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ORIGINAL ARTICLE

# Outcomes With Intermediate Left Main Disease: Analysis From the ISCHEMIA Trial

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**BACKGROUND:** Patients with significant (≥50%) left main disease (LMD) have a high risk of cardiovascular events, and guidelines recommend revascularization to improve survival. However, the impact of intermediate LMD (stenosis, 25%–49%) on outcomes is unclear.

**METHODS:** Randomized ISCHEMIA (International Study of Comparative Health Effectiveness With Medical and Invasive Approaches) participants who underwent coronary computed tomography angiography at baseline were categorized into those with (25%–49%) and without (<25%) intermediate LMD. The primary outcome was a composite of cardiovascular mortality, myocardial infarction (MI), or hospitalization for unstable angina, heart failure, or resuscitated cardiac arrest. The primary quality of life outcome was the Seattle Angina Questionnaire summary score.

**RESULTS:** Among the 3699 participants who satisfied the inclusion criteria, 962 (26%) had intermediate LMD. Among invasive strategy participants with intermediate LMD on coronary computed tomography angiography, 49 (7.0%) had significant (≥50% stenosis) left main stenosis on invasive angiography. Patients with intermediate LMD had a higher risk of cardiovascular events in the unadjusted but not in the fully adjusted model compared with those without intermediate LMD. An invasive strategy increased procedural MI and decreased nonprocedural MI with no significant difference for other outcomes including the primary end point. There was no meaningful heterogeneity of treatment effect based on intermediate LMD status except for nonprocedural MI for which there was a greater absolute reduction with invasive management in the intermediate LMD group (−6.4% versus −2.0%; $P_{interaction}$=0.049). The invasive strategy improved angina-related quality of life and the benefit was durable throughout follow-up without significant heterogeneity based on intermediate LMD status.

**CONCLUSIONS:** In the ISCHEMIA trial, there was no meaningful heterogeneity of treatment benefit from an invasive strategy regardless of intermediate LMD status except for a greater absolute risk reduction in nonprocedural MI with invasive management in those with intermediate LMD. An invasive strategy increased procedural MI, reduced nonprocedural MI, and improved angina-related quality of life.

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**Key Words:** coronary artery disease ■ follow-up studies ■ humans ■ prognosis ■ quality of life

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### WHAT IS KNOWN

- Patients with significant (≥50%) left main disease (LMD) have a high risk of cardiovascular events, and guidelines recommend revascularization to improve survival.
- The impact of intermediate LMD (25%–49% left main stenosis) is not known.

### WHAT THE STUDY ADDS

- In the ISCHEMIA trial (International Study of Comparative Health Effectiveness With Medical and Invasive Approaches), 26% of participants had intermediate LMD (25%–49% left main stenosis) on coronary computed tomography angiography, and this was a marker for extensive atherosclerosis.
- Invasive management increased procedural myocardial infarction, reduced nonprocedural myocardial infarction, and improved angina-related quality of life when compared with conservative management regardless of intermediate LMD status.
- Invasive management resulted in a greater reduction in nonprocedural myocardial infarction compared with conservative management in those with intermediate LMD than in those without intermediate LMD.

### Nonstandard Abbreviations and Acronyms

| | |
|---|---|
| **CABG** | coronary artery bypass graft |
| **CAD** | coronary artery disease |
| **CCTA** | coronary computed tomography angiography |
| **CONFIRM** | Coronary CT Angiography Evaluation for Clinical Outcomes: An International Multicenter |
| **ISCHEMIA** | International Study of Comparative Health Effectiveness With Medical and Invasive Approaches |
| **LAD** | left anterior descending |
| **LM** | left main |
| **LMD** | left main disease |
| **MI** | myocardial infarction |
| **QoL** | quality of life |

In patients with stable ischemic heart disease without significant left main disease (LMD), routine revascularization is not associated with improvement in survival when compared with initial medical therapy alone.[1–3] However, patients with significant (≥50% stenosis) LMD have improved survival with coronary artery bypass graft (CABG) surgery, as shown in a meta-analysis of CABG versus no CABG trials from the 1980s in an era of minimal medical therapy.[4] Nevertheless, based on this evidence, contemporary guidelines recommend revascularization of patients with significant LMD to improve survival.[5] Accordingly, ISCHEMIA (International Study of Comparative Health Effectiveness With Medical and Invasive Approaches) excluded patients with significant LMD. To address the paucity of outcomes data in patients with LMD who do not have flow-limiting stenosis (≥50% coronary diameter reduction), we sought to address the prevalence and outcomes of patients with intermediate LMD (25%–49%) as assessed by coronary computed tomography angiography (CCTA).[1] The principal objective of this post hoc analysis was to compare the clinical and quality-of-life (QoL) outcomes with intermediate LMD on CCTA and to evaluate whether there was any difference between an invasive versus a conservative strategy.

## METHODS

### Study Population

The design and the principal results of the ISCHEMIA trial have been published before.[1,6] In brief, 5179 participants with site-determined moderate-to-severe ischemia on stress testing were randomized 1:1 to either an invasive strategy or to a conservative strategy. Most enrolled participants with normal renal function first underwent blinded CCTA to exclude those with LMD (≥50% stenosis) and without obstructive coronary artery disease (CAD; <50% stenosis in all major epicardial coronary artery).

