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CLINICAL RESEARCH

# Coronary CT Angiography Followed by Invasive Angiography in Patients With Moderate or Severe Ischemia-Insights From the ISCHEMIA Trial

G.B. John Mancini, MD,[a] Jonathan Leipsic, MD,[a] Matthew J. Budoff, MD,[b] Cameron J. Hague, MD,[a,c] James K. Min, MD,[d] Susanna R. Stevens, MS,[e] Harmony R. Reynolds, MD,[f] Sean M. O'Brien, PHD,[e] Leslee J. Shaw, PHD,[g] Cholenahally N. Manjunath, MD,[h] Kreton Mavromatis, MD,[i] Marcin Demkow, MD,[j] Jose Luis Lopez-Sendon, MD,[k] Alexander M. Chernavskiy, MD, PHD,[l] Gilbert Gosselin, MD,[m] Herwig Schuchlenz, MD,[n] Gerard P. Devlin, MD,[o] Anoop Chauhan, MD,[p] Sripal Bangalore, MD, MHA,[f] Judith S. Hochman, MD,[f] David J. Maron, MD[q]

## ABSTRACT

**OBJECTIVES** This study aimed to examine the concordance of coronary computed tomographic angiography (CCTA) assessment of coronary anatomy and invasive coronary angiography (ICA) as the reference standard in patients enrolled in the International Study of Comparative Health Effectiveness with Medical and Invasive Approaches (ISCHEMIA).

**BACKGROUND** Performance of CCTA compared with ICA has not been assessed in patients with very high burdens of stress-induced ischemia and a high likelihood of anatomically significant coronary artery disease (CAD). A blinded CCTA was performed after enrollment to exclude patients with left main (LM) disease or no obstructive CAD before randomization to an initial conservative or invasive strategy, the latter guided by ICA and optimal revascularization.

**METHODS** Rates of concordance were calculated on a per-patient basis in patients randomized to the invasive strategy. Anatomic significance was defined as ≥50% diameter stenosis (DS) for both modalities. Sensitivity analyses using a threshold of ≥70% DS for CCTA or considering only CCTA images of good-to-excellent quality were performed.

**RESULTS** In 1,728 patients identified by CCTA as having no LM disease ≥50% and at least single-vessel CAD, ICA confirmed 97.1% without LM disease ≥50%, 92.2% with at least single-vessel CAD and no LM disease ≥50%, and only 4.9% without anatomically significant CAD. Results using a ≥70% DS threshold or only CCTA of good-to-excellent quality showed similar overall performance.

**CONCLUSIONS** CCTA before randomization in ISCHEMIA demonstrated high concordance with subsequent ICA for identification of patients with angiographically significant disease without LM disease.
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From the [a]Center for Cardiovascular Innovation, University of British Columbia, Vancouver, British Columbia, Canada; [b]Lundquist Institute, Torrance, California, USA; [c]St. Paul's Hospital Department of Radiology, Vancouver, British Columbia, Canada; [d]Cleerly, Inc., New York, New York, USA; [e]Duke Clinical Research Institute, Durham, North Carolina, USA; [f]New York University Grossman School of Medicine, New York, New York, USA; [g]Weill Cornell Medicine, New York, New York, USA; [h]Sri Jayadeva Institute of Cardiovascular Sciences and Research, Bangalore, India; [i]Emory University School of Medicine, Atlanta, Georgia, USA; [j]Institute of Cardiology, Warsaw, Poland; [k]Hospital Universitario La Paz-IdiPaz- CIBER-CV, Madrid, Spain; [l]E.Meshalkin National Medical Research Center of the Ministry of Health of the Russian Federation, Novosibirsk, Russia; [m]Montréal Heart Institute, Montréal, Québec, Canada; [n]LKH Graz II, Department fuer Kardiologie und Intensivmedizin, Graz, Austria; [o]Gisborne Hospital, Gisborne, New Zealand; [p]Blackpool Teaching Hospitals, Lancashire, United Kingdom; [q]Department of Medicine, Stanford University School of Medicine, Stanford, CA, USA. Jagat Narula, MD, served as Guest Editor for this paper.

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**ABBREVIATIONS AND ACRONYMS**

**CAD** = coronary artery disease

**CCTA** = cardiac computed tomographic angiography

**CX** = circumflex

**DS** = diameter stenosis

**ICA** = invasive coronary angiography

**LAD** = left anterior descending

**LM** = left main

**OMT** = optimal medical therapy

**RCA** = right coronary artery

The ISCHEMIA (International Study of Comparative Health Effectiveness With Medical and Invasive Approaches) assessed whether patients with moderate or severe ischemia on functional testing would have improved outcome if treated with an initial invasive strategy that included optimal medical therapy (OMT) compared with OMT alone with cardiac catheterization reserved for failure of medical therapy (1,2). The protocol included a pre-randomization blinded coronary computed tomographic angiogram (CCTA) in the majority of participants to address 3 issues. First, it was a pragmatic way to address safety and commensurately to facilitate physician willingness to randomize patients by excluding those with important left main (LM) disease. Second, CCTA helped avoid randomization of patients with no significant obstructive coronary artery disease (CAD) who would not benefit from revascularization and who would dilute statistical power of the trial. Finally, it overcame concerns that randomization at the time of invasive coronary angiography (ICA) might dissuade physicians from randomizing patients in the catheterization laboratory with knowledge of the presence of high anatomic burden of disease (2,3). The use of CCTA to address these issues was based upon the strong relationship between CCTA and ICA and the rapidly emerging role of CCTA as a tool to improve use of angiography suites (4–13). The primary aim of this analysis was to identify the per-patient concordance between CCTA and ICA for identification of obstructive CAD and absence of LM disease. We also explored discordance for absence of significant LM and concordance for burden of disease as reflected by 1-, 2- or 3-vessel disease, location of disease per major vessel, and for assessment of proximal disease in the left anterior descending (LAD) artery.

