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Meta-Analysis and Systematic Review of the Long-Term Predictive Value of Assessment of Coronary Atherosclerosis by Contrast-Enhanced Coronary Computed Tomography Angiography

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Objectives We conducted a systematic review and meta-analysis to determine the predictive value of findings of coronary computed tomography angiography for incident cardiovascular events.

Background Initial studies indicate a prognostic value of the technique; however, the level of evidence as well as exact independent risk estimates remain unclear.

Methods We searched PubMed, EMBASE, and the Cochrane Library through January 2010 for studies that followed up ≥100 subjects for ≥1 year and reported at ≥1 hazard ratio (HR) of interest. Risk estimates for the presence of significant coronary stenosis (primary endpoint; ≥50% diameter stenosis), left main coronary artery stenosis, each coronary stenosis, 3-vessel disease, any plaque, per coronary segment containing plaque, and noncalcified plaque were derived in random effect regression analysis, and causes of heterogeneity were determined in meta-regression analysis.

Results We identified 11 eligible articles including 7,335 participants (age 59.1 ± 2.6 years, 62.8% male) with suspected coronary artery disease. The presence of ≥1 significant coronary stenosis (9 studies, 3,670 participants, and 252 outcome events [6.8%] with 62% revascularizations) was associated with an annualized event rate of 11.9% (6.4% in studies excluding revascularization). The corresponding HR was 10.74 (98% confidence interval [CI]: 6.37 to 18.11) and 6.15 (95% CI: 3.22 to 11.74) in studies excluding revascularization. Adjustment for coronary calcification did not attenuate the prognostic significance ($p = 0.79$). The estimated HRs for left main stenosis, presence of plaque, and each coronary segment containing plaque were 6.64 (95% CI: 2.6 to 17.3), 4.51 (95% CI: 2.2 to 9.3), and 1.23 (95% CI: 1.17 to 1.29), respectively.

Conclusions Presence and extent of coronary artery disease on coronary computed tomography angiography are strong, independent predictors of cardiovascular events despite heterogeneity in endpoints, categorization of computed tomography findings, and study population. (J Am Coll Cardiol 2011;57:2426–36) © 2011 by the American College of Cardiology Foundation

Computed tomography (CT) technology has progressed rapidly, and state-of-the-art equipment quickly disseminates, so that coronary computed tomography angiography (CTA) increasingly penetrates clinical practices. Coronary CTA has been well validated as an accurate noninvasive modality to detect coronary artery stenoses (1), but also detects the presence and extent of nonobstructive coronary artery disease (CAD). However, the lack of robust outcome data has limited the level of supportive recommendations from clinical practice guidelines (2).

In addition to its potential diagnostic value in patients with acute and chronic chest pain, growing evidence indicates that the presence and severity of CAD as defined by coronary CTA is also associated with the risk for future cardiac events. However, evidence from available individual studies is limited by the large uncertainty around their individual risks estimates,

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mostly as a result of the limited number of outcomes but also due to differences among the populations investigated and the outcomes reported. Thus, the actual risk associated with specific findings in coronary CTA remains largely unclear, but it is necessary to appropriately design future outcome studies including risk modification in prospective, randomized intervention trials and consideration of the public health impact of an increased use of noninvasive cardiac imaging using coronary CTA. Therefore, we performed a systematic review of studies that assessed the prognostic value of coronary CTA findings on a combined cardiovascular endpoint and pooled available evidence in a meta-analysis.

Methods

Study selection. We searched PubMed, EMBASE, and the Cochrane library through January 2010 using medical subject headings "cardiac/coronary CT" or "cardiac/coronary computed tomography" or "cardiac/coronary CT angiography" or "cardiac/coronary CTA" or "cardiac/coronary MDCT," in combination with the text words "atherosclerosis complications" or "mortality" or "survival analysis" or "outcome" or "death" or "prognosis/prognostic." In addition, we obtained expert opinions (S.A., K.N., U.H., and C.R.B.) whether any potentially relevant study was missed. We limited our search to articles published in English, German, French, or Italian, and to those conducted on human adults over the age of 18 years. Reference lists of all retrieved original papers and of review articles were hand-searched to identify further relevant studies (Fig. 1). Finally, we searched for multiple publications of retrieved articles to obtain the most complete and up-to-date study results.

Abbreviations and Acronyms

CAD = coronary artery disease
CI = confidence interval
CT = computed tomography
CTA = computed tomography angiography
HR = hazard ratio
MI = myocardial infarction

Inclusion and exclusion criteria. Pre-specified study inclusion criteria were cohort studies (prospective or retrospective) of >100 subjects who were followed up for >1 year. Studies that included subjects with suspected or known CAD were eligible for inclusion in the present analysis. Per definition, we included studies using ≥16-slice CT and electron-beam CT given that both techniques have been comparably used for CTA in the past.

Given the different clinical scenario and very limited availability of long-term data, we excluded studies involving patients with acute presentation, such as acute chest pain.

Data abstraction and definitions. Among potentially eligible studies, 12 were excluded from the analysis. Six studies did not provide any hazard ratio (HR) of interest (merely provided raw data and described the occurrence of events on a case basis) (3,4), included <100 subjects (5), included a duplicate publication with a different focus of the analysis (6,7), reported on costs (8), or exclusively reported on noncalcified plaque (9).

Two independent investigators abstracted information on all variables listed in Table 1. Discrepancies between the 2 investigators were resolved by discussion and reexamination of the corresponding studies with a senior investigator (S.A., C.R.B., and U.H.) or by contacting the authors of the individual studies. To determine whether the predictive value of the cardiac CT findings on plaque and stenosis was independent of coronary artery calcification (as measured in native examinations), we abstracted HR from the source data with and without adjustment for coronary artery calcification separately.

Study quality indicators included the presence or absence of an endpoint committee, blinded CT results and outcome assessment, exclusion of subjects after enrollment, and endpoint definition. The total subject number was defined as the number of participants in whom the risk estimates were derived.

