PROTOCOL 10-389

EXCEL Clinical Trial

Evaluation of XIENCE versus Coronary Artery Bypass Surgery for Effectiveness of Left Main Revascularization

Principal Investigators	Gregg W. Stone, MD Columbia University Medical Center New York, NY, USA Patrick W. Serruys, MD Erasmus Medical Center Rotterdam, The Netherlands Joseph Sabik, MD Cleveland Clinic Main Campus Cleveland, OH, USA A. Pieter Kappetein, MD Erasmus Medical Center Rotterdam, The Netherlands
Planned Number of Sites and Region	Approximately 165 sites in USA, Canada, Europe, South America, South Korea and Australia
Sponsor	Abbott Vascular ("Abbott") 3200 Lakeside Drive Santa Clara, CA 95054, USA
Trial Type	*Randomized Clinical Trial:* Prospective, unblinded, randomized multicenter trial of approximately 1900 subjects with unprotected left main coronary artery (ULMCA) disease and treatment groups of stenting with commercially approved XIENCE Family Stent System (inclusive of XIENCE PRIME®, XIENCE V®, XIENCE Xpedition™ and XIENCE PRO [for use outside the United States only]) versus coronary artery bypass grafting. *Universal Registry:* Approximately 1000 subjects who have angiographically significant left main disease but are not eligible for the randomized trial.
Data Monitoring	Novella Clinical Morrisville, NC 27560, USA

Data Management	Cardialysis 3012 KM, Rotterdam, The Netherlands
Data Analysis	The Cardiovascular Research Foundation New York, NY 10022, USA
Angiographic Core Laboratory	The Cardiovascular Research Foundation New York, NY 10022, USA
Electronic Data Capture	Medidata RAVE New York, NY 10003, USA
Quality of Life and U.S. Health Economics Analysis	Health Economics and Technology Assessment Group Mid America Heart Institute Saint Luke's Health System Kansas City, MO64134, USA
Randomization Service	ICON Clinical Research, L.P. North Wales, PA19454, USA
Clinical Events Committee	The Cardiovascular Research Foundation New York, NY 10022, USA
Data Safety Monitoring Board	Lars Wallentin, MD, Chair University Hospital Uppsala, Sweden
Protocol Contact	Jennifer Jones-McMeans, PhD Associate Director Clinical Research

Version 10.0
08 February 2016

Table of Contents

LIST OF TABLES

LIST OF FIGURES

COMPLIANCE STATEMENT

This trial will be conducted in accordance with this Protocol/Clinical Investigational Plan, the Declaration of Helsinki, applicable good clinical practices and regulations (e.g., US 21 CFR Part 50, 21 CFR Part 56, and 21 CFR Part 812, OUS ISO14155) and the appropriate local legislation(s). The most stringent requirements, guidelines or regulations must always be followed. The conduct of the trial will be approved by the appropriate Institutional Review Board (IRB)/ Medical Ethics Committee (MEC) of the respective investigational site and by the applicable regulatory authorities (e.g., FDA, PMDA, MHRA, etc.

PROTOCOL SUMMARY

Trial Name and Number	**EXCEL Clinical Trial: 10-389** Evaluation of XIENCE versus Coronary Artery Bypass Surgery for Effectiveness of Left Main Revascularization
Objectives	To establish the safety and efficacy of the commercially approved XIENCE Family Stent System (inclusive of XIENCE PRIME, XIENCE V, XIENCE Xpedition and XIENCE PRO [for use outside the United States [OUS] only]) in subjects with unprotected left main coronary artery disease (either isolated to the left main trunk or associated with disease in other coronary arteries) by demonstrating that compared to coronary artery bypass graft surgery, treatment of the left main stenosis ± other significant coronary lesions with the XIENCE stent will result in non-inferior or superior rates of the composite measure of all-cause mortality, myocardial infarction or stroke at an anticipated median follow-up duration of three years.
Study Device	**Commercial XIENCE Family Stent Systems, including:** • **Commercial XIENCE PRIME EECSS:** Stent diameter: 2.25*, 2.5, 2.75, 3.0, 3.5 and 4.0 mm Stent lengths: 8, 12, 15, 18, 23, 28, 33 and 38 mm • **Commercial XIENCE V EECSS :** Stent diameter: 2.25, 2.5, 2.75, 3.0, 3.5, 4.0 mm Stent lengths: 8, 12, 15, 18, 23, and 28 mm • **Commercial XIENCE Xpedition Stent System:** Stent diameter: 2.25*, 2.5, 2.75, 3.0, 3.25, 3.5, 4.0 mm Stent lengths: 8, 12, 15, 18, 23, 28, 33 and 38 mm • **Commercial XIENCE PRO EECSS (for OUS use only):** Stent diameter: 2.25*, 2.5, 2.75, 3.0, 3.5, 4.0 mm Stent lengths: 8, 12, 15, 18, 23, 28, 33 and 38 mm * 2.25 mm diameter stents do not include stent lengths of 33 and 38 mm

Study Design	**Randomized Clinical Trial (RCT)** Prospective, unblinded, randomized multicenter trial of about 1900 subjects at approximately 165 U.S. and international centers. Following diagnostic angiography demonstrating significant left main disease and consensus of the local Heart Team that the subject meets the study entry criteria, subjects will be consented and randomized 1:1 to: a) PCI using XIENCE (N~950),or b) CABG (N~950) Follow-up for all randomized subjects will continue for five years with an option for additional follow-up to 10 years **Universal Registry** An additional group of approximately 1000 subjects who are not eligible for randomization or for other reasons are not randomized will be consented for the Universal Registry. All patients with left main disease without prior CABG in whom the visual estimated diameter stenosis is greater than or equal to 50% will be eligible for entry into EXCEL registry. These subjects will be consented for the Universal Registry, and followed through the time of initial treatment per standard of care with either PCI, CABG or medical therapy. Approximately 100 consecutive subjects from the Universal Registry with a ≥50% and <70% visually estimated angiographic diameter stenosis who otherwise meet all eligibility criteria, but without significant ischemia by noninvasive testing consistent with significant left main disease, and in whom IVUS shows a MLA >6.0 mm^2 and/or a FFR >0.80, will be analyzed separately as intermediate lesion subjects, and followed through the time of initial treatment per standard of care with either PCI, CABG or medical therapy.

Primary and Key Secondary Endpoints	**RCT** • **<u>Primary Endpoint</u>:** Composite measure of all-cause death, myocardial infarction (MI) or stroke (modified Rankin Scale (mRS) ≥1 and increase by ≥1 from baseline) at 3 years post randomization. The primary endpoint will be estimated via Kaplan-Meier failure rate. The primary endpoint analysis will be conducted at the time when approximately 50% of the patients have reached the 3-year follow-up AND all patients have reached the 2-year follow-up, whichever time point is latest. All available data through 3-year follow-up will be used. • **<u>Major Powered Secondary Endpoints:</u>** • Composite measure of all-cause mortality, MI or stroke (mRS≥1 and increase by ≥1 from baseline) at 30 days • Composite measure of all-cause mortality, myocardial infarction, stroke (mRS≥1 and increase by ≥1 from baseline) or unplanned revascularization for ischemia at 3 years post randomization. This powered endpoint will be estimated via Kaplan-Meier failure rate. The analysis will be conducted at the time when approximately 50% of the patients have reached the 3-year follow-up AND all patients have reached the 2-year follow-up, whichever time point is latest. All available data through 3-year follow-up will be used.
Quality of Life (QoL) and Health Economics	Health-related quality of life (HRQoL) and treatment costs will be assessed in 1800 randomized patients alongside the core clinical trial to evaluate the impact of the PCI and CABG strategies on a range of relevant quality of life (QoL) domains and also to evaluate the cost-effectiveness of the two treatment strategies. HRQoL and functional status will be assessed using a combination of generic and disease-specific measures selected to cover a broad range of health domains that may be affected by coronary artery disease, its treatment, and its complications. Disease-specific QoL will be assessed using the Seattle Angina Questionnaire (SAQ) and the London School of Hygiene Dyspnea Questionnaire. Mental health and depression will be assessed using the Patient Health Questionnaire-9 (PHQ-9). Generic health status will be assessed using the Medical Outcomes Study 12-item Short Form (SF-12), and health utilities will be assessed using the EuroQoL (EQ-5D) with U.S.-specific weights. These measures will be assessed using standardized, written questionnaires at baseline (prior to randomization), 1 month, 12 months, 3 years, and 5 years. Data on cardiovascular-specific resource utilization will be collected prospectively for the index hospitalization and the full follow-up period for all subjects using standardized case report forms. Procedural costs will be assessed

	using a resource-based approach to convert standard measures such as procedural duration and utilization of items into costs. Other hospital costs will be assessed using an "event-driven" approach in which specific complications and outcomes are assigned standard costs based on external data. The cost and quality of life data will be integrated in order to perform a formal cost-effectiveness analysis. The primary analysis will be performed from the perspective of the U.S. healthcare system using a lifetime time horizon. Secondary analyses will be performed from the perspective of other health care systems with the collaboration of a local health economist.
Targeted Number of Subjects to Receive Study Device	A total of about 2900 subjects, as outlined below, will be targeted at up to approximately 165 U.S. and international sites. **RCT:** Approximately 1900 subjects will be randomized. **Universal Registry:** Approximately 1000 consecutive subjects will be registered, which includes approximately 100 consecutive subjects with intermediate lesions.
Subject Follow-Up	**RCT:** Clinical follow-up at in-hospital, 30 days, 6 months, 1 year, 2 years, 3 years, 4 years, and 5 years, with an option for additional follow-up to 10 years. **Universal Registry:** Follow up through the time of initial treatment as per standard of care with PCI, CABG or medical therapy.
Treatment Strategy	• All subjects participating in this clinical trial will have informed consent obtained after diagnostic angiography and prior to randomization. "Ad hoc" unprotected left main PCI is not permitted. • It is strongly recommended that the timing from randomization to treatment (PCI or CABG) be ≤1 week. It is mandatory that revascularization be performed ≤2 weeks after randomization in all cases in both treatment arms. Reasons for delay beyond 2 weeks will be tracked. • Target lesion(s) will be treated in accordance with the randomization schedule after satisfying the general and angiographic inclusion and exclusion criteria as defined in the protocol. If more than one target lesion will be treated, all lesions must receive the treatment that has been assigned as per the randomization.

Inclusion Criteria for RCT	**Inclusion criteria** (following criteria must be present): • Unprotected left main coronary artery (ULMCA) disease with angiographic diameter stenosis (DS) ≥70% (visually estimated) requiring revascularization as assessed by both a participating interventional cardiologist and cardiac surgeon (local Heart Team), ***OR*** • ULMCA disease with angiographic DS ≥50% but <70% (visually estimated) requiring revascularization as assessed by both a participating interventional cardiologist and cardiac surgeon (local Heart Team), with one or more of the following present: ◦ Non-invasive evidence of ischemia referable to a hemodynamically significant left main lesion (large area of ischemia in both the LAD and LCX territories, or in either the LAD or LCX territory in the absence of other obstructive coronary artery disease to explain the LAD or LCX defect), or stress-induced hypotension, or stress-induced fall in LVEF, or stress-induced transient ischemic dilatation of the left ventricle, or stress-induced thallium/technetium lung uptake, and/or ◦ IVUS MLA ≤6.0 mm^2, and/or ◦ FFR ≤0.80 **OR** • Left Main Equivalent Disease: Left main Medina classification 0,1,1 bifurcation disease (diameter stenosis of both the true ostial LAD and LCX [within 5 mm of the left main distal bifurcation]) ≥50%, in the absence of significant angiographic stenosis in the left main coronary artery, may also be randomized if one of the two following conditions are present: ◦ Both the ostial LAD and ostial LCX stenoses are ≥70% stenotic by visual estimation, *or* ◦ If one or both of the ostial LAD and ostial LCX stenoses are ≥50% and <70% stenotic by visual estimation, then this lesion(s) is demonstrated to be significant either by ▪ a) non-invasive evidence of ischemia in its myocardial distribution; and/or ▪ b) FFR ≤0.80; and/or ▪ c) IVUS MLA ≤4.0 mm^2 (FFR is preferred). Note: if both the ostial LAD and ostial LCX stenoses are ≥50% and <70% stenotic by visual estimation, then both lesions must be significant by these criteria for the patient to be eligible for randomization.

Inclusion Criteria for RCT (continued)	• Clinical and anatomic eligibility for both PCI and CABG as agreed to by the local Heart Team ◦ Interventionalist determines PCI appropriateness and eligibility ◦ Surgeon determines surgical appropriateness and eligibility • Silent ischemia, stable angina, unstable angina or recent MI ◦ If recent MI, CK-MB must have returned to normal prior to randomization • Ability to sign informed consent and comply with all study procedures including follow-up for at least three years • The subject must be ≥18 years of age
Exclusion Criteria for RCT	**Clinical exclusion criteria** (the subject is not eligible for randomization if any of the following are present): • Prior PCI of the left main trunk at any time prior to randomization • Prior PCI of any other (non-left main) coronary artery lesions within one year prior to randomization • Prior CABG at any time prior to randomization • Need for any concomitant cardiac surgery other than CABG (e.g. valve surgery, aortic repair, etc.), or intent that if the subject randomizes to surgery, any cardiac surgical procedure other than isolated CABG will be performed • CK-MB greater than the local laboratory upper limit of normal, or recent MI with CK-MB levels still elevated Note: A subject with a recent MI in whom the troponin levels are still elevated but falling and in whom the CK-MB has returned to within normal range may be randomized, with the CK-MB levels used to assess peri-procedural MI. • Subjects unable to tolerate, obtain or comply with dual antiplatelet therapy for at least one year • Subjects requiring or who may require additional surgery (cardiac or non-cardiac) within one year • The presence of any clinical condition(s) which leads the participating interventional cardiologist to believe that clinical equipoise is not present (i.e. the subject should not be treated by PCI, but rather should be managed with CABG or medical therapy [reasons will be documented in the Heart Team worksheet] • The presence of any clinical condition(s), which leads the participating cardiac surgeon to believe that clinical equipoise is not present (i.e. the subject should not be treated by CABG, but rather should be managed with PCI or medical therapy (reasons will be documented in the Heart Team worksheet)

Exclusion Criteria for RCT	**Clinical exclusion criteria** (the subject is not eligible for randomization if any of the following are present): • Prior PCI of the left main trunk at any time prior to randomization • Prior PCI of any other (non-left main) coronary artery lesions within one year prior to randomization • Prior CABG at any time prior to randomization • Need for any concomitant cardiac surgery other than CABG (e.g. valve surgery, aortic repair, etc.), or intent that if the subject randomizes to surgery, any cardiac surgical procedure other than isolated CABG will be performed • CK-MB greater than the local laboratory upper limit of normal, or recent MI with CK-MB levels still elevated Note: A subject with a recent MI in whom the troponin levels are still elevated but falling and in whom the CK-MB has returned to within normal range may be randomized, with the CK-MB levels used to assess peri-procedural MI. • Subjects unable to tolerate, obtain or comply with dual antiplatelet therapy for at least one year • Subjects requiring or who may require additional surgery (cardiac or non-cardiac) within one year • The presence of any clinical condition(s) which leads the participating interventional cardiologist to believe that clinical equipoise is not present (i.e. the subject should not be treated by PCI, but rather should be managed with CABG or medical therapy [reasons will be documented in the Heart Team worksheet]) • The presence of any clinical condition(s) which leads the participating cardiac surgeon to believe that clinical equipoise is not present (i.e. the subject should not be treated by CABG, but rather should be managed with PCI or medical therapy (reasons will be documented in the Heart Team worksheet)

Exclusion Criteria for RCT (continued)	• Pregnancy or intention to become pregnant (female subjects of child bearing potential must have a negative pregnancy test within 7 days of the index procedure) • Non cardiac co-morbidities with life expectancy less than 3 years • Other investigational drug or device studies that have not reached their primary endpoint **Angiographic exclusion criteria** (the subject is not eligible for randomization if any of the following are present): • Left main diameter stenosis <50% (visually assessed by the consensus of the local Heart Team), unless left main equivalent disease is present • SYNTAX score ≥33, as determined by the consensus of the local Heart Team • Visually estimated left main reference vessel diameter <2.25 mm or >4.25 mm (post dilatation up to 4.5 mm is allowed) • The presence of specific coronary lesion characteristics or other cardiac condition(s) which leads the participating interventional cardiologist to believe that clinical equipoise is not present (i.e. the subject should not be treated by PCI, but rather should be managed with CABG or medical therapy reasons will be documented) • The presence of specific coronary lesion characteristics or other cardiac condition(s) which leads the participating cardiac surgeon to believe that clinical equipoise is not present (i.e. the subject should not be treated by CABG, but rather should be managed with PCI or medical therapy - reasons will be documented)
Primary Analytical Population	For the RCT, the primary analysis of the composite endpoint of all-cause mortality, MI and stroke will be performed on the intent-to-treat (ITT) population.

Statistical Method	For the RCT, the primary endpoint is a composite of all-cause mortality, MI or stroke (mRS≥1 and increase by ≥1 from baseline) at 3 years post randomization. The primary endpoint will be estimated via Kaplan-Meier failure rate and Greenwood's formula for estimating the standard error. The primary endpoint analysis will be conducted at the time when approximately 50% of the patients have reached the 3-year follow-up AND all patients have reached the 2-year follow-up, whichever time point is latest. All available data through 3-year follow-up will be used. The study is powered for sequential non-inferiority and superiority testing. If the non-inferiority of PCI to CABG test is met for the primary endpoint, then superiority testing will be performed. The primary endpoint will be evaluated using the difference in Kaplan-Meier failure rates in the intent-to-treat population using all available data. The hypothesis test is designed to show non-inferiority of PCI to CABG for the primary endpoint with a one-sided alpha of 0.025. Assuming the following: • primary endpoint event rate is 11% in each treatment arm at 3 years (using 3-year event rates from the SYNTAX trial, the most contemporary reference dataset) • minimum time to follow-up is years • median time to follow-up is approximately 3 years • 8% lost to follow-up at 3 years • non-inferiority margin $\Delta = 4.2\%$ • one-sided alpha = 0.025 • accrual time of 29 months then a sample size population of 1900 subjects (~950 per arm) will provide 80% power to demonstrate non-inferiority. If non-inferiority is met, superiority testing will be performed with a one-sided alpha of 0.025. The trial will have 80% power to demonstrate superiority with a difference of 3.84% of PCI arm to CABG arm (e.g. 7.16% in PCI arm vs. 11% in CABG arm).

1. INTRODUCTION

The primary objective of this study is to evaluate the safety and efficacy of the commercially approved XIENCE Family Stent System (inclusive of XIENCE PRIME, XIENCE V, XIENCE Xpedition and XIENCE PRO [for OUS use only]) in selected subjects with unprotected left main coronary artery disease (either isolated to the left main trunk or associated with disease in the other coronary arteries) by testing the principal hypothesis that compared to coronary artery bypass graft surgery, treatment of the left main stenosis and other significant coronary lesions with the XIENCE stent will result in non-inferior or superior rates of the composite measure of all-cause mortality, myocardial infarction or stroke at an anticipated median follow-up duration of three years.

All subjects will be screened per the protocol inclusion and exclusion criteria and randomized subjects will have clinical follow-up at 30 and 180 days, and 1, 2, 3, 4, and 5 years with potential follow-up continuing annually to 10 years.

2. BACKGROUND

2.1. Evolution in Surgical Revascularization

Coronary artery bypass grafting (CABG) was introduced in 1967 and rapidly became the accepted standard treatment for subjects with obstructive coronary artery disease who were deemed necessary for coronary revascularization.[1]

The Coronary Artery Surgery Study (CASS) trial in the 1970's[2] showed that obstructive left main disease was best treated with CABG compared to medical treatment. Mortality was reduced by CABG in these subjects and thus has been the standard of care for over 30 years.

Recent advances in coronary surgery include improvements in pre-operative risk assessment and management, anesthesia, the use of arterial grafts, and improvement in post-operative care.[3,4,5,6]

These have resulted in further improvements with reduced hospital morbidity and mortality. Furthermore, with the use of arterial grafts the occlusion rate of bypass graft has been reduced and improved quality of life.

With the introduction of drug-eluting stents (DES), long-term outcomes after percutaneous coronary intervention (PCI) have markedly improved in patients with complex coronary anatomy, justifying randomized trials of PCI vs. CABG. This resulted in the recent 1800 randomized patient Synergy between PCI with TAXUS and Cardiac Surgery (SYNTAX) trial, which showed that PCI with paclitaxel-eluting stents (PES) in a cohort of subjects with three vessel disease and left main disease with few other exclusion criteria was inferior to CABG for the composite primary endpoint of death, MI, stroke or unplanned revascularization at 1 year. However, post-hoc and subgroup analysis from the 705 left main stem subjects according to the anatomic SYNTAX score demonstrated that those subjects with low and intermediate SYNTAX scores had comparable or improved results with PCI compared to CABG.[7] However, as an underpowered subgroup analysis, this observation is considered hypothesis generating.

Most large-scale comparative trials of surgery vs. PCI have found higher rates of stroke in those undergoing CABG.[8, 9, 10] In the SYNTAX trial, the incidence of stroke at one year was significantly higher in the CABG cohort than with PCI (2.2% vs. 0.6%, respectively, P=0.003).[11]This has been perceived by many surgeons as possibly not representative of current surgical results. The surgical community believes that the stroke incidence may be further reduced by selective screening of the cerebral circulation, a shorter waiting time from randomization to CABG, more careful management of the ascending aorta, and improved adjunctive pharmacotherapy.

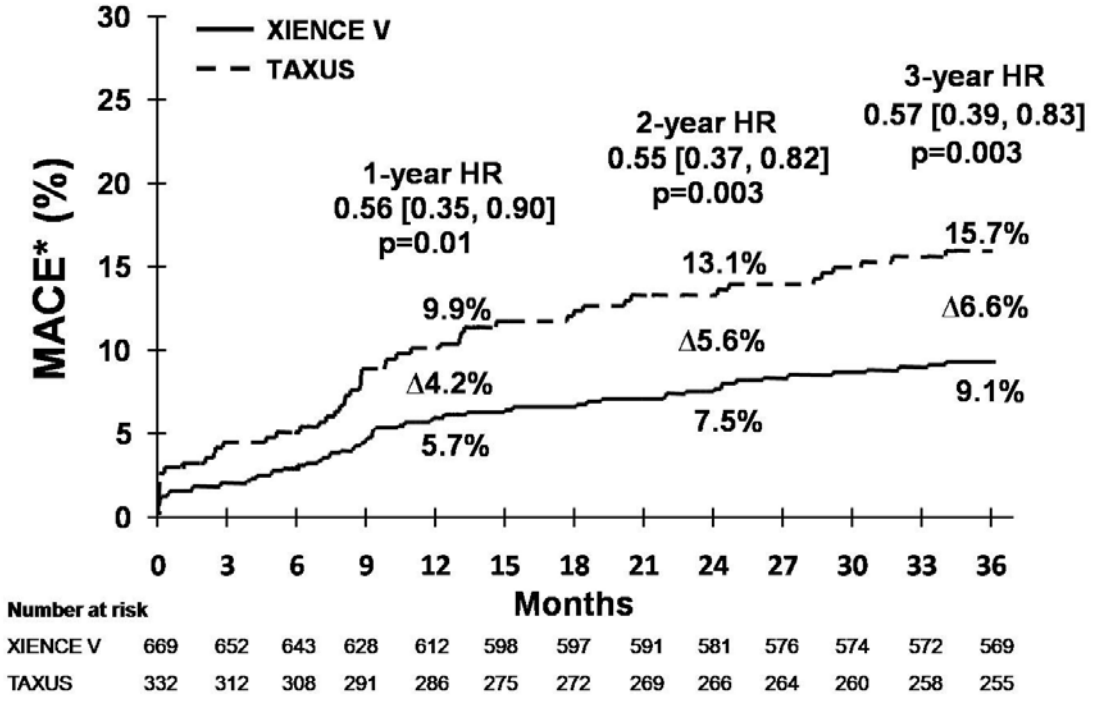
2.2. Percutaneous Coronary Intervention

PCI was introduced into clinical practice in 1977, almost 10 years later than CABG, and was initially considered appropriate only for subjects with single-vessel disease.[12] However, as experience and technology have advanced, the indication has been expanded to treat subjects with multivessel and more complex disease.

In the last decade, several randomized controlled trials (ARTS I, MASS II, ERACI-II) examined the relative benefits of PCI and CABG in subjects with single or multivessel coronary artery disease.[13, 14] The validity of these conclusions has been questioned because of (1) subsequent improvements in both percutaneous and surgical techniques as well as (2) strict inclusion criteria limiting relevance to subjects treated in the 'real world'.

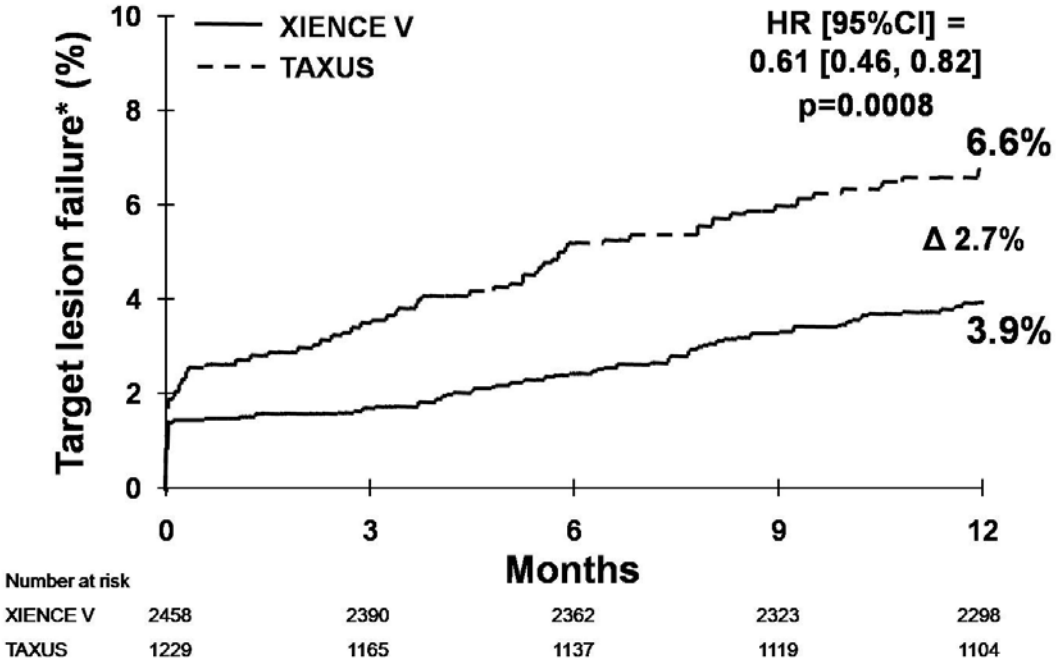
Re-evaluation may be especially important in the case of PCI as stenting is applied to increasingly complex subjects. Moreover, the durability of the benefit of stenting to 5 years has been challenged.[15] The most appropriate treatment for left main disease subjects remains a matter of considerable debate, especially since the introduction of drug-eluting stents (with sirolimus or paclitaxel).[16, 17, 18, 19, 20] More recently, the second generation everolimus-eluting stent, XIENCE V, has shown superiority in angiographic outcomes compared to the first generation PES in the SPIRIT III trial. The clinical outcomes for the XIENCE V stent compared to the first generation PES were superior at both three years in the SPIRIT III trial and at one year in the SPIRIT IV trial as shown in Figure 2.1 and Figure 2.2, respectively. The COMPARE randomized trial also showed marked improvements in both safety and efficacy with the everolimus-eluting stent compared to the paclitaxel DES in an 1800 patient randomized trial which randomized patients with unprotected left main stem disease.[21] Thus, clinical outcomes may be further improved with left main and multivessel stenting with the XIENCE V stent compared to drug-eluting stents used in earlier randomized trials.

Figure 2.1 SPIRIT III Trial: Major Adverse Cardiac Events at 3 Years (n=1,002)



* MACE = cardiac death, MI, or ischemia-driven TLR

Figure 2.2 SPIRIT IV Trial: Target Lesion Failure at 1 Year (n=3,690)

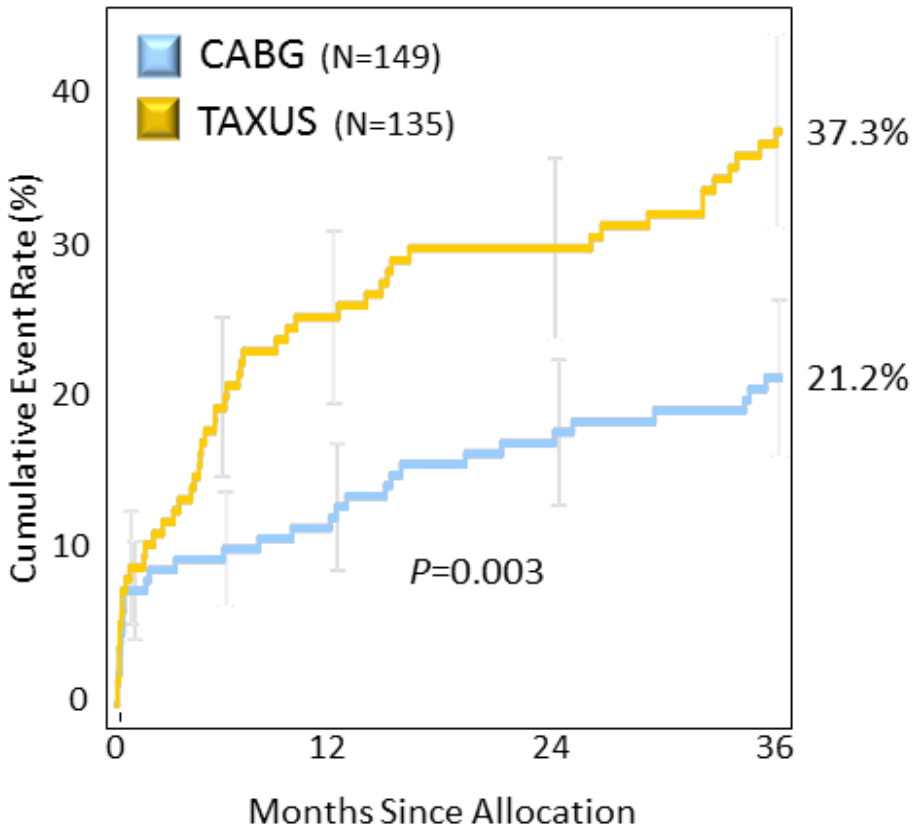


* Target lesion failure = cardiac death, target vessel MI, or ischemia-driven TLR

2.3. The SYNTAX Trial – Influence of Anatomic Complexity

The potential influence of anatomic complexity in the SYNTAX trial was evaluated by examining the outcomes of TAXUS DES vs. CABG in different subgroups from this trial according to the SYNTAX score.[7] Subjects within the highest SYNTAX tertile (score of 33 or greater) had superior overall clinical outcomes (including lower mortality) when treated with CABG. (Figure 2.3 and Table 2-1). Conversely, the approximately two-thirds of the left main subjects with a SYNTAX score of 32 or below had comparable or superior clinical overall outcomes (including lower mortality) achieved with PCI at 3years follow-up which may justify the use of PCI with DES in these subjects (Figure 2.4 and Table 2-2). However, these subgroup analyses were post hoc and underpowered, and as such must be considered hypothesis- generating. It is also possible that, based on the recent data on XIENCE V from the SPIRIT Trials, the new second-generation DES would have competed more favorably with CABG.

Figure 2.3 SYNTAX Trial: Major Adverse Cardiac and Cerebrovascular Events at 3 Years in the Left Main Subgroup with the Highest SYNTAX Score Tertile (SYNTAX Scores ≥33)

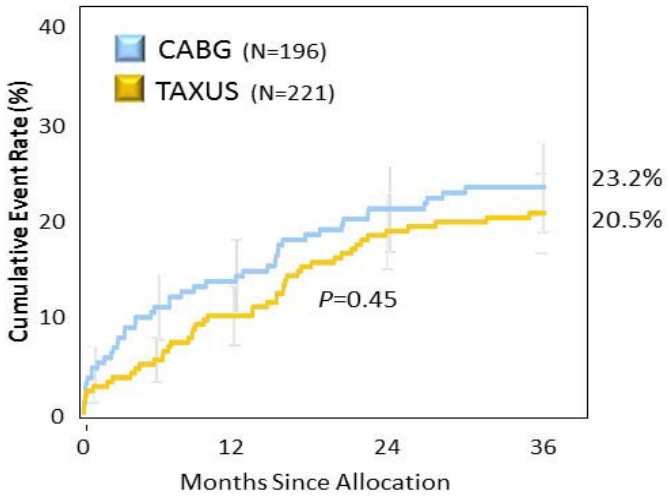


Cumulative KM Event Rate = 1.5 SE; log-rank *P* value; site-reported data; ITT population

Table 2-1 SYNTAX Trial: Components of Major Adverse Cardiac and Cerebro vascular Events at 3 Years in the Left Main Subgroup with the Highest SYNTAX Score Tertile (SYNTAX Scores ≥33)

Outcome	CABG (N=149)	TAXUS (N=135)	*P*-value
Death	7.6%	13.4%	0.10
CVA	4.9%	1.6%	0.13
MI	6.1%	10.9%	0.18
Death, CVA, or MI	15.7%	20.1%	0.34
Revascularization	9.2%	27.7%	<0.001

Figure 2.4 SYNTAX Trial: Major Adverse Cardiac and Cerebrovascular Events at 3 Years for the Left Main Subgroup in Subjects with the Lowest and Intermediate SYNTAX Score Tertiles (SYNTAX Scores 0-32)



Cumulative KM Event Rate = 1.5 SE; log-rank *P* value; site-reported data; ITT population

Table 2-2 SYNTAX Trial: Components of Major Adverse Cardiac and Cerebro vascular Events at 3 Years for the Left Main Subgroup in Subjects with the Lowest and Intermediate SYNTAX Score Tertiles (SYNTAX Scores 0-32)

Outcome	CABG (N=196)	TAXUS (N=221)	*P*-value
Death	9.0%	3.7%	0.02
CVA	3.3%	0.9%	0.09
MI	2.6%	4.6%	0.33
Death, CVA, or MI	13.2%	8.7%	0.12
Revascularization	13.7%	15.7%	0.61

2.4. Other Studies Comparing PCI and CABG for Unprotected Left Main Coronary Artery (ULMCA) Disease

Other studies specifically examining PCI for ULMCA disease include:

- The LEMANS randomized trial, while only studying 105 patients, demonstrated a benefit of PCI compared to CABG in the primary endpoint of LVEF after left main revascularization: a significant increase in LVEF at 12-month follow-up was noted only in the PCI group (mean 3.3% vs. 0.5% with CABG, P=0.047).[22] Moreover, the LeMANS trial reinforced the well-known benefits of PCI compared to CABG in reducing peri-procedural and short-term morbidity. In this trial, major adverse events within 30 days (including death, myocardial infarction, stroke, major bleeding, major arrhythmia, unstable angina, acute heart failure, unplanned surgery or revascularization, renal failure, infection, post-cardiotomy syndrome, and sternal refixation) occurred in 8% of PCI patients versus 28% of CABG patients (P=0.006). Subjects undergoing PCI compared to CABG also had significantly shorter hospitalization (mean 6.8 days vs. 12.0 days; P=0.0007).
- The LEMANS Registry and the large scale LEFT MAIN-COMPARE registry demonstrated that stenting of ULMCA is feasible and offers good long-term outcome. Implantation of DES for ULMCA decreased the risk of long-term Major Adverse Cardiac and Cerebrovascular Events (MACCE), and particularly improved survival in subjects with distal ULMCA disease.[23,24]
- The ISAR-LEFT MAIN randomized trial demonstrated that implantation of either paclitaxel eluting stent (PES) or sirolimus eluting stent (SES) in ULMCA lesions is safe and effective; both of these drug-eluting stents provide comparable clinical and angiographic outcomes.[25]
- Recent meta-analysis[26] of multiple trials among selected subjects with first generation DES showed that death, myocardial infarction, or stroke (major adverse cardiovascular or cerebrovascular events) were similar in the PCI and CABG subjects at 1 year (odds ratio [OR]: 0.84 [95% confidence interval: 0.57 to 1.22]). Target vessel revascularization was significantly higher in the PCI group at 1 year (OR: 4.36 [95% CI: 2.60 to 7.32]), 2 years (OR: 4.20 [95% CI: 2.21 to 7.97]), and 3 years (OR: 3.30 [95% CI: 0.96 to 11.33]). There was no difference in mortality in PCI versus CABG subjects at 1 year (OR: 1.00 [95% CI: 0.70 to 1.41]), 2 years (OR: 1.27 [95% CI: 0.83 to 1.94]), and 3 years (OR: 1.11

[95% CI: 0.66 to 1.86]). The meta-analysis concluded that most studies demonstrate no significant difference in mortality or the composite of mortality, MI, or stroke, for up to 3 years, between PCI and CABG for the treatment of ULMCA stenosis in selected subjects. However, PCI subjects have a significantly higher risk of target vessel revascularization. In selected subjects with ULMCA stenosis (especially in those without complex concomitant coronary artery disease, as seen in the SYNTAX trial), PCI is emerging as an acceptable option. Reflecting these findings, PCI for stenting of non-complex ULMCA disease has recently been given a class IIb recommendation in the guidelines of the American College of Cardiology and American Heart Association.[27]

2.5. Quality of Life and U.S. Health Economics Sub-Studies

Until very recently, most physicians viewed the field of medical economics as an academic exercise that was irrelevant to daily practice (see also Section 17, Appendix B). Typically, new therapeutic strategies and medical technologies were adopted by practitioners prior to any definitive evaluation of their effectiveness. Such is no longer the case. As health expenditures have continued to grow, it is no longer sufficient for a therapeutic strategy to simply demonstrate improved efficacy in order to be accepted into the mainstream of medical practice. Today, physicians, payers, and policy-makers have become increasingly interested in understanding the value of therapies by evaluating their cost-effectiveness. Such economic evaluations assume particular importance when the disease under consideration is either highly prevalent or very costly.

Since the earliest days of health economic studies, there has been interest in understanding the relative costs and benefits of percutaneous coronary intervention (PCI) and bypass surgery (CABG). These studies have been motivated by both the frequency and costs of these procedures, which currently account for more than $20 billion in annual health care expenditures in the U.S. alone.[28] In the early 1980's, Weinstein and Stason[29] first used data from the VA Cooperative Study and the European Coronary Surgery Study to develop projections of life-expectancy and symptomatic status for subjects with coronary disease treated with CABG or medical therapy. They estimated that for subjects with multivessel CAD, the cost-effectiveness ratio for CABG (compared with medical therapy) ranged from $15,000 - $70,000 per quality-adjusted year of life (QALY) gained (costs adjusted to 1997 dollars). Lower ratios were associated with treatment of subjects with more extensive disease and more severe anginal symptoms. More recently, Wong and colleagues[30] used a Markov simulation model to predict long-term medical care costs and quality-adjusted life expectancy for subjects with chronic stable angina treated with either medication or coronary revascularization. In contrast to Weinstein, they also considered balloon angioplasty (PTCA) as a potential form of revascularization. Since their model was developed in the late 1980s, they did not incorporate the results of any of the more recent randomized trials of PTCA vs. either medical therapy[31,32,33] or CABG.[19,34,35] Nonetheless, based on observational data regarding the symptomatic and survival benefits of PTCA, they estimated that for subjects with one- or two-vessel disease and moderate to severe angina, PTCA was economically attractive with a cost-effectiveness ratio of $10,000 - $40,000 per quality-adjusted year of life gained (costs in 1997 dollars). For subjects with mild or no symptoms, however, PTCA did not appear particularly attractive, with a cost-effectiveness ratio of $140,000-$200,000/QALY.

Currently, the best long-term data regarding the cost-effectiveness of PCI vs. CABG are from the Bypass Angioplasty Revascularization Investigation (BARI). Within BARI, Hlatky and colleagues performed a prospective cost-effectiveness substudy among 934 of the 1829 trial participants.[36] Based on 12-year follow-up data, they estimated that the mean cumulative cost of CABG was $123,000 vs. $121,000 for PCI. [37] Despite these higher costs, however, after accounting for the greater overall life expectancy with CABG (8.48 vs. 8.42 years) the incremental cost-effectiveness ratio for CABG vs. PCI was highly favorable at $14,300 per year of life gained. Given the substantial differences in subject populations (BARI specifically excluded subjects with left main disease) and revascularization techniques (BARI pre-dated the use of either stents or drug-eluting stents as well as contemporary use of high dose statins and dual antiplatelet therapy), however, these results provide only limited insight into the cost-effectiveness of PCI with DES vs. CABG for subjects with left main disease.

To date, the only available data regarding the cost-effectiveness of PCI for left main disease are derived from the 1-year follow-up of the SYNTAX trial (Cohen DJ, ACC Scientific Sessions 2009). For the overall population of subjects with either 3-vessel or left main disease, initial revascularization costs were ~$6000/subject greater with CABG than with PCI. Over the subsequent 12 months, repeat revascularization was significantly more common with initial PCI such that follow-up costs were ~$2500/subject greater with PCI. Thus, at 12 months, total medical care costs remained greater with CABG, by approximately $3500/subject. Because there were no differences in overall survival yet short-term quality of life was better with PCI, quality adjusted life expectancy was also slightly greater with PCI at this early timepoint. Consequently, PCI with DES was an economically dominant strategy at this relatively early timepoint. Results were even more favorable for the subgroup of subjects (n=701) with left main disease. Among this subset, 1-year costs were $6300/subject higher with CABG and quality-adjusted life expectancy also favored PCI (by 0.03 QALYs) rendering PCI a highly dominant strategy at this relatively early timepoint. Although these results suggest that PCI could be a highly attractive strategy from both a clinical and economic perspective for subjects undergoing revascularization for left main CAD, longer term follow-up and additional confirmatory data will be required to determine the durability and reproducibility of these findings.

2.6. Justification for a Contemporary Large-Scale Trial Comparing PCI and CABG for LMCA Disease

The SYNTAX trial is the largest contemporary trial of DES vs. CABG in patients with complex coronary artery disease, and with a primary endpoint of death, MI, stroke or repeat revascularization at one year, confirmed the superiority of CABG compared to PES. As a result the SYNTAX investigators concluded that "CABG remains the standard of care for patients with three-vessel or left main coronary artery disease, since the use of CABG, as compared with PCI, resulted in lower rates of the combined end point of major adverse cardiac or cerebrovascular events at one year."[7] However, SYNTAX was not powered to examine the outcomes of patients only with left main coronary artery disease (with or without other diseased coronary vessels).

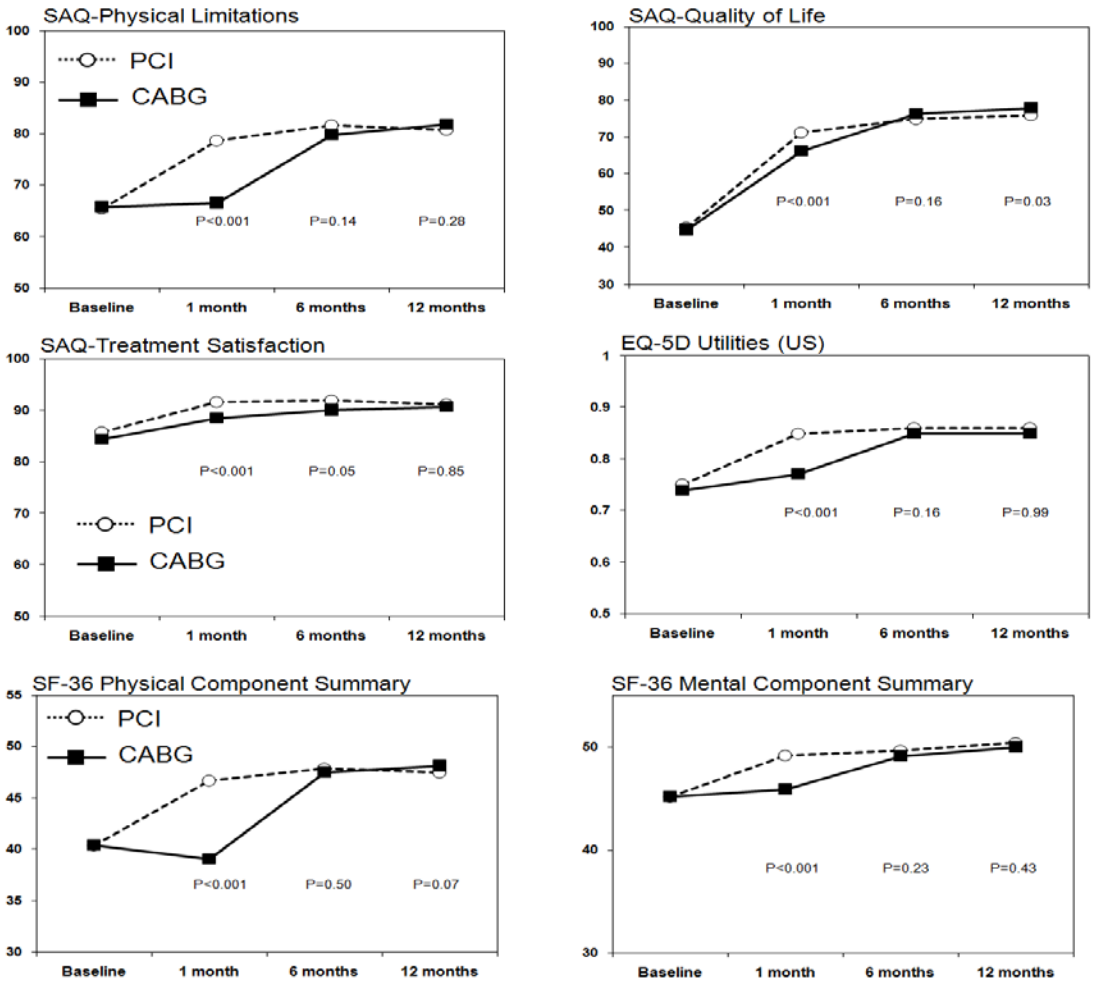
Indeed, the results of SYNTAX, as well as the numerous other trials discussed above suggest equipoise between PCI with first generation DES and CABG for the composite of mortality,

myocardial infarction or stroke, albeit with higher rates of repeat revascularization for PCI.