## METHODS

The study population consisted of the participants randomized to the invasive group who had core laboratory-interpreted, pre-randomization CCTAs and core laboratory-interpreted baseline ICA within 6 months of CCTA. Exclusion criteria for this analysis were: 1) previous coronary artery bypass grafting; 2) noninterpretable CCTA or ICA; 3) ≥50% diameter stenosis (DS) LM disease on CCTA; 4) absence of ≥50% DS on CCTA for participants enrolled after stress imaging tests; 5) absence of ≥70% DS on CCTA for participants enrolled after nonimaging exercise tolerance tests; 6) >6 months between pre-randomization CCTA and ICA; and 7) post-randomization revascularization procedure before the date of the baseline diagnostic angiogram (Supplemental Figure 1, Supplemental Table 1). A total of 1,757 participants were available for analyses, representing 67.9% of the total number randomized to the invasive arm (n = 2,588) and 91.9% of the scans received by the core CCTA laboratory for participants randomized to the invasive strategy (n = 1,913). There were 1,728 patients with complete information to make overall patient level assessment for the primary per-patient analysis and the remaining (n = 29) were suitable only for inclusion in various vessel and segment-level analyses. There were 1,296 patients with complete information for analysis of agreement between CCTA and ICA for the number of vessels diseased; a case was considered not evaluable for the number of vessels diseased if certain designated segments could not be interpreted for the presence of ≥50% DS: for example, the mid-right coronary artery (RCA), because of cardiac motion or other artifact.

The primary analysis was based upon use of the ≥50% DS threshold in all suitable patients and applied to both ICA and CCTA. Secondary analyses (shown in the Supplemental Appendix and Supplemental Tables 2 to 6) used: 1) only those participants enrolled after use of stress imaging to assess ischemic burden, and the ≥50% DS threshold (n = 1,260, excluding those enrolled only after nonimaging exercise tolerance testing because randomization of such patients was based upon a ≥70% DS threshold on CCTA); 2) ≥70% DS threshold applied to all patients for both CCTA and ICA; and 3) a ≥70% DS threshold applied to CCTA compared with a ≥50% threshold applied to ICA. Finally, sensitivity analyses of the primary and secondary aims were performed using only good- or excellent-quality CCTA. CCTA image quality was recorded based on assessment of overall image

The authors attest they are in compliance with human studies committees and animal welfare regulations of the authors' institutions and Food and Drug Administration guidelines, including patient consent where appropriate. For more information, visit the Author Center.

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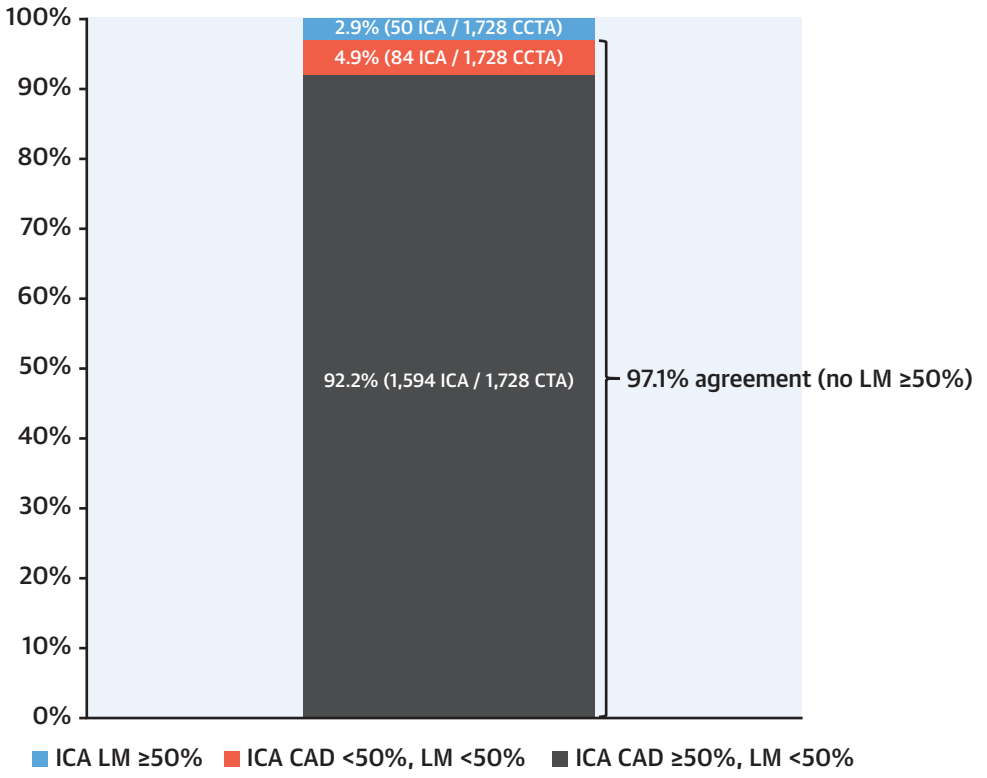
**CENTRAL ILLUSTRATION** **Overall Percent Agreement Between ICA and CCTA**