RISK ESTIMATES. To summarize the available evidence, we abstracted the HR of the individual studies pertaining to each CT category of interest. To minimize the effect of confounding, we included the most extensively adjusted HR (with associated 95% confidence interval [CI] derived from multivariate regression analysis) from each original study, if available. For studies that did not provide multivariate adjusted HRs for each predictor of interest, the univariate

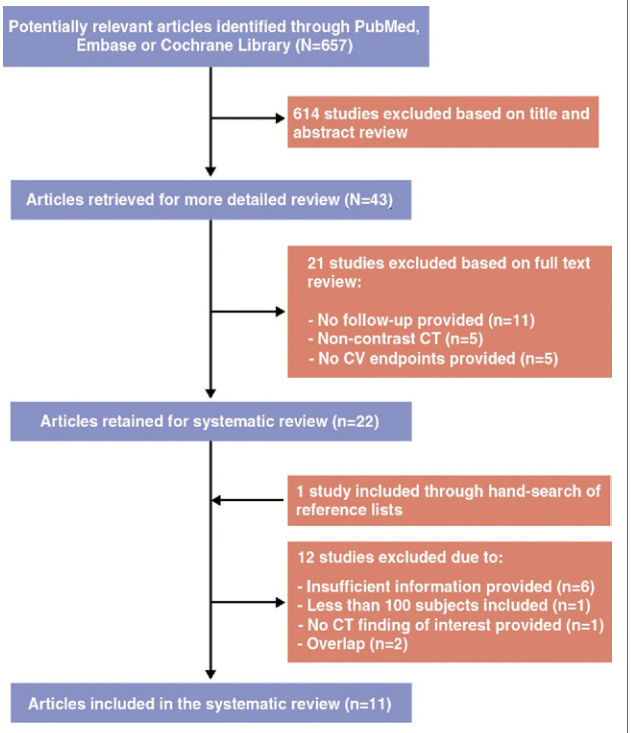

Figure 1 Literature Research and Selection Process of Studies Included in Analysis

CT = computed tomography; CV = cardiovascular. Figure by Craig Skaggs.

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Table 1 Study Characteristics

First Author, Year (Ref. #)	Region	Sample Type	N	Age (yrs)	Men	History of CAD/Diabetes/BMI (kg/m^2)	CT Scanner	Excluded Subjects/ Segments
Pundziute, 2007 (11)	Europe	Suspected or known CAD	100	59.0	0.59	0.35/0.14/N.R.	16/64-slice	4 (arrhythmia)/ 0.3% (stent, motion) vessels ≤1.5 mm
Min, 2007 (13)	United States	Suspected CAD, asymptomatic with multiple CVRF	1,127	61.7	0.43	0/0.17/N.R.	16-slice	N.R./N.R.
Gaemperli, 2008 (20)	Europe	Suspected or known CAD	220	63.0	0.65	0.17/0.15/27	64-slice	3/0.02% (stent, motion)
Ostrom, 2008 (22)	United States	Suspected CAD	2,538	59.0	0.70	0/0.14/29.4	EBCT	N.R.
Carrigan, 2009 (14)	United States	Suspected CAD	227	54.0	0.61	0/0.09/N.R.	64-slice	N.R.
Gopal, 2009 (21)	United States	Suspected CAD, intermediate risk	493	58.0	0.70	0/0.15/N.R.	EBCT	N.R.
Hadamitzky, 2009 (10)	Europe	Suspected CAD	1,150	60.2	0.69	0/0.08/25.7	64-slice	45/segments ≤1.5 mm
Rubinshtein, 2009 (23)	Middle East	Suspected CAD	545	58.0	0.68	0/0.14/N.R.	64-slice	0.015% (motion, calcium, size)
Aldrovandi, 2009 (19)	Europe	Suspected CAD	187	62.5	0.64	0/0.11/0.21 obese	64-slice	N.R.
van Werkhoven, 2009 (12)	Europe	Suspected CAD	432	58.0	0.59	0/0.28/0.21 obese	64-slice	59 (24 uninterpretable, 35 lost to FU/N.R.
van Werkhoven, 2009 (24)*	Europe	Suspected CAD	316	57.0	0.61	0/0.40/0.23 obese	64-slice	15 (motion, SNR)/0

	CT Findings Studied	Follow-Up (Months)	Endpoint	Events	AC/CV Mortality	Nonfatal MI	UAP	PCI/ CABG	Multivariable Adjustment
Pundziute, 2007 (11)	Presence of plaque Obstructive CAD (≥50%) LM obstructive CAD Segment any plaque Segment obstructive CAD Segment MCAP, CAP, NCAP	13.0	Combined CV	26	0/1	3	3	24/7	Scanner type, age, hyperlipidemia, hypertension, family history of CAD, smoking
Min, 2007 (13)	Obstructive CAD (≥50%) Obstructive CAD (≥70%) LM obstructive CAD Segment any plaque 3-vessel obstructive disease	15.3	AC mortality	39	39/0	0	0	0/0	Age, hyperlipidemia, family history of CAD
Gaemperli, 2008 (20)	Obstructive CAD (≥50%) LM obstructive CAD Presence of plaque Segment with any plaque Segment with NCAP, CAP, MCAP	14.0	Combined CV	59	3/1	3	2	58/16	None
Ostrom, 2008 (22)	Presence of plaque 1/2/3 vessel nonobstructive CAD 1/2/3 vessel obstructive CAD	78.0	AC mortality	86	86/0	0	0	0/0	Age, sex, CVRF (CAC)
Carrigan, 2009 (14)	Obstructive CAD (≥50%) LM obstructive CAD (≥30%) Segment plaque (0–10) Segment NCAP, MCAP, CAP	27.6	Combined CV	18	0/1	3	0	14/7	Age, dyslipidemia, statin use, aspirin
Gopal, 2009 (21)	Obstructive CAD (≥50%)	40.0	Combined CV	21	0/0	21	0	0/0	Age, sex, CVRF (CAC)
Hadamitzky, 2009 (10)	Obstructive CAD (≥50%)	18.0†	Combined CV (revasc. ≥30 days)	21	0/0	1	5	15/0	None
Aldrovandi, 2009 (19)	Obstructive CAD (≥50%)	24.0	Combined CV	20	0/0	3	1	16/0	N.R.
Rubinshtein, 2009 (23)	Obstructive CAD (≥25%)	18.2	Combined CV (revasc. ≥30 days)	53	0/13	18	0	38/0	Age, sex, CAC, risk factors
van Werkhoven, 2009 (12)	Obstructive CAD (≥50%) Segments with obstructive CAD Presence of plaque Segment of any plaque Segment with MCAP, NCAP, CAP	22.3	Combined CV	13	5/0	3	5	0/0	Age, sex (CAC)
van Werkhoven, 2009 (24)*	Obstructive CAD (≥50%) Presence of plaque	20.4†	Combined CV	21	6/0	8	7	0/0	CVRF

*In 2009, the same lead author published in *Heart* (12) and the *European Heart Journal* (24). †Median provided.

