

ORIGINAL RESEARCH

Selective Referral Using CCTA Versus Direct Referral for Individuals Referred to Invasive Coronary Angiography for Suspected CAD



A Randomized, Controlled, Open-Label Trial

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ABSTRACT

OBJECTIVES This study compared the safety and diagnostic yield of a selective referral strategy using coronary computed tomographic angiography (CCTA) compared with a direct referral strategy using invasive coronary angiography (ICA) as the index procedure.

BACKGROUND Among patients presenting with signs and symptoms suggestive of coronary artery disease (CAD), a sizeable proportion who are referred to ICA do not have a significant, obstructive stenosis.

METHODS In a multinational, randomized clinical trial of patients referred to ICA for nonemergent indications, a selective referral strategy was compared with a direct referral strategy. The primary endpoint was noninferiority with a multiplicative margin of 1.33 of composite major adverse cardiovascular events (blindly adjudicated death, myocardial infarction, unstable angina, stroke, urgent and/or emergent coronary revascularization or cardiac hospitalization) at a median follow-up of 1-year.

RESULTS At 22 sites, 823 subjects were randomized to a selective referral and 808 to a direct referral strategy. At 1 year, selective referral met the noninferiority margin of 1.33 ($p = 0.026$) with a similar event rate between the randomized arms of the trial (4.6% vs. 4.6%; hazard ratio: 0.99; 95% confidence interval: 0.66 to 1.47). Following CCTA, only 23% of the selective referral arm went on to ICA, which was a rate lower than that of the direct referral strategy. Coronary revascularization occurred less often in the selective referral group compared with the direct referral to ICA (13% vs. 18%; $p < 0.001$). Rates of normal ICA were 24.6% in the selective referral arm compared with 61.1% in the direct referral arm of the trial ($p < 0.001$).

CONCLUSIONS In stable patients with suspected CAD who are eligible for ICA, the comparable 1-year major adverse cardiovascular events rates following a selective referral and direct referral strategy suggests that both diagnostic approaches are similarly effective. In the selective referral strategy, the reduced use of ICA was associated with a greater diagnostic yield, which supported the usefulness of CCTA as an efficient and accurate method to guide decisions of ICA performance. (Coronary Computed Tomographic Angiography for Selective Cardiac Catheterization [CONSERVE]; [NCT01810198](https://doi.org/10.1016/j.jcmg.2018.09.018)) (J Am Coll Cardiol Img 2019;12:1303-12) Published by Elsevier on behalf of the American College of Cardiology Foundation.

ABBREVIATIONS AND ACRONYMS

ACC = American College of Cardiology

AHA = American Heart Association

CAD = coronary artery disease

ICA = invasive coronary angiography

CCTA = coronary computed tomographic angiography

MACE = major adverse cardiovascular event

PCI = percutaneous coronary intervention

Invasive coronary angiography (ICA) is a commonly performed diagnostic test for evaluation of stable symptomatic patients with suspected coronary artery disease (CAD) to guide decisions of coronary revascularization (1-4). Although current professional guidance documents offer direction for appropriate selection of patients for elective ICA, previous studies observed that most individuals who underwent nonemergent ICA did not have actionable CAD (5,6). For these patients, ICA is an invasive, expensive procedure that may be unnecessary. When CAD is identified, ICA is frequently associated with ad hoc percutaneous coronary intervention (PCI) at the time of ICA, but whether this approach improves clinical outcomes is not clear (7-9).

SEE PAGE 1313

Coronary computed tomographic angiography (CCTA) is a noninvasive anatomic imaging method that enables identification and exclusion of CAD (10-12). Previous multicenter studies have consistently demonstrated the high diagnostic performance of CCTA to exclude obstructive CAD by 99% to 100%, a finding that is associated with favorable outcomes. These data have advanced the concept of the use of CCTA as a “gatekeeper” that more precisely selects individuals for ICA (6,13). For stable patients already referred for nonemergent ICA, it is not known how the safety and downstream clinical outcomes of a selective ICA referral strategy, informed by CCTA findings,

compare to a direct ICA referral strategy, because patients would have otherwise undergone ICA.

The objective of the CONSERVE (Coronary Computed Tomographic Angiography for Selective Cardiac Catheterization) trial (NCT01810198) was to compare the cardiovascular outcomes of a selective referral strategy, in which CCTA was performed before ICA, versus a direct referral strategy. The primary hypothesis of the CONSERVE trial was that a selective referral strategy would be noninferior to a direct referral strategy for major adverse cardiovascular events (MACE).