Although the importance of mortality, MI and stroke as essential endpoints is universally accepted, no single trial has been adequately powered to examine whether CABG has superior, comparable, or non-inferior rates of the composite endpoint of mortality, MI, or stroke compared expressed that the inclusion of unplanned revascularization into the primary SYNTAX endpoint (which was necessitated for sample size requirements) biased the trial against PCI, as many other endpoints of equal or more important impact to patient well-being might have been selected instead. As discussed above, most trials (including SYNTAX) have shown that stroke rates are higher after CABG than PCI, an endpoint significantly more important to physicians and subjects than repeat revascularization. Peri-procedural bleeding is significantly more common after CABG compared to PCI, and is a powerful independent predictor of early and late mortality in this setting.[38, 39, 40]Subjects undergoing CABG compared to PCI have prolonged hospital stays (for example, mean 3.4 days after PCI vs. 9.5 days after CABG, P<0.001),[7] greater and prolonged incisional chest pain, and delayed return to work and activities of daily life. The impact of all of these adverse events, including the benefits from the greater prevention of recurrent ischemia and repeat revascularization with CABG compared to PCI, may be captured in quality of life measures. As reported from the One-Year Quality of Life SYNTAX Substudy,[41]

PCI as compared to CABG had superior measures of quality of life in most measures at one month, though these outcomes had equalized by 6 and 12 months (Figure 2.5).

Figure 2.5 SYNTAX Trial: Quality of Life Measures Comparing PCI and CABG



Moreover, as described above, the SYNTAX trial had few exclusion criteria, and post hoc analyses using the SYNTAX score have demonstrated a clear advantage of CABG for those subjects with the highest risk SYNTAX tertile (score ≥33). In contrast, for subjects randomized to PES vs. CABG with a SYNTAX score of ≤32 (approximately two thirds of the left main cohort), mortality was lower with PCI at 3 years, and a trend was present for reduced composite death, MI or stroke with PCI, with nonsignificantly different rates of unplanned revascularization between PCI and CABG. However, as a post hoc, subgroup analysis, these findings must be considered hypothesis-generating, warranting testing in an appropriately powered randomized trial. Furthermore, the primary endpoint of SYNTAX was measured at one year, a period which may be too early to capture the intermediate term outcomes between PCI and CABG.

In addition, as described below, the XIENCE V stent has been shown to be superior to the PES, with lower rates of stent thrombosis, MI and target lesion revascularization demonstrated in four randomized trials (SPIRIT II, SPIRIT III, SPIRIT IV and COMPARE). Use of XIENCE V may therefore further improve outcomes in the PCI arm. Since the SYNTAX trial was conducted, improvements in PCI technique and adjunct pharmacotherapy have occurred (e.g. strategies to manage the bifurcation, use of intravascular ultrasound and fractional flow reserve, bivalirudin and optimal thienopyridine use), as well as improvements in CABG (optimal use of arterial conduits, screening for and management of peri-procedural stroke risk, e.g., with epi-aortic ultrasound, and optimal use of pre-, intra-, and post-procedural pharmacotherapy).

Thus, an appropriate trial to evaluate PCI vs. CABG in subjects with disease of the left main stem is justified, and would:

- be restricted to those patients in whom clinical equipoise is present between PCI and CABG (SYNTAX score ≤32);
- utilize optimal interventional and surgical techniques (allowing for acceptable variation between centers);
- be adequately powered for a primary endpoint of mortality, MI or stroke, and at a later endpoint than one year (e.g. at 3 years); and
- evaluate other important secondary endpoints including not only revascularization, but also in-hospital, short-term and as well as late outcomes, and quality of life and cost-effectiveness at different intervals so a complete assessment of the risks vs. the benefits of PCI compared to CABG may be appreciated.

2.7. Device Overview

2.7.1. XIENCE V EECSS Clinical Experience

After a small first-in-man trial, SPIRIT FIRST, in which the XIENCE V stent was shown to reduce angiographic late loss in comparison with the bare-metal MULTI-LINK VISION stent,[42] the safety and efficacy of the XIENCE V stent was further studied in larger randomized trials of subjects with noncomplex lesions in which XIENCE V stent was compared to the widely used

TAXUS stent (Boston Scientific). In both the 300-subject randomized SPIRIT II trial and the 1002-subject randomized SPIRIT III trial, XIENCE V stent proved superior to TAXUS stent in

terms of the primary end point of in-stent late loss at 6 months (SPIRIT II)[43] and in-segment late loss at 8 months (SPIRIT III).[44] In the SPIRIT III trial, XIENCE V stent was also found to be non-inferior to TAXUS stent for the co-primary end point of ischemia-driven target vessel failure (cardiac death, myocardial infarction [MI] or ischemia-driven target vessel revascularization [TVR]) at 9 months.[45] In a pooled analysis from the 1302 subjects in the SPIRIT II and SPIRIT III trials, XIENCE V stent resulted in reduced rates of major adverse cardiac events (MACE; cardiac death, MI or ischemia-driven target lesion revascularization [TLR]: 5.2% vs. 10.0%, P=0.02) at 1 year, driven by a significantly reduced rate of TLR (3.1% vs. 5.8%, P=0.02)and a trend toward less cardiac death or MI (2.7% vs. 4.5%, P=0.10), with nonsignificantly different rates of stent thrombosis (0.7% vs. 0.8%, P=0.90).[46] These findings have been robust to three years. In SPIRIT III, treatment with XIENCE V stent compared with TAXUS stent resulted in a 28.5% reduction in target vessel failure (14.3% vs. 20.0%) and a 40.9% reduction in MACE (9.7% vs. 16.4%) at 3 years.[47] However, neither SPIRIT II nor SPIRIT III were powered for statistical superiority testing in clinical end points, nor were they adequately sized to elicit potential differences in low frequency safety events between the two stent platforms. Of note, routine angiographic follow-up was prespecified in all subjects at 6 months in SPIRIT II and in 564 subjects at 8 months in SPIRIT III, a protocol-specific process which may artificially enhance the absolute difference in TLR between the two stents by provoking angiographically induced revascularization procedures, the so-called "oculostenotic reflex".[48, 49] Although this process may not affect the relative difference in clinical efficacy between two stents,[47, 50] routine angiographic follow-up should ideally not be performed prior to the primary clinical end point if an accurate and realistic assessment of treatment related differences is to be obtained.[51]

Thus, the SPIRIT IV trial was performed with clinical endpoints only and represents an adequately-powered, single- blind, multicenter prospective trial comparing the XIENCE V stent to the TAXUS EXPRESS stent in 3690 subjects (2:1 ratio of XIENCE V to TAXUS EXPRESS). The primary endpoint was target lesion failure (TLF) defined as the composite of cardiac death, target vessel MI and ischemia-driven target lesion revascularization (TLR), and was superior for XIENCE V stent compared to TAXUS EXPRESS stent (TLF 3.9% vs. 6.6%, respectively, P=0.0008).[50] In addition, both TLR (2.5% vs. 4.6%, P=0.001), MI (1.9%. vs. 3.0%, P=0.02), and ARC definite or probable stent thrombosis (ST) (0.29% vs. 1.06%, P=0.003) favored the XIENCE V stent group. These results were duplicated in the investigator-sponsored COMPARE trial (also performed without routine angiographic follow-up), in which 1800 subjects were randomized to the XIENCE V stent vs. the TAXUS Liberté stent.[21] Compared to TAXUS at one year, XIENCE V stent resulted in statistically lower rates of the primary composite endpoint of death, MI or TVR (6.2% vs. 9.1%, P=0.02), as well as MI (2.8% vs. 5.4%, P=0.007), ARC definite or probable ST (0.7% vs. 2.6%, P=0.002), TLR (1.7% vs. 4.8%, P=0.0002).

2.7.2. XIENCE V Stent in Unprotected Left Main Coronary Artery (ULMCA) Disease Background

The French multicenter prospective observational LeMAX study assessed 1-year outcomes in 174 subjects treated with the XIENCE V stent who had ULMCA disease and were treated with protocol mandated provisional T-stenting. The subjects represented a high-risk cohort with a mean EuroSCORE of 4.67, mean SYNTAX score of 25.1, and the presence of multi-vessel disease in 46% of subjects. 76.2% of subjects had a SYNTAX score 0-32 and left ventricular

function was well preserved. Importantly, despite 81% of lesions involving the distal left main stenosis (74% bifurcation, 7% trifurcation), a mean of only 1.2 stents were implanted, and final kissing balloon inflation was used in 95% of lesions. The rate of MACCE, death, MI, stroke and target lesion revascularization was 14.7%, 4.1%, 2.5%, 1.6% and 2.5% respectively. The rate of MACCE-free survival at 1-year stratified according to SYNTAX score tertiles <22, 23-32 and ≥33 was 90%, 88.4% and 72.4%. MACCE is defined as the composite of all-cause death, MI, TLR and cerebrovascular events.[52]

2.7.3. XIENCE V Stenting in Multiple and Complex Lesions

There is evidence that event rates with the XIENCE V stent are lower than with TAXUS stent in subjects with multiple vessels treated. Data from the SPIRIT III trial suggest numerically lower rates for XIENCE V stent in dual vessel treatment compared to TAXUS stent[53]. In the SPIRIT IV trial, subgroup analysis demonstrated that the relative benefits of XIENCE V stent compared to TAXUS stent in reducing Target Lesion Failure rates (TLF: cardiac death, target vessel myocardial infarction, or target lesion revascularization) were consistent in most subgroups examined, although the absolute differences were greater in complex subjects, such as those with long lesions, small reference vessel diameter, and multiple lesions[54].

In a recent pooled analysis of the SPIRIT II (n=300), SPIRIT III (n=1002) and SPIRIT IV (n=3687) trials in which XIENCE V stent was compared to TAXUS stent (randomized 3:1 or 2:1) in 4689 subjects, clinical outcomes atone year were analyzed in subjects with either a single vessel treated (n=4152), or two or more treated vessels (n=1648)[55].

- **Single treated vessel:** Adverse outcomes trended lower in XIENCE V stent vs. TAXUS stent subjects with a single treated vessel for major adverse cardiac events (MACE: cardiac death, MI or TLR) (4.1% vs. 6.5%) and TLF (4.0% vs. 6.3%). Stent thrombosis rates were comparable between the XIENCE V single vessel treated subgroup and the TAXUS subgroup for both protocol and ARC-defined
- **Multiple treated vessels:** The observed TLF and MACE rates trended toward lower rates in the XIENCE V subgroup compared to the TAXUS subgroup. The one year observed rates for TLF were 6.1% for the XIENCE V subgroup and 13.0% for the TAXUS subgroup. The observed rates at one year for MACE were 6.3% for the XIENCE V subgroup and 13.4% for the TAXUS subgroup. The observed difference in overall stent thrombosis rates at one year was 1.3% (protocol defined) and 1.5% (ARC defined) between the XIENCE V subgroup and the TAXUS subgroup, in favor of the XIENCE V subgroup.
- In summary, for the one-year results of the SPIRIT II, III, and IV pooled analysis, the XIENCE V arm consistently showed numerically lower event rates for composite clinical endpoints than the TAXUS arm.

Finally, in the SPIRIT V single-arm study of 2700 real-world subjects receiving an XIENCE V stent, the composite rate of cardiac death, target vessel MI and TLR (i.e. TLF) was predictably higher in subjects with multiple vessels treated, compared to single vessel treatment, driven by a numerically higher TLR rate with multiple vessels treated; yet, the absolute TLF rate of 7.79% was low in this complex subject population, confirming the efficacy and safety of the XIENCE V stent in these subjects[56].

2.7.4. XIENCE V Stenting in Medically Treated Diabetics

In both the SPIRIT III[44] and SPIRIT IV[50] trials, a significant interaction was observed between stent type and diabetes mellitus. In this regard, with a pre-specified stratified randomization of 1,185 diabetic subjects in SPIRIT IV (a larger cohort than the entire SPIRIT III trial), SPIRIT IV represents the largest comparative experience to date evaluating the outcomes of different DES in subjects with diabetes mellitus. The relative reduction in TLF with XIENCE V stent compared to TAXUS stent in subjects with diabetes mellitus was 6% (0.5% absolute reduction), compared to 53% (3.6% absolute reduction) in subjects without diabetes mellitus. While the point estimate for the primary endpoint favored XIENCE V stent compared to TAXUS stent in both diabetic and non-diabetic subjects, the differences in relative effect size suggests that the mechanisms of restenosis and/or response to antiproliferative agents may vary in subjects with insulin resistance or deficiency[57]. Longer-term follow-up is required to determine whether differences between XIENCE V stent and TAXUS stent in subjects with diabetes mellitus emerge over time.

In the COMPARE trial, in a stratified analysis of the primary endpoint (all death, non-fatal MI and TVR) that was not pre-specified in the protocol, there was no difference between the everolimus-eluting and the PES among subjects with diabetes mellitus (RR 1.00 [95% CI, 0.53-1.89], P=0.99) but confidence intervals were wide, and the results of a test of interaction were not significant.[58] Thus, as in the SPIRIT IV trial, in the COMPARE trial as well, the XIENCE V stent and TAXUS stent appear to have similar clinical outcomes in the population of subjects with diabetes mellitus. In the SPIRIT V single-arm study of 2700 real-world subjects receiving a XIENCE V stent, composite rates of all death, MI and TVR were predictably higher in subjects with diabetes mellitus as compared to subjects without diabetes mellitus at one year, but composite rates of cardiac death, target vessel MI and TLR (i.e., TLF) were no different (5.73% vs. 4.80, P=0.3285).[56] Overall, SPIRIT V confirms low event rates with everolimus-eluting coronary stent in real world subjects with diabetes mellitus.

2.7.5. XIENCE V Everolimus Eluting Coronary Stent System (EECSS)

2.7.5.1. Indication

The XIENCE V EECSS is indicated for improving coronary luminal diameter in subjects with symptomatic heart disease due to *de novo* native coronary artery lesions (length ≤ 28 mm) with reference vessel diameters of 2.25 mm to 4.25 mm.

2.7.5.2. Description of XIENCE V Stent System

The XIENCE V EECSS is comprised of the XIENCE V EECS, a delivery system, and a drug eluting coating. The coating is composed of two polymers and the anti-proliferative drug everolimus. Both polymers have been previously CE Marked and FDA/MHLW approved for blood contacting applications. Zortress®, the oral formulation of everolimus developed by Novartis Pharmaceuticals Corporation, has been evaluated in clinical trials and is approved in the United States for the prevention of organ rejection in adult kidney transplant recipients at the dose of 1.5 mg/day.

Outside the U.S., Zortress is sold under the brand name, Certican®, in more than 70 countries. Everolimus is also approved in the United States under the name of Afinitor® for patients with advanced renal cell carcinoma (cancer) at doses of 5 to 20 mg/day when taken by mouth.

Table 2-3 XIENCE V EECS Product Sizes

Diameter→ Length ↓	**2.25 mm**	**2.5 mm**	**2.75 mm**	**3.0 mm**	**3.5 mm**	**4.0 mm**
8 mm	X	X	X	X	X	X
12 mm	X	X	X	X	X	X
15 mm	X	X	X	X	X	X
18 mm	X	X	X	X	X	X
23 mm	X	X	X	X	X	X
28 mm	X	X	X	X	X	X

The everolimus-eluting coronary stent (EECS, manufactured and distributed by Abbott Vascular, Santa Clara, CA, as XIENCE V) is a medical grade L-605 cobalt chromium (CoCr) alloy MULTI-LINK VISION or MULTI-LINK MINI VISION balloon-expandable stent with 0.0032-in strut thickness which is coated with a conformal coating of a non-erodible polymer loaded with 100 μg/cm^2 of everolimus [40-O-(2-hydroxyethyl)-rapamycin], a semisynthetic macrolide immunosuppressant, inhibits growth factor-stimulated cell proliferation by causing cell-cycle arrest in the late G1 stage, thereby suppressing neointimal formation.[59,60]Comparative analysis in an *in vivo* rabbit aortoiliac model has shown more rapid endothelialization with the EECS compared to sirolimus eluting stents, paclitaxel eluting stents, and zotarolimus eluting stents.[61] Clinical trials are required, however, to determine whether this finding translates into improved human safety or efficacy.

2.7.6. XIENCE PRIME Everolimus Eluting Coronary Stent System (EECSS)

While the data in Section 2.7.1 to 2.7.4, were obtained using the XIENCE V stent, the next iteration of this stent XIENCE PRIME, is now commercially available in the U.S., EU and some Asia-Pacific countries and includes stent lengths of 33 and 38 mm. A U.S. single arm trial,

SPIRIT PRIME, of 500 subjects is currently ongoing under an investigational device exemption (IDE) from the FDA (IDE # G090068).

2.7.6.1. Indication

The XIENCE PRIME stent system is indicated for improving coronary luminal diameter in subjects with symptomatic heart disease due to *de novo* native coronary artery lesions (length ≤ 32 mm) with reference vessel diameters of ≥2.25 mm to ≤4.25 mm.

2.7.6.2. Description of XIENCE PRIME Stent System

The XIENCE PRIME stent system is composed of a drug coated stent and balloon expandable delivery system. The drug coating is composed of two polymers and the anti-proliferative drug everolimus, which are identical to XIENCE V stent. The delivery system used in this trial utilizes the same principle of operation as other Abbott Vascular Rapid Exchange (RX) coronary stent systems and coronary dilation catheters.

Table 2-4 XIENCE PRIME EECS Product Sizes

Diameter → Length ↓	**2.25 mm**	**2.5 mm**	**2.75 mm**	**3.0 mm**	**3.5 mm**	**4.0 mm**
8 mm	X	X	X	X	X	X
12 mm	X	X	X	X	X	X
15 mm	X	X	X	X	X	X
18 mm	X	X	X	X	X	X
23 mm	X	X	X	X	X	X
28 mm	X	X	X	X	X	X
33 mm	n/a	X	X	X	X	X
38 mm	n/a	X	X	X	X	X

The everolimus-eluting coronary stent (EECS, manufactured and distributed by Abbott Vascular, Santa Clara, CA, as XIENCE PRIME) is a balloon expandable stent manufactured from a flexible cobalt chromium alloy with a multicellular design and 0.0032-in strut thickness which is coated with a thin non-adhesive, durable, biocompatible acrylic polymer and fluorinated copolymer releasing everolimus.

2.7.7. XIENCE XPEDITION STENT SYSTEM

The XIENCE Xpedition Stent System is a new iteration of XIENCE PRIME with a new stent delivery system. XIENCE Xpedition is now commercially available in the U.S., EU and some Asia-Pacific countries. The stent and stent contacting balloon materials, and the drug coating formulation and drug dose density (100 ug/cm²) are identical to the XIENCE PRIME EECSS. XIENCE Xpedition also includes stent lengths of 33 and 38 mm and stent diameter of 3.25 mm.

2.7.7.1. Indication

The XIENCE Xpedition stent system is indicated for improving coronary artery luminal diameter in patients with symptomatic heart disease due to *de novo* native coronary artery lesions (length ≤32 mm) with reference vessel diameters of ≥2.25 mm to ≤4.25 mm.

2.7.7.2. Description of XIENCE Xpedition Stent System

The XIENCE Xpedition stent systems are device/drug combination products consisting of a drug-coated stent and a balloon expandable delivery system. The stent is coated with a formulation

containing everolimus, the active ingredient, embedded in a non-erodible polymer, which is identical to the FDA approved XIENCE V and XIENCE PRIME EECSS. The XIENCE Xpedition Stent System is available in two delivery system configurations: Rapid Exchange (RX) and Over-the-Wire (OTW).

Table 2-5 XIENCE Xpedition Product Sizes

Diameter → Length ↓	**2.25 mm**	**2.5 mm**	**2.75 mm**	**3.0 mm**	**3.25 mm**	**3.5 mm**	**4.0 mm**
8 mm	X	X	X	X	X	X	X
12 mm	X	X	X	X	X	X	X
15 mm	X	X	X	X	X	X	X
18 mm	X	X	X	X	X	X	X
23 mm	X	X	X	X	X	X	X
28 mm	X	X	X	X	X	X	X
33 mm	n/a	X	X	X	X	X	X
38 mm	n/a	X	X	X	X	X	X

2.7.8. XIENCE PRO Everolimus Eluting Coronary Stent System (EECSS)

The XIENCE PRO EECSS is a rebranding (re-labeling) of the commercially approved XIENCE V EECSS and the XIENCE PRIME LL EECSS. XIENCE PRO is only approved for use outside the U.S. It is not commercially available in the U.S.

2.7.8.1. Indication

The XIENCE PRO EECSS (with stent length up to 28 mm) is indicated for improving coronary luminal diameter in patients with symptomatic ischemic heart disease due to discrete *de novo* native coronary artery lesions (length ≤28 mm) with a reference vessel diameter of 2.25 mm 4.0 mm.

The XIENCE PRO LL EECSS (with 33 mm and 38 mm stent length) is indicated for improving coronary luminal diameter in patients with symptomatic ischemic heart disease due to discrete *de novo* native coronary artery lesions. The treated lesion length should be less than the nominal stent length (33 mm or 38 mm) with a reference vessel diameter of ≥2.50 mm and ≤4.25 mm.

2.7.8.2. Description of XIENCE PRO EECSS

The XIENCE PRO is comprised of a balloon-expandable everolimus eluting stent pre-mounted on a dedicated delivery system. The XIENCE PRO utilities the identical stent, delivery system, drug coating as the commercially approved XIENCE V EECSS and XIENCE PRIME LL EECSS.

Table 2-6 XIENCE PRO EECS Product Sizes

Diameter → Length ↓	**2.25 mm**	**2.5 mm**	**2.75 mm**	**3.0 mm**	**3.5 mm**	**4.0 mm**
8 mm	X	X	X	X	X	X
12 mm	X	X	X	X	X	X
15 mm	X	X	X	X	X	X
18 mm	X	X	X	X	X	X
23 mm	X	X	X	X	X	X
28 mm	X	X	X	X	X	X
33 mm	n/a	X	X	X	X	X
38 mm	n/a	X	X	X	X	X

3. STUDY OBJECTIVE

The primary objective of this study is to establish the safety and efficacy of the XIENCE Stent System in subjects with unprotected left main coronary artery (ULMCA) disease (either isolated to the left main trunk or associated with disease in other coronary arteries) by demonstrating that compared to coronary artery CABG, treatment of the left main stenosis ± other significant coronary lesions with the XIENCE stent will result in non-inferior or superior rates of the composite measure of all-cause mortality, myocardial infarction or stroke at the anticipated median follow-up of three years.

4. STUDY DESIGN

4.1. Study Design

A total of approximately 2900 subjects will be targeted in the study.

The prospective, unblinded, randomized multicenter trial will randomize about 1900 subjects at approximately 165 U.S. and international centers. Following diagnostic angiography demonstrating significant ULMCA disease and the consensus of the local Heart Team (qualified participating interventional cardiologist and cardiac surgeon) that the subject meets all the study entry criteria, subjects will be consented and randomized 1:1 to: a) PCI using the XIENCE stent, or b) CABG. Follow-up for all randomized subjects will continue for 5 years with a potential for additional follow-up to 10 years.

An additional group of approximately 1000 subjects who are not eligible for randomization or for other reasons are not randomized will be consented for the Universal Registry. All patients with left main disease without prior CABG in whom the visual estimated diameter stenosis is greater than or equal to 50% will be eligible for the EXCEL registry. These subjects will be consented for the Universal Registry, and followed through the time of initial treatment as per

standard of care with either PCI, CABG or medical therapy. No adverse event data will be collected for Universal Registry subjects.

Approximately 100 consecutive subjects from the Universal Registry with a ≥50% and <70% visually estimated angiographic diameter stenosis who otherwise meet all enrolment criteria, but without significant ischemia by noninvasive testing consistent with significant ULMCA disease, and in whom IVUS shows a MLA >6.0 mm^2 and/or a FFR >0.80 will be analyzed separately as intermediate lesion subjects, and followed through the time of initial treatment as per standard of care with either PCI, CABG or medical therapy.

4.2. Subject Follow-up

All randomized subjects will be followed for at least a five-year period post-procedure. All randomized subjects will have a follow-up telephone contact or office visit (preferred) at 30 days, at 6 months, and then at 1, 2, 3, 4, and 5 years post procedure. To support the 3 year endpoint analysis, clinical sites will be asked to obtain the 3 year adverse event status on all subjects. Therefore, at the time the last subject reaches the minimal follow-up duration, an additional adverse event (AE) check will be performed in order for data up to 3 years (365 days*3=1095 days) from date of randomization to be established equally in both arms (see Section 8.2 for further details).

The randomized subject consent form will also contain the potential for possible follow-up for a total of 10 years, with data collected from subject telephone contact or office visits at 6, 7, 8, 9 and 10 years. Follow-up after 5 years and for up to 10 years will be performed at the sole discretion of the Sponsor, if funding is available. Prior to the 5 year follow-up visit date for the first randomized subject, all sites will be notified if follow-up will continue for 5 or 10 years.

4.3. Treatment Strategy

The treatment strategy for all subjects randomized in the trial is as follows:

- All subjects participating in the randomized portion of clinical trial will have ***informed consent*** obtained after diagnostic angiography and prior to randomization. "Ad hoc" ULMCA PCI is not permitted (with one exception – see Section 20.1.3.).
- It is strongly recommended that the ***timing from randomization to treatment*** (PCI or CABG) be ≤1 week, but it is mandatory that revascularization be performed ≤2 weeks after randomization in all cases in both treatment arms. Reasons for delay beyond 2 weeks will be tracked.
- Target lesion(s) will be treated in accordance with the randomization schedule after satisfying the general and angiographic inclusion and exclusion criteria as defined in the protocol. If more than one target lesion will be treated, all lesions must receive the treatment that has been assigned as per the randomization.

5. ENDPOINTS

5.1. Primary Endpoint and Key Secondary Endpoints

Primary Endpoint. The primary endpoint of the randomized trial is the composite measure of all-cause mortality, myocardial infarction, or stroke (modified Rankin Scale (mRS) ≥1 and increase by ≥1 from baseline) at 3 years post randomization. The primary endpoint will be estimated via Kaplan-Meier failure rate measured from randomization and Greenwood's formula for estimating the standard error. The primary endpoint analysis will be conducted at the time when approximately 50% of the patients have reached the 3-year follow-up AND all patients have reached the 2-year follow-up, whichever time point is latest. All available data through 3-year follow-up will be used.

Major Powered Secondary Endpoints:

1. The composite of all-cause mortality, MI and stroke (mRS≥1 and increase by ≥1 from baseline) at 30 days post randomization. This powered endpoint will be estimated via Kaplan-Meier failure rate defined from randomization and Greenwood's formula for estimating the standard error.

2. The composite measure of all-cause mortality, MI, stroke (mRS≥1 and increase by ≥1 from baseline), or unplanned revascularization for ischemia at 3 years post randomization. This powered endpoint will be estimated via Kaplan-Meier failure rate defined from randomization and Greenwood's formula for estimating the standard error. The analysis will be conducted at the time when approximately 50% of the patients have reached the 3-year follow-up AND all patients have reached the 2-year follow-up, whichever time point is latest. All available data through 3-year follow-up will be used.

5.2. Other Secondary Endpoints

The primary endpoint composite event rate (all-cause death, MI or stroke) and powered secondary endpoints at all time points other than median of 3 years will be other secondary endpoints.

Time points for all other secondary endpoints, unless specified otherwise, are in-hospital, 30 days, 6 months, 1, 2, 3, 4, and 5 years post-procedure. The other secondary endpoints are:

- All-cause mortality
  - Cardiac death
  - Non-cardiac death
- All MI (peri-procedural, spontaneous, Q-wave and non Q-wave) including large and small MIs
- Protocol-defined MI
- MI adjudicated per Universal MI Definition
- Stroke (all, ischemic, and hemorrhagic)
- Disability following stroke event at 90 days± 2 weeks

- Ischemia-driven revascularization
    - Ischemia-driven target lesion revascularization (TLR)
    - Ischemia-driven target vessel revascularization (TVR)
    - Ischemia-driven non target vessel revascularization (Non-TVR)
- All revascularization (ischemia driven and non-ischemia driven)
    - All target lesion revascularization (TLR)
    - All target vessel revascularization (TVR)
    - All non-target vessel revascularization (non-TVR)
- Complete revascularization at baseline procedure, anatomic and functional (see Section 19. Appendix D).
- Stent thrombosis (ARC definition) symptomatic or asymptomatic
- Symptomatic graft stenosis or occlusion (since this requires angiographic documentation, this endpoint will be compared to symptomatic ARC definite stent thrombosis)
- Bleeding complications
    - Requirement for blood product transfusion
    - TIMI scale (major or minor)
    - BARC scale
- Requirement for blood product transfusion
- Time from randomization to procedure; time from procedure to discharge; ICU days; time from procedure to return to work
- Major adverse events (MAE) defined as composite of the following components. MAE will be assessed in-hospital and at 30 days only.
    - death
    - myocardial infarction
    - stroke
    - Transfusion of ≥2 units of blood
    - TIMI major or minor bleeding
    - major arrhythmia
    - unplanned coronary revascularization for ischemia
    - any unplanned surgery or therapeutic radiologic procedure
    - renal failure
    - sternal wound dehiscence
    - infection requiring antibiotics for treatment
    - intubation for >48 hours
    - post-pericardiotomy syndrome.

Definitions of terms and endpoints are located in Sections 16.1 and 16.2. Acronyms and abbreviations are defined in Section 16.0. Other secondary endpoints are included in the QoL sub-study.

5.3. Pre-Specified Sub-Groups

The present trial is underpowered for comparative assessment of PCI vs. CABG in any subgroup. Proposals for analysis that could lead to publications and hypothesis generation are included in Section 21.2.

6. SELECTION AND WITHDRAWAL OF SUBJECTS

6.1. Subject Population

Subjects randomized into this trial will be comprised of male and female subjects from the general interventional cardiology population. The randomized trial will randomize approximately 1900 subjects who meet all eligibility criteria and provide written informed consent. Each site should randomize a minimum of one subject, and may not randomize more than a maximum of 250 subjects.

6.2. Subject Screening

Once local IRB or ethics committee approval is obtained, potential subjects will be identified by qualified investigators in this trial and screened for study eligibility by the local Heart Team. Subjects eligible for randomization per the general inclusion and exclusion criteria will be asked to sign an informed consent for the randomized trial. Subjects who do not satisfy inclusion and exclusion criteria or who are otherwise not randomized will be documented on the Heart Team Worksheet, and asked to sign a consent form for data collection for the Universal Registry.

6.3. Stroke Assessment

All patients to be randomized into the Excel RCT will have a modified Rankin Scale (mRS) assessment conducted by mRS trained personnel at baseline and each visit and telephone interview. Additionally, the site research coordinator will evaluate each subject at 30 days, 6 months 1, 2, 3, 4 and 5 Y follow-up time points and at the primary endpoint follow up time point (either at annual follow up or at subject contact for primary endpoint AE check) using a Transient Ischemic Attack (TIA)/Stroke Questionnaire (Appendix J) and mRS disability questions. This questionnaire is a National Institute of Health Stroke Scale (NIHSS) validated questionnaire used in the CREST clinical trial. The disability questions are adapted from a structured interview developed for stroke patients.[1] If the responses to this questionnaire indicates a possible stroke or a

[1] Wilson JTL, Hareendran A, Grant M, Baird T, Shultz UGR, Muir KW, and Bone I. "Improving the Assessment of Outcomes in Stroke: Use of a Structured Interview to Assign Grades on the Modified Rankin Scale." Stroke. 2002; 33; 2243-46.

change in the mRS, then a vascular neurologist or stroke specialist or a mRS certified personnel blinded to the treatment type will confirm the mRS scale, determine whether a stroke has occurred

and determine the stroke severity using the NIHSS TIA/Stroke questionnaire. If a new stroke is diagnosed at the site, the investigators at the site will prepare a short narrative that describes the findings that support the diagnosis. All stroke events will be adjudicated by the Clinical Events Committee (CEC). Furthermore, if there is an increase in the mRS by one or more points noted at any visit, then an evaluation will be carried out to determine if a stroke or other outcome event has occurred.

Post-procedure, if a patient is diagnosed and adjudicated with a stroke event by the Clinical Events Committee (CEC), a disability assessment must be performed at 90 days ±2 weeks after the diagnosis of stroke using the mRS assessment instrument.

6.4. Informed Consent

Trial-specific subject procedures will not be started until a signed informed consent has been obtained. The Investigator and/or a person designated by the Investigator who has been trained on the protocol, will explain the nature and scope of the trial, potential risks and benefits of participation, and answer questions for the subjects. If the subject agrees to participate, the informed consent form must be signed and personally dated by the subject or legally authorized representative. The Investigator or a person designated by the Investigator must also sign the informed consent form, prior to subject participation in this trial. Any additional persons required by the local Institutional Review Board (IRB) or Ethics Committee (EC) to sign the informed consent form will also do so as required by the IRB/EC. No subjects belonging to a vulnerable population will participate in the trial. A copy of the executed informed consent form will be provided to the subject. In addition, the signed informed consent must be kept in the subject's medical records. A statement from the IRB/EC as to the requirements of additional signatures is to be provided to the Sponsor.

All subjects must provide informed consent in accordance with the local IRB/EC, using an IRB/EC-approved informed consent form. The final eligibility for the trial will be confirmed based on the pre-intervention angiography.

For trials with investigational product:

For live cases at congresses, the subject needs to sign a specific Live Case ICF, approved by the IRB/EC and by AV, as well as by the competent authorities (e.g., FDA), as applicable. The investigator must request AV approval prior to performing a Live Case.

For trials with commercial product:

For live cases at congresses, the subject needs to sign a specific Live Case ICF approved by the IRB/EC. The investigator must notify AV prior to performing a Live Case.

At U.S. sites, an authorization for use and disclosure of the subjects' protected health information as that term is defined by the Health Insurance Portability and Accountability Act (HIPAA) shall be obtained. Per individual site procedures, this authorization may be included as part of the subject informed consent.

6.5. Eligibility Criteria

Assessment for general eligibility criteria is based on medical records of the site and interview with a candidate subject. If some of the clinical and laboratory tests are not included in site standard tests, they must be done but after written informed consent is obtained. Subjects must meet ALL of the inclusion criteria to be considered for the clinical evaluation. If ANY of the exclusion criteria are met, the subject is excluded from the clinical evaluation and cannot be randomized.

The subjects who do not meet the eligibility criteria for the randomized clinical trial can participate in the Universal Registry.

6.5.1. Inclusion Criteria

- Unprotected left main coronary artery (ULMCA) disease with angiographic diameter stenosis (DS) ≥70% (visually estimated) requiring revascularization as assessed by both a participating interventional cardiologist and cardiac surgeon (local Heart Team),

or

- ULMCA disease with angiographic DS ≥50% but <70% (visually estimated) requiring revascularization as assessed by both a participating interventional cardiologist and cardiac surgeon, *with one or more of the following present:*
  - Non-invasive evidence of ischemia referable to a hemodynamically significant left main lesion (large area of ischemia in both the LAD and LCX territories, or in either the LAD or LCX territory in the absence of other obstructive coronary artery disease to explain the LAD or LCX defect), or stress-induced hypotension or stress-induced fall in LVEF, or stress-induced transient ischemic dilatation of the left ventricle or stress-induced thallium/technetium lung uptake, and/or
  - IVUS minimum lumen area (MLA) ≤6.0 mm^2, and/or
  - Fractional Flow Reserve (FFR) ≤0.80
    - Note: IVUS is strongly preferred to FFR for ULMCA interrogation unless there is no other disease in both the LAD and LCX territories (i.e. isolated left main disease), in which case either is acceptable (see Section 18. Appendix C.)

or

- Left Main Equivalent Disease: Left main Medina classification 0,1,1 bifurcation disease (diameter stenosis of both the true ostial LAD and LCX [within 5 mm of the left main distal bifurcation]) ≥50%, in the absence of significant angiographic stenosis in the left main coronary artery, may also be randomized if one of the two following conditions are present:
  - Both the ostial LAD and ostial LCX stenoses are ≥70% stenotic by visual estimation, *or*
  - If one or both of the ostial LAD and ostial LCX stenoses are ≥50% and <70% stenotic by visual estimation, then this lesion(s) is demonstrated to be significant either by
    - a) non-invasive evidence of ischemia in its myocardial distribution; and/or
    - b) FFR ≤0.80; and/or
    - c) IVUS MLA ≤4.0 mm^2 (FFR is preferred).

Note: if both the ostial LAD and ostial LCX stenoses are ≥50% and <70% stenotic by visual estimation, then both lesions must be significant by these criteria for the patient to be eligible for randomization.

- Clinical and anatomic eligibility for both PCI and CABG as agreed to by the local Heart Team
  - Interventionalist determines PCI appropriateness and eligibility
  - Surgeon determines surgical appropriateness and eligibility
- Silent ischemia, stable angina, unstable angina or recent MI
  - If recent MI, CK-MB must have returned to normal prior to randomization.
- Ability to sign informed consent and comply with all study procedures including follow-up for at least three years
- The subject must be ≥18 years of age

6.5.2. Clinical Exclusion Criteria

- Subject is part of a vulnerable population who, in the judgment of the investigator, is unable to give Informed Consent for reasons of incapacity, immaturity, adverse personal circumstances or lack of autonomy. This may include: Individuals with mental disability, persons in nursing homes, children, impoverished persons, persons in emergency situations, homeless persons, nomads, refugees, and those permanently incapable of giving informed consent. Vulnerable populations also may include members of a group with a hierarchical structure such as university students, subordinate hospital and laboratory personnel, employees of the Sponsor, members of the armed forces, and persons kept in detention.
- Prior PCI of the left main trunk at any time prior to randomization
- Prior PCI of any other (non-left main) coronary artery lesions within 1 year prior to randomization
- Prior CABG at any time prior to randomization
- Need for any concomitant cardiac surgery other than CABG (e.g. valve surgery, aortic repair, etc.), or intent that if the subject randomizes to surgery, any cardiac surgical procedure other than isolated CABG will be performed
- CK-MB greater than the local laboratory upper limit of normal or recent MI with CK-MB levels still elevated.
  - Note: A subject with a recent MI in whom the troponin levels are still elevated but falling and in whom the CK-MB has returned to within normal range prior to randomization may be randomized, with CK-MB levels used to assess peri-procedural MI.
- Subjects unable to tolerate, obtain or comply with dual antiplatelet therapy for at least 1 year
- Subjects requiring or who may require additional surgery (cardiac or non cardiac) within 1 year

- The presence of any clinical condition(s) which leads the participating interventional cardiologist to believe that clinical equipoise is not present (i.e. the subject should not be treated by PCI, but rather should be managed with CABG or medical therapy - reasons will be documented in the Heart Team worksheet)
- The presence of any clinical condition(s) which leads the participating cardiac surgeon to believe that clinical equipoise is not present (i.e. the subject should not be treated by CABG, but rather should be managed with PCI or medical therapy - reasons will be documented in the Heart Team worksheet)
- Pregnancy or intention to become pregnant (female subjects of child bearing potential must have a negative pregnancy test within 7 days of the index procedure)

  Note: Female patients should be instructed to use safe contraception (e.g. intrauterine devices, hormonal contraceptives: contraceptive pills, implants, transdermal patches, hormonal vaginal devices, injections with prolonged release. It is accepted in certain cases to include subjects having a sterilized regular partner or subjects using a double barrier contraceptive method. However, this should be explicitly justified in special circumstances arising from the study design, product characteristics and/or study population.
- Non cardiac co-morbidities with life expectancy less than 3 years
- Other investigational drug or device studies that have not reached their primary endpoint

6.5.3. Angiographic Exclusion Criteria

- Left main diameter stenosis <50% (visually assessed), unless left main equivalent disease is present
- SYNTAX score ≥33, as determined by the consensus of at least one participating interventional cardiologist and one surgeon of the local Heart Team
- Visually estimated left main reference vessel diameter <2.25 mm or >4.25 mm (post dilatation up to 4.5 mm is allowed)
- The presence of specific coronary lesion characteristics or other cardiac condition(s) which leads the participating interventional cardiologist to believe that clinical equipoise is not present (i.e. the subject should not be treated by PCI, but rather should be managed with CABG or medical therapy - reasons will be documented)
- The presence of specific coronary lesion characteristics or other cardiac condition(s) which leads the participating cardiac surgeon to believe that clinical equipoise is not present (i.e. the subject should not be treated by CABG, but rather should be managed with PCI or medical therapy - reasons will be documented)

6.6. Subject Flow

Every subject who presents with ULMCA or left main equivalent disease to any qualified interventional cardiologist or cardiac surgeon participating in this trial will be evaluated by the local Heart Team including detailed assessment of the inclusion and exclusion criteria, the SYNTAX score calculated from diagnostic angiogram, history, physical examination and laboratory evaluations. If the information is not adequate for the local Heart Team to make their decision, then further testing and/or an angiogram will be performed after informed consent is obtained from the subject.

The Study Coordinators should facilitate the local team conference. Each site will take minutes of each conference for the investigators sites. The members will review the collected baseline information e.g. the angiogram (including the SYNTAX score), and demographic characteristics. During the local Heart Team conference, the members will jointly decide whether the subject is eligible for randomization or for the Universal Registry.

If both members of the local Heart Team determine that the subject meets the eligibility criteria of the Randomized Study, the subject will be deemed meeting randomization criteria and enters the "Randomized Clinical Trial" (Figure 6.1).

- Note: If all the eligibility criteria are met *except* that the diagnostic angiography demonstrates a ULMCA lesion or left main equivalent lesion(s) which either the interventional cardiologist and/or cardiac surgeon of the local Heart Team believes is ≥50% but <70% in diameter stenosis by visual estimate, the subject is not yet eligible for randomization without further evaluation. If non-invasive evidence of ischemia referable to a hemodynamically significant ULMCA lesion as defined in Section 6.5.1 is not present, the subject must have IVUS (preferably) or FFR assessment of the ULMCA lesion. In this case, the subject will be consented for randomization prior to the invasive IVUS/FFR procedure. If the IVUS/FFR procedure demonstrates that the ULMCA lesion is significant, the subject may be randomized at that point in the catheterization laboratory, and PCI performed if the randomization is to PCI. If the randomization is to CABG, the catheterization laboratory procedure is terminated and CABG performed as per standard of care.

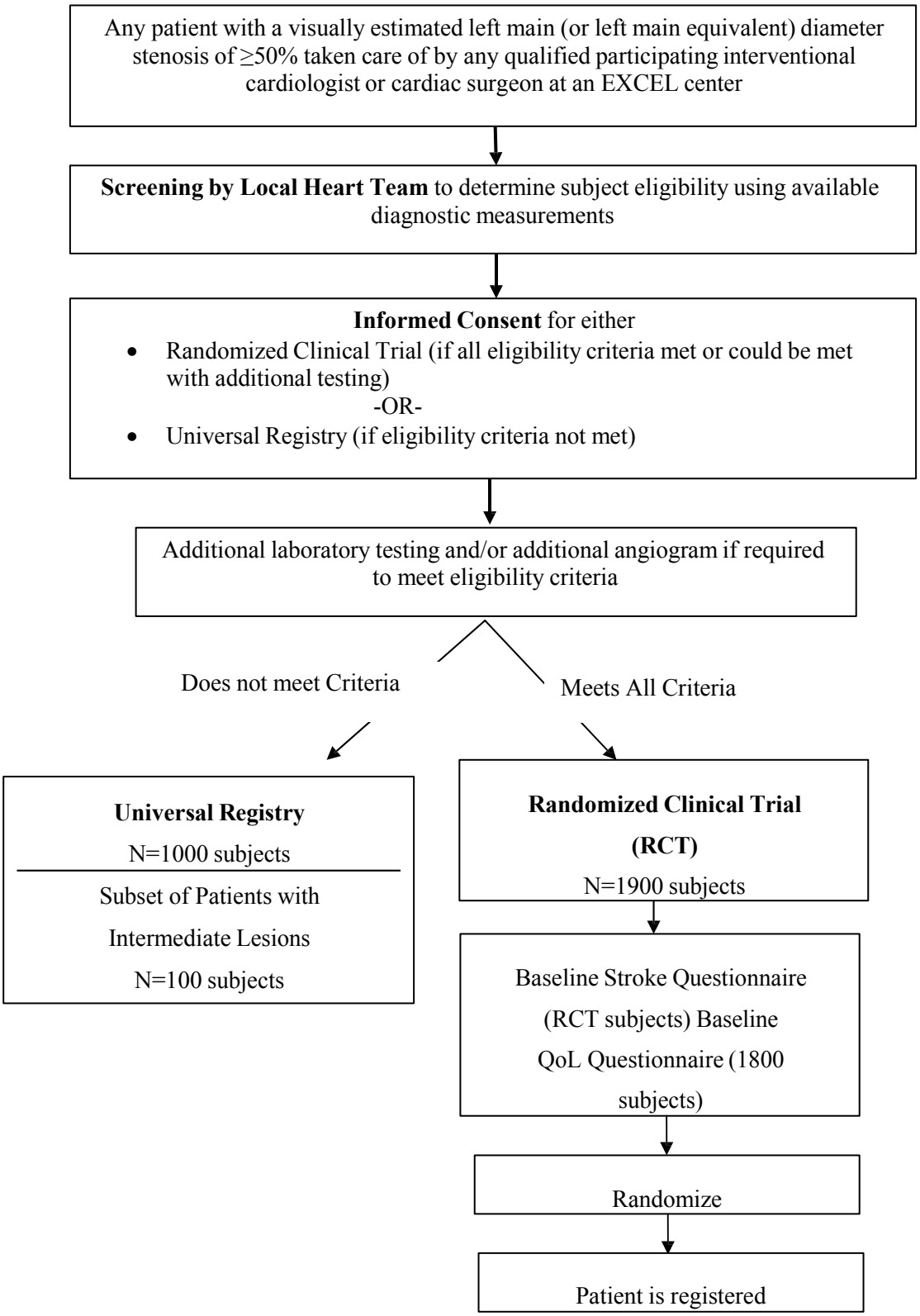
The local Heart Team may also decide that the subject does not meet randomization criteria. The reasons for this will be documented in a worksheet (Heart Team Worksheet). These subjects will be approached for inclusion into the Universal Registry (Figure 6.1).

