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Prognostic Significance of Nonobstructive Left Main Coronary Artery Disease in Women versus Men: Long-Term Outcomes from the CONFIRM Registry

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An Abstract of

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Abstract

Prognostic Significance of Nonobstructive Left Main Coronary Artery Disease in Women versus Men: Long-Term Outcomes from the CONFIRM Registry

By Joe X. Xie

Background: Patients with obstructive (≥50% stenosis) left main (LM) coronary artery disease (CAD) are at high risk for future adverse events; prior studies have also documented worse outcomes among women than men with severe multivessel/LM CAD. However, clinical outcomes associated with nonobstructive (1-49% stenosis) LM CAD have not been previously examined and as a result, the optimal management strategy of nonobstructive left main disease is not clear.

Objective: To assess the prognostic significance of nonobstructive left main (LM) coronary artery disease (CAD) and examine sex differences in subjects with suspected underlying CAD.

Methods: In the long-term COronary CT Angiography EvaluatioN For Clinical Outcomes: An InteRnational Multicenter (CONFIRM) registry, patients underwent elective coronary computed tomographic angiography (CCTA) for suspected CAD and were followed for 5 years. After excluding obstructive LM CAD, 5,166 patients were categorized as having normal LM or nonobstructive LM. Kaplan-Meier and multivariable Cox proportional hazards models, adjusted for baseline demographics, CAD risk factors, and obstructive CAD burden in other vessels, were used to estimate the composite risk of death, myocardial infarction (MI), or revascularization in women and men by LM status.

Results: Non-obstructive LM was detected in 18% of patients. The composite incidence of death, myocardial infarction, or revascularization was higher among patients with nonobstructive LM than normal LM, 27.3% versus 17.2% ($p<0.0001$). A significant interaction existed between sex and LM status for the composite outcome ($p =0.001$). In multivariable Cox regression, the presence of nonobstructive LM plaque increased the risk for the composite outcome in women (HR_{adj} 1.63, [1.26-2.10], $p<0.001$), but not in men (HR_{adj} 0.99 [0.82-1.19], $p=0.879$) (p_{adj}-for-interaction=0.002). Among those with nonobstructive LM CAD, women had a nearly 80% higher risk for events than men with nonobstructive LM CAD (HR_{adj} 1.78 [1.31-2.25], $p=0.017$).

Conclusion: Nonobstructive LM CAD was frequently detected on CCTA and significantly associated with adverse events. While in men the association was confounded by comorbid CAD risk factors and co-occurring CAD burden, in women, nonobstructive LM remained associated with downstream events even after multivariable adjustment. Recognizing the prognostic significance of nonobstructive LM plaque in women may augment risk stratification efforts.

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BACKGROUND

Coronary heart disease (CHD) is defined as the clinical symptoms or complications that arise from insufficient blood flow to the myocardium, such as angina or myocardial infarction (MI), and typically due to progressive atherosclerosis and narrowing of the coronary arteries.[1] In 2010, an estimated 17.6 million adults in the United States (US) had a diagnosis of CHD, with 610,000 new cases annually.[1] Although rates of death from acute MI have decreased substantially due to continued advancements in diagnostic and therapeutic techniques, CHD remains the number one cause of death in the US.[1]

The left main (LM) coronary artery, which arises from the root of the aorta and branches into the left anterior descending artery (LAD) and left circumflex artery (LCX), is responsible for the majority of the blood flow to the myocardium. Given the anatomic significance of the LM, obstructive stenosis (defined as ≥50% luminal narrowing from plaque) in the LM has been found to be associated with significant CHD morbidity and mortality.[2] Abundant prognostic evidence and numerous clinical trials in the past 40 years have examined optimal management strategies and clinical outcomes of patients with obstructive LM coronary artery disease (CAD).[3] Furthermore, prior studies have described worse outcomes among women than men with severe multivessel or LM CAD, including after revascularization, despite a higher prevalence and burden of obstructive CAD among men.[4-7] However, the prevalence and prognostic significance of nonobstructive stenosis (<50% luminal narrowing) in the LM coronary artery, including sex-specific differences in outcomes, has not been previously evaluated.

Importantly, nonobstructive CAD (in general) is frequently identified on coronary angiography among stable patients with CHD. From a recent report by Patel et al, among nearly 400,000 US adults without a known history of CAD, obstructive CAD was only detected in ~37%

of patients on elective cardiac catheterization; another one-third of patients had nonobstructive CAD, which was also reported in the Patel study and by several others to be more prevalent in symptomatic women (~60%) than men (~30%).[6,8,9] Furthermore, several investigations have described a strong association between nonobstructive CAD and adverse cardiovascular events in both invasive and noninvasive angiographic cohorts, with gradations of risk based on the extent of nonobstructive plaque.[10] Comparative prognostic data of women versus men with nonobstructive CAD, however, have been more limited, despite clear sex-related epidemiologic differences and numerous studies describing disproportionately worse outcomes among women than men with obstructive CAD.[11-17] The recent emergence and recognition of nonobstructive CAD as clinically significant atherosclerotic coronary disease have thus prompted increased efforts to examine nonobstructive CAD, including characterizing sex-specific disparities in outcomes, as a means to improve risk stratification efforts and target preventive care for a large number of at-risk women and men.[9] Notably, nonobstructive CAD within the LM has not been an emphasis within any of these studies to date.

Accordingly, we sought to examine the prognostic significance of nonobstructive LM CAD in a large, 'real-world' cohort of patients who underwent elective coronary computed tomographic angiography (CCTA) for the evaluation of suspected CAD. Our study aims were to (1) assess the association between nonobstructive LM CAD as detected on CCTA with clinical outcomes including all-cause mortality, nonfatal MI, and coronary revascularization; and (2) determine whether sex-specific differences in risk exist among patients with nonobstructive LM CAD vs normal LM anatomy. Our hypotheses were that patients with nonobstructive LM CAD would have a higher risk of death, nonfatal MI and revascularization compared to patients with no LM CAD

(for Aim 1), and that sex modifies the association between nonobstructive LM CAD and composite clinical outcomes with a higher hazard ratio in women as compared to me men (for Aim 2).