AC = all cause; BMI = body mass index; CABG = coronary artery bypass graft; CAC = coronary artery calcification; CAD = coronary artery disease; CAP = coronary atherosclerotic plaque; CT = computed tomography; CV = cardiovascular; CVRF = cardiovascular risk factors; EBCT = electron-beam computed tomography; LM = left main; MCAP = mixed atherosclerotic plaque; MI = myocardial infarction; NCAP = non-calcified atherosclerotic plaque; N.R. = not reported; PCI = percutaneous coronary intervention; revasc. = revascularization; SNR = signal-to-noise-ratio; UAP = unstable angina pectoris.

risk estimate was included in the analysis (with the associated 95% CI).

EVENT RATES. To provide information on absolute risks, we derived the number and type of events for the presence and absence of CT findings from the original studies. All events were annualized by using the provided average follow-up time (median was used in 3 studies [10–12]) and summarized by weighting by sample size.

ASSUMPTIONS. To harmonize the CT predictors of interest, we made the following assumptions. We excluded the predictor "severe" stenosis (defined as >70% luminal narrowing) as a too optimistic assumption from the analysis for the primary predictor of interest in 1 study (13), according to the lead author's recommendation. Also, to derive the pooled risk estimate for the presence of left main coronary artery stenosis, we included 1 study that reported the risk associated with the presence of ≥30% luminal narrowing (14), and 1 study that reported a combined predictor additionally including the proximal left anterior descending coronary artery (11). As 1 study reported on the risk associated with the absence of any atherosclerotic plaque (13), the risk associated with any atherosclerotic plaque was derived by the reciprocal.

Data analysis and statistical methods. The primary objective of this systematic review was to assess the relationship between the coronary CTA finding of a significant coronary stenosis (>50% luminal narrowing) and a combined cardiovascular endpoint. Secondary predictors of interest included the presence of any atherosclerotic plaque, presence of a significant left main stenosis, and the risk associated with each coronary segment containing plaque (17-segment model of the American Heart Association) (15).

We used the metafor package in the statistical software package R (version 2.10.0) to pool the natural logarithms (ln) of the HR, using a random effect model (restricted maximum-likelihood estimator). Between-study heterogeneity was examined using the Q statistic and the I^2 statistic (16). Publication bias was assessed using plots of study results against precision of the study (funnel plots). Symmetry of the funnel plots was tested using the methods suggested by Egger et al. (17) and Begg and Mazumdar (18).

Given the detected high degree of heterogeneity of the risk ratios, we subsequently conducted meta-regression analysis to explore pre-defined sources of heterogeneity of our primary predictor of interest. The following pre-specified variables were analyzed: average age, proportion of males, proportion of subjects with body mass index ≥30 kg/m^2, history of CAD, CT technology employed (64-slice vs. other), follow-up time (average), type of endpoint (all-cause mortality vs. combined endpoint), multivariate adjustment (yes/no), potential of model overfitting (yes/no, defined by the presence of >1 covariate for 9 to 10 outcome events in the multivariate models), and study quality (score containing number of quality indicators). For all these pre-specified variables, subgroup analysis for the primary predictor of interest was performed to further investigate effect modification, and HRs were estimated for each subgroup (stratified by median). A p value ≥0.1 was selected to indicate absence of significant heterogeneity of the estimates. For obesity, body mass index was converted to the prevalence of obesity (body mass index >30 kg/m^2) by assuming normal distribution.

To determine whether the predictive value was independent of coronary artery calcification, we fitted a mixed regression model for the occurrence of events and modeled a binary variable whether the study was adjusted for coronary artery calcification or not, as a covariate. Again, the most adjusted estimated variable was included and statistical difference of the covariate was determined.

All analysis was performed using R (version 2.10.0), and a p value <0.05 was considered to indicate statistical significance.

Results

We identified 11 studies that met the inclusion criteria and provided at least 1 risk ratio (Fig. 1) (10–14,19–24). Characteristics of all selected studies are detailed in Table 1. Overall, we included a total of 7,335 subjects (average age 59.1 ± 2.6 years, 62.8% male) with an average follow-up ranging between 14 and 78 months (median 20.4 months). The majority of included studies had a single-center design (82%, 9 of 11) and were conducted in Europe or the United States (55% and 36%, respectively); only 1 study was from the Middle East (23).

The study population consisted of patients referred for suspected coronary artery disease (100%). Two studies (18%) additionally included subjects with known coronary artery disease. There was substantial heterogeneity among the reported CT findings (Table 1), and several studies did not provide all pre-specified parameters. The 64-slice CT technology was used in 7 studies (64%), 16-slice technology was used in 2 studies (18%) (11,13), and 2 studies used electron-beam CT (18%) (21,22). The number of observed outcome events as well as type of event by study is detailed in Table 1.