- The purpose of the Universal Registry is to assess the proportion and reasons for which subjects with angiographically significant ULMCA disease requiring revascularization during the time course of this study are not randomized; to compare the baseline characteristics (including the SYNTAX score) of the randomized and non-randomized subjects, and between those in the registry who undergo PCI versus CABG; and to assess the site to site variability in randomization eligibility and treatment patterns.
- Up to 100 consecutive subjects with a visually estimated angiographic left main diameter stenosis of ≥50% but <70% but who did not meet the ischemia, IVUS, or FFR criteria will be entered into the Universal Registry but evaluated separately as intermediate lesion subjects. The purpose of the evaluation of intermediate lesion subjects is to document the proportion and characteristics of subjects with an angiographically intermediate lesion (visually estimated angiographic left main diameter stenosis of ≥50% but <70%) in whom ischemia cannot be demonstrated and/or the lesion does not appear significant by IVUS using standard accepted criteria, and to assess the treatments these subjects undergo

The decision for the subject's inclusion into the Randomized Clinical Trial or the Universal Registry must be documented and signed by both members of the local Heart Team (Heart Team Worksheet).

Figure 6.1 outlines the screening and randomization process and illustrates the point where informed consent should be obtained.

Figure 6.1 Subject Flow



6.7. Subject Discontinuation

Every subject should remain in the trial until completion of the required follow-up period. However, a subject's participation in any clinical trial is voluntary and the subject has the right to withdraw at any time without penalty or loss of benefit. Should this occur, the reason for withdrawal must be recorded in the source documentation. Conceivable reasons for discontinuation may include, but not be limited to, the following:

- **Subject Withdrawal:** Subject participation in a clinical trial is voluntary and the subject may discontinue participation (refuse all subsequent testing/follow-up) at any time without loss of benefits or penalty.
- **Lost-to-Follow-up:** Subject does not complete the scheduled follow-up visits but has not officially withdrawn from the trial (does not apply to missed visits). Site personnel should make all reasonable efforts to locate and communicate with the subject, including the following, at each contact time point:
    - A minimum of two telephone calls to contact the subject should be recorded in the source documentation, including date, time, and initials of site personnel trying to make contact.
    - If these attempts are unsuccessful, a letter should be sent to the subject.
    - If the subject misses two consecutive scheduled contact time points and the above mentioned attempts at communicating with the subject are unsuccessful, the subject will be considered lost-to-follow-up.

Note: If a subject misses one or more of the follow-up contact time points this will be considered a missed visit. Subject may then return for subsequent visits.

All subjects have the right to withdraw at any point during the course of the study without prejudice. It will be documented whether or not each subject completed the clinical study. If the study treatments or observations are discontinued in any subject, the reason will be recorded and the Sponsor must be notified promptly. It is imperative to obtain complete follow-up data for all subjects (other than those who withdraw their consent), whether or not they receive their assigned treatments. Every attempt should be made to collect follow-up information on all subjects randomized in the study through the entire five years of follow-up (or up to ten years optional). All procedures and laboratory specimens or tests requested for evaluation following administration of the study device/CABG surgery should be carried out when possible, whether or not a subject continues to receive treatment according to the protocol.

If a subject withdraws from the study due to problems related to the investigational device safety or performance, the investigator shall ask for the subject's permission to follow his/her status/condition outside of the clinical investigation.

A Study Completion Form must be completed:

- when the subject is considered lost to follow-up (per the above definition)
- when the subject withdraws from the study
- upon study completion

The Sponsor must be notified of the reason for subject discontinuation. The site will provide this information on the Study Completion Form. Investigators must also report this to their IRB/EC as defined by their institution's procedure. Subjects will not be replaced.

7. TREATMENT OF SUBJECTS

7.1. Schedule of Events – Randomized Trial

	Screening	Pre-procedure / Baseline	Procedure	Post-procedure	visit preferred [1] 1M ± 7d	Phone or office visit 6M ± 14d	visit preferred [1] 1Y (-30d, +60d)	visit preferred [1] 2Y (-30d, +60d)	visit preferred [1] 3Y,4Y, 5Y (-30d, +60d)	possible visits 6Y, 7Y, 8Y, 9Y, 10Y (-30d, +60d)
Local Heart Team meeting	x									
Estimate LM disease severity	x									
Angina status	x			x	x	x	x	x	x	x
Eligibility criteria	x									
SYNTAX score	x									
Physical examination	x									
LVEF (echo, MRI or cath)[10]	x									
Informed consent		x								
FFR / IVUS(if DS ≥50 and <70%)[2]		x								
Demographics, Medical History		x								
12 lead ECG		x[3]		x[3]			x[4]			
Laboratory tests										
$HgbA_{1c}$ (required), hsCRP & BNP (recommended)		x								
Hgb, WBC, Platelets		x								
CK / CK-MB		x[5]		x[6]						
Serum creatinine		x								
mRS assessment		x[7]			X[9]	X[9]	X[9]	X[9]	X[9]	
Stroke Assessment (TIA Questionnaire)*					X[9]	X[9]	X[9]	X[9]	X[9]	
Cardiac medication		x	x	x	x	x	x	x	x	x
QoL questionnaire		x			x		x		x[8]	x
Treatment assignment		x								
Safety assessment & reporting		←---------- (S)AE AND Study event REPORTING----------→								
Event related source docs		←----------collecting source documents related to events----------→								
CABG / PCI treatment			x							
Document resource utilization				x	x	x	x	x	x	x

1 Office visits are strongly recommended. If that is not possible, phone contact with subject or subject's local physician is acceptable. As a last resort, notification of death by civil registry will be accepted.

2 For an intermediate left main lesion (≥50 - <70% visual DS) without non-invasive evidence of a hemodynamically significant ULMCA lesion; prior to randomization, a cath lab procedure must document left main IVUS ≤6mm^2 (preferred) or FFR ≤0.80.
3 ECGs to be collected for independent core lab assessment at baseline, within 24 hours post procedure (ideally at the same time as the first CK-MB draw), at discharge, and during any adverse cardiac event.
4 ECG to be collected for independent core lab assessment at 1Y visit. If the 1Y contact is by phone, the ECG must be done at a local institution and submitted to investigative site.
5 CK/CK-MB is required at baseline and to assess peri-procedural MI; troponin levels are optional. At baseline prior to randomization, the CK-MB must be within normal limits, or if recent MI and troponin is still elevated, the CK-MB must have returned within the laboratory normal range prior to randomization.
6 For assessment of post procedural myocardial damage, CK-MB must be drawn at 12h (±2 hrs; i.e. 10-14 hrs) and 24h (±2 hrs; i.e. 22-26 hrs) post procedure or at discharge if sooner. Additional serial troponins or CK-MBs should be drawn in hospital or at any time during follow-up to assess any adverse cardiac event.
7. At baseline assessment is performed using mRS scale
8. QoL questionnaire is not done at 4 year follow-up.
9.Stroke Assessment: performed using Stroke/TIA and mRS stroke assessment. In case of an event of stroke, a mRS questionnaire disability assessment will also be done at 90 days±2 weeks after the event
10.LVEF must be assessed at baseline within 14 days prior to randomization.

Schedule of Events – Universal Registry

	Screening	Pre-Treatment
Estimate LM disease severity	x	
Local Heart Team meeting	x	
Angina status	x	
Eligibility criteria	x	
SYNTAX score	x	
Informed consent		X
FFR / IVUS(if DS ≥50 and <70%)[1]		x
Demographics, Medical Hx, Physician exam, intended LVEF (recommended), basic labs (Hgb, creatinine)		x
CABG / PCI / medical treatment		x

1 Intermediate lesion (visually estimated left main diameter stenosis ≥50 - <70%) registry only; no evidence of any of the following: 1) non-invasive ischemia consistent with hemodynamically significant ULMCA disease; 2) FFR ≤0.8; 3) IVUS MLA ≤6mm^2

7.2. Baseline and Pre-Procedure

Subject preparation will occur in accordance with standard hospital policy for the care of interventional cardiology or CABG subjects.

7.2.1. Demographics and Medical History

In all study subjects (randomized or registry), demographics and medical history will be captured in the eCRF.

7.2.2. Pre-PCI Medication

Aspirin. Preloading with aspirin 300 to 325 mg at least 2 hrs before the PCI is mandatory. For subjects already receiving chronic aspirin therapy, the loading dose of 300 to 325 mg of aspirin must still be given. Either chewable or intravenous aspirin is mandatory for the loading dose in subjects not on chronic aspirin who will receive only one dose of aspirin before the ULMCA PCI.

ADP antagonists. ADP antagonist pre-loading therapy is mandatory. In patients undergoing PCI, the ADP antagonist must be given prior to the start of the interventional procedure according to the timing for the selected agent below. For subjects already receiving chronic ADP antagonist therapy, pre-loading is still mandatory. The choice of either clopidogrel, prasugrel or ticagrelor is left to the discretion of the investigator. The one exception where ADP antagonist loading may be first given after the procedure is in the case of the patient who qualifies for randomization except for the presence of a visually estimated 50% - <70% diameter stenosis of the left main in whom IVUS or FFR will be performed for confirmation of lesion severity. In this case, since the patient will be randomized in the catheterization laboratory after IVUS or FFR, ADP antagonist pre-loading is permitted but is not mandatory; if the patient randomizes to PCI, however, and had not been preloaded, ADP antagonist preloading must be administered within 2 hours post PCI. In case of preloading, the following schedule is recommended:

- clopidogrel 600 mg >6 hrs before PCI, or 300 mg >12 hrs before PCI (even if the subject is on chronic ADP antagonist therapy); or
- prasugrel 60 mg >1 hr before PCI (even if the subject is on chronic ADP antagonist therapy); or
- ticagrelor with dosing per labeling >1 hr before PCI (even if the subject is on chronic ADP antagonist therapy) if approved by the local regulatory authorities during the randomization period of this protocol.

Pre-PCI statin therapy. Recent randomized trials[62, 63,64, 65, 66] have demonstrated that high dose statin therapy decreases PCI-related myonecrosis in subjects undergoing stent implantation, whether or not the subject is already taking chronic statin therapy. Therefore, in the absence of absolute contraindications to statin use (e.g. severe allergy with prior use), it is strongly recommended to give the statins 12 hours in advance (at least one dose), but in all cases at least 1 hour before the PCI, regardless of LDL level and history of prior statin use.

- atorvastatin 80 mg
- rosuvastatin 40 mg

The above statin regimens are required per the protocol. In certain circumstances, sites may not be able to follow the protocol required statin regimen. In these cases, the site must agree to an alternative regimen with the sponsor in writing prior to randomizing any patients. Failure to prospectively document and obtain approval of the alternative therapy will lead to the assessment of a protocol deviation.

Other medications. The use of other medications prior to PCI (e.g. beta-blockers, ACE inhibitors) is left to the discretion of the treating physicians.

7.2.3. Pre-CABG Medication

It is strongly recommended that subjects are treated with aspirin, statins, and antihypertensive medications prior to surgical revascularization. For subjects on clopidogrel, prasugrel, or ticagrelor prior to CABG, these agents should be discontinued and CABG postponed for at least 5 days, 7 days or 5days, respectively, if the subject is stable. Subjects receiving amiodarone prophylaxis should be loaded prior to surgery, and have their treatment continued for a minimum of five days after surgery. It is strongly recommended that ACE inhibitors be stopped sufficiently before surgery to ensure they are no longer effective at the time of surgery.

7.2.4. 12-Lead ECG

12-lead ECGs must be collected only in the randomized cohort, at pre-procedure, within 24 hours post procedure, at discharge, and at one year follow-up. If the one year follow-up is performed through phone contact, the mandatory ECG must be performed at a local institution and submitted to the investigative site. In addition, 12-lead ECG should be recorded during clinical episodes of ischemia or other adverse cardiac event and included in the event source documentation of the subject.

7.2.5. Laboratory Tests

In the randomized cohort, the following lab tests will be required pre-procedure: HbA_{1c}, CK-MB, hemoglobin, WBC, platelet count and serum creatinine, whereas hsCRP and BNP are highly recommended.

Initial screening must show that CK-MB is within normal limits. If the subject has had a recent MI and the troponin level is still >ULN, the CK-MB must have fallen to within normal limits to qualify the subject for randomization. If the CK-MB is still elevated the subject is not eligible for randomization until the CK-MB has fallen to <ULN. Cardiac markers must be measured in all subjects at baseline and twice within 24 hours following the revascularization procedure: at 12 ± 2 hours (i.e. 10-14 hours) and at 24 ± 2 hours (i.e. 22-26 hours) post procedure or at discharge if sooner. In addition, with any significant new clinical episodes of angina or adverse cardiac events, cardiac markers should be repeated and followed for 6-18 hours post ischemia. CK-MB levels must be used to assess baseline entry criteria and post procedure myonecrosis. Either CK-MB or Troponin I or T levels may be used to assess myonecrosis >48 hours post procedure.

Note: Discharge is considered when subject leaves the treating or referral hospital.

7.2.6. Left Ventricular Ejection Fraction

Left ventricular ejection fraction (LVEF) must be assessed at baseline within 14 days prior to randomization, either by echocardiography, MRI, or contrast left ventriculography. For registry patients this is only recommended.

7.2.7. Angiography

Baseline angiography of the target vessel(s) will be completed as per the Angiographic Core Lab Protocol. (Refer to Section 23, Appendix H.)

7.2.8. IVUS / FFR

Prior to randomization, all subjects with an angiographically intermediate left main lesion (≥50 - <70 DS% by consensus visual assessment by the Heart Team) without noninvasive evidence of a hemodynamically significant left main lesions must undergo additional invasive investigation after informed consent such as IVUS (preferred) or FFR to document lesion severity. If these tests provide data that the patient meets the inclusion criteria, the subject may be randomized; if not, the subject should be included in the Universal Registry. (Refer to Section 18, Appendix C.)

7.2.9. TIA/Stroke Questionnaire

All patients randomized into the EXCEL RCT will have a modified Rankin Scale (mRS) assessment conducted by mRS-trained personnel at baseline and each visit and telephone interview. Additionally, the site research coordinator will evaluate each subject at 30 days, 6 months, 1, 2, 3, 4 and 5 Y follow-up time points and at the primary endpoint follow-up time point (either at annual follow-up or at subject contact for primary endpoint AE check) using a Transient Ischemic Attack (TIA)/Stroke Questionnaire and mRS disability questions (Appendix J). This questionnaire is the National Institute of Health Stroke Scale (NIHSS) validated questionnaire used in Abbott Vascular's CREST clinical trial. The disability questions are adapted from a structured interview developed for stroke patients. If a subject's response to this questionnaire indicates a possible stroke or a change in the mRS, then a vascular neurologist/ stroke specialist/mRS certified personnel blinded to the treatment type will confirm the mRS scale, determine whether a stroke has occurred and determine the stroke severity using the NIHSS TIA/Stroke Questionnaire. If a new stroke is diagnosed at the site, the investigators at the site will prepare a short narrative that describes the findings that support the diagnosis. All stroke events will be adjudicated by the Clinical Events Committee (CEC). Furthermore, if there is an increase in the mRS by one or more points noted at any visit, then an evaluation will be carried out to determine if a stroke or other outcome event has occurred.

Post procedure, if a patient is diagnosed and adjudicated with a stroke event by the Clinical Events Committee (CEC), a disability assessment will be performed at least 90 days after the diagnosis of stroke using the mRS assessment instrument.

7.2.10. QoL Questionnaire

Subjects in the QoL substudy of the randomized trial should complete the Quality of Life (QoL) questionnaires after being determined to be eligible for randomized study participation but prior to randomization. Subjects who have intermediate lesions who require an additional angiogram to determine eligibility should complete the QoL questionnaire prior to the additional angiogram in case the randomization assignment is to PCI and the angiogram procedure continues into the PCI treatment without leaving the catheterization laboratory.

Disease-specific QoL will be assessed using the Seattle Angina Questionnaire (SAQ) and the London School of Hygiene Dyspnea Questionnaire in 1800 selected patients. Mental health and depression will be assessed using the Patient Health Questionnaire-9 (PHQ-9). Generic health status will be assessed using the Medical Outcomes Study 12-item Short Form (SF-12), and health utilities will be assessed using the EuroQoL (EQ-5D) with U.S.-specific weights. These measures will be assessed using standardized, written questionnaires at baseline (prior to randomization), 1 month, 12 months, 3 years, and 5 years. Questionnaires will be presented in each subject's native language using culturally-validated translations. When an appropriate translation does not exist for the instrument, it will be omitted from the specific country but the remainder of the questionnaires will still be administered. Data entry for each questionnaire into the study database will be the responsibility of an appropriate contract research organization (CRO).

See Section 17, Appendix B. for details regarding Quality of Life and U.S. Health Economics Sub-Studies.

7.2.11. Resource Utilization

Data on cardiovascular-specific resource utilization will be collected prospectively for each randomized U.S. subject for the index hospitalization and the full follow-up period for all subjects using standardized case report forms.

7.2.12. IVRS Randomization

After informed consent has been obtained and all eligibility criteria have been confirmed, the central allocation service (Interactive Voice Response System: IVRS) should be contacted (ICON Clinical Research, L.P.). Prior to randomization, the IVRS will prompt the study coordinator to provide the subject's SYNTAX score and diabetes status (whether or not medically treated for stratification purposes). The IVRS will randomize the subject to either PCI with the XIENCE stent (depending on availability) or CABG treatment on a one to one basis using a randomized block design. Randomization will be stratified by the presence vs. absence of medically treated diabetes, SYNTAX score <23 vs. ≥23, and study center. Patients with significant ULMCA disease who are otherwise not eligible for randomization should be entered into the Universal Registry through the IVRS, ideally prior to revascularization.

7.3. Procedure- PCI

It is recommended that the treatment for subjects randomized to PCI will be according to the product labeling and instructions for use as well as the following instructions:

7.3.1. General Considerations

- ***Procedural "staging"*** in PCI subjects is defined as a planned elective second PCI procedure at a separate setting to optimally complete the PCI. Given the complexity of the ULMCA subjects randomized in this clinical trial, it is anticipated that a substantial proportion of PCI subjects may fall into the category of staged procedures. The criteria for staging are left to the operator's best judgment, and there is expected variability among operators and sites. In general, the decision to stage is based on the overall extent and complexity of coronary

  disease, the case complexity (intra-procedure difficulty encountered by the operator), the duration of the procedure, assessment of radiation exposure, the total volume of contrast utilized, the clinical stability of the subject, and other subject-related factors (diabetes, renal function, etc.). The recommended timing of a planned elective staged second PCI procedure is optimally within 2 weeks post index procedure, but in all subjects it is strongly recommended that it be completed within 4 weeks post index procedure.

  The reason(s) for the staged procedure must be documented in the eCRF and source documents. Furthermore, the need for staging, and all specific lesions planned to be treated during the staged procedure should be declared beforehand in the eCRF at the time of initial baseline procedure.

  Unless otherwise planned, stented segment(s) treated during the initial baseline procedure

should not be treated again during the staged procedure. If the e-CRF from the first procedure did not indicate that such re-intervention was planned, the re-PCI will be considered to be clinically indicated, and will be analyzed as an event (although not necessarily ischemia-related – the Clinical Events Committee will make this determination).

Only randomized study stents should be used during staged procedures, if possible. During a staged procedure the same study assessments (such as ECG and cardiac biomarker collection) apply as during the baseline procedure. All subjects must be taking the protocol required post ULMCA medications (such as aspirin and ADP antagonists) prior to staged procedure. The staged procedures will not affect the original follow-up schedule.

- ***Hemodynamic support*** for PCI subjects with ULMCA lesions is usually not required but there is significant variability in the perceived need for hemodynamic support among experienced operators and sites. Criteria for required hemodynamic support may include systemic hypotension, severe pulmonary hypertension, severely reduced ejection fraction, extreme anatomic complexity (e.g. severely calcified left main lesion with intended use of rotational atherectomy), and/or subject instability before or during the procedure. The decision regarding the use hemodynamic support, either elective and planned or urgently required due to subject instability, and the type of support device is left to the operator's best judgment.
- The choice of ***vascular access*** for PCI (e.g. femoral or radial) is left to the operator's best judgment.
- The choice and use of ***vascular closure devices*** is left to the operator's best judgment.

7.3.2. Optimal ULMCA PCI – General Considerations

- Determination of ***ULMCA lesion severity.*** At the time of the PCI procedure, all ULMCA lesions which appear visually to be <70% stenotic (even if the angiographic stenosis appeared to be ≥70% in severity on the earlier qualifying angiogram), should not be treated with PCI unless there is evidence of ischemia or morphologic severity defined as either:
  - noninvasive functional evidence of ischemia in the territory of the lesion (not explained by another coronary stenosis), and/or
  - IVUS minimal luminal area ≤6.0 mm^2 (see IVUS procedural guidelines), and/or
  - FFR ≤0.80 (see FFR procedural guidelines).

  If the subject has been randomized to PCI and the ULMCA stenosis is no longer believed to be significant by these criteria, PCI should in most cases be performed of other significant lesions, but the ULMCA should not undergo intervention. Exceptions might include cases in which there is ostial LAD or LCX disease abutting the borderline left main lesion which must be treated; when the left main stenosis is rapidly progressive on the basis of serial angiograms; or when the left main lesion is irregular or disrupted in appearance or has other high risk features for continued medical therapy. Whether or not the ULMCA is treated, once randomized, the subject will remain in the randomized trial by intention to treat.
- In subjects with ***"other coronary disease"*** outside of the ULMCA complex, the following treatment sequences are recommended:
  - If LAD and/or LCX disease is present, treat the LAD and/or LCX first (distal to proximal,

as per usual PCI practice), unless the severity of the LM stenosis (e.g. >70% stenosis) requires primary treatment of the LM first.

- If the ULMCA lesion is critical (e.g. >90% visually assessed stenosis or clinical instability), treat the ULMCA first, either with balloons or definitive stenting as randomized to insure subject safety.
- If the RCA has a severe culprit lesion in a large vessel and the ULMCA stenosis is <70%, the operator may choose to treat the RCA before the ULMCA lesion; otherwise the ULMCA lesion should usually be treated before the RCA.
- Chronic total occlusions (CTOs) should usually be treated after completion of the ULMCA lesion (frequently as a planned second staged procedure).

- ***Left main lesion preparation***, defined as pre-treatment with balloons or other approved devices (including rotational atherectomy for heavily calcified vessels), of the ULMCA complex is left to the operator's best judgment, but is strongly recommended. Direct stenting of the ULMCA is strongly discouraged.
- Adequate lesion pre-dilatation requires dilatation with a balloon no smaller than 0.5 mm smaller than the distal RVD. Furthermore, when moderate or greater calcification is evident by either angiography or IVUS, all possible steps should be taken to ensure that full balloon expansion with the anticipated final stent size is achievable before the stent is implanted. This might require pre-dilatation with a non-compliant balloon sized 1:1 to the distal RVD (either alone or in conjunction with a cutting/scoring balloon and/or high-speed rotational atherectomy), and/or successful passage of an IVUS catheter after pre-dilatation demonstrating adequate lumen dimensions. Strong consideration should be given to additional pre-dilatation or lesion preparation if an IVUS catheter will not cross the lesion prior to stent implantation.
- To provide continuous branch vessel access and to ensure subject safety, ***two separate guidewires*** must always be in place in both the LAD and LCX during treatment of a distal LM bifurcation lesion.
- In subjects randomized to PCI, only the commercially available ***XIENCE stent*** can be used –

  this is mandatory. The XIENCE DES should be used if it is available in the appropriate diameter and length. The XIENCE PRIME DES is available in diameters from 2.25 mm to 4.0 mm and lengths from 8 mm to 38 mm (see Table 2-4 for size matrix). The XIENCE V DES is available in diameters from 2.25 mm to 4.0 mm and lengths from 8 mm to 28 mm (see Table 2-3 for size matrix). The XIENCE Xpedition is available in diameters from 2.25 mm to 4.0 mm and lengths from 8 mm to 38 mm (see Table 2-5 for size matrix). The XIENCE PRO DES (for OUS use only) is available in diameters from 2.25 mm to 4.0 mm and lengths from 8 mm to 38 mm (see Table 2-6 for size matrix). The 4.0 mm diameter XIENCE stent can be post-dilated up to 4.5 mm diameter using appropriately sized balloons. It is strongly recommended not to overlap XIENCE V stents due to the absence of longer XIENCE V stent lengths to match the XIENCE PRIME, XIENCE Xpedition or XIENCE PRO (for OUS use only) 33 and 38 mm stent lengths.
- The following techniques are strongly recommended to optimally deploy the XIENCE DES:
  - good lesion preparation with balloons or other approved devices as above
  - selection of the stent diameter according to the distal reference vessel diameter (1.0 – 1.1 : 1.0 ratio)

- deployment of the XIENCE PRIME (at 8 to 18 atm), XIENCE Xpedition (at 8 to 18 atm), XIENCE PRO (at 8 to 18 atm, for OUS use only) or XIENCE V DES (at 8 to 16 atm)
- optional post-dilation using properly sized non-compliant balloons at high pressures contained within the stent margins, especially if there is an area of incomplete expansion (noted by IVUS or as a "waist" on the deployment balloon or angiographic narrowing post-deployment).

In the rare case where a XIENCE stent is not available in the size and/or length needed, or the XIENCE stent cannot be delivered to the target site, subjects should be managed per the standard of care at the hospital site in the best interest of the subject.

IVUS guidance for ULMCA PCI is found in Section 20.2

- Devices not approved by the FDA may not be used during the procedure.

7.3.3. Left Main Ostial and Shaft Lesions

- After adequate lesion preparation and in the optimal deployment view, a ***single stent*** should be implanted in the ULMCA, beginning at the ostium (placed 1-2 mm in the aorta to ensure aorto-ostial coverage) and ending in either the ULMCA segment if the ULMCA length is >8 mm, or "crossing-over" to end in either the LAD (usually) or LCX (less commonly) if the ULMCA length is <8 mm.
- ***Post-dilatation*** with short high pressure (≥18 atm) non-compliant balloons within the stent margins is strongly recommended unless IVUS guidance indicates flush apposition and appropriate CSA (minimum CSA >8.5 mm^2).

7.3.4. Left Main Distal Bifurcation Lesions

- A ***single stent crossover provisional technique*** is strongly recommended whenever possible with the stent size selected to match the distal branch reference vessel (usually the LAD). If the side branch origin (usually the ostial LCX) has a residual stenosis <50% with TIMI 3 flow, and without a significant dissection, the decision to dilate the side branch is left to the discretion of the operator. If the decision is made not to dilate the side branch, a short (usually 8 mm) non-compliant balloon contained within the left main segment should be used to fully expand the stent in the left main. If there is uncertainty concerning the adequacy of side branch patency, an FFR determination is recommended, with a value of ≤0.80 indicating that side branch dilatation should be performed.[67, 68] If there is significant (>50%) stenosis or other signs of sub-optimal side branch appearance (e.g. dissection or FFR ≤0.80), it is strongly recommended to utilize kissing balloons after a single stent crossover technique, with long inflations of 60 seconds or more if tolerated by the subject to attempt to manage the ostial LCX without additional stent implantation. The technique of post-stent kissing balloons in this circumstance includes the use of non-compliant short balloons in both branches with balloon sizing according to the distal reference vessel diameters, initial dilation of the side branch balloon at moderate pressures (8 to 12 atm), followed by simultaneous inflation/deflation of both balloons (8 to 12 atm).
- Guidelines for a ***provisional second stent***: After single stent crossover stent placement, if the branch vessel origin appears sub-optimal based upon angiographic, FFR or IVUS

assessment, subsequent kissing balloon angioplasty is strongly recommended as above. If the side branch is still suboptimal in appearance despite multiple balloon inflations, based upon the following criteria: severe dissection (≥grade B), TIMI flow <3, or "severe stenosis" >70% DS (visual estimate) or IVUS MLA ≤4.0 mm^2 with plaque burden >60%, or FFR ≤0.80 – a provisional second stent should be strongly considered.

- The ***technique for a provisional second stent*** is left to the operator's best judgment and may include any the following: T-stent, TAP, mini-crush (reverse crush), or culotte bifurcation stent techniques. The use of ***kissing balloons after provisional second stents*** is strongly recommended. The technique of post-stent kissing balloons in this circumstance includes the use of non-compliant short balloons in both branches with balloon sizing according to the distal reference vessel diameters, initial dilation with the side branch balloon at high pressures (≥18 atm), followed by simultaneous inflation and deflation of both balloons (8-12 atm).
- The decision to use a ***primary two stent technique*** strategy rather than a single crossover stent technique should be considered when the side branch (usually the LCX) is large (>3 mm), with significant disease (by angiographic or IVUS assessment) and lesion length >5 mm, or when there are other special anatomic considerations (e.g. heavy calcification). Considering the anatomic variability of the distal LM bifurcation, the final decision to select a primary two stent technique strategy is left to the operator's best judgment. The choice of a particular distal bifurcation stent strategy is also left to the operator's best judgment and may include T-stenting, TAP, crush, or culotte stent techniques. A "V-stent" distal bifurcation stent approach is discouraged unless the ULMCA segment is very short, or there is focal ULMCA distal bifurcation disease which extends into the branch vessel origins and the procedure can be completed with a short segment (<3 mm) of two stents in the distal ULMCA segment.
- The use of ***kissing balloons after primary two stent technique*** is strongly recommended. The technique of post-stent kissing balloons in this circumstance includes the use of non-compliant short balloons within the margins of the stents in both branches with balloon sizing according to the distal reference vessel diameters, initial dilation of the side branch balloon at high pressures (≥18 atm), followed by simultaneous inflation/deflation of both balloons (8-12 atm).

7.3.5. Optimal PCI of Other Coronary Lesions

- For all ***"borderline or intermediate non left main lesions"*** (40-70% diameter stenosis by angiographic visual estimate), it is strongly recommended to confirm the lesion significance before treatment using FFR evaluation (preferred) or IVUS assessment (alternate). In the case of FFR this may need to be performed after successful stenting of the left main stenosis. (See Section 20) Non left main lesions which are not severe either by angiographic, IVUS or FFR assessment should not undergo PCI.
- For all non-left main lesions, ***IVUS guidance pre-treatment and assessment post-treatment*** to optimize lumen dimensions is recommended (especially for LAD lesions, with exceptions including distal lesions, tortuous vessels, or focal proximal lesions in large vessels). IVUS guidance to optimize the results of intervention in the left main segment

is strongly recommended. (See Section 20. Appendix E.)

- The liberal use of ***additional guidewires*** to protect side branches during complex angioplasty is recommended as per the operator's best judgment.
- ***Lesion preparation*** using balloons or any approved device is left to the operator's best judgment to be able to deliver the stent to the lesion and achieve full stent expansion.
- It is mandatory that only a ***XIENCE stent*** is used for all non left main coronary lesions which are stented. If the XIENCE stent is either unavailable or cannot be delivered to lesion site, it is recommended to follow standard of care at the site.
- Liberal use of short non-compliant ***post-dilation balloons*** (≥18 atm) within the stent margins of all stents is recommended to optimize luminal results, unless IVUS otherwise shows optimal expansion and lumen dimensions.
- ***Criteria for optimal PCI of ULMCA and non LM lesions*** are as follows: visual diameter stenosis <10% is acceptable (0% stenosis is strongly preferred), and there should be no edge dissections > type A, with no residual edge stenosis >20% by angiography.
- ***Specific lesion categories***, such as chronic total occlusions, bifurcation disease, diffuse lesions, thrombus-containing lesions or heavily calcified lesions should be treated according to the operator's best judgment using acknowledged best PCI practices. In situations of diffuse disease or tandem lesions it is recommended to use single long stents rather than either two shorter side-by-side or overlapping stents. A liberal staging strategy should be used, especially for subjects with complex double vessel or triple vessel disease, or if high doses of radiation and/or contrast are used in the first procedure. Refer to Section 7.3.1.

7.3.6. Intra-procedure Adjunctive Pharmacology

- Either bivalirudin, unfractionated heparin or low molecular weight heparin is acceptable (according to proper dose guidelines, adjusted for renal insufficiency). Bivalirudin is recommended for this protocol based on a recent large scale study in more than 127,000 subjects demonstrating a reduction in mortality with bivalirudin compared to heparin + GPIIb/IIIa inhibitors across a broad cross section of subjects undergoing PCI.[69] Moreover, two additional recent studies in more than 1.5 million patients and 13,500 patients have shown that bivalirudin results in a marked reduction in major bleeding compared to other anticoagulants, especially when used in concert with vascular closure devices.[70, 71] Bivalirudin should be administered as an intravenous bolus of 0.75 mg/kg and an infusion of 1.75 mg/kg/hr, started 5 minutes before PCI. In patients with an estimated creatinine clearance <60 ml/min (as calculated by the Cockcroft-Gault formula), the bolus dose of bivalirudin is unchanged, but the infusion dose should be reduced as follows:

Calculated Cl_{cr} (ml/min)	Bivalirudin Half-life (min)	Reduction in Infusion Dosage (%)
>90	25	0
60-90	22	0
30-59	34	20
10-29	57	60
<10	210	90

As a direct thrombin inhibitor, bivalirudin increases the activated clotting time (ACT). However, use of the ACT level to guide bivalirudin dosing has not been found to be helpful; i.e. high ACT levels have not correlated with bleeding, and low ACT levels have not correlated with lack of efficacy with bivalirudin. ACT levels are therefore not required in this protocol. However, it is recommended that an ACT is drawn just to be certain that the bivalirudin bolus and infusion have been delivered.

In nearly all cases, the bivalirudin infusion should be discontinued at the end of the procedure. If manual compression is to be used, femoral sheaths may be removed in 2 hours without checking an ACT or a PTT level. Of course, hemostasis may be obtained at any earlier time by use of a vascular closure device, the use of which is per operator discretion.

- If unfractionated heparin is used as a procedural anticoagulant, it is recommended that an initial bolus of 60 U/kg be administered, with subsequent boluses titrated to an ACT of 250 seconds. However, the exact manner of use of unfractionated heparin is left to the discretion of the operator and local practice. Low molecular weight heparin may be used as a procedural anticoagulant as per local practice and expertise, but is not recommended in subjects with an estimated creatinine clearance <60 ml/min. Fondaparinux is not permitted as a procedural anticoagulant. Procedural anticoagulants should usually be discontinued at the end of the procedure, but in rare cases may be continued at low dose as per physician discretion (e.g. for subjects with an indwelling intra-aortic balloon pump). The routine use of post procedural low molecular weight heparin for prophylaxis of deep venous thrombosis is not permitted.

7.3.7. GP IIb/IIIa inhibitors

GP IIb/IIIa inhibitors are strongly discouraged in subjects adequately pre-loaded with an ADP antagonist (clopidogrel, prasugrel, or ticagrelor), especially if bivalirudin is used. GP IIb/IIIa inhibitors may be used, however, in subjects with large amounts of thrombus, or for thrombotic or ischemic complications arising during the procedure (provisional or bail-out use) – e.g. for refractory thrombus or no reflow resistant to repeat balloon dilatation and intracoronary use of nitroprusside or calcium channel blockers in the absence of a mechanical complication. Provisional GP IIb/IIIa inhibitors may not be used for "soft" indications such as lesion haziness or a small dissection as their use in these situations will increase bleeding complications, without clear benefit.

7.4. Procedure – CABG

The treatment for subjects randomized to CABG is as follows:

7.4.1 Optimal CABG Requirements

- ***Conduct of Surgery.*** Coronary artery bypass grafting may be performed with or without the assistance of cardiopulmonary bypass, depending on the expertise of the center. Robotic surgery techniques may not be used.

  On-pump, surgical revascularization may be performed with an arrested heart or beating

heart strategy. Cannulation for cardiopulmonary bypass should be ascending aortic for arterial return, unless there is ascending aortic atherosclerosis or dilatation (≥4 cm in diameter), and right atrial for venous drainage. In cases of aortic atherosclerosis or dilatation, an alternate arterial cannulation strategy must be performed (see below). Cardiopulmonary bypass blood flow should be maintained at least at 2.0 liters/m^2/minute. Systemic arterial blood pressure should be at maintained at a minimum of 60 mm Hg during cardiopulmonary bypass, and should be increased in the elderly and in those with cerebrovascular disease to ensure adequate cerebral blood flow. During cardiopulmonary bypass the subject's temperature may be cooled or allowed to drift down as determined by local practice. Use of a single cross-clamp technique for subjects undergoing CABG on CPB is strongly recommended and multiple applications of an aortic clamp is strongly discouraged. When weaning from cardiopulmonary bypass it is recommended that the subject be normothermic.

Sites will be advised to follow their own insulin protocols for glucose level management intra-and postoperatively if these are consistent with the STS practice guidelines. If no guidelines exist, then sites will be advised to follow an insulin protocol similar to the one included in Appendix I.

In off-pump and on-pump beating heart surgery, coronary stabilization devices must be used. Coronary artery exposure and cardiac manipulation may be performed with apical suction positioners and/or pericardial sutures. Intravascular shunts may be used to prevent ischemia and allow for hemostasis during performance of the distal anastomoses. Proximal vessel loops may be used to obtain hemostasis during construction of the distal anastomoses or placement of intravascular shunts. Distal vessel loops are to be avoided whenever possible. The use of a humidified blower during the performance of the distal anastomoses to improve visibility is highly recommended. Every effort should be made to keep the subjects normothermic during off-pump revascularization.

After completion of proximal and distal anastomoses, graft patency assessment is strongly recommended with either transit time Doppler flow measurements or with intra-operative angiography with immunofluorescence or standard radiographic angiography. If a bypass graft is determined to be functioning poorly, the graft should be evaluated and revised.

- ***Aortic Assessment.*** It is strongly recommended that intra-operative assessment of the ascending aorta by transesophageal echocardiography and/or epi-aortic echocardiography be performed. Aortic assessment should be performed prior to manipulation, cannulation, or clamping of the ascending aorta. If ascending aortic atherosclerosis or dilatation is identified, a surgical strategy must be used that does not manipulate, cannulate, or clamp the atherosclerotic or dilated aorta. For on-pump revascularization a strongly recommended option is alternate site arterial cannulation (axillary or femoral artery) with no ascending clamping, and for off-pump revascularization a strategy with a no-touch aortic technique should be implemented. Hypothermic circulatory arrest with ascending aortic replacement should be used as a last resort for subjects with ascending aortic atherosclerosis. Locally approved proximal aortic connectors and facilitators (that do not involve aortic clamping) may be used to perform proximal anastomoses.
- ***Cardioplegia for On-Pump, Arrested Heart Surgery.*** Intermittent, cold blood cardioplegia is the preferred myocardial protection strategy for on-pump, arrested heart surgery. However, intermittent cold crystalloid cardioplegia or continuous warm blood cardioplegia is allowed if local standard of care. Cold blood cardioplegia should be administered initially at 10 to 15

cc/kg to arrest and protect the heart, and then re-administered every 20 to 30 minutes at a minimum of 5 cc/kg. Delivery of cardioplegia should be initially antegrade to arrest the heart in the absence of important aortic insufficiency. If important aortic insufficiency is present and antegrade delivery of cardioplegia is not feasible, cardioplegia should be administered retrograde to arrest the heart and additional right ventricular protection methods should be performed, such as ice slush to the surface of the right ventricle and cardioplegia administered via the completed bypass graft to the right coronary artery system. During the remainder of the cross-clamp period, cardioplegia may be administered antegrade, retrograde via a coronary sinus catheter, and/or via completed saphenous vein grafts. If available, a nutrient rich hot shot given prior to removing the aortic cross-clamp is highly recommended.

- ***Conduit Selection.*** Arterial grafts are the preferred conduits for coronary revascularization. It is strongly recommended for all subjects to have the left internal thoracic artery used to graft the left anterior descending coronary artery system. In most cases this may be the left internal thoracic artery. In subjects less than seventy years of age, additional arterial grafts are highly recommended. The right internal thoracic artery is the preferred second arterial graft, and should be used to graft the next most important and stenotic coronary artery system. It may be used as an in-situ graft or free graft. Other arterial grafts that may be used in this study include the radial, in-situ gastroepiploic, and free inferior epigastric arteries. When using the radial artery as a bypass graft, it should be preferentially used to revascularize a left coronary artery system branch with severe (>70%) stenosis. The in-situ gastroepiploic artery may be used to graft severely stenotic (preferentially occluded) branches of the right coronary artery or posterior descending of a left dominant system. The inferior epigastric artery is best used as a "Y" or "T" graft.

  Saphenous vein grafts may be used for coronary revascularization in the study. Since internal thoracic artery grafting of the left anterior descending is standard of care for surgical revascularization, saphenous veins may be used to bypass the left anterior descending only when the left internal thoracic is an inadequate conduit.

Although arterial grafts are the preferred conduit, each center should use a conduit revascularization strategy that they are experienced and comfortable performing. When selecting conduits, the effects of native coronary competitive blood flow must be considered.

Details of non-use of arterial grafts and non-use of internal mammary artery grafts including the reasons for such non- use will be recorded in the EXCEL trial eCRF.

- ***Intraoperative Transesophageal Echocardiography Assessment.*** It is highly recommended that intraoperative transesophageal echocardiography be performed prior to cannulation to assess left ventricular function, cardiac valves, and ascending aorta. For subjects with intraoperatively identified important valve dysfunction or aortic aneurysmal disease, the surgeon may repair or replace the valve or aorta as deemed necessary. Intraoperatively, after coronary revascularization is complete, it is strongly recommended that transesophageal echocardiography be used to assess for new ventricular wall abnormalities. If new ventricular wall abnormalities are identified, then the bypass graft supplying that myocardial area should be evaluated and revised if necessary.

7.5. Completeness of Revascularization

All ischemic myocardial areas, such as those subtended by coronary arteries with visually assessed ≥50% diameter stenosis, should be revascularized.

For subjects randomized to PCI: In prior PCI vs. CABG trials, the determination of and execution of "completeness of revascularization" strategy has been an important consideration. In this trial, the philosophical approach is to perform PCI of all significant ischemia-producing lesions as opposed to all lesions which appear to be significant by angiographic visual assessment, especially if the angiographic lesions are 40-70% diameter stenosis. Moreover, it is strongly recommended that PCI is performed only in ischemia-producing lesions, in most cases not treating non ischemia-producing lesions. Ischemia-producing lesions are defined as those which (1) are ≥70% angiographic diameter stenosis (visually assessed), or if <70% diameter stenosis, are either (2a) associated with noninvasive functional evidence of ischemia in the territory of the lesion (not explained by another coronary stenosis), and/or (2b) intra-procedure FFR ≤0.80 (note FFR procedure guidelines), and/or (2c) IVUS minimal luminal area ≤4.0 mm^2 (for non left main lesions) with plaque burden >60% (note IVUS procedure guidelines).

For subjects randomized to CABG: Since all subjects in this study have important ULMCA stenosis, according to contemporary surgical standards, all subjects should have at least one bypass graft to the left anterior descending coronary artery system and a second graft to circumflex coronary artery system. All coronary arteries with ≥50% stenosis and ≥1.5 mm in diameter should be revascularized.

7.6. Post-Procedure Assessments and Medications

Following the procedure, mandated medication is specified below; beyond that, the subject will be treated in accordance with hospital standard of care.

7.6.1. Laboratory Assessments

The laboratory assessments need to be obtained according to the Schedule of Events included in Section 7.1.

7.6.2. Post-PCI Medications

Aspirin. Mandatory dosing with aspirin will be ≥75 mg post-PCI per day in the hospital, and then aspirin ≥75 mg per day indefinitely. Daily aspirin must be given for the duration of the trial. Aspirin must not be discontinued for CABG or other reasons unless absolutely necessary.

ADP antagonists. Chronic daily ADP antagonist therapy is mandated for at least one year after PCI in subjects who received a ULMCA DES, with the choice of agent left to the discretion of the investigator, either:

- clopidogrel 75 mg per day, or 150 mg per day for 7-30 days then reduced to 75 mg per day, unless clopidogrel hyporesponsive;
- prasugrel 10 mg per day (5 mg per day may be used in patients <60 kg in body weight or in other circumstances, but in general the 5 mg per day prasugrel dose is discouraged given

minimal clinical experience with this prescribed amount);

- ticagrelor per labeling and recommended guidelines if approved by the local regulatory authorities during the treatment period of this protocol.

"Hypo-responders" to anti-platelet therapy based on point of care testing are managed according to local standard of care. A daily ADP antagonist must be given for at least one year in the absence of major complications, and is recommended for the duration of the trial in the absence of major bleeding or other complications.

ADP antagonists must not be discontinued within the first year after DES implantation unless absolutely necessary for major bleeding, major trauma, or major surgery necessitating discontinuation of antiplatelet therapy (e.g. intracranial surgery). Many surgeries can safely be performed while the subject is on dual antiplatelet therapy. If a subject on dual antiplatelet therapy requires surgery, strong consideration should be given to performing the surgery without antiplatelet agent discontinuation. If a particular dual antiplatelet therapy must be discontinued, a GP IIb/IIIa bridging strategy up until the time of surgery may be considered, followed by re-loading of the ADP antagonist as soon as possible post surgery.

Statin therapy. See Section 22.2 for recommendations for statin use after PCI.

Other medications. For medication use post PCI, see Section 22.2.

7.6.3. Post-CABG Medications

Aspirin (≥75 mg) must be given within six hours after surgery intravenously, orally, rectally, or via a nasogastric tube if there is no important bleeding (≤50 cc/hr), and daily for the duration of the trial. All subjects should be treated postoperatively with daily statins and beta-blockers, unless contraindicated, see Section 22.2.

Beta-blockers are recommended for prophylaxis of post-operative atrial fibrillation. Amiodarone may be considered for subjects in whom beta-blockers are contraindicated and as therapy for postoperative sinus rhythm control. For subjects receiving amiodarone prophylaxis for atrial fibrillation, amiodarone should be continued for five days postoperatively.

It is recommended that ACE inhibitors be given in subjects with depressed left ventricular function.

Clopidogrel is not required but may be administered as per local standard of care in subjects with saphenous vein grafts or in those who underwent off-pump surgery.

7.6.4. Post-Operative Atrial Fibrillation – CABG

Post-operative atrial fibrillation should be treated with either rate control and anticoagulation, or chemical or electrical cardioversion. Subjects being treated with rate control and anticoagulation should be treated with warfarin and may be bridged with heparin as per local protocol. Subjects undergoing cardioversion may undergo cardioversion without anticoagulation if the duration of atrial fibrillation is less than 36 hours. Subjects undergoing cardioversion where the duration of atrial fibrillation is greater than 36 hours should be adequately anticoagulated with either heparin or warfarin as per local practice. If atrial fibrillation recurs or is resistant to cardioversion,

anticoagulation with warfarin with or without heparin bridging is strongly recommended. Warfarin anticoagulation should be continued as per local practice, but at a minimum until atrial fibrillation has resolved. Subjects on warfarin anticoagulation for atrial fibrillation should be maintained with an INR of 2.0 to 2.5.