Randomized participants who underwent CCTA were included for this study. Participants with LMD ≥50% on CCTA, those with prior CABG, and those with nonevaluable or missing data on left main (LM) stenosis were excluded. Participants were categorized into those with (25%–49%) and without (<25%) intermediate LMD, as determined by the computed tomography core laboratory by visual interpretation. Luminal diameter stenosis severity was scored as none (0%), mild (1%–49% luminal stenosis), moderate (50%–69% luminal stenosis), or severe (70% luminal stenosis).[7] Percentage obstruction of coronary artery lumen was based on a comparison of the luminal diameter of the segment exhibiting obstruction to the luminal diameter of the most normal-appearing site immediately proximal to the plaque. In instances in which plaque was highly calcified, 2-dimensional oblique images were also visualized without maximal intensity projection (ie, 0.625- to 0.75-mm isotropic voxel resolution) or multiplanar reformats with cross-sectional views to minimize partial volume averaging artifact of calcium. The final assessment was by visual assessment and by consensus using whatever display and reconstruction methods were deemed warranted by the individual readers. Quantitative algorithms that might be affected by calcium were not used. CCTA and not invasive coronary angiography was used to identify those with intermediate LMD, as invasive angiography was not performed routinely in those randomized to conservative management. The trial was approved by the institutional review board, and informed consent was obtained from all patients. Regarding data sharing, we will follow the National Institutes of Health data sharing plan, effective from April 1, 2022. We will make data and materials publicly available after March 30, 2022.

We will not make the data, methods used in the analysis, and materials used to conduct the research available to any researcher for purposes of reproducing the results or replicating the procedure before that date.

## Study Procedures and Follow-Up

Participants randomized to the invasive strategy underwent coronary angiography followed by revascularization with either percutaneous coronary intervention or CABG surgery, when feasible. Participants randomized to conservative management underwent coronary angiography and revascularization for failure of optimal medical therapy or for a suspected clinical event. Both groups were recommended aggressive secondary prevention that included lifestyle and pharmacological interventions. Site investigators were blinded to the results of the CCTA and hence were unaware of the intermediate LMD status of trial participants.

## Study Outcomes

The primary clinical outcome was a composite of cardiovascular mortality, myocardial infarction (MI), or hospitalization for unstable angina, heart failure, or resuscitated cardiac arrest (primary outcome of the ISCHEMIA trial). Secondary clinical outcomes included the composite of cardiovascular mortality or MI; composite of cardiovascular mortality, MI, or stroke; primary end point or stroke; and individual components of the composite outcomes. The definitions of study outcomes have been published before,[1] and the definition of MI is also outlined in the Supplemental Material. The primary QoL outcome was the Seattle Angina Questionnaire summary score.[8] Individual components of the Seattle Angina Questionnaire summary score (Angina Frequency score, QoL score, and Physical Limitation score) and the Rose Dyspnea scale and the EQ-5D visual analogue scale were likewise evaluated.

## Statistical Analysis

Participants were categorized into those with and without intermediate LMD. Participants were further categorized based on the randomized treatment allocation (invasive versus conservative strategy). Categorical variables were presented as counts (percentages), and differences between groups were assessed using the $\chi^2$ test. For categorical variables with ordered levels, the Cochran-Armitage test for trend was applied. Continuous variables were presented as the number of nonmissing values and median (Q1–Q3); differences between groups are assessed using the Wilcoxon rank-sum test. Cox proportional-hazards regression models were fit for the primary and each of the secondary clinical event end points. Covariates in the unadjusted models include intermediate LMD, randomized treatment, and the LM-by-treatment interaction. Models were repeated, adjusting for the same covariates used in the primary ISCHEMIA manuscript (age, sex, estimated glomerular filtration rate, ejection fraction, and diabetes). In addition, the fully adjusted model additionally adjusted for hypertension, number of diseased vessels, and the presence or absence of 50% stenosis in the proximal left anterior descending (LAD) artery. Given the violation of the proportional hazard assumptions, as observed in the published main analysis,[1] cumulative end point event rates at 4 years according to intermediate LMD and randomized treatment, along with the difference in cumulative incidence for the treatment groups, were computed. Rates were derived from the cumulative incidence function to account for the competing risk of death. *P* values testing for a difference in the differences in treatment groups according to intermediate LMD or not were calculated. All analyses were performed using SAS, version 9.4 (Cary, NC).

The analysis of the QoL outcomes mirrored the approach of the primary QoL analyses of the ISCHEMIA trial.[9] In brief, for descriptive purposes, unadjusted mean scores were reported by treatment group at each assessment. The effect of treatment was evaluated using mixed-effects proportional odds models of follow-up health status scores. Models included fixed effects for baseline score, LM stenosis severity, treatment group, LM stenosis by treatment interaction, time since randomization, time interactions with all preceding effects, and patient-level random intercepts and time effects. Piecewise linear splines were used to model time trends, with knots at 3, 6, 12, 18, and 24 months for the fixed effect of time and knots at 6 months for patient-level random effects. Restricted cubic splines were used to allow for nonlinear effects of baseline scores. All models were fit using Bayesian methods with weakly informative priors to directly estimate the probability distribution of the treatment effect, which can be interpreted as the probability of different effect sizes given the observed data. All analyses were conducted using SAS, version 9.4, R, version 3.5.3, Stan, version 2.18.1, and R packages rstan, rstanarm, brms, and tidyverse.[10–15]

# RESULTS

Among the 3913 participants who underwent CCTA, 3699 satisfied the inclusion criteria (Figure S1). Of these participants, 962 (26%) had intermediate LMD and 2737 (74%) did not (770 had 0% stenosis and 1967 had 1%–24% LM stenosis).

## Baseline Characteristics

Patients with intermediate LMD were older, and a greater proportion had hypertension and diabetes when compared with the cohort without intermediate LMD. There was a greater proportion of patients with intermediate LMD who had severe ischemia on stress imaging, 3-vessel disease, LAD stenosis, and proximal LAD stenosis. There was no significant difference in baseline QoL in the group with and without intermediate LMD (Table 1). In addition, there were no significant differences in baseline characteristics between those randomized to an invasive versus conservative strategy in the 2 cohorts with and without intermediate LMD (Table S1).

## Invasive Angiographic Characteristics

In the subgroup of patients randomized to the invasive strategy, 7% of patients with intermediate LMD on CCTA had significant (≥50% stenosis on quantitative coronary angiography) LMD on invasive angiography (Table S2).

