JACC: CARDIOVASCULAR IMAGING
VOL. 9, NO. 9, 2016

ISSN 1936-878X/$36.00
PUBLISHED BY ELSEVIER
http://dx.doi.org/10.1016/j.jcmg.2015.09.028

CT Angiography for the Detection of Coronary Artery Stenoses in Patients Referred for Cardiac Valve Surgery

Systematic Review and Meta-Analysis

Maksymilian P. Opolski, MD,[a] Adam D. Staruch, MD,[a] Michal Jakubczyk, PhD,[b] James K. Min, MD,[c] Heidi Gransar, MS,[d] Michal Staruch, MS,[e] Adam Witkowski, MD,[a] Cezary Kepka, MD,[f] Won-Keun Kim, MD,[g] Christian W. Hamm, MD,[g,h] Helge Möllmann, MD,[g] Stephan Achenbach, MD[i]

JACC: CARDIOVASCULAR IMAGING CME

CME Editor: Ragavendra R. Baliga, MD.

This article has been selected as this issue's CME activity, available online at http://www.acc.org/jacc-journals-cme by selecting the CME tab on the top navigation bar.

Accreditation and Designation Statement

The American College of Cardiology Foundation (ACCF) is accredited by the Accreditation Council for Continuing Medical Education (ACCME) to provide continuing medical education for physicians.

The ACCF designates this Journal-based CME activity for a maximum of 1 *AMA PRA Category 1 Credit(s)* ™. Physicians should only claim credit commensurate with the extent of their participation in the activity.

Method of Participation and Receipt of CME Certificate

To obtain credit for this CME activity, you must:

1. Be an ACC member or *JACC: Cardiovascular Imaging subscriber*.
2. Carefully read the CME-designated article available online and in this issue of the journal.
3. Answer the post-test questions. At least 2 out of the 3 questions provided must be answered correctly to obtain CME credit.
4. Complete a brief evaluation.
5. Claim your CME credit and receive your certificate electronically by following the instructions given at the conclusion of the activity.

CME Objective for This Article: After reading this article the reader should be able to: 1) review the evaluation and management of coronary artery disease in patients with valvular heart disease scheduled for cardiac valve surgery; 2) understand the relationship between the diagnostic accuracy of noninvasive coronary CTA and the type of valvular heart disease as well as the technical specifications of the CT scanner; and 3) review the role of coronary CTA as a gatekeeper to other diagnostic examinations in patients with suspected coronary artery disease.

CME Editor Disclosure: *JACC: Cardiovascular Imaging* CME Editor Ragavendra R. Baliga, MD, has reported that he has no relationships to disclose.

Author Disclosure: Dr. Opolski has received a scholarship from the Foundation for Polish Science. Dr. Min has served on the medical advisory boards of GE Healthcare, Arineta, AstraZeneca, and Bristol-Myers Squibb; serves on the Speakers Bureau of GE Healthcare; received research support from GE Healthcare, Vital Images, and Phillips Healthcare; and received grants from the National Institutes of Health/National Heart, Lung and Blood Institute (R01HL111141, R01HL115150, R01HL118019, and U01HL105907) and from the Qatar National Research Foundation (NPRP09-370-3-089). Dr. Kim has served as a proctor for Symetis SA and St. Jude Medical. Dr. Achenbach has received grant support and serves on the Speakers Bureau of Siemens Healthcare. All other authors have reported that they have no relationships relevant to the contents of this paper to disclose.

Medium of Participation: Print (article only); online (article and quiz).

CME Term of Approval

Issue Date: September 2016
Expiration Date: August 31, 2017

From the [a]Department of Interventional Cardiology and Angiology, Institute of Cardiology, Warsaw, Poland; [b]Institute of Econometrics, Warsaw School of Economics, Warsaw, Poland; [c]Department of Radiology, The New York-Presbyterian Hospital and Weill Cornell Medical College, New York, New York; [d]Department of Imaging and Division of Cardiology, Department of Medicine, Cedars-Sinai Heart Institute, Cedars-Sinai Medical Center, Los Angeles, California; [e]Medical University of Warsaw, Warsaw, Poland; [f]Department of Coronary and Structural Heart Diseases, Institute of Cardiology, Warsaw, Poland; [g]Department of Cardiology, Kerckhoff Heart Center, Bad Nauheim, Germany; [h]Department of Cardiology and Angiology, Justus-Liebig University of Giessen, Giessen, Germany; and the [i]Department of Internal Medicine 2 (Cardiology), University of Erlangen, Erlangen, Germany. Dr. Opolski has received a scholarship from the Foundation for Polish Science. Dr. Min has served on the medical advisory boards of GE Healthcare, Arineta, AstraZeneca, and Bristol-Myers Squibb; serves on the Speakers Bureau of GE Healthcare; received research support from GE Healthcare, Vital Images, and Phillips Healthcare; and received grants from the National Institutes of Health/National Heart, Lung and Blood Institute (R01HL111141, R01HL115150, R01HL118019, and U01HL105907) and from the Qatar National Research Foundation (NPRP09-370-3-089). Dr. Kim has served as a proctor for Symetis SA and St. Jude Medical. Dr. Achenbach has received grant support and serves on the Speakers Bureau of Siemens Healthcare. All other authors have reported that they have no relationships relevant to the contents of this paper to disclose. João Lima, MD, served as Guest Editor for this paper.

Manuscript received September 8, 2015; accepted September 24, 2015.

JACC: CARDIOVASCULAR IMAGING, VOL. 9, NO. 9, 2016
SEPTEMBER 2016:1059–70

CT Angiography for the Detection of Coronary Artery Stenoses in Patients Referred for Cardiac Valve Surgery

Systematic Review and Meta-Analysis

Maksymilian P. Opolski, MD,[a] Adam D. Staruch, MD,[a] Michal Jakubczyk, PhD,[b] James K. Min, MD,[c] Heidi Gransar, MS,[d] Michal Staruch, MS,[e] Adam Witkowski, MD,[a] Cezary Kepka, MD,[f] Won-Keun Kim, MD,[g] Christian W. Hamm, MD,[g,h] Helge Möllmann, MD,[g] Stephan Achenbach, MD[i]

ABSTRACT

OBJECTIVES This study aimed to evaluate the diagnostic accuracy of coronary computed tomography angiography (CTA) for detecting coronary artery stenoses in patients with valvular heart disease undergoing valve surgery.

BACKGROUND Coronary CTA is currently not routinely recommended for detecting coronary artery stenoses before cardiac valve surgery. However, recent improvements in computed tomography technology may enable the identification of the most appropriate candidates for coronary CTA before valve surgery.

METHODS A systematic review was performed of PubMed, EMBASE, and the Cochrane databases for all studies that used ≥16-detector row computed tomography scanning to perform coronary CTA in patients with valvular heart disease scheduled for valve surgery and validated the results against invasive angiography. Summary diagnostic accuracies were calculated by using a bivariate random effects model, and a generalized linear mixed model was applied for heterogeneity analysis.

RESULTS Seventeen studies analyzing 1,107 patients and 12,851 coronary segments were included. Patient-based analysis revealed a pooled sensitivity of 93% (95% confidence interval [CI]: 86 to 97), specificity of 89% (95% CI: 86 to 91), a negative likelihood ratio (LR) of 0.07 (95% CI: 0.04 to 0.16), and a positive LR of 8.44 (95% CI: 6.49 to 10.99) for coronary CTA to identify individuals with stenosis ≥50%. Specificity and positive LR were higher in patients without aortic stenosis (AS) versus those with AS (96% vs. 87% and 21.2 vs. 7.4, respectively), as well as with ≥64 detectors versus <64 detectors (90% vs. 86% and 9.5 vs. 6.9). Heterogeneity analysis revealed a significant impact of AS and the number of detectors on specificity of CTA.