METHODS

Study Design and Study Population

We performed a retrospective cohort study using data from Phase 2 of the CONFIRM (COronary CT Angiography EvaluatioN For Clinical Outcomes: An InteRnational Multicenter) registry. CONFIRM was a large, community-based registry that enrolled stable outpatients undergoing elective CCTA in the evaluation of clinically suspected CAD and were followed for 5 years (Phase 1 of the registry had 3-year follow-up). Although invasive coronary angiography has traditionally been used as the gold standard in the diagnosis and evaluation of patients presenting with symptoms suggestive of CAD, recent developments in CT technology including improvements in temporal resolution, spatial resolution, and volume coverage now allow routine and accurate examination of the coronary arteries using CCTA.[18] As a result, CCTA has emerged as a promising noninvasive anatomic imaging modality with an extensive randomized trial and observational registry evidence base and has since been incorporated within national guidelines for the diagnostic evaluation of CAD.[4,19,20] The primary aim of CONFIRM was to assess the prognostic value of CCTA-derived findings for the prediction of adverse cardiovascular events. A total of 17 participating sites from 9 countries (United States, Canada, Germany, Switzerland, Italy, Portugal, Austria, Israel, and South Korea) enrolled 12,086 patients between 2002 and 2009. All sites received institutional review board approval and oversight. Patient and site identifiers were not entered into the CONFIRM database. Additional details regarding the CONFIRM registry's design, rationale, site eligibility, and patient recruitment have been previously described in detail.[21]

Inclusion and Exclusion Criteria

The inclusion criteria for our analysis reflected the enrollment indications of the CONFIRM registry, including: (1) adults ≥18 years of age, (2) referral for CCTA to evaluate for suspected CAD given presenting symptoms or for risk stratification using a ≥64-detector row scanner, (3) prospective data collection of CAD risk factors and CCTA data, and (4) standardized reporting of segmental coronary stenosis, as per Society of Cardiovascular Computer Tomography (SCCT) guidelines.[22,23] Specific to our study (CONFIRM had no explicit exclusion criteria), we excluded patients with obstructive LM CAD (n=426), history of known CAD or coronary revascularization (n=1,416), missing LM stenosis severity (n=721; missing at random, complete case analysis performed), and incomplete adjudication of clinical events (n=4,357; not missing at random, complete case analysis performed) for a final cohort size of 5,166 patients. All CONFIRM investigators have reviewed and approved our study.

CCTA Protocol and Anatomic Definitions

Each CONFIRM site followed standardized protocols for performing CCTA as defined by guidelines of the SCCT.[22,23] The percent luminal stenosis in the LM was coded as normal (0% stenosis) or nonobstructive (1-49% stenosis) by visual assessment. Luminal stenosis in non-LM vessels, including the left anterior descending (LAD) artery, left circumflex (LCx) artery, and right coronary artery (RCA) were also gathered and coded as normal (0% stenosis), nonobstructive (1-49% stenosis), or obstructive (≥50% stenosis), which were consistent with previous CCTA-derived definitions for obstructive and nonobstructive CAD.[4]

Clinical Descriptive Data

All patients enrolled in CONFIRM underwent evaluation by a physician or nurse prior to CCTA. Each participating site uniformly collected self-reported baseline clinical data including age, gender, history of hypertension (HTN), diabetes mellitus (DM), hyperlipidemia (HLD),

smoking status, early family history of early CAD (father <55 or mother <65 years of age), left ventricular ejection fraction (LVEF), and presenting symptom characteristics categorized as no chest pain, non-cardiac chest pain, atypical angina, or typical angina.

Outcome Data Collection and Follow-up Methods

Our primary outcome was a composite of incident all-cause mortality (n=349), nonfatal MI (n=471), or coronary revascularization (n=364). Each individual endpoint was also evaluated as a secondary outcome. The National Death Index was queried for death within the United States, or determined through direct interview with the patient's family or physician, telephone call, or review of medical records for events outside of the United States. The specific causes of death were not delineated further in CONFIRM. MI events were confirmed through review of the patient's medical records for hospital documentation of biomarker elevation and electrocardiographic alterations consistent with the Universal Definition of MI.[24] Four out of the seventeen sites did not have complete adjudication of MI events. Coronary revascularization events were also confirmed through review of medical records, however, target vessel revascularization was not reported. Additional information on ascertainment and adjudication methods have been previously described.[21]

Statistical Analyses

Patients were categorized by their LM status as having nonobstructive LM CAD (1-49% stenosis) or normal LM (0% stenosis). Using chi-squared tests for categorical variables and t-tests for continuous variables, baseline characteristics were compared between patients with nonobstructive LM and normal LM.

Using the Kaplan-Meier method, we assessed for differences in the composite incidence of all-cause mortality, nonfatal MI, or coronary revascularization according to LM status through

5 years of follow-up. After the proportional hazards assumption was met by graphical assessment (**Appendix A**), we used Cox proportional hazards models to assess the association between nonobstructive LM and the composite outcome, and tested for an interaction between sex and LM status. Three multivariable Cox proportional hazards models were created using covariables defined a priori based on clinical judgment. Model 1 included age, HTN, DM, HLD, smoking history, and the presence of typical angina to control for baseline demographics, CAD risk factors, and pretest probability for obstructive CAD. Model 2 included the covariables from Model 1 plus the total number of non-LM coronary artery segments with obstructive plaque (scored 0 to 15) to adjust for differences in obstructive plaque burden between LM strata.[19] As an alternative method to adjust for the extent of co-occurring obstructive plaque, Model 3 included the covariables from Model 1 plus the number of non-LM vessels with obstructive plaque (scored 0 to 3).

In additional subgroup and sensitivity analyses, (1) we assessed time-to-event by LM status in a subset of 3,325 patients without any obstructive CAD to further account for baseline differences in plaque burden. (2) We also examined sex-specific differences in risk (women compared directly to men) in subgroups of patients based on the location (LM, LAD, LCX, or RCA) or extent (per-segment and per-vessel) of nonobstructive plaque. (3) Since target vessel revascularization was not known and may have been subject to biases by gender or the extent of obstructive CAD, we removed revascularization from the composite endpoint and repeated our analysis using death or nonfatal MI as the primary outcome. (4) Since we excluded non-randomly missing data (4 sites without complete adjudication of MI events), baseline characteristics of patients who were excluded were compared to those included in the final cohort. Kaplan-Meier analysis was also repeated for the endpoint of all-cause mortality in a pooled cohort (n=9,523). A

two-tailed p-value <0.05 was considered statistically significant for each analysis. All statistical analyses were performed using SAS version 9.4 (Cary, NC).