Coronary stenosis by coronary CT angiography. Among the included publications, 9 studies analyzed a combined cardiovascular endpoint and provided an HR for the presence of significant coronary stenosis (10–12,14,19–21,23,24). They included a total of 3,670 participants who were followed up to 27.6 months (average 21.9 months). Based on 252 (6.8%) outcome events (6% all-cause, 6% cardiovascular mortality, 23% nonfatal MI, 4% unstable angina requiring hospitalization, and 62% revascularizations), the combined estimated HR was 10.74 (95% CI: 6.37 to 18.11) (Table 2, Fig. 2), indicating an approximately 10-fold higher risk among subjects with any detectable coronary stenosis by CTA compared with subjects without coronary stenosis. The annualized (and weighted by sample size) event rates among subjects with and without significant coronary stenosis (weighted prevalence 70.7% and 29.3%, respectively) were 11.9% and 1.1%, respectively (Table 3) with substan-

Table 2 Summary Estimates of Relative Risks Associated With Secondary Coronary CT Angiographic Findings

CT Angiography Finding	$n_{Studies}$	$n_{Participants}$	Events	Hazard Ratio* (95% CI)	I^2	p Value	Z	p Value
Significant coronary stenosis	9	3,670	252	10.74 (6.4–18.1)	85%	<0.001	1.34	0.18
Left main coronary artery stenosis	4	1,674	142	6.64 (2.6–17.3)	71.9%	0.009	0.49	0.62
Each significant coronary stenosis	4	1,879	145	1.35 (1.1–1.7)	95.1%	<0.001	0.41	0.52
3-vessel disease	2	3,665	125	2.50 (1.9-3.3)	0%	0.55	0.32	0.87
Any atherosclerotic plaque	6	4,733	244	4.51 (2.2–9.3)	26.7%	0.33	0.96	0.32
Each coronary segment containing plaque	5	2,106	163	1.23 (1.17–1.29)	7.6%	0.35	−0.7	0.50
Each coronary segment containing noncalcified plaque	4	979	124	1.29 (1.2–1.4)	0%	0.13	0.27	0.91

Data are summarized hazard ratios (95% confidence intervals [CIs]). *As derived from meta-regression analysis.
CT = computed tomography; $n_{Participants}$ = number of subjects included in analysis; $n_{Studies}$ = number of studies included in analysis.

tial variability being present (i.e., annualized event rate in subjects with a significant coronary stenosis: 3.3% to 57.7%).

There was significant between-study heterogeneity (Q statistic, $p < 0.001$), and according to the I^2 test, 71.8% of the variability could be explained by between-study heterogeneity. The funnel plot revealed no statistical sign of asymmetry ($z = 1.34$, $p = 0.18$).

In meta-regression analysis (Table 4), the risk estimate derived from studies that included revascularization in their endpoint was significantly higher than studies excluding revascularization from their endpoint ($p = 0.03$), indicating a substantial source of heterogeneity. After exclusion of revascularization from the endpoint, the annualized total event rate was 6.4% (overall annualized event rate dropped from 5.0% to 1.7% for all studies vs. studies excluding revascularization from the endpoint, respectively). Also, average age in the source population and study quality score were identified to be a significant source of heterogeneity ($p = 0.02$ and $p = 0.001$, respectively). In contrast, there was no significant source of heterogeneity associated with the proportion of males, obesity, history of CAD, CT technology used (64-slice vs. other), follow-up time, and potential overfitting of the models (Table 4).

Incremental value beyond calcium scoring. Three studies including 3,465 participants and 128 cardiovascular events provided analyses of the incremental value of coronary CTA beyond coronary calcification through multivariate analysis (21,22,24). The association between the presence of significant coronary stenosis or any plaque and cardiovascular events remained highly significant after adjustment for coronary calcium (HR: 11.24 vs. 10.42, $p = 0.79$, respectively).

Secondary predictors. Combined risk estimates as well as study characteristics for the secondary CT predictors of interest are detailed in Table 2 and Figures 3 and 4). The estimated increased risk associated with each coronary stenosis (maximum of 17) was ~35% (HR: 1.35, 95% CI:

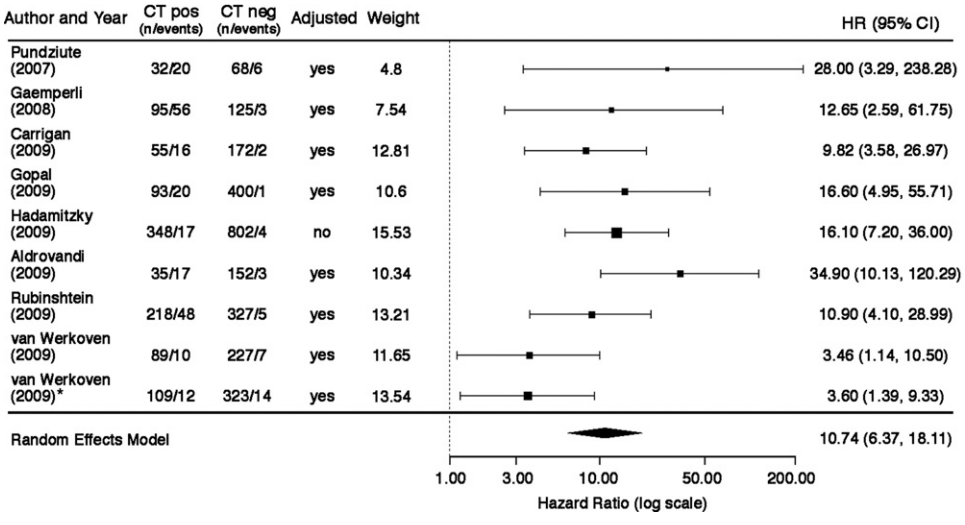

Figure 2 Forest Plot of Single Studies in Analysis for Risk Associated With Significant Coronary Stenosis

"Adjusted" indicates whether multivariate adjustment was performed. **Horizontal lines** represent 95% confidence intervals (CIs). The **rectangles** represent the point estimate, and the size of the rectangle is proportional to the weight given to each study in the meta-analysis. The **diamond** represents the summary estimate (**size of the diamond** = 95% CI). The **dashed vertical line** represents the reference of no increased risk. *In 2009, the same lead author published in *Heart* (12) and the *European Heart Journal* (24). CT = computed tomography; HR = hazard ratio; neg = negative; pos = positive. Figure illustration by Craig Skaggs.