CONCLUSIONS Coronary CTA using currently available technology is a reliable imaging alternative to invasive angiography with excellent sensitivity and negative LR for the detection of significant coronary stenoses in patients undergoing cardiac valve surgery. The specificity of coronary CTA may be decreased against the background of AS (Computed Tomography Angiography for the Detection of Coronary Artery Disease in Patients Referred for Cardiac Valve Surgery: A Meta-Analysis; CRD42015016213) (J Am Coll Cardiol Img 2016;9:1059–70) © 2016 by the American College of Cardiology Foundation.

Valvular heart disease (VHD) that requires surgery is common in industrialized countries (1). In the majority of such patients, pre-operative evaluation for coronary artery disease (CAD) with invasive coronary angiography (ICA) is recommended (1,2), although most patients are found to have no significant coronary stenoses (3). In recent years, several studies have tested the diagnostic performance of coronary computed tomography angiography (CTA) in patients undergoing cardiac valvular surgical treatment (4–20). However, all of these studies were limited by small sample sizes in single centers, which may introduce bias that obfuscates the actual diagnostic performance of coronary CTA compared with ICA. We thus performed a comprehensive meta-analysis of all available studies comparing coronary CTA with ICA for the detection of significant coronary stenoses in patients scheduled for elective valve surgery.

METHODS

SEARCH STRATEGY. This study followed the protocol specified in the Preferred Reporting Items for Systematic Reviews and Meta-analyses statement (21). Database searches for papers reporting on patients with VHD, pre-operatively examined by using coronary CTA and invasive angiography, were performed by 2 independent reviewers (A.D.S. and M.S.). The PubMed, EMBASE, and Cochrane Library databases were used. We used the search terms and corresponding Medical Subject Headings for “computed tomography” AND “heart valve disease.” The search was limited to English-language studies of humans and adults (>18 years of age) in peer-reviewed journals up to July 2015. The references of all papers retrieved were also searched. All studies were carefully examined to exclude potential duplicates or overlapping data. Trials in abstract form without a published manuscript were excluded.

SEE PAGE 1071

ELIGIBILITY CRITERIA. We included a study if: 1) it used at least 16-slice computed tomography (CT) scan as a diagnostic test for the detection of coronary stenoses in the pre-operative assessment of patients referred for heart valve surgery; 2) it selected 50% diameter stenosis as the cut-off criterion for significant CAD using ICA as the standard of reference; and 3) absolute numbers of true-positive, true-negative, false-positive, and false-negative results were provided or could be derived at the per-patient or per-segment level. Studies were excluded if they were performed in patients with aortic valve stenosis (AS) referred for transcatheter aortic valve replacement.

DATA EXTRACTION AND QUALITY ASSESSMENT. Data extraction of the selected studies was performed by 2 independent investigators (M.P.O. and A.D.S) using a standardized data extraction form. The form included the following characteristics of each trial: first author, year of publication, and journal; study population characteristics, including sample size (number of subjects screened and evaluated with both tests, and number of subjects excluded), sex, mean age, mean body mass index, type of VHD, and mean heart rate during CTA scanning; prevalence of CAD; and technical characteristics of the intervention (number of detector rows, effective radiation dose, beta-blocker or ivabradine use, nitroglycerin use, and amount of contrast agent). Differences between reviewers were resolved by consensus whenever necessary. The methodological quality of included studies was assessed by 2 independent reviewers (M.P.O. and A.D.S.) using the modified Quality Assessment of Studies of Diagnostic Accuracy Included in Systematic Reviews-2 criteria (22), and discrepancies were resolved by consensus.

STATISTICAL ANALYSIS. Categorical variables from individual studies are presented as frequency (%), and continuous variables are presented as mean ± SD. Measures of diagnostic accuracy are reported as point estimates with 95% confidence intervals (CIs). The primary analysis was performed at the per-patient level, with secondary analyses evaluating the available per-segment and per-vessel data. Sensitivity, specificity, and positive and negative likelihood ratios (LRs) were computed based on the true-positive, true-negative, false-positive, and false-negative rates for each study. Both LRs are independent from prevalence rates, and there is consensus that a positive LR >10 and a negative LR <0.1 provide reliable evidence of satisfactory diagnostic performance (23). The ratio of positive LR to negative LR

ABBREVIATIONS AND ACRONYMS

AS = aortic valve stenosis

CAD = coronary artery disease

CI = confidence interval

CTA = computed tomography angiography

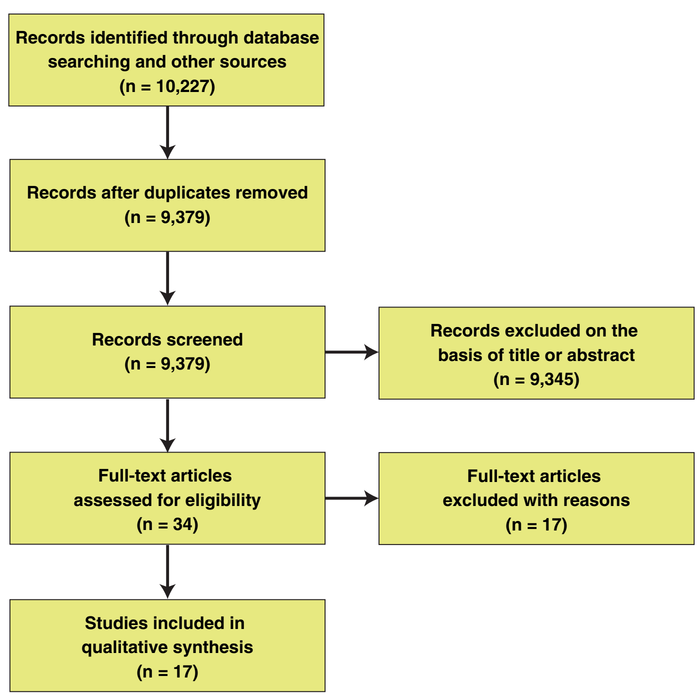
ICA = invasive coronary angiography

LR = likelihood ratio

ROC = receiver-operating characteristic

VHD = valvular heart disease

FIGURE 1 Flow Diagram of the Review Process



Seventeen articles were excluded from the final analysis due to incomplete or unsystematic data.