8. EVALUATION OF SAFETY AND EFFECTIVENESS

Safety and efficacy will be evaluated at several timepoints throughout the trial as described in the Schedule of Events.

8.1. Laboratory Tests, ECGs, and Other Measures

Tests will be performed periodically on all subjects as follows (Section 7.1, Schedule of Events):

8.2. Clinical Follow-up

Subjects will have clinical follow-up as a telephone contact or office visit, at the time points listed below. Day 0 is the date of the randomization assignment which can be on the same date or earlier than the date of the randomized procedure. All adverse events (AE) will be recorded from Day 0. Patient follow-up will occur from the day of randomized procedure as shown below. Office visits are strongly recommended for the annual clinical follow-up. If that is not possible, phone contact with subject or subject's local physician is acceptable. As a last resort, notification of death by civil registry will be accepted.

- 30 ± 7 days (office visit preferred)
- 6 months ± 14 days (telephone contact or office visit)
- Visits at 1, 2, 3, 4, and 5 years with windows of -30 days, +60 days (office visit preferred)
- Potential visits:
  - Yearly visits at 6, 7, 8, 9, and 10 years with window of-30 days, +60 days (office visit preferred)

All efforts must be made to obtain follow-up information on subjects who have visited a clinic or hospital, underwent procedures or have been treated for adverse events in a non-study-related hospital(s). Non study hospital related material will be collected and reviewed at the study coordinating centers. All follow-up angiograms must be collected (whether at the study hospital or an outside hospital) and sent to the angiographic core laboratory for independent analysis.

The following data will be collected at 30 days, 6 mo, 1 year, 2 years, 3 years, 4 years and 5 years follow-up time points (and potential 6-10 year visits).

- Data regarding adverse events (with related laboratory tests results), including but not limited to death, MI, stroke, TIA, bleeding, renal insufficiency, repeat revascularization procedures, repeat hospitalization for any reason, ECGs, details of any subsequent repeat coronary angiography and results of such, if applicable.

- Details of any subsequent coronary interventions (for example, repeat PCI or CABG). The physician must record in the source documents whether a revascularization was carried out during the period between the index procedure and the follow-up visit. The physician must then document whether the revascularization was based on clinical signs and symptoms and available ancillary data and whether the procedure was ischemia driven according to the definition specified in this protocol (Refer to Section 16, Appendix A).
- Compliance to protocol-required medications
- Use and changes in chronic concomitant medications (Refer to Section 16, Appendix A).

Additional Follow-up Visits

Additional subject visits may occur as clinically warranted. The same information as specified in Section 8.2, Clinical Follow-up, will be collected.

To support the 3 year endpoint analysis, clinical sites will be asked to obtain the 3 year adverse event status on all subjects. Therefore, an adverse event (AE) check should be performed in order for data up to 3 years (365 days*3=1095 days) from date of randomization to be established equally in both arms. The AE check will commence the day after the 2 year follow-up of the last subject enrolled. At this time, all clinical sites must contact subjects to collect AE information if one of the following has occurred:

- Subject had a 3 year visit >28 days prior to 1095 days; or
- Subject has completed their 2 year visit but has not yet completed the 3-year visit, and follow-up is beyond 730+28 days.

For subjects who have completed visits at ≥ (1095 – 28= 1067) days, no further contact is needed concerning the AE check.

8.3. Guidelines for Follow-up Non-Invasive Testing, Angiography and Reintervention

8.3.1. Follow-up Non-Invasive Testing

The decision whether to perform routine stress testing after ULMCA treatment should depend on the symptomatic state of the subject, as follows:

- The asymptomatic subject. Routine stress testing is strongly discouraged in the asymptomatic subject.
- The subject with atypical symptoms. Routine stress testing may be performed in the subject with atypical symptoms according to the discretion of the treating physicians, or such subjects may be treated conservatively.
- The subject with typical angina or other progressive cardiac symptoms or signs. Subjects with typical cardiac symptoms or evidence of progressive heart disease should in most cases undergo repeat cardiac catheterization; stress testing should not be performed, especially in the subject with possible recurrent disease in the left main stem.

Because of the risk of exercise-induced stent thrombosis, in no case should routine follow-up exercise stress testing be performed within 8 weeks after stent implantation.

Follow-up echocardiography (without exercise) is not mandated by protocol but may be performed at any time during follow-up per the discretion of the treating physicians. Similarly, multislice CT scanning but may be performed at any time during follow-up per the discretion of the treating physicians. However, the use of MSCT in accurately determining in-stent restenosis has not been validated, and thus should in general not be used to guide decision making. MSCT may be useful, however, in determining bypass graft patency.

8.3.2. Follow-up Angiography

Routine follow-up angiography in the asymptomatic subject is not permitted in this study. Prior studies have not demonstrated a benefit of routine follow-up angiography after ULMCA disease, and routine follow-up angiography can result in non clinically indicated revascularization procedures (the "oculostenotic reflex").[48,49] In the SYNTAX trial, routine follow-up angiography was performed at 15 months in 268 surviving asymptomatic subjects with ULMCA disease randomized to PCI with TAXUS PES vs. CABG. In the PCI group, the mean late loss in the left main stem with PES was only 0.2 mm, and thrombus was present in only 2 subjects (1%). The composite rate of death, MI, stroke or repeat revascularization among PCI subjects undergoing routine angiography was 13% at 15 months (compared to 15.8% in all PCI subjects at 12 months, including those who were symptomatic). Numerous prior studies of drug-eluting stents in subjects with ULMCA disease have demonstrated very low rates (<0.5%) of left main stent thrombosis,[25, 72, 73] and no prior study of routine angiographic follow-up has been shown to improve outcomes after drug-eluting stents. Routine angiographic follow-up after left main intervention is not recommended by the current ACC/AHA PCI guidelines.[27]

For subjects who develop atypical chest pain or other symptoms that might reflect ischemia, it is strongly recommended that a nuclear stress test, echocardiographic stress test, or MSCT scan be performed, with subsequent angiography only for positive non-invasive results. Valid indications for follow-up angiography in the present study include any of the following:

- the recurrence of typical angina;
- a positive noninvasive study indicating moderate or severe ischemia, a significant decline in left ventricular function or progressive valve disease;
- progressive heart failure or unstable arrhythmias;
- cardiac arrest;
- or other clinical conditions for which the treating physician believes follow-up angiography is indicated.

The reasons for follow-up angiography will be closely tracked in the case report form.

8.3.3. Repeat Intervention (PCI or CABG)

In subjects who do undergo follow-up angiography, repeat PCI or CABG may only be performed with evidence of ischemia, requiring one of the following to be present:

- ≥70% diameter stenosis of the treated or new lesions by visual angiographic assessment
- In the case of a visually estimated diameter stenosis of ≥50% to <70%, either
  - evidence of definite ischemia in the territory of the diseased vessel by prior non-invasive stress testing with imaging evaluation showing ischemia in the questioned myocardial territory, and/or
  - IVUS minimal stent area ≤6.0 mm^2 (see IVUS procedure guidelines) for left main lesions or ≤4.0 mm^2 for non-left main lesions, and/or
  - intra-procedure FFR ≤0.80 (see FFR procedure guidelines).

IVUS is preferred for assessment of left main lesions, and FFR is preferred for assessment of non-left main lesions. In particular, after left main stent implantation, the ostial LCX may often appear significantly or even severely stenosed in the absence of symptoms or ischemia ("pseudo-stenosis"). All subjects with a suspected ostial LCX stenosis, regardless of the degree of angiographic severity (unless occluded), are highly recommended to have demonstrated an FFR ≤0.80 in the LCX prior to repeat revascularization, unless there is unequivocal evidence of lateral wall ischemia on non-invasive stress testing.

If repeat revascularization is to be performed, the decision whether to perform PCI or CABG should be made according to the discretion of the treating physicians, ideally by local Heart Team consensus.

8.4. Adverse Events

An adverse event (AE) is any untoward medical occurrence, unintended disease or injury, or untoward clinical signs (including abnormal laboratory findings) in subjects, users or other persons, whether or not related to the investigational medical device.

NOTE 1: This definition includes events related to the investigational medical device or the comparator.

NOTE 2: This definition includes events related to the procedures involved.

NOTE 3: For users or other persons, this definition is restricted to events related to investigational medical devices.

An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not related to the medicinal (investigational) product.

Stable, chronic, pre-existing conditions are not to be reported as AEs. However, worsening of a pre-existing condition that occurs after a subject's participation in the trial is considered an AE and must be reported as such.

Planned procedures (scheduled prior to the index procedure) that occur after the index procedure are not considered AEs and are not to be reported as such. Complications from such procedures, however, are considered AEs and must be reported.

Non-cardiac related abnormal laboratory values will not be considered AEs unless:

- the investigator determined that the value is clinically significant,

- the abnormal lab value required intervention, or
- the abnormal lab value required subject termination from the study.

The investigator should report the event(s) to the IRB/EC according to the institution's reporting requirements.

Adverse Event Reporting

The Investigator will monitor the occurrence of adverse events for each subject during the course of the study. For the purpose of this protocol, the reporting of adverse events begins directly after randomization. All adverse events (AEs) reported by the subject, observed by the Investigator, or documented in medical records will be listed on the Adverse Event Case Report Forms.

Adverse events will be monitored throughout the course of the

study. Serious Adverse Events

If the adverse event meets any of the criteria below, it is regarded as a serious adverse event (SAE):

a) Led to a death,
b) Led to a serious deterioration in health that either:
1) Resulted in a life-threatening illness or injury, or
2) Resulted in a permanent impairment of a body structure or a body function, or
3) Required in-patient hospitalization or prolongation of existing hospitalization, or
4) Resulted in medical or surgical intervention to prevent life threatening illness or injury or permanent impairment to a body structure or a body function.

c) Led to fetal distress, fetal death or a congenital abnormality or birth defect.
d) An important medical event that may not result in death, be life-threatening, or require hospitalization but may be considered serious when, based upon appropriate medical judgment, may jeopardize the patient or subject and/or may require intervention to prevent one of the outcomes listed in this definition.

NOTE 1: This includes device deficiencies that might have led to a serious adverse event if a) suitable action had not been taken or b) intervention had not been made or c) if circumstances had been less fortunate. These are handled under the SAE reporting system.
NOTE 2: A planned hospitalization for pre-existing condition, or a procedure required by the Clinical Investigation Plan, without a serious deterioration in health, is not considered to be a serious adverse event.

The investigator will report serious adverse events to the IRB/EC according to the institution's reporting requirements.

8.4.1. Serious Adverse Event Reporting

Serious adverse events and device deficiencies must be reported no later than 3 calendar days from

the site becoming aware of the event or as per the investigative site's local requirements if the requirement is more stringent than those outlined. The date the site staff became aware of the serious adverse event must be recorded in the source document. The Investigator will further report the event to the local IRB/EC according to the institution's IRB/EC reporting requirements.

Serious adverse events should be reported on the SAE Notification Form in the occurrence that the electronic data capture (EDC) system is not available. This does not replace the EDC reporting system. All information must still be entered in the EDC system once the system is back to normal function.

Serious adverse events that occurred in the user or persons other than the study subject should not be entered in the EDC system, however they need to be reported on the fax notification form titled SAE Notification Form.

8.4.2. Unanticipated Serious Adverse Device Effects (USADE)

Unanticipated serious adverse device effect (USADE) refers to any serious adverse effect on health or safety or any life-threatening problem or death caused by, or associated with, a device, if that effect, problem, or death was **not previously identified in nature, severity, or degree of incidence** in the investigational plan or application (including a supplementary plan or application), or any other unanticipated serious problem associated with a device that relates to the rights, safety, or welfare of subjects.

Abbott Vascular requires the Investigator to report any USADE to the sponsor within 3 calendar days of the investigator's knowledge of the event and to the IRB/EC per IRB/EC requirements.

8.4.3. Device Relationship

Determination of whether there is a reasonable possibility that an investigational product or device caused or contributed to an adverse event is to be **determined by the Investigator** and recorded on the appropriate CRF form. Determination should be based on assessment of temporal relationships, biologic plausibility, association (or lack of association) with underlying disease, and presence (or absence) of a more-likely cause.

8.5. Safety Monitoring – Data Safety Monitoring Board (DSMB)

The Data Safety Monitoring Board (DSMB) is useful to ensure safety by reviewing cumulative data from the clinical trial at pre-scribed intervals for the purpose of safety guarding the interest of trial participants. The DSMB will serve as an advisory role. The composition, guiding policies, and operating procedures governing the DSMB are described in a separate DSMB charter. Based on safety data, the DSMB may recommend a modification to the protocol or that the sponsor stops the clinical trial/investigation. All final decisions regarding clinical trial/ investigation modifications, however, rest with the Sponsor.

8.6. Event Adjudication – Clinical Events Committee (CEC)

The Clinical Events Committee is comprised of qualified physicians who are not investigators in the trial. The Clinical Events Committee is responsible for adjudicating specified clinical endpoints based on the specific criteria used for the categorization of clinical events in the trial. The composition, guiding policies, and operating procedures governing the CEC are described in a separate CEC Manual of Operations.

9. STATISTICAL DESIGN AND ANALYSIS

This section describes the statistical considerations and analysis plans for the EXCEL trial. The study is powered for both the primary and the 2 major secondary endpoints through an anticipated median follow-up of three years.

In general, binary variables will be summarized using counts, percentages, and exact 95% confidence intervals. For continuous variables, percentiles, means, standard deviations, and 95% confidence intervals for the mean using the Gaussian approximation will be calculated. Time to event data will be summarized using Kaplan-Meier estimates and 95% confidence intervals. Kaplan-Meier curves will be constructed for the primary and major secondary endpoints and differences in treatment will be tested using the difference in Kaplan-Meier failure rates on all available data through 3-year follow-up at the time of the analysis (event driven analysis). All primary analyses will be measured from randomization onward and will be by intention to treat according to randomized assignment, regardless of what therapy was actually received. A sensitivity analysis will be performed on the primary endpoint defined from the index procedure date. The composite of all-cause mortality, MI, stroke (mRS≥1 and increase by ≥1 from baseline), or unplanned revascularization for ischemia at 3 years post randomization will also be classified as a sensitivity analysis. Secondary analyses will be performed for the per protocol (PP) population (see also Section 9.1.5.2).

9.1. Randomized Cohort

9.1.1. Primary Endpoint

The primary endpoint is a composite of all-cause mortality, MI or stroke (mRS≥1 and increase by ≥1 from baseline) at 3 years post randomization. The primary endpoint will be estimated via Kaplan-Meier failure rate measured from randomization and Greenwood's formula for estimating the standard error. The primary endpoint analysis will be conducted at the time when approximately 50% of the patients have reached the 3-year follow-up AND all patients have reached the 2-year follow-up, whichever time point is latest. All available data through 3-year follow-up will be used.

The analysis will also be performed at 3 years post index procedure, as a sensitivity analysis.

9.1.2. Major Powered Secondary Endpoints

The major powered secondary endpoints are:

- The composite of all-cause mortality, MI, or stroke (mRS≥1 and increase by ≥1 from baseline) at 30 days post randomization. This powered endpoint will be estimated via Kaplan-Meier failure rate measured from randomization and Greenwood's formula for estimating the standard error.
- The composite of all-cause mortality, MI, stroke (mRS≥1 and increase by ≥1 from baseline), or unplanned revascularization for ischemia at 3 years post randomization. This powered endpoint will be estimated via Kaplan-Meier failure rate measured from randomization and Greenwood's formula for estimating the standard error. The analysis will be conducted at the time when approximately 50% of the patients have reached the 3-year follow-up AND all patients have reached the 2-year follow-up, whichever time point is latest. All available data through 3-year follow-up will be used.

Sensitivity analyses will also be performed on all of the endpoints above from the index procedure date. The composite of all-cause mortality, MI, stroke (mRS≥1 and increase by ≥1 from baseline), or unplanned revascularization for ischemia at 3 years post randomization will also be classified as a sensitivity analysis.

9.1.3. Other Secondary Endpoints

The primary endpoint composite event rate (all-cause death, MI or stroke) and powered secondary endpoints at all time points other than median of 3 years will be analyzed as other secondary endpoints.

Time points for all other secondary endpoints, unless specified otherwise, are in-hospital, 30 and 180 days, 1, 2, 3, 4 and 5 years post-procedure.

Survival analysis techniques will be used to analyze the time-to-event variables. All of these analyses will be performed for these endpoints with time defined from date of randomization and (as a sensitivity analysis) from date of index procedure.

The other secondary endpoints are:

- All-cause mortality
    - Cardiac death
    - Non-cardiac death
- All myocardial infarctions (periprocedural, spontaneous, Q-wave and non Q-wave) including large and small MIs
- Protocol-defined MI
- MI adjudicated per Universal Definition
- Protocol-defined stroke

- All stroke (all, ischemic and hemorrhagic)
- Disability following stroke event at 90 days± 2 weeks
- Ischemia-driven revascularization
    - Ischemia-driven target lesion revascularization (TLR)
    - Ischemia-driven target vessel revascularization (TVR)
    - Ischemia-driven non target vessel revascularization (Non-TVR)
- All revascularization (ischemia driven and non-ischemia driven)
    - All target lesion revascularization (TLR)
    - All target vessel revascularization (TVR)
    - All non target vessel revascularization (non-TVR)
- Complete revascularization at baseline procedure, anatomic and functional (see Section 19. Appendix D)
- Stent thrombosis (ARC definition) symptomatic or asymptomatic
- Symptomatic graft stenosis or occlusion (since this requires angiographic documentation, this endpoint will be compared to symptomatic ARC definite stent thrombosis)
- Requirement for blood product transfusion
- Bleeding complications
    - Requirement for blood product transfusion
    - TIMI scale (major or minor)
    - BARC scale
- Time from randomization to procedure; time from procedure to discharge; ICU days; time from procedure to return to work
- Major adverse events (MAE) defined as composite of the following components. MAE will be assessed in-hospital and at 30 days only.
    - death
    - myocardial infarction
    - stroke
    - transfusion of ≥2 units of blood
    - TIMI major or minor bleeding
    - major arrhythmia
    - unplanned coronary revascularization for ischemia
    - any unplanned surgery or therapeutic radiologic procedure
    - renal failure
    - sternal wound dehiscence
    - infection requiring antibiotics for treatment
    - intubation for > 48 hours
    - post-pericardiotomy syndrome

9.1.4. Subgroup Analyses

Subgroup analysis will be performed in the intent-to-treat population. However, these comparisons are not powered for hypothesis testing, and the analysis results are considered exploratory. The proposed subgroups are listed in Section 21.2.

9.1.4.1. Gender-specific Subgroup Analysis

In particular, the primary and powered secondary endpoints will be further examined for differences between males and females. A test for interaction will be performed to evaluate the potential differences in treatment effect for these two groups. Details of the analysis will be specified in the SAP.

9.1.5. Analysis Populations

Hypothesis testing for the primary endpoint and the major powered secondary endpoints will be performed based on the intent-to-treat (ITT), the as-treated and per-protocol (PP) populations. Other endpoints, including the Economic Outcomes/Cost-Effectiveness Analysis will be performed on both the ITT and PP populations. Adverse events collected for safety will be summarized for the ITT population only.

9.1.5.1. Intent-to-Treat Population

The intent-to-treat population will consist of all subjects randomized to the study, regardless of the treatment actually received. Subjects will be analyzed in the treatment group to which they were randomized. This is the primary analysis population.

9.1.5.2. Per-Protocol Population

The per-protocol population consists of subjects with the following characteristics:

- subjects who received the initial treatment to which they were randomized
- assigned treatment must have been for their first revascularization
- no major protocol violations (defined in the statistical analysis plan)

9.1.5.3. As-Treated Population

The as-treated population consists of subjects who received a protocol defined treatment. Subjects will be included in the treatment arm corresponding to the first study treatment actually received.

9.1.6. Sample Size Calculations and Assumptions

Sample size calculations for the Com-Nougue approach[74], which utilizes the difference in Kaplan-Meier estimates, were derived using simulations. Sample size calculations were performed using the PASS 2008 software.[75]

9.1.6.1. Primary Endpoint: Composite of All-Cause Mortality, MI, or Stroke (mRS≥1 and increase by ≥1 from baseline) at 3 years

The primary endpoint of all-cause mortality, MI or stroke will be evaluated using the difference in Kaplan-Meier failure rates measured from randomization in the intent-to-treat population using all available data. The hypothesis test is designed to show non-inferiority of PCI to CABG for the primary endpoint with a one-sided alpha of 0.025. The null (H_0) and alternative (H_A) hypotheses are:

$$H_0: F_{PCI\text{-}PE}(T) - F_{CABG\text{-}PE}(T) \geq \Delta_{PE}$$

$$H_A: F_{PCI\text{-}PE}(T) - F_{CABG\text{-}PE}(T) < \Delta_{PE.}$$

$F_{PCI\text{-}PE}$ and $F_{CABG\text{-}PE}$ are the Kaplan-Meier estimates of failure rate of the primary endpoint at 3 years in the PCI and CABG arms, respectively. Δ_{PE} is the non-inferiority margin for the primary endpoint.

The sample size calculation is based on the following assumptions:

- primary endpoint event rate is 11% in each treatment arm at 3 years (using 3-year event rates from the SYNTAX trial, the most contemporary reference dataset)
- minimum time to follow-up is 2 years
- median time to follow-up is approximately 3 years
- 8% lost to follow-up at 3 years
- non-inferiority margin Δ_{PE} = 4.2%
- one-sided alpha = 0.025
- accrual time of 29 months

A sample size population of 1900 subjects (~950 per arm) will provide approximately 80% power to demonstrate non-inferiority of PCI to CABG.

For the PCI arm to pass the non-inferiority test for the primary endpoint of the composite of death, MI and stroke at 3 years, the maximum allowable event rate would be approximately 12.1%. Comparing to the 11% event rate of the CABG arm, the average difference per year is only ~ 0.4%. The criteria for an acceptable non-inferiority delta has been carefully considered by the principal investigators, executive committee, PCI and surgical committees and country leaders of this protocol, representing more than 100 physicians not related to the study Sponsor, 50% of whom are interventional cardiologists and 50% of whom are cardiac surgeons. A non- inferiority margin of 4.2% for the primary endpoint in this protocol has been agreed upon by this balanced study leadership to represent clinical therapeutic interchangeability[76] between PCI and CABG, given the substantially lower peri-procedural morbidity of PCI, the likelihood for fewer strokes with PCI, especially in the first 30 days to 1 year (which in most cases is a clinically more important endpoint than MI, although the trial will not be powered to demonstrate a reduction in stroke), and the likely higher rate of subsequent unplanned revascularization for PCI.

If non-inferiority is met, superiority testing will be performed with a one-sided alpha of 0.025.

The null (H_0) and alternative (H_A) hypotheses for the superiority test are:

$$H_0: F_{PCI\text{-}PE}(T) - F_{CABG\text{-}PE}(T) \geq 0$$

$$H_A: F_{PCI\text{-}PE}(T) - F_{CABG\text{-}PE}(T) < 0.$$

Using a one-sided alpha of 0.025, assuming 8% lost to follow-up at 3 years, the trial will have approximately 80% power to demonstrate superiority with a difference of 3.84% of PCI arm to CABG arm (e.g. 7.16% in PCI arm vs. 11% in CABG arm).

9.1.6.2. Major Powered Secondary Endpoints

Composite of All-Cause Mortality, MI, or Stroke (mRS≥1 and increase by ≥1baseline) at 30 Days

The first major powered secondary endpoint of all-cause mortality, MI or stroke at 30 days will be evaluated using the difference in Kaplan-Meier failure rates measured from randomization in the intent to treat population using all available data. Loss to follow-up is considered to be minimal at this time point. This endpoint is a major powered secondary endpoint, based on data from the SYNTAX trial, and has historical relevance. The hypothesis is designed to show non-inferiority of PCI to CABG with a one-sided alpha of 0.05. The null (H_0) and alternative (H_A) hypotheses for non- inferiority of this powered secondary endpoint are:

$$H_0: F_{PCI\text{-}PE}(T) - F_{CABG\text{-}PE}(T) \geq \Delta_{PE}$$

$$H_A: F_{PCI\text{-}PE}(T) - F_{CABG\text{-}PE}(T)_{\text{-}PCI} < \Delta_{PE}.$$

$F_{PCI\text{-}PE}(T) - F_{CABG\text{-}PE}(T)$ are the Kaplan-Meier estimates of failure rates measured from randomization at 30 days between CABG and PCI andΔ_{PE} is the non-inferiority difference for this powered secondary endpoint.

The power calculation is based on the following assumptions:

- composite rate is 3.0% in each treatment arm at 30 days
- non-inferiority $\Delta_{PE} = 2\%$
- one-sided alpha = 0.05
- accrual time = 29 months

A sample size population of 1900 subjects (~ 950 per arm) will provide approximately 80% power to demonstrate non-inferiority between the two treatment groups.

The second major powered secondary endpoint has been defined to provide direct comparison to the results of the SYNTAX trial.

Composite of All-Cause Mortality, MI, Stroke (mRS≥1 and increase by ≥1 from baseline), or Unplanned Revascularization for Ischemia at 3 Years

The powered secondary endpoint of the composite of all-cause mortality, MI, stroke, or unplanned revascularization for ischemia will be evaluated using the difference in Kaplan-Meier failure rates from randomization to 3 years between CABG and PCI in the intent to treat population using all

available data. This endpoint is a powered endpoint, based on data from the SYNTAX trial, and has historical relevance, although in terms of clinical relevance is not necessarily considered weighted greater than is quality of life measures or other secondary endpoints. The hypothesis is designed to show non-inferiority of PCI to CABG with a one-sided alpha of 0.05. The null (H_0) and alternative (H_A) hypotheses for non-inferiority of this powered secondary endpoint are:

$$H_0: F_{COMP\text{-}PCI}(T) - F_{COMP\text{-}CABG}(T) \geq \Delta_{COMP}$$

$$H_A: F_{COMP\text{-}PCI}(T) - F_{COMP\text{-}CABG}(T) < \Delta_{COMP.}$$

$F_{COMP\text{-}PCI}(T) - F_{COMP\text{-}CABG}(T)$ is the difference in failure rates at 3 years between CABG and PCI and Δ_{COMP} is the non-inferiority margin for this powered secondary endpoint.

Assuming the following:

- major secondary endpoint event rate is 22% in each treatment arm at 3 years (using 3-year event rates from the SYNTAX trial)
- median time to follow-up is approximately 3 years
- minimum time to follow-up is 2 years
- 8% lost to follow-up at 3 years
- non-inferiority $\Delta_{COMP} = 8.4\%$
- one-sided alpha = 0.05
- accrual time of 29 months

then a sample size of 1900 subjects (~950 per arm) will provide an approximately 99% power to demonstrate non-inferiority of CABG to PCI using the Com-Nougue approach.

9.1.7. Statistical Analysis

9.1.7.1. Analysis of Primary and Major Powered Secondary Endpoints

The primary and the two major powered secondary endpoints will be analyzed for the intent-to-treat population, the as-treated population and the per-protocol population. Formal hypothesis testing will be based on the intent-to-treat population. Hierarchical testing will be employed following the order below:

- Primary endpoint-All cause mortality, MI or Stroke from randomization to median follow-up of 3 years (non-inferiority)
- First major powered secondary endpoint-All cause mortality, MI or Stroke from randomization to 30 days
- Second major powered secondary endpoint-All cause mortality, MI, Stroke or Unplanned Revascularization for Ischemia from randomization to median of 3 years
- Primary endpoint – All cause mortality, MI, or stroke from randomization to median follow-up of 3 years (superiority)

Formal hypothesis testing of the first major powered secondary endpoint will occur only if non-inferiority for the primary endpoint is met. Simultaneous formal hypothesis testing of the second major powered secondary endpoint and the superiority test of the primary endpoint will occur only if non-inferiority for the first major powered secondary endpoint is met.

9.1.7.2. Analysis of Other Endpoints

For binary variables, counts, percentages, and exact 95% confidence intervals will be calculated. For continuous variables, percentiles, means, standard deviations, and 95% confidence intervals for the mean using the Gaussian approximation will be calculated. P values will be reported for descriptive purposes only. Logistic regression and ANOVA models will be used to determine if the data exhibit any trends. For time-to-event variables, such as stent thrombosis, survival curves will be constructed using Kaplan-Meier estimates, and log-rank test or Cox proportional hazard model results will be displayed for hypothesis-generating purposes only.

9.1.8. Procedures for Accounting for Missing Data

Although every effort will be made to minimize the amount of missing data, some loss to follow-up is unavoidable. For time-to-event hypothesis tests, subjects will be censored at their last known follow-up. The percentage of subjects with follow-up in each treatment arm will be summarized. The reasons for loss to follow-up will be collected and summarized. All of these comparisons will be performed using descriptive analyses only.

9.1.9. Measures Taken to Minimize Bias

9.1.9.1. Randomization

Assessment of eligibility must be done prior to randomization. Suitable subjects will be randomized to procedure with PCI or CABG in a ratio of 1:1. Randomization will be stratified by medically treated diabetes mellitus (diabetic vs. non-diabetic), SYNTAX score (<23 vs. ≥23) and by center.

The randomization will be managed by a central IVRS randomization. See Section 7.2.12 for randomization details. Once randomized the subject is analyzed as part of the intent-to-treat (ITT) population.

9.1.9.2. Clinical Events Committee and Angiographic Core Laboratory

In order to minimize bias, the clinical events committee (CEC) will assess specified clinical events per the Manual of Operation and independent core laboratories will assess imaging data.

9.1.10. Pooling Strategy

Analyses will be performed pooling data across study sites, study regions, and study stents. Additional analyses will be conducted to evaluate the potential differences in treatment effect for different sites/regions/study stents for the primary and powered secondary endpoints. Details of the analyses will be specified in the SAP.

9.1.11. Interim Analysis

No formal interim analysis is planned for this study. Interim study reports with descriptive analysis may be produced for regulatory or reimbursement purposes.

9.2. Universal Registry

The key baseline characteristics including reasons for exclusion from randomization, SYNTAX score and clinician treatment allocation will be summarized descriptively. For binary variables, percentages, and exact 95% confidence intervals will be calculated. For continuous variables, percentiles, means, standard deviations, and 95% confidence intervals for the mean using the Gaussian approximation will be calculated. The baseline features and treatment allocation of subjects in the registries will be compared to those in the randomized trial for descriptive purposes.

9.3. Health-Related Quality of Life (HRQoL) and Treatment Costs

Health-related quality of life (HRQoL) and treatment costs will be assessed alongside the core clinical trial in about 1800 patients to evaluate the impact of the PCI and CABG strategies on a range of relevant quality of life (QoL) domains and also to evaluate the cost-effectiveness of the two treatment strategies. Details regarding the QoL and U.S. Health Economics Sub-Studies can be found in Section 17, Appendix B.

9.3.1. Endpoints

Quality of life will be assessed using five patient reported outcome instruments administered at the following time points: baseline, 1 month, 1 year, 3 years, and 5 years. Score ranges for each instrument are as follows: SAQ: 0-100; PHQ-8: 0-24; SF-12: 0-100; EQ-5D: 0-1; Rose Dyspnea: 0-4. Means and standard deviations for these scores will be presented.

9.3.2. Quality of Life

HRQoL and functional status will be assessed using a combination of generic and disease-specific measures selected to cover a broad range of health domains that may be affected by coronary artery disease, its treatment, and its complications in about 1800 patients. Disease-specific QoL will be assessed using the Seattle Angina Questionnaire (SAQ)[77, 78] and the London School of Hygiene Dyspnea Questionnaire.[79, 80] Mental health and depression will be assessed using the Patient Health Questionnaire-9 (PHQ-9).[81] Generic health status will be assessed using the Medical Outcomes Study 12-item Short Form (SF-12),[82] and health utilities will be assessed using the EuroQoL (EQ-5D) with U.S.-specific weights.[83, 84] Further details regarding the rationale for selection of these instruments and specific analytic approaches are detailed in Section 17. These measures will be assessed using standardized, written questionnaires at baseline (prior to randomization), 1 month, 12 months, 3 years, and 5 years.

9.3.3. Economic Outcomes/Cost-Effectiveness

Data on cardiovascular-specific resource utilization and will be collected prospectively for the index hospitalization and the full follow-up period for 1800 subjects using standardized case report forms. Procedural costs will be assessed using a resource-based (e.g., "bottom up") approach to convert standard measures such as procedural duration and utilization of "big ticket" items (e.g., stents, balloons, wires, contrast, etc.) into costs. Other hospital costs will be assessed using an "event-driven" approach in which specific complications and outcomes (e.g. myocardial infarction, bleeding complications, post-operative infection, etc.) are assigned standard costs based on external data. Additional costs will be assigned for follow-up hospitalizations and repeat revascularization procedures, emergency room visits, outpatient diagnostic testing, cardiovascular medications, and rehabilitation services (including skilled nursing services). In each case, costs will be assessed from the perspective of the U.S. healthcare system. Finally, the cost and quality of life data will be integrated in order to perform a formal cost-effectiveness analysis. The primary analysis will be performed from the perspective of the U.S. healthcare system using a lifetime time horizon. Secondary analyses will be performed from the perspective of other health care systems with the collaboration of a local health economist.

If there are no significant differences in prognostically important endpoints (e.g., death, non-fatal MI, non-fatal stroke) between the two groups then the analysis will be based on the observed cost and QoL data from the trial itself (under the assumption that long-term survival would be comparable for the two groups). If there are differences in one or more of these endpoints (or their composite), however, then it will be important to account for differences in long-term survival between the two groups in the analysis. In this case, the data from the trial itself will be used along with external data in order to project long-term survival for each trial participant and use these estimates in order to estimate differences in quality-adjusted life expectancy over each subject's lifetime. Consistent with current guidelines for health economic analyses, the trial data will be used to calculate an incremental cost-effectiveness ratio (cost per quality-adjusted year of life gained) for the more expensive technique compared with the less expensive technique, and by comparing this ratio with those for other medical interventions, determine whether one treatment strategy is preferred on economic grounds.[85] Additional analyses will be performed using intermediate, disease-specific endpoints including cost per major adverse cardiovascular event avoided and cost per repeat revascularization avoided.[86]

The primary cost-effectiveness and quality of life analyses will be performed when all randomized subjects have completed a minimum of 3-years of follow-up. Although this time frame is slightly different from that for the main clinical endpoint, the longer follow-up duration for the economic analysis will minimize the need for extrapolation beyond the observed data.

Additional details of the approaches to U.S.-specific costing and the formal cost-effectiveness analysis are provided in Section 17.4 and Section 17.5.

9.4. Other Analysis

An IVUS substudy (Section 18) is planned (see Appendix C).

10. DIRECT ACCESS TO SOURCE DATA/DOCUMENTS

The Investigator/institution will permit direct access to source data/documents in order for trial-related monitoring, audits, IRB/EC review and regulatory inspections to be performed.

Subjects providing informed consent are agreeing to allow the Sponsor access and copying rights to pertinent information in their medical records concerning their participation in this trial, both at the study hospital and subsequent hospitals where the subject may receive subsequent care after randomization. The Investigator will obtain, as part of the informed consent, permission for trial monitors or regulatory authorities to review, in confidence, any records identifying the subjects in this trial. This information may be shared with regulatory agencies; however, the Sponsor undertakes not to otherwise release the subject's personal and private information.

11. QUALITY CONTROL AND QUALITY ASSURANCE

11.1. Selection of Clinical Sites and Investigators

The Sponsor will select Investigators who are qualified by training and experience and are legally entitled to perform clinical research and to participate in the investigation of the study device. Sites will be selected based upon review of a recent site assessment and the qualifications of the Primary Investigator at the site. Each site will have an interventional cardiologist and cardiac surgeon as "joint" principal investigators. All participating investigators will be trained to the protocol and study procedures prior to enrolling subjects.

11.2. Protocol and Informed Consent Approval

Institutional Review Board (IRB) or Ethics Committee (EC) approval for the protocol, informed consent form, and other study related documents will be obtained by the Primary Investigator at each investigational site prior to participation in this trial. The approval letter must be signed by the IRB/EC chairman or authorized representative prior to the start of this trial and a copy for U.S. sites must be provided to the Sponsor. In addition, the investigator or designee will provide the Sponsor with all required documentation necessary for initial and ongoing study approval at their site.

In accordance with the investigational site IRB/EC requirements, the investigator will (a) advise the IRB/EC of the progress of this trial on a regular basis until study completion; (b) obtain written IRB/EC approval at predetermined timepoints to continue the trial as required by country regulations; and (c) submit any amendments to the protocol as well as associated informed consent form changes and obtain written IRB/EC approval obtained prior to implementation.

No investigative procedures other than those defined in this protocol will be undertaken on the study subjects without the written agreement of the IRB/EC and the Sponsor.

11.2.1. Protocol Amendments

Approved protocol amendments will be provided to the Investigators by the Sponsor prior to implementing the amendment. The Primary Investigator will be responsible for notifying the IRB/EC of the protocol amendment (administrative changes) or obtaining IRB/EC approval of the protocol amendment (changes in subject care or safety), according to the instructions provided by the Sponsor with the protocol amendment.

Acknowledgment/approval by the IRB/EC of the protocol amendment must be documented in writing prior to implementation of the protocol amendment. Copies of this documentation must also be provided to the Sponsor.

11.3. Protocol Deviations

It is the Investigator's responsibility to ensure that there are no deviations from the protocol and to stay in full compliance with all established procedures of the IRB/EC. The Investigator will not deviate from the protocol for any reason except in cases of medical emergencies, when the deviation is necessary to protect the life or physical well-being of the subject. All deviations must be reported to the Sponsor. Protocol deviations are determined by the Sponsor. In subject-specific deviations from the protocol, a protocol deviation eCRF will be completed. The occurrence of protocol deviations will be monitored by the Sponsor. Investigators will inform their IRB/EC of all protocol deviations in accordance with their specific IRB/EC reporting policies and procedures.

In the event that an Investigator does not comply with the Investigator Agreement or protocol, the Sponsor will notify the Investigator of the site’s non-compliance. Continued non-compliance may result in further escalation in accordance with the Sponsor’s SOP.

11.4. Training

11.4.1. Site Training

All Investigators/trial personnel are required to attend Sponsor training sessions, which may be conducted at an Investigator's meeting, a site initiation visit or other appropriate training sessions. Also, training by telephone may take place as required. Training of Investigators/trial personnel will include, but is not limited to, the investigational plan, investigational device usage, protocol requirements, electronic case report form completion and trial personnel responsibilities. All Investigators/trial personnel that are trained must sign a training log (or an equivalent) upon completion of the training. Prior to being trained, Investigator/trial personnel must not perform any trial-related activities that are not considered standard of care at the site.

11.4.2. Training of Sponsor’s Monitors

The Sponsor’s monitors or designee will be trained to the protocol, electronic case report forms and investigational device usage, if appropriate. The Sponsor or designee is responsible for the training. Training may be conducted in accordance with the Sponsor’s SOP.

11.5. Monitoring

Sponsor and/or designee will monitor the study over its duration according to the pre-specified monitoring plan. The study monitor will visit each site at appropriate intervals to review investigational data for accuracy and completeness and ensure compliance with the protocol.

Medical records/source documents (office, clinic or hospital) will be reviewed for 100% of subjects looking for primary end-point events.

In cases of all-cause mortality and SAE, the study monitor will perform inspection for pertinent documents and records for these events. The monitor will be assisting sites to resolve any data queries and ensuring that relevant source documents related to study events are being retrieved from the sites. The Investigator/site will permit access to such records. Source documentation must be available to substantiate proper informed consent procedures, adherence to protocol procedures, adequate reporting and follow-up of adverse events, accuracy of data collected on case report forms, and device information. A monitoring visit sign-in log will be maintained at the site. The Investigator and/or research coordinator will be available for monitoring visits. It is expected that the Investigator will provide the study monitor with a suitable working environment for review of study-related documents.

11.6. Quality Assurance Assessments

The Sponsor/designee may conduct periodic compliance assessments (on-site audits) at various study sites. A Sponsor representative or designee may request access to all trial records, including source documentation, for inspection and duplication during a compliance assessment.

The Investigator and research coordinator must be available to respond to reasonable requests and queries made during the compliance assessment process.

11.7. Regulatory Agency Inspection

In the event that an Investigator is contacted by a Regulatory Agency in relation to this study, the Investigator will notify the Sponsor immediately. The Investigator and research coordinator must be available to respond to reasonable requests and inspection queries made during the inspection process. The Investigator must provide the Sponsor with copies of all correspondence that may affect the review of the current study (e.g., Form FDA 483, Inspectional Observations, and warning letters). The Sponsor will provide any needed assistance in response to regulatory inspections.

11.8. Executive Operations Committee

The Executive Operations Committee (EOC) is responsible of the overall management of the study at the highest level. The EOC is comprised of four voting members who are the Co-PIs, as well of non-voting members: representatives from the Sponsor, the heads of the PCI and CABG committees, a neurology expert as well as representative from both Cardialysis and CRF.

12. DATA HANDLING AND RECORD KEEPING

For the trial duration, the Investigator will maintain complete and accurate documentation including but not limited to medical records, trial progress records, laboratory reports, case report forms, signed informed consent forms, device accountability records, correspondence with the IRB/EC and trial monitor/Sponsor, adverse event reports, and information regarding subject discontinuation or completion of the trial.

12.1. Source Documentation

Regulations require that the Investigator maintain information in the subject's medical records that corroborates data collected on the case report forms. In order to comply with these regulatory requirements the following information should be included in the subject record at a minimum:

- Medical history/physical condition of the subject before involvement in the trial sufficient to verify protocol entry criteria
- Dated and signed notes on the day of entry into the trial referencing the Sponsor, protocol number, subject ID number, treatment assigned and a statement that informed consent was obtained
- Dated and signed notes from each subject visit (for specific results of procedures and exams)
- Adverse events reported and their resolution including supporting documents such as discharge summaries, catheterization laboratory reports, ECGs, and lab results, including documentation of site awareness of SAEs and of investigator device relationship assessment of SAEs
- Study required lab reports and 12-lead ECGs, signed and dated for review and annotated for clinical significance of out of range results
- Notes regarding protocol-required and prescription medications taken during the trial (including start and stop dates)
- Subject's condition upon completion of or withdrawal from the trial
- Any other data required to substantiate data entered into the CRF

Source documents will be requested for events that require adjudication. Source documents requested for adjudication must be redacted of all protected health information prior to submission.

12.2. Electronic Case Report Form (eCRF) Completion

Primary data collection based on source-documented hospital chart reviews will be performed clearly and accurately by research coordinators (RC) at each clinical site trained on the protocol and case report form completion. The eCRF data will be collected for all subjects that are randomized. This data will be monitored by the Sponsor's Site Monitors. The Sponsor will provide clinical monitoring to include review of case report forms and parity checks with the source documentation, including operator worksheets retained with case report form documentation and hospital charts.

12.3. Record Retention

The sponsor will archive and retain all documents pertaining to the trial as per the applicable regulatory record retention requirements. The Primary Investigator will maintain all records pertaining to this study until instructed by the Sponsor. Investigator will be notified by the Sponsor of the date of marketing approval or discontinuation of the study. The Investigator will obtain permission from the Sponsor in writing before destroying or transferring control of any study records.

12.4. Investigational Device Management

Sites will use only commercially available XIENCE stents.

12.5. Maintenance of Randomization Codes

The Sponsor will maintain a complete record of randomization codes for all subjects randomized in the trial.

13. ETHICAL CONSIDERATIONS

This study will be conducted in accordance with the Declaration of Helsinki ISO 14155-2011(E) standards, as well as with applicable country specific requirements.

All subjects must provide written informed consent in accordance with the site's IRB/EC for the respective Countries, using an IRB/EC-approved informed consent form. The final eligibility for the study will be confirmed based on the decision of the local Heart Team. Study-specific procedures must not be performed until a signed informed consent has been obtained. The

Investigator or designee, who has been trained on the protocol, will explain the nature and scope of the study, potential risks and benefits of participation, and answer questions for the subject. If the subject agrees to participate, the informed consent form must be signed and personally dated by the subject or legally authorized representative. The Investigator or a person designated by the Investigator must also sign the informed consent form. The informed consent must be completed by both the subject and Investigator prior to any protocol specified testing and prior to subject participation. Any additional persons required by the site's IRB/EC to sign the informed consent form must also comply. In addition, for U.S. sites an authorization for use and disclosure of the subjects' protected health information (PHI) according to the Health Insurance Portability and Accountability Act (HIPAA) may be included as part of the subject informed consent process in accordance with individual site procedures.

Figure 6.1 outlines the screening and randomization process and illustrates the point where informed consent should be obtained.

14. PUBLICATION POLICY

14.1. Publication Policy

The Executive Operations Committee, Sponsor and Investigators are committed to the publication and widespread dissemination of the results of the study. Data from this study will not be withheld regardless of the findings. The Excel Clinical Trial is a scientifically driven study sponsored by Abbott Vascular. All public presentations and manuscript generation and submissions will be led under the auspices of the four Principal Investigators who will organize and lead a Publications Committee. However, this Study represents a joint effort between investigators and Sponsor, and as such, the parties agree that the recommendation of any party concerning manuscripts or text shall be taken into consideration in the preparation of final scientific documents for publication or presentation.

Copies of the final locked database will be housed at both Cardialysis and CRF. Neither CRF nor Cardialysis will publicly release any data or study related material, presentations, or manuscripts without the express permission of both organizations as well as agreement of the four Principal Investigators. All four Principal Investigators will be listed as authors on all abstracts and publications, and as such must agree to their submission. The publication and/or presentation of results from a single trial site are not allowed until publication and/or presentation of the multi-center results. All single site data for public dissemination must be generated from the central database – local database projects are not permitted. All proposed publications and presentations resulting from or relating to the study (whether from multicenter data or single site analysis) must be submitted to the Publications Committee for review and approval prior to submission for publication or presentation.