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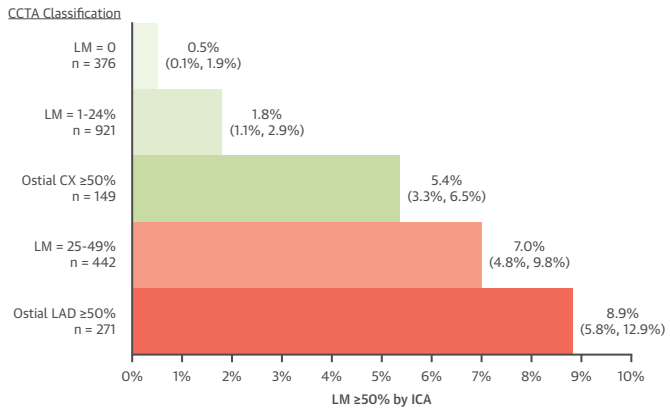
There was 97.1% concordance for the absence of LM disease and 92.2% concordance for the designation of at least single-vessel coronary disease without LM. There were 50 cases of the 1,728 patients in total (2.9%) who had ICA evidence of LM disease ≥50% DS despite CCTA reports of <50% DS. CCTA = cardiac computed tomographic angiography; ICA = invasive coronary angiography; LM = left main. The 1,728 denominator comes from 1,757 patients eligible for the overall study minus 21 patients with nonevaluable CCTAs and 8 with missing ICA information for ≥50% CAD.

noise, presence of motion artifacts, poor contrast, misregistration, adequacy of field of view, calcium affecting ease of segmental analysis or difficult to assess stents, among other factors. Each scan was also graded as either excellent, good, fair, or poor. All CCTA segmental assessments were determined by consensus of at least 2 independent readers, and cases of LM disease were also reviewed and finalized by a third reader. Readers assessed 17 segments (14), with additional identification of whether lesions were in the ostium of the LAD artery or the circumflex (CX). The lesions were graded categorically as 0%, 1% to 24%, 25% to 49%, 50% to 69%, and 70% or greater. Quantitative coronary angiography was performed as previously described (15). All patients provided informed consent for participation in the ISCHEMIA trial. The protocol was approved by the institutional review board at New York University Grossman School of Medicine (the clinical coordinating center) and by the institutional review board and ethics committee at each participating site (Supplemental Appendix).

Statistical analysis focused on estimating the probability that patients who were classified as having significant CAD and no significant LM disease on CCTA would be classified as the same by ICA. We also examined the frequency of CCTA and ICA agreeing on the number of diseased vessels and the presence or absence of stenosis in specific vessels. The study's main concordance measures were the percent of participants with CCTA-defined CAD ≥50% and no LM disease ≥50% whose ICA result was concordant in the sense of having ICA-defined CAD ≥50% and no ICA LM disease ≥50%, the

**FIGURE 1 ICA Detection of LM ≥ 50% DS as a Function of CCTA Classification**




The CCTA classification of LM (0%, 1% to 24% and 25% to 49% DS) or the classification of ostial CX or ostial LAD is shown on the **left**, with the number of individual reports. The length of the horizontal bars represents the percentage of cases (with 95% exact binomial confidence intervals) having LM ≥50% DS by ICA for each of the CCTA classifications. Note that 18 CCTAs were not interpretable for the presence of LM ≥50% DS, leaving a sample size of 1,739. CCTA = cardiac computed tomographic angiography; CX = circumflex; DS = diameter stenosis; ICA = invasive coronary angiography; LAD = left anterior descending; LM = left main. Note that 18 CCTAs were not interpretable for the presence of LM ≥50% DS, leaving a sample size of 1,739.

percent who were discordant because of ICA CAD <50%, and the percent who were discordant because of ICA LM disease ≥50%. Rates of discordance due to ICA LM disease ≥50% were estimated overall and across subgroups based on CCTA-defined number of diseased vessels and degree of stenosis in specific vessels. All concordance measures in this study were conditional on having CCTA-defined CAD ≥50% and no LM disease ≥50%. Patients who failed screening because of CCTA-defined LM disease ≥50% or no CAD ≥50% did not receive study ICAs in ISCHEMIA and were therefore excluded. Traditional accuracy measures treating ICA as the reference standard could not be calculated because of missing ICA results for the patients who failed screening. The exclusion of such patients prevented us from estimating sensitivity and specificity but did not invalidate estimation of concordance probabilities as defined here for patients meeting inclusion and exclusion criteria for ISCHEMIA.

## RESULTS

The median (25th, 75th percentile) time between CCTA and ICA was 29 (18, 46) days with a mean and standard deviation of 35.7 ± 27.1 days.