TABLE 1 Baseline Characteristics of Included Studies

First Author (Ref. #), Year	Detectors	Patients (Initial Group)	Excluded Patients	Nonevaluable Segments (%)	Valve Disease (%)	Male (%)	Age (yrs)	BMI (kg/m²)	HR (beats/min)	Use of Beta-Blocker or Ivabradine	Use of Nitrate	Effective Radiation Dose (mSv)	Contrast (ml)	CAD Prevalence (%)	Analysis Type
Bettencourt et al. (4), 2009	64	237 (237)	0	5.2 (included in analysis)	AR, 14 AS, 68 MR, 17 MS, 11	48	67	27	67	Yes	Yes	12.5	80–100	18	Patient, vessel, segment
Bonmassari et al. (5), 2006	16	33 (33)	11	13 (excluded from analysis)	AR, 22 AS, 48 MR, 27 MS, 3	70	70	NR	65	No	NR	NR	100–125	42	Patient, segment
Gilard et al. (6), 2006	16	55 (55)	0	NA	AS, 100	38	70	NR	66	Yes	NR	NR	120	20	Patient
Goffinet et al. (7), 2009	64	38 (42)	0	NA	AR, 100	81	54	NR	67	NR	NR	14.9	90	7	Patient
Jakamy et al. (8), 2012	64	48 (48)	0	1.4 (included in analysis)	AR, 38 AS, 32 MR, 21 MS, 9	62	63	NR	NR	Yes	NR	NR	120	27	Patient, vessel, segment
Laissy et al. (9), 2007	16	40 (40)	0	NR	AS, 100	63	68	NR	65	No	NR	15–18	100–120	33	Patient, segment
Larsen et al., (10), 2013	64 and 320	181 (181)	10	NR	AS, 100	59	71	26	65	Yes	Yes	19–26	NR	47	Patient
Lee at al. (11), 2012	DS-64	22 (262*)	0	10 (included in analysis)	AR, 44* AS, 56*	58*	54*	23*	68*	Yes	Yes	10.3	100–110	95	Vessel, segment
Manghat et al. (12), 2006	16	36 (40)	1	8 (excluded from analysis)	AS, 100	67	71	26	62	Yes	NR	NR	100	42	Patient, segment
Meijboom et al. (13), 2006	64	70 (70)	0	NR	AR, 13 AS, 44 MR, 34 MS, 3 TR, 1 TS, 1 PR, 3	70	63	NR	60	Yes	NR	15.2–21.4	100	26	Patient, vessel, segment
Pontone et al. (14), 2012	64	40 (80)	0	1 (included in analysis)	MR, 100	50	61	23	60	Yes	NR	2.55	NR	17	Patient, segment
Pouleur et al. (15), 2007	40	82 (82)	0	1.5 (included in analysis)	AR, 34 AS, 37 MR, 29	64	62	NR	69	Yes	NR	13.9	120	18	Patient, vessel, segment
Reant, et al. (16), 2006	16	40 (40)	0	23.7 (excluded from analysis)	AR, 10 AS, 68 MR, 15 MS, 7	50	70	26	65	Yes†	NR	NR	80	33	Patient, segment
Rodríguez-Palomares et al. (17), 2011	16	106 (106)	0	3.2 (excluded from analysis)	AR, 14 AS, 62 MR, 16 MS, 4 AVD/MVD, 4§	60	67	28	62	Yes	Yes‡	8–12	80–100	30	Patient, vessel, segment

Continued on the next page

TABLE 1 Continued

First Author (Ref. #), Year	Detectors	Patients (Initial Group)	Excluded Patients	Nonevaluable Segments (%)	Valve Disease (%)	Male (%)	Age (yrs)	BMI (kg/m^2)	HR (beats/min)	Use of Beta-Blocker or Ivabradine	Use of Nitrate	Effective Radiation Dose (mSv)	Contrast (ml)	CAD Prevalence (%)	Analysis Type
Scheffel et al. (18), 2007	64	50 (50)	0	1.8 (excluded from analysis)	AR, 100	76	54	25	65	Yes	NR	8.8–13.6	90	26	Patient, vessel, segment
Stagnaro et al. (19), 2009	64	55 (55)	2	NR	AR, 16 AS, 56 MR, 25 MS, 2	53	74	NR	NR	Yes	No	16–23	90–110	36‖	Patient, vessel, segment
Takaoka et al. (20), 2013	320	20 (21)	0	NR	TR, 100	52	68	NR	NR	NR	NR	NR	95	15	Patient, segment

Concomitant aortic valve stenosis (AS) and aortic valve regurgitation were regarded as AS; concomitant mitral valve stenosis (MS) and mitral regurgitation (MR) were regarded as MS. *The values are presented for the initial but not analyzed group of patients. †No beta-blockers were administered in case of AS or left ventricular systolic dysfunction. ‡No nitrates were administered in case of AS. §These patients were reported to have either aortic valve disease (AVD) or mitral valve disease (without further specification of valve disease). ‖The prevalence of significant coronary artery disease (CAD) is calculated for patients with evaluable computed tomography images.

AR = aortic regurgitation; BMI = body mass index; DS = dual-source; HR = heart rate; MVD = mitral valve disease; NA = not applicable; NR = not reported; PR = pulmonary regurgitation; TR = tricuspid regurgitation; TS = tricuspid stenosis.

was combined in a single global accuracy measure, the diagnostic odds ratio (24).

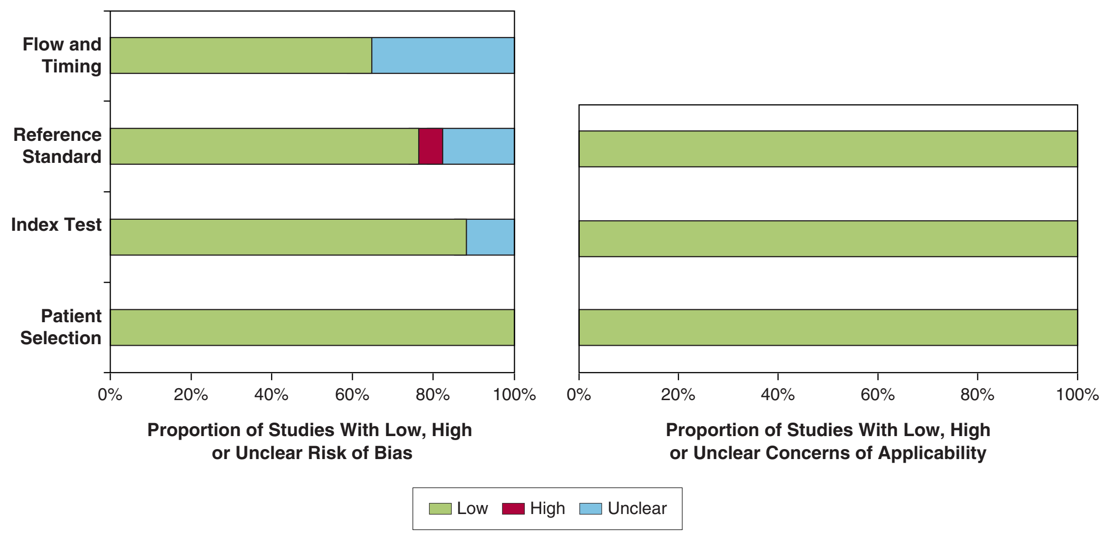
Summary sensitivity and specificity, positive and negative LRs, and diagnostic odds ratios were estimated by using a bivariate random effects model. This approach assumes bivariate normal distributions for the logit transformations of sensitivity and specificity from individual studies (25,26). In addition, the hierarchical summary receiver-operating characteristic (ROC) curve presenting the point estimates for each study, the joint ROC curve, and the pooled characteristics, including the 95% confidence region and the 95% prediction region, was constructed (27).

Sources of clinical and statistical heterogeneity were explored at the patient level by using the bivariate generalized linear mixed model (2 outcomes, sensitivity and specificity, modeled jointly) as previously described (28,29). We assessed the following covariates, which were selected a priori: sample size (divided by a median of 50 patients), average age of patients (divided by a median of 67 years), percentage of male subjects (divided by a median of 60%), number of CT detector rows (defined as either <64 detectors or ≥64 detectors), and the presence of any patient with AS. Publication bias was assessed for each analysis by using the Deeks test (30). The κ statistic was calculated for the inter-rater reliability between 2 investigators for quality assessment. Statistical computations were performed using Stata version 14 (Stata Corporation, College Station, Texas) and R version 3.1.0 statistical software (R Foundation for Statistical Computing, Vienna, Austria). Significance testing was at the 2-tailed 0.05 level.

RESULTS

STUDY SELECTION. After exclusion of duplicates, the systematic review retrieved 9,379 potentially relevant papers that were screened according to title or abstract for possible inclusion (**Figure 1**). Thirty-four full-text reports were selected for further evaluation, from which 17 studies were excluded for the following reasons: no systematic ICA was performed (9 papers)—it was either completely absent (31,32) or was used only to confirm abnormal and/or nondiagnostic CTA findings (33–39); data to calculate diagnostic accuracies were not provided or could not be derived (4 papers) (40–43); no reference to valve surgery was present (1 paper) (43); and a heterogeneous patient population inclusive of patients without VHD was included (4 papers) (44–47) or no values for true-positive and false-negative observations were reported (i.e., variance is infinite and CIs as well as sensitivity could not be computed)

FIGURE 2 **Assessment of Methodological Quality of Included Studies Using the QUADAS-2 Criteria**



Stacked bars represent the proportion of studies with a low **(green)**, high **(red)**, or unclear **(blue)** risk of bias or concerns of applicability. QUADAS-2 = Quality Assessment of Studies of Diagnostic Accuracy Included in Systematic Reviews-2.