**Table 1. Baseline Characteristics According to Randomized Treatment Assignment and LM Disease Severity on CCTA**

| | <25% LM stenosis (n=2737) | 25%–49% LM stenosis (n=962) | *P* value |
|---|---|---|---|
| Demographics | | | |
| Age, y | | | <0.001 |
| Median (Q1–Q3) | 63 (57–70) | 65 (59–71) | |
| Female sex | 21.4% | 19.8% | 0.267 |
| Race | | | 0.620 |
| White | 64.6% | 64.8% | |
| Asian | 30.3% | 30.9% | |
| Black | 4.3% | 3.4% | |
| Other | 0.8% | 0.9% | |
| Ethnicity | | | 0.890 |
| Hispanic or Latino | 16.6% | 16.8% | |
| Not Hispanic or Latino | 83.4% | 83.2% | |
| Clinical history | | | |
| Hypertension | 68.5% | 72.8% | 0.012 |
| Diabetes | 39.8% | 44.0% | 0.024 |
| Prior MI | 16.9% | 15.1% | 0.196 |
| Cigarette smoking | | | 0.465 |
| Never | 41.7% | 43.2% | |
| Former | 44.7% | 44.6% | |
| Current | 13.6% | 12.2% | |
| QoL (baseline) | | | |
| SAQ-7 Summary Score | 76.4 (62.2–89.2) | 78.1 (64.7–91.7) | 0.038 |
| SAQ-7 Angina Frequency Score | 80 (70–100) | 90 (70–100) | 0.037 |
| SAQ-7 QoL Score | 62.5 (37.5–87.5) | 62.5 (50.0–87.5) | 0.061 |
| SAQ-7 Physical Limitation Score | 87.5 (66.7–100) | 71.7 (75.0–100) | 0.172 |
| Rose Dyspnea Scale | 1 (0–2) | 1 (0–2) | 0.228 |
| EQ-5D visual analogue scale | 70 (60–80) | 70 (60–80) | 0.506 |
| Laboratory values | | | |
| Estimated eGFR from enrollment, mL/min | | | 0.494 |
| Median (Q1–Q3) | 85 (73–101) | 86 (72–100) | |
| LDL-C, mg/dL | | | 0.654 |
| Median (Q1–Q3) | 83 (63–112) | 84 (63–108) | |
| Stress test (core lab interpretation) | | | |
| Ischemia severity by imaging modality | | | |
| Stress imaging overall | 72.6% | 71.2% | 0.395 |
| Severity | | | 0.040 |
| Severe | 46.4% | 49.1% | |
| Moderate | 40.3% | 41.8% | |
| Mild | 8.3% | 5.3% | |
| None | 4.8% | 3.8% | |
| Uninterpretable | 0.3% | 0.0% | |
| Exercise tolerance test | 27.4% | 28.8% | |
| Severity | | | 0.959 |
| Severe | 84.6% | 85.5% | |
| Moderate | 7.9% | 7.3% | |
| Mild | 2.0% | 1.8% | |
| None | 2.0% | 1.5% | |

(*Continued*)

**Table 1. Continued**

| | <25% LM stenosis (n=2737) | 25%–49% LM stenosis (n=962) | *P* value |
|---|---|---|---|
| Uninterpretable | 3.5% | 4.0% | |
| CCTA, findings | | | |
| Disease defined as ≥50% stenosis | | | |
| No. of diseased vessels | | | <0.001 |
| 1 vessel disease | 27.6% | 14.1% | |
| 2 vessel disease | 34.5% | 24.5% | |
| 3 vessel disease | 37.9% | 61.4% | |
| Left anterior descending | 86.2% | 93.0% | <0.001 |
| Proximal left anterior descending disease | 39.4% | 64.4% | <0.001 |
| Right coronary artery | 67.4% | 80.0% | <0.001 |
| Left circumflex | 70.6% | 82.5% | <0.001 |
| Disease defined as ≥70% stenosis | | | |
| No. of diseased vessels | | | <0.001 |
| 0 | 12.3% | 9.1% | |
| 1 | 43.4% | 34.8% | |
| 2 | 27.9% | 31.3% | |
| 3 | 16.4% | 24.7% | |
| Left anterior descending | 64.9% | 70.3% | 0.007 |
| Proximal left anterior descending disease | 18.7% | 27.0% | <0.001 |
| Right coronary artery | 50.0% | 60.0% | <0.001 |
| Left circumflex | 53.1% | 60.0% | 0.002 |

CCTA indicates coronary computed tomography angiography; eGFR, estimated glomerular filtration rate; EQ-5D, EuroQol-5 Dimension; LDL-C, low density lipoprotein-cholesterol; LM, left main; MI, myocardial infarction; QoL, quality of life; and SAQ, Seattle Angina Questionnaire.



The LM stenosis characteristics, coronary angiography, and revascularization details of the 49 (7%) patients with angiographically severe LMD are outlined in Table S3. The majority of these patients had bifurcation lesion of the LM (69%) and 55% had moderate or severe calcification on angiography (Table S3). Moreover, 61% of these patients underwent CABG (93% with an internal mammary graft to the LAD artery) and 26% underwent percutaneous coronary intervention (Table S3).

A higher percentage of participants with intermediate LMD had angiographic LMD, 3-vessel disease, proximal LAD disease, and a higher SYNTAX score when compared with those without intermediate LMD (Table 2). A greater percentage of participants with intermediate LMD underwent CABG (32.1% versus 18.2%) when compared with those without intermediate LMD. The LM stenosis characteristics, coronary angiography, and revascularization details of the patients with intermediate LMD on coronary computed tomography who underwent coronary angiography are outlined in Table S4.