**PER-PATIENT ANALYSIS.** ICA and CCTA were concordant for the identification of at least single-vessel CAD and absence of LM ≥50% in 92.2% of cases (95% confidence interval [CI]: 90.9% to 93.5%). In 4.9% (95% CI: 3.9% to 6.0%) of cases, ICA did not confirm presence of CAD ≥50% DS. And in 2.9% (95% CI: 2.2 to 3.8%) of cases, CCTA missed ICA identified LM ≥50% DS (**Central Illustration**). Thus, ICA and CCTA were concordant in 97.1% (1,678 of 1,728) for the absence of significant LM disease ≥50%.

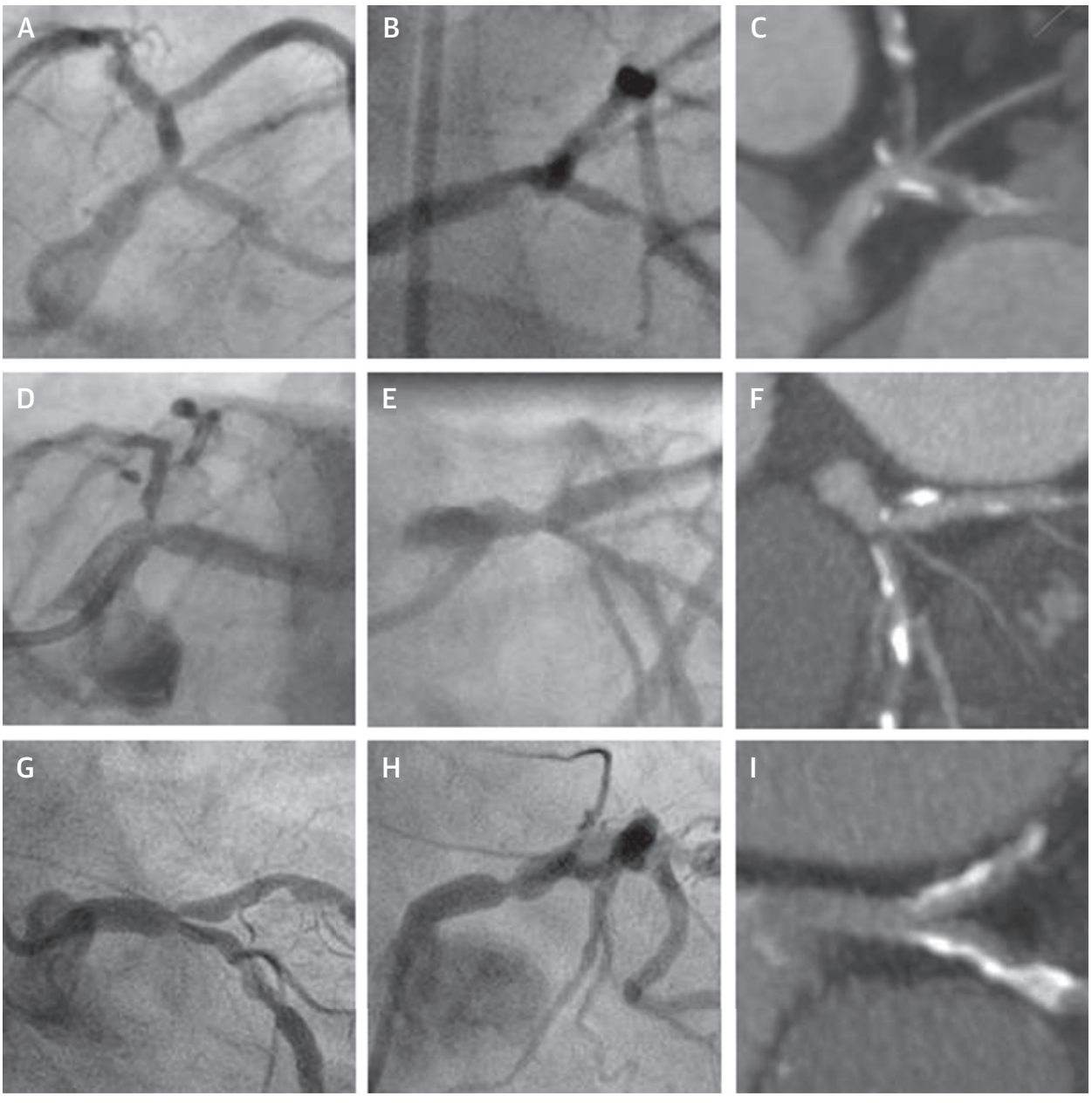
**ASSESSMENT OF LM DISEASE DISCORDANCE.** When CCTA identified LM = 0% DS (376 patients), it was rare (2 patients, 0.5%) for ICA to report LM ≥50% DS. Of 921 patients with CCTA findings of 1% to 24% DS, 1.8% (17 patients) had LM ≥50% DS on ICA. Of 442 patients with CCTA reports of LM 25% to 49% DS, 7% (31 patients) had LM disease ≥50% on ICA. The average percent of DS of the significant LM stenosis detected by ICA was 62 ± 3% (mean ± SD), 62 ± 14% and 64 ± 10%, respectively, for these 3 CCTA categories of LM assessment (0, 1% to 24%, 25% to 49%). When CCTA identified ≥50% DS in the ostial CX (149 patients) or ostial LAD (271 patients), but <50% DS in the LM, there were 5.4% (8 patients) and 8.9% (24 patients) with ICA showing ≥50% DS in the LM, respectively (**Figure 1**). Examples of discrepancies in 3 patients are shown in **Figure 2**.

