Prognostic value of coronary anatomy and myocardial innervation imaging in cardiac disease

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Chapter 2

Prognostic value of coronary vessel dominance in relation to significant coronary artery disease determined with non-invasive computed tomography coronary angiography

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ABSTRACT

Aims:

Limited information is available regarding the relationship between coronary vessel dominance and prognosis. Therefore, the purpose of this study was to determine the prognostic value of coronary vessel dominance in relation to significant coronary artery disease (CAD) in patients referred for computed tomography coronary angiography (CTA).

Methods and Results:

The study population consisted of 1425 patients (869 men, 57±12 years) referred for CTA. To evaluate the impact of vessel dominance and significant CAD on CTA on outcome, patients were followed during a median period of 24 months for the occurrence of non-fatal myocardial infarction and all-cause mortality. The presence of a left dominant system was identified as a significant predictor for non-fatal myocardial infarction and all-cause mortality (HR 3.20; 95%CI 1.67-6.13, p<0.001) and had incremental value over baseline risk factors and severity of CAD on CTA. In addition, in the subgroup of patients with significant CAD on CTA, patients with left dominant system had worse outcome compared to patients with a right dominant system (cumulative event rates: 9.5% and 35% at 3-year follow-up for right and left dominant coronary artery system, respectively, log-rank p<0.001).

Conclusions:

The presence of a left dominant system was identified as an independent predictor of non-fatal myocardial infarction and all-cause mortality, especially in patients with significant CAD on CTA. Therefore, the assessment of coronary vessel dominance on CTA may further enhance risk stratification beyond the assessment of significant CAD on CTA.

INTRODUCTION

Non-invasive computed tomography coronary angiography (CTA) is increasingly used in clinical practice for visualization of the coronary arteries in patients with suspected or known coronary artery disease (CAD)[1-3]. Multiple studies demonstrated high diagnostic accuracy of CTA in detection of CAD. In addition to the good diagnostic performance, CTA also provides important prognostic information[4,5]. Several studies have shown that patients with significant CAD detected on CTA have worse overall outcome compared to patients without significant CAD[6,7]. However, CTA not only provides information about the presence and degree of coronary stenosis, it also allows the evaluation of cardiac anatomy including coronary vessel dominance. As a result, coronary vessel dominance is routinely determined on CTA. In the general population, right dominant coronary artery system is most prevalent, approximately 87% to 89%, while left dominant coronary artery system has a prevalence of 7% to 8% and balanced coronary artery system is present in approximately 4% of the population[8-10]. Although coronary vesssel dominance is easily assessed on CTA, limited information is available considering the prognostic value of coronary vessel dominance in patients referred for CTA. Moreover, the relation between coronary vessel dominance and the prognostic importance of a significant stenosis remains unclear. Therefore, the purpose of this study was to evaluate the prognostic relevance of coronary vessel dominance in the presence and absence of CAD determined on CTA.

METHODS

Patients and study protocol

The study population consisted of consecutive patients who were clinically referred for CTA because of typical chest pain or atypical chest pain in combination with an elevated risk profile for cardiovascular disease. Patients were enrolled at the Leiden University Medical Center in the Netherlands and at the University Hospital Zurich in Switzerland. Exclusion criteria were: 1) previous coronary artery bypass graft surgery (CABG); 2) (supra)ventricular arrhythmias; 3) renal insufficiency (defined as a glomerular filtration rate <30 ml/min); 4) known allergy to iodinated contrast agent; 5) severe claustrophobia and 6) pregnancy. Patient data were entered consecutively into the departmental patient information systems and retrospectively analysed. Patients with uninterpretable CTA examination were excluded from analysis. Patients referred for revascularization after CTA remained in the study population.

CTA data Acquisition

Patients were scanned using a 64-row CT scanner (Aquillion64, Toshiba Medical Systems, Otawara, Japan; General Electrics LightSpeed VCT, Milwaukee, WI, USA) or with a 320-row CT scanner (Aquilion ONE, Toshiba Medical Systems). Before examination patient's heart rate and blood pressure were monitored. In absence of contra-indications patients with a heart rate exceeding 65 beats/min received 50 or 100 mg oral metoprolol, or 5 to 10 mg metoprolol, intravenously. Scan acquisition parameters have been previously described[5,11,12]. A reconstruction dataset with the least motion artifacts was evaluated typically acquired during a mid-diastolic phase.