Table 3 CT Angiographic Finding of Any Significant Coronary Stenosis and Any Atherosclerotic Plaque, Number of Events (%), and Annualized Event Rates

First Author, Year (Ref. #)	N	All Annualized Event Rate		CT Positive			CT Negative		
		All	Excluding Revasc.	Prevalence (%)	No. of Events (%)	Annualized Event Rate	Prevalence (%)	No. of Events (%)	Annualized Event Rate
Presence of significant coronary stenosis									
Pundziute, 2007 (11)	100	24.0%	6.4%	32 (32.0%)	20 (62.5%)	57.7%	68 (68.0%)	6 (8.8%)	8.1%
Gaemperli, 2008 (20)	220	23.0%	3.5%	95 (43.2%)	56 (58.9%)	50.5%	125 (56.8%)	3 (2.4%)	2.1%
Carrigan, 2009 (14)	227	3.5%	0.7%	55 (24.2%)	16 (29.1%)	12.7%	172 (75.8%)	2 (1.2%)	0.5%
Gopal, 2009 (21)	493	1.2%	1.2%	93 (18.9%)	20 (21.5%)	6.5%	400 (81.1%)	1 (0.3%)	0.09%
Hadamitzky, 2009 (10)	1,150	1.2%	0.3%	348 (30.3%)	17 (4.9%)	3.3%	802 (69.7%)	4 (0.5%)	0.33%
Aldrovandi, 2009 (19)	187	5.4%	1.0%	35 (18.7%)	17 (48.6%)	24.3%	152 (81.3%)	3 (2.0%)	1.0%
Rubinshtein, 2009 (23)	545	6.4%	3.0%	218 (40.0%)	48 (22.0%)	14.5%	327 (60.0%)	5 (1.5%)	0.99%
van Werkhoven, 2009 (12)	316	2.2%	1.3%	89 (28.2%)	10 (11.2%)	6.0%	227 (71.8%)	7 (3.1%)	1.7%
van Werkhoven, 2009 (24)	432	2.9%	1.9%	109 (25.2%)	12 (11.0%)	6.5%	323 (74.8%)	14 (4.3%)	2.5%
Weighted average		5.0%	1.7%	29.3%		11.9%	70.7%		1.1%
Presence of any atherosclerotic plaque									
Pundziute, 2007 (11)	100	24.0%	6.4%	80 (80%)	26 (32.5%)	30.0%	20 (20%)	0 (0%)	0%
Gaemperli, 2008 (20)	220	23.0%	3.5%	177 (80.5%)	59 (33%)	28.3%	43 (19.5%)	0 (0%)	0%
Ostrom, 2008 (22)	2,538	0.5%	0.02%	1,453 (57.3%)	68 (4.7%)	0.72%	1,085 (42.7%)	18 (1.7%)	0.26%
van Werkhoven, 2009 (12)	316	2.2%	1.3%	231 (73.1%)	15 (6.5%)	3.5%	85% (26.9%)	1 (1.2%)	0.64%
van Werkoven, 2009 (24)*	432	2.9%	1.9%	299 (69.2%)	24 (8.4%)	4.9%	133 (39.8%)	3 (2.3%)	1.35%
Weighted average		3.0%	0.08%	62.3%		4.0%	37.8%		0.4%

Prevalence of computed tomography (CT) angiographic finding of any significant coronary stenosis (top part of the table) and any atherosclerotic plaque (bottom part of the table), number of events (%), and annualized event rates among all subjects (also excluding revascularization [Revasc.] as an endpoint) and in subjects with CT positive and CT negative findings (presence and absence of CT angiographic finding) as derived from crude event numbers provided in the source publications. Averages of risks are weighted by sample size. One study (Min, 2007 [13]) was excluded from the table because events according to CT finding category was not provided. *In 2009, the same lead author published in *Heart* (12) and the *European Heart Journal* (24).

1.1 to 1.7) (Fig. 3B) and ~550% (HR: 6.64, 95% CI: 2.60 to 17.3) (Fig. 3A) for the presence of left coronary artery stenosis compared with subjects without left main coronary artery stenosis. There was significant variability of the risk estimate (I^2 = 71.9% and 77.7%, respectively), which was attributed to higher risk in studies including revascularization in their endpoint (p = 0.04 and p = 0.05, respectively) and a higher prevalence of history of CAD (both p = 0.05). The presence of 3-vessel disease was associated with a 2.5-fold risk compared with subjects without 3-vessel disease (HR: 2.50, 95% CI: 1.9 to 3.3) (Fig. 3C); no heterogeneity and no publication bias were detected (p = 0.55 and 0.87, respectively).

On average, presence of any atherosclerotic plaque was detected in the majority of subjects (weighted average 62.2%) with an event rate of 0.4% among subjects without any plaque (Table 3). Subjects with any plaque detected by CT were at a ~4.5-fold risk for events compared with subjects without plaque detected (HR: 4.51, 95% CI: 2.2 to 9.3) (Fig. 4A). Also, significant increased risk was associated with each segment containing any detectable plaque (HR: 1.23, 95% CI: 1.17 to 1.29) (Fig. 4B), and noncalcified plaque (HR: 1.29, 95% CI: 1.2 to 1.4) (Fig. 4C); no heterogeneity or publication bias was detected.

Discussion

To our knowledge, this is the first study combining available evidence on the predictive value of coronary CTA in a comprehensive analysis of the associated risks and identifying sources of heterogeneity of the existing data. These data may be particularly relevant to homogenize reporting standards for cardiac CT, to determine appropriate design of prospective randomized trials for risk modification on the basis of cardiac CT findings, and to estimate the potential impact of noninvasive CT imaging on healthcare systems (25).

The results of this systematic review and meta-analysis indicate that CT-based findings of coronary plaque and stenosis are strong independent predictors of future cardiovascular events. Specifically, the presence of significant coronary stenosis was associated with a 10-fold higher risk for all cardiovascular events (cardiovascular death, nonfatal MI, unstable angina requiring hospitalization, and revascularization) and 6-fold risk for death, MI, and unstable angina requiring hospitalization independent of coronary artery calcification. Moreover, our results show that there is a 4.5-fold risk associated with the presence of any CAD and that each diseased coronary segment portraits a 23% higher risk for adverse outcomes. We also demonstrated that choice of endpoints, classification of CT findings, study quality, and study population (age) introduced substantial heterogeneity with respect to risk prediction among existing studies.