**ASSESSMENT OF NUMBER OF DISEASED VESSELS.** The agreement between CCTA and ICA for the designation of presence of single-, double-, or triple-vessel disease without LM disease was 54.5% (**Figure 3**). Overestimation of disease by CCTA occurred in 25.3% of cases and underestimation—including underestimation of LM disease—in 20.2% of cases.

**ASSESSMENT OF LOCATION OF DISEASE.** **Per-vessel analysis.** **Figure 4** demonstrates concordance between ICA and CCTA for the presence of ≥50% DS in the LAD, CX, and RCA (including their major branches; see Definitions in Supplemental Appendix) of 84.1%, 81.3%, and 83.3% of patients, respectively. Conversely, concordance for <50% DS was 56.9%, 70.2%, and 74.3%, respectively.

**Assessment of LAD artery segments.** Because of the importance attached to LAD artery disease, and because of variable visual cues for segmentation between ICA and CCTA (e.g., septals are infrequently used to define proximal LAD on CCTA, whereas this is more feasible with ICA), we analyzed concordance between CCTA and ICA for the LAD artery as a whole, for an "extended" proximal LAD or mid-LAD segment, and for the isolated proximal LAD artery (**Figure 5**). This shows an expected decrease in

**FIGURE 2** **Left Main ICA and CCTA Discordance**

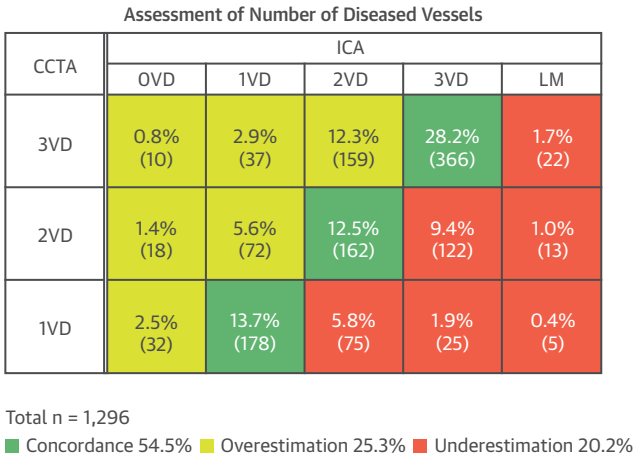



**Each row** represents 1 of 3 patients with ICA detection of LM ≥50% and CCTA report of LM <50% DS. **A, B, D, E, G, and H** are 2 ICA frames showing a potential stenosis in the LM ≥50% for each patient. A single corresponding CCTA reconstruction for each patient is shown at the **end of each row in C, F, and I**. Abbreviations as in Figure 1.

concordance for presence of significant stenosis as one progresses from considering the entire LAD vessel (84.1%), the proximal or mid-LAD vessel (76.7%), and only the proximal LAD vessel itself (54.0%). Conversely, exclusion of significant disease improved progressively from LAD vessel overall (56.9%) to the proximal or mid-LAD vessel (70.8%) and the proximal LAD vessel itself (79.3%).

**SENSITIVITY ANALYSES.** Other secondary and sensitivity analyses for the main per-patient results are provided in the Supplemental Appendix and showed similar results. In particular, use of a ≥70%

**FIGURE 3 Concordance Matrix Between CCTA and ICA for Detection of Single-, Double-, or Triple-Vessel Disease**




Shading in **green** identifies concordance between the 2 imaging methods. Shading in **red** identifies underestimation, and, in **yellow**, overestimation. Designation of LM <50% by CCTA but ≥50% by ICA was considered an underestimation by CCTA. The n per cell is provided and expressed as a percent of the total N = 1,296. The overall concordance was 54.5% (95% confidence interval: 51.7% to 57.2%). Note that, in 426 CCTAs and 35 ICAs, certain designated segments could not be interpreted for the presence of ≥ 50% DS, leaving a sample size of 1,296 for which the number of diseased vessels is known. Abbreviations as in Figure 1.

DS threshold applied to CCTA and a ≥50% DS threshold applied to ICA did not improve per-patient performance. In addition, a focus on the subset (n = 830 of 1,757, 47%) with CCTA quality rated as good or excellent did not change performance (Supplemental Tables 5 and 6).