CTA image analysis

CTA reconstructions were transferred to dedicated workstations (Vitrea2, Vital Images, USA and Advantage, GE Healthcare, USA). CTA image analysis was performed by 2 observers in consensus, experienced in the evaluation of CTA. Coronary anatomy and coronary vessel dominance was assessed in a standardized manner by dividing the coronary artery tree into 17 segments according to the guidelines of the American Heart Association[13]. A coronary artery system was classified as right dominant when the posterior descending artery (PDA) originated from the right coronary artery (RCA), whereas a coronary artery system was considered left dominant if the PDA originating from the left circumflex artery (LCX). A coronary artery system was classified as balanced, when the PDA originated from the RCA in combination with a large postero-lateral branch originating from the LCX reaching near the posterior interventricular groove. Subsequently, the presence of CAD was assessed by scrolling through axial images, simultaneous with visual assessment of curved multiplanar reconstructions in at least 2 orthogonal planes. All 17 coronary segments were scored as 1) normal CTA or minor wall irregularities <30%, 2) non-obstructive CAD (defined as 30-50% luminal narrowing) or 3) significant CAD (defined as ≥50% luminal narrowing), as previously described[5]. In case of stented coronary segments, the presence of in-stent restenosis was analyzed as described before[14,15]. CTA results on a per patient basis were scored according to the 5 step score assessing both degree of stenosis and number of vessels affected, as previously described by Chow et al.[16]. The 5 categories were normal coronaries or minimal wall irregularities <30%, non-obstructive CAD and 1-, 2-, and 3-vessel disease.

Patient follow-up

Patients were entered prospectively into the departmental patient information system over a period of three years time. Follow-up information was obtained for all patients six months post-index CTA of the last patient entering the study. Based on the difference in inclusion date, follow-up time varied among patients with a minimal follow-up time of 6 months and a maximal follow-up of 3.5 years. Patient follow-up data were gathered by 3

observers blinded to the baseline CTA results using clinical visits or standardized telephone interviews.

Outcome measures

The primary endpoint was the composite of non-fatal myocardial infarction (MI) and all-cause mortality. Non-fatal MI was defined based on the criteria of typical chest pain, elevated cardiac enzyme levels, and typical changes on the ECG[17]. A secondary outcome was the occurrence of cardiac adverse events, defined as the composite of non-fatal MI and cardiac death. To obtain the cause of death, the electronic health records of the cardiology department were first consulted. If the cause of death could not be retrieved from these health records, general practitioners were contacted. Cases that remained unidentified were classified as unknown.

Statistical Analysis

Continuous variables were expressed as means and standard deviations (SD) and categorical baseline data were expressed in numbers and percentages. Kaplan Meier analyses stratified for coronary vessel dominance were performed to estimate the cumulative incidences of the primary and secondary endpoint in the total population, in patients without significant CAD on CTA and in patients with significant CAD on CTA. Annual event rates were calculated by dividing the Kaplan-Meier event rates by mean number of years follow-up.

Subsequently, Cox regression analysis for the primary and secondary endpoint was used to determine the prognostic value of coronary vessel dominance and CAD on CTA. The number of covariables included in the multivariate analysis was adjusted to the number of events. According to univariate significance and baseline differences between groups, age, smoking and diabetes were included in the multivariate model, together with the confounding factors gender and known CAD. The increase in global chi-square value was used to determine the incremental prognostic value of coronary vessel dominance over CAD on CTA and clinical risk factors. To avoid potential of overfitting in this extensive multivariate Cox regression model, two additional models were created only correcting for age, gender and overall plaque burden (model 1) and for age, gender and proximally located CAD (model 3). Furthermore, the prognostic value of significant stenosis location was determined for all patients, patients with right dominant coronary artery system and patients with left dominant coronary artery system. Adjusted hazard ratios (HR) with 95% confidence intervals (CIs) were reported. Statistical analysis was performed using SPSS software (version 16.0, SPSS Inc., Chicago, IL, USA). A p-value <0.05, 2-sided test, was considered statistically significant.

RESULTS

Patient population

The study population consisted of 1467 consecutive patients clinically referred for CTA at the Leiden University Medical Center (n=999, 68%) and at the University Hospital Zurich (n=468, 32%). In the total population the CTA examination was uninterpretable due to poor image quality in 42 (2.9%) patients. As a result, a total of 1425 patients (57±12 years old, 58% men) remained for analysis. In total, 1256 patients (88%) had a right dominant coronary artery system, while 131 patients (9.2%) had a left dominant and 38 patients (2.7%) had a balanced coronary artery system. The baseline characteristics of the patient population, categorized by coronary vessel dominance, are presented in Table 1. Overall baseline characteristics were similar between groups, although significant differences were observed for the presence of diabetes (22%, 34% and 45% for right, left and balanced coronary artery system, respectively, p=0.003).