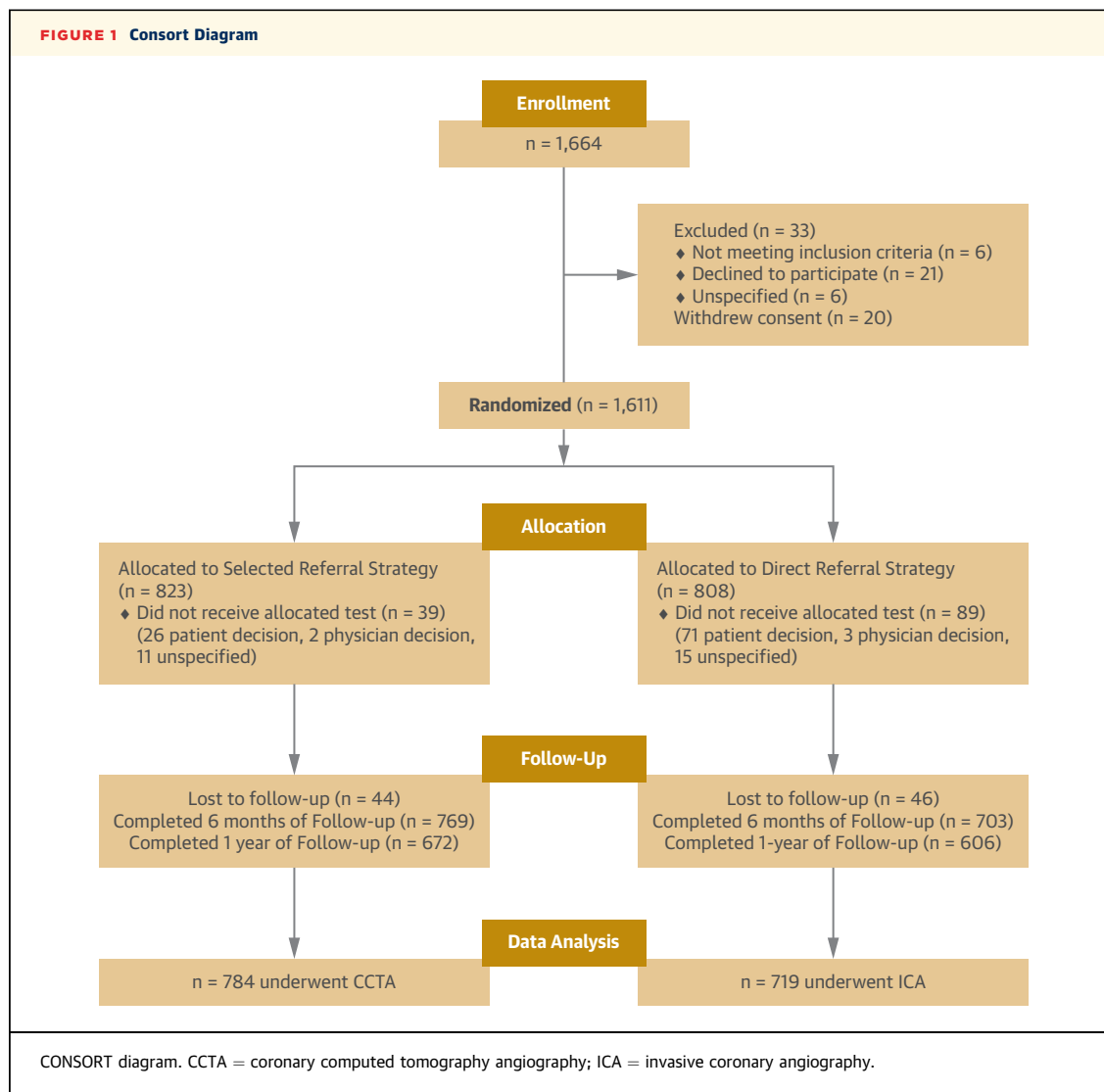
METHODS

STUDY DESIGN. CONSERVE was a 1:1 randomized, controlled, open-label, international, multicenter trial at 22 hospitals and cardiology practices in North America, East Asia, Europe, and India. The study protocol was approved at each enrolling site by the local institutional review board or ethics committee. After randomization to selective referral versus direct referral, ICA and CCTA performance and interpretation were executed locally, and downstream clinical decision-making was at the sole discretion of the local physicians. A total of 20 patients (14 in the selective referral and 6 in the direct referral arm) withdrew consent and were not included in our analysis (Figure 1).