## DISCUSSION

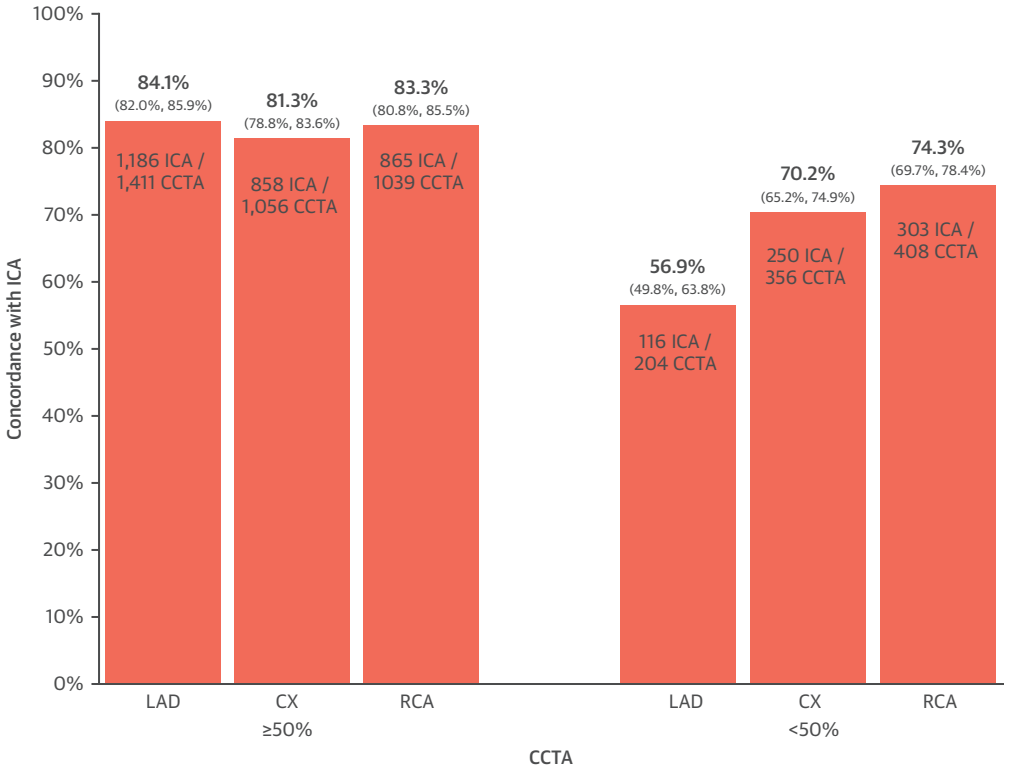
In this cohort with a very high a priori likelihood of obstructive CAD, CCTA was highly concordant with ICA in patients randomized to the invasive arm of ISCHEMIA (97.1% for excluding LM disease ≥50% and 92.2% for identifying patients with at least 1-vessel CAD and no LM disease). Concordance for burden of disease based on numbers of diseased vessels (1, 2, or 3 and without LM disease) was modest (54.5%). Overestimation of disease burden by CCTA occurred in 1 in 4 and underestimation in 1 in 5 cases compared with ICA. Thus, CCTA successfully ensured that randomization of patients with noninvasive evidence of moderate-to-severe ischemia would be limited as much as possible to those without LM disease and avoided as much as possible those patients without significant CAD. It also enabled avoidance of the pitfalls of study enrolment at the time of ICA when biases might have compromised randomization to OMT of patients with higher burdens of disease and disease in locations such as the ostial or proximal LAD artery.

**STUDY LIMITATIONS.** The analysis of LM disease in this report is limited by necessity: first, to only those patients thought to be eligible for randomization after excluding LM disease through use of CCTA and, second, to those randomized to the invasive strategy. It has already been reported that of the 5,757 patients undergoing a study CCTA, 434 were not eligible for randomization, based upon a CCTA core laboratory report of LM disease ≥50% (7.5% of subjects) (16). But ICA core laboratory corroboration is not available in those patients. It is conceivable that the percentage of patients having ICA-confirmed LM disease might be <7.5%, based on the potential for overestimation by CCTA and the imperative for CCTA readers to maximize patient safety, possibly leading to "overcalling" of LM disease. But of those who proceeded to ICA, detailed analysis of the small number of discordant cases allowed us to identify some CCTA findings associated with a higher likelihood of finding LM ≥50% DS on ICA, most notably CCTA reporting of ostial LAD vessel or CX DS ≥50% or LM 25% to 49% DS. One may argue that ICA, a 2-dimensional imaging modality, may not be an appropriate gold standard for determining the precise difference between a distal LM stenosis and an ostial LAD artery or ostial CX stenosis compared with CCTA (17). The sample images in Figure 2 may be taken to support this hypothesis. Regardless, exclusion of LM disease by CCTA in 97.1% of cases proceeding to ICA was excellent.

Although concordance between CCTA and ICA for identifying severe disease in specific major vessels (LAD vs. CX vs. RCA) was high (81.3% to 84.1%), excluding disease in each specific vessel was only modest (56.9% to 74.3%) (Figure 4). Such analyses are affected by the binary categorization based upon the 50% threshold. We did not see material differences with secondary analyses using only good to excellent scans or using a higher stenosis threshold (≥70%).