Our data show that the heterogeneity among studies can be partially attributed to differences in the classification and reporting of CT findings. In fact, there was no single CT predictor of interest uniformly reported across all 11 studies

Table 4 Random Effect Meta-Analysis of Relationship Between CT Angiographic Finding on Coronary Plaque and Stenosis Risk of Combined Cardiovascular Event Stratified According to Potential Sources of Heterogeneity

Variable	Studies	Events/Participants	Hazard Ratio (95% CI)	p Value for Difference
Average age, yrs				
>58*	4	126/1,657	19.83 (10.04–39.16)	0.02
≤58	5	126/2,013	7.17 (4.23–12.15)	
Proportion of males				
>65%*	5	180/2,508	15.25 (7.23–32.21)	0.21
≤65%	4	72/1,162	8.04 (4.13–15.67)	
Obesity (BMI ≥30 kg/m^2)				
>22.6%*	2	77/447	12.75 (4.51–36.12)	0.43
≤22.6%	4	75/2,085	7.07 (2.5–19.95)	
History of CAD				
Any history	2	85/320	17.27 (3.81–78.27)	0.51
None	7	167/3,350	10.06 (5.66–17.87)	
CT technology				
64-slice CT	7	205/3,077	9.63 (5.42–25.07)	0.34
16-slice/EBCT	2	47/597	19.56 (5.10–75.01)	
Follow-up time, months				
>22.3*	4	80/1,339	11.65 (5.42–25.07)	0.72
≤22.3	3	172/2,331	14.39 (5.86–35.37)	
Revasc. in endpoint				
Revasc. not included	3	55/1,241	6.15 (3.22–11.74)	0.03
Revasc. included	6	197/2,429	15.41 (8.92–26.62)	
Adjusted analysis				
Adjusted	7	213/2,520	8.18 (4.79–13.99)	0.28
Unadjusted	1	21/1,150	16.1 (5.28–49.10)	
Study quality				
Higher	5	106/2,157	16.83 (10.08–28.11)	0.001
Lower	4	146/1,513	5.86 (3.34–10.29)	
Potential model overfitting				
No	3	133/1,915	13.27 (5.41–32.57)	0.57
Yes	6	119/1,755	9.58 (4.88–18.80)	

*Stratified by median.
Revasc. = revascularization defined as percutaneous coronary intervention or bypass; other abbreviations as in Tables 1 and 2.

(Table 1). That severely limits the comparability and pooling of available outcome data. Our study demonstrates that the following CT findings are associated with worse outcomes and thus should be included as standard reporting elements in clinical reports as well as in future research studies: 1) the presence of at least 1 coronary artery stenosis exceeding ≥50% diameter stenosis per patient; 2) the number of coronary segments containing at least 1 coronary artery stenosis exceeding ≥50% diameter; 3) left main coronary artery disease; 4) the presence of any detectable atherosclerotic plaque (regardless of severity) per patient; and 5) the number of segments containing any nonobstructive plaque, calcified, noncalcified, and mixed plaque (noncalcified and calcified plaque components).

Another major difference across studies was related to the choice of outcomes. Forty percent of studies (data not shown) reported on multiple events per subject with subjects reaching soft and hard endpoints subsequently (i.e., unstable angina followed by revascularization procedure). Although in each study the relative risks were adequately derived, further pooled analysis on hard and soft endpoints was unattainable.

We detected higher risk associated with CT findings in studies including revascularization compared to studies without CT findings. That is particularly relevant as 62% of all endpoints were revascularizations, and whereas the annualized overall event rate was 5% across all studies, it dropped significantly to 1% for death, nonfatal MI, and unstable angina requiring hospitalization. Because coronary revascularization in this context is a management option without any proven effect of health outcomes, it should be reported in conjunction with test utilization and efficiency of cardiac CTA rather than efficacy and effectiveness. As virtually all CT results were unblinded, differences in outcomes and strength of associations may therefore also be an expression of the substantial work-up bias/confounding by indication. However, although a number of studies excluded revascularizations within 30 days after CT imaging, its choice as an endpoint in prognostic studies remains questionable. It appears that classical endpoints such as death, MI, and unstable angina requiring revascularization should be used for imaging studies as well. Therefore, it is clear that a prospective study focusing on clinically more