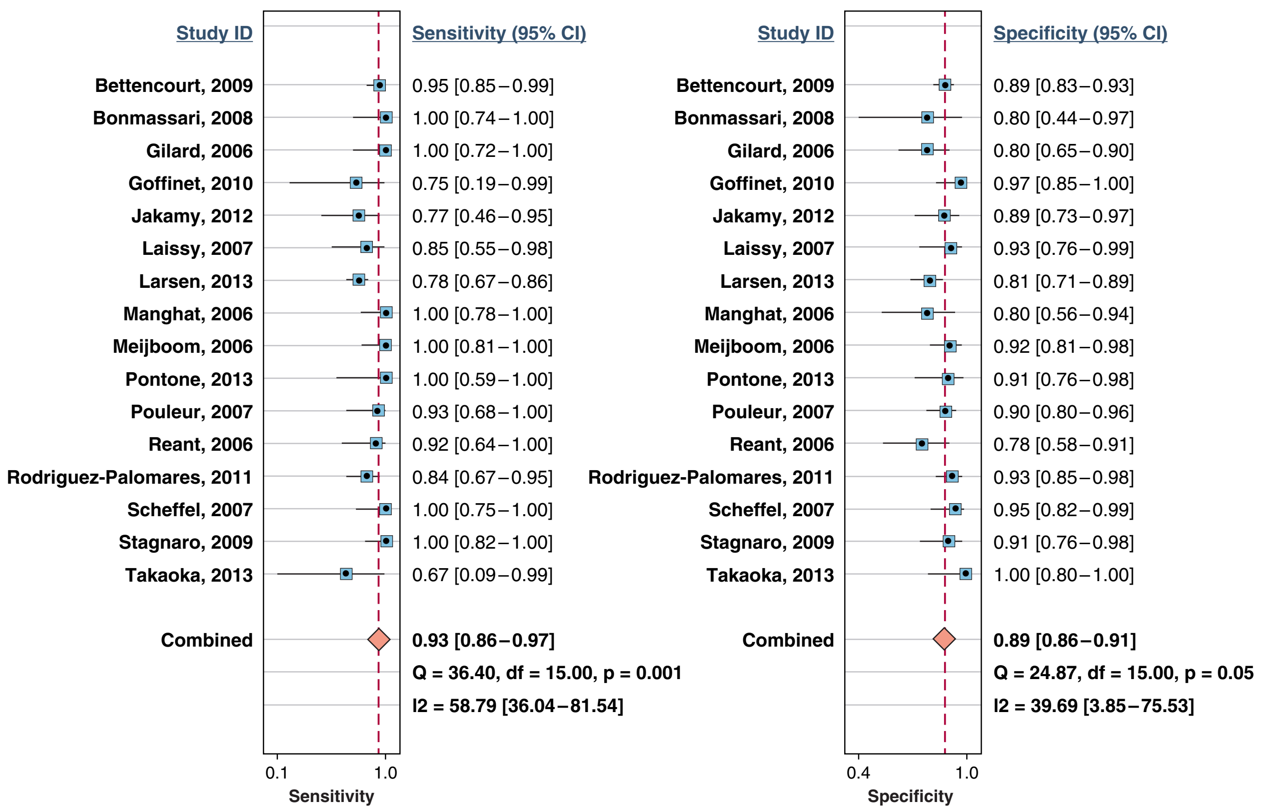
(2 papers) (44,45). Seventeen studies were included in the final analysis (Table 1).

BASELINE CHARACTERISTICS. Overall, a total of 1,153 patients (mean age 65.0 ± 6.4 years; 60% male) were included. The mean heart rate at the time of coronary CTA was 65 beats/min (60 to 68 beats/min), and 13 studies used beta-blockers for reduction of heart rate. The use of contrast media ranged from 80 to 125 ml, and the radiation dose ranged from 2.55 to 26.0 mSv. Of the 17 studies, 4 studies analyzing 321 patients (mean age 70.0 ± 1.4 years; 57% male) evaluated only patients with AS (6,9,10,12). Of the remaining 13 studies, 9 studies analyzed 693 patients (mean age 66.0 ± 5.8 years; 59% male) with various types of VHD (the percentage of patients with AS ranged from 32% to 68%) (4,5,8,11,13,15-17,19). Four studies included 148 patients (mean age 59.0 ± 6.7 years; 65% male) with a single type of valvular disease that was not AS (2 studies with aortic regurgitation, 1 study with mitral regurgitation, and 1 study with tricuspid regurgitation) (7,14,18,20). In 10 studies analyzing 761 patients (mean age 63.0 ± 7.2 years; 61% male) at least a 64-slice CTA was used (4,7,8,10,11,13,14,18-20), whereas 7 studies evaluated 16- or 40-slice CTA in a total of 392 patients (mean age 68.0 ± 3.1 years; 59% male) (5,6,9,12,15-17). All studies reported a ≥50% stenosis cutoff to determine the presence of significant CAD (in 1 study that originally used a ≥70% stenosis cutoff, the corresponding author was approached to provide supplementary accuracy data for ≥50% stenosis cutoff) (10).

QUALITY ASSESSMENT. Overall, the selected studies showed excellent quality in terms of applicability and satisfactory quality scores in terms of the risk of bias (Figure 2), with an inter-rater agreement of κ = 0.91. Risk of bias was high in 1 study regarding blinding the reference standard result from the assessor of the index test (11); however, because this study failed to provide diagnostic accuracy data on the per-patient basis, it was not included in the primary endpoint analysis. Four studies manifested an unclear risk of bias and did not explain whether the reference standard (3 papers) (7,14,20) or index test (2 papers) (5,20) was interpreted in a blinded fashion. Similarly, risk of bias regarding flow and timing was unclear in 6 studies because not all recruited patients were analyzed, and timing between the index test and the reference standard was unknown (5,7,10,11,19,20).

PUBLICATION BIAS. Using the Deeks test, there was no indication of publication bias for any of the analyses ($p = 0.28$ for the per-patient evaluation, $p = 0.87$ for the per-vessel evaluation, and $p = 0.24$ for the per-segment evaluation).

FIGURE 3 Forest Plots of Per-Patient Sensitivity and Specificity of CTA Compared With Invasive Coronary Angiography



The size of the **square-plotting symbol** is proportional to the size of the study. **Horizontal lines** are the 95% confidence intervals (CIs). CTA = computed tomography angiography.

PATIENT-BASED ANALYSIS. In the per-patient analysis, results from 16 studies with a total of 1,107 patients, after exclusion of 24 patients (2%), were pooled. Overall, 313 patients (28%) had evidence of at least 1 significant stenosis in ICA. The pooled sensitivity, specificity, positive and negative LRs, and a diagnostic odds ratio for CTA were 93% (95% confidence interval [CI]: 86 to 97), 89% (95% CI: 86 to 91), 8.44 (95% CI: 6.49 to 10.99), 0.07 (95% CI: 0.04 to 0.16), and 113.74 (95% CI: 47.98 to 269.64), respectively (**Figures 3 to 5**). Analyses of diagnostic accuracy, stratified according to the presence of AS, found more favorable specificity (96%) and positive LR (21.2) in studies without AS compared with specificity (87%) and positive LR (7.4) in studies with AS, with equally high values of sensitivity and negative LR in both groups. Similarly, an analysis stratified according to the number of CT detectors demonstrated more favorable specificity (90%) and positive LR (9.5) for ≥64 detectors compared with the specificity (86%) and positive LR (6.9) for <64 detectors, with equally high values of sensitivity and negative LR in both groups (**Table 2**). Statistical heterogeneity was found for sensitivity (I^2 = 58.8%; p = 0.001), negative LR (I^2 = 59.0%; p = 0.001), and diagnostic odds ratio (I^2 = 100.0%; p = 0.001). Vessel-based and segment-based analyses are presented in the Online Appendix.