RESULTS

Clinical and CCTA Characteristics of the Study Cohort

Of 5,166 patients, 82% had normal LM and 18% had nonobstructive LM CAD (**Table 1**). Patients with nonobstructive LM were older and had higher baseline rates of CAD risk factors including HTN, DM, and HLD ($p<0.001$). Furthermore, patients with nonobstructive LM CAD had more extensive (per-segment and per-vessel) co-occurring obstructive plaque in non-LM vessels ($p<0.001$). Neither baseline LVEF ($p=0.232$) nor presenting symptoms ($p=0.424$) were significantly different by LM status.

Association between Nonobstructive LM CAD and Death, Myocardial Infarction, or Revascularization

Through a mean 5.3±1.8 years of follow-up (median 5.5 years [IQR 1.2]), the cumulative incidence of the composite outcome was 27.3% for patients with nonobstructive LM CAD compared to 17.2% for patients with normal LM ($p<0.0001$, **Figure 1**). Differences in the incidence for the individual endpoints of all-cause mortality (10.0% versus 5.5%, $p<0.0001$), nonfatal MI (12.1% versus 8.6%, $p=0.0004$), and coronary revascularization (10.7% versus 6.2%, $p<0.0001$) by LM status are also shown. Compared to normal LM, nonobstructive LM was associated with a higher risk for the composite outcome (HR 1.69 [1.47-1.95], $p<0.001$). Importantly, a significant interaction existed between sex and LM status for the composite endpoint ($p=0.001$) as well as for the individual endpoints of death ($p=0.027$) and revascularization ($p=0.027$), but not MI ($p=0.182$).

Sex-specific Differences in Outcomes

Sex-specific disparities in outcomes according to LM status were further explored. Differences in baseline clinical characteristics by gender are provided in **Appendix B**; women had

a lower burden (per-segment and per-vessel) of obstructive CAD than men (p<0.001). In both women (n=1,911) and men (n=3,255), those with nonobstructive LM had higher cumulative incidence of events than those with normal LM: women (34.3% versus 15.4%, p<0.0001); men (24.6% versus 18.2%, p<0.0001) (**Figure 2**). Compared to normal LM, nonobstructive LM CAD increased the composite risk by 2.4-fold risk in women and 1.4-fold in men; however, after multivariable adjustment, the association between nonobstructive LM and the composite outcome remained significant in women (HR_{adj} 1.63 [1.26-2.10], p<0.001), but not in men (HR_{adj} 0.99 [0.82-1.19], p=0.879) (**Tables 2a and 2b**). Similarly, the association between nonobstructive LM and the individual endpoints of death, nonfatal MI, and revascularization also differed by sex and are presented in **Tables 2a and 2b**.

Additional Subgroup and Sensitivity Analyses

In a subgroup of 3,325 patients without any obstructive CAD, the cumulative 5-year incidence of the composite outcome remained significantly lower among those with nonobstructive LM than those with normal LM (18.6% versus 10.7%, p<0.0001, **Figure 3**), and was also consistent in women and men, separately: women (28.3% versus 10.5%, p<0.0001); men (14.0% versus 10.8%, p=0.036).

Next, we examined whether sex-related differences in outcomes varied by nonobstructive plaque location or extent. As shown in **Figure 4**, in subgroups of patients with nonobstructive LM CAD, women had a significantly higher risk for adverse events than men (HR_{adj} 1.78 [1.31-2.25], p=0.017). In contrast, outcomes were not significantly comparing women to men in other subgroups of nonobstructive plaque either based on location (LAD, LCX, RCA) or extent (per-segment or per-vessel scoring).

Furthermore, after removing revascularization events from the composite endpoint, nonobstructive LM remained at a higher risk for death or MI than normal LM in women (HR_{adj} 1.40 [1.04-1.87], p=0.025), but not in men (HR_{adj} 0.99 [0.79-1.24], p=0.937) (**Table 3**, p-for-interaction=0.047).

In addition, we examined the baseline characteristics of the patients from the four excluded sites. Patients excluded were younger, more often female, but had higher rates of family history with early CAD and more often presented with typical angina (p<0.001, **Appendix C**). However, rates of HTN, DM, and HLD were similar between the included and excluded patients (p>0.05) and the extent of co-occurring obstructive CAD was nearly identical between groups (p=0.844). Finally, in a pooled Kaplan-Meier analysis including patients from all sites (n=9,523), patients with nonobstructive LM CAD had a consistent and elevated incidence of death compared to those with normal LM (10.4% versus 6.4%, p<0.0001, **Appendix D**).

DISCUSSION

Although prognosis is well established in the setting of obstructive LM CAD, our findings were the first to reveal an association between nonobstructive LM CAD and adverse cardiovascular events, and importantly, sex-specific differences in outcomes among patients with nonobstructive LM CAD. The presence of nonobstructive LM CAD increased the composite event risk by over 60% among women; in contrast, the association between nonobstructive LM CAD and future events was not significant among men after adjustment for CAD burden in non-LM vessels. Furthermore, women with nonobstructive LM plaque had a nearly 1.8-fold higher risk for future events than men with nonobstructive LM plaque; sex-specific differences in outcomes were not observed across other patterns of nonobstructive CAD. These findings provide evidence that nonobstructive LM plaque carries important sex-specific prognostic value that should be considered during risk stratification.

Surprisingly, there has been a paucity of data regarding the prognostic implication of nonobstructive LM plaque within the published literature. One reason may be that previous studies have frequently represented nonobstructive CAD as having a uniform level of risk. For instance, in the Women's Ischemia Syndrome Evaluation (WISE) study[12], 5-year event rates for MI were estimated to be 3.9% for patients with any nonobstructive CAD. However, the extent and lesion-specific distribution of nonobstructive CAD were not further delineated.