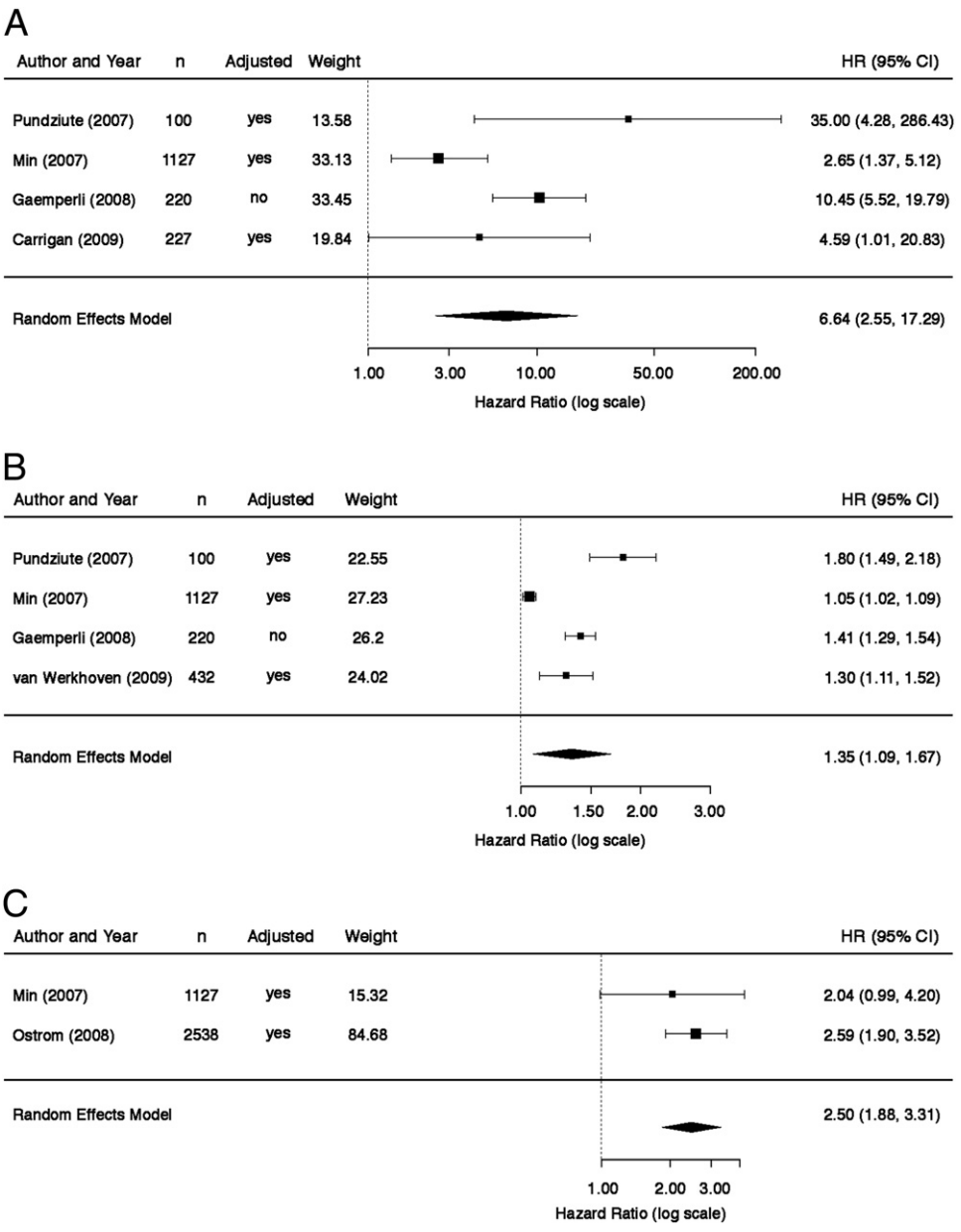

Figure 3 **Risk Estimates for the Presence of Left Main Stenosis, per Significant Stenosis, and 3-Vessel Disease**

(A) Presence of left main coronary artery stenosis. **(B)** Each significant coronary artery stenosis (maximum of 17). **(C)** Presence of 3-vessel obstructive disease. "Adjusted" indicates whether multivariate adjustment was performed. **Horizontal lines** represent 95% confidence intervals (CIs). The **rectangles** represent the point estimate, and the **size of the rectangle** is proportional to the weight given to each study in the meta-analysis. The **diamond** represents the summary estimate (**size of the diamond** = 95% CI). The **dashed vertical line** represents the reference of no increased risk. Figure by Craig Skaggs. HR = hazard ratio.

relevant endpoints would need a very high sample size, as these event rates are very low. An example is the ongoing 10,000-patient PROMISE (PROspective Multicenter Imaging Study for the Evaluation of Chest Pain) trial, which compares hard endpoints for functional versus anatomic testing in patients with suspected CAD.

The importance of exact outcome and population definitions is further supported by substantial variability of the annualized event rates and prevalence of CT findings among subjects with and without significant coronary stenosis (~3 up to 58% annualized event rate), which was clearly dependent on whether revascularization was included in the endpoint or not (annualized event rate 11.9% vs. 6.4% for studies including vs. excluding revascularization, respectively). Also, partially, the variability may be attributable to population difference and differences in clinical setting as the prevalence of CT findings was similarly heterogeneous (18% up to