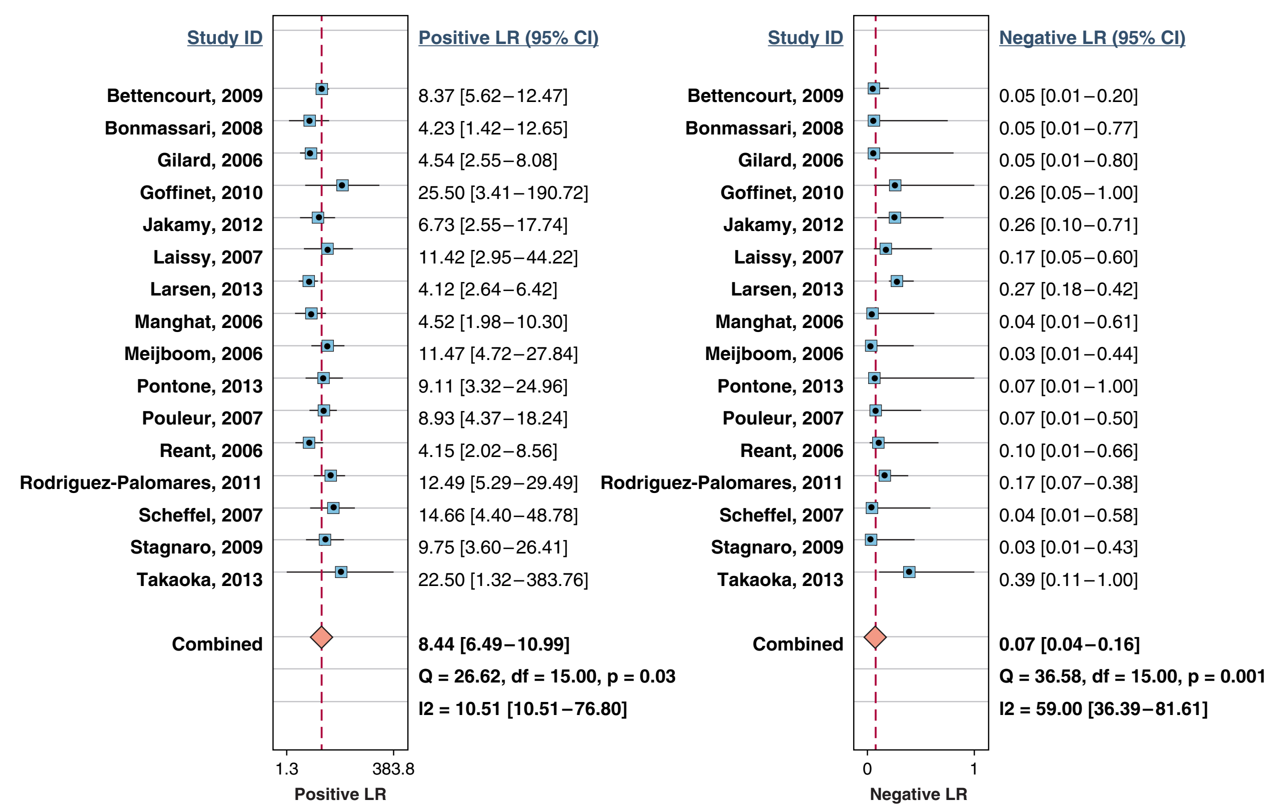
HETEROGENEITY ANALYSES. The generalized linear mixed model showed significant interactions between the presence of ≥64 detectors, absence of patients with AS, fewer male subjects, and lower age, as well as smaller sample size and higher specificity of coronary CTA for the detection of significant coronary stenoses. Conversely, male sex was the only covariate with a negative effect on sensitivity (**Figure 6**). Statistical heterogeneity was present for AS (I^2 = 69.0%; p = 0.04) and age (I^2 = 71.0%; p = 0.03) only.

DISCUSSION

This meta-analysis investigated the diagnostic accuracy of coronary CTA with ≥16 slices for the detection of significant coronary stenoses in patients undergoing cardiac valve surgery. Our main finding

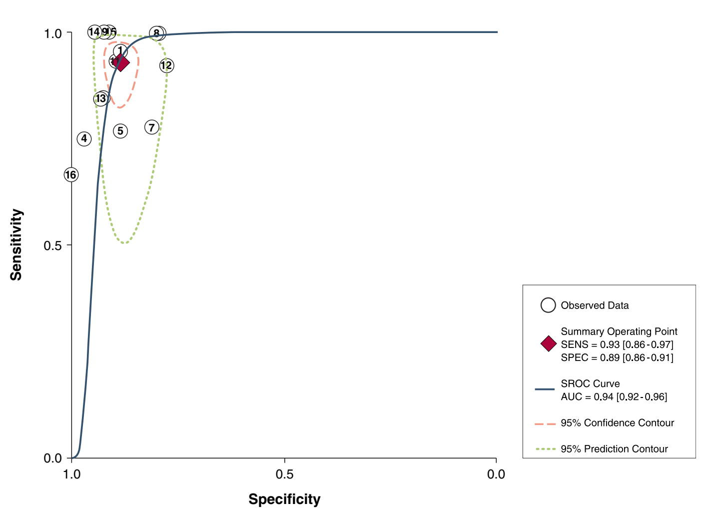
JACC: CARDIOVASCULAR IMAGING, VOL. 9, NO. 9, 2016
SEPTEMBER 2016:1059-70

FIGURE 4 Forest Plots of Per-Patient Positive and Negative LRs of CTA Compared With Invasive Coronary Angiography



LR = likelihood ratio; other abbreviations as in Figure 3.

FIGURE 5 Hierarchical SROC Plot Showing Average Sensitivity and Specificity Estimate of the Study Results at the Per-Patient Level With 95% Confidence Region



The 95% prediction region represents the confidence region for a forecast of the true sensitivity (SENS) and specificity (SPEC) in a future study. The **red diamond** indicates per-patient level. AUC = area under the curve; SROC = summary receiver-operating characteristic.

was that coronary CTA using currently available technology can effectively rule out significant coronary stenoses in patients scheduled for valve surgery compared with the clinical standard of ICA, and it may thus serve as a gatekeeper for ICA before cardiac valve surgery. Importantly, the ability for coronary CTA to detect significant coronary stenoses in patients with VHD is not universal and was lower for patients with AS, a finding possibly reflective of the higher prevalence of atherosclerosis.