More recently, both invasive angiographic and CCTA series have characterized gradations of risk based on the extent of nonobstructive CAD. Maddox et al described 1-year MI event rates of 0.24%, 0.56% and 0.59%, respectively, among patients with 1-vessel, 2-vessel, and 3-vessel nonobstructive CAD (defined as 20%-49% stenosis on invasive angiography).[15] Similarly in CCTA cohorts, proportional increases in 3-year mortality rates were reported with increasing

nonobstructive vessel involvement with estimated HRs ranging from 1.43 to 4.75 for 1- to 3-vessel nonobstructive CAD.[26] In contrast to our study, these prior investigations had shorter follow-up times, and nonobstructive LM plaque was classified as '1-vessel' nonobstructive CAD, as a lesion within the LAD territory, or incorporated as part of the segment involvement score.[4,5,11,13,26] One exception was a small, single-center CCTA study of 76 patients with nonobstructive LM CAD, of whom, none experienced an event after 20 months of follow-up.[27] Thus, our investigation expands upon previous findings with longer, 5-year follow-up, and to our knowledge, is the first study sufficiently powered to assess the prognostic significance of nonobstructive LM CAD.

Specifically, our study revealed that nonobstructive LM plaque was more strongly associated with adverse events in women than men, independent of obstructive CAD burden in other vessels. These sex-specific differences in outcomes were not observed for other subgroups of patients with multi-segment or multi-vessel nonobstructive CAD. Our results are in concordance with prior studies by Leipsic and others, who have not found that outcomes in women versus men differed based on the extent of nonobstructive CAD; however, disparities in prognosis based upon the location of nonobstructive plaque (e.g. LM versus other vessel) was not previously explored.[14,17] Similarly, Shaw et al described both higher in-hospital and 4-year mortality among women with significant atherosclerotic burden or high-risk lesions such as obstructive multivessel or LM CAD as compared to men;[4-6] we now extend these observations of sex-based differences in outcomes of LM disease to patients with nonobstructive plaque.

Mechanistically, women are known to have smaller coronary arterial sizes than men, including the luminal area of the LM, which has been associated with worse outcomes in women following percutaneous or surgical revascularization and may also increase susceptibility to thrombotic occlusion.[28] Numerous postmortem pathological examinations and intravascular

ultrasound (IVUS) studies have also characterized differences in coronary atherosclerotic composition and progression between women and men.[29-33] In autopsy series of individuals post-cardiovascular death, women were noted to have less severe and extensive CAD as well as higher rates of plaque erosion than men, which has been shown to frequently lead to distal microemboli and microvascular obstruction in addition to acute epicardial coronary thrombosis.[29,31-33] Furthermore, in an IVUS sub-study of WISE, positive coronary artery remodeling was detected in the majority of women without obstructive CAD on angiography; these vulnerable nonobstructive plaques have been proposed to serve as precursor lesions at risk for future erosion or rupture.[30] Hypothetically, given that the LM subtends a large proportion of the myocardium, any sex-based differences in rates of nonobstructive but vulnerable LM plaques that have undergone positive remodeling could conceivably place women at a significant and higher risk for downstream adverse events. These 'hidden' plaques may also lead to an underestimation of true atherosclerotic burden and therapeutic delay. Further characterization of sex-specific changes in vessel morphology and plaque remodeling are needed to improve discrimination of at-risk lesions,[34] and may further elucidate disparities in outcomes between women and men with nonobstructive LM CAD.

Our findings add to the growing body of evidence that depict a heterogeneous distribution of risk among patients with nonobstructive CAD; both the extent and location of nonobstructive plaque appear to confer varying prognostic value. Despite high rates of nonobstructive CAD on elective cardiac catheterization and a disproportionately higher prevalence of nonobstructive CAD among women compared to men, guideline recommendations on the management of this large cohort of patients with nonobstructive CAD have not been well-defined, and multiple studies have shown that patients with nonobstructive CAD are not as aggressively or consistently managed with

the same anti-atherosclerotic or ischemic medications that are reserved for obstructive CAD. [8,35,36,37] Although optimal medical therapy among patients with nonobstructive CAD remains unclear, simple reassurance and complacency in clinical management are likely not appropriate. In this context, elucidating and recognizing high-risk patterns of nonobstructive CAD, including the sex-specific prognostic significance of nonobstructive LM plaque, may help provide a more granular understanding of cardiovascular risk that can ultimately be used to guide preventive care efforts.

Study Limitations

Inherently, we were unable to account for all (unmeasured) confounders given our retrospective study design, however, we utilized several multivariable regression models that incorporated all available and pertinent clinical characteristics. Potential selection biases also limit our analysis. The proportion of women in our cohort was 37%, suggesting possible sex-related selection biases during patient enrollment in CONFIRM and highlights the need for external validation in a registry with a more equal representation of women and men. Similarly, we excluded non-randomly missing data from four enrollment sites thus introducing selection bias, however, no significant differences in event rates were observed from our pooled survival analysis. Although both external (including invasive angiographic cohorts) and prospective validation of our results remain to be performed, however, we chose the CONFIRM registry for our analysis as it still represents the largest CCTA cohort (of women or men) and with the longest duration of patient follow-up. Moreover, we did not have further details on plaque composition, progression or remodeling, which may have yielded additional predictive information and should be included in future analyses. Finally, the CONFIRM registry did not collect information regarding post-CCTA medication use and clinical management, which may have differed by sex and impacted patient outcomes. Prospective randomized trials assessing the effect of aspirin, statins, and anti-

ischemic medications on clinical endpoints of women and men with nonobstructive CAD are needed.

Conclusion

Although abundant prognostic data have documented poor clinical outcomes among patients with obstructive LM CAD, our findings were the first to reveal an elevated 5-year risk for death, MI, or revascularization associated with nonobstructive LM CAD. Notably, women with nonobstructive LM CAD were at higher risk for adverse downstream events compared to men and may be contributing to disparities in outcomes among women and men with nonobstructive CAD. Recognizing the sex-specific prognostic significance of nonobstructive LM plaque may improve future risk stratification efforts in patients undergoing evaluation for CAD.