Our findings are in line with the findings of the recent SYNTAX (TAXUS Drug-Eluting Stent Versus Coronary Artery Bypass Surgery for the Treatment of Narrowed Arteries) II trial, in which participants underwent CCTA and ICA with SYNTAX scores calculated from both modalities (18). The SYNTAX scores from CCTA overestimated the disease burden compared with the invasive gold standard. Thus, CCTA is a good tool to help enrich the population referred for ICA compared with stress testing alone

**FIGURE 4** **Concordance Between CCTA and ICA for Location of Significant CAD in Major Vessels**

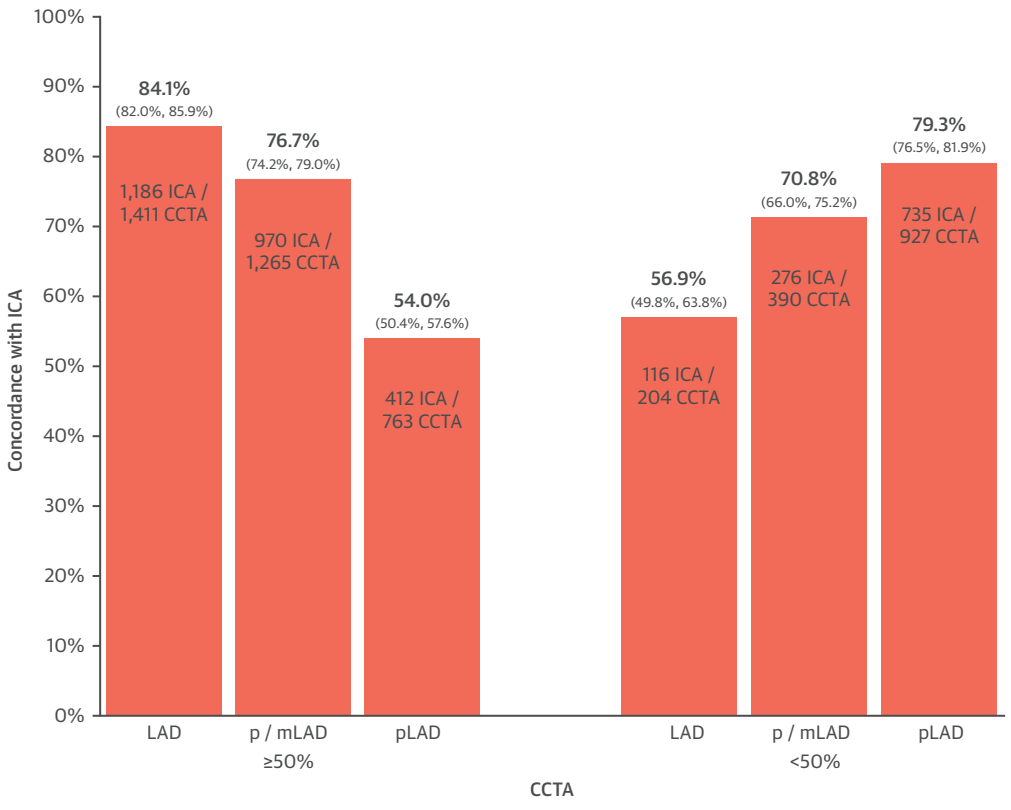



The **x-axis** shows CCTA reports of disease ≥50% and <50% DS in the LAD, the CX, or the RCA. The **y-axis** shows the percent concordance with ICA as derived from the numbers shown within the **bars** (numerator = cases that agree with ICA; denominator = number of cases with the CCTA result shown); 95% confidence intervals are provided in brackets. CAD = coronary artery disease; RCA = right coronary artery; other abbreviations as in Figure 1.

but should not be considered adequate for precise planning of any specific revascularization strategy without ICA corroboration. Others have also highlighted these types of discrepancies (19-22).

Elements of this study may limit the application to routine clinical CCTA or to more broad populations, particularly those with much lower a priori likelihood of CAD. The analyses were based upon core-laboratory assessment and were all determined by consensus (23). This element of quality control does not occur in routine practice. The analyses are based solely on those patients eligible by CCTA and subsequently undergoing core-laboratory analysis of ICA. We do not have ICA comparisons for those patients deemed by CCTA to have either no significant CAD or LM ≥50% DS, thereby precluding valid calculations of sensitivity, specificity, and positive and negative predictive values. The highly selected cohort had a very high probability of significant underlying CAD based on selection by previous evidence of moderate or severe stress-induced ischemia and history of angina in 89%. This feature, however, is also a unique strength of the analyses because the majority of previous studies comparing the performance of CCTA with ICA have been undertaken in populations with a much lower risk and extent of underlying CAD, accounting for the well-known high negative predictive value of CCTA (4-10). It is worth emphasizing that calcium remains an impediment to the facile reading of CCTA scans, and calcium sufficient to potentially impair segmental analysis was present in 31% of scans (Supplemental Table 5) (24,25). Accordingly, only 75% of CCTA studies could be included in the analysis of number of vessels diseased because key segments were not evaluable for ≥50% DS in the remaining 25%, because of calcification, motion, or other artifacts. Stents (noted in 17% of patients in this study) provide similar challenges to CCTA reading. All readings of calcified or stented segments were performed using the principle

**FIGURE 5** Assessment of LAD Segments




The **x-axis** shows CCTA reports of disease ≥50% and <50% DS in the entire LAD vessel, in an extended segment consisting of both the proximal (p) and mid (m) LAD, and solely in the pLAD. The **y-axis** shows the concordance with ICA in percent as derived from the numbers shown within the **bars** (numerator = cases that agree with ICA; denominator = number of cases with the CCTA result shown); 95% confidence intervals are provided in brackets. m = mid; p = proximal; other abbreviations as in Figure 1.

of "best effort;" use of appropriate views, reconstructions, filters, windows, and levels by the individual readers; and then reaffirmed by the consensus process. Although exact concordance for segments within major vessels was suboptimal, this segmentation problem is recognized from studies attempting to correlate lesion-specific fractional flow reserve measured invasively with values derived from CCTA (26). Finally, CCTA-derived fractional flow reserve was not calculated so correlation with fractional flow reserve performed in some patients at the time of ICA was not possible.