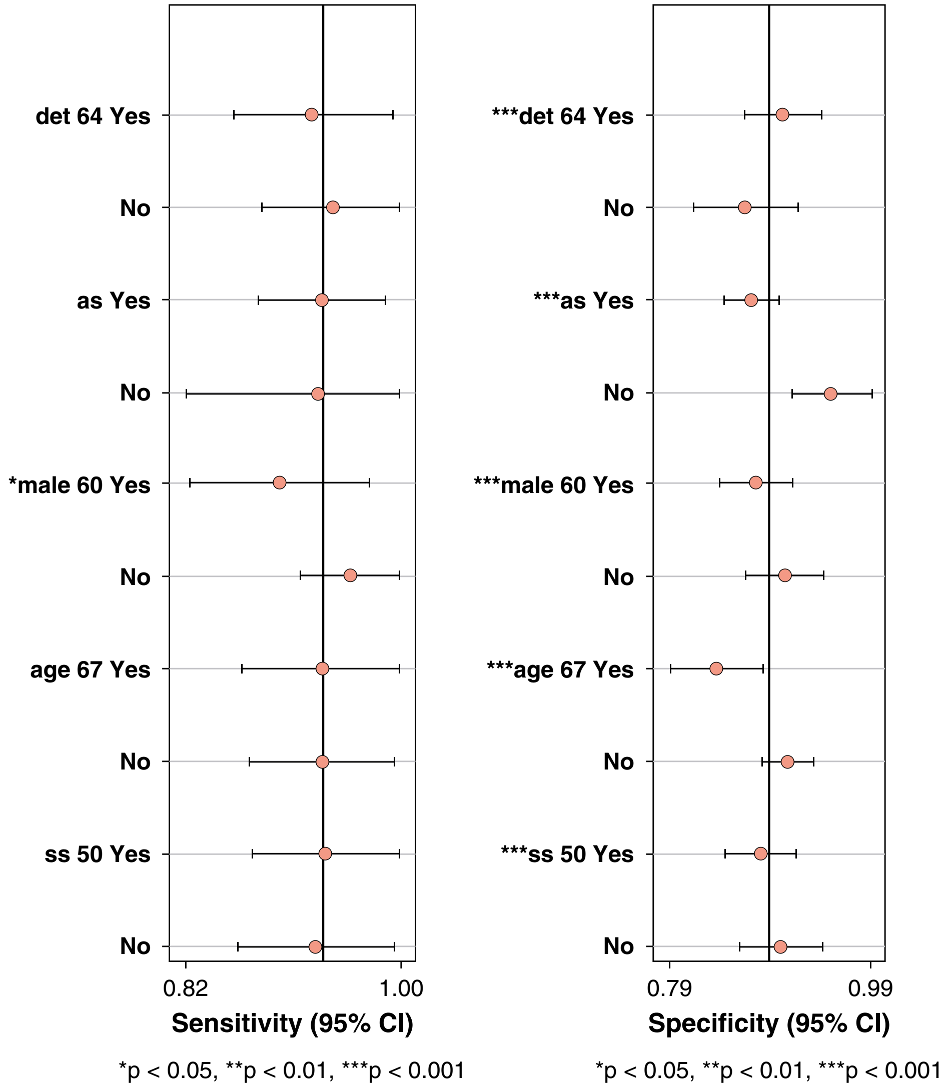
The presence of concomitant CAD in patients undergoing cardiac valvular surgery is related to worse clinical outcomes (48), and various clinical studies have suggested that combined valve and bypass surgery reduces early and late mortality (48,49). Consequently, pre-surgical assessment of CAD is essential for risk stratification and determination if concomitant coronary revascularization is indicated. According to current guidelines for the management of valvular heart disease, ICA remains the gold standard for the identification of coronary stenoses in all male patients >40 years of age, post-menopausal women,

TABLE 2 Summary Estimates for Pooled Measures of Diagnostic Accuracy of Coronary CTA for Evaluating the Presence of Significant Coronary Stenoses Compared With Invasive Coronary Angiography on a Per-Patient Basis

	No. of Studies	Prevalence of CAD	Sensitivity (95% CI)	Specificity (95% CI)	Positive LR (95% CI)	Negative LR (95% CI)	DOR (95% CI)
Total	16	28%	93 (86–97)	89 (86–91)	8.4 (6.5–11)	0.07 (0.04–0.16)	114 (48–270)
Studies with <64 detectors	7	29%	94 (84–98)	86 (80–91)	6.9 (4.7–10.3)	0.07 (0.02–0.19)	105 (35–315)
Studies with ≥64 detectors	9	28%	94 (84–98)	90 (86–93)	9.5 (6.4–14.3)	0.06 (0.02–0.19)	148 (39–558)
Studies with AS	12	30%	93 (85–97)	87 (84–90)	7.4 (5.9–9.4)	0.08 (0.03–0.18)	95 (37–244)
Studies without AS	4	18%	94 (60–99)	96 (89–98)	21.2 (8.0–55.7)	0.07 (0.01–0.56)	325 (31–3,402)

CI = confidence interval; CTA = computed tomography angiography; DOR = diagnostic odds ratio; LR = likelihood ratio; other abbreviations as in Table 1.

FIGURE 6 Graphical Presentation of the Generalized Linear Mixed Model Exploring the Impact of Selected Variables on Sensitivity and Specificity of CTA



Continuous variables were dichotomized according to its median values. as = aortic stenosis; det = detectors; ss = sample size; other abbreviations as in Figures 3 and 5.

and pre-menopausal women with any risk factors for CAD (1,2). However, ICA imparts a non-negligible risk for catheter-related complications and can be time-consuming (1,13). Furthermore, ICA should be avoided when its risk outweighs potential benefits (e.g., in acute aortic dissection or aortic vegetation) (2).

On the basis of large multicenter clinical trials and meta-analyses, coronary CTA can accurately rule out coronary stenoses in the general population with a low or intermediate pre-test probability of CAD (50–52). However, to date, only a limited number of single-center studies have tested the accuracy of coronary CTA to detect coronary stenoses in patients before cardiac valve surgery, and definitive evidence advocating for the use of coronary CTA in VHD requires further validation (4–20). In this regard, the present meta-analysis provides a stronger basis for clinical application of coronary CTA in patients with VHD. Using ICA as a reference standard, coronary CTA exhibited an excellent pooled negative LR (0.07) for exclusion of significant coronary stenoses in patients with VHD. Based on our data, ICA could have been avoided in 64% (703 of 1,107) of patients with a true-negative CTA result, whereas in 3% (34 of 1,107) of patients, the correct diagnosis of obstructive CAD would have been missed on the basis of a false-negative CTA finding. These results are clinically relevant because they indicate that coronary CTA may be a reasonable gatekeeper to ICA before valve surgery. Consequently, our findings support the potential for reduction of unnecessary downstream testing and catheter-related complications and costs. By relevance, a normal CTA examination confers an excellent prognosis, thus supporting its clinical utility if used in patients with suspected CAD (53). In contrast to the excellent ability to exclude obstructive CAD, the pooled positive LR (8.44) of coronary CTA to identify significant coronary stenoses was modest, further substantiating the additional need for ICA to confirm or refute a positive CTA test result in patients with VHD.

Given that the risk factors for CAD vary among different valve diseases (3), a subanalysis of diagnostic performance of coronary CTA for specific VHD is desirable. Particularly germane to this concept, patients with AS are older and have a higher prevalence of CAD compared with other valve diseases (48). Indeed, this scenario has been consistently emphasized in several studies that have observed a limited specificity of coronary CTA for the detection of significant stenoses in patients with AS (6,9,10,12). These findings are in line with the present meta-analysis demonstrating decreased specificity (87%) and positive LR (7.4) of coronary CTA against the background of AS. Conversely, the presence of AS did not affect the ability of CTA to reliably exclude significant CAD as confirmed by the high negative LR (0.08) and heterogeneity analysis. Of note, coronary CTA showed excellent diagnostic performance both to detect and rule out significant coronary stenoses in patients without AS, highlighting the need for the assessment of the pre-test probability of CAD.

Although coronary CTA with ≥64 detectors was associated with improved specificity compared with <64 detectors in the generalized linear model analysis, sensitivity remained high for both ≥64 and <64 detectors. These results are clinically important because they indicate that coronary CTA could be used effectively to rule out significant CAD in patients with VHD across a wide range of technical scanners. In contrast, the use of CTA with <64 detectors was inadequate for the detection of significant coronary stenoses, likely as a result of worse spatial and temporal resolution.

Beyond its use in the identification of CAD, coronary CTA offers information incremental to that of ICA for the assessment of cardiac valve morphology. Indeed, coronary CTA may contribute to the evaluation of the severity of valve disease, either by quantifying valvular calcification or through the measurement of valve planimetry (11). It can also provide practical knowledge to the cardiac surgeon about the intrathoracic anatomy, including aortic arch calcification and dimensions, course of arteries, or presence of congenital anomalies (2).