## Clinical and QoL Outcomes

When compared with patients without intermediate LMD, those with intermediate LMD had a significantly higher risk of the composite primary outcome, the composite of the primary outcome or stroke, composite of cardiovascular death/MI or stroke, and the individual end points of cardiovascular death, heart failure, and stroke even after adjustment for baseline variables (Table 3; Figure 1). In the fully adjusted models, patients with intermediate LMD had a higher risk of stroke. However, the QoL scores were similar during follow-up between the group with and without intermediate LMD (Figure S2).

## Heterogeneity of Randomized Treatment Effect

There was no significant difference between an invasive and conservative strategy for the primary and secondary outcomes. However, there was an increase in procedural MI and decrease in nonprocedural MI with the invasive strategy as compared with the conservative strategy. There was no heterogeneity of treatment effect based on intermediate LMD status on CCTA except for the outcome of nonprocedural MI. There was a greater absolute risk reduction in nonprocedural MI with invasive management in the intermediate LMD group (−6.4% versus −2.0%; $P_{interaction}$=0.049; Figure 2) when compared with those without intermediate LMD. Of note, there was a numerically higher rate of procedural MI in those with intermediate LMD, but the test for interaction was not significant. An invasive strategy improved angina-related QoL, and the benefit was durable through the length of follow-up without a significant heterogeneity based on LMD severity on CCTA (Figure 3). The benefit was largely in patients with symptoms of angina,

**Table 2. Anatomy by Coronary Angiography and Revascularization Status in the Invasive Group**

| | No intermediate LMD (n=1379) | Intermediate LMD (n=467) | *P* value |
|---|---|---|---|
| Angiographic characteristics | | | |
| 50% stenosis threshold | | | |
| LMD | 1.4% | 7.0% | <0.001 |
| Proximal LAD | 33.2% | 42.7% | <0.001 |
| No. of diseased vessels | | | <0.001 |
| 0 | 6.1% | 3.2% | |
| 1 | 26.6% | 17.2% | |
| 2 | 31.9% | 32.8% | |
| 3 | 35.4% | 46.8% | |
| 70% stenosis threshold | | | |
| LMD | 0.2% | 2.7% | <0.001 |
| Proximal LAD | 21.3% | 25.6% | 0.060 |
| No. of diseased vessels | | | <0.001 |
| 0 | 18.4% | 12.2% | |
| 1 | 39.9% | 34.6% | |
| 2 | 28.1% | 34.2% | |
| 3 | 13.6% | 19.0% | |
| Syntax score | | | <0.001 |
| n | 1304 | 442 | |
| Median (Q1–Q3) | 15 (8–23) | 21 (12–29) | |
| Revascularization status | | | <0.001 |
| PCI | 61.5% | 49.7% | |
| Drug-eluting stent | 98.0% | 97.1% | 0.428 |
| CABG surgery | 18.2% | 32.1% | |
| Internal mammary artery to LAD | 83.3% | 84.6% | 0.734 |
| None | 20.3% | 18.2% | |

Patients with both PCI and CABG are classified according to first procedure. CABG indicates coronary artery bypass graft; LAD, left anterior descending; LMD, left main disease; and PCI, percutaneous coronary intervention.

and no benefit was seen in the subgroup without symptoms (Figure 4). Results were largely similar for other QoL components (Seattle Angina Questionnaire-7 QoL score, Seattle Angina Questionnaire-7 Physical Limitation score, Rose dyspnea scale, and EQ-5D visual analogue scale; Figure S2).

## DISCUSSION

While current clinical practice guidelines continue to advocate revascularization for the management of patients with LM stenosis ≥50% by coronary angiography based on randomized trials from the 1970s and 1980s, the optimal management in patients with lesser degrees of LM stenosis is unknown. In this analysis of the ISCHEMIA trial, 26% of patients who underwent CCTA had intermediate LM stenosis (25%–49%) of whom 7% had angiographically significant (≥50% stenosis on quantitative coronary angiography) LM stenosis. Of note, while patients with intermediate LMD at baseline had more severe ischemia, a greater extent of CAD indicating greater atherosclerotic burden, and a higher risk of cardiovascular events despite a similar QoL, including angina-specific QoL, there were no differences between treatment groups for primary and major secondary clinical outcomes when compared with patients without intermediate LMD. As seen in the ISCHEMIA trial as a whole, the invasive strategy increased the risk of procedural MI but decreased the risk of nonprocedural MI when compared with the conservative strategy, but there was no evidence of meaningful heterogeneity of treatment effect across LM stenosis severity other than that for nonprocedural MI ($P_{interaction}$=0.049) where there was a quantitative interaction (greater absolute benefit in those with intermediate LMD with invasive strategy). There were significant and durable benefits of an invasive strategy in improving angina-related QoL in symptomatic patients regardless of LM stenosis severity.

### LM Disease

The data on survival benefit of CABG when compared with no CABG in those with LMD shown in the trials done in the 1980s are based on 150 patients with LMD enrolled in these trials.[4] Since then, randomized