PATIENT ENROLLMENT. The study participants were stable patients with suspected but without known CAD referred for nonemergent ICA based upon the American College of Cardiology/American Heart

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Manuscript received August 15, 2018; revised manuscript received September 4, 2018, accepted September 19, 2018.



Association (ACC/AHA) guidelines for coronary angiography (2), and included indications based on abnormal stress testing or suspected CAD symptoms. Patients were recruited during a clinic visit at the point of referral to ICA. Exclusion criteria included known history of CAD, ACC/AHA Class I or III indication for ICA, known complex congenital heart disease, planned ICA for reasons other than CAD evaluation, or other reasons that precluded randomization to either group for reasons of safety (Supplemental Appendix).

TRIAL RANDOMIZATION. After enrollment and baseline data collection, block randomization stratified by Korean and non-Korean sites was performed with 1:1 allocation to the selective referral or direct referral groups using web-based computer randomization (MDDX, San Francisco, California). Subjects

and physicians were not blinded to allocation or study results.

TRIAL PROCEDURES. After receiving written informed consent, eligible patients were randomly assigned to a selective referral or a direct referral strategy. A selective referral strategy was defined by initial performance of CCTA, with ICA performed at the discretion of the local physician informed by the CCTA findings. A direct referral strategy allowed performance of ICA as otherwise planned before study enrollment.

An initial sample size calculation yielded a necessary and sufficient sample size of 1,463 patients, assuming a 10% dropout and an annualized event rate of 5.2% based on 80% power to detect a noninferiority multiplicative margin of 1.33. A hypothesis of non-inferiority allowed us to evaluate the safety of a

TABLE 1 Downstream Procedural Use Following Randomization

	Selective Referral (n = 784 Underwent Index CCTA)		Direct Referral (n = 719 Underwent Index ICA)		p Value
	Total	%	Total	%	
Invasive procedures					
Invasive coronary angiography	179	23	30	4	<0.001
Fractional flow reserve	0	0	41	6	<0.001
Percutaneous coronary intervention	89	11	109	15	<0.001
Coronary artery bypass surgery	9	1	18	3	0.075
Revascularization	98	13	127	18	0.007
Noninvasive CAD tests					
CCTA	3	0.4	1	1	<0.001
Exercise electrocardiography	108	14	79	11	0.12
Stress nuclear	14	2	10	1	0.67
Stress echocardiogram	9	1	9	1	0.95
Rest echocardiogram	281	36	95	13	<0.001
Overall % of downstream testing	1,204	153	199	29	<0.001

CAD = coronary artery disease; CCTA = coronary computed tomography angiography.

selective referral strategy compared with the standard of care, that is, direct referral to invasive angiography. On October 22, 2015, we proposed to expand enrollment to a larger sample of a minimum of 1,600 patients and to obtain a median follow-up time of 12 months as reflective of the diagnostic episode of care for initial referral to ICA. All changes to the protocol, including the sample size calculation, was performed under the guidance of a Data Safety and Monitoring Board.

All sites were instructed to perform ICA and CCTA in accordance with local site practice and societal guidelines. For both ICA and CCTA, presence or absence of angiographic stenoses $\geq 50\%$ using a Society of Cardiovascular Computed Tomography coronary tree model was recorded by local site physicians, and the maximum on per-patient basis was used to define obstructive CAD (14). Normal ICAs were considered to be ICAs that demonstrated no stenosis $\geq 50\%$.

Data collection was performed prospectively in a central electronic data capture system. We acquired baseline data related to demographic characteristics, clinical CAD risk factors, angina typicality, ACC/AHA guideline indication for ICA, and cardiovascular medications. Follow-up was performed in person or by telephone communication at regular prescribed intervals, as well as last date of follow-up for those who did not reach 365 days at study closure. At each follow-up, patients were queried as to the occurrence of any MACE. Further data were collected for downstream invasive coronary and noninvasive cardiac procedures, as well as cardiovascular and all-cause hospitalizations. The primary endpoint was analyzed at 1 year of follow-up. Of event-free

survivors, 6-month follow-up was complete in 98% and 98% of patients in the selective and direct referral arms groups, respectively; similarly, 1-year follow-up (± 1 month) was complete in 86% and 84% of selective and direct referral patients, respectively (Figure 1).