In the present meta-analysis, the reported dose of radiation was 2.55 to 26.0 mSv, and the dose of contrast agent ranged from 80 to 125 ml, which are somewhat higher compared with ICA. However, with the growing use of CTA imaging, newer techniques to lower radiation exposure are constantly being developed. Recently, ultra-low-dose protocols with mean estimated radiation doses <1 mSv and preserved image quality have been documented (54). Moreover, the use of low concentration contrast medium protocols might effectively reduce the risk of contrast nephropathy by obtaining the same quality of CTA (55).

STUDY LIMITATIONS. The results of our meta-analysis are limited to studies with both a retrospective and prospective design. Nonetheless, this study was based on the largest currently available pooled cohort of patients with VHD, and it can thus recognize the most optimal candidates for the identification of coronary stenoses with CTA. Furthermore, patients with severely impaired renal function, known contrast allergy, cardiac arrhythmias, and hemodynamic instability were excluded from the majority of the analyzed studies. Thus, the possibility of selection bias that is present in all meta-analyses cannot be discounted. Also, none of the included studies reported details concerning the clustered nature of the per-segment and per-vessel data. Finally, not all studies provided data regarding patient, vessel, and segment levels.

CONCLUSIONS

The present meta-analysis showed that coronary CTA provides, across a wide range of diverse clinical centers, high diagnostic performance for the exclusion of significant coronary stenoses in patients scheduled for valve surgery. Considering the differences in the pre-test probabilities of CAD among various valvular diseases, the diagnostic accuracy of coronary CTA to detect significant CAD decreased against the background of AS.

REPRINT REQUESTS AND CORRESPONDENCE: Dr. Maksymilian P. Opolski, Department of Interventional Cardiology and Angiology, Institute of Cardiology, Alpejska 42, Warsaw 04-628, Poland. E-mail: opolski.mp@gmail.com.

PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE: Coronary CTA using currently available technology has excellent diagnostic performance for the exclusion of significant coronary stenoses in patients scheduled for valve surgery, and it can serve as a gatekeeper for ICA before cardiac valve surgery. The diagnostic ability of coronary CTA to detect significant CAD may be decreased against the background of AS.

TRANSLATIONAL OUTLOOK: Future studies are needed to test whether the routine performance of coronary CTA in broad populations of patients scheduled for cardiac valve surgery may help reduce downstream testing as well as catheter-related complications and costs. Furthermore, whereas the image acquisition and reconstruction protocols of coronary CTA are constantly being developed, large-scale prospective clinical trials comparing radiation and contrast exposure between ICA and coronary CTA among patients with valvular heart disease now seem warranted.

REFERENCES

1. Nishimura RA, Otto CM, Bonow RO, et al. 2014 AHA/ACC guideline for the management of patients with valvular heart disease: executive summary: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. J Am Coll Cardiol 2014;63:2438–88.

2. Vahanian A, Alfieri O, Andreotti F, et al. Guidelines on the management of valvular heart disease (version 2012). Eur Heart J 2012;33:2451–96.

3. Ramsdale DR, Bennett DH, Bray CL, et al. Angina, coronary risk factors and coronary artery disease in patients with valvular disease. A prospective study. Eur Heart J 1984;5:716–26.

4. Bettencourt N, Rocha J, Carvalho M, et al. Multislice computed tomography in the exclusion of coronary artery disease in patients with presurgical valve disease. Circ Cardiovasc Imaging 2009;2:306–13.

5. Bonmassari R, Muraglia S, Centonze M, et al. Noninvasive detection of coronary artery stenosis with 16-slice spiral computed tomography in a population at low to moderate risk for coronary artery disease. J Cardiovasc Med (Hagerstown) 2006;7:817–25.

6. Gilard M, Cornily JC, Pennec PY, et al. Accuracy of multislice computed tomography in the preoperative assessment of coronary disease in patients with aortic valve stenosis. J Am Coll Cardiol 2006;47:2020–4.

7. Goffinet C, Kersten V, Pouleur AC, et al. Comprehensive assessment of the severity and mechanism of aortic regurgitation using multidetector CT and MR. Eur Radiol 2010;20:326–36.

8. Jakamy R, Barthélémy O, Le Feuvre C, et al. Accuracy of multislice computed tomography in the preoperative assessment of coronary disease in patients scheduled for heart valve surgery. Arch Cardiovasc Dis 2012;105:424–31.

9. Laissy JP, Messika-Zeitoun D, Serfaty JM, et al. Comprehensive evaluation of preoperative patients with aortic valve stenosis: usefulness of cardiac multidetector computed tomography. Heart 2007;93:1121–5.

10. Larsen LH, Kofoed KF, Dalsgaard M, et al. Assessment of coronary artery disease using coronary computed tomography angiography in patients with aortic valve stenosis referred for surgical aortic valve replacement. Int J Cardiol 2013;168:126–31.

11. Lee SC, Ko SM, Song MG, et al. Morphological assessment of the aortic valve using coronary computed tomography angiography, cardiovascular magnetic resonance, and transthoracic echocardiography: comparison with intraoperative findings. Int J Cardiovasc Imaging 2012;28 Suppl 1:33–44.

12. Manghat NE, Morgan-Hughes GJ, Broadley AJ, et al. 16-Detector row computed tomographic coronary angiography in patients undergoing evaluation for aortic valve replacement: comparison with catheter angiography. Clin Radiol 2006;61:749–57.

13. Meijboom WB, Mollet NR, Van Mieghem CA, et al. Pre-operative computed tomography coronary angiography to detect significant coronary artery disease in patients referred for cardiac valve surgery. J Am Coll Cardiol 2006;48:1658–65.

14. Pontone G, Andreini D, Bertella E, et al. Pre-operative CT coronary angiography in patients with mitral valve prolapse referred for surgical repair: comparison of accuracy, radiation dose and cost versus invasive coronary angiography. Int J Cardiol 2013;167:2889–94.

15. Pouleur AC, le Polain de Waroux JB, Kefer J, et al. Usefulness of 40-slice multidetector row computed tomography to detect coronary disease in patients prior to cardiac valve surgery. Eur Radiol 2007;17:3199–207.

16. Reant P, Brunot S, Lafitte S, et al. Predictive value of noninvasive coronary angiography with multidetector computed tomography to detect significant coronary stenosis before valve surgery. Am J Cardiol 2006;97:1506–10.

17. Rodríguez-Palomares JF, Cuéllar H, Martí G, et al. Coronary angiography by 16-slice computed tomography prior to valvular surgery. Rev Esp Cardiol 2011;64:269–76.

18. Scheffel H, Leschka S, Plass A, et al. Accuracy of 64-slice computed tomography for the preoperative detection of coronary artery disease in patients with chronic aortic regurgitation. Am J Cardiol 2007;100:701–6.

19. Stagnaro N, Della Latta D, Chiappino D. Diagnostic accuracy of MDCT coronary angiography in patients referred for heart valve surgery. Radiol Med 2009;114:728–42.

20. Takaoka H, Funabashi N, Kataoka A, et al. Utilities of 320-slice computed-tomography for evaluation of tricuspid valve annular diameter before tricuspid-valve-plasty compared with the direct-measurement of tricuspid valve annular diameter during open heart-surgery. Int J Cardiol 2013;168:2889–93.

21. Liberati A, Altman DG, Tetzlaff J, et al. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate health care interventions: explanation and elaboration. Ann Intern Med 2009;151:W65–94.

22. Whiting PF, Rutjes AW, Westwood ME, et al. QUADAS-2 Group. QUADAS-2: a revised tool for the quality assessment of diagnostic accuracy studies. Ann Intern Med 2011;155:529–36.