The Sponsor will receive any proposed publication and/or presentation materials prior to submission of the presentation or the initial submission of the proposed publication in order for the materials to be reviewed by the Sponsor. If any such proposed publication or presentation contains patentable subject matter which in Sponsor's sole discretion, warrants intellectual proprietary protection, the Sponsor may delay any publication or presentation for up to sixty (60) days after Executive Operations Committee approval for the purpose of pursuing such protection. The prior notwithstanding, however, the results of the study will not be considered confidential or patentable information after the multicenter primary endpoint data is presented, and the Investigators' rights to present and publish such data representing the scientific results of this study will not be restricted.

The primary endpoint presentation and publication will state that the study has been performed in a selected patient population with left main disease.

14.2. Publication Committee

The Publication Committee is composed of the Principal Investigators, representatives from Abbott Vascular Clinical Research, and other personnel as determined by the committee Chairperson and approved by the Executive Operations Committee. This team will oversee presentation and/or publication aspects of the study. The Publication Committee will determine

policy and strategies regarding individual presentations and/or publications arising from study generated data. The committee will also review all external requests for accessing study related data and strategies aligning with Abbott Vascular presentation and publication team expectations. The committee will also follow Abbott Vascular applicable policies and standard operating procedures regarding Abbott Vascular-sponsored clinical studies.

15. RISK ANALYSIS

15.1. Potential Risks - PCI

15.1.1. Risks from Cardiac Catheterization, Stenting, and PTCA

There is extensive clinical and commercial experience worldwide with cardiac catheterization and interventional procedures and it is expected that the surgical and procedural risks will not be significantly different in this clinical trial. For a list of anticipated adverse events from each stent system, refer to XIENCE PRIME, XIENCE V, XIENCE Xpedition and XIENCE PRO (for OUS use only) device IFU.

Some of the complications of stenting procedure are:

- Death, stroke, shock, kidney failure, squeezing of the heart due to accumulation of blood in the sac around the heart (cardiac tamponade), access site infection, decreased blood supply to a part of the heart muscle, arms or leg, inadvertent injury to the aorta and/or its branches may occur in <2% of the patients.
- Vascular complications at the access site that might need vessel repair including hematoma or hemorrhage, blockage of the coronary artery.
- Rapid/ slow heartbeat, heart attack, development of blood clots, abnormal connection between an artery and a vein next to it (arterio-venous fistula), abnormal blood pressure, fluid development in the lungs (pulmonary edema), emergency or non-emergency surgery may occur in 2-5% of the patients.
- Chest pain or discomfort, access site pain, allergic reaction or hypersensitivity to contrast agent or cobalt, chromium, nickel, tungsten, acrylic and fluoropolymers and drug reactions to antiplatelet drugs or contrast agent, repeat closure of the coronary artery over time may occur in 5-10% of the patients.
- The rates of surgical and procedural risks for patients being treated for LM disease or Left Main Equivalent disease may be higher than the experience worldwide with cardiac catheterization and interventional procedures.
- The adverse events and potential device issues associated with the particular techniques (e.g., T- stent, TAP, mini-crush (reverse crush) or culotte bifurcation)) associated with the treatment of Left Main disease and allowed for in this study may result in adverse events or device issues not previously identified. As the study progresses and the experience with these techniques are better understood, the protocol may be updated with additional risks.

15.1.2. Associated Risks of Everolimus

The risks of everolimus when used in a blood vessel (as in the Trial) are unknown. Zortress®, the oral formulation of everolimus developed by Novartis Pharmaceuticals Corporation, has been evaluated in clinical trials and is approved in the United States for the prevention of organ rejection in adult kidney transplant recipients at low-moderate immunologic risk, at the dose of 1.5 mg/day.

Outside the U.S., Zortress is sold under the brand name, Certican®, in more than 70 countries. Everolimus is also approved in the United States under the name of Afinitor® for the treatment of patients with advanced renal cell carcinoma (cancer) after failure of treatment with sunitinib or sorafenib, at doses of 5 to 20 mg/day when taken by mouth. The amount of drug in the blood from the XIENCE stent is several folds lower than obtained with oral doses (1.5 mg to 20 mg/day).

The list below includes the known risks of everolimus at the oral doses indicated above. There may be other potential adverse events that are unforeseen at this time.

- Abdominal pain (including upper abdominal pain)
- Anemia
- Angioedema
- Anorexia
- Asthenia
- Constipation
- Cough
- Delayed wound healing/fluid accumulation
- Diarrhea
- Dyslipidemia (including hyperlipidemia and hypercholesterolemia)
- Dyspnea
- Dysgeusia
- Dyspepsia
- Dysuria
- Dry skin
- Edema (peripheral)
- Epistaxis
- Fatigue
- Headache
- Hematuria
- Hyperglycemia (may include new onset of diabetes)
- Hyperlipidemia
- Hyperkalemia
- Hypertension
- Hypokalemia
- Hypomagnesemia
- Hypophosphatemia
- Increased serum creatinine

- Infections and serious infections: bacterial, viral, fungal, and protozoal infections (may include herpes virus infection, polyoma virus infection which may be associated with BK virus associated nephropathy, and/or other opportunistic infections)
- Insomnia
- Interaction with strong inhibitors and inducers of CY3PA4
- Leukopenia
- Lymphoma and other malignancies (including skin cancer)
- Male infertility (azospermia and/or oligospermia)
- Mucosal inflammation (including oral ulceration and oral mucositis)
- Nausea
- Neutropenia
- Non-infectious pneumonitis
- Pain: extremity, incision site and procedural, and back
- Proteinuria
- Pruritus
- Pyrexia
- Rash
- Stomatitis
- Thrombocytopenia
- Thrombotic microangiopathy (TMA)/Thrombotic thrombocytopenic purpura (TTP)/ Hemolytic uremic syndrome (HUS)
- Tremor
- Urinary tract infection
- Upper respiratory tract infection
- Vomiting

Live vaccines should be avoided and close contact with those that have had live vaccines should be avoided. Fetal harm can occur when administered to a pregnant woman. There may be other potential adverse events that are unforeseen at this time.

Exposure to drug and polymer on the XIENCE stent is directly related to the number and lengths of the stents implanted. The use of multiple XIENCE stents will result in receiving larger amounts of drug and polymer. It should be noted that a kidney or heart transplant patient or a patient with advanced renal cell carcinoma usually receives a daily dose of the drug everolimus by mouth that is several times higher than the maximum dose of the drug contained on one XIENCE stent.

Everolimus, when given by mouth daily to organ transplant patients or renal cell carcinoma patients, may interact with other drugs or substances. Patient should notify the physician about any medications they might be taking.

The XIENCE Xpedition stent system is similar to XIENCE PRIME with a new stent delivery system optimized for acute performance. The XIENCE PRIME and XIENCE Xpedition stent systems are similar to the clinically proven XIENCE V EECSS. XIENCE PRO (for OUS use only) is just rebranding of XIENCE V EECSS and XIENCE PRIME LL EECSS. The XIENCE V EECSS has been shown to be safe and effective in four clinical trials, SPIRIT FIRST, SPIRIT

II, SPIRIT III and SPIRIT IV. The SPIRIT PRIME clinical trial is Abbott Vascular's pivotal US trial evaluating the XIENCE PRIME stent system. The SPRIIT PRIME trial has met all pre-specified performance goals with statistical significance for its primary endpoint of target lesion failure at 1 year. Long-term risks and benefits associated with the XIENCE PRIME stent system are currently unknown.

15.1.3. Drug Interactions with Everolimus

Everolimus is extensively metabolized by the cytochrome P4503A4 (CYP3A4) in the gut wall and liver and is a substrate for the counter transporter P-glycoprotein. Therefore, absorption and subsequent elimination of everolimus may be influenced by drugs that also affect this pathway. Everolimus has also been shown to reduce the clearance of some prescription medications when it was administered orally along with cyclosporine (CsA). Formal drug interaction studies have not been performed with the XIENCE stent because of limited systemic exposure to everolimus eluted from the XIENCE stent. However, due consideration should be given to the potential for both systemic and local drug interactions in the vessel wall when deciding to place the XIENCE stent in a subject taking a drug with known interaction with everolimus.

Everolimus, when prescribed as an oral medication, may interact with the drugs/foods[87, 88] listed below. Medications that are strong inhibitors of CYP3A4 might reduce everolimus metabolism *in vivo*. Hence, co-administration of strong inhibitors of CYP3A4 may increase the blood concentrations of everolimus while co-administration of inducers of CYP3A4 may decrease the blood concentrations of everolimus.

- CYP3A4 isozyme inhibitors (ketoconazole, itraconazole, voriconazole, ritonavir, erythromycin, clarithromycin, fluconazole, calcium channel blockers (verapamil and diltiazem), aprepitant atazanavir, nefazodone, amprenavir, indinavir, nelfinavir, delavirdine, fosamprenavir, saquinavir and telithromycin)
- Inducers of CYP3A4 isozyme (rifampin, rifabutin, carbamazepine, phenobarbital, phenytoin, dexamethasone)
- Antibiotics (ciprofloxacin, ofloxacin)
- Glucocorticoids
- HMG CoA reductase inhibitors (simvastatin, lovastatin)
- Digoxin
- Cisapride (theoretical potential interaction)
- Sildenafil (Viagra®) (theoretical potential interaction)
- Antihistaminics (terfenadine, astemizole)
- Grapefruit / grapefruit juice

15.1.4. Associated Risks of XIENCE Polymer

The safety and biocompatibility of acrylic and fluoro deposited polymer coatings have been demonstrated based upon XIENCE PRIME stent system biocompatibility testing per ISO 10993-1 and the long term use of these polymers in medical implants. These polymers are the same as those of the FDA approved XIENCE V EECS. However, the long-term outcome of the XIENCE PRIME/XIENCE Xpedition stent system polymer as a permanent implant is presently unknown.

15.1.5. Genotoxicity, Carcinogenicity and Reproductive Toxicity of XIENCE

The carcinogenicity, genotoxicity, and reproductive toxicity of the XIENCE PRIME and XIENCE Xpedition stent have not been evaluated; however, long term carcinogenicity and teratology studies were performed with the XIENCE V EECS, a similar everolimus eluting subcutaneously in transgenic mice. Based on the results of this study, the XIENCE V EECS does not appear to be carcinogenic when implanted in transgenic mice for 26 weeks. In the reproductive toxicity studies, XIENCE V EECS was implanted in rats and showed no effect on their fertility or reproductive capability. Additionally, there were no teratogenic effects in the offspring in this study[89].

15.1.5.1. Pregnancy/Fertility

There are no adequate studies in pregnant women or men intending to father children regarding the safety of everolimus or the XIENCE stent. Everolimus when administered at oral doses of 0.1 mg/kg and above showed effects on pre- and post-natal rat development limited to slight body weight changes and fetal survival without any specific toxic potential.[87]

Therefore, pregnant subjects and those planning pregnancy up to one year following the index procedure are excluded from this study. Women of child bearing age must have a recent negative pregnancy test prior to randomization. If a female subject does get pregnant, the risks to the fetus are unknown. Effective contraception must be used before implanting a XIENCE stent system. The method of contraception is a personal choice but needs to be made with respect to the subject's values with adequate medical information on the effectiveness and safety of the method. Except for surgical removal of the uterus and ovaries or total abstinence, all methods of birth control have a failure rate. Intrauterine devices (IUD), hormonal contraceptives (birth control pills, injections or implants), tubal ligation or partner's vasectomy and barrier contraceptives (condoms, diaphragms, and cervical caps) are available means of birth control. The primary care provider or a gynecologist should be consulted concerning the best birth control method for the subject given his/her medical history and lifestyle choices.

15.1.5.2. Lactation

It is unknown whether everolimus is distributed in human milk. Everolimus pharmacokinetic and safety profiles have not been determined in infants. Consequently, mothers should be advised of potential serious adverse reactions to everolimus in nursing infants. Prior to XIENCE stent system implantation, a decision should be made regarding whether to discontinue nursing or conduct an alternate percutaneous coronary intervention procedure.

15.2. Potential Risks – CABG

The potential benefits, risks and complications of CABG have been extensively studied and documented over the last five decades.

In contemporary surgical practice overall hospital mortality for CABG is approximately 2% (1% for elective subjects). For example in the whole cohort of 113,000 subjects undergoing CABG in the United Kingdom in the four year period 2005 to 2008, including those who were urgent, the

overall mortality was 1.8% (1.1% in the 78,000 elective subjects).[90]

Complications of CABG are:

- Death, stroke, shock, prolonged healing of the surgical incision on the chest due to separation of the sides of the wound, sternal surgical infection, in-advertent injury to the aorta and/or its branches, emergency or non-emergency need for reoperation or angioplasty may occur in < 2% of the patients.
- Excessive bleeding, heart attack, kidney failure, a state of subnormal or depressed amount of blood being pumped by the heart (low cardiac output syndrome) requiring intravenous medicine support and/or mechanical assistance from an intra-aortic balloon pump, development of blood clots, abnormal blood pressure, fluid development in the lungs (pulmonary edema), may occur in 2% to 5% of the patients.
- Chest pain, respiratory failure, need for mechanical support for breathing, rapid or slow heart beat, post-op impaired neurocongnitive functioning, fever, nausea may occur in 5-10% of the patients.

The rates of surgical and procedural risks for patients being treated for LM disease or Left Main Equivalent disease may be higher than the experience worldwide with cardiac catheterization and interventional procedures.

15.3. Major Adverse Event Rates in Left Main Studies

Long term adverse event data for PCI in the LM population has not been extensively studied or reported and is therefore not provided in the risk analysis section. Recent literature on major cardiac event rates in left main procedures[1,2,3,4,5,6,7,8] is limited and emerging. In trials conducted in patients with LM disease treated with either PCI or CABG, the following range of major adverse event rates were observed: death (2.0% at one year to 11.2% at 5 years), myocardial infarction (1.0% at one year to 15.7% at 5 years), stroke (0.1% at one year to 5.9% at 5 years) and revascularization (3.4% at one year to 19.7% at 5 years).

15.4. Gender/ Race Specific Prevalence

Coronary artery disease (CAD) continues to be the leading cause of morbidity and mortality among women in the United States and throughout the world.[91,92] The prevalence of coronary artery disease in United States is estimated at 17.6 million for both sexes of which 8.5 million are

reported to be in females.[93] The age-adjusted death rate resulting from coronary artery disease (CAD) in females, which accounts for about half of all cardiovascular disease (CVD) deaths in women, was 95.7 per 100, 000 females in 2007 which was a third of what was observed in 1980.[94,95] Despite a decline in the overall cardiovascular deaths in females, recently CAD rates in US women 35 to 54 years age appear to be increasing, likely associated with obesity.[96]

Limited race specific data available has shown African-American women to have higher coronary heart disease mortality risk in comparison to white women since the 1940s[97] attributed mainly to substantially lower rate of awareness of heart disease and stroke that has been documented among black versus white women.[98, 99] In contrast, Hispanics have the lowest percentage of cardiovascular deaths (21.7%) compared with non-Hispanics (26.3%) despite their lower

socioeconomic status, and inadequate access to healthcare in United States (known as 'Hispanic Paradox').[100,101,102]

[1] Serruys, P. TCT 2011. 4 year outcomes of the Syntax trial in a subset of patients with left main disease.

[2] Salvatella N., Morice MC., Darremont O., et al. (2011). Unprotected left main stenting with a second generation drug eluting stent: 1 year outcomes for the LEMAX Pilot study. Eurointervention. 7(6):689-96.

[3] Carrie D., Eltchanionoff H., Lefevre T., et al. (2011). Early and long term results of unprotected left main coronary artery stenosis with paclitaxel eluting stents: the FRIEND registry. Eurointervention. 7(6):680-88.

[4] Seung KB, Park DW, Kim YK et al. (2008). Stents versus coronary artery bypass grafting for left main coronary artery disease. NEJM. 358:1781-92.

[5] Park SJ, Kim YK, Park DW, et al. (2011). Randomized Trial of stents versus bypass surgery for left main coronary artery disease. NEJM. 364:1718-27.

[6] Park SJ. PRECOMBAT Trial. ACC 2011.

[7] Park DK., Kim YK, Yun SC, et al. (2010). Long term outcomes after stenting versus coronary artery bypass grafting for unprotected left main coronary artery disease. 10 year results of bare metal stents and 5 year results of drug eluting stents from the ASAM-MAIN registry. JACC; 56(17):1366-75.

[8] Capodanno, D, Stone GW, Morice MC, et al. (2011). Percutaneous coronary intervention versus coronary artery bypass graft surgery in left main coronary artery disease. JACC; 58(14):1426-32.

In the EXCEL clinical trial, the intended patient population is a group with unprotected left main coronary artery (ULMCA) disease. Literature for Left Main (LM) disease with respect to gender shows a lower prevalence in women than men particularly in the definite angina group. In the CASS study, it was observed that in men 50 years or older, 50% had three-vessel or left main disease whereas in women left main disease or three-vessel disease occurred in over 40% of women older than 60 years of age.[103]

15.4.1. Gender-specific and Race-specific Diagnosis and Treatment Patterns

It is well documented in literature that men and women present with CAD differently in terms of epidemiology, pathophysiology, clinical presentation, diagnosis and management.[104, 105, 106, 107,108,109]

In general, women are less likely to be referred for functional testing of ischemia and that a lower rate of diagnostic angiograms and interventional procedures are performed compared with men.[110] A study that used referral to cardiac catheterization as an indication of perceived patient risk observed that approximately 42% women underwent cardiac catheterization compared to approximately 50% men.[111]

Although men and women share most classic risk factors, the significance and the relative weighting of these factors are different for the two genders. In women, menopause is associated with a worsening of CAD risk profile.[112] The clinical presentation of CAD and the interpretation of noninvasive diagnostic testing is less reliable in women (atypical symptoms) compared with men, especially in the age group below 55 years when the prevalence of coronary artery disease is still relatively low.[113] Thus, women in this age group are significantly less likely than men to have ECGs suggestive of myocardial ischemia.[114] Additionally, women presenting with chest pain are less likely to undergo diagnostic testing and are less likely to have a positive exercise test or imaging study.[115] In general, women usually experience a delay in the clinical diagnosis, which may easily translate into increased procedural morbidity and mortality. Additionally, disparities have been found in the administration and performance of both noninvasive testing and cardiac catheterization. Four times as many men as women receive device therapy for sudden cardiac arrest prevention.[99,100]

Gender/race specific data on diagnosis and treatment patterns in the intended population is not available in literature.

15.4.2. Proportions of Women Included in Past Trials

Limited gender specific data is available on key trials related to Left Main disease and CABG trials. However, Table 15-1 summarizes the proportions of women included in the past trials (both AV sponsored and non-AV sponsored clinical trials).

Table 15-1 Proportions of Women Included in Past Trials

Study No.	Trial Name	Total number of patients	Men (%)	Women (%)
Abbott PCI (DES) Trials				
1	SPIRIT II	300	219 (73%)	81 (27%)
2	SPIRIT III	1002	687 (68.6%)	314 (31.4%)
3	SPIRIT IV	3687	2499 (67.8%)	1188 (32.2%)
4	SPIRIT PRIME (CSR+LLR)	525	361 (68.8%)	164 (31.2%)
5	XV USA	5054	3478 (68.8%)	1576 (31.2%)
Non-Abbott DES and CABG Trials				
6	Pooled data from RAVEL, SIRIUS, E-SIRIUS, C-SIRIUS[116]	1748	1251 (71.6%)	497 (28.4%)
7	ENDEAVOR clinical trial program[117]	2132	1524 (71.5%)	608 (28.5%)
8	TAXUS Women[118]	810	642 (79.3%)	168 (20.7%)
9	CABG (Effect of gender on post-operative outcomes)[119]	1743	1220 (70%)	523 (30%)
10	CABG (Gender differences in clinical and angiographic outcomes)[120]	954	766 (80%)	188 (20%)
Trials for Target Indication (Left Main Disease)				
11	SYNTAX Trial[121]	1800	1398 (77.6%)	402 (22.4%)
12	Left Main DES[122]	1452	1048 (72.2%)	404 (27.8%)

Typically in a drug eluting stent trial, 20-33% women participated which is comparable to the proportion of women participated in CABG, SYNTAX, and Left Main DES trials.

Within Abbott sponsored trials, the participation of African American men ranged from approximately 3-6% compared to 4-10% women of the same race; percentage of Hispanic men ranged from 1.4-3.2% compared to women (0.9-3.2%) whereas white men represented 89-95% of the male population compared to white women representing 85-88% of the female population.

15.4.3. Clinically Significant Gender Differences in Outcomes Related to Safety or Effectiveness

The recognition of gender disparities in the epidemiology, diagnosis and treatment of cardiovascular disease are well-established. However, there is limited literature regarding the influence of gender on treatment patterns and outcomes of coronary revascularization. Due to a higher baseline risk profile and more complex angiographic characteristics, women tend to have worse clinical outcomes compared to men.[123,124,125]

Several studies indicate that women are less likely than men to undergo diagnostic catheterization.[126,127,128] However, in recent drug eluting trials as discussed below, it is indicated that women who underwent stent based PCI procedures or CABG procedures irrespective of the type of DES including the left main disease, had similar clinical outcomes as observed in men.

Despite less favorable baseline clinical and angiographic features in women compared with men, the angiographic and clinical benefits are independent of gender using different drug eluting stents.[116,117,129,130,131] Similar observations have been reported for men and women undergoing by-pass surgery after accounting for differences in the risk variables.[119,120,121] Of particular

interest is the observation by the Investigators of SYNTAX trial where despite gender related differences in baseline co-morbidities, the outcomes between CABG and PCI at 12 months were similar for men and women in the most challenging group of patients with three vessel and/or left main disease.[122]

15.5. Risk Management Procedures

Subjects will be monitored closely throughout the trial duration. Subjects will be evaluated clinically at pre-determined timepoints to assess their clinical status.

An independent DSMB will monitor safety of the subjects throughout the trial.

15.5.1. Post PCI

As part of the dual antiplatelet strategy, aspirin ≥75 mg per day indefinitely is mandatory post procedure. Additionally chronic daily ADP antagonist therapy is mandated following PCI with choices including either:

- clopidogrel 75 mg per day, or 150 mg per day for 7-30 days then reduced to 75 mg per day, unless subject is hyporesponsive to clopidogrel, or
- prasugrel 5 or 10 mg per day, or
- ticagrelor per labeling and recommended guidelines if approved by the local regulatory authorities during the treatment period of this protocol.

In subjects who received a ULMCA DES, a daily ADP antagonist must be given for at least one year, and is recommended for the duration of the trial in the absence of major bleeding complications or other major complications. ADP antagonists must not be discontinued within the first year after DES implantation unless absolutely necessary for major bleeding complications, major trauma, major surgery necessitating discontinuation of antiplatelet therapy (e.g. intracranial surgery), etc. If an ADP antagonist must be discontinued, a GP IIb/IIIa bridging strategy up until the time of surgery may be considered, followed by re-loading of the ADP antagonist as soon as possible post surgery.

15.5.2. Post CABG

Aspirin must be used daily for the duration of the trial. Subjects who are treated with CABG should receive the following medications as per the local institution standard of care unless medically contraindicated: beta blocker and statins. If there is left ventricular dysfunction, an ACE inhibitor should also be prescribed.

Section 22 outlines the recommended care of post-CABG subjects.

15.5.3. Gender-specific

Abbott Vascular plans to encourage investigators participating in this trial to randomize women that meet inclusion/exclusion criteria of this study. Site staff will be trained by way of the investigator training material to encourage randomization of women in the EXCEL trial. It is

pertinent to note that the study inclusion or exclusion criteria are open to both genders except the exclusion criteria where pregnant women or women who are planning to be pregnant within one year of the study after randomization are excluded from this study. This exclusion is because the effects of the XIENCE Drug Eluting Stents have not been studied in pregnant females in the past and any potential iatrogenic effects of the drug/device on the pregnant female and the fetus remain unknown.

In an effort to better understand any potential gender differences from this trial, the gender subgroup has been prespecified in the EXCEL protocol (Section 9.1 Gender-specific subgroup analysis, Section 17.5 QoL subgroup analyses and Section 21.2 Pre-specified subgroups). These analyses will be descriptive and hypothesis generating and may provide further insights in understanding any potential gender differences.

Abbott Vascular believes that the proportion of women randomized in the EXCEL clinical trial will reflect the proportion of women reaching the catheterization laboratory. Moreover, the data obtained from the prespecified gender subgroup analysis in the EXCEL trial will provide robust descriptive data in terms of diagnosis, treatment, and clinical outcomes in men and women.

15.6. Potential Benefits

15.6.1. Potential benefits of stenting.

The XIENCE PRIME and XIENCE Xpedition stent systems are very similar to the approved XIENCE V EECSS. The XIENCE V EECSS has been evaluated in the SPIRIT FIRST, SPIRIT II, SPIRIT III and SPIRIT IV trials and demonstrated safety and efficacy.

Additionally, the SPIRIT PRIME study, a prospective, two-arm, open-label, multi-center registry using the XIENCE PRIME Stent system (XIENCE PRIME and XIENCE PRIME LL EECSS) in 500 subjects is being conducted at up to 75 global sites. Overall, the long-term effects and potential benefits of XIENCE PRIME stent system are not yet known.

Drug eluting stents have been associated with a reduction in the need for repeat revascularization without an increase in the risk of death or myocardial infarction for subjects with ULMCA stenosis compared to bare metal stent.[89] In another study by Tamburino et al, in a large population of subjects with acute coronary syndrome and ULMCA disease, DES were more effective than BMS in reducing myocardial infarction and target lesion revascularization.[132] The LEMANS Registry has shown good long term outcome with implantation of DES for ULMCA coronary artery disease. DES stenting of ULMCA decreased the risk of long-term MACCE with improved survival in subjects with distal ULMCA disease.[133] The ISAR-Left Main randomized clinical trial has shown that implantation with either paclitaxel or sirolimus eluting stents in ULMCA lesions is safe and effective with comparable clinical and angiographic outcomes. Additionally, for both stent types, definite stent thrombosis rates at two years were low and comparable with no new events beyond 30 days post index procedure.[23]

These studies not only demonstrate the safety and effectiveness of drug eluting stents in the treatment of ULMCA disease but also indicate the absence of signal suggesting an increased safety risk with DES stenting of the ULMCA.[25,134]

15.6.2. Potential benefits of CABG.

Indications for CABG can either be classified as symptomatic, prognostic or a combination. Traditional prognostic indications for CABG include subjects with significant left main stem stenosis and those with two or three vessel coronary artery disease particularly involving the proximal left anterior descending coronary artery and thus far CABG procedure has been the standard of care for the treatment of left main disease. CABG may also be indicated in subjects who remain symptomatic with angina and/or breathlessness despite optimal medical therapy even in the absence of a prognostic indication. Numerous studies have demonstrated that improvement in symptoms correlates well with significant improvements in quality of life.[90]

16. APPENDIX A: DEFINITIONS, ABBREVIATIONS, AND ACRONYMS

16.1. Primary and Major Secondary Endpoint Definitions

16.1.1. Definition of Death

The cause of death will be adjudicated as being due to cardiovascular causes, non cardiovascular causes, or undetermined causes.

- Cardiovascular Death includes sudden cardiac death, death due to acute myocardial infarction, death due to heart failure or cardiogenic shock, death due to stroke, death due to other cardiovascular causes, and death due to bleeding as follows:
  - **Sudden Cardiac Death** refers to death that occurs unexpectedly and includes the following deaths:
    - Witnessed and instantaneous without new or worsening symptoms
    - Witnessed within 60 minutes of the onset of new or worsening cardiac symptoms
    - Witnessed and attributed to an identified arrhythmia (e.g., captured on an electrocardiographic (ECG) recording or witnessed on a monitor by either a medic or paramedic)
    - Subjects unsuccessfully resuscitated from cardiac arrest
    - Subjects successfully resuscitated from cardiac arrest but who die without identification of a non-cardiac etiology (Post-Cardiac Arrest Syndrome)
    - Unwitnessed death or other causes of death (information regarding the subject's clinical status preceding death should be provided, if available)
  - **Death due to Acute Myocardial Infarction** refers to an acute myocardial infarction (MI) leading inexorably to death, generally within 30 days. Death due to known sequelae of MI including mechanical complications, arrhythmia, and/or pump failure, as well as death resulting from a procedure to treat myocardial ischemia or to treat a complication resulting from myocardial infarction should be considered death due to acute MI. The acute myocardial infarction should be verified either by the diagnostic criteria outlined for acute myocardial infarction or by autopsy findings showing recent myocardial infarction or recent coronary thrombus, and there should be no conclusive evidence of another cause of death.

    If death occurs before biochemical confirmation of myocardial necrosis can be obtained, adjudication should be based on clinical presentation and ECG evidence.

    Death due to a myocardial infarction that occurs as a direct consequence of a cardiovascular investigation, procedure, or operation should be classified as death due to other cardiovascular cause.
  - **Death due to Heart Failure or Cardiogenic Shock** refers to death occurring in the context of clinically worsening symptoms and/or signs of heart failure without evidence of another cause of death.

Death due to heart failure or cardiogenic shock should include sudden death occurring during an admission for worsening heart failure as well as death from progressive heart failure or cardiogenic shock following implantation of a mechanical assist device.

New or worsening signs and/or symptoms of congestive heart failure (CHF) include any of the following:

- New or increasing symptoms and/or signs of heart failure requiring the initiation of, or an increase in, treatment directed at heart failure or occurring in a subject already receiving maximal therapy for heart failure
- Heart failure symptoms or signs requiring continuous intravenous therapy or chronic oxygen administration for hypoxia due to pulmonary edema
- Confinement to bed predominantly due to heart failure symptoms
- Pulmonary edema sufficient to cause tachypnea and distress not occurring in the context of an acute myocardial infarction, worsening renal function, or as the consequence of an arrhythmia occurring in the absence of worsening heart failure
- Cardiogenic shock not occurring in the context of an acute myocardial infarction or as the consequence of an arrhythmia occurring in the absence of worsening heart failure. Cardiogenic shock is defined as systolic blood pressure (SBP) <90 mm Hg for greater than 1 hour, not responsive to fluid resuscitation and/or heart rate correction, and felt to be secondary to cardiac dysfunction and associated with at least one of the following signs of hypoperfusion:
  - Cool, clammy skin or
  - Oliguria (urine output < 30 mL/hour) or
  - Altered sensorium or
  - Cardiac index < 2.2 L/min/m^2

  Cardiogenic shock can also be defined if SBP < 90 mm Hg and increases to ≥ 90 mm Hg in less than 1 hour with positive inotropic or vasopressor agents alone and/or with mechanical support.

  Note: Heart failure may have a number of underlying causes, including acute or chronic ischemia, structural heart disease (e.g. hypertrophic cardiomyopathy), and valvular heart disease. Where treatments are likely to have specific effects, and it is likely possible to distinguish between the various causes, then it may be reasonable to separate out the relevant treatment effects. In other cases, the aggregation implied by the definition above may be more appropriate.

◦ **Death due to Stroke (Cerebrovascular Event: intracranial hemorrhage or non-hemorrhagic stroke)** refers to a cerebrovascular event or a complication of a cerebrovascular event that leads inexorably to death, generally within 30 days after the suspected event. These deaths may be based on clinical signs and symptoms as well as neuroimaging and/or autopsy. There should be no conclusive evidence of another cause of death.

◦ **Death due to Other Cardiovascular Causes** refers to death due to a cardiovascular cause not included in the above categories (e.g. dysrhythmia, pulmonary embolism,

cardiovascular intervention, aortic aneurysm rupture, or peripheral arterial disease). Mortal complications of cardiac surgery or PCI, even if "non-cardiovascular" in nature, should be classified as cardiovascular deaths.

- **Death Due to Bleeding** refers to fatal bleeding or bleeding which contributes to death, with categories being mutually exclusive.
  - **Fatal Bleeding:** death in which a bleeding event directly leads to death within 7 days. Examples of fatal bleeding include an intracranial hemorrhage that leads to herniation of the brain and death within 24 hours, or a massive gastrointestinal hemorrhage that results in shock, hemodynamic collapse, and death. If a bleeding event is considered fatal, then the cause of death should be either intracranial or non-intracranial bleeding.
  - **Bleeding Contributes to Death:** death in which a bleeding event is part of a causal chain of medical events that ultimately leads to death within 30 days of the bleed, but bleeding is not directly and/or immediately related to the subject's death. An example of bleeding that contributes to death is a large retroperitoneal bleed that leads to surgical evacuation and subsequent development of an abscess in the area of bleeding that leads to sepsis, multiorgan failure, and death 10 days after the onset of bleeding. If bleeding contributes to death (but the bleeding is not categorized as "fatal"), then the cause of death should be recorded as something other than intracranial/non-intracranial bleeding.

- **Non-Cardiovascular Death** is defined as any death not covered by cardiac death or vascular death. Categories include but are not limited to:
  - Pulmonary causes
  - Renal causes
  - Gastrointestinal causes
  - Infection (includes sepsis)
  - Non-infectious (e.g., systemic inflammatory response syndrome (SIRS))
  - Malignancy (i.e., new malignancy, worsening of prior malignancy)
  - Accidental/Trauma
  - Suicide
  - Non-cardiovascular system organ failure (e.g., hepatic failure)
  - Non-cardiovascular surgery
  - Other non-cardiovascular
- **Undetermined cause of death** refers to a death not attributable to one of the above categories of cardiovascular death or to a non-cardiovascular cause. *For this trial all deaths with undetermined causes will be included in the cardiovascular category.*

16.1.2. Definition of Myocardial Infarction

Different criteria for spontaneous and peri-procedural MI will be utilized.

- **Spontaneous MI** (occurring >72 hours after any PCI or CABG)

Detection of rise and/or fall of cardiac biomarkers (CK-MB or troponin) with at least one value

above the upper reference limit (URL)* together with evidence of myocardial ischemia with at least one of the following:

- ECG changes indicative of new ischemia [ST-segment elevation or depression as defined below, in the absence of other causes of ST-segment changes such as left ventricular hypertrophy (LVH) or bundle branch block (BBB)] *or*
- Development of pathological Q waves (≥0.04 seconds in duration and ≥1 mm in depth) in ≥2 contiguous precordial leads or ≥2 adjacent limb leads) of the ECG, *or*
- Angiographically documented graft or native coronary artery occlusion or new severe stenosis with thrombosis and/or diminished epicardial flow, *or*
- Imaging evidence of new loss of viable myocardium or new regional wall motion abnormality

  *If the upper reference limit (URL) from the respective laboratory performing the assay is not available, then the URL for myocardial necrosis from the laboratory should be used. If the URL or the URL for myocardial necrosis is not available, the MI decision limit for the particular laboratory should be used as the URL. Reference limits from the laboratory performing the assay are preferred over the manufacturer's listed reference limits in an assay's instructions for use.

  - **ST elevation**

    New ST elevation at the J point in two anatomically contiguous leads with the cut-off points: ≥0.2 mV in men (>0.25 mV in men <40 years) or ≥0.15 mV in women in leads V2-V3 and/or ≥0.1 mV in other leads
  - **ST depression**

    New horizontal or down-sloping ST depression ≥0.05 mV in two contiguous leads.

  The above ECG criteria illustrate patterns consistent with myocardial ischemia

- **Procedure-Related Myocardial Infarction** (occurring within 72 hours of either PCI or CABG)

  In the present study it is essential to have an identical definition for MI after both PCI and CABG to eliminate ascertainment bias. Furthermore, given that MI represents one component of the primary composite endpoint of death, stroke or MI, and that death and stroke are devastating complications, only prognostically important MI that has clearly been associated with subsequent mortality will be included in the primary endpoint. In this regard, small levels of cardiac enzyme elevation after PCI reflect the underlying degree of atherosclerosis [135] and seem to have little or no prognostic significance, [136, 137] Large-scale studies in the stent era have shown that peak post-PCI levels of ≥8x the upper limits of normal ULN or ≥10x ULN are required before an association with subsequent mortality emerges, [138] although some studies have suggested that a CPK-MB of CPK-MB ≥5x ULN may be prognostically important. [137, 139, 140] Myocardial infarction may be difficult to diagnosis in the peri-surgical period given an obligate release of cardiac enzymes from all CABG procedures, although post CABG CPK-MB levels of ≥5 fold or ≥10 fold increased have been shown to be prognostically related to subsequent mortality. [141, 142, 143, 144] Moreover, cardiac troponin elevations after PCI are of uncertain prognostic importance, in contrast to

spontaneous troponin elevations in subjects with myonecrosis unrelated to revascularization procedures (spontaneous MI), for which numerous studies have shown to be strongly predictive of subsequent mortality.[140,145,146,147,148,149,150] Thus, in the present study only CK-MB elevations will be used for determination of peri-procedural MI, whereas troponin or CK-MB elevations may be used to diagnose spontaneous MI.

CK-MB levels will be drawn at baseline and at 12±2 hrs and at 24±2 hrs post procedure (or at discharge if this occurs before 24±2 hrs), and more frequently for signs or cardiac symptoms of clinical or hemodynamic instability. 12-lead EKGs will be recorded at baseline, within 24 hours after the procedure (at the same time as the CK-MB draw if possible) and at discharge.

The baseline CK-MB must be normal for subject enrolment in this study. A post procedure MI will be defined as the occurrence within 72 hours after either PCI or CABG of either:

- CK-MB above 10 x URL (*determined on a single measurement), OR
- CK-MB above 5 x URL (*determined on a single measurement), PLUS
  - new pathological Q waves in at least 2 contiguous leads or new persistent non-rate related LBBB, *or*
  - angiographically documented graft or native coronary artery occlusion or new severe stenosis with thrombosis and/or diminished epicardial flow, *or*
  - imaging evidence of new loss of viable myocardium or new regional wall motion abnormality

Symptoms of cardiac ischemia (which are of course difficult to assess in the post CABG patient either because of intubation or incisional pain) are not required for the diagnosis of peri-procedural MI.

For each MI identified by the CEC, the type of MI will also be described as:

- ST-Elevation MI (STEMI)
  - Also categorize as:
    - Q-wave**
    - Non-Q-wave
    - Unknown (no ECG or ECG not interpretable)
- Non-ST-Elevation MI (NSTEMI)
  - Also categorize as:
    - Q-wave**
    - Non-Q-wave
    - Unknown (no ECG or ECG not interpretable)
- Unknown (no ECG or ECG not interpretable)

** Development of new (i.e., not present on the subject's ECG before allocation) pathological Q-waves (≥0.04 seconds in duration and ≥1 mm in depth) in ≥2 contiguous precordial leads or ≥2 adjacent limb leads.

16.1.3. Definition of Stroke

Stroke is defined as the rapid onset of a new persistent neurologic deficit attributed to an obstruction in cerebral blood flow and/or cerebral hemorrhage with no apparent non-vascular cause (e.g., trauma, tumor, or infection). Available neuroimaging studies will be considered to support the clinical impression and to determine if there is a demonstrable lesion compatible with an acute stroke. Strokes will be classified as ischemic, hemorrhagic, or unknown.

All patients to be randomized into the Excel RCT will have a modified Rankin Scale (mRS) assessment conducted by mRS trained personnel at baseline and each visit and telephone interview. Additionally, the site research coordinator will evaluate each subject at 30 days, 6 months, 1, 2, 3, 4 and 5 Y follow-up time points and at the primary endpoint follow-up time point (either at annual follow-up or at subject contact for primary endpoint AE check) using a Transient Ischemic Attack (TIA)/Stroke Questionnaire and mRS Disability Questions (Appendix J). This questionnaire is a National Institute of Health Stroke Scale (NIHSS) validated questionnaire used in the CREST clinical trial. The mRS disability questions are adapted from a structured interview developed for stroke patients[1]. If a subject's response to this questionnaire indicates a possible stroke or a change in the mRS, then a vascular neurologist or stroke specialist or a mRS certified personnel will confirm the mRS scale, determine whether a stroke has occurred and determine the stroke severity using the NIHSS TIA/Stroke questionnaire.

If a new stroke is diagnosed at the site, the investigators at the site will prepare a short narrative that describes the findings that support the diagnosis. All stroke events will be adjudicated by the Clinical Events Committee (CEC). Furthermore, if there is an increase in the mRS by one or more points noted at any visit, then an evaluation will be carried out to determine if a stroke or other outcome event has occurred. Post procedure, if a patient is diagnosed and adjudicated with a stroke event by the Clinical Events Committee (CEC), a disability assessment will be performed at least 90 days±2 weeks after the diagnosis of stroke using the mRS assessment instrument.

Any certification or mRS training for the personnel should be based on the structured interview version as in Appendix J (Modified Rankin Disability Questionnaire).

A. For the diagnosis of stroke, the following four criteria should be fulfilled:
    1. Rapid onset* of a focal/global neurological deficit with at least one of the following:
        - Change in level of consciousness
        - Hemiplegia
        - Hemiparesis
        - Numbness or sensory loss affecting one side of the body
        - Dysphasia/Aphasia
        - Hemianopia (loss of half of the field of vision of one or both eyes)

[1] Wilson JTL, Hareendran A, Grant M, Baird T, Shultz UGR, Muir KW, and Bone I. "Improving the Assessment of Outcomes in Stroke: Use of a Structured Interview to Assign Grades on the Modified Rankin Scale." Stroke. 2002; 33; 2243-46.

- Amaurosis fugax (transient complete/partial loss of vision of one eye)
- Other new neurological sign(s)/symptom(s) consistent with stroke

*If the mode of onset is uncertain, a diagnosis of stroke may be appropriate provided that there is no plausible non-stroke cause for the clinical presentation

2. Duration of a focal/global neurological deficit ≥24 hours or<24 hours if any of the following conditions exist:
   i. at least one of the following therapeutic interventions:
      a. Pharmacologic (i.e., thrombolytic drug administration)
      b. Non-pharmacologic (i.e., neurointerventional procedure such as intracranial angioplasty)
   ii. Available brain imaging clearly documents a new hemorrhage or infarct
   iii. The neurological deficit results in death
3. No other readily identifiable non-stroke cause for the clinical presentation (e.g., brain tumor, trauma, infection, hypoglycemia, other metabolic abnormality, peripheral lesion, or drug side effect). Patients with non-focal global encephalopathy will not be reported as a stroke without unequivocal evidence based upon neuroimaging studies.
4. Confirmation of the diagnosis by a neurology or neurosurgical specialist and at least one of the following:
   a. Brain imaging procedure (at least one of the following):
      i. CT scan
      ii. MRI scan
      iii. Cerebral vessel angiography
   b. Lumbar puncture (i.e. spinal fluid analysis diagnostic of intracranial hemorrhage)

B. If the acute focal signs represent a worsening of a previous deficit, these signs must have either
   1. Persisted for more than one week, or
   2. Persisted for more than 24 hours and were accompanied by an appropriate new CT or MRI finding

C. Strokes may be sub-classified as follows:
   1. Ischemic (Non-hemorrhagic): a stroke caused by an arterial obstruction due to either a thrombotic (e.g., large vessel disease/atherosclerotic or small vessel disease/lacunar) or embolic etiology.
   2. Hemorrhagic: a stroke due to a hemorrhage in the brain as documented by neuroimaging or autopsy. This category will include strokes due to primary intracerebral hemorrhage (intraparenchymal or intraventricular), ischemic strokes with hemorrhagic transformation (i.e., no evidence of hemorrhage on an initial imaging study but appearance on a subsequent scan), subdural hematoma,* and primary subarachnoid hemorrhage.

      *All subdural hematomas that develop during the clinical trial should be recorded and classified as either traumatic versus nontraumatic.
   3. Unknown: the stroke type could not be determined by imaging or other means (e.g., lumbar puncture, neurosurgery, or autopsy) or no imaging was performed.

D. Stroke Disability

All strokes with stroke disability of Modified Rankin Scale (mRS) ≥1 will be included in the primary endpoint. All diagnosed strokes (even with mRS 0) will also be tabulated. Stroke disability will be classified using an adaptation of the modified Rankin Scale as follows, the assessment of which will be based on the Modified Rankin Disability Questionnaire (Appendix J.)

Scale	Disability
0	No stroke symptoms at all. (May have other complaints)
1	No significant disability; symptoms present but no physical or other limitations.
2	Slight disability; limitations in participation in usual social roles, but independent for activities of daily living (ADL)
3	some need for assistance but able to walk without assistance
4	Moderately severe disability; need for assistance with some basic ADL, but not requiring constant care
5	Severe disability; requiring constant nursing care and attention.
Stroke: Modified Rankin score ≥1 and increase by ≥1 from baseline	

E. Transient Ischemic Attack (as compared to stroke) is defined as:

- New focal neurologic deficit with rapid symptom resolution, usually 1-2 hours, always within 24 hours
- Neuroimaging without tissue injury

16.1.4. Definition of Coronary Revascularization Procedures

A coronary revascularization procedure may be either a coronary artery bypass graft (CABG) surgery or a percutaneous coronary intervention (PCI) (for example, angioplasty, stenting), regardless of procedural success.

Coronary revascularization procedures may be further classified as follows:

- Urgent: an urgent procedure is one that is performed within 48 hours of upon diagnosis of the subject's status due to urgency of the medical condition, but is not otherwise considered emergent
- Emergent: an emergent procedure is one that is performed as soon as possible (usually within 6 hours)
- Elective: an elective procedure is one that is scheduled and is not urgent or emergent

Procedural Success may be defined as follows:

- CABG: the successful placement of at least one conduit with either a proximal and distal anastomosis or a distal anastomosis only

- PCI: successful balloon inflation with or without stenting and the achievement of a residual stenosis <50% of the left anterior descending coronary artery and/or the left circumflex artery. The balloon inflation and/or stenting could have been preceded by adjunctive device use (e.g., Angiojet, rotational atherectomy etc.)

Target Lesion: A lesion revascularized in the index procedure (or during a planned or provisional staged procedure). The LM target lesion extends from the left main stem ostium to the end of the 5 mm proximal segments of the left anterior descending and left circumflex arteries as well as the ramus intermedius if the latter vessel has a vessel diameter of ≥2 mm.

Target Vessel: The target vessel is defined as the entire major coronary vessel proximal and distal to the target lesion including upstream and downstream branches and the target lesion itself. The left main and any vessel originating from the left main coronary artery or its major branches is, by definition, considered a target vessel for the purposes of this trial (unless either the LAD or LCX are occluded at baseline and no attempt was made to revascularize these territories by either PCI or CABG).

Target Vessel-Non-Target Lesion: The target vessel but non-target lesion consists of a lesion in the epicardial vessel/branch/graft that contains the target lesion; however, this lesion is outside of the target lesion by at least 5 mm distal or proximal to the target lesion determined by quantitative coronary angiography (QCA)

Non-Target Vessel: For the purposes of this trial, the only possible non-target vessel would be the right coronary artery and its major branches that were not treated by either PCI or CABG at the index procedure (unless either the LAD or LCX are occluded at baseline and no attempt was made to revascularize these territories by either PCI or CABG).