MACEs. Independent investigators blinded to study allocation adjudicated adverse events. The primary endpoint was a composite of MACEs that included death, nonfatal myocardial infarction, unstable angina, stroke, urgent or emergent coronary revascularization, and cardiovascular hospitalization (endpoint definitions provided in the Supplemental Appendix). Secondary clinical endpoints included the primary MACE endpoint plus major bleeding, need for urgent or emergent surgery due to hemorrhage, major transfusion, and rates of test-related complications. The secondary endpoints also included evaluation of downstream resource use, including coronary revascularization, invasive and noninvasive CAD diagnostic testing, and hospitalizations. An independent clinical events committee, blinded to randomization assignment, adjudicated all clinical endpoints. Supervision of the accrual and evaluation of all suspected endpoints was performed under the guidance of a Data Safety and Monitoring Board.

STATISTICAL METHODS. Statistical analyses were pre-specified. Baseline demographic, CAD risk factors, angina typicality, and ACC/AHA guideline indications for ICA were summarized as frequencies and proportions for categorical variables and mean $\pm$ SD for continuous variables. Categorical comparisons were made using chi-square tests, whereas

continuous variables were compared using Student's *t*-tests.

The null hypothesis was that the ratio of hazard rates of the direct referral arm compared with the selective referral arm (≥ 1.33). Additional comparisons of the selective and direct referral arms used a time-to-first MACE analysis using a Cox proportional-hazards model. MACE-free survival probabilities were calculated using Kaplan-Meier survival curves. ICA normalcy was calculated using the first ICA that occurred within 1 year of enrollment. Modeled radiation dose (in millisieverts) was estimated for the initial test using the dose-length product for CCTA and published survey data for ICA (15-17). Finally, we modeled diagnostic cost using a hybrid approach in which utilization data (from Table 1) were multiplied by published cost estimates, including Medicare payment rates for fiscal year 2016 (18). All analyses were performed with SAS 9.4 (SAS Institute Inc., Cary, North Carolina).

RESULTS

DESCRIPTIVE STATISTICS. Enrollment was initiated on December 2012 and completed on July 2015. A total of 1,611 patients were randomized, with follow-up data available for 1,503 patients (90.3%) at the time of study completion (Figure 1). Among the 823 patients randomized to the selective referral strategy, 784 underwent CCTA, and among the 808 patients randomized to the direct referral strategy, 719 underwent ICA. Additional analyses can found in the Supplemental Appendix.

The mean age of the study population was 60 ± 12 years; 46.2% were women (Table 2). CAD risk factors were prevalent: 58% were hypertensive, 34% were dyslipidemic, 28% had diabetes, and 30% were current or former smokers. The pre-test likelihood of CAD was largely intermediate risk. Most patients were symptomatic, with typical and atypical angina reported in 31% and 40% of patients, respectively. On the index procedure, the prevalence of obstructive CAD was 28% for CCTA and 39% for the direct referral to ICA arm ($p < 0.001$).

MACE RATES. The median follow-up was 12.3 months (interquartile range: 11.7 to 13.2 months). During follow-up, 4.6% ($n = 36$) of the selective referral arm and 4.6% ($n = 33$) of the direct referral arm experienced MACEs ($p = 0.99$) (Table 3, Figure 2). For the primary outcome, the hazard ratio was 0.99 (95% confidence interval: 0.66 to 1.47; $p = 0.026$ for the 1-sided test of noninferiority). Pre-specified