**Table 3. Association Between Degree of LM Stenosis on CCTA and Outcomes**

| | <25% LM stenosis | | 25%–49% LM stenosis | | Unadjusted | | Adjusted | | Fully adjusted | |
|---|---|---|---|---|---|---|---|---|---|---|
| Variable label | Events, n | CIF | Events, n | CIF | HR (95% CI) | *P* value | HR (95% CI) | *P* value | HR (95% CI) | *P* value |
| Primary end point | 280 | 11.49 (10.16–12.91) | 130 | 14.64 (12.22–17.28) | 1.36 (1.11–1.68) | 0.0035 | 1.31 (1.06–1.61) | 0.0123 | 1.12 (0.90–1.39) | 0.3067 |
| Cardiovascular death/MI | 254 | 10.56 (9.27–11.95) | 113 | 12.92 (10.57–15.51) | 1.30 (1.04–1.62) | 0.0207 | 1.24 (0.99–1.55) | 0.0574 | 1.07 (0.85–1.35) | 0.5526 |
| Primary end point or stroke | 303 | 12.46 (11.07–13.93) | 146 | 16.84 (14.23–19.64) | 1.42 (1.17–1.73) | 0.0005 | 1.37 (1.12–1.67) | 0.0021 | 1.19 (0.97–1.47) | 0.0945 |
| Cardiovascular death/MI/stroke | 279 | 11.56 (10.21–13.01) | 129 | 15.11 (12.57–17.87) | 1.36 (1.10–1.67) | 0.0042 | 1.30 (1.05–1.60) | 0.0143 | 1.14 (0.92–1.42) | 0.2284 |
| Cardiovascular death | 72 | 3.26 (2.52–4.14) | 42 | 4.51 (3.13–6.25) | 1.72 (1.18–2.52) | 0.0051 | 1.63 (1.11–2.39) | 0.0122 | 1.31 (0.88–1.96) | 0.1811 |
| MI | 201 | 8.10 (6.99–9.30) | 88 | 10.37 (8.26–12.75) | 1.27 (0.99–1.64) | 0.0588 | 1.22 (0.94–1.56) | 0.1293 | 1.06 (0.81–1.38) | 0.6682 |
| Spontaneous MI | 140 | 5.79 (4.84–6.85) | 60 | 7.43 (5.61–9.59) | 1.24 (0.91–1.67) | 0.1674 | 1.20 (0.88–1.62) | 0.2498 | 1.06 (0.77–1.45) | 0.7315 |
| Procedural MI | 43 | 1.62 (1.18–2.17) | 26 | 2.83 (1.89–4.07) | 1.78 (1.10–2.90) | 0.0200 | 1.64 (1.00–2.67) | 0.0487 | 1.36 (0.81–2.26) | 0.2415 |
| Resuscitated cardiac arrest | 4 | 0.19 (0.06–0.47) | 1 | 0.11 (0.01–0.58) | 0.72 (0.08–6.41) | 0.7656 | 0.76 (0.08–6.91) | 0.8088 | 0.78 (0.08–7.42) | 0.8268 |
| Unstable angina | 17 | 0.61 (0.36–0.98) | 11 | 1.39 (0.72–2.44) | 1.85 (0.87–3.96) | 0.1110 | 1.89 (0.88–4.05) | 0.1020 | 1.92 (0.85–4.32) | 0.1172 |
| Heart failure | 25 | 0.89 (0.56–1.36) | 17 | 2.00 (1.17–3.20) | 2.09 (1.13–3.86) | 0.0196 | 2.06 (1.10–3.84) | 0.0239 | 1.83 (0.95–3.52) | 0.0704 |
| Stroke | 32 | 1.32 (0.88–1.91) | 20 | 2.62 (1.60–4.04) | 1.85 (1.06–3.24) | 0.0306 | 1.82 (1.04–3.20) | 0.0362 | 1.89 (1.05–3.42) | 0.0338 |

Adjusted models adjusted for age, sex, eGFR, ejection fraction, and diabetes. Fully adjusted model additionally adjusted for hypertension, number of diseased vessels, and presence or absence of 50% stenosis in the proximal LAD. CCTA indicates coronary computed tomography angiography; CIF, cumulative incidence function; eGFR, estimated glomerular filtration rate; HR, hazard ratio; LAD, left anterior descending; LM, left main; and MI, myocardial infarction.



strategy trials testing routine revascularization versus initial medical therapy have excluded patients with LMD. Unlike other coronary territories where a visual estimate of ≥70% stenosis is considered angiographically significant, for the LM artery, a coronary stenosis of ≥50% is conventionally considered to be angiographically significant and is generally considered in guidelines to warrant routine revascularization.

There are, however, no robust data validating this threshold. In fact, in the Veterans Administration Cooperative Study of Coronary Bypass Surgery, the absolute benefit with CABG over no CABG on clinical outcomes was greatest in high-risk patients with >75% LM stenosis. Furthermore, there was only a nonsignificant trend toward benefit in patients with 50% to 75% stenosis.[16] This suggests that there may be a continuum of risk and a gradient effect for the degree of angiographic LMD on either events or effects of therapy, but this has not been subjected to careful prospective study, nor have lesser degrees of LMD been evaluated as they relate to subsequent clinical outcomes. In the CONFIRM (Coronary CT Angiography Evaluation for Clinical Outcomes: an International Multicenter) registry of stable outpatients who underwent elective CCTA for evaluation of clinically suspected CAD, 18% had nonobstructive (1%–49%) LM stenosis.[17] However, the proportion of patients with intermediate LMD (25%–49% stenosis) was not presented. In our analysis from the ISCHEMIA trial, 26% of patients had intermediate LMD on CCTA. The greater proportion of patients with intermediate LMD is likely due to the requirement of moderate or severe ischemia for trial entry in ISCHEMIA when compared with CONFIRM. In CONFIRM, nonobstructive LMD in women, but not men, was associated with worse outcomes, including increased mortality even after adjusting for baseline risk factors and CAD burden. In our study, intermediate LMD was associated with overall worse clinical outcomes, but in the fully adjusted models taking into account the extent of CAD, patients with intermediate LMD had a higher risk of stroke but not other end points, suggesting that the prognostic value of intermediate LMD is, in part, a reflection of greater burden of atherosclerosis.[18]

Finally, given this greater burden of atherosclerosis and potential progression to significant LMD, we explored whether there is heterogeneity of treatment effect of invasive and conservative strategy based on LM stenosis severity. In our study, 7% of those with intermediate LMD on CCTA were considered to have significant obstructive (≥50% stenosis on quantitative coronary angiography) LMD on coronary angiography, perhaps emphasizing the differences between the two imaging modalities.[7] The majority of these patients had moderate or severe calcification on angiography. As outlined in a recent publication, the discordance is likely due to ostial