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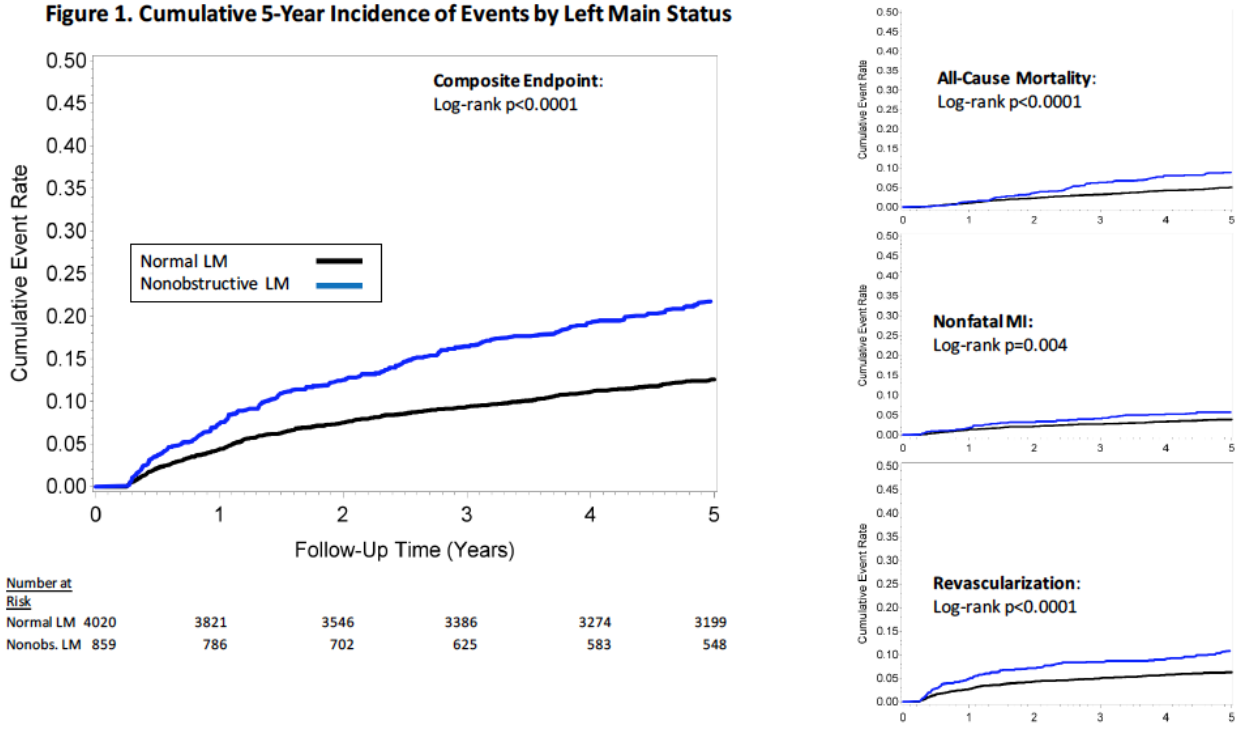
FIGURES

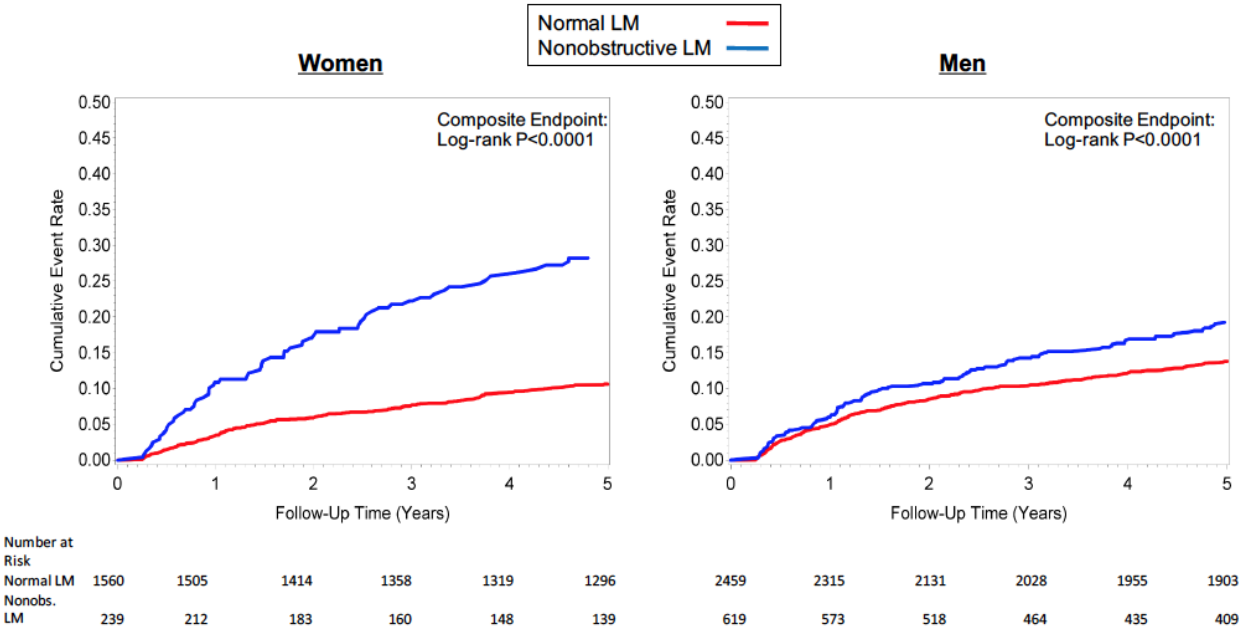
Figure 1. Cumulative 5-Year Incidence of Events by Left Main Status



Cumulative incidence of the primary composite outcome of all-cause mortality, nonfatal myocardial infarction or coronary revascularization is displayed using a 90-day landmark time. Cumulative events rates for the secondary endpoints of death, nonfatal myocardial infarction, and revascularization are also shown. Patients are stratified as having normal LM or nonobstructive LM.