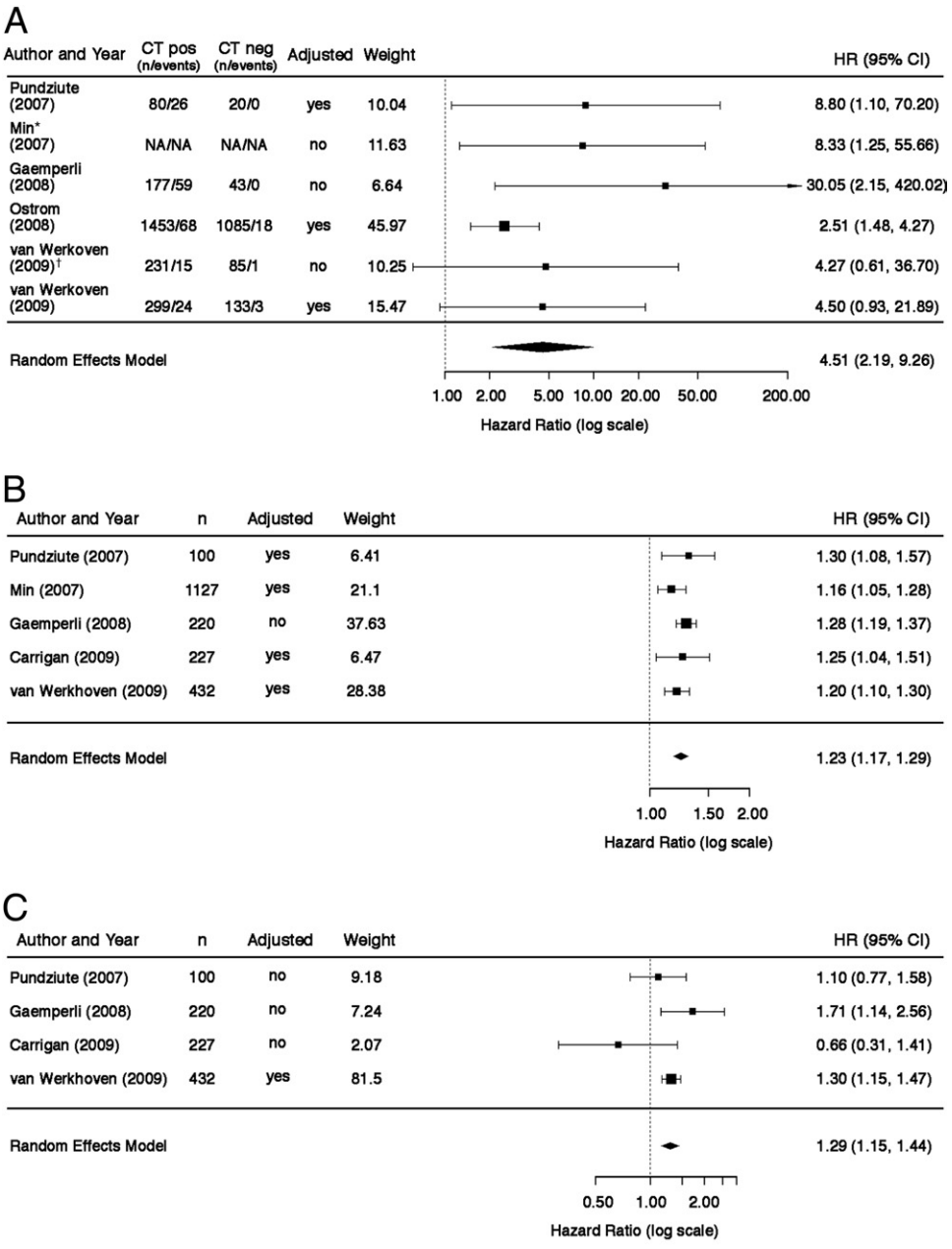

Figure 4 **Risk Estimates for the Presence of Plaque, per Segment of Any Plaque, per Segment of Noncalcified Plaque**

(A) Any atherosclerotic plaque within the coronary artery tree. **(B)** Each coronary segment containing any atherosclerotic plaque (maximum of 17). **(C)** Each coronary segment containing noncalcified atherosclerotic plaque. *As derived by the reciprocal. †In 2009, the same lead author published in *Heart* (12) and the *European Heart Journal* (24). "Adjusted" indicates whether multivariate adjustment was performed. **Horizontal lines** represent 95% confidence intervals (CIs). The **rectangles** represent the point estimate, and the **size of the rectangle** is proportional to the weight given to each study in the meta-analysis. The **diamond** represents the summary estimate (**size of the diamond** = 95% CI). The **dashed vertical line** represents the reference of no increased risk. Figure by Craig Skaggs. CT = computed tomography; HR = hazard ratio; N/A = not applicable.

40% for the presence of significant stenosis), of which we identified age as a major source.

Our results further indicate that coronary CTA may provide incremental prognostic information beyond the analysis of coronary calcium. However, this finding is only based on 3 studies and will thus need to be confirmed in larger, dedicated analyses. That is specifically relevant as the incremental value of CAC beyond established risk factors is well known (2), and coronary calcium scores are easily obtainable whereas coronary CTA requires more sophisticated equipment, injection of contrast, and higher radiation exposure. Interestingly, in a large meta-analysis on the

predictive value of CAC by Pletcher et al. (26), the investigators derive a 10-fold pooled estimate associated with an Agatston score ≥400, similar to our derived estimates for the presence of significant coronary stenosis. An interesting objective for future research will be to determine whether an Agatston score ≥400 is associated with a similar risk as the presence of significant coronary stenosis.

We also present initial summary risk estimates for the presence and extent of exclusively noncalcified plaque, which may be 1 of the potential benefits of cardiac CTA as it represents up to 80% of the total atherosclerotic plaque burden (27), and on a case basis is considered to be associated with acute coronary syndrome (28). Our results indicate that the extent of noncalcified plaque was associated with a slightly higher risk as any atherosclerotic plaque (HR: 1.29 vs. 1.23, respectively); however, we did not have the statistical power to detect true difference between the 2 entities of atherosclerotic plaque as the finding was based on 3 smaller studies only (11,20,24). Thus, further research is necessary to elucidate the incremental value of noncalcified plaque beyond the calcified plaque component.

Study limitations. Notably, our results were derived from cohorts enrolling symptomatic subjects, and all subjects underwent cardiac CTA for clinically suspected CAD. Thus, our results do exclusively apply to these symptomatic patients and cannot be generalized to an asymptomatic population. That is in line with recommendations from clinical practice guidelines (2), which recommend cardiac CTA in the diagnostic setting by ruling out significant coronary artery disease in low-risk to intermediate-risk populations. Nevertheless, in these subjects, the prognostic information pertaining to distinct CT findings is available at no extra cost and can potentially help to improve risk assessment. Potentially, further advances in technology to reduce radiation exposure, including prospective triggering and high-pitch protocols, will make scanning of asymptomatic subjects for risk stratification more amenable.

We were not able to analyze the incremental predictive value of CT findings on plaque and stenosis beyond other markers of cardiovascular risk as only 1 study assessed the prognostic value over single-positron emission CT myocardial perfusion imaging (6). In this study, Van Werkhoven et al. (6) found a synergistic role of both modalities covering anatomical and functional information for risk stratification. Clearly, upcoming studies should focus on the incremental value of cardiac CT in comparison with other imaging techniques, such as single-positron emission CT and echocardiography as well as serum biomarkers or clinical prediction rules of increased risk.

Importantly, a general limitation of this analytic technique is that the validity of the results depends on each single original study. Also, our meta-analytic approach relied on combining the aggregate HR and associated 95% CI from each trial using random-effect modeling accounting for heterogeneity among the original studies. Also, the number of potential confounders we investigated in meta-regression was high, with the risk of false positive findings. Given the nature of published reports, we were unable to combine individual patient outcome data of each study, which may have provided more insight into particular subgroups of patients. (Fig. 3)

Conclusions

In this meta-analysis, we identify a set of coronary CTA findings based on the presence and extent of CAD that are strong predictors of cardiovascular events in symptomatic subjects clinically referred for cardiac CT, independent of coronary artery calcification and cardiovascular risk factors. We also demonstrate that choice of endpoints, classification of CT findings, and study population (age) introduced substantial heterogeneity with respect to risk prediction among existing studies.

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Key Words: cardiac computed tomography ■ coronary calcification ■ meta-analysis ■ noninvasive imaging ■ prognostic value.