TABLE 2 Baseline Characteristics of the Patients Enrolled in the CONSERVE Trial

	Selective Referral Strategy (n = 784)	Direct Referral Strategy (n = 719)
Age, yrs	59.9 $\pm$ 12.1	60.8 $\pm$ 11.5
Sex		
Female	378 (48.3)	316 (43.9)
Race/ethnicity		
Asian	671 (85.6)	604 (84.0)
White	103 (13.1)	102 (14.2)
African American	4 (0.5)	10 (1.4)
Hispanic	4 (0.5)	3 (0.4)
Unknown	2 (0.3)	0 (0.0)
Body mass index (kg/m ²)	25.6 $\pm$ 4.0	25.7 $\pm$ 4.0
Risk factors		
Hypertension	446 (56.9)	424 (59.0)
Dyslipidemia	259 (33.0)	249 (34.6)
Diabetes	203 (25.9)	212 (29.5)
Current smoker (≤ 3 months)	108 (13.8)	98 (13.6)
Former smoker (> 3 months)	126 (16.1)	124 (17.2)
Premature family history of CAD	67 (8.5)	57 (7.9)
Pre-test likelihood of obstructive CAD, %	51 $\pm$ 30	52 $\pm$ 30
Angina type		
Typical angina	243 (31.0)	216 (30.1)
Atypical angina	315 (40.2)	278 (38.7)
Noncardiac chest pain	18 (2.3)	10 (1.4)
Asymptomatic	90 (11.5)	76 (10.6)
Other symptoms	117 (14.9)	138 (19.2)
Dyspnea	106 (13.5)	127 (17.7)
Palpitations	5 (0.6)	6 (0.8)
Dizziness or syncope	6 (0.7)	4 (0.5)
Arrhythmia	0 (0.0)	1 (0.1)
Nonemergent indications for ICA		
NIST findings	227 (29.0)	201 (28.0)
Symptomatic with abnormal NIST	183 (23.4)	165 (23.0)
Asymptomatic with > 2 CAD risk factors and an abnormal NIST	39 (5.0)	32 (4.5)
Worsening NIST	5 (0.6)	4 (0.6)
Symptoms	533 (68.0)	477 (66.3)
Persistent angina despite optimized medical therapy	201 (25.6)	205 (28.5)
Any angina, not evaluable by NIST	286 (36.5)	231 (32.1)
Heart failure with normal ejection fraction of unknown etiology	46 (5.9)	41 (5.7)
Other clinical indications	24 (3.1)	41 (5.7)
Low-risk surgery, stable angina, high-risk surgery with equivocal NIST or vascular surgery with ≥ 2 risk factors	17 (2.2)	19 (2.6)
Asymptomatic, high-risk occupation or other miscellaneous	7 (0.9)	22 (3.1)
No. of vessels with obstructive CAD $\geq 50\%$ on the index procedure		
No CAD	269 (34.4)	174 (24.2)
Nonobstructive CAD	294 (37.6)	265 (36.9)
1-vessel CAD	126 (16.1)	127 (17.7)
2-vessel CAD	52 (6.6)	82 (11.4)
3-vessel or left main stenosis	41 (5.2)	71 (9.9)

Values are mean $\pm$ SD or n (%).

ICA = invasive coronary angiography; NIST = non-invasive stress testing; other abbreviations as Table 1.

TABLE 3 MACE Rate by Randomization to Selective Referral Versus Direct Referral to ICA

	Selective Referral (n = 784)	Direct Referral (n = 719)	Hazard Ratio (95% CI)	p Value
Any MACE (primary endpoint)	36 (4.6)	33 (4.6)	0.99 (0.62-1.58)	0.99
Death	2 (0.3)	1 (0.1)		
Acute myocardial infarction	2 (0.3)	2 (0.3)		
Unstable angina	9 (1.1)	8 (1.1)		
Cardiac hospitalization	33 (4.2)	31 (4.3)		
Stroke	2 (0.3)	2 (0.3)		
Composite of MACE or major bleed	36 (4.6)	35 (4.9)	0.93 (0.58-1.48)	0.75
Major bleed	0 (0.0)	2 (0.3)		
Need for major transfusion	0 (0.0)	1 (0.1)		

Values are n (%) unless otherwise indicated.

CI = confidence interval; MACE = major adverse cardiovascular event; other abbreviation as in Table 2.

secondary clinical endpoints were rare, with major bleeding occurring in 2 patients in the direct referral arm that required 1 major transfusion. No bleeding or requirement for transfusion occurred in the selective referral arm (Table 3). There was no significant difference in the secondary clinical endpoints (4.6% vs 4.5%, $p = 0.48$) (Supplemental Appendix).

FOLLOW-UP INVASIVE AND NONINVASIVE TESTING. The rate of follow-up ICA was lower in the selective referral group; 23% of patients underwent follow-up ICA compared with 100% of the direct referral patients. An additional 4% of patients in this latter arm underwent repeat ICA (Table 1). Similarly, rates of PCI were lower in the selective referral patients (11% vs. 15% in the direct referral arm; $p < 0.001$) (Table 1). In contrast, the proportion of patients who underwent any downstream exercise

electrocardiography, stress nuclear, or stress echocardiography was higher in the selective referral arm (14% vs. 11%; $p = 0.04$). No differences were noted in the proportion of patients who were reported as free from angina at the completion of follow-up (60% in the selective referral arm vs. 62% in the direct referral arm, $p = 0.52$).