LM: Left main

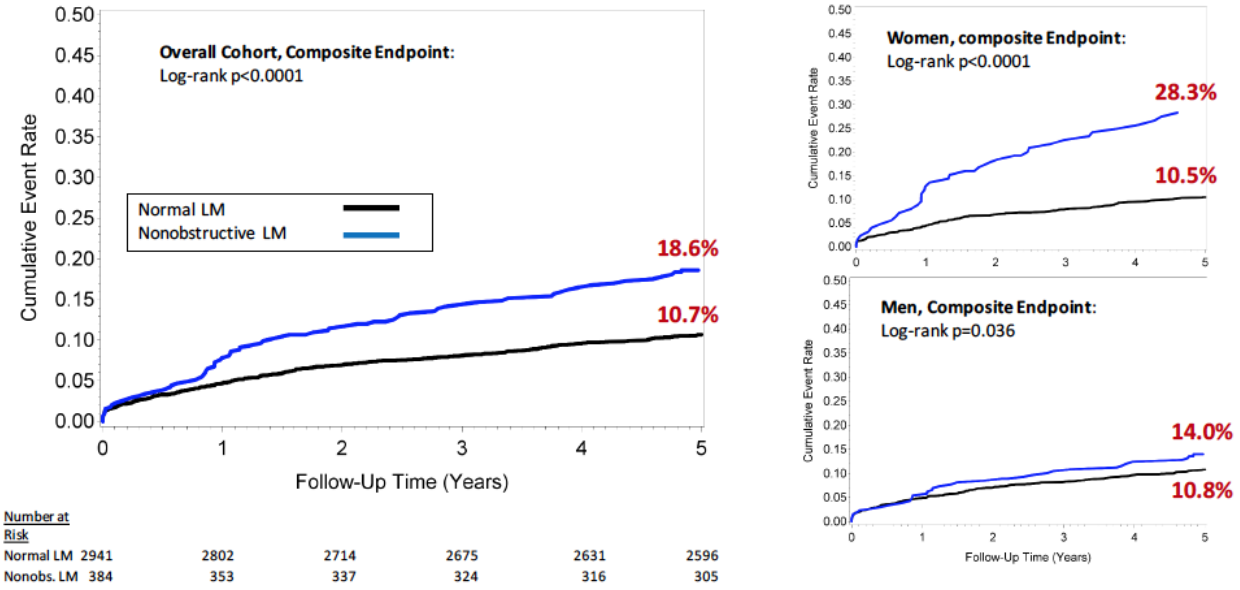
Figure 2. Cumulative 5-Year Incidence of Events in Women and Men



Cumulative incidence of the composite outcome of all-cause mortality, nonfatal myocardial infarction or coronary revascularization are displayed by LM status in women and men.

LM: Left main

Figure 3. Cumulative Incidence of Events among Patients without any Obstructive CAD

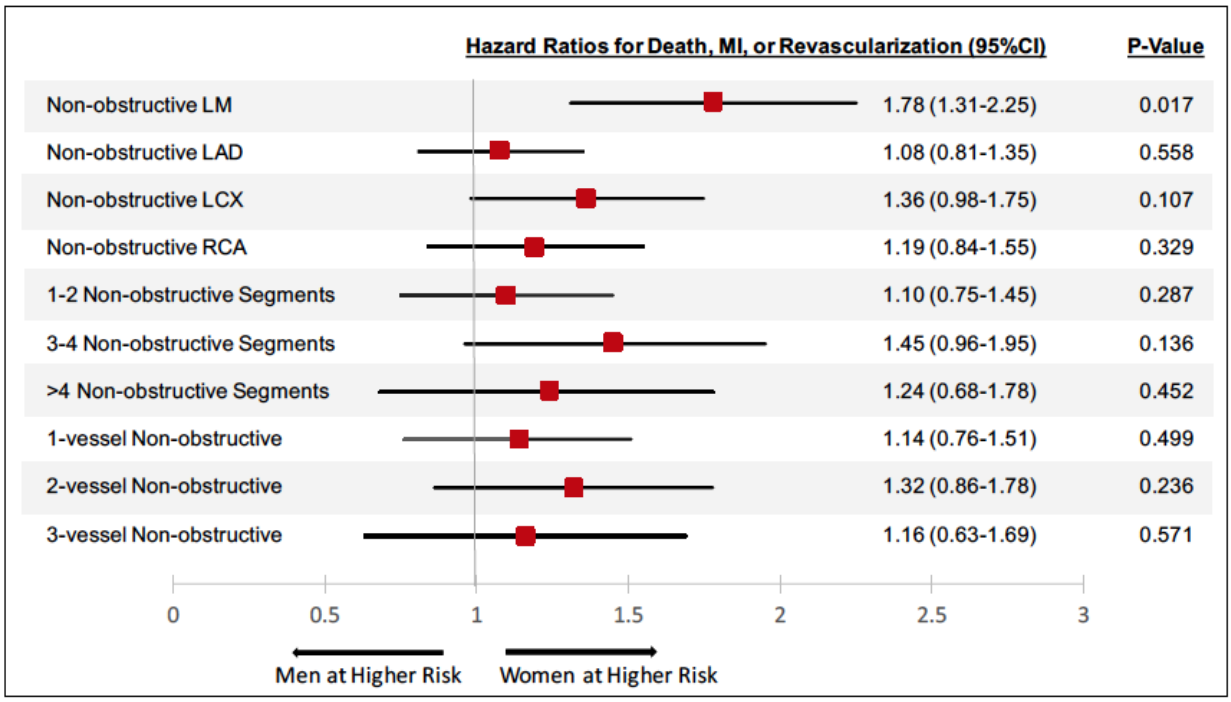


Cumulative 5-year incident event rates for the composite outcome of all-cause mortality, nonfatal myocardial infarction or coronary revascularization are displayed among patients without any obstructive CAD. Patients are stratified as having normal LM or nonobstructive LM.

Cumulative incidence curves are also displayed in women and men, separately.

CAD: Coronary artery disease; LM: Left main

Figure 4. Sex-specific Differences in Risk by Nonobstructive Plaque Location and Extent



Risk-adjusted hazard ratios comparing women to men for the composite outcome of all-cause mortality, nonfatal myocardial infarction, or revascularization are shown in different subgroups of nonobstructive CAD. All models adjusted for age, hypertension, hyperlipidemia, diabetes, smoking, and angina.