23. Deville WL, Buntinx F, Bouter LM, et al. Conducting systematic reviews of diagnostic studies: didactic guidelines. BMC Med Res Methodol 2002; 2:9.

24. Glas AS, Lijmer JG, Prins MH, Bonsel GJ, Bossuyt PM. The diagnostic odds ratio: a single indicator of test performance. J Clin Epidemiol 2003;56:1129–35.

25. Arends LR, Hamza TH, van Houwelingen JC, Heijenbrok-Kal MH, Hunink MG, Stijnen T. Bivariate random effects meta-analysis of ROC curves. Med Decis Making 2008;28:621–38.

26. Reitsma JB, Glas AS, Rutjes AW, Scholten RJ, Bossuyt PM, Zwinderman AH. Bivariate analysis of sensitivity and specificity produces informative summary measures in diagnostic reviews. J Clin Epidemiol 2005;58:982–90.

27. Rutter CM, Gatsonis CA. A hierarchical regression approach to meta-analysis of diagnostic test accuracy evaluations. Statist Med 2001; 20:2865–84.

28. Hamza TH, Arends LR, van Houwelingen HC, Stijnen T. Multivariate random effects meta-analysis of diagnostic tests with multiple thresholds. BMC Medical Research Methodology 2009; 9:1–15.

29. Harbord RM, Whiting P. Metandi: meta-analysis of diagnostic accuracy using hierarchical logistic regression. Stata Journal 2009;9:211–29.

30. Deeks JJ, Macaskill P, Irwig L. The performance of tests of publication bias and other sample size effects in systematic reviews of diagnostic test accuracy was assessed. J Clin Epidemiol 2005;58:882–93.

31. Feng J, Wang XM, Ji XP, et al. Comparison of low-dose sequences of dual-source CT and echocardiography for preoperative evaluation of aortic valve disease. Chin Med J 2013;126:4423–9.

32. Diab AY, Gonsorcik J, Dobrovicova A, Gibarti C, Javorsky M, Stancak B. Degenerative aortic valve stenosis: diagnostic value of noninvasive evaluation in elderly. Cardiology sk 2010;19:369–74.

33. Wen LY, Yang ZG, Peng LQ, Li Y, Chen J. Preoperative assessment of coronary arteries in patients undergoing thoraco-abdominal and noncoronary cardiovascular surgery with dual-source computed tomography angiography. J Card Surg 2014;29:59–65.

34. Morris MF, Suri RM, Akhtar NJ, et al. Computed tomography as an alternative to catheter angiography prior to robotic mitral valve repair. Ann Thorac Surg 2013;95:1354–9.

35. Catalán P, Leta R, Hidalgo A, et al. Ruling out coronary artery disease with noninvasive coronary multidetector CT angiography before noncoronary cardiovascular surgery. Radiology 2011;258: 426–34.

36. Cornily JC, Gilard M, Bezon E, et al. Cardiac multislice spiral computed tomography as an alternative to coronary angiography in the preoperative assessment of coronary artery disease before aortic valve surgery: a management outcome study. Arch Cardiovasc Dis 2010;103: 170–5.

37. Nardi P, Pellegrino A, Romagnoli A, et al. Multidetector computed tomographic coronary angiography as an alternative to conventional coronary angiography in non-coronary surgical patients. J Cardiovasc Surg (Torino) 2011;52: 429–35.

38. Buffa V, De Cecco CN, Cossu L, et al. Preoperative coronary risk assessment with dual-source CT in patients undergoing noncoronary cardiac surgery. Radiol Med 2010;115:1028–37.

39. Russo V, Gostoli V, Lovato L, et al. Clinical value of multidetector CT coronary angiography as a preoperative screening test before non-coronary cardiac surgery. Heart 2007;93:1591–8.

40. Chow BJ, Freeman MR, Bowen JM, et al. Ontario multidetector computed tomographic coronary angiography study: field evaluation of diagnostic accuracy. Arch Intern Med 2011;171: 1021–9.

41. Galas A, Hryniewiecki T, Kępka C, et al. May dual-source computed tomography angiography replace invasive coronary angiography in the evaluation of patients referred for valvular disease surgery? Kardiol Pol 2012;70:877–82.

42. Killeen RP, Arnous S, Martos R, Abbara S, Quinn M, Dodd JD. Chronic mitral regurgitation detected on cardiac MDCT: differentiation between functional and valvular aetiologies. Eur Radiol 2010;20:1886–95.

43. Tanaka H, Shimada K, Yoshida K, Jissho S, Yoshikawa J, Yoshiyama M. The simultaneous assessment of aortic valve area and coronary artery stenosis using 16-slice multidetector-row computed tomography in patients with aortic stenosis comparison with echocardiography. Circ J 2007;71:1593–8.

44. Plass A, Grünenfelder J, Leschka S, et al. Coronary artery imaging with 64-slice computed tomography from cardiac surgical perspective. Eur J Cardiothorac Surg 2006;30:109–16.

45. Plass A, Azemaj N, Scheffel H, et al. Accuracy of dual-source computed tomography coronary angiography: evaluation with a standardised protocol for cardiac surgeons. Eur J Cardiothorac Surg 2009;36:1011–7.

46. Leschka S, Scheffel H, Husmann L, et al. Effect of decrease in heart rate variability on the diagnostic accuracy of 64-MDCT coronary angiography. AJR Am J Roentgenol 2008;190: 1583–90.

47. Leschka S, Stolzmann P, Desbiolles L, et al. Diagnostic accuracy of high-pitch dual-source CT for the assessment of coronary stenoses: first experience. Eur Radiol 2009;19:2896–903.

48. Mullany CJ, Elveback LR, Frye RL, et al. Coronary artery disease and its management: influence on survival in patients undergoing aortic valve replacement. J Am Coll Cardiol 1987;10: 66–72.

49. Lund O, Nielsen TT, Pilegaard HK, Magnussen K, Knudsen MA. The influence of coronary artery disease and bypass grafting on early and late survival after valve replacement for aortic stenosis. J Thorac Cardiovasc Surg 1990;100: 327–37.

50. Meijboom WB, Meijs MF, Schuijf JD, et al. Diagnostic accuracy of 64-slice computed tomography coronary angiography: a prospective, multicenter, multivendor study. J Am Coll Cardiol 2008;52:2135–44.

51. Schuetz GM, Zacharopoulou NM, Schlattmann P, Dewey M. Meta-analysis: noninvasive coronary angiography using computed tomography versus magnetic resonance imaging. Ann Intern Med 2010;152:167–77.

52. von Ballmoos MW, Haring B, Juillerat P, Alkadhi H. Meta-analysis: diagnostic performance of low-radiation-dose coronary computed tomography angiography. Ann Intern Med 2011; 154:413–20.

53. Otaki Y, Arsanjani R, Gransar H, et al. What have we learned from CONFIRM? Prognostic implications from a prospective multicenter international observational cohort study of consecutive patients undergoing coronary computed tomographic angiography. J Nucl Cardiol 2012;19: 787–95.

54. Achenbach S, Marwan M, Ropers D, et al. Coronary computed tomography angiography with a consistent dose below 1 mSv using prospectively electrocardiogram-triggered high-pitch spiral acquisition. Eur Heart J 2010;31:340–6.

55. Zhang LJ, Qi L, Wang J, et al. Feasibility of prospectively ECG-triggered high-pitch coronary CT angiography with 30 mL iodinated contrast agent at 70 kVp: initial experience. Eur Radiol 2014;24:1537–46.

KEY WORDS coronary angiography, coronary computed tomography angiography, meta-analysis, valvular heart disease

APPENDIX For supplemental results and figures, please see the online version of this article.

CME **Go to http://www.acc.org/jacc-journals-cme to take the CME quiz for this article.**