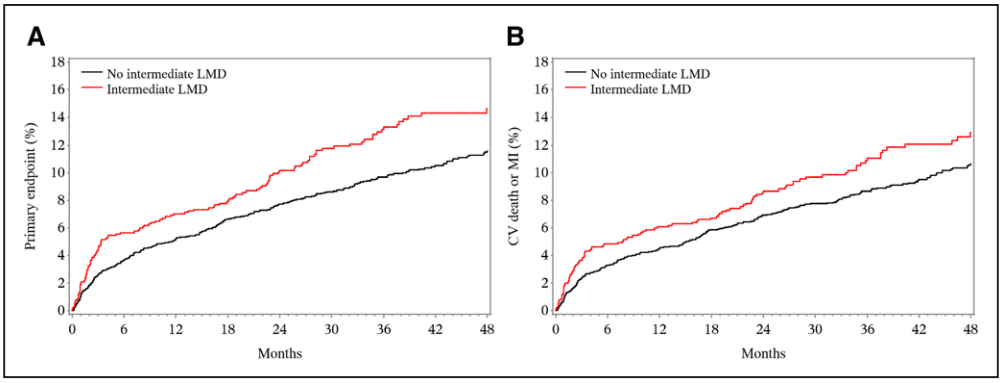


**Figure 1. Risk of clinical outcomes based on the severity of left main disease (LMD) on coronary computed tomography angiography.**
**A**, Risk of primary clinical outcome; (**B**) risk of key secondary clinical outcome. CV indicates cardiovascular; and MI, myocardial infarction.

LAD or ostial left circumflex CAD that might have led to discordance with invasive angiography, generally due to the limited views on invasive angiography.[7] Despite this, we did not observe any meaningful heterogeneity of treatment effect. Similar to the overall findings in the ISCHEMIA trial, the invasive strategy increased procedural MI, reduced nonprocedural MI, and showed no significant difference for other clinical outcomes. There was an interaction for the outcome of nonprocedural MI ($P_{interaction}$=0.049), with a greater absolute benefit of the

| Event | 4-year Cumulative Incidence (95% CI) | | Difference in Event Rate, INV - CON (95% CI) | Interaction P-value |
|---|---|---|---|---|
| | INV | CON | | |
| **CV death, MI, hHF, hUA, or RCA** | | | | 0.616 |
| No intermediate LMD | 10.8% (9.0%, 12.7%) | 12.2% (10.3%, 14.3%) | -1.5% (-4.2%, 1.3%) | |
| Intermediate LMD | 13.0% (10.0%, 16.5%) | 16.0% (12.4%, 19.9%) | -2.9% (-7.9%, 2.1%) | |
| **CV death or MI** | | | | 0.346 |
| No intermediate LMD | 10.0% (8.2%, 11.9%) | 11.2% (9.3%, 13.2%) | -1.2% (-3.9%, 1.5%) | |
| Intermediate LMD | 10.8% (8.0%, 14.1%) | 14.7% (11.2%, 18.7%) | -3.9% (-8.7%, 1.0%) | |
| **Primary endpoint or stroke** | | | | 0.896 |
| No intermediate LMD | 11.4% (9.6%, 13.4%) | 13.5% (11.5%, 15.7%) | -2.1% (-4.9%, 0.8%) | |
| Intermediate LMD | 15.9% (12.5%, 19.6%) | 17.5% (13.7%, 21.7%) | -1.7% (-7.0%, 3.7%) | |
| **CV death, MI, or stroke** | | | | 0.811 |
| No intermediate LMD | 10.6% (8.8%, 12.6%) | 12.5% (10.5%, 14.6%) | -1.9% (-4.7%, 0.9%) | |
| Intermediate LMD | 13.7% (10.5%, 17.2%) | 16.3% (12.5%, 20.5%) | -2.6% (-7.8%, 2.6%) | |
| **CV death** | | | | 0.115 |
| No intermediate LMD | 2.7% (1.8%, 3.9%) | 3.8% (2.7%, 5.2%) | -1.0% (-2.7%, 0.6%) | |
| Intermediate LMD | 5.4% (3.3%, 8.3%) | 3.6% (2.1%, 6.0%) | 1.8% (-1.3%, 4.9%) | |
| **MI** | | | | 0.121 |
| No intermediate LMD | 8.0% (6.4%, 9.7%) | 8.2% (6.7%, 10.0%) | -0.2% (-2.6%, 2.1%) | |
| Intermediate LMD | 8.2% (5.8%, 11.1%) | 12.4% (9.1%, 16.1%) | -4.2% (-8.6%, 0.2%) | |
| **Non-procedural MI** | | | | 0.049 |
| No intermediate LMD | 4.8% (3.5%, 6.2%) | 6.8% (5.4%, 8.4%) | -2.0% (-4.1%, -0.0%) | |
| Intermediate LMD | 4.1% (2.4%, 6.5%) | 10.5% (7.5%, 14.1%) | -6.4% (-10.3%, -2.6%) | |
| **Procedural MI** | | | | 0.239 |
| No intermediate LMD | 2.3% (1.6%, 3.2%) | 0.9% (0.4%, 1.6%) | 1.5% (0.5%, 2.4%) | |
| Intermediate LMD | 4.3% (2.7%, 6.4%) | 1.4% (0.6%, 3.0%) | 2.9% (0.7%, 5.1%) | |
| **UA hospitalization** | | | | 0.573 |
| No intermediate LMD | 0.4% (0.1%, 0.8%) | 0.9% (0.5%, 1.5%) | -0.5% (-1.1%, 0.1%) | |
| Intermediate LMD | 0.9% (0.3%, 2.1%) | 1.9% (0.8%, 3.7%) | -1.0% (-2.6%, 0.7%) | |
| **HF hospitalization** | | | | 0.215 |
| No intermediate LMD | 1.1% (0.6%, 2.0%) | 0.6% (0.3%, 1.2%) | 0.5% (-0.3%, 1.3%) | |
| Intermediate LMD | 3.0% (1.6%, 5.0%) | 1.1% (0.3%, 2.7%) | 1.9% (-0.1%, 3.9%) | |
| **Stroke** | | | | 0.168 |
| No intermediate LMD | 1.0% (0.6%, 1.8%) | 1.6% (0.9%, 2.6%) | -0.6% (-1.6%, 0.5%) | |
| Intermediate LMD | 3.3% (1.9%, 5.3%) | 2.0% (0.8%, 4.2%) | 1.3% (-1.1%, 3.7%) | |