CAD: Coronary artery disease; LM: Left main; LAD: left anterior descending artery; LCX: left circumflex artery; RCA: right coronary artery

TABLES

Table 1. Baseline Characteristics of Study Cohort by Left Main Status				
	All Patients (N=5,166)	**Normal LM (N=4,241)**	**Nonobstructive LM (N=925)**	**P- Value***
Age, years	60±12	60±12	65±10	<0.001
Male	3,255 (63)	2,592 (61)	663 (71)	<0.001
Hypertension	2,769 (54)	2230 (53)	539 (59)	0.001
Diabetes	865 (17)	676 (16)	189 (21)	0.001
Hyperlipidemia	2,717 (53)	2,128 (50)	589 (64)	<0.001
Smoking History	1,030 (20)	827 (20)	203 (22)	0.099
Family History of Early CAD	1,490 (29)	1,204 (29)	286 (31)	0.118
LVEF, %	60±13	60±13	61±15	0.232
Symptom Characteristics				0.424
Typical angina	696 (15)	582 (16)	114 (14)	
Atypical angina	1,587 (35)	1,295 (35)	292 (35)	
Non-cardiac	409 (9)	341 (9)	68 (8)	
No chest pain	1,867 (41)	1,515 (41)	352 (43)	
Extent of Obstructive CAD (by Segment)	0.8±1.5	0.7±1.4	1.5±1.9	<0.001
Extent of Obstructive CAD (by Vessel)				<0.001
1-vessel	986 (19)	723 (17)	263 (30)	
2-vessel	496 (10)	340 (8)	156 (18)	
3-vessel	207 (6)	205 (5)	102 (11)	

Values reported as mean ± standard deviation or N (%)

*Comparison of patients with normal LM and nonobstructive LM using

chi-squared test for categorical variables and t-test for continuous variables

CAD: Coronary artery disease; LM: Left main; LVEF: Left ventricular ejection fraction;

Table 2a. Risk of Death, Myocardial Infarction, and Revascularization by Left Main Status in Women

	Unadjusted		Model 1*		Model 2**		Model 3***	
	HR (95% CI)	P-Value	HR (95% CI)	P-Value	HR (95% CI)	P-Value	HR (95% CI)	P-Value
Composite Endpoint								
Normal LM	1.00	Reference	1.00	Reference	1.00	Reference	1.00	Reference
Nonobstructive LM	2.37 (1.87-3.01)	<0.001	2.02 (1.57-2.58)	<0.001	1.67 (1.30-2.15)	<0.001	1.63 (1.26-2.10)	<0.001
All-Cause Mortality								
Normal LM	1.00	Reference	1.00	Reference	1.00	Reference	1.00	Reference
Nonobstructive LM	2.52 (2.31-2.90)	<0.001	1.96 (1.55-2.36)	0.001	1.92 (1.51-2.32)	0.002	1.87 (1.45-2.29)	0.003
Nonfatal MI								
Normal LM	1.00	Reference	1.00	Reference	1.00	Reference	1.00	Reference
Nonobstructive LM	1.75 (1.21-2.52)	0.003	1.60 (1.10-2.33)	0.015	1.29 (0.88-1.89)	0.195	1.25 (0.85-1.83)	0.254
Revascularization								
Normal LM	1.00	Reference	1.00	Reference	1.00	Reference	1.00	Reference
Nonobstructive LM	2.62 (2.18-3.06)	<0.001	2.33 (1.87-2.80)	<0.001	1.94 (1.47-2.44)	0.006	1.86 (1.38-2.34)	0.011

Table 2b. Risk of Death, Myocardial Infarction, and Revascularization by Left Main Status in Men

	Unadjusted		Model 1*		Model 2**		Model 3***	
	HR (95% CI)	P-Value	HR (95% CI)	P-Value	HR (95% CI)	P-Value	HR (95% CI)	P-Value
Composite Endpoint								
Normal LM	1.00	Reference	1.00	Reference	1.00	Reference	1.00	Reference
Nonobstructive LM	1.44 (1.21-1.71)	<0.001	1.18 (0.99-1.42)	0.065	1.07 (0.90-1.29)	0.438	0.99 (0.82-1.19)	0.879
All-Cause Mortality								
Normal LM	1.00	Reference	1.00	Reference	1.00	Reference	1.00	Reference
Nonobstructive LM	1.57 (1.16-2.12)	0.004	1.14 (0.84-1.55)	0.412	1.13 (0.83-1.54)	0.448	1.04 (0.75-1.44)	0.817
Nonfatal MI								
Normal LM	1.00	Reference	1.00	Reference	1.00	Reference	1.00	Reference
Nonobstructive LM	1.32 (1.01-1.72)	0.041	1.20 (0.91-1.58)	0.203	1.06 (0.80-1.41)	0.677	0.98 (0.74-1.30)	0.887
Revascularization								
Normal LM	1.00	Reference	1.00	Reference	1.00	Reference	1.00	Reference
Nonobstructive LM	1.46 (1.11-1.91)	0.007	1.18 (0.89-1.57)	0.232	1.05 (0.79-1.40)	0.743	0.98 (0.73-1.31)	0.888

*Model 1: covariables include age, hypertension, diabetes, hyperlipidemia, smoking, and presence of typical angina

**Model 2: covariables include those in Model 1 plus the total number of non-LM coronary artery segments with obstructive CAD

***Model 2: covariables include those in Model 1 plus the total number of non-LM vessels with obstructive CAD

CI: Confidence Interval; HR: Hazard ratio; LM: Left main; MI: Myocardial infarction

Table 3. Risk of Death or Myocardial Infarction by Left Main Status

	Unadjusted		Model 1*		Model 2**		Model 3***	
	HR (95% CI)	P-Value	HR (95% CI)	P-Value	HR (95% CI)	P-Value	HR (95% CI)	P-Value
Women								
Normal LM	1.00	Reference	1.00	Reference	1.00	Reference	1.00	Reference
Nonobstructive LM	1.99 (1.51-2.61)	<0.001	1.67 (1.26-2.22)	<0.001	1.44 (1.08-1.91)	0.014	1.40 (1.04-1.87)	0.025
Men								
Normal LM	1.00	Reference	1.00	Reference	1.00	Reference	1.00	Reference
Nonobstructive LM	1.41 (1.15-1.73)	0.001	1.17 (0.94-1.44)	0.152	1.08 (0.87-1.34)	0.475	0.99 (0.79-1.24)	0.937

*Model 1: covariables include age, hypertension, diabetes, hyperlipidemia, smoking, and presence of typical angina