Target Vessel Revascularization (TVR): Target vessel revascularization is any repeat percutaneous intervention of the target vessel or bypass surgery of the target vessel

Target Lesion Revascularization (TLR): Target lesion revascularization is defined as any repeat percutaneous intervention of the target lesion or bypass surgery of the target vessel

All revascularization events will be adjudicated as either ischemia-driven or non ischemia-driven

Ischemia-Driven Target Lesion (or Vessel) Revascularization: A target lesion (vessel) revascularization will be considered ischemia-driven if the target lesion diameter stenosis is ≥50% by QCA (analysis segment measurement, involving the lesion itself and 5 mm of proximal and/or distal margin) and any of the following criteria for ischemia are met:

- A positive functional study corresponding to the area served by the target lesion; or
- Ischemic ECG changes at rest in a distribution consistent with the target vessel; or
- Typical ischemic symptoms referable to the target lesion; or
- IVUS of the target lesion with a minimal lumen area (MLA) of ≤4mm^{2}for non left main lesions or ≤6mm^{2}for left main lesions. If the lesions are *de novo* (i.e. not restenotic), the plaque burden must also be ≥60%; or
- FFR of the target lesion ≤0.80

Note: A target lesion revascularization for a diameter stenosis less than 50% might also be considered ischemia-driven by the CEC if there was a markedly positive functional study or ECG changes corresponding to the area served by the target lesion.

Ischemia-Driven Non-Target Vessel Revascularization: A non target vessel revascularization will be considered ischemia-driven if any lesion the non target vessel has a diameter stenosis ≥ 50% by QCA with any of the above criteria for ischemia met.

Unplanned revascularization for ischemia: Any repeat revascularization of either a target vessel or non-target vessel with any of the above criteria for ischemia met.

16.2. Other Definitions

Adverse Device Effect

Represents a possibly, probably or definitely device-related Adverse Event.

Adverse Event

An adverse event (AE) is any untoward medical occurrence, unintended disease or injury, or untoward clinical signs (including abnormal laboratory findings) in subjects, users or other persons, whether or not related to the investigational medical device.

Bleeding Complication

Bleeding will be classified by the TIMI hemorrhage classification.

Severity	
Major	• Intracranial hemorrhage –OR– • A ≥5 g/dL decrease in the hemoglobin concentration –OR– • A ≥15% absolute decrease in the hematocrit
Minor	• Observed blood loss: o A ≥3 g/dL decrease in the hemoglobin concentration –OR– o A ≥10% absolute decrease in the hematocrit • No observed blood loss: o A ≥4 g/dL decrease in the hemoglobin concentration –OR– o A ≥12% absolute decrease in the hematocrit
Minimal	• Any clinically overt sign of hemorrhage (including imaging) that is associated with a <3 g/dL decrease in hemoglobin concentration or <9% decrease in the hematocrit

All TIMI definitions take into account blood transfusions, so that hemoglobin and hematocrit values are adjusted by 1 g/dl or 3%, respectively, for each unit of blood transfused. Therefore, the true change in hemoglobin or hematocrit if there has been an intervening transfusion between two blood measurements is calculated as follows:

- Δ Hemoglobin = [baseline Hgb – post-transfusion Hgb] + [number of transfused units];
- Δ Hematocrit = [baseline Hct – post-transfusion Hct] + [number of transfused units X 3].

Bleeding Academic Research Consortium (BARC) Definition for Bleeding[1]

Type 0: no bleeding

Type 1: bleeding that is not actionable and does not cause the patient to seek unscheduled performance of studies, hospitalization, or treatment by a healthcare professional; may include episodes leading to self-discontinuation of medical therapy by the patient without consulting a healthcare professional

Type 2: any overt, actionable sign of hemorrhage (eg, more bleeding than would be expected for a clinical circumstance, including bleeding found by imaging alone) that does not fit the criteria for type 3, 4, or 5 but does meet at least one of the following criteria: (1) requiring nonsurgical, medical intervention by a healthcare professional, (2) leading to hospitalization or increased level of care, or (3) prompting evaluation

Type 3

Type 3a

- Overt bleeding plus hemoglobin drop of 3 to < 5 g/dL* (provided hemoglobin drop is related to bleed)
- Any transfusion with overt bleeding

Type 3b

- Overt bleeding plus hemoglobin drop ≥5 g/dL* (provided hemoglobin drop is related to bleed)
- Cardiac tamponade
- Bleeding requiring surgical intervention for control (excluding dental/nasal/skin/hemorrhoid)
- Bleeding requiring intravenous vasoactive agents

Type 3c

- Intracranial hemorrhage (does not include microbleeds or hemorrhagic transformation, does include intraspinal)
- Subcategories confirmed by autopsy or imaging or lumbar puncture
- Intraocular bleed compromising vision

Type 4: CABG-related bleeding

- Perioperative intracranial bleeding within 48 h
- Reoperation after closure of sternotomy for the purpose of controlling bleeding
- Transfusion of ≥ 5 U whole blood or packed red blood cells within a 48-h period†
- Chest tube output ≥ 2L within a 24-h period

[1] Mehran R, Rao SV, Bhatt DL, et al. Stnadardized Bleeding Definitions for Cardiovascular Clinical Trials: A Consensus Report From the Bleeding Academic Research Consortium.Circulation.2011.123:2736-2747.

Type 5: fatal bleeding

Type 5a

Probable fatal bleeding; no autopsy or imaging confirmation but clinically suspicious

Type 5b

Definite fatal bleeding; overt bleeding or autopsy or imaging confirmation

Note: CABG indicates coronary artery bypass graft. Platelet transfusions should be recorded and reported but are not included in these definitions until further information is obtained about the relationship to outcomes. If a CABG-related bleed is not adjudicated as at least a type 3 severity event, it will be classified as not a bleeding event. If a bleeding event occurs with a clear temporal relationship to CABG (ie, within a 48-h time frame) but does not meet type 4 severity criteria, it will be classified as not a bleeding event.

*Corrected for transfusion (1 U packed red blood cells or 1 U whole blood =1 g/dL hemoglobin).
†Cell saver products are not counted.

Chronic Concomitant Medications

Medication that:

- has been prescribed or is an over the counter (OTC) medication that has been taken or will continue to be taken regularly for at least a period of 6 months, *or*
- is required to be taken indefinitely by the subject, *or*
- has been prescribed or is an OTC medication that has been taken multiple times (each time for at least 6 months)

Complete Revascularization

See Section 19, Appendix D for the definitions of complete anatomic and ischemic revascularization.

Major Adverse Event (assessed in-hospital and 30 days only)

Composite of death, myocardial infarction, stroke, transfusion of ≥ 2 units of blood, major arrhythmia, unplanned coronary revascularization for ischemia, any unplanned surgery or radiologic procedure, renal failure, sternal wound dehiscence, infection requiring antibiotics for treatment, intubation for >48 hours, or post-pericardiotomy syndrome.

Major Arrhythmia

Ventricular tachycardia or fibrillation requiring cardioversion or countershock; atrial fibrillation lasting >24 hours; bradycardia or conduction system disease requiring a permanent pacemaker.

Myocardial Infarction from Universal Definition

The analysis of RCT data will include the incidence of MI using the Universal Definition[151] for each treatment group evaluated descriptively as a secondary endpoint.

The term myocardial infarction should be used when there is evidence of myocardial necrosis in a clinical setting consistent with myocardial ischemia. Under these conditions any one of the following criteria meets the diagnosis for myocardial infarction:

- Detection of rise and/or fall of cardiac biomarkers (preferably troponin) with at least one value above the upper reference limit together with evidence of myocardial ischemia with at least one of the following:
- Symptoms of ischaemia;
- ECG changes indicative of new ischemia (new ST-T changes or new left bundle branch block);
- Development of pathological Q waves in the ECG;
- Imaging evidence of new loss of viable myocardium or new regional wall motion abnormality.
- Sudden, unexpected cardiac death, involving cardiac arrest, often with symptoms suggestive of myocardial ischemia, and accompanied by presumably new ST

  elevation, or new LBBB, and/or evidence of fresh thrombus by coronary angiography and/or at autopsy, but death occurring before blood samples could be obtained, or at a time before the appearance of cardiac biomarkers in the blood.
- For percutaneous coronary interventions (PCI) in patients with normal baseline troponin values, elevations of cardiac biomarkers above the URL are indicative of peri-procedural myocardial necrosis. By convention, increases of biomarkers greater than 3 X URL have been designated as defining PCI-related myocardial infarction. A subtype related to a documented stent thrombosis is recognized.
- For coronary artery bypass grafting (CABG) in patients with normal baseline troponin values, elevations of cardiac biomarkers above the URL are indicative of peri-procedural myocardial necrosis. By convention, increases of biomarkers greater than 5 X URL plus either new pathological Q waves or new LBBB, or angiographically documented new graft or native coronary artery occlusion, or imaging evidence of new loss of viable myocardium have been designated as defining CABG-related myocardial infarction.
- Pathological findings of an acute myocardial infarction.

Renal Failure

Serum creatinine increase by ≥1 mg/dL from baseline or need for dialysis.

Serious Adverse Event

If the adverse event meets any of the criteria below, it is regarded as a serious adverse event (SAE).

- a) Led to a death,
  b) Led to a serious deterioration in health that either:
  1) Resulted in a life-threatening illness or injury, or

2) Resulted in a permanent impairment of a body structure or a body function, or
3) Required in-patient hospitalization or prolongation of existing hospitalization, or
4) Resulted in medical or surgical intervention to prevent life threatening illness or injury or permanent impairment to a body structure or a body function.

c) Led to fetal distress, fetal death or a congenital abnormality or birth defect.

d) An important medical event that may not result in death, be life-threatening, or require hospitalization but may be considered serious when, based upon appropriate medical judgment, may jeopardize the patient or subject and/or may require intervention to prevent one of the outcomes listed in this definition.

Stent Thrombosis

For this trial, stent thrombosis will be defined as the occurrence of definite or probable stent thrombosis according to the ARC criteria.

1. Stent Thrombosis: Timing

Type	Timing
Acute stent thrombosis*	0 to 24 hours after stent implantation
Subacute stent thrombosis	>24 hours to 30 days after stent implantation
Late stent thrombosis†	>30 days to 1 year after stent implantation
Very late stent thrombosis†	>1 year after stent implantation
Stent thrombosis will be reported as a cumulative value over time and at the various individual timepoints specified above. Time 0 is defined as the timepoint after the guiding catheter has been removed and the subject has left the catheterization laboratory.	
*Acute or subacute can also be replaced by the term early stent thrombosis. Early stent thrombosis (0 to 30 days) will be used in the remainder of this document.	
†Includes primary as well as secondary late stent thrombosis; secondary late stent thrombosis is a stent thrombosis after a target lesion revascularization.	

2. ARC Definitions of Definite, Probable, and Possible Stent Thrombosis

- **Definite Stent Thrombosis**

Definite stent thrombosis is considered to have occurred by *either* angiographic or pathological confirmation:

a. Angiographic confirmation of stent thrombosis†

The presence of a thrombus‡ that originates in the stent or in the segment 5 mm proximal or distal to the stent and presence of at least 1 of the following criteria within a 48-hour time window:

1. Acute onset of ischemic symptoms at rest
2. New ischemic ECG changes that suggest acute ischemia

3. Typical rise and fall in cardiac biomarkers (refer to definition of spontaneous MI: Troponin or CK-MB > 99th percentile of URL)
4. Nonocclusive thrombus
   a. Intracoronary thrombus is defined as a (spheric, ovoid, or irregular) noncalcified filling defect or lucency surrounded by contrast material (on 3 sides or within a coronary stenosis) seen in multiple projections, or persistence of contrast material within the lumen, or a visible embolization of intraluminal material downstream
5. Occlusive thrombus
   a. TIMI 0 or TIMI 1 intrastent or proximal to a stent up to the most adjacent proximal side branch or main branch (if originates from the side branch)

b. Pathological confirmation of stent thrombosis

Evidence of recent thrombus within the stent determined at autopsy or via examination of tissue retrieved following thrombectomy

- **Probable Stent Thrombosis**

Clinical definition of probable stent thrombosis is considered to have occurred after intracoronary stenting in the following cases:
a. Any unexplained death within the first 30 days
b. Irrespective of the time after the index procedure, any MI that is related to documented acute ischemia in the territory of the implanted stent without angiographic confirmation of stent thrombosis and in the absence of any other obvious cause

- **Possible Stent Thrombosis**

Clinical definition of possible stent thrombosis is considered to have occurred with any unexplained death from 30 days after intracoronary stenting until end of trial follow-up.

†The incidental angiographic documentation of stent occlusion in the absence of clinical signs or symptoms is not considered a confirmed stent thrombosis (silent occlusion)

‡Intracoronary thrombus

Symptomatic Graft Stenosis or Occlusion

Ischemic symptoms in the presence of ≥50% diameter stenosis in a coronary bypass graft.

Unplanned Revascularization, Surgery, or Radiologic Procedure

Vascular access complications, sternal refixation or other complications requiring the subject to return to the cath lab or surgical rooms.

Disability After Stroke

In case of an event of stroke disability at 90-days±2 weeks will be an overall measurement of severity of stroke as assessed by mRS scale as defined in Section 16.1.3.

Left Main Equivalent Disease

Left main Medina classification 0, 1, 1 bifurcation disease (diameter stenosis of both the true ostial LAD and LCX [within 5 mm of the left main distal bifurcation]) ≥50%, in the absence of significant angiographic stenosis in the left main coronary artery, may also be randomized if one

of the two following conditions are present:

- Both the ostial LAD and ostial LCX stenoses are ≥70% stenotic by visual estimation, *or*
- If one or both of the ostial LAD and ostial LCX stenoses are ≥50% and <70% stenotic by visual estimation, then this lesion(s) is demonstrated to be significant either by
  - a) non-invasive evidence of ischemia in its myocardial distribution; and/or
  - b) FFR ≤0.80; and/or
  - c) IVUS MLA ≤4.0mm^2 (FFR is preferred).

Note: If both the ostial LAD and ostial LCX stenoses are ≥50% and <70% stenotic by visual estimation, then both lesions must be significant by these criteria for the patient to be eligible for randomization.

16.3 Abbreviations and Acronyms

Acronym	Definition
ACEF	Age, creatinine and left ventricle ejection fraction.
ACS	Acute coronary syndrome
ADP	Adenosine diphosphate (as in ADP antagonist)
AE	Adverse event
ARC	Academic Research Consortium
Atm	Atmospheres (measurement of pressure)
BARC	Bleeding Academic Research Consortium
BNP	Brain natriuretic peptide
CABG	Coronary artery bypass graft
CASS	Coronary Artery Surgery Study (a trial that has contributed a standard map of coronary artery system)
CEC	Clinical Events Committee
CK-MB	Creatine kinase – muscle brain
CRF/eCRF	Case report form / electronic case report form
CRO	Contract research organization -or- Clinical research organization
hsCRP	High sensitivity C-reactive protein
CTO	Chronic total occlusion
CSA	Cross-sectional area
DES	Drug eluting stent
DS	Diameter stenosis (%)
DSMB	Data Safety Monitoring Board
EC	Ethics Committee
ECG	Electrocardiogram
EDC	Electronic data capture
EECS / EECSS	Everolimus eluting coronary stent / everolimus eluting coronary stent system
EOC	Executive Operations Committee
EU	Europe
FDA	Food and Drug Administration
FFR	Fractional flow reserve
GPIIb/IIIa	Glycoprotein IIb/IIIa
$HgbA_{1c}$	Glycated or glycosylated hemoglobin (average blood glucose concentration over prolonged periods of time)
HR	Hazard ratio
IRB	Institutional Review Board
ITA	Internal thoracic artery
ITT	Intent-to-treat

Acronym	Definition
IVRS	Interactive voice response system
IVUS	Intravascular ultrasound
LAD	Left anterior descending artery
LCX	Left circumflex artery
LM	Left main (coronary artery)
LVEF	Left ventricular ejection fraction
MACE	Major Adverse Cardiac Event
MACCE	Major Adverse Cardiac and Cerebrovascular Events
MI	Myocardial infarction
MLA	Minimum lumen area
MRI	Magnetic resonance imaging
mRS	Modified Rankin Scale
OUS	Outside the U.S.
PCI	Percutaneous coronary intervention
PES	Paclitaxel eluting stent
QALY	Quality adjusted year of life
QoL	Quality of life
RCA	Right coronary artery
RCT	Randomized clinical trial
RHI	Regular Human Insulin
SAE	Serious adverse event
SAQ	Seattle Angina Questionnaire
SOP	Standard operating procedure
ST	Stent thrombosis
STS	Society of Thoracic Surgeons
TEE	Transesophageal echocardiogram
TIA	Transient ischemic attack
TIMI	Thrombolysis In Myocardial Infarction (a trial that has contributed definitions for bleeding as well as coronary artery blood flow)
TLF	Target lesion failure
TLR	Target lesion revascularization
TVR	Target vessel revascularization
UADE	Unanticipated adverse device effect
U.S.	United States
ULMCA	Unprotected left main coronary artery
ULN	Upper limit of normal

17. APPENDIX B: QUALITY OF LIFE AND U.S. HEALTH ECONOMICS SUB-STUDIES

As described in the main clinical protocol, the EXCEL trial will randomize approximately 1900 selected subjects with unprotected left main disease to the XIENCE DES vs. CABG and follow them for up to 10 years; the primary endpoint of the trial is death, MI, or stroke at a median follow-up of 3-years. Given the large sample size and extended follow-up duration, EXCEL will provide an ideal setting in which to definitively examine the relative costs, quality of life benefits, and cost-effectiveness of PCI for this important subject population. In this proposal, the specific goals of the proposed health economic and quality of life studies are outlined as well as the general analytic plans.

The proposed analyses will be directed in about 1800 subjects by David J. Cohen, M.D., M.Sc. in conjunction with the Health Economics and Technology Assessment (HETA) Group of Saint Luke's Mid America Heart Institute. Of note, since cost-effectiveness is dependent on the perspective of the analysis, the health economic analyses described in this proposal will be performed specifically from the U.S. perspective. If additional perspectives from other countries are desired, it should be possible to collaborate with local health economists to extend these methods to these additional countries.

17.1. Study Objectives

17.1.1. Cost Studies

- To compare long-term medical care costs for subjects with unprotected left main coronary disease treated with either PCI (using the XIENCE drug-eluting stent) or CABG from the perspective of the U.S. healthcare system
- To identify factors in addition to treatment assignment that are associated with variations in long-term medical care costs in subjects undergoing revascularization for unprotected left main coronary disease.

17.1.2. Quality of Life Studies

- To compare health-related quality of life between alternative strategies of percutaneous or surgical coronary revascularization, according to the design of the EXCEL trial.
- To identify factors, in addition to treatment assignment, those are associated with variations in quality of life for subjects with left main coronary disease.

17.1.3. Cost-effectiveness Studies

- Within the context of the EXCEL trial, to evaluate the relative cost-effectiveness of PCI with drug-eluting stents and CABG, measured as cost per quality-adjusted year of life gained, over a 3 to 5-year time horizon.

- To evaluate the relative cost-effectiveness of PCI with drug-eluting stents vs. CABG in terms of additional endpoints including cost per life-year gained, cost per death, MI, or stroke avoided, and cost per repeat revascularization procedure avoided.

17.2. Subject Population

The population for the quality of life and cost-effectiveness sub-studies will consist of 1800 subjects. The primary analyses will be conducted on an intention-to-treat (ITT) basis. In particular, any subjects who die prior to receiving their initial revascularization procedure will be retained in the ITT analyses and considered as part of their randomization group. Secondary analyses will be performed based on the per-protocol population (i.e., sub-study subjects who receive their assigned treatment) and a treatment-received population (sub-study subjects based on the initial revascularization procedure performed).

17.3. Quality of Life Assessment

Health-related quality of life will be measured using an instrument incorporating both disease-specific and generic health status measures appropriate for the assessment of subjects with coronary artery disease. Each of the individual health status measures described below has been selecting from an existing instrument that has undergone extensive reliability and validity testing and is appropriate for the subject population being studied in the EXCEL trial.

17.3.1. Disease-specific measures

The goal of the disease-specific measures is to detect differences in health-related quality of life related directly to the two revascularization strategies under consideration. Thus, the primary focus of the disease-specific measures will be to detect differences in symptoms or in quality of life directly attributable to coronary artery disease and its principal complications.

Cardiovascular-specific quality of life will be measured using the Seattle Angina Questionnaire (SAQ)[77] along with the London School of Hygiene Dyspnea Questionnaire.[79] The SAQ is a 19-item questionnaire that measures five domains of CAD-related health status: angina frequency, physical limitations, disease perception/QoL, angina stability, and treatment satisfaction. Scores range from 0 to 100 with higher scores indicating fewer symptoms and thus better health status. The SAQ has undergone extensive reliability and validity testing[77, 78]and has been shown to correlate with long-term survival and ACS hospitalization among subjects with chronic CAD.[152]The London School of Hygiene Dyspnea Questionnaire was originally adapted from the Rose Angina Questionnaire and assesses the individual's level of dyspnea with common activities.[79] Previous research has demonstrated that this scale measures an important component of HRQoL in subjects with chronic coronary disease that is independent of traditional angina scales.[80] In addition to their established validity and reliability in subjects with coronary artery disease, these instruments are easily administered either by written questionnaire or direct interview.

17.3.2. Generic quality of life measures

The principal generic quality of life measure for this study will be the Medical Outcomes Study 12-item Short Form Health Status questionnaire (SF-12).[82]The SF-12 is derived from the larger Medical Outcomes Study Short-Form 36 (SF-36), a 36 item questionnaire that has undergone extensive consistency, reliability, and validity testing and has been used to assess quality of life outcomes in more than 250 clinical trials.[153,154] The SF-12 produces two summary scales that assess both physical and mental/emotional health; these summary scores have been shown to correlate well with those obtained from the longer, more time consuming SF-36.[82] In addition to limiting subject burden, a specific advantage of the SF-12 for the purposes of this study is that the summary scales are scored such that the U.S. population mean is 50 and the population standard deviation is 10, thus providing highly interpretable data relative to other populations and health states.

17.3.3. Mental Health/Depression

In both anecdotal experience and uncontrolled observations, depression has been reported to be a relatively common and debilitating late-term complication of CABG. Therefore, in addition to the mental health index provided by the SF-12, a more detailed assessment of depression using the PHQ-8 will be performed. This 8-item module derived from the larger Patient Health Questionnaire has been shown to be a highly valid and reliable measure of depression. Scores range from 0 to 24 with levels ≥5 generally considered to represent mild depression and levels ≥10 representing moderate depression. [155] It differs from the original PHQ-9 only in the elimination of the suicidality question, which may be considered to be inappropriate for many clinical trial population.[81] Similar to the SAQ and SF-12, culturally valid translations are available in multiple languages including virtually all of the countries that are expected to contribute subjects to the EXCEL trial.

17.3.4. Utility measurement

For the purposes of cost-effectiveness analysis, quality of life must also be measured in terms of "utility", a global rating (on a 0-1 scale) that reflects an individual's preference for his or her current health state relative to perfect health.[29] Although in the past, it had been customary to measure utility directly from trial participants using time-tradeoff techniques,[156,157] there is an emerging consensus that cost-effectiveness analyses designed to inform societal resource allocation use community-based (rather than subject-based) preferences.[158]

There are a number of potential techniques for measurement of subject-specific, population-based utility weights within the EXCEL trial. These include the Health Utilities Index (HUI),[159] the Quality of Well-Being Scale (QWB),[160] the EuroQol (EQ-5D),[83] and recently published algorithms that allow mapping of the SF-36 or SF-12 to health state utilities.[161,162] Although each of these approaches has intrinsic advantages (and disadvantages), the preferred utility instrument for the EXCEL trial is the EQ-5D. The EQ-5D is a multiattribute health status classification system with an empirically-derived preference based scoring system based on analysis of time trade-off utilities for selected health states among 2997 randomly-selected members of the adult population of the U.K.[163]Recently, analogous preference-weights have been developed for U.S. population utilities.[84]

Although the EQ-5D was not specifically developed for use in subjects with coronary artery disease, it offers several specific advantages for this trial. First, it is based on a health state classification system that includes five specific domains of health: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. By incorporating many of the domains that are likely to be affected by coronary artery disease and its complications, such as pain, physical limitations, and role limitations, the EQ-5D should capture important differences in health within the study population. Second, the EQ-5D may be administered by either a five item written questionnaire or telephone interview and thus should add little burden to the overall data collection task. By comparison, both the HUI and the QWB questionnaires are substantially longer and, in previous experience, are often too burdensome for chronically-ill subjects. Finally, considerable practical experience with the EQ-5D exists as it has been used successfully as the principal utility measure in the Benestent II Trial (n=823)[164] and the PAMI Stent trial (n=900),[165] and most recently in the SYNTAX trial.

17.3.5. Economic Data Collection

The following data elements will be obtained from the EXCEL trial database for use in this sub-study:

- Measures of global medical resource utilization for each hospitalization including length of stay and number of ICU days.
- Cardiac catheterization laboratory resource utilization for the index procedure as well as any subsequent catheterizations or PCI procedures required during the follow-up period. Data collected will include total procedure duration; numbers of angioplasty balloons, stents (bare and drug-eluting), guidewires, ultrasound catheters, and guiding catheters used; adjunctive medications used including glycoprotein IIb/IIIa antagonists and direct thrombin inhibitors; and the amount and type of contrast dye required. These data will provide a direct measure of resource utilization for the two strategies, and will be used to examine the true costs of initial PCI based on standard, "bottom-up" accounting measures.[85,166]
- Measures of global resource utilization for each initial and follow-up hospitalization for treatment of cardiovascular disease, its direct complications, and potential complications of treatment. For each hospital admission, these data will include total length of stay, number of ICU days, principal diagnosis, and major procedures performed during the hospitalization (e.g., coronary revascularization, pacemaker or ICD implantation, peripheralvascular surgery). Hospital admissions unrelated to treatment of cardiovascular disease or potential complications of its treatment will be identified by an independent review committee, blinded to initial treatment assignment and excluded from the economic analysis, since any differences in these events are unlikely to be related to the assigned treatment strategy. Thus, their inclusion in the economic analysis would only increase the variance of the cost estimates and reduce statistical power.
- Detailed listing of outpatient medications for treatment of cardiovascular disease at each follow-up subject contact.
- Subject estimates (by self-report) of utilization of outpatient cardiovascular services including diagnostic testing (e.g., ETT, nuclear stress testing, echocardiography, cardiac

CT); outpatient procedures (e.g., diagnostic catheterization, cardioversion); and physician visits.

- Number and duration of admissions to rehabilitation hospitals, nursing homes, and other chronic care facilities.

17.4. Cost Measurement

17.4.1. Procedural Costs

Catheterization laboratory and bypass costs will be calculated for each subject using standard, "bottom-up" cost accounting methods using the most current unit costs available at the time of each analysis.[85] For example, if the 1-year analysis is performed in 2013, every effort will be made to obtain updated unit costs for 2013. Similarly, if the 5-year analysis is performed in 2015, unit costs for that year will be used as the basis for the cost analysis. The rationale for using updated costs is that the goal of the cost-effectiveness analysis is to inform ongoing policy development and not merely to describe historically-relevant costs.

For major disposable items (including angioplasty balloons, bare metal and drug-eluting stents, guidewires, and guiding catheters), costs will be based on a survey of U.S. hospital and catheterization laboratory administrators as to the acquisition costs for the item at the time of the analysis. Drug costs for procedural anticoagulants including glycoprotein 2b/3a antagonists, direct thrombin inhibitors, and thrombolytic agents will be determined in a similar fashion. Updated cost data for the final calculations and analysis will ensure that the cost estimates are accurate at the time of publication. The cost of other disposables, depreciation, and overhead for catheterization laboratory maintenance, and non-physician personnel will be estimated based on the average cost per procedure at 3-5 geographically diverse U.S. medical centers during the same time frame and adjusted for measured procedure duration. Similar methods will be applied to estimate the procedural cost of CABG.

17.4.2. Non-procedural Hospitalization Costs

The non-procedural costs of hospitalizations will be estimated in two ways. The primary method will utilize an event-based approach to estimating costs; the secondary approach will utilize a resource-based approach. The advantage of the event-based approach to hospitalization costs is that it does not rely on an assumption of comparability of length of stay between U.S. and non-U.S. subjects. Rather, nationally-representative data will be used to estimate the cost of an uncomplicated hospital admission and also the relationship between specific procedural complications and hospital costs. This approach is identical to one that has recently been employed for calculation of costs in the SYNTAX trial. Details of this estimation process are outlined below.

The event-based approach relies on the Medicare Provider and Review (MedPAR) database. The MedPAR file is an administrative database maintained by the Centers for Medicare and Medicaid Services containing all claims submitted by hospitals for services provided to Medicare beneficiaries. For each hospitalization, the MedPAR record includes information on age, sex, race, date of admission, date of discharge; the principal diagnosis code (ICD-9-CM), eight secondary ICD-9-CM diagnosis codes, six ICD-9-CM procedure codes, discharge status, total

charges, total reimbursement, and the hospital's Medicare provider number.

Estimating costs consists of three steps. In the first step, the MedPAR database will be used to model the relationship between the total index hospitalization costs and the costs associated with various complications occurring after the procedure of interest but during the index hospitalization. Estimates of the costs of these complications will be obtained via a regression using a model with structure:

$$TC_i = A + X_i\beta + Z_i\delta + u_i$$

where TC_i is the total cost of the index hospitalization for subject i, X_i is a set of indicator variables for subject i denoting whether particular complications occurred, β is an associated parameter vector representing the estimated costs of the complications, Z_i is a set of individual baseline subject characteristics (e.g., age, sex, etc.), δ is an associated parameter vector representing the incremental cost of the characteristics, A represents the sum of procedural costs and any other costs for an uncomplicated hospitalization, and u_i is a residual. This model will be estimated separately for each procedure type.

The second step will be to obtain an estimate of the mean cost of uncomplicated hospitalizations. Letting UHC be uncomplicated hospitalization costs (excluding procedural costs), and PC be procedural costs, for each subject is defined as:

$$W_i = UHC_i + PC_i,$$

which would imply

$$\overline{W} = \overline{UHC} + \overline{PC}.$$

Since the regression in step 1 does not specify a separate intercept for each subject, it is reasonable to think of A as an average across all subjects, i.e., that $\hat{A}$ is an estimate of $\overline{W}$. Then a straightforward way to estimate mean uncomplicated hospital costs ($\overline{UHC}$) is to subtract an estimate of mean procedure costs ($\overline{PC}$) from the estimate of A, i.e.,

$$\hat{\overline{UHC}} = \hat{A} - \hat{\overline{PC}}$$

Mean procedure costs for use in this step will be obtained from the REPLACE-2 trial (14) or a comparable multicenter registry or trial that reflects contemporary PCI practice in a broad, relatively unselected subject population.

The third step is to combine the previously obtained parameter values to produce an estimate of U.S.-relevant costs based on the data from the EXCEL trial. First, an estimate of subject-specific variable costs (Q_i) will be obtained by the estimates of β and δ (as previously derived from the MedPAR analyses) to the EXCEL subject data, i.e.,

$$\hat{Q}_i = X_i \hat{\beta} + Z_i \hat{\delta},$$

where $\hat{\beta}$ and $\hat{\delta}$ are the estimates of β and δ, respectively. An estimate of non-procedural costs

($\hat{NPC}_i$) is then obtained for each subject i by adding subject specific variable costs to the average cost of an uncomplicated subject

$$\hat{NPC}_i = \overline{\hat{UHC}} + \hat{Q}_i .$$

We will then calculate total hospital cost by adding the resource-based procedure costs to the estimated non-procedural costs, i.e.

$$\hat{TC}_i = \hat{NPC}_i + \hat{PC}_i .$$

Finally, in order to preserve subject variability in the cost data, residuals drawn from the step (1) regression will be added to the expected values. The approach outlined above will be used to calculate the cost of each index hospitalization as well as any subsequent hospitalizations during which a coronary revascularization procedure is performed.

For all other cardiovascular hospitalizations, data on principal and secondary diagnoses and any major procedures performed will be used to assign a DRG to the hospitalization. This mapping procedure will be performed in a blinded fashion by the MAHI HETA group working in conjunction with a trained Medicare coder. For each subsequent hospitalization, costs will be assigned based on the average cost for the relevant DRG based on MedPAR data. As noted previously, prior to performing the economic analysis, all rehospitalizations will be reviewed by an independent review committee (blinded to treatment group) to determine those hospitalizations that are unrelated to cardiovascular disease or its direct complications that will be excluded from the analysis.

As a sensitivity analysis, a more direct, resource-based approach to estimating non-procedural hospital costs will be considered. For this approach, either the MEDPAR database or a large, single-center database (e.g., Mid America Heart Institute) will be used to develop a regression model for non-procedural hospital costs based on subject characteristics, length of stay (LOS) elements (ICU, non-ICU), as well as specific procedures and in-hospital complications. The regression coefficients from the associated models will then be used to estimate non-procedural hospitalization costs based on the observed resource utilization data from the EXCEL population. All other costs (e.g., procedural costs, cardiovascular hospitalizations without revascularization procedures) will be calculated in the identical fashion to the "event-based" approach described previously.

17.4.3. Other costs

For all hospitalizations associated with coronary revascularization procedures, physician costs will be estimated on the basis of standard procedural codes and the Medicare Fee Schedule. For all other hospitalizations, physician costs will be estimated as a percentage of hospital costs according to DRG and corresponding Medicare physician cost to hospital cost ratio.[167,168] Costs for outpatient medical care resource utilization (office visits, ER visits, non-protocol diagnostic tests) will be applied according to the Medicare Fee Schedule, and skilled nursing facility and rehabilitation stays will be estimated using Medicare reimbursement rates. Medication costs will be estimated based on an average per subject per month cost for each medication class. The mean cost for each class of medication will be based on an analysis of managed care pharmacy claims for subjects with coronary artery disease.

17.5. Analytic Plan

17.5.1. Quality of Life Endpoints

Since quality of life is a multidimensional construct for which different subjects may have different individual preferences, no specific scale will be considered as the "primary" QoL endpoint of the EXCEL trial. Rather, the goal of the study will be to describe any differences in the various quality of life scales over the time-frame of the trial. To limit any "false positive" results due to the large number of scales and timepoints evaluated, all QoL analyses will be performed using a p-value of <0.01 as an indicator of statistical significance.

For each of the quality of life measures in this study, data analysis will proceed in two stages. First, a simple descriptive and comparative analyses of cross-sectional data by intention-to-treat will be performed. For these cross-sectional analyses, comparisons will be performed at each follow-up timepoint using analysis of covariance to adjust for any baseline differences, including baseline score, between the treatment groups. Second, in order to account for missing data, longitudinal random coefficient growth curve models will be used to examine the effect of CABG versus PCI over time on each health status/QoL outcome. These models readily accommodate linear and nonlinear changes over time, as well as missing data patterns commonly seen in longitudinal studies. These analyses will incorporate all available QoL scores including those for subjects who die, withdraw from the study, or are lost to follow-up. Variables included in the longitudinal models for each outcome will include treatment (according to intention to treat), follow-up time (using linear, quadratic, and cubic terms), and interactions between treatment and each time term. In addition, these analyses will adjust for any baseline sociodemographic and clinical factors that differ between the two groups.

A particular challenge in the analysis of quality of life data relates to the problem of missing data (due to death, incapacity, subject refusal, or loss to follow-up). The proposed analytic strategy assumes that measurements are missing at random, however it is possible that subjects with impaired quality of life may be less likely to complete the interview. The sensitivity of the results to a variety of alternative assumptions regarding the relationship between quality of life and the likelihood of completing the QoL questionnaires will be examined. Potential approaches will include imputing missing values with the natural "worst case" score for each of the quality of life endpoints and application of multiple imputation techniques.[169]

17.5.2. Exploratory Analyses: Impact of Events on Quality-Adjusted Life Expectancy

One of the secondary goals of this study is to better understand the relative impact of outcome events on overall subject health. For these analyses, the longitudinal growth curve models to estimate quality of life over time for the two treatment groups will be used. Similar to the approach described above, these analyses will incorporate all available QoL scores including those for subjects who die, withdraw from the study, or are lost to follow-up. Variables included in the longitudinal models for each outcome will include treatment (according to intention to treat), follow-up time (using linear, quadratic, and cubic terms), and interactions between treatment and each time term. In addition, a broad range of baseline sociodemographic and clinical characteristics will be included. Finally, these models will include terms for each outcome variable of interest including myocardial infarction, stroke, and the occurrence of one or more repeat revascularization procedures (as time-dependent covariates). The interpretation of these analyses will be focused on the beta coefficients, which will indicate the independent impact of each outcome event on the various health status domains (including utility weights) for subjects undergoing revascularization for left main disease.

17.5.3. Cost and Resource Use Comparisons

The primary endpoints for the cost analysis will be total cardiovascular-related health care costs at 3 years. Because of concerns that extreme cost outliers may be driven by unobserved factors unrelated to the study, all cost data will be censored at the upper 99th percentile to limit the impact of any such high-cost outliers.

Health economic decisions regarding the efficient allocation of scarce resources involve consideration of the total costs of treating all subjects with a specific disease with the particular treatment in question. In such settings it is the arithmetic mean, which is the per-person cost of implementing the treatment or intervention that is the most relevant measure for summarizing and comparing cost.[170] Characteristics of cost distributions can complicate the task of the data analyst needing to carry out a formal comparison of mean costs, however. The distribution of cost data tends to be skewed, with a large proportion of costs at the lower end of the distribution and a long right tail. As the appropriateness of many statistical tests and models relies on an approximately normal underlying distribution of the data, many common tests, such as the two-sample *t* test for the comparison of means, may not be appropriate.

Statistical inference for all cost endpoints will therefore be performed by means of the non-parametric bootstrapping.[171] Use of this approach avoids making any parametric assumptions regarding the sampling distribution of a statistic by deriving an empirical estimate of the sampling distribution by drawing a large number of samples *with replacement* form the original data. The statistic of interest is then calculated for each of the samples, and the bootstrap replicates of the original sample yield an empirical estimate of the sampling distribution. The bootstrap approach has been advocated as a preferred method for testing hypotheses, particularly with relatively modest sample sizes, because it can be more accurate than tests based on asymptotic approximations. For each comparison, an expected difference for the two treatment groups and an associated 95% confidence interval based on bootstrap resampling will be

calculated.

17.5.4. Cost-Effectiveness Analyses

Cost effectiveness will be expressed in terms of the incremental cost-effectiveness ratio, comparing the more effective treatment (Treatment A) to the less effective treatment (Treatment B). The cost-effectiveness ratio is calculated as:

$$\frac{\textit{Mean Cost (Treatment A)} - \textit{Mean Cost (Treatment B)}}{\textit{Effectiveness (A)} - \textit{Effectiveness (B)}}$$

where effectiveness is measured either in terms of quality-adjusted life years, life-years, or in terms of the proportion of subjects experiencing a major adverse event (death, MI, stroke +/- repeat revascularization). For the purposes of these analyses, all costs will be expressed in constant dollars and both future costs and quality-adjusted life years will be discounted at 3%/year, consistent with current guidelines. [172] For each analysis, a cost-effectiveness acceptability curve to relate any specific cost-effectiveness threshold to the probability of treatment A being cost-effective at that threshold will be constructed.

17.5.5. Lifetime Cost-Effectiveness

If there are important differences in irreversible clinical outcomes between the PCI and CABG groups, a life-time cost-effectiveness analysis will be performed in addition to the within-trial analysis described above. For this analysis, the data from the in-trial analysis to project life-expectancy and quality-adjusted life expectancy for each surviving subject will be used, contingent on the observed clinical outcomes during the trial. If there are differences in survival, the remaining life-expectancy for the two treatment groups will be estimated by relating the observed annual follow-up mortality to the mortality that would have been predicted based on a comparable age- and gender-matched U.S. population.[173] Quality-adjusted life expectancy will be calculated by assuming that each subjects' health status remains unchanged beyond the last observation in the trial.

On the other hand, if there are differences in other non-fatal outcomes but not survival, a state-transition (Markov) model will be developed to project lifetime costs, survival, and quality-adjusted life expectancy for each treatment group.[174] The model will be developed based on the observed within-trial data and calibrated to match the 3-year outcomes (in terms of aggregate costs and quality-adjusted life-expectancy) for the two treatment groups. Under this approach, standard one-way, multi-way, and probabilistic sensitivity analyses will also be performed to explore the impact of plausible variations in the assumptions on the incremental cost-effectiveness ratios.

17.5.6. Evaluation of Heterogeneity by Country

Given that the primary cost-effectiveness analysis will be based on approximately 1800 patients of EXCEL trial population, a series of heterogeneity tests will be performed to identify whether it is appropriate to generalize these results to the U.S. as a whole or whether an analysis based specifically on U.S. subjects is more appropriate.[175]Although heterogeneity in terms of costs and

clinical outcomes can be evaluated through standard statistical techniques and interaction tests, heterogeneity in cost-effectiveness results will be evaluated using a net benefit regression approach through the use of country by treatment group interaction terms.[176] Because of the inherently low power of these tests, clinical outcomes, resource use, and cost and cost-effectiveness results will be stratified by country as well, in an effort to identify countries with markedly outlying clinical, economic or cost-effectiveness outcomes. If important heterogeneity is detected, results for a particular country may need to be based on the individual country data or on pooled data with other countries with comparable outcomes and resource use.

17.5.7. Subgroup Analyses

In addition to each of the main analyses specified above, each of the cost and cost-effectiveness analyses will be performed on several pre-specified subgroups of interest. These subgroups will include diabetic vs. non-diabetic subjects, type of left main disease (ostium/shaft vs. distal bifurcation), terciles of angiographic complexity (by SYNTAX score), [7] age subgroups (<65, 65-75, >75), gender, and U.S. vs. non-U.S. subjects. Additional subgroup analyses for the cost and cost-effectiveness calculations will be performed for any subject subgroups identified as clinically-relevant based on the main clinical outcomes as well.

17.6. Approach to Unanticipated Protocol Modifications

Finally, it is important to note that in contrast to traditional statistical analyses which are designed to test a specific hypothesis, cost-effectiveness analyses are inherently descriptive. As a result, it may be the case that the analysis plan above may be modified as a result of unanticipated data sources or results from the clinical trial. Such modifications will be at the discretion of the MAHI HETA group and will be reviewed by the Executive Committee of the EXCEL trial.

17.7. Independence of Research

Increasing scientific scrutiny of cost-effective analysis has led to the recent development of generally-accepted guidelines for the conduct of industry-sponsored cost-effectiveness research.[177] Such guidelines are necessary to ensure the independence of the investigators and thus to establish the scientific validity and credibility of the research. Publication of results will be normally governed by Publication Policy mentioned elsewhere in this document and as approved by the EOC.

18. APPENDIX C: IVUS SUBSTUDY

The IVUS substudy will explore whether procedural use of IVUS improves outcomes of left main stenting, as well as determine the IVUS parameters that most strongly correlate with left main stent thrombosis or restenosis. Although in this regard a randomized trial would be ideal, the current protocol is already sufficiently complex such that adding another level of randomization is not practical. Moreover, although assessment of minimal luminal area by IVUS is relatively simple, not all sites are expert in the use of IVUS guidance for complex left main stenoses. Therefore, the potential utility of IVUS guidance in improving the acute and late results of left main stenting with the XIENCE stent will be determined from a multivariable and propensity adjusted non randomized analysis of the outcomes based on IVUS usage. All left main lesions in which IVUS was used will undergo rigorous core laboratory evaluation. The principal events to be analyzed according to IVUS use will be procedural success and complications, MACE, TLR and stent thrombosis, both on a subject level (all lesions) and adjudicated to those adverse events arising from the left main lesion.

Analyses to be performed:

- PCI outcomes according to IVUS use on a subject level. The outcomes of subjects undergoing PCI will be compared according to the frequency of left main IVUS use for procedural guidance. The results will be adjusted by differences in baseline clinical and angiographic characteristics between the subjects and lesions in the 2 groups (IVUS used vs. not used for procedural guidance), including the use of a propensity score for IVUS guidance. In addition, propensity analysis will be used to create 2 matched groups with 100% vs. 0% left main IVUS guidance for comparison of procedural and late outcomes.
- PCI outcomes according to IVUS use on a site level. The outcomes in the upper 50% of sites according to left main IVUS guidance will be compared to the lower 50% of sites according to left main IVUS guidance. The results will be adjusted by differences in baseline clinical and angiographic characteristics between the subjects and lesions in the 2 groups, including the use of a propensity score for IVUS guidance. Results will also be examined according to tertiles of IVUS use frequency on a site level.
- IVUS predictors of clinical events. Among subjects undergoing left main IVUS guided intervention, the univariate and multivariable IVUS predictors of TLR, stent thrombosis and MACE will be determined, and the incremental value of IVUS variables in predicting adverse outcomes will be analyzed. The primary hypotheses will be that MACE will be inversely predicted by minimal stent area (MSA). Radiofrequency IVUS parameters will also be collected for analysis of relationship of pre-stent and post–stent plaque morphology to subsequent MACE.

19. APPENDIX D: OPTIMAL REVASCULARIZATION DEFINITIONS

Numerous prior studies have attempted to determine the differences in the extent of revascularization between CABG and PCI, and whether complete vs. incomplete revascularization is prognostically important with either modality. The results of these studies have been extremely inconsistent, with limitations including: 1) different definitions for complete revascularization used for PCI and CABG; 2) different definitions for complete revascularization used between studies; 3) definitions created and applied post hoc; 4) use of operator assessment to determine the extent of revascularization, rather than independent committee; 5) sample size and follow-up duration limitations; 6) analysis of varying subgroups; 7) lack of distinction between the extent of anatomic and ischemic revascularization.

EXCEL is a large-scale, multicenter, prospective trial in which subjects with coronary artery disease will undergo surgical or percutaneous revascularization and be followed for a minimum of 5 years. EXCEL will employ comprehensive angiographic core laboratory analysis and an independent clinical events committee to adjudicate events. This affords an opportunity to pre-specify criteria and methodology for analysis of the impact of the extent of anatomic and ischemic revascularization in subjects undergoing PCI and CABG.