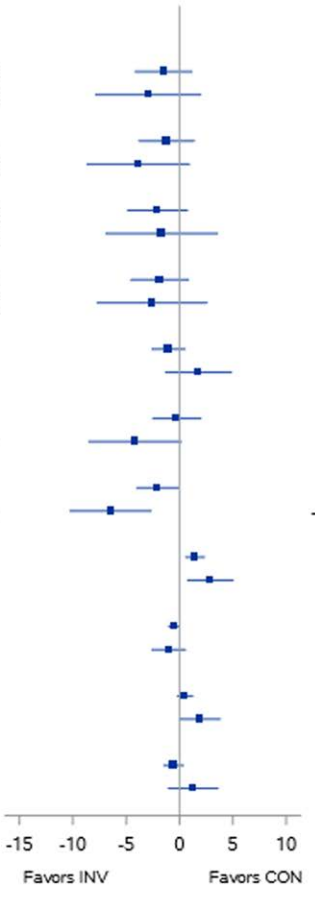


**Figure 2. Heterogeneity of treatment effect based on randomized treatment group and left main severity on coronary computed tomography angiography for the primary and secondary clinical outcomes.**
CON indicates conservative; CV, cardiovascular; hHF, hospitalization for heart failure; hUA, hospitalization for unstable angina; INV, invasive; LMD, left main disease; MI, myocardial infarction; and RCA, resuscitated cardiac arrest.

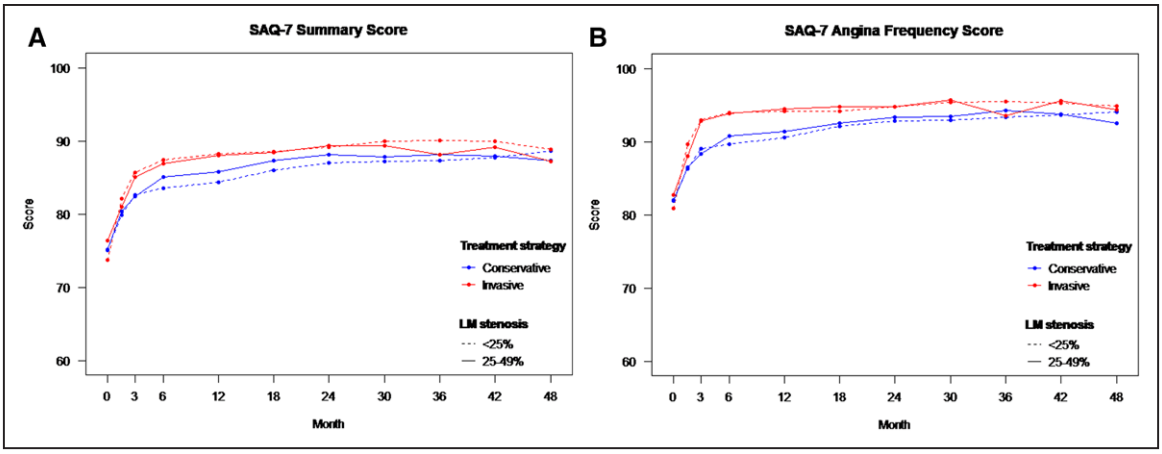


**Figure 3. Heterogeneity of treatment effect based on randomized treatment group and left main (LM) severity on coronary computed tomography angiography for the quality of life outcomes.**
**A**, Effect on Seattle Angina Questionnaire (SAQ)-7 summary score; (**B**) effect on SAQ-7 angina frequency score.

invasive strategy in those with intermediate LMD when compared with the cohort without intermediate LMD. This could, in part, be explained by the greater proportion of patients who underwent CABG (versus percutaneous coronary intervention) in those with intermediate LMD when compared with those without intermediate LMD (32.1% versus 18.2%). The prognostic value of procedural versus spontaneous MI is controversial. We recently showed that type 1 MI events that occurred in ISCHEMIA were associated with an increased risk for all-cause death, cardiovascular death, and the composite of cardiovascular death or heart failure admission in comparison with patients without an MI.[19] In contrast, the risk of subsequent all-cause death or cardiovascular death after procedural MI in comparison with patients without an MI was less than type 1 MI[19] suggesting that spontaneous MI may be associated with higher mortality.[20]

Finally, despite a greater extent of atherosclerosis in those with intermediate LMD, baseline symptom status was similar. During follow-up, the invasive strategy improved angina-related QoL without significant heterogeneity of treatment effect based on LMD severity, and the benefits were largely confined to participants with symptoms of angina at the time of randomization.

The clinical implications of the study are severalfold. First, the presence of intermediate LMD on CCTA is a marker of extensive atherosclerotic burden and as such may warrant aggressive medical therapy. Second, the presence of intermediate LMD may point to greater absolute benefit from an invasive strategy when compared with a conservative strategy for the reduction of spontaneous MI ($P_{interaction}$=0.049) although there was no difference in death. Finally, the decision to pursue an invasive strategy should be driven mainly by patient symptom status, which was better with invasive management.