Table 1. Patient characteristics

	Total n=1425	Right Dominant n=1256	Left Dominant n=131	Balanced n=38	p-value
Gender (male)	824 (58%)	733 (58%)	74 (57%)	17 (45%)	0.233
Age (years)	57 ± 12	57 ± 12	56 ± 12	54 ± 15	0.095
Reason for Referral					
Typical chest pain	213 (15%)	190 (15%)	18 (14%)	5 (13%)	0.870
Atypical chest pain and elevated risk profile	1212 (85%)	1066 (85%)	113 (86%)	33 (87%)	0.870
Clinical Risk Factors					
Diabetes	338 (24%)	276 (22%)	45 (34%)	17 (45%)	0.003
Hypercholesterolemia[a]	551 (39%)	495 (39%)	44 (34%)	12 (32%)	0.232
Hypertension[b]	683 (48%)	599 (48%)	61 (47%)	23 (61%)	0.299
Family history of CAD[c]	543 (38%)	476 (38%)	51 (39%)	16 (42%)	0.894
Current Smoking	354 (25%)	302 (24%)	43 (33%)	9 (24%)	0.102
Obesity (BMI ≥30 kg/m^2)	257 (18%)	222 (19%)	24 (18%)	11 (29%)	0.227
Known CAD					
Previous myocardial infarction	126 (8.8%)	116 (9.2%)	8 (6.1%)	2 (5.3%)	0.357
Previous PCI	155 (11%)	140 (11.1%)	10 (7.6%)	5 (13.2%)	0.423

Data are presented as mean values ± SD or n (%).

[a] Serum total cholesterol ≥230 mg/dl and/or serum triglycerides ≥200 mg/dl or treatment with lipid lowering drugs

[b] Defined as systolic blood pressure ≥140 mm Hg and/or diastolic blood pressure ≥90 mm Hg and/or the use of antihypertensive medication

[c] Defined as presence of coronary artery disease in first degree family members at <55 years in men and <65 years in women

BMI: body mass index; CAD: coronary artery disease; PCI: percutaneous coronary intervention.

Follow-up was obtained for 1347 (94.5%) patients, while 78 (5.5%) patients were lost to follow-up. The distribution of coronary vessel dominance was comparable between patients with and without complete follow-up. Furthermore, patients lost to follow-up were younger (53±11 years old), had less hypertension (28.2%) and diabetes (9.0%) and were less often known with CAD (3.8%) compared to patients with follow-up.

CTA Results

CTA was classified as normal CTA or minor wall irregularities < 30% in 503 (35%) patients, non-significant CAD in 479 (34%) patients, and significant CAD in 443 (31%) patients (Table 2). Of those patients with significant CAD on CTA, 246 patients had 1-vessel disease, 125 patients had 2-vessel disease and 72 patients were diagnosed with 3-vessel disease. Furthermore, the distribution of significant CAD on CTA did not differ significantly among patients with a right dominant, left dominant and balanced coronary artery systems. However, normal CTA or minor wall irregularities <30% were observed less frequently in patients with right dominant coronary artery system compared to patients with a left dominant and balanced coronary artery systems (34%, 44% and 45%, respectively, p=0.031)

Table 2. CTA results

	Total n=1425	Right Dominant n=1256	Left Dominant n=131	Balanced n=38	p-value
CAD on CTA					
Normal CTA or minor wall irregularities (<30%)	503 (35%)	428 (34%)	58 (44%)	17 (45%)	0.031
Non-significant CAD on CTA (30-50%)	479 (34%)	428 (34%)	38 (29%)	13 (34%)	0.504
Significant CAD on CTA (>50%)	443 (31%)	400 (32%)	35 (27%)	8 (21%)	0.186
1 vessel disease (>50%)	246 (17%)	224 (18%)	18 (14%)	4 (11%)	0.268
2 vessel disease (>50%)	125 (8.7%)	110 (7.7%)	13 (9.9%)	2 (5.3%)	0.670
3 vessel disease (>50%)	72 (5.1%)	66 (5.3%)	4 (3.1%)	2 (5.3%)	0.548
Significant stenosis location					
RCA	217 (15%)	205 (16%)	9 (7.2%)	3 (8.0%)	0.020
LM	27 (1.9%)	25 (2.0%)	1 (0.8%)	1 (2.6%)	0.325
LAD	324 (23%)	290 (23%)	27 (21%)	7 (18%)	0.723
LCX	163 (11%)	140 (11%)	19 (15%)	4 (11%)	0.484
Overall plaque burden					
Mean number of diseased segments (>30%)	3.1 ± 3.5	3.2 ± 3.5	2.5 ± 3.2	3.6 ± 4.3	0.697
Mean number of proximal diseased segments (>30%)	1.3 ± 1.4	1.3 ± 1.4	1.1 ± 1.3	1.4 ± 1.5	0.071

Comparison of CTA results between coronary vessel dominance groups. Data are presented as mean values ± SD or n (%).

CAD: coronary artery disease; CTA: computed tomography coronary angiography; RCA: right coronary artery; LAD: left anterior descending artery; LCX: left circumflex artery; LM: left main artery.