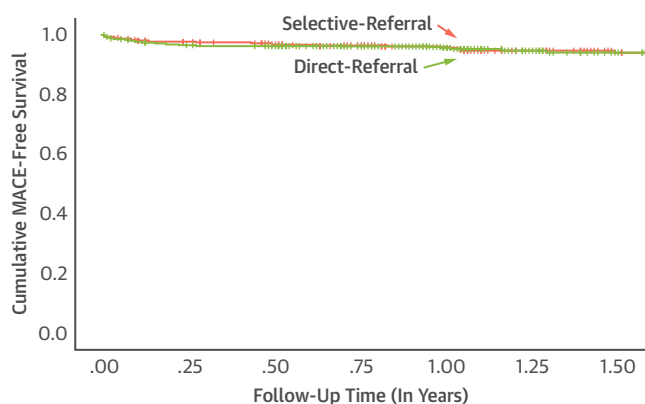
DETECTION OF OBSTRUCTIVE CAD AT ICA. The ICA normalcy rate, defined as no obstructive CAD, was 25% (24 of 114 patients) in the selective referral arm compared with 61% (439 of 719 patients) in the direct referral arm ($p < 0.001$). Among the 219 patients identified with obstructive CAD by CCTA in the selective referral arm, only 52% went on to ICA during follow-up; a lower proportion of patients with obstructive CAD by the index study underwent revascularization in the selective referral group (34% of 219 vs. 43% of 280; $p = 0.04$). Of these patients, functional evaluation by stress testing or fractional flow reserve was performed before revascularization in 73 of 74 (99%) patients in the selective referral group compared with 113 of 121 (93%) patients in the direct referral group ($p < 0.001$). Although higher rates of follow-up testing were reported in the selective referral arm, cumulative diagnostic test costs remained 57% lower in the selective referral arm, which was solely due to the higher upfront costs associated with ICA (Figure 3).

RADIATION EXPOSURE. The median effective dose for diagnostic ICA is 7 to 9 mSv (16,17). By comparison, the observed CCTA median effective dose in the CONSERVE trial was 6.5 mSv.

DISCUSSION

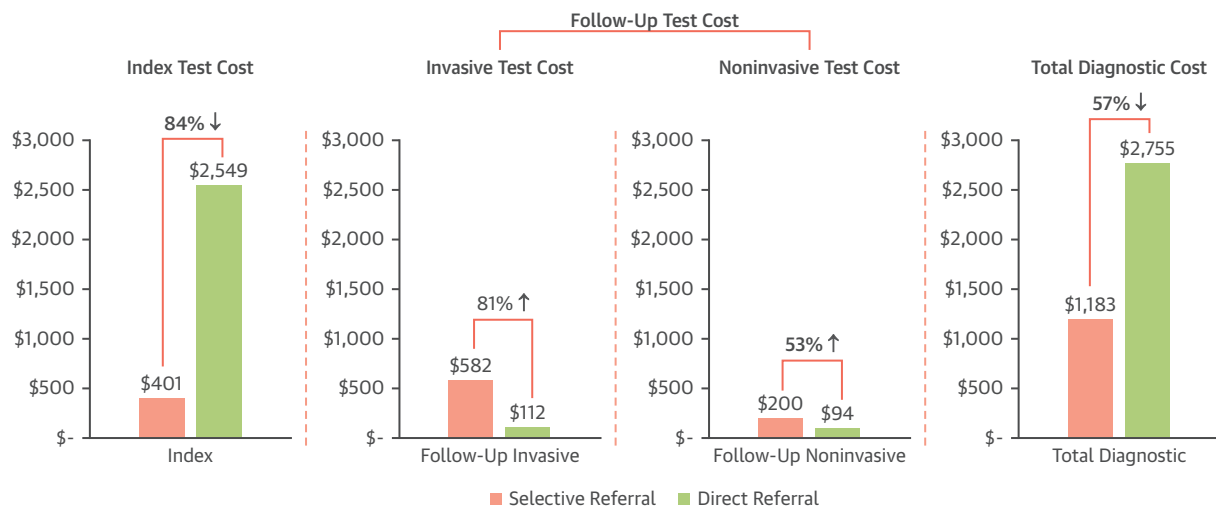
The CONSERVE trial was a multinational, randomized clinical trial with a pragmatic strategy design for patients with stable but suspected CAD who were eligible based on guideline indications of non-emergent ICA. In this trial, we observed that a selective referral strategy, in which decisions to proceed to ICA were informed by CCTA findings, met the noninferiority multiplicative margin of 1.33 ($p = 0.026$), with similar MACE event rates of 4.6% in both arms. However, additional observations revealed that compared with patients in the direct referral group, 77% of patients in the selective referral group avoided ICA, and, as such, diagnostic evaluation costs were reduced by 57%. In addition, a strategy of CCTA followed by selective ICA significantly improved the diagnostic yield, with an improved detection of obstructive CAD compared with those who underwent direct ICA. This enriched yield of a CCTA arm was expected based on this

FIGURE 2 MACE-Free Survival



Kaplan-Meier major adverse cardiovascular event (MACE)-free survival by randomization to selective referral versus direct referral to invasive coronary angiography ($p = 0.95$).