19.1. Principles:

1) The same criteria for complete revascularization should apply for PCI and CABG
2) The importance of the extent of anatomic vs. ischemic revascularization should be differentiated (which is prognostically more useful, and how much overlap there is between the two)
3) The extent of revascularization will be determined by independent committees and core laboratories (i.e. not the treating physician) using pre-specified definitions and methodology
4) The significance of complete vs. incomplete revascularization will be assessed in each study for the primary and major secondary endpoint, as well as for death, repeat revascularization and QoL in all subjects, and in subsets of subjects with a) normal vs. depressed LVEF; b) CTOs vs. no CTOs; c) diabetics vs. non diabetics; d) LAD vs. non LAD disease and/or complete revascularization (includes left main disease in subjects without significant LAD disease)
5) The implications of revascularization of non ischemic vessels (deleterious effect) will be determined by analysis of subjects with complete ischemic vs. “potentially excessive” revascularization
6) Revascularization will be defined as complete (all significant lesions revascularized as determined by the core laboratory), vs. incomplete. Incomplete revascularization will be further subdivided into 1 vs. 2 or more non revascularized territories, and to LAD vs. non LAD non revascularized territories. The implications of incomplete revascularization will also be defined according to the non revascularized myocardial jeopardy score.

19.2. Anatomic revascularization:

1) Complete anatomic revascularization requires revascularization of all vessels ≥2.0 mm reference vessel diameter with a DS ≥60% (both as measured by core angiographic laboratory analysis).

   - While this will be the pre-specified criteria for anatomically significant lesions, sensitivity analysis will be performed using different criteria (e.g. ≥2.5 mm vessels, DS ≥70%, etc.)

2) From the baseline angiogram, the angiographic core lab will identify and designate those lesions and vessels requiring revascularization in all subjects according to this definition, prior to knowledge of the extent of actual revascularization.

   Contrast dye used in angiography may cause allergy, bradycardia, hypotension, renal dysfunction, decreased contractility, heart failure and fluid overload. Such risks are reported in <5% of the patients. Patients will be given intravenous fluids to protect from such risks from the contrast dye.

3) Following PCI, the angiographic core lab will determine the extent of revascularization (after all planned (i.e. staged) procedures)

   - Only vessels with TIMI 2 or 3 flow post procedure with a core laboratory DS <50% will be considered successfully revascularized.

4) Following CABG, the angiographic core lab will determine the extent of revascularization (by review of the operative note, which will need to be routinely collected), or if there is a repeat angiogram during the index hospitalization.

   - It is acknowledged that there will be some grafted vessels which are incorrectly identified in the operative note, and some grafts that will close immediately post op that will not be detected by this methodology. However, routine post operative angiography is not standard of care, and is not recommended as a substudy as it could affect clinical event rates.

19.3. Ischemic revascularization:

1) Complete ischemic revascularization requires revascularization of all vessels containing lesions with a core laboratory diameter stenosis of ≥50% with any of the following:

   a) noninvasive evidence of ischemia in that territory regardless of vessel size. If by angiographic core laboratory analysis there is more than one lesion with diameter stenosis ≥50% or more than one vessel containing lesions with diameter stenosis ≥50% in the ischemic territory, complete revascularization requires treatment of all such lesions and vessels with reference vessel diameter ≥2.0 mm; OR

   b) lesions in vessels with reference vessel diameter ≥2.0 mm with either IVUS MLA ≤4 mm^2 + plaque burden ≥60%, and/or FF≤0.80; OR

   c) an angiographic core lab DS ≥70% with ≥2.0 mm reference vessel diameter, unless FFR and/or IVUS criteria above are negative, or the vessel subtends non-viable myocardium as demonstrated by either perfusion imaging or akinesis

(Note: this is a practical definition – some cases of hibernating myocardium may be missed).

- For assessment of the completeness of ischemic revascularization, physiologic significance "trumps" anatomic severity. e.g. If the angiographic diameter stenosis is >70% but the FFR is >0.80, that lesion does not require treatment for ischemic revascularization to be considered complete.

3) The angiographic core lab will determine the extent of revascularization in both groups by review of baseline functional tests, angiograms, cath reports (for IVUS and FFR results) and op notes (note – source documents need to be collected)

20. APPENDIX E: IVUS AND FFR RECOMMENDATIONS

20.1. Pre-Revascularization Assessment of Intermediate ULMCA Lesions

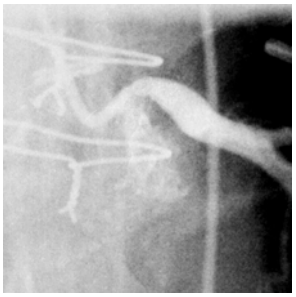
20.1.1. Prior to Randomization

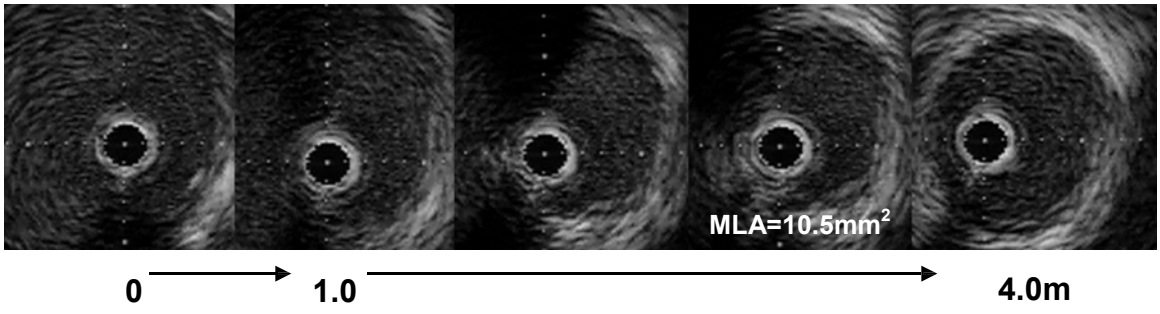
If the ULMCA lesion is intermediate (≥50% and <70% by angiographic visual estimate) without a markedly positive noninvasive test (see Section 6.5.1 – inclusion criteria): either IVUS (strongly recommended) or FFR (alternatively) must be performed for the subject to qualify for randomization.

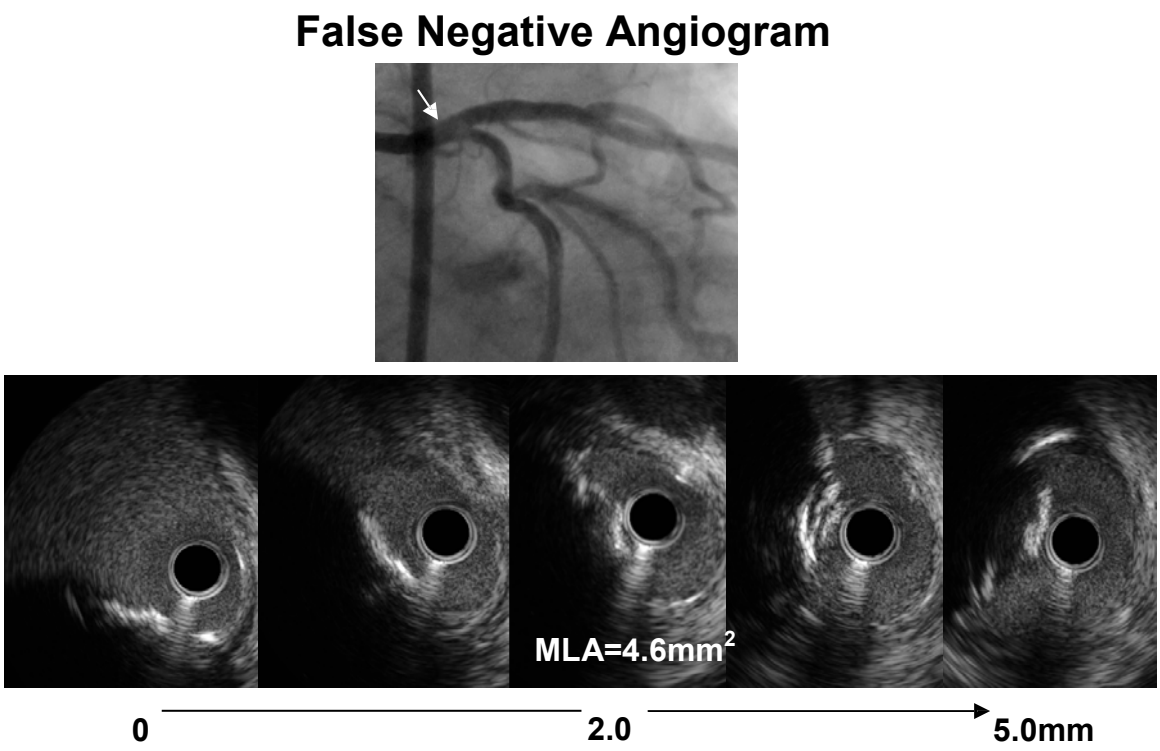
20.1.2. IVUS Criteria

IVUS criteria to *defer* revascularization of the ULMCA and not randomize subjects into the study is a ULMCA minimum lumen area (MLA) >6.0 mm^2.[178] Conversely, if the MLA is ≤6.0 mm^2, the ULMCA lesion may be considered to be hemodynamically significant and subject may be randomized. In order to determine the true MLA in the ULMCA, it may be necessary to image back to the aorto-ostial junction from both the LAD and LCX; the *smaller* of the two MLAs is the more accurate and should be used for decision-making. Practically, however, this is only necessary if the first pullback shows an MLA >6.0 mm^2. Examples of false positive and false angiograms appear in the figures below.

False Positive Angiogram



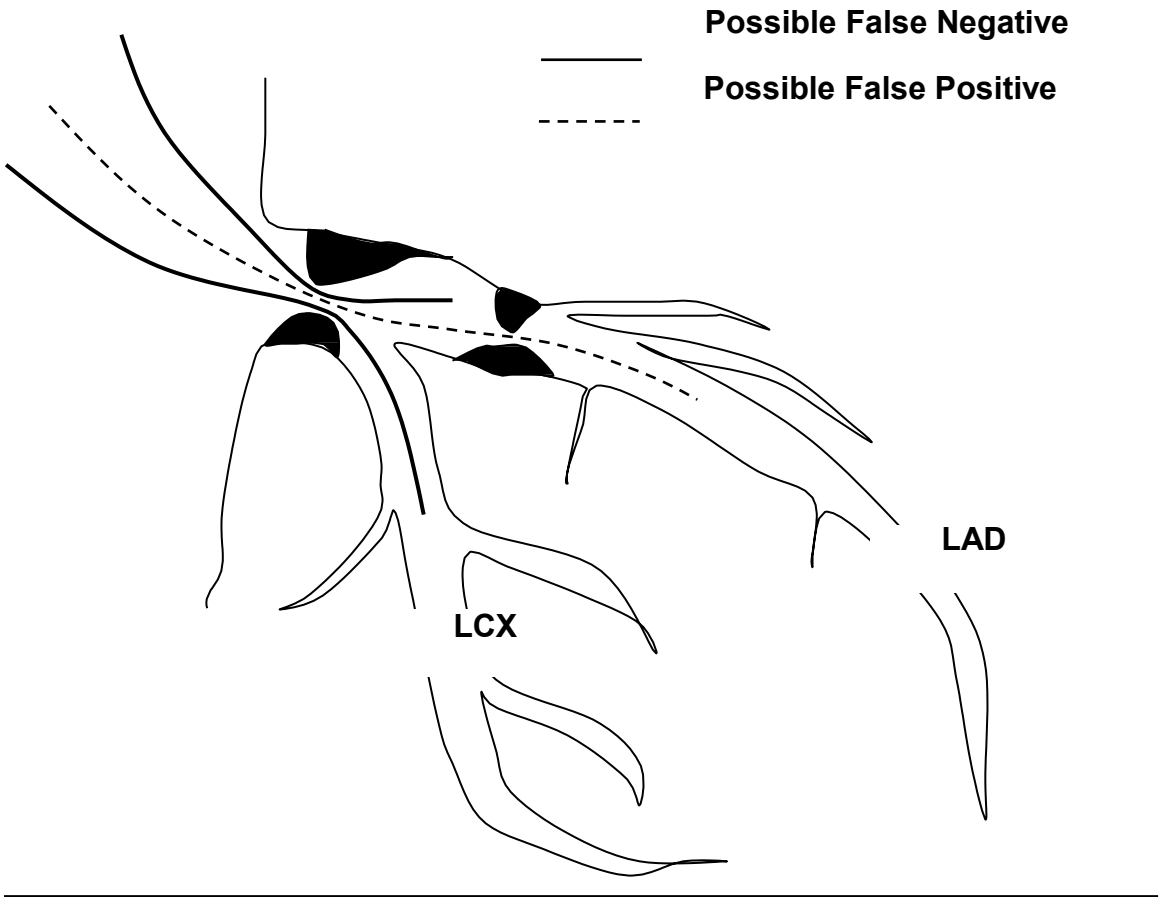




20.1.3. FFR Criteria

Deferral of borderline left main lesions with a negative FFR has been demonstrated to be safe.[179] In the present study, the FFR criteria used to *defer* revascularization of the ULMCA and not randomize subjects into the study is an FFR >0.80.[180,181] This is most useful if there are no other lesions in both the LAD and LCX (otherwise there may be false positive and false negative FFR measurements in the ULMCA). The pressure wire transducer should be positioned just distal to the ULMCA lesion and proximal to any secondary lesions, as long as there is a major branch after the left main which appears angiographically nearly normal for adequate runoff (e.g. the LAD or a large diagonal).

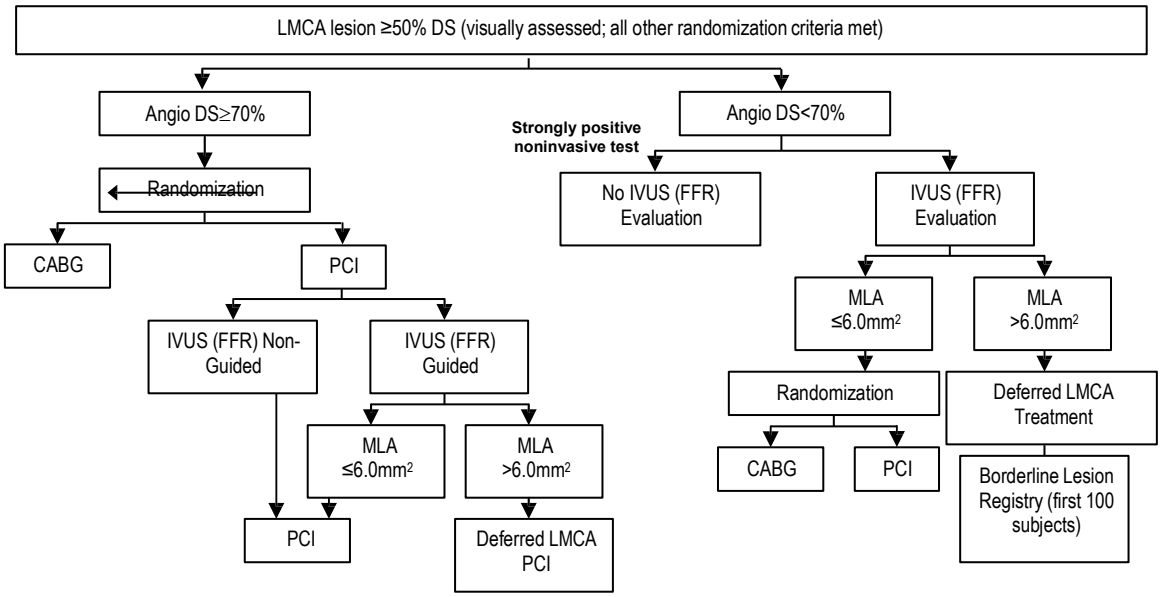
Note: See figure below. If there is also a tight stenosis in the proximal LAD distal to the ULMCA bifurcation lesion, and the FFR transducer is placed between these lesions, FFR may be false negative (>0.80); if the transducer is placed distal to a second hemodynamically significant lesion, the FFR may be false positive (≤0.80); therefore, IVUS evaluation is strongly preferred in most scenarios except to assess an isolated borderline left main stenosis.



For subjects who meet all eligibility criteria for randomization, except that either the interventional cardiologist or cardiac surgeon on the local Heart Team (or both) believe that the ULMCA diameter stenosis is visually assessed to be ≥50% - <70% stenotic without clear noninvasive evidence demonstrating hemodynamic significance of the ULMCA lesion (see Section 6.5.1 – inclusion criteria), consent for the randomized trial can be obtained pre-catheterization. Cardiac catheterization is then performed, with either IVUS (strongly recommended) or alternatively FFR assessment of the ULMCA. Randomization can be performed on the cath lab table if IVUS or FFR then demonstrates a significant left main lesion. If the subject randomizes to PCI, intervention may be directly performed. If the subject randomizes to CABG, the procedure is terminated and CABG performed as soon as logistically appropriate. Alternatively, if the subject with an intermediate lesion was not consented pre-cath, the subject must be removed from the table, sedation allowed to completely reverse, the protocol explained, consent obtained, and randomization and revascularization performed during a separate procedure.

If IVUS or FFR evaluation was not done before randomization, and if the subject was randomized to PCI, and if at the time of the planned ULMCA intervention the ULMCA lesion was found to be intermediate (<70% by angiographic visual estimate, without a positive nuclear or echocardiographic noninvasive study demonstrating ischemia which cannot be attributed to

other lesions) prior to PCI (see Section 6.5.1 – inclusion criteria), either IVUS (strongly recommended) or FFR (alternatively) must be performed to verify the significance of the lesion before randomization. Refer to section 20.1.2 for IVUS criteria and Section 20.1.3 for FFR criteria. If the ULMCA lesion is deemed insignificant, the left main lesion should in most cases not be treated (unless, for example, treatment of an ostial LAD or ostial LCX lesion necessitates LM treatment, or the lesion is irregular or otherwise disrupted), and PCI of other lesions should be performed as clinically indicated. The subject will remain in the PCI arm by intention to treat.



20.2. IVUS for PCI Guidance of ULMCA PCI

The use of IVUS to guide ULMCA intervention is strongly recommended as a recent publication describing the results of a large non randomized but adjusted registry[182] suggests that 3-year mortality may be improved with IVUS-guided DES implantation of the ULMCA.

In subjects in whom IVUS is used to guide PCI, it is strongly recommended that both the LAD and LCX be imaged *prior to* intervention back to the aorto-ostial junction to assist with stent size and length selection. If it is unexpectedly discovered that the ULMCA lesion is not significant (MLA >6.0 mm^2 in both pullback directions), the left main lesion should not be treated, and PCI of other lesions performed as clinically indicated. If ULMCA disease extends into the ostial/proximal LAD (as it does in the majority of subjects), it is recommended that stent length be selected so as to end the stent in a segment of LAD with a plaque burden <50%. While there are no IVUS criteria for selecting a one-stent (cross-over) vs. a two-stent strategy, in general a LCX ostium lumen area >4.0 mm^2 or a plaque burden ≤60% in a short segment of disease may indicate that a one-stent (cross-over) strategy will be adequate.

Iterative IVUS and post-dilation should be performed until the ULMCA minimum stent area is >8.5mm^2 and the ostial/proximal LAD minimum stent area is at least >5.5mm^2 and preferably matched to the distal reference vessel diameter if larger. Observational data in non-LMCA lesions has shown that in general the larger the minimal stent area the lower the likelihood of restenosis and stent thrombosis[183, 184, 185] and thus post-dilation with non compliant balloons sized up to 0.25-0.5mm less than the IVUS determined true vessel diameter (average media-media dimension) to safely achieve the largest maximal luminal dimension is recommended. It is strongly recommended that IVUS is also performed post-LMCA stenting from at least one epicardial coronary artery, usually the LAD, with pullback into the aorta (disengaging the guide to ensure the ostium is not missed). If a 1-stent technique is used (most commonly from the ULMCA into the LAD, "crossing over" the LCX), it is desirable but not mandatory that the ostial LCX also be imaged post-intervention if possible. If a 2-stent technique is used, IVUS pullback across the LAD and LCX is strongly recommended if the IVUS catheter passes easily into the LCX. *LCX or side branch imaging should not be pursued aggressively to avoid IVUS-related (or pressure wire-related) complications.* If the IVUS catheter or pressure wire can be safely positioned into the LCX, then, in general, an LCX ostium lumen area >4.0mm^2 (single stent strategy) or >5.5mm^2 (two stent strategy) or an FFR >0.80 (single stent strategy) indicates that no further intervention is necessary.

Severe dissections present by IVUS (residual true lumen within the dissection flap ≤8.5mm^2 in the ULMCA either proximal or distal to the stent or ≤5.5mm^2 in the proximal LAD or LCX distal to the stent) should in general receive an additional stent. Malapposition with stent area ≤8.5mm^2 in the ULMCA or ≤5.5mm^2 in the proximal LAD or LCX should in general be treated by additional post-dilatation with larger balloons.

20.3. IVUS and FFR for Guidance of Non-ULMCA Lesion PCI

20.3.1. Pre-intervention non-ULMCA lesion assessment

To avoid unnecessary interventions with subsequent peri-procedural and late myocardial infarctions and repeat revascularization procedures[139] PCI of non ischemia producing lesions should in general not be performed. Whereas IVUS is strongly recommended (preferable to FFR) to assess intermediate ULMCA stenoses, it is just as strongly recommended that FFR be performed (preferable to IVUS) in all intermediate non-LMCA lesions (those with an angiographic diameter stenosis <70% by visual estimate), unless there is a positive nuclear or echocardiographic noninvasive study with ischemia clearly present in the distribution of that lesion. In the setting of serial stenoses, stenting should only be performed if the FFR beyond all narrowings is ≤0.80[138]. Under maximum intravenous hyperemia (140 μg/kg/min IV adenosine for at least 3 minutes, or until peak hyperemia is observed), the pressure sensor is pulled back by hand slowly under fluoroscopic guidance, and the pressure curves are recorded. If the FFR is 0.81 or 0.82, increasing the intravenous adenosine to 280 μg/kg/min for at least 3 minutes, or until peak hyperemia is observed may demonstrate that the lesion is hemodynamically significant (FFR decreases to ≤0.80), warranting treatment. The investigator should first stent the stenosis that appears most significant or is responsible for the largest pressure gradient during pullback of the pressure sensor. After stenting the first lesion, FFR is measured again and any residual narrowing causing an FFR ≤0.80 is stented. (Note: for all FFR procedures, intravenous adenosine is required as opposed to intracoronary adenosine to ensure optimal coronary vasodilatation, and because intravenous adenosine provides prolonged hyperemia allowing adequate time to perform pullback of the pressure wire and localize pressure gradients.)

For sites that do not use FFR, it is strongly recommended that pre-interventional IVUS is used in all intermediate lesions (those with a visually estimated angiographic stenosis of <70% (unless there is a positive nuclear or echocardiographic noninvasive study with ischemia clearly present in the distribution of that lesion). A significant lesion by IVUS criteria that should be stented has both a minimal luminal area (MLA) of ≤4 mm^2 *and* a plaque burden of >60%. In the absence of extenuating circumstances (e.g. plaque rupture, etc.), lesions that do not have both of these criteria should not undergo PCI.

20.3.2. IVUS guidance of non-ULMCA stenting

If IVUS is used to guide treatment of ULMCA lesions, it is recommended that IVUS also be used to guide treatment of important non-LMCA lesions in the LAD, LCX, and RCA circulations. XIENCE stent size and length should be selected and optimized to achieve a minimum stent area >5.5mm^2 in non ULMCA lesions (with post-dilation with non compliant balloons sized up to 0.25-0.5mm less than the IVUS determined true vessel diameter (average media-to-media dimension), and to end the stents in arterial segments with a plaque burden <50%. Severe dissections present by IVUS (residual true lumen within the dissection flap ≤5.5mm^2 either proximal or distal to the stent) should in general receive an additional stent. Malapposition with stent area ≤5.5mm^2 should in general be treated by additional post-dilatation with larger balloons.

20.4. Follow-up

Since the site of restenosis after distal ULMCA bifurcation intervention is typically the ostium of the LCX, and since many presumed ostial LCX restenoses are angiographic artifacts (i.e. appear angiographically severe, but in fact are not hemodynamically significant),[68] it is strongly recommended that FFR be performed before treating any presumed restenotic lesions in the ostial LCX location (regardless of angiographic severity, unless totally occluded) unless there is unequivocal lateral wall ischemia by nuclear or echocardiographic noninvasive testing. If the FFR is >0.80, the ostial LCX lesion should not be treated and, thus, TLR (and possible procedural complications) avoided. For sites that do not use FFR, it is strongly recommended that pre-interventional IVUS of the ostial LCX be performed instead with an MLA >4.0mm^2 used as the criteria to defer intervention and avoid TLR.[186] Similarly, prior to performing a repeat intervention elsewhere in the coronary tree, if the visually assessed angiographic diameter stenosis is <70%, ischemia should be documented according to either a positive nuclear or echocardiographic noninvasive test in the distribution of the recurrent lesion, or an FFR ≤0.80, or IVUS with a MLA ≤4.0 mm^2.

20.5. Technical Considerations

IVUS should be performed using motorized transducer pullback at 0.5 mm/sec using only sheath-based, rotating, mechanical transducers. The pullback should start at least 1 cm distal to the lesion or stent, and conclude at least 1 cm proximal to the lesion or stent.

FFR should be performed using intravenous adenosine infusion (140 µg/kg/min) for at least 3 minutes or until maximal hyperemia is achieved. Occasionally doses as high as 280 µg/kg/min will lead to a positive FFR when a lower dose did not. To avoid turbulence, the pressure transducer should be placed 2-3 cm beyond the lesion to be assessed.

21. APPENDIX F: PROPOSED ANALYSES FOR SECONDARY PUBLICATIONS

The following endpoints and analysis will be considered for publication. Analysis will be performed on available data with no additional data collected specifically for these analyses.

21.1. Other Endpoints

- Utility of the SYNTAX score, ACEF score, clinical SYNTAX score, and novel predictive instruments
- Multivariable predictors of the primary and major secondary endpoints and their components in all subjects and in the PCI and CABG arms individually
- Weighted Composite Endpoint
- Competing Risk Analysis

PCI arm:

- Frequency and impact of IVUS and/or FFR guidance
- Frequency and impact of involvement of the distal left main vs. left main ostial/body lesions
- Frequency and impact of different treatment strategies for the distal left main bifurcation
- Frequency and impact of lesion preparation
- Frequency and impact of chronic total occlusions and bifurcation lesions

CABG arm:

- Frequency and impact of on vs. off pump CABG
- Frequency and impact of single vs. bilateral ITA vs. multiple arterial graft use
- Frequency and impact of endoscopic versus open saphenous vein harvest technique
- Frequency and impact of epi-aortic ultrasound and/or TEE
- Impact of prophylactic and management strategies for atrial fibrillation
- Value of carotid screening

21.2. Pre-specified subgroups

Subgroup analysis will be considered exploratory and hypothesis-generating only. Details of the subgroup analysis will be provided in the SAP. The following subgroups are of particular interest:

- Diabetics, women, elderly, poor left ventricular function, chronic kidney disease (CKD),

# of diseased vessels, distal bifurcation involvement, chronic total occlusion (CTO), geographic location

- SYNTAX score, clinical SYNTAX score, ACEF score

22. APPENDIX G: OPTIMAL MEDICAL THERAPIES

Optimal medical therapy (secondary prevention plus angina therapy) in the EXCEL trial will be intensive and evidence-based, and will be applied equally to both treatment groups. Every subject should undergo individual risk assessment followed by aggressive risk factor reduction with tailored lifestyle intervention and pharmacological therapy to control risk factors, prevent future cardiovascular events, and manage symptoms (angina).[187,188,189] These recommendations should be given in writing to all subjects, with a plan in place prior to discharge for close follow-up care to optimize long-term medical therapy. Table 22-1 illustrates the risk factor goals which are recommended.

Table 22-1 Risk Factor Modification Goals

Risk Factor	**Goal**
Smoking	Cessation
Total Dietary Fat / Saturated Fat	<30% calories / <7% calories
Dietary Cholesterol	<200 mg/day
Sodium	<2,400 mg/day
Fish	≥2 servings per week
Physical Activity	≥30 minutes of moderate intensity, ≥5 times/week
Body Weight by Body Mass Index (kg/m^2)	Initial BMI — Weight Loss Goal 25-27.5 kg/m^2 — BMI < 25 kg/m^2 >27.5 kg/m^2 — 10% relative weight loss
Blood Pressure	<130/80 mm/Hg
LDL cholesterol (primary goal)	<70 mg/dL (<1.8 mmol/L)
Non-HDL cholesterol (secondary goal)	<100 mg/dL (<2.6 mmol/L) if TG ≥150 (≥1.69 mmol/L)
Triglycerides (secondary goal)	<150 mg/dL (<1.7 mmol/L)
HDL cholesterol (secondary goal)	>40 mg/dL (>1.0 mmol/L) for men; >50 mg/dL (>1.3 mmol/L) for women
Diabetes	HbA_{1c}<7.0%
Influenza Vaccination	All subjects annually

Table 22-2 Waist Circumference Thresholds for Abdominal Obesity

Ethnicity	**Waist Circumference Threshold**	
European descent	Men >102 cm (40 in)	Women >88 cm (35 in)
Asian or ethnic Central & South American	Men >90 cm (35 in)	Women >80 cm (32 in)
Mediterranean or sub-Saharan African	Men >94 cm (37 in)	Women >80 cm (32 in)

22.1. General Recommendations and Goals

22.1.1. Smoking

All subjects who are smokers should enter a smoking cessation program (or practice-based counseling with nurse coordinators) with a focus upon quitting, avoiding relapses, and minimizing exposure to secondhand smoke.[187, 188, 189]

22.1.2. Dietary and Weight Goals

In subjects with an initial BMI of between 25-27.5 (kg/m^2) the goal should be a BMI of less than 25 kg/m^2. If BMI is greater than 27.5, the goal is 10% relative weight loss.

Table 22-2 lists waist circumference thresholds for abdominal obesity. Although these are not in themselves therapeutic targets, they are a useful screening tool for abdominal obesity as one of the components of the metabolic syndrome.

An ideal diet should comprise less than 30% of calories as total fat and less than 7% of calories as saturated fat. Dietary cholesterol should be limited to less than 200 mg per day, sodium less than 2400 mg per day, and at least 2 servings of fish per week are recommended.

22.1.3. Physical Activity

Physical activity goals are 30-60 minutes of moderate intensity exercise five or more times per week. Based upon evidence of contemporary cardiac rehabilitation programs and taking into account that subjects in the EXCEL trial will have undergone coronary revascularization there should be little concern in regard to ischemic risk from exercise training. An exercise prescription based upon the guidelines from the American Association of Cardiovascular Pulmonary Rehabilitation and the American College of Sports Medicine may be prescribed. Specifics are frequency of five or more times per week, an intensity based upon a resting heart rate plus 20 beats per minute, a Borg rating of perceived exertion (RPE) of 11-13 ("fairly light to somewhat hard"), or below the subject's angina-ischemia threshold. The duration should be 30-60 minutes and the modes include walking, treadmill, cycling, elliptical, rowing, stair climbing, or other.[190, 191]

22.1.4. Influenza Vaccination

Influenza vaccination should be encouraged on an annual basis for all subjects.

22.1.5. Diabetes

The goals for diabetes management are to maintain fasting blood glucose levels between 80 to 125 mg/dL (4.44 – 7.49 mmol/L) and hemoglobin A_{1c} levels of less than 7% in accordance with published recommendations.[192, 193, 194] More stringent goals, i.e., a hemoglobin A_{1c} level of less than 6%, can be considered in individual subjects. All subjects with hemoglobin A_{1c} levels of greater than 7% should be referred to a diabetes clinic or a physician with expertise in the management of diabetes. Management will be in accordance with published guidelines and recommendations.

22.1.6. Lipid Goals

Aggressive lipid-lowering therapy is advocated with the primary goal being LDL cholesterol of less than 70 mg/dL (less than 1.8 mmol/L).[188, 189,195,196] Secondary goals including increasing the levels of HDL cholesterol to greater than 40 mg/dL (greater than 1.0 mmol/L) for men and greater than 50 mg/dL (greater than 1.3 mmol/L) for women. Other secondary goals include maintaining triglyceride levels below 150 mg/dL (less than 1.7 mmol/L), non-HDL cholesterol below 100 mg/dL (<2.6 mmol/L), and total cholesterol/HDL cholesterol ratio of less than 4.0. Fasting lipid profiles should be analyzed at baseline, 6 weeks after starting therapy, 6 months, and then annually throughout the trial but are not a protocol requirement.

22.1.7. Hypertension

The goal is a blood pressure of less than 130/80 mmHg. All subjects with hypertension will receive lifestyle counseling focused on sodium restriction, weight loss, and exercise. Medications will be prescribed if necessary.

22.2. Pharmacologic Therapy

Table 22-3 lists the recommended drugs to be used for each condition and the indications for therapy (Subject to modification, pending finalization and subsequent changes to ACC/AHA and ESC clinical practice guidelines for stable and unstable ischemic heart disease). Goals of therapy are to achieve the desired level of risk factors and to control symptoms according to the subject's individual tolerance of medications, so as to maintain an acceptable quality of life.

Table 22-3 Pharmacologic Therapy Indications

Medication Class	Indication
Aspirin	See Sections 7.6.2 and 7.7.3.
Thienopyridine	See Sections 7.6.2 and 7.6.3
ACE inhibitor	Hypertension, diabetes, left ventricular systolic dysfunction, chronic kidney disease
Angiotensin receptor blocker	Individuals with hypertension, diabetes, left ventricular systolic dysfunction, chronic kidney disease who are intolerant of ACE inhibitors
Beta-blocker	All post-MI subjects unless contraindicated[1], all others[2]
Thiazide diuretic	Hypertension, as indicated
Calcium antagonist	Hypertension, angina/ischemia
Long-acting nitrate	Angina/ischemia
Late inward Na^+ current inhibitor: ranolazine	Angina/ischemia
Other anti-anginal agents: ivabradine, trimetazadine, nicorandil	Angina/ischemia
Statin	All subjects

Medication Class	Indication
Niacin: extended-release niacin	LDL >70 mg/dL (1.8 mmol/L), non-HDL >100 mg/dL (2.6 mmol/L) if TG >150 mg/dL (1.7 mmol/L) on statin; HDL < 40 mg/dL (1.0 mmol/L) in men, HDL < 50 mg/dL (1.3 mmol/L in women
Cholesterol absorption inhibitor: ezetimibe	LDL >70 mg/dL (1.8 mmol/L) on maximally-tolerated dose of statin
Bile acid sequestrant	LDL >70 mg/dL (1.8 mmol/L) on maximally-tolerated dose of statin
Fibrate	TG >10 mg/dL (1.7 mmol/L) on statin (not recommended for low HDL when TG < 150 mg/dL (1.69 mmol/L)
Omega-3 fatty acids	All subjects receive 1 gm/d; 2-4 gm/d to lower non-HDL <100 mg/dL (2.6 mmol/L)

ACE=angiotensin converting enzyme; HDL=high density lipoprotein cholesterol; LDL=low density lipoprotein cholesterol; LVEF=left ventricular ejection fraction; MI=myocardial infarction; TG=triglycerides
[1]Class IA recommendation according to ACC/AHA guidelines
[2]Class IB recommendation according to ACC/AHA guidelines

22.2.1. Antiplatelet Therapy

See Section 7.6.2 and Section 7.6.3 for specific recommendations for antiplatelet therapy after PCI and CABG, respectively.

22.2.2. Treatment of Hypertension

The overall goal of therapy for hypertension is to provide maximal protection against cardiovascular consequences with minimal side effects. There remains, however, some uncertainty with regard to which drug should be used and in what order.

Since all subjects in this trial have symptomatic coronary artery disease, initial therapy should be an angiotensin converting enzyme inhibitor (ACE-I) or a beta-blocker. If the goal blood pressure is not reached, the next step is the addition of a diuretic or a calcium-channel blocker. All subjects should be on a beta blocker and an ACE-I prior to the addition of other agents. If there are contraindications to use, side effects, or blood pressure is not controlled, subjects should be referred to the principal investigator for further consultation. An ACE-I or angiotensin receptor blocker (ARB) should be administered to all subjects with diabetes, left ventricular systolic dysfunction, and/or chronic kidney disease.

22.2.3. Lipid Lowering Therapy

After the procedure, all subjects should be started on a high dose "statin" based on LDL level according to the recommended regimens included in Table 22-4.

Table 22-4 Lipid Lowering Recommendations

Medication	Baseline LDL 70-100 mg/dL	Baseline LDL ≥ 100 mg/dL
Atorvastatin (Lipitor)	40 mg	80 mg
Rosuvastatin (Crestor)	20 mg	40 mg

If lipid goals are not reached after the maximum tolerated dose of a statin, then the preferred

option is to add Niacin ER 500 mg daily for 4 weeks to be titrated over a period of 4 weeks for each increase in dosage up to a maximum of 2000 mg daily. Other options if the triglycerides are less than or equal to 200 mg/dL (2.3 mmol/L) are to add a bile acid sequestrant such as colesevelam 6 tablets daily or 3 tablets twice per day with a meal and liquid or ezetimibe 10 mg daily. If triglycerides are greater than or equal to 200 mg/dL (greater than 2.3 mmol/L) add either Tricor (fenofibrate) 145 mg per day or fish oils up to a dose of 4 gm daily. If subject still does not reach lipid goals, the principal investigator should be consulted.

22.2.4. Anti-anginal Therapy

All subjects should receive sublingual nitroglycerin for pain relief and prophylaxis. The choice between beta blockers and calcium channel blockers for first line anti-anginal therapy is not clear cut but in general, beta-blockers are advised as initial therapy, particularly in subjects with hypertension, left ventricular systolic dysfunction, and/or a history of myocardial infarction. Absolute contraindications to beta-blockers are severe resting sinus bradycardia, pre-existing second degree AV block, sick sinus node syndrome, asthma of at least moderate severity, or decompensated (class IV) heart failure. Most diabetics and subjects with chronic obstructive pulmonary disease but without frank bronchospasm will tolerate beta blockers although close monitoring is recommended.

Subsequent steps include the addition of drugs not already utilized, e.g., the addition of a calcium channel-blocker, long-acting nitrate, or ranolazine in subjects already on a beta-blocker. Conversely, the addition of a beta-blocker to subjects who are already on a calcium-channel blocker should be considered.

New anti-anginal agents such as Trimetazidine (approved for use in Europe) and Ivabradine (approved for use in Europe) may be tried in selected subjects.

22.2.5. Vitamin Supplementation

Vitamin supplementation with vitamin E, folic acid, vitamin B6, and vitamin B12 are *not recommended*. Although the evidence for vitamin D deficiency as a risk factor for CAD is growing, evidence for vitamin D supplementation as effective secondary prevention is lacking. Vitamin D supplementation is therefore not currently recommended, but may be considered if new evidence emerges during the course of the trial as appropriate, depending on results from two large ongoing trials.

23. APPENDIX H: ANGIOGRAPHIC CORE LABORATORY INSTRUCTIONS

Angiographic core laboratory is at Cardiovascular Research Foundation, New York, NY,

USA. Instruction to the sites

- DICOM CD-R should be acquired at 15-30 frames/second for baseline and post procedural angiograms. Please specify the frame rate on the Technician's Worksheet
- Use ≥ 6 Fr diagnostic or guiding catheters, and provide the size of the catheter on the log.
- Use 50-200 mcg IC nitroglycerin and record on the Technician's Worksheet at baseline, during, and after the coronary intervention.
- Please provide a full baseline diagnostic angiogram with at least 3 different views of every major epicardial vessel.
- The left main bifurcation must be imaged in at least 3 orthogonal views to minimize vessel overlap and or foreshortening, making every effort to display the left main lesion in its most severe and least foreshortened view.
- For subjects undergoing CABG, please provide detailed operative report to core laboratory for determination of complete revascularization.
- For subjects undergoing PCI, please provide 2 matched orthogonal views of the lesion at baseline, and after final intervention.
- Please film as much detail of the intervention as possible (pre and post stent placement, complications etc).
- Please film all stent deployments so that an accurate assessment can be made for the areas of stent overlap/gap.
- Please ensure that **at least 5 cardiac cycles** are captured on film for each coronary vessel imaged to ensure optimal TIMI flow assessment at baseline and final intervention.
- Left ventriculography should be performed in the 30 degree RAO view ensuring that at least 2 consecutive sinus beats are available for analysis.
- Labels are provided and must include your site ID, the subject ID, the procedure date, and the event.

Shipping Instruction for Procedural and Event Angiograms

- Original Technician's Worksheet (please keep a photocopy of the Technician's Worksheet at the Clinical Site).
- Cardiac catheterization and procedure report
- Procedural Film
- All unscheduled event films should be sent to the Angiographic Core Laboratory.

Ship Films and Reports to:
Katharine Lymberis
Attn: EXCEL TRIAL Angiographic
Core Laboratory Cardiovascular
Research Foundation
111 East 59th Street, 12th Floor
New York, NY 10022
Phone: (212)851-9193
Fax: (212)851-9330
Email: klymberis@crf.org

24. APPENDIX I: EXCEL Insulin Protocol for Glycemic Control

Note: Do not use for diabetic ketoacidosis (DKA).

This protocol is only for patients who are NPO (nothing by mouth) or are receiving continuous enteral or parenteral nutrition. It is not appropriate for those taking scheduled meals or tube feeding boluses or Type I diabetics.

Goal Blood Glucose

Goal blood glucose is 110-150 mg/dL. In addition, the goal blood glucose at 6:00 a.m. on POD #1 and #2 is <200 mg/dL.

- At the time of ICU admission:
  - If blood glucose is ≥140 mg/dL and the patient is not receiving insulin infusion, then initiate infusion at 0.05 units/kg/hr.
  - If blood glucose is 110-150 mg/dL and the patient is receiving insulin infusion, then reduce the infusion by 50%, unless the rate has already been reduced by 50% in operating room.
- If blood glucose is <200 mg/dL on day of surgery, POD (post-operative day) #1 or #2, follow Insulin Infusion Adjustment Protocol found in Table A.

Table A Insulin Infusion Adjustment

*****DO NOT ADJUST INSULIN RATE EVERY HOUR. ONLY MAKE ADJUSTMENTS TO THE INSULIN RATE EVERY TWO HOURS.*****

Blood Glucose (mg/dL)	If blood glucose DECREASES ≥30 mg/dL since last level	If blood glucose is STABLE (change in blood glucose is <30 mg/dL since last level)	If blood glucose INCREASES ≥30 mg/dL since last level
≤70	Stop insulin infusion See Hypoglycemia Protocol	Stop insulin infusion See Hypoglycemia Protocol	--
71-79	Stop insulin infusion See Hypoglycemia Protocol	Stop insulin infusion	--
80-109	Stop insulin infusion	Decrease rate by 50%	--
110-150	Decrease rate by 50%	Continue current rate	Increase rate by 25%
151-170	Decrease rate by 50%	Increase rate by 25%	Increase rate by 50%
171-200	Decrease rate by 25%	Increase rate by 25%	Bolus 2 units Increase rate by 25%
201-250	Continue current rate	Bolus 2 units Increase rate by 25%	Bolus 4 units Increase rate by 25%
251-300	Continue current rate	Bolus 4 units Increase rate by 50%	Bolus 6 units Increase rate by 50%
301-350	Continue current rate	Bolus 6 units Increase rate by 50%	Bolus 8 units Increase rate by 50%
351-400	Continue current rate	Bolus 8 units Increase rate by 50%	Bolus 10 units Increase rate by 50%
>400	Notify medical staff	Notify medical staff	Notify medical staff

Note: If insulin rate is ≥30 units/hr or if blood glucose is not being controlled using the protocol, notify the medical staff. If the protocol requires RHI rates to be <0.5 cc/hr, hold infusion and recheck blood glucose level in one hour.

- If blood glucose is ≥200 mg/dL on day of surgery, POD #1 or #2:
  - Bolus with 4 units regular insulin IV and either change rate to 0.05 unit/kg/hr or increase rate by 25%, whichever is greater.
  - If diabetic or on epinephrine, bolus 6 units regular insulin IV and either change rate to 0.1 unit/kg/hr or increase rate by 50%, whichever is greater.
  - Note: Patients who require insulin rates greater than 20 units per hour must have blood glucose monitoring every 1 hour. If blood glucose is <180 mg/dL and has decreased by more than 100 mg/dL from the previous reading done one hour earlier, call the medical staff to inquire whether regular insulin dose reduction per protocol is sufficient.
  - Note: If patient is on epinephrine and blood glucose is >300mg/dL and lactate is >10 mmol/L and blood glucose is not decreasing, call the medical staff to consider changing from epinephrine to dobutamine.
  - Note: Expect a rapid decrease in insulin needs after stopping epinephrine.
- Caution: Treating hyperkalemia with insulin and glucose may be associated with poor glycemic control. Inform the medical staff if pretreatment blood glucose is ≥180 mg/dL or if two post-treatment blood glucoses are outside the goal range of 110-150 mg/dL.
- Measure blood glucose every hour in the following circumstances:
  - If blood glucose is ≥200 mg/dL. If so, continue monitoring and treating every hour until blood glucose is <170 mg/dL for two consecutive hours then measure blood glucose every 2 hours.
  - If blood glucose is <200 mg/dL and the blood glucose has increased or decreased by ≥50 mg/dL from the previous measurement.
  - If insulin infusion rate is >20 units/hr.
  - As required under Section "Hypoglycemia Protocol".

Insulin Continuous Infusion

Do NOT use for diabetic ketoacidosis (DKA).

- Regular insulin 100 units/100 ml in 0.9% normal saline; concentration 1 unit/ml
- If patient is not on insulin infusion and blood glucose is 150-170 mg/dL, repeat blood glucose measurement after 2 hours.
- If blood glucose is 150-170 mg/dLl for 2 consecutive measurements:
  - Bolus dose: 0.05 units/kg (maximum bolus is 5 units)
  - Then initiate continuous infusion with initial rate of 0.05 units/kg/hr (maximum initial rate is 5 units/hr).
- If blood glucose >170 mg/dL, do not repeat the measurement after 2 hours. Instead, give bolus and start infusion immediately as above.
- See Table A for adjustment of insulin rate.