## Study Limitations

This is a post hoc analysis of data from a randomized trial, and as such, the findings are hypothesis generating. The subgroups by themselves were underpowered for clinical outcomes. The definition of the cohort was based on CCTA, not invasive angiography, which many consider the gold standard. In addition, in depth plaque composition analysis was not performed on the coronary computed tomography. However, LM stenosis characteristics in the subset that underwent invasive angiography were included. Moreover, in the group that underwent invasive angiography, intravascular imaging was not mandated, and as such, intravascular correlation of the LM findings seen on CCTA is not available for comparison. Use of intravascular imaging to optimize stent implantation was low in the trial. Moreover, the trial excluded patients with ejection fraction <35% as this was tested in the STICH trial (Surgical Treatment for Ischemic Heart Failure).[21] In addition, longer term follow-up (ISCHEMIA-EXTEND [International Study of Comparative Health Effectiveness With Medical and Invasive Approaches Extended Follow-Up]) may provide additional insights into outcomes between invasive and conservative management. Given the low prevalence of isolated intermediate LMD on CCTA in ISCHEMIA (by design), the current study does not provide guidance on the management of such patients.

## Conclusions

Among ISCHEMIA trial participants with intermediate LMD, defined by CCTA as a 25% to 49% diameter stenosis, there was a 31% higher rate of cardiovascular events, but similar QoL, as compared with participants without intermediate LMD (<25% stenosis). However, this increased risk was not significant after accounting for extent of CAD. Regardless of intermediate LMD status, there was no evidence that the invasive strategy reduced the composite primary outcome and the secondary

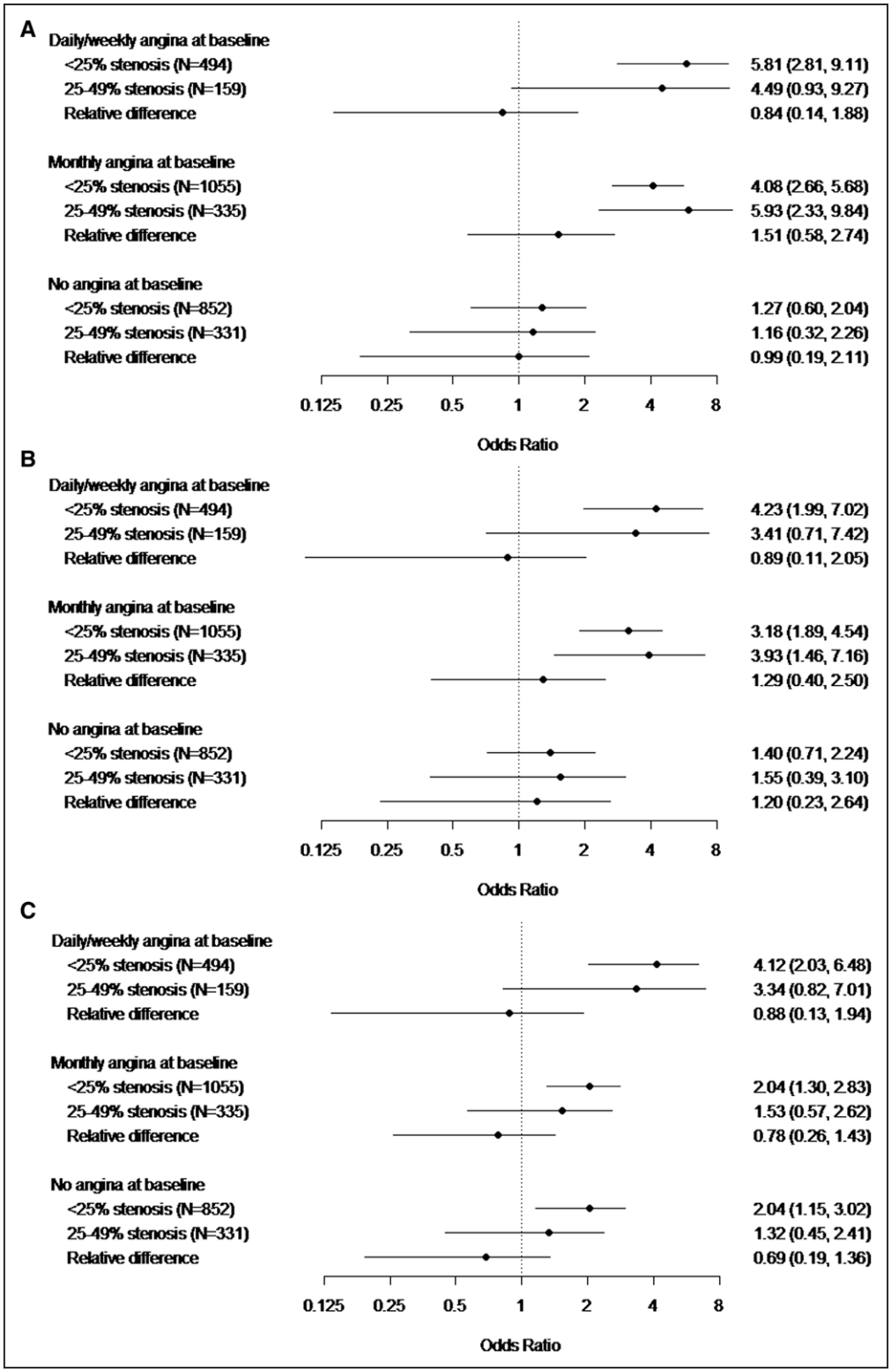


**Figure 4. Heterogeneity of treatment effect based on randomized treatment group and left main severity on coronary computed tomography angiography stratified by baseline symptom status for the Seattle Angina Questionnaire-7 angina frequency score.** Odds ratio >1.0 favors invasive strategy. At 3 mo (**A**), at 12 mo (**B**), and at 36 mo (**C**).

outcome of cardiovascular death or MI. Invasive management increased procedural MI, reduced nonprocedural MI (with greater absolute risk reduction in those with intermediate LMD), and improved angina-related QoL, with no significant difference for other clinical outcomes in patients with or without intermediate LMD.

## ARTICLE INFORMATION

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### Supplemental Material

Supplemental Methods
Figures S1 and S2
Tables S1–S4

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