FIGURE 3 Diagnostic Procedural Cost



Estimated cost for diagnostic procedures in the CONSERVE trial: a comparison of selective- versus direct-referral to invasive coronary angiography. Costs are presented as average per patient costs on the index test, follow-up (invasive and noninvasive) testing, and total diagnostic costs. A comparison of costs in the selective referral arm versus the direct referral arm is presented at the top of each set of the columns (e.g., index costs were 84% lower for the selective referral arm versus the direct referral arm of the trial).

selective testing approach because patients proceeding to ICA would be more often those with evidence of obstructive CAD.

COMPARATIVE EVIDENCE FROM OTHER TRIALS AND REGISTRIES. These data supported that CCTA exhibits excellent diagnostic performance and provides, for the first time, a demonstration of a strategy of care not previously illustrated in previous randomized trials. Previous pragmatic trials largely compared CCTA with functional testing, such as the National Institutes of Health-National Heart, Lung, and Blood Institute PROMISE (Prospective Multi-center Imaging Study for Evaluation of Chest Pain Trial) and other trials (19–23). Our results contrasted with previous trials, which generally demonstrated increased revascularization in the CCTA groups compared with functional testing. In contrast, the CONSERVE trial evaluated CCTA in higher risk patient groups at a later stage in clinical decision-making (because most patients were enrolled following an abnormal stress test or for persistent or worsening symptoms despite medical therapy) as a “gatekeeper” to identify candidates who might have safely avoided ICA (19). A similar gatekeeper strategy was reported in the Cost-Effectiveness of functional Cardiac Testing in the diagnosis and management of CAD trial that revealed ICA was reduced by 20% to 25% in the 898 patients who underwent stress

imaging compared with direct referral to ICA. In addition, the single-center Coronary Artery Disease Management trial of 340 patients also evaluated CCTA as a gatekeeper to ICA for a narrower range of indications restricted to a chest pain evaluation (24). This report by Dewey et al. (24) noted reductions in ICA of >80%. However, they used a shorter duration of follow-up through only 48 h to assess near-term safety of major procedural complications ($p = 1.00$). Our trial could be contrasted with this previous finding because we broadened enrollment to patients with diverse indications and from multiple centers around the world, and extended follow-up to 12 months, which was a sufficient duration to capture the entire episode of care.

Our low event rate was not atypical from current a priori designed clinical trials, but it did limit our strength of evidence and causal statements that might be inferred from the CONSERVE trial. Suggested inferences from our trial should support the documented similar safety profile for a selective referral strategy guided by CCTA findings compared with direct referral to ICA in largely lower risk patients referred for nonemergent indications. The reduction in the use of ICA in the selective referral arm guided by CCTA findings was noteworthy, and its findings might have applicability to current diagnostic testing approaches. Moreover, our data were in accord with randomized trials that examined the

safety of an initial trial of optimal medical therapy versus an angiographically-guided coronary revascularization strategy (9,25).

Often, a criticism of CCTA is the potential for overuse of ICA, but in the CONSERVE trial, post-test management relied upon ischemia-guided care and resulted in the use of stress testing to further select candidates for ICA and revascularization. Our study demonstrated an overall 28% reduction in coronary revascularization rates in the selective referral group, with increased stress testing and decreased revascularization even among those with obstructive CAD by the index study. This exhibited the “diagnostic-therapeutic cascade,” in which the temporal coupling of ICA with the ability to perform revascularization resulted in more liberal use of ad hoc PCI (26).

ENRICHING THE DIAGNOSTIC YIELD GUIDED BY CCTA. The CONSERVE trial had clinical applicability for patients referred for nonemergent ICA because a selective strategy guided by CCTA could avoid approximately 4 of 5 ICA procedures, and reduce the rate of ICA normalcy by nearly two-thirds. We used a simple diagnostic test that was interpreted on site by treating site physicians, required no central core laboratory analysis, and was applicable to a wider patient population who were referred for ICA. From a policy perspective, implementation of a selective referral strategy might result in markedly fewer invasive diagnostic and revascularization procedures, with increased noninvasive testing. Our results might provide insights as to the potential magnitude of impact of the updated United Kingdom National Institute for Clinical Excellence (UK-NICE) guidelines, which recommend CCTA as the first-line test for coronary artery disease (27). We proposed that results from the CONSERVE trial are generalizable to contemporaneous ICA for several reasons. First, the patient indications used for inclusion were still considered appropriate by contemporary professional societal guidance documents, and reflected common and routine practices across our varied enrolling centers (4). Moreover, post-CCTA often relied on noninvasive stress testing to further refine the selective referral arm and inform the use of ICA. Approximately 40% of patients in the ACC CathPCI registry underwent ICA without previous stress testing (28). This registry reported a high rate of no obstructive CAD and suggested that alternative approaches should be used to avert unnecessary ICA, if possible. Our results also extended the findings from the PLATFORM (Prospective Longitudinal Trial of FFR-CT: Outcome and Resource Impacts) study,