Blood Glucose Monitoring

Monitor blood glucose every 2 hours (exceptions noted in Section Hypoglycemia Protocol and Section Goal Blood Glucose)

Sampling site and lab analysis should remain consistent. Arterial sampling is preferred method for obtaining blood glucose measurements.

Verify blood glucose results using an alternate method (e.g. fingerstick) for:

- Variations in blood glucose lab results ≥100mg/dL on consecutive blood draws
- Suspicion of false lab results or contaminated specimen
- Blood glucose results reading "I" or "Lo" on the accu- check meter

Hypoglycemia Protocol

- **If blood glucose ≤ 70 mg/dL** – stop insulin infusion, give 25-50 mL of 50% dextrose solution, notify medical staff, obtain BG level every 30 minutes until blood glucose is >80 mg/dL for three consecutive levels, and then check blood glucose every 2 hours.
- **If blood glucose DECREASES ≥30 mg/dL since last level and blood glucose is 71-79 mg/dL** – stop infusion, obtain blood glucose level every 30 minutes until blood glucose level is >80 mg/dL for three consecutive levels, then check blood glucose level every 2 hours.
- **If enteral nutrition or total parenteral nutrition is stopped**, decrease insulin infusion rate by 50% and monitor blood glucose levels every 1 hour until blood glucose >80 mg/dl for three consecutive levels, then check blood glucose every 2 hours.

Resuming Insulin Infusion:

- Restart insulin infusion when first blood glucose value is ≥ 150 mg/dL. Do not bolus. Restart insulin infusion at half the previous rate. Obtain blood glucose in 1 hour and reevaluate.

Important Notes

Insulin sensitivity will usually improve over time in the critically ill patient. Because of this, the need for insulin may decrease throughout the ICU stay.

Insulin requirements will usually increase when starting glucocorticoid therapy. Large fluctuations in blood glucose may occur, requiring more frequent blood glucose measurements.

Prior to discharge from the ICU, patients should be evaluated for transition to the standardized subcutaneous insulin order set.

Subcutaneous insulin (combination of intermediate/long acting plus sliding scale/prandial insulin) is appropriate for ICU patients taking meals or receiving boluses of tube feeding.

Patients who develop hypoglycemia while receiving subcutaneous insulin (combination of intermediate/long acting plus sliding scale/prandial insulin) may require a different hypoglycemia protocol to account for the prolonged effect of insulin.

Calculation of Insulin Infusion

Use current weight when starting the insulin infusion for the first time.

- If DECREASING RATE by 50% New rate = Current rate X 0.5
- If DECREASING RATE by 25% New rate = Current rate X 0.75
- If INCREASING RATE by 50% New rate = Current rate X 1.5

25. APPENDIX J: Transient Ischemic Attack (TIA)/Stroke Questionnaire

A. Transient Ischemic Attack (TIA)/Stroke Questionnaire

Site # _____Pt # ____ _____ ___ ___ ___

Follow-up

(Questionnaire for Verifying Stroke-Free Status)

Exam Time Interval

30 Days 6 Month 1 Year 2 Year 3 Year
4 Year 5 Year

Other_____

Instructions: This form is to be used during the EXCEL follow-up contacts either in clinic visits or telephone. Remind respondent of date of last contact.

Date and time of form completion: __ __ / __ __ / __ __ __ __ (mm/dd/yyyy)

__ __: __ __ (Hr/min (24 hr. format))

1. Since the last routine EXCEL contact by phone or clinic, have you been told by a physician that you have had a stroke?	YES	NO	Don't know/Not sure
2. Since the last routine EXCEL contact by phone or in the clinic, have you been told by a physician that you had a TIA, mini-stroke, or transient ischemic attack?	YES	NO	Don't know/Not sure
3. Since the last routine EXCEL contact by phone or in the clinic, have you had sudden painless weakness on one side of your body?	YES	NO	Don't Know/ Not sure
4. Since the last routine EXCEL contact by phone or	YES	NO	Don't Know/ Not sure

in the clinic, have you had sudden numbness or a dead feeling on one side of your body?			
5. Since the last routine EXCEL contact by phone or in the clinic, have you had sudden painless loss of vision in one or both eyes?	YES	NO	Don't Know/ Not sure
6. Since the last routine EXCELcontact by phone or in the clinic, have you suddenly lost one half of your vision?	YES	NO	Don't Know/ Not sure
7. Since the last routine EXCEL contact by phone or in the clinic, have you suddenly lost the ability to understand what people were saying?	YES	NO	Don't Know/ Not sure
8. Since the last routine EXCEL contact by phone or in the clinic, have you suddenly lost the ability to express yourself verbally or in writing?	YES	NO	Don't Know/ Not sure

If any of questions 1 – 8 are answered "YES", follow procedures for a potential stroke; that is, submit the Major Event Form, Neurological Event Form, NIHSS TIA/Stroke Questionnaire, etc.

B.Modified Rankin Disability Questionnaire

A. Rankin 5-Severe disability; requiring constant nursing care and attention.

Question: Does the person require constant care? < YES < NO

B. Rankin 4-Moderately severe disability; need for assistance with some basic ADL, but not requiring constant care.

Question: Is assistance essential for eating, using the toilet, daily hygiene, or walking? < YES < NO

C. Rankin 3-some need for assistance but able to walk without assistance.

Question: Is assistance essential for preparing a simple meal, doing household chores, looking after money, shopping, or traveling locally? < YES < NO

D. Rankin 2-Slight disability; limitations in participation in usual social roles, but independent for ADL.

Questions: Has there been a change in the person's ability to work or look after others? < YES < NO

Question: Has there been a change in the person's ability to participate in previous social and leisure activities? < YES < NO <

Question: Has the person had problems with relationships or become isolated? < YES < NO

E. Rankin 1-No significant disability; symptoms present but no physical or other limitations.

Question: Does the person have symptoms that do not interfere with the ability to carry out all usual activities ? < YES < NO

F. Rankin 0-No symptoms at all.

Score Rankin 0 if answers to all questions A-E are "No".

26. APPENDIX K: REFERENCES

[1] Favaloro RG. Saphenous vein autograft replacement of severe segmental coronary artery occlusion: operative technique. Ann Thorac Surg 1968; 5(4):334-9.

[2] CASS Principal Investigators And Their Associates. Coronary artery surgery study (CASS): a randomized trial of coronary artery bypass surgery. Circulation 1983; 68:939-50.

[3] Janssen DP, Noyez L, Wouters C, et al. Preoperative prediction of prolonged stay in the intensive care unit for coronary bypass surgery. Eur J Cardiothorac Surg 2004; 25 (2):203-7.

[4] Tavilla G, Kappetein AP, Braun J, et al. Long term follow-up of coronary artery bypass grafting in three-vessel disease using exclusively pedicled bilateral internal thoracic and right gastroepiploic arteries. Ann Thorac Surg 2004; 77(3):794-99.

[5] Buxton BF, Komeda M, Fuller JA, et al. Bilateral internal thoracic artery grafting may improve outcome of coronary artery surgery. Risk-adjusted survival. Circulation 1998; 98 (19 Suppl):II1-6.

[6] Flynn M, Reddy S, Shepherd W, et al. Fast-tracking revisited: routine cardiac surgical patients need minimal intensive care. Eur J Cardiothorac Surg 2004; 25(1):116-22.

[7] Morice MC, Serruys PW, Kappetein AP, et al. Outcomes in patients with de novo left main disease treated with either percutaneous coronary intervention using paclitaxel-eluting stents or coronary artery bypass graft treatment in the Synergy Between Percutaneous Coronary Intervention With TAXUS and Cardiac Surgery (SYNTAX) Trial. Circulation. 2010; 121:2645-2653.

[8] Hlatky MA, Boothroyd DB, Bravata DM, et al. Coronary artery bypass surgery compared with percutaneous coronary interventions for multivessel disease: a collaborative analysis of individual patient data from ten randomized trials. Lancet 2009; 373:1190-97.

[9] Kapoor JR, Gienger AL, Ardehali R, et al. Isolated disease of the proximal left anterior descending artery: comparing the effectiveness of percutaneous coronary interventions and coronary artery bypass surgery. J Am Coll Cardiol: Cardiovascular Interventions 2008; 1(5):483-91.

[10] Hannan EL, Racz MJ, Walford G, et al. Long-term outcomes of coronary-artery bypass grafting versus stent implantation. N Engl J Med 2005; 352:2174-83.

[11] Serruys PW, Morice MC, Kappetein AP, et al. Percutaneous coronary intervention versus coronary-artery bypass grafting for severe coronary artery disease. N Engl J Med 2009; 360(10):961-72 plus Supplementary Appendix.

[12] Gruntzig AR, Senning A, Siegenthaler WE. Nonoperative dilatation of coronary-artery stenosis: percutaneous transluminal coronary angioplasty. N Engl J Med 1979; 301(2):61-8.

[13] Serruys PW, Unger F, Sousa JE, et al. Arterial revascularization therapies study group. N Engl J Med 2001; 344(15):1117-24.

[14] Rodriguez A, Bernardi V, Navia J, et al. Argentine randomized study: coronary angioplasty with stenting versus coronary bypass surgery in patients with multiple-vessel disease (ERACI II): 30-day and one-year follow-up results. J Am Coll Cardiol 2001; 37(1):51-58.

[15] Serruys PW. ARTS I: 5-year clinical follow-up of the Arterial Revascularization Therapy Study. ESC 2004; abstract #3601.

[16] The BARI Study Group. Comparison of coronary bypass surgery with angioplasty in patients with multivessel disease. N Engl J Med 1996; 335(4):217-25. Erratum in: N Engl J Med 1997; 336(2):147.

[17] The CABRI Study Group. First-year results of CABRI (Coronary Angioplasty versus Bypass Revascularisation Investigation). Lancet 1995; 346(8984):1179-84.

[18] Hamm CW, Reimers J, Ischinger T, et al. A randomized study of coronary angioplasty compared with bypass surgery in patients with symptomatic multivessel coronary disease. N Engl J Med 1994; 331(16):1037-43.

[19] King SB 3rd, Lembo NJ, Weintraub WS, et al. A randomized trial comparing coronary angioplasty with coronary bypass surgery. N Engl J Med 1994; 331(16):1044-50.

[20] The RITA Study Group. Coronary angioplasty versus coronary artery bypass surgery: the Randomized Intervention Treatment of Angina (RITA) trial. Lancet 1993;341(8845):573-80.

[21] Kedhi E, Joesoef KS, McFadden E, et al. Second-generation everolimus-eluting and paclitaxel-eluting stents in real-life practice (COMPARE): a randomised trial. Lancet 2010; 375: 201-09.

[22] Buszman PE, Kiesz SR, Bochenek A, et al. Acute and late outcomes of unprotected left main stenting in comparison with surgical revascularization. J Am Coll Cardiol 2008; 51:538-45.

[23] Buszman PE, Buszman PP, Kiesz RS, et al. Early and long-term results of unprotected left main coronary artery stenting: The LE MANS (Left Main Coronary Artery Stenting) Registry. J Am Coll Cardiol 2009; 54:1500-11.

[24] Jones RH. Percutaneous interventions vs. coronary-artery bypass grafting in left main coronary disease (MAIN-COMPARE). N Engl J Med 2008; 358:1851-53.

[25] Mehilli J, Kastrati A, Byrne RA, et al. Paclitaxel- versus sirolimus-eluting stents for unprotected left main coronary artery disease. J Am Coll Cardiol 2009; 53:1760-68.

[26] Naik H, White AJ, Chakravarty T, et al. A meta-analysis of 3,773 patients treated with percutaneous coronary intervention or surgery for unprotected left main coronary artery stenosis. J Am Coll Cardiol Intv. 2009; 2:739-47.

[27] Kushner FG, Hand M, Smith SC, et al. 2009 focused updates: ACC/AHA guidelines for the management of patients with ST-elevation myocardial infarction (Updating the 2004 guideline and 2007 focused update) and ACC/AHA/SCAI guidelines on percutaneous

coronary intervention (Updating the 2005 guideline and 2007 focused update): A report of the American College of Cardiology Foundation/American Heart Association Task Force on practice guidelines. Circulation 2009; 120:2271-306.

[28] American Heart Association. Heart Disease and Stroke Statistics — 2009 Update, On-line publication.

[29] Weinstein MC, Stason WB. Foundations of cost-effectiveness analysis for health and medical practices. N Engl J Med 1977;296:716-21.

[30] Wong JB, Sonnenberg FA, Salem DN, Pauker SG. Myocardial revascularization for chronic stable angina. Analysis of the role of percutaneous transluminal coronary angioplasty based on data available in 1989. Ann Intern Med 1990;113:852-71.

[31] Parisi AF, Folland ED, Hartigan P. A comparison of angioplasty with medical therapy in the treatment of single-vessel coronary artery disease. Veterans Affairs ACME Investigators. N Engl J Med 1992;326:10-16.

[32] RITA-2 trial participants.Coronary angioplasty versus medical therapy for angina: the second Randomised Intervention Treatment of Angina (RITA-2) trial. Lancet 1997;350:461-68.

[33] Boden WE, O'Rourke RA, Teo KK, et al. Optimal medical therapy with or without PCI for stable coronary disease. N Engl J Med 2007;356:1503-16.

[34] RITA trial participants.Coronary angioplasty versus coronary artery bypass surgery: the Randomized Intervention Treatment of Angina (RITA) trial. Lancet 1993;341:573-80.

[35] The Bypass Angioplasty Revascularization Investigation (BARI) Investigators. Comparison of coronary bypass surgery with angioplasty in patients with multivessel disease. N Engl J Med 1996;335:217-25.

[36] Hlatky MA, Rogers WJ, Johnstone I, et al. Medical care costs and quality of life after randomization to coronary angioplasty or coronary bypass surgery. N Engl J Med 1997;336:92-99.

[37] Hlatky MA, Boothroyd DB, Melsop KA, et al. Medical costs and quality of life 10 to 12 years after randomization to angioplasty or bypass surgery for multivessel coronary artery disease. Circulation 2004;110:1960-6.

[38] Koch CG, Li L, Sessler DI, et al. Duration of red-cell storage and complications after cardiac surgery. N Engl J Med 2008;358;1229-39.

[39] Engoren MC, Habib RH, Zacharias A, et al. Effect of blood transfusion on long-term survival after cardiac operation. Ann Thorac Surg 2002; 74:1180-6.

[40] Koch CG, Li L, Duncan AI, et al. Morbidity and mortality risk associated with red blood cell and blood-component transfusion in isolated coronary artery bypass grafting. Crit Care Med 2006; 34:1608-16.

[41] Cohen DJ. Health related quality of life and U.S. based economic outcomes of PCI with drug-eluting stents vs. bypass surgery for patients with 3-vessel and left main coronaryartery disease: 1-year results from the SYNTAX Trial. ACC2009 Scientific Sessions, Late Breaking Clinical Trials Presentation (2402-10).

[42] Serruys PW, Ong ATL, Piej JJ, et al. A randomised comparison of a durable polymer everolimus-eluting coronary stent with a bare metal coronary stent. EuroIntervention 2005; 1:58-65.

[43] Serruys PW, Ruygrok P, Neuzner J, et al. A randomised comparison of an everolimus-eluting coronary stent with a paclitaxel-eluting coronary stent: the SPIRIT II trial. EuroIntervention 2006; 2:286-94.

[44] Stone GW, Midei M, Newman W, et al. Comparison of an everolimus eluting stent and a paclitaxel-eluting stent in patients with coronary artery disease: a randomized trial. JAMA 2008; 299:1903-13.

[45] Stone GW, Midei M, Newman W, et al. Randomized comparison of everolimus-eluting and paclitaxel-eluting stents: two-year clinical follow-up from the clinical evaluation of the XIENCE V everolimus eluting coronary stent system in the treatment of patients with de novo native coronary artery lesions (SPIRIT III trial). Circulation 2009;119:680-86.

[46] Miu R, Serruys PW, Stone GW. Performance of everolimus-eluting stents: pooled analysis from the SPIRIT trials. J of Intervent Cardiol 2009; 22:S41-S47.

[47] Internal Progress Report titled, "Three Year Follow-up Progress Report SPIRIT III Clinical Trial" , Version 1.0, Report date: 06-Nov-2009

[48] ten Berg J, Kelder J, Suttorp M, et al. Influence of planned six-month follow-up angiography on large outcome after percutaneous coronary intervention: a randomized study. J Am Coll Cardiol 2001; 38:1061-9.

[49] Pinto DS, Stone GW, Ellis SG, et al. Impact of routine angiographic follow-up on the clinical benefits of paclitaxel-eluting stents: results from the TAXUS-IV trial. J Am Coll Cardiol 2006; 48:32-36.

[50] Stone GW. The SPIRIT IV trial. Presented at TCT2009, Sep 2009, San Francisco, CA.

[51] Stone GW, Lansky AJ, Pocock SJ, et al. Paclitaxel-eluting stents versus bare-metal stents in acute myocardial infarction. N Engl J Med 2009; 360:1946-59.

[52] Salvatella N, Morice MC, Carrie D, et al. Unprotected left main stenting with a second generation drug-eluting stent. Preliminary results of the LEMAX pilot study. Circulation 2009; 120 (18): S976-S977 Supplement.

[53] Applegate RJ, Hermiller JB, Sanz M, et al. Comparison of everolimus-eluting and paclitaxel-eluting coronary stents in patients with two treated vessels: 2-year results from the SPIRIT III randomized trial. Am J Cardiol (Suppl). 2009; 104(6):150D.

[54] Stone GW, Rizvi A, Newman W, et al. A large-scale randomized comparison of everolimus-eluting and paclitaxel-eluting stents: one-year clinical outcomes from the SPIRIT IV Trial. Am J Cardiol (Suppl). 2009; 104(6): XV.

[55] One-Year Follow-up Progress Report SPIRIT II, SPIRIT III, and SPIRIT IV Pooled Analysis; Date of report: March 11, 2010. .

[56] Kaul U, for the SPIRIT V Investigators. SPIRIT V registry: one year follow-up of complex lesion and patient sub-groups. J Am Coll Cardiol 2010; 55(10) Supplement 1:A209.E1972.

[57] Rocic P. Differential phosphoinositide 3-kinase signaling: Implications for PTCA? Am J Physiol Heart Circ Physiol. 2009;297:1970-71

[58] Sheiban I, Villata G, Bollati M, et al. Next-generation drug-eluting stents in coronary artery disease: focus on everolimus-eluting stent (XIENCE V). Vasc Health Risk Manag 2008; 4:31-38.

[59] Schuler W, Sedrani R, Cottens S, et al. SDZ RAD, a new rapamycin derivative: pharmacological properties in vitro and in vivo. Transplantation 1997; 64:36-42.

[60] Carter AJ, Brodeur A, Collingwood R, et al. Experimental efficacy of an everolimus eluting cobalt chromium stent. Catheter Cardiovasc Interv 2006;68:97-103.

[61] Joner M, Nakazawa G, Finn AV, et al. Endothelial cell recovery between comparator polymer-based drug-eluting stents. J Am Coll Cardiol 2008; 52:333-42.

[62] Pasceri V, Patti G, Nusca A, et al. Randomized trial of atorvastatin for reduction of myocardial damage during coronary intervention: Results from the ARMYDA (Atorvastatin for Reduction of Myocardial Damage during Angioplasty) Study. Circulation2004; 110: 674-78.

[63] Patti G, Pasceri V, Colonna G, et al. Atorvastatin pre-treatment improves outcomes inpatients with acute coronary syndromes undergoing early percutaneous coronary intervention: Results of the ARMYDA-ACS Randomized Trial. J Am Coll Cardiol 2007; 49:1272-78.

[64] Di Sciascio G, Patti G, Pasceri V, et al. Efficacy of atorvastatin reload in patients on chronic statin therapy undergoing percutaneous coronary intervention: Results of the ARMYDA-RECAPTURE (Atorvastatin for Reduction of Myocardial Damage During Angioplasty) Randomized Trial. J Am Coll Cardiol 2009; 54:558-65.

[65] Briguori C, Visconti G, Focaccio A, et al. Novel Approaches for Preventing or Limiting Events (Naples) II Trial: Impact of a single high loading dose of atorvastatin on periprocedural myocardial infarction. J Am Coll Cardiol 2009; 54:2157-63.

[66] Briguori C, Colombo A, Airold F, et al. Statin administration before percutaneous coronary intervention: Impact on periprocedural myocardial infarction. Eur Heart J 2004; 25:1822-28.

[67] Koo BK, Park KW, Kang HJ, et al. Physiological evaluation of the provisional side-branch intervention strategy for bifurcation lesions using fractional flow reserve. Eur Heart J 2008 Mar; 29(6):726-32.

[68] Koo BK, Kang HJ, Youn TJ, et al. Physiologic assessment of jailed side branch lesions using fractional flow reserve. J Am Coll Cardiol 2005 Aug 16; 46(4):633-7.

[69] Rassen JA, Mittleman MA, Glynn RH, et al. Safety and effectiveness of bivalirudin in routine care of patients undergoing percutaneous coronary intervention. Eur Heart J 2010; 31:561-72.

[70] Marso SP, Amin AP, House JA, et al. National Cardiovascular Data Registry. Association between use of bleeding avoidance strategies and risk of periprocedural bleeding among patients undergoing percutaneous coronary intervention. JAMA. 2010; 303:2156-64.

[71] Sanborn TA, Ebrahimi R, Manoukian SV, et al. Impact of femoral vascular closure devices and antithrombotic therapy on access site bleeding in acute coronary syndromes: The Acute Catheterization and Urgent Intervention Triage Strategy (ACUITY) trial. Circ Cardiovasc Interv. 2010; 3:57-62.

[72] Toyofuku M, Kimura T, Morimoto T, et al. Three-year outcomes after sirolimus-eluting stent implantation for unprotected left main coronary artery disease: Insights from the J-Cypher Registry. Circulation 2009; 120:1866-74.

[73] Seung KB, Park D-W, Kim Y-H, et al. Stents versus coronary-artery bypass grafting for left main coronary artery disease. N Engl J Med 2008; 358:1781–92.

[74] Com-Nougue C, Rodary C, Patte C, How to establish equivalence when data are censored: a randomized trial of treatments for B non-Hodgkin lymphoma. Statist. Med. 1993. 12, 1353–1364.

[75] Hintze J. PASS 2008. NCSS, LLC. Kaysville, Utah. www.ncss.com.

[76] Ware JH, Antman EM. Equivalence trials. N Engl J Med 1997; 337:1159-61.

[77] Spertus JA, Winder JA, Dewhurst TA, et al. Monitoring the quality of life in patients with coronary artery disease. Am J Cardiol 1994; 74:1240-44.

[78] Spertus JA, Winder JA, Dewhurst TA, et al. Development and evaluation of the Seattle Angina Questionnaire: a new functional status measure for coronary artery disease. J Am Coll Cardiol 1995; 25:333-41.

[79] Cleary PD, Epstein AM, Oster G, et al. Health-related quality of life among patients undergoing percutaneous transluminal coronary angioplasty Med Care 1991;29:939-50. Published erratum appears in Med Care 1992 Jan;30(1):76.

[80] Arnold SV, Spertus JA, Jones PG, et al. The impact of dyspnea on health-related quality of life in patients with coronary artery disease: results from the PREMIER registry. Am Heart J 2009; 157:1042-49.

[81] Kroenke K, Spitzer RL. The PHQ-9: A new depression diagnostic and severity measure. Psychiatric Annals 2002, 32 (9):509-15.

[82] Ware JE, Kosinski M, Keller SD. A 12-item short-form health survey (SF-12): construction of scales and preliminary tests of reliability and validity. Medical Care 1996; 32:220-33.

[83] The EuroQol Group. EuroQol - a new facility for the measurement of health-related quality of life. Health Policy 1990; 16:199-208.

[84] Shaw JW, Johnson JA, Coons SJ. US valuation of the EQ-5D health states: development and testing of the D1 valuation model. Med Care 2005; 43:203-20.

[85] Eisenberg J. Clinical economics: A guide to the economic analysis of clinical practices. JAMA 1989; 262:2879-86.

[86] Ryan JW, Cohen DJ. Are drug-eluting stents cost-effective? It depends on whom you ask. Circulation 2006; 114:1736-44.

[87] *Certican® Investigator's Brochure.* Novartis Pharmaceuticals Corporation, 2007.

[88] *Afinitor Prescribing Information.* Novartis Pharmaceuticals Corporation, 2009.

[89] On file at Abbott Vascular: Toxikon protocol numbers: ABV/VIVO/001-06/000/SS, ABV/VIVO/002-06/000/SS; Toxikon report numbers: 05-5305-G1, 06-2512-G1.

[90] Abu-Omar Y, Taggart DP. Review: The present status of off-pump coronary artery bypass grafting. Eur J Cardiothorac Surg 2009; 36(2):312-21.

[91] Mosca L, Appel LJ, Benjamin EG, et al. American Heart Association. Evidence based guidelines for cardiovascular disease prevention in women. Circulation. 2004; 109(5):672-93.

[92] Mazzaferri EL, Limacher MC. Changing patterns of CAD therapy and hormone usage for women. Cardiology Review. 2005; 22(3):32–37.

[93] Lloyd-Jones D, Adams R, Carnethon M, et al. Heart disease and stroke statistics--2009 update: a report from the American Heart Association Statistics Committee and Stroke Statistics Subcommittee. Circulation. 2009; 119(3):e21-181.

[94] Xu JQ, Kochanek KD, Murphy SL, et al. Deaths: Final Data for 2007: National Vital Statistics Reports. Hyattsville, MD: National Center for Health Statistics. 2010.

[95] Rossouw JE, Anderson GL, Prentice RL, et al. Writing Group for the Women's Health Initiative Investigators. Risks and benefits of estrogen plus progestin in healthy postmenopausal women: principal results from the Women's Health Initiative randomized controlled trial [summary for patients appears in CMAJ.2002; 2167:2377-2378 and J Fam Pract.2002; 2051:2821]. JAMA.2002; 288:321-33.

[96] Roger VL, Go AS, Lloyd-Jones DM, et al. on behalf of the American Heart Association Statistics Committee and Stroke Statistics Subcommittee. Heart disease and stroke statistics-2011 update: a report from the American Heart Association [published correction appears in Circulation.2011.123:e240]. Circulation.2011; 123:e18-e209.

[97] Bransford TL and Ofili E. The Paradox of Coronary Heart Disease in African-American Women. J Natl Med Assoc. 2000;. 92:327-33.

[98] Mosca L, Mochari-Greenberger H, Dolor RJ, et al. Twelve-year follow-up of American women's awareness of cardiovascular disease risk and barriers to heart health. Circ Cardiovasc Qual Outcomes. 2010; 3:120-27.

[99] Ferris A, Robertson RM, Fabunmi R, et al. American Heart Association; American Stroke Association. American Heart Association and American Stroke Association national survey of stroke risk awareness among women. Circ. 2005; 111:1321-26.

[100] Heron M. Deaths: Leading Causes for 2006. Hyattsville, MD: National Center for Health Statistics. 2010.

[101] Gallo LC, Penedo FJ, Espinosa de los Monteros K, et al. Resiliency in the face of disadvantage: do Hispanic cultural characteristics protect health outcomes? J Pers. 2009;77:1707–46.

[102] Markides KS, Eschbach K. Aging, migration, and mortality: current status of research on the Hispanic paradox. J Gerontol B Psychol Sci Soc Sci. 2005; 60 (spec No. 2):68-75.

[103] Chaitman BR, Bourassa MG, Davis K et al. Angiographic prevalence of high-risk coronary artery disease in patient subsets (CASS).1981; 64(2):362-67.

[104] Bello N, Mosca L. Epidemiology of coronary heart disease in women. Prog Cardiovasc Dis. 2004; 46(4):287-92.

[105] Wenger NK. Cardiovascular health and disease in women–problems and prospects. Circ. 2004; 109:558-60.

[106] Berger JS, Brown DL. Impact of gender on mortality following primary angioplasty for acute myocardial infarction. Prog Cardiovasc Dis. 2004; 46(4):297-304.

[107] Peterson P, Masoudi F, Rumsfeld J. Gender differences in the epidemiology and treatment of heart failure. Cardiol Review.2005; 22(3):24-29.

[108] Jacobs AK, Eckel RH. Evaluating and managing cardiovascular disease in women understanding a woman's heart. Circulation. 2005; 111(4):383-84.

[109] Redberg RF, Shaw LJ. Diagnosis of coronary artery disease in women.Prog Cardiovasc Dis. 2003; 46(3):239-58.

[110] Daly CA, Clemens F, Sendon JL, et al. The clinical characteristics and investigations planned in patients with stable angina presenting to cardiologists in Europe: from the Euro Heart Survey of Stable Angina. Eur Heart J. 2005; 26:996-1010.

[111] Bugiardini R, Yan RT, et al. Factors influencing underutilization of evidence-based therapies for women. Eur Heart J. 2011; DOI: 10.1093/eurheartj/ehr027.

[112] Matthews KA, Meilahn EN, Kuller LH, et al. Menopause and risk factors for coronary heart disease. N Engl J Med. 1989; 321:641-6.

[113] Mieres JH, Shaw LJ, Arai A, et al. Role of non-invasive testing in the clinical evaluation of women with suspected coronary artery disease. Circ. 2005; 111:682-96.

[114] Arnold AL, Milner KA, Vaccarino V. Sex and race differences in electrocardiogram use (the National Hospital Ambulatory Medical Care Survey). Am J Cardiol. 2001; 88(9):1037-40.

[115] Scirica BM, Moliterno DJ, Every NR, et al. Differences between men and women in the management of unstable angina pectoris (The GUARANTEE Registry). The GUARANTEE Investigators. Am J Cardiol. 1999; 84(10):1145-50.

[116] Solinas E, Nikolsky E, Lansky AJ, et al. Gender-specific outcomes after sirolimus-eluting stent implantation. JACC. 2007; 50(22):2111-16.

[117] Brown RA, Williams M, Barker CM, et al. Sex-specific outcomes following revascularization with zotarolimus-eluting stents: Comparison of angiographic and late-term clinical results. Cath and Cardiovasc Interv.2010; 76:804-13.

[118] Mikhail GW, Gerber RT, Cox DA, et al. Influence of sex on long-term outcomes after percutaneous coronary intervention with the paclitaxel-eluting coronary stent. Results of the "TAXUS Women" analysis. JACC: Cardiovasc Interv. 2010; 3(12):1250-59.

[119] Aldea GS, Gaudiani JM, Shapira OM, et al. Effect of gender on postoperative outcomes and hospital stays after coronary artery bypass grafting. Ann Thorac Surg. 1999; 67:1097-103.

[120] Fukui T, Takanashi S. Gender differences in clinical and angiographic outcomes after coronary artery bypass surgery. Circ J. 2010; 74:2103-8.

[121] Morice M-C, Eltchaninoff H, Serruys PW, et al. Effect of gender on one-year outcomes in the Synergy between Percutaneous Coronary Intervention and Cardiac Surgery (SYNTAX) Trial. ACC 2009.

[122] Sheiban I, Spina CL, Cavallero E, et al. Sex-related differences in patients undergoing percutaneous unprotected left main stenting. EuroInterv. 2010; 5:795-800.

[123] Mahoney EM, Jurkovitz CT, Chu H, et al. Cost and cost-effectiveness of an early invasive vs. conservative strategy for the treatment of unstable angina and non-ST-segment elevation myocardial infarction. JAMA. 2002; 288(15):1851-58.

[124] Akhter N, Milford-Beland S, Roe MT, et al. Gender differences among patients with acute coronary syndromes undergoing percutaneous coronary intervention in the American College of Cardiology-National Cardiovascular Data Registry (ACC-NCDR). Am Heart J. 2009; 157(1):141-48.

[125] Vaina S, Voudris V, Morice M-C,. et al. Effect of gender differences on early and mid-term clinical outcome after percutaneous or surgical coronary revascularization in patients with multivessel coronary artery disease: Insights from ARTS I and ARTS II. EuroInterv. 2009; 4(4):492-501.

[126] Anand SS, Xie CC, Mehta S, et al. CURE Investigators. Differences in the management and prognosis of women and men who suffer from acute coronary syndromes. J Am Coll Cardiol. 2005; 46:1845-51.

[127] Jani SM, Montoye C, Mehta R, et al. ACC Foundation Guidelines Applied in Practice Steering Committee. Sex differences in the application of evidence-based therapies for the treatment of acute myocardial infarction: The ACC Guidelines applied in practice projects in Michigan. Arch Intern Med 2006; 166:1164-70.

[128] Kudenchuk PJ, Maynard C, Martin JS, et al. Comparison of presentation, treatment, and outcome of acute myocardial infarction in men versus women. Am J Cardiol 1996; 78:9-14.

[129] Presbitero P, Belli G, Zavalloni D, et al. Gender paradox in outcome after percutaneous coronary intervention with paclitaxel eluting stents. EuroInterv. 2008; 4:345-50.

[130] Lansky AJ, Yaqub M, Sood P, et al. Performance of everolimus and paclitaxel-eluting coronary stents in women: Two-year outcomes from the SPIRIT IV Trial. CRT 2011.

[131] Lansky AJ, Ng VG, Mutlu H, et al. Gender-based evaluation of the XIENCE V everolimus-eluting coronary stent system: Clinical and angiographic results from the SPIRIT III randomized trial. Catheter Cardiovasc Interv. 2009; 74(5):719-27.

[132] Kim Y, Park D, Lee S, et al. Long term safety and effectiveness of unprotected left main stenting with drug eluting stents compared with bare metal stents (MAIN-COMPARE Study). Circulation 2009; 120:400-407.

[133] Tamburino C, Di Salvo M, Capoddano D, et al. Comparison of drug eluting stents and bare metal stents for the treatment of unprotected left main coronary artery disease in acute coronary syndromes. Am J Cardiol 2009; 103:187-93.

[134] Kandzari D, Colombo A, Park S, et al. Revascularization for unprotected left main disease. J Am Coll Cardiol 2009; 54:1576-88.

[135] Stone GW, Mehran R, Dangas G, et al. Differential impact on survival of electrocardiographic Q-wave versus enzymatic myocardial infarction after percutaneous intervention. Circulation 2001; 104:642-47.

[136] Javaid A, Buch AN, Steinberg DH, et al. Does creatine kinase-MB (CK-MB) isoenzyme elevation following percutaneous coronary intervention with drug-eluting stents impact late clinical outcome? Catheter Cardiovasc Interv 2007; 70:826-31.

[137] Saucedo JF, Mehran R, Dangas G, et al. Long-term clinical events following creatine kinase–myocardial band isoenzyme elevation after successful coronary stenting. J Am Coll Cardiol 2000; 35(5):1134-41.

[138] Brener SJ, Ellis SG, Schneider J, et al. Frequency and long-term impact of myonecrosis after coronary stenting. Eur Heart J 2002; 23(11):869-76.

[139] Ellis SG, Chew D, Chan A, et al. Death following creatine kinase-MB elevation after coronary intervention. Identification of an early risk period: Importance of creatine kinase-MB level, completeness of revascularization, ventricular function, and probable benefit of statin therapy. Circulation 2002; 106:1205-10.

[140] Kini AS, Lee P, Marmur JD, et al. Correlation of postpercutaneous coronary intervention creatine kinase-MB and troponin I elevation in predicting mid-term mortality. Am J Cardiol 2004; 93(1):18-23.

[141] Brener SJ, Lytle BW, Schneider JP, et al. Association between CK-MB elevation after percutaneous or surgical revascularization and three-year mortality. J Am Coll Cardiol 2002; 40(11):1961-67.

[142] Ramsay J, Shernan S, Fitch J, et al. Increased creatine kinase MB level predicts postoperative mortality after cardiac surgery independent of new Q waves. J Thorac Cardiovasc Surg 2005; 129:300-06.

[143] Mahaffey KW, Roe MT, Kilaru R, et al.Creatine kinase-MB elevation after coronary artery bypass grafting surgery in patients with non-ST-segment elevation acute coronary syndromes predict worse outcomes: results from four large clinical trials. Eur Heart J 2007; 28(4):425-32.

[144] Klatte K, Chaitman BR, Theroux P, et al. Increased mortality after coronary artery bypass graft surgery is associated with increased levels of postoperative creatine kinase-myocardial band isoenzyme release: Results from the GUARDIAN trial. J Am Coll Cardiol 2001; 38:1070-77.

[145] Antman EM, Tanasijevic MJ, Thompson B, et al. Cardiac-specific troponin I levels to predict the risk of mortality in patients with acute coronary syndromes. N Engl J Med 1996; 335:1342-49.

[146] Prasad A, Gersh BJ, Bertrand ME, et al. Prognostic significance of periprocedural versus spontaneously occurring myocardial infarction after percutaneous coronary intervention in patients with acute coronary syndromes: an analysis from the ACUITY (Acute Catheterization And Urgent Intervention Triage Strategy) Trial. J Am Coll Cardiol 2009; 54:477-86.

[147] Nienhuis MB, Ottervanger JP, Bilo HJG, et al. Prognostic value of troponin after elective percutaneous coronary intervention: A meta-analysis. Catheter Cardiovasc Interv 2008; 71:318-24.

[148] Prasad A, Rihal CS, Lennon RJ, et al. Significance of periprocedural myonecrosis on outcomes after percutaneous coronary intervention: An analysis of preintervention and postintervention Troponin T levels in 5487 patients. Circ Cardiovasc Intervent2008; 1:10-19.

[149] van Domburg RT, Cobbaert C, Kimman G-J, et al. Long-term prognostic value of serial Troponin T bedside tests in patients with acute coronary syndromes. Am J Cardiol 2000; 86:623-27.

[150] Tanasijevic MJ, Cannon CP, Antman EM. The role of cardiac Troponin-I (cTnI) in risk stratification of patients with unstable coronary artery disease. Clin. Cardiol 1999; 22:13-16.

[151] Thygesen K, Alpert JS, Jaffe AS. Third universal definition of myocardial infarction. J Am Coll Cardiol 2012;60:1581-98.

[152] Spertus JA, Jones P, McDonell M, et al. Health status predicts long-term outcome in outpatients with coronary disease. Circulation 2002; 106:43-49.

[153] Stewart AL, Greenfield S, Hays RD, et al. Functional status and well-being of patients with chronic results from the Medical Outcomes Study. JAMA 1989; 262:907-13.

[154] Ware JE, Jr., Sherbourne CD. The MOS 36-item short-form health survey (SF-36). I. Conceptual framework and item selection. Med Care 1992; 30:473-83.

[155] Kroenke K, Spitzer RL, Williams JBW. The PHQ-9: Validity of a brief depression severity measure. J Gen Intern Med 2001; 16:606-13.

[156] Gore JM, Granger CB, Simoons ML, et al. Stroke after thrombolysis. Mortality and functional outcomes in GUSTO-I trial. Circulation 1995; 92:2811-18.

[157] Oldridge N, Furlong W, Feeny D, et al. Economic evaluation of cardiac rehabilitation soon after acute myocardial infarction. Am J Cardiol 1993; 72:154-61.

[158] Gold M, Patrick D, Torrance G, et al., eds. Identifying and valuing outcomes. New York, NY: Oxford University Press; 1996.

[159] Torrance GW, Feeny DH, Furlong WJ, et al. Multiattribute utility function for a comprehensive health status classification system. Health Utilities Index Mark2. Med Care 1996; 34:702-22.

[160] Kaplan R, Anderson J, Ganiats T, eds. The Quality of Well Being Scale: rationale for a single quality of life index. Dordrecht: Kluwer Academic Publishers; 1993.

[161] Fryback DG, Lawrence WF, Martin PA, et al. Predicting Quality of Well-being scores from the SF-36: results from the Beaver Dam Health Outcomes Study. Med Decis Making 1997; 17:1-9.

[162] Johannesson M, Isacson DGL, Borgquist L. The relationship between health-state utilities and the SF-12 in a general population. Med Decis Making 1999; 19:128-40.

[163] Dolan P. Modeling valuations for EuroQol health states. Medical Care 1997; 35:1095-108.

[164] Van Hout BA, Cohen DJ, Koens BAH, et al. Costs and effects of stent implantation versus balloon angioplasty (abstract). J Am Coll Cardiol 1998;31:50A.

[165] Rinfret S, Grines CL, Cosgrove RS, et al. Quality of life after balloon angioplasty or stenting for acute myocardial infarction. One-year results from the Stent-PAMI trial. J Am Coll Cardiol 2001; 38:1614-21.

[166] Finkler SA. The distinction between cost and charges. Ann Intern Med 1982; 96:102-9.

[167] Mitchell JB, Burghe RT, Lee AJ, et al. Per case prospective payment for episodes of hospital care. Springfield, VA; U.S. Dept of Commerce National Technical Information Service; Publication PB95226023.

[168] Mahoney EM, Jurkovitz CT, Chu H, et al. Cost and cost-effectiveness of an early invasive vs. conservative strategy for the treatment of unstable angina and non-ST segment elevation myocardial infarction. JAMA 2002; 288:1851-58.

[169] Shafer J. Analysis of incomplete multivariate data. London: Chapman and Hall; 1997.

[170] Barber JA, Thompson SG. Analysis of cost data in randomized trials: an application of the non- parametric bootstrap. Stat Med 2000; 19:3219-36.

[171] Efron B, Tibshirani RJ. An introduction to the bootstrap. New York, NY: Chapman and Hall; 1993.

[172] Gold M, Siegel J, Russel L, Weinstein M, eds. Cost-effectiveness in health and medicine. New York, NY: Oxford University Press; 1996.

[173] Hlatky MA, Boothroyd DB, Melsop KA, et al. Economic outcomes of treatment strategies for type 2 diabetes mellitus and coronary artery disease in the bypass angioplasty revascularization investigation 2 diabetes trial. Circulation 2009; 120:2550-58.

[174] Beck JR, Pauker SG. The Markov process in medical prognosis. Med Decis Making 1983; 3:419-58.

[175] Cook JR, Drummond M, Glick H, et al. Assessing the appropriateness of combining economic data from multinational clinical trials. Stat Med 2003; 22:1955-76.

[176] Hoch JS, Briggs AH, Willan AR. Something old, something new, something borrowed, something blue: a framework for the marriage of health econometrics and cost- effectiveness analysis. Health Econ 2002; 11:415-30.

[177] Hillman AL, Eisenberg JM, Pauly MV, et al. Avoiding bias in the conduct and reporting of cost-effectiveness research sponsored by pharmaceutical companies. N Engl J Med 1991; 324:1362-65.

[178] Abizaid AS, Mintz GS, Abizaid A, et al. One-year follow-up after intravascular ultrasound assessment of moderate left main coronary artery disease in patients with ambiguous angiograms. J Am Coll Cardiol 1999; 34:707-15.

[179] Hamilos M, Muller O, Cuisset T, et al. Long-term clinical outcome after fractional flow reserve - Guided treatment in patients with angiographically equivocal left main coronary artery stenosis. Circulation 2009; 120:1505-1512.

[180] Fearon WF, Tonino PAL, De Bruyne B, et al. Rationale and design of the fractional flow reserve versus angiography for multivessel evaluation (FAME) study. Am Heart J 2007; 154:632-36.

[181] Tonino PAL, De Bruyne B, Pijls NHJ, et al. Fractional flow reserve versus angiography for guiding percutaneous coronary intervention. N Engl J Med 2009; 360:213-24.

[182] Park S-J, Kim Y-H, Park D-W. Impact of intravascular ultrasound guidance on long-term mortality in stenting for unprotected left main coronary artery stenosis. Circ Cardiovasc Intervent 2009; 2:167-177.

[183] Fujii K, Carlier SG, Mintz S et al. Stent under expansion and residual reference segment stenosis are related to stent thrombosis after sirolimus-eluting stent implantation: An intravascular ultrasound study. J Am Coll Cardiol 2005; 45:995-98.

[184] Okabe T, Mintz GS, Buch AN, et al. Intravascular ultrasound parameters associated with stent thrombosis after drug-eluting stent deployment. Am J Cardiol. 2007; 100:615-20.

[185] Liu X, Doi H, Maehara A, et al. A volumetric intravascular ultrasound comparison of early drug-eluting stent thrombosis versus restenosis. JACC Cardiovasc Interv2009; 2:428-34.

[186] Doi H, Maehara A, Mintz GS, et al. Impact of in-stent minimal lumen area at 9 months post stent implantation on 3-year target lesion revascularization–free survival. A serial intravascular ultrasound analysis from the TAXUS IV, V, and VI Trials. Circ Cardiovasc Interv 2008; 1:111-18.

[187] Grundy SM, Cleeman JI, Merz CN, et al. Implications of recent clinical trials for the National Cholesterol Education Program Adult Treatment Panel III guidelines. Circulation 2004; 110:227-39.

[188] Smith SC, Jr., Allen J, Blair SN, et al. AHA/ACC guidelines for secondary prevention for patients with coronary and other atherosclerotic vascular disease: 2006 update: endorsed by the National Heart, Lung, and Blood Institute. Circulation 2006; 113:2363-72.

[189] European guidelines on cardiovascular disease prevention in clinical practice: Executive summary. Eur Heart J 2007; 28:2375-414.

[190] American Heart Association of Cardiovascular and Pulmonary Rehabilitation. Guidelines for cardiac rehabilitation and secondary prevention. 4th Edition. Champaign IL, Human Kinetics, 2004.

[191] The American College of Sports Medicine. Guidelines for exercise testing and prescription. 7th Edition. Philadelphia Pennsylvania, Williams and Wilkens 2006.

[192] Boden WE, O'Rourke RA, Teo KK, et al. Design and rationale of the Clinical Outcomes Utilizing Revascularization and Aggressive DruG Evaluation (COURAGE) trial: Veterans Affairs Cooperative Studies Program no. 424. Am Heart J 2006; 151:1173-79.

[193] American Diabetes Association. Standards of medical care for patients with diabetes mellitus. Diabetes Care 1999; 22(Suppl 1):S32-S42.

[194] The Diabetes Control and Complications Trial Research Group. The effect of intensive diabetes treatment on the development and progression of long-term complications in insulin-dependent diabetes mellitus. N Eng J Med 1993; 329:977-86.

[195] Third Report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III) final report. Circulation 2002; 106:3143-421.

[196] Gibbons RJ, Abrams J, Chatterjee K, et al. ACC/AHA 2002 guideline update for the management of patients with chronic stable angina. Summary article: a report of the American College of Cardiology/American Heart Association Task Force on practice guidelines (Committee on the Management of Patients With Chronic Stable Angina). J Am Coll Cardiol 2003; 41:159-68.