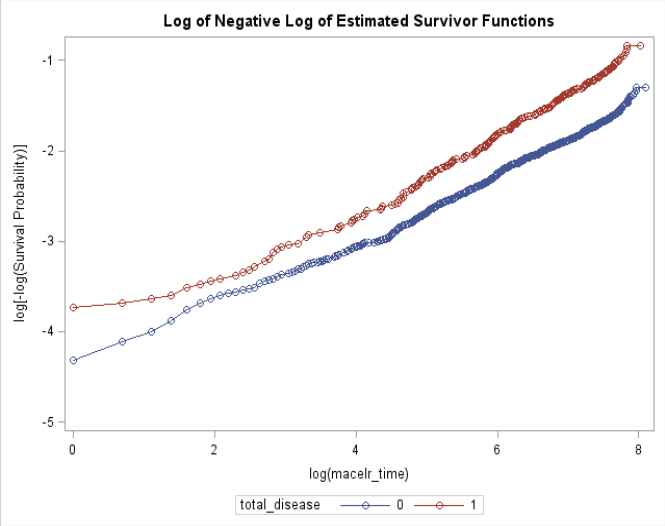
**Model 2: covariables include those in Model 1 plus the total number of non-LM coronary artery segments with obstructive CAD

***Model 2: covariables include those in Model 1 plus the total number of non-LM vessels with obstructive CAD

CI: Confidence Interval; HR: Hazard ratio; LM: Left main; MI: Myocardial infarction

APPENDIX

Appendix A. Graphical Evaluation of the Proportional Hazards Assumption



Appendix B. Baseline Characteristics of Study Cohort by Gender

Baseline Characteristics of Study Cohort by Gender						
	All Women (N=1,911)	All Men (N=3,255)	P- Value*	Women with Nonobstructive LM (N=261)	Men with Nonobstructive LM (N=663)	P- Value**
Age, years	62±11	59±12	<0.001	67±10	63±10	<0.001
Hypertension	1,135 (60)	1,634 (50)	<0.001	185 (71)	354 (54)	<0.001
Diabetes	329 (17)	536 (16)	0.474	57 (22)	132 (20)	0.516
Hyperlipidemia	1,033 (54)	1,683 (52)	0.095	170 (65)	418 (63)	0.578
Smoking Histo	263 (14)	767 (24)	<0.001	53 (20)	150 (23)	0.434
Family History	602 (32)	887 (28)	0.001	87 (34)	198 (30)	0.288
LVEF, %	61±14	60±13	0.326	63±16	61±15	0.448
Symptom Characteristics			<0.001			0.003
Typical angin	282 (17)	414 (14)		43 (18)	71 (12)	
Atypical angi	646 (38)	941 (33)		93 (40)	199 (34)	
Non-cardiac	188 (11)	221 (8)		21 (9)	47 (8)	
No chest pain	571 (34)	1,295 (45)		77 (33)	274 (46)	
Extent of Obstructive CAD (by	0.6±1.2	1.0±0.9	<0.001	1.2±1.7	1.6±1.9	0.012
Extent of Obstructive CAD (by Vessel)			<0.001			0.046
1-vessel	291 (16)	695 (22)		73 (29)	190 (30)	
2-vessel	115 (6)	381 (12)		37 (15)	119 (19)	
3-vessel	74 (4)	232 (7)		21 (8)	80 (13)	

Values reported as mean ± standard deviation or N (%)

*Comparison of women and men using

chi-squared test for categorical variables and t-test for continuous variables

**Comparison of women and men with nonobstructive LM CAD using chi-squared test

for categorical variables and t-test for continuous variables

CAD: Coronary artery disease; LM: Left main; LVEF: Left ventricular ejection fraction;

Appendix C. Baseline Characteristics of the Excluded Sites

Baseline Characteristics of Excluded Patients			
	Included (n=5,166)	Excluded (n=4,357)	P- Value*
Age, years	61±12	57±14	<0.001
Male	3255 (63)	2082 (48)	<0.001
Hypertension	2769 (54)	2314 (53)	0.509
Diabetes	865 (17)	793 (18)	0.071
Hyperlipidemia	2717 (53)	2287 (53)	0.803
Smoking Histo	1030 (20)	1189 (27)	<0.001
Family History	1,490 (29)	2,197 (50)	<0.001
LVEF, %	60±14	58±10	<0.001
Symptom Characteristics			<0.001
Typical angin	696 (15)	1021 (27)	
No chest pain	1867 (41)	617 (16)	
Nonobstructive LMCAD	925 (18)	332 (8)	<0.001
Extent of Obstructive CAD			0.844
None	3,274 (65)	2,779 (65)	
1-vessel	986 (19)	808 (19)	
2-vessel	496 (10)	419 (10)	
3-vessel	307 (6)	273 (6)	

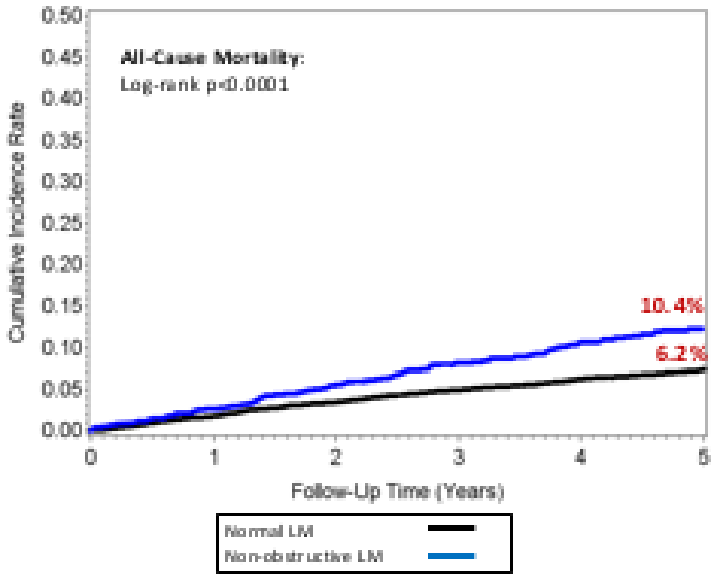
Values reported as mean ± standard deviation or N (%)

*Comparison of included and excluded sites using

chi-squared test for categorical variables and t-test for continuous variables

CAD: Coronary artery disease; LM: Left main; LVEF: Left ventricular ejection fraction

Appendix D. Cumulative 5-Year Incidence of Death Including All Sites



Cumulative 5-year incident death rates are displayed for a pooled cohort of included and Excluded patients (n=9,523) comparing patients with nonobstructive LM and normal LM.

LM: Left main