which was an observational registry that enrolled a subgroup of patients who were candidates for ICA (29). From the PLATFORM ICA cohort, a combined strategy of CCTA in addition to noninvasive fractional flow reserve resulted in an ICA cancellation rate of 61% and a marked reduction in the finding of no obstructive CAD at ICA. However, in this study, a CCTA-alone arm was not evaluated. In this regard, the CONSERVE findings offered insight into the efficacy of CCTA alone, to serve as an efficient gatekeeper of ICA, with a 77% reduction in ICA and a similar 1-year safety profile of few reported major adverse clinical events, as observed in the PLATFORM study. The present study results suggested that, at least for the purposes of guiding referral to ICA, that CCTA alone might represent an effective approach.

STUDY LIMITATIONS. Our pragmatic trial was generalizable to real-world clinical practice patterns, with referral decisions to ICA and revascularization based on the overall judgment of site physicians from a wide array of international sites, as opposed to protocolized care that would increase uniformity within the trial. Our trial was typical of most in which accrual of lower risk patients resulted in lower than expected MACE rates. We performed a post hoc power calculation, and based on the reported MACE rate of 4.6%, the available power was 62% ($\alpha = 0.05$) to detect noninferiority between the randomized arms of our trial. The CONSERVE trial was also powered to include “softer” endpoints; a trial for the use of only “hard” clinical outcomes would have required a substantially larger sample size because of the identical frequency of adverse clinical events in each trial arm. For any trial, patients who are lost to follow-up are an important consideration. We compared those patients included in the present analysis and compared with those who were lost, which revealed similarities in presenting symptoms, risk factor prevalence, and pre-test likelihood of CAD (Supplemental Appendix). The lower rate of observed obstructive CAD might challenge whether direct referral should have been an option, but indications for referral to ICA were in accordance to societal guidelines, and reflected the high rate of normal ICA often quoted in the published literature (5,30). Finally, because of the null results of the Veteran Affairs–sponsored Clinical Outcomes Using Revascularization and Aggressive Drug Evaluation trial, some might argue that direct referral should be compared with no testing rather than to a selective referral strategy. Further investigation now appears warranted to address this question, (9).

CONCLUSIONS

In this trial of stable patients with suspected CAD who were referred for guideline-directed ICA, a selective referral strategy was found to result in similar MACE rates at 1 year of follow-up compared with a direct-referral strategy. Growing evidence supports that noninvasive anatomic testing by CCTA alone, as a gatekeeper procedure, may prove advantageous in promptly and accurately identifying candidates for downstream procedures. These data and similarly relevant findings from other randomized trials call for revisions to the current ischemic heart disease guidelines for the evaluation of patients with stable ischemic heart disease (3).

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PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE: Evidence supports that most patients undergoing elective ICA do not have obstructive CAD. We compared 1-year MACE-free survival and downstream resource use of a selective referral strategy using CCTA compared with a direct referral strategy to ICA. Our results noted similar 1-year MACE rates ($p = 0.95$). The selective referral strategy was noninferior to the direct referral strategy at a margin of 1.33 ($p = 0.026$), albeit with reduced statistical power. In patients who underwent initial CCTA or the selective referral arm, we observed a marked reduction in the use of follow-up ICA (by $\sim 80\%$) and diagnostic cost savings of 57%. These results supported the use of CCTA as a front-line diagnostic procedure, followed by selective referral to ICA of a greater proportion of patients with obstructive CAD.

TRANSLATIONAL OUTLOOK: The CONSERVE trial aimed to evaluate, in a randomized trial setting, the potential to safely shift lower risk patients eligible for elective ICA to less expensive CCTA. Because of the high rate of ICA across the United States, the implications of findings from the CONSERVE trial could expedite a patient's diagnosis of CAD while providing for a prompt and efficient diagnostic pathway guided by CCTA findings.

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KEY WORDS coronary computed tomographic angiography, invasive coronary angiography, major adverse cardiac events, stable ischemic heart disease

APPENDIX For the list of participating centers, an expanded Methods section, and a supplemental table and figure, please see the online version of this paper.