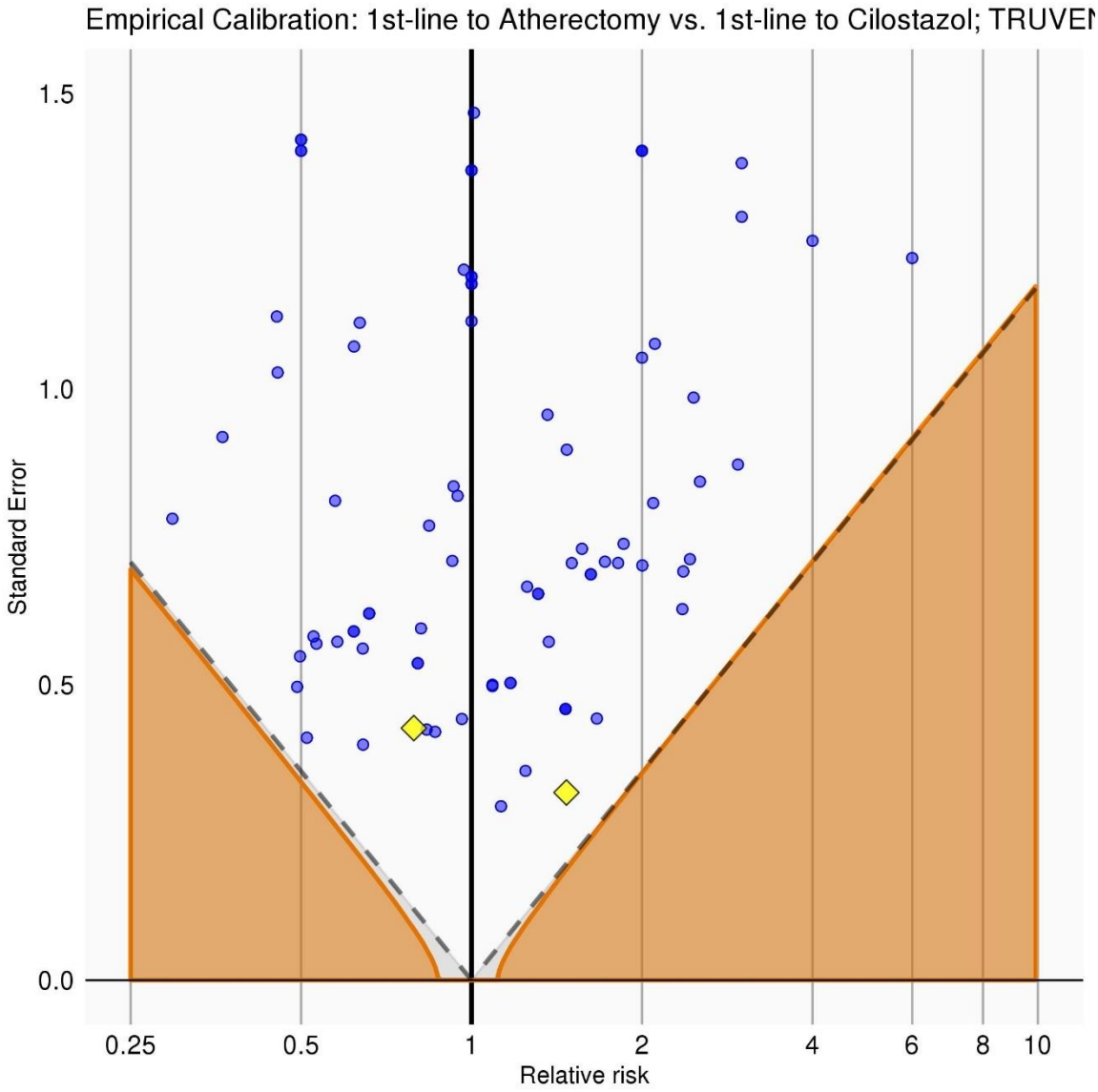


Figure 45: Empirical Calibration Plot, Percutaneous Transluminal Angioplasty with Stent vs Cilostazol.

(Blue dot = negative control effect estimate; yellow diamond = outcome of interest effect estimate; area under dashed line = traditional *p*-value; area under orange shading = empirically calibrated *p*-values; "First-line" = first line treatment of statins, clopidogrel, or aspirin)



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