The utility of CCTA in this research protocol of high-risk patients may have important implications for clinical practice and for expanding appropriate-use criteria for CCTA in patients with moderate or severe ischemia, despite the limitations noted here (27). It has been shown in the CONSERVE (Coronary Computed Tomographic Angiography for Selective Cardiac Catheterization) trial that use of CCTA in patients with a lower probability of CAD compared with the ISCHEMIA trial helps to avoid unnecessary ICA, diminish ICA costs, and improve overall use (28). After stress testing and before randomization, 21% of subjects undergoing CCTA were excluded because of the absence of significant CAD (16). Thus, the total experience of using CCTA in this trial and the unique, high-risk cohort suggest that an expanded role for CCTA before ICA may be warranted even when the ischemic burden is moderate or severe (11).

## CONCLUSIONS

We demonstrated that, in patients first shown to have moderate or severe ischemia on stress testing, CCTA was an effective method to identify patients with significant CAD and without LM disease as determined by ICA.

## AUTHOR DISCLOSURES

This project was funded by National Institutes of Health (NIH) grants U01HL105907, U01HL105462, and U01HL105561 (NCT01471522). Dr. Mancini has received grants from National Heart, Lung and Blood Institute. Dr. Leipsic has served as Consultant and has reported stock options in HeartFlow and CIRCLE CVI; has received a research grant from GE Healthcare. Dr. Budoff has received grant support from General Electric. Dr. Hague has received grants from National Heart, Lung and Blood Institute. Dr. Min has received grants from National Heart, Lung, and Blood Institute, support from Cleerly Inc., grants and other support from GE Healthcare, and support from Arineta. Ms. Stevens has received grants from National Heart, Lung and Blood Institute. Dr. Reynolds has received grants from National Heart, Lung and Blood Institute and nonfinancial support from Abbott Vascular, Siemens, and BioTelemetry. Drs. O'Brien, Shaw, Manjunath, Mavromatis, Demkow, Lopez-Sendon, Chernyavskiy, Gosselin,. Schuelenz, Devlin, and Chauhan have received grants from National Heart, Lung and Blood Institute. Dr. Bangalore has received grants from National Heart, Lung and Blood Institute; and has served on advisory boards for Abbott Vascular, Pfizer, Amgen, Biotronik, Meril, Reata Pharmaceuticals, and Abbott Vascular. Dr. Hochman has served as Principal Investigator for the International Study of Comparative Health Effectiveness with Medical and Invasive Approaches (ISCHEMIA) trial, for which—in addition to support by a National Heart, Lung, and Blood Institute grant—devices and medications were provided by Abbott Vascular, Medtronic Inc., St. Jude Medical Inc., Volcano Corporation, Arbor Pharmaceuticals LLC, AstraZeneca, Merck Sharp and Dohme Corp., Omron Healthcare Inc.; and has received financial support from Arbor Pharmaceuticals LLC and AstraZeneca. Dr. Maron has received grants from National Heart, Lung, and Blood Institute.

**ADDRESS FOR CORRESPONDENCE:** Dr. G.B. John Mancini, University of British Columbia, Diamond Centre, Room 9111, 2775 Laurel Street, Vancouver, British Columbia V57 1M9, Canada. E-mail: mancini@mail.ubc.ca.

## PERSPECTIVES

**COMPETENCY IN MEDICAL KNOWLEDGE:** Cardiac computed tomographic angiography was used in a novel fashion to determine coronary anatomy eligibility for a randomized trial that compared a conservative strategy with an invasive strategy for the management of patients with chronic coronary artery disease. Patients had very high a priori likelihood of underlying coronary disease by virtue of moderate or severe ischemia documented by stress testing. Subsequent evaluation by cardiac computed tomographic angiography before invasive angiography served well to ensure presence of angiographically significant coronary artery disease and to exclude left main disease and nonobstructive disease.

**COMPETENCY IN PATIENT CARE:** This analysis demonstrates that patients suspected of coronary artery disease with stress tests showing moderate or severe ischemia can be effectively stratified further using cardiac computed tomography to assess left main stenosis and to ensure that when intervention may be warranted, procession to invasive angiography is reserved for patients with verified anatomic burden of disease.

**TRANSLATIONAL OUTLOOK:** The results of this study potentially expand the appropriate use of computed tomographic angiography before referral to invasive angiography when there is evidence of moderate or severe ischemia. This sequence more precisely identifies patients who truly have anatomically significant underlying coronary atheroma when intervention is being considered.

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**KEY WORDS** cardiac computed tomographic angiography, cardiac catheterization, invasive coronary angiography, ischemia, left main coronary artery disease

**APPENDIX** For supplemental figures and tables, please see the online version of this paper.