(Table 2). In addition, there was no difference in the extent of CAD, since the number of vessels affected and the overall plaque burden were comparable between groups (Table 2). Specifically looking at significant stenosis location, the prevalence of a significant stenosis in the RCA was higher in patients with right dominant coronary artery system as compared to patients with a left dominant and balanced coronary artery system (16%, 7% and 8%, respectively, p=0.020), while the prevalence of a stenosis in the LAD and LCX did not differ among groups (Table 2).

Cardiac events

During a median follow-up time of 24 months (25^{th}-75^{th} percentile: 15-37 months), the composite endpoint occurred in 57 (4.0%) patients. Specifically, non-fatal myocardial infarction was reported in 18 (1.3%) patients, while cardiac death occurred in 9 (0.6%) patients and 30 (2.1%) patients died due to non-cardiac death. Causes of the 30 non-cardiac deaths were malignancy (6 deaths), sepsis (5 deaths), respiratory insufficiency (4 deaths), vascular events (3 deaths), post-operative non-cardiac complications (3 deaths) and other causes (7 deaths). In two cases the reason of death remained unknown. A total of 120 (8.4%) patients underwent revascularization, in 87 (6.1%) by percutaneous coronary intervention (PCI) and in 33 (2.3%) by CABG. No differences in referral for coronary revascularization after CTA were observed between the different coronary vessel dominance groups (revascularization rate of 8.6%, 7.6% and 5.3% in patients with right dominant, left dominant and balanced coronary artery systems respectively, p=0.706). Peri-procedural complications were observed in 4 (0.3%) patients. These 4 patients had a right dominant coronary artery system and experienced a non-fatal MI within 90 after revascularization by PCI.

Event rates during follow-up in relation to CAD on CTA and coronary vessel dominance

When comparing difference in event-free survival in the total study population according to coronary vessel dominance, the cumulative incidence of non-fatal myocardial infarction and all-cause mortality after 3 years of follow-up was 17% in patients with a left dominant coronary artery system, compared to 4.8% and 2.7% in patients with right dominant and balanced coronary artery systems, respectively (log-rank p<0.001, Figure 1). After stratification according to the absence or presence of significant CAD on CTA, patients without significant CAD showed to have good prognosis with low annual event rates for adverse cardiac events of 0.3%, as well as low annual event rates for the composite of non-fatal MI and all-cause mortality of 0.9% (Table 3). Furthermore, in patients without significant CAD no significant difference was observed in event-free survival between right dominant and left dominant coronary artery systems, with cumulative event rates of 2.4% and 7.4%

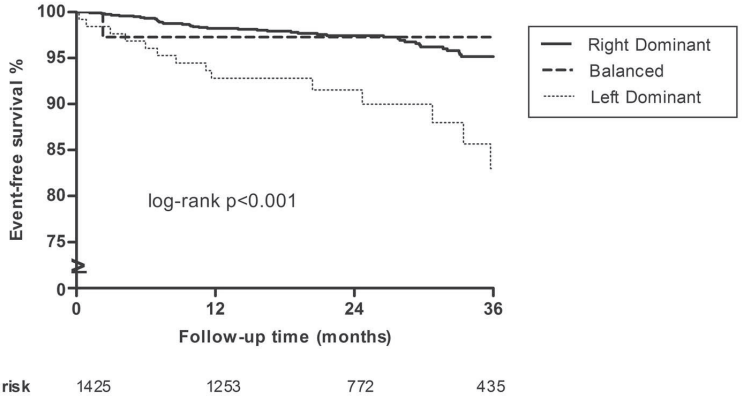

Figure 1. Kaplan Meier survival curve for non-fatal myocardial infarction and all-cause mortality in patients with right dominant, left dominant and balanced coronary artery system.
In the total study population statistically significant difference in event-free survival according to coronary vessel dominance was observed, showing a worse outcome in patients with a left dominant coronary artery system (log-rank p<0.001).

Table 3. Adverse (Cardiac) Events in patients with right and left dominant coronary artery systems stratified for significant CAD on CTA

	n	All Death	Cardiac Death	Non-Fatal MI	Combined Cardiac Death, Non-Fatal MI	Annual Event Rate	Combined All Death, Non-Fatal MI	Annual Event Rate
Total	1387	38* (2.7%)	9 (0.7%)	18 (1.2%)	27 (1.9%)	1.0%	56 (4.0%)	1.9%
Right dominant	1256	27 (2.1%)	4 (0.3%)	14 (1.1%)	18 (1.4%)	0.8%	41 (3.3%)	1.6%
Left dominant	131	11 (8.4%)	5 (3.8%)	4 (3.1%)	9 (6.9%)	2.8%	15 (11.5%)	4.5%
Log-rank p value		<0.001	0.061	0.047	<0.001		<0.001	
No significant CAD	952	15 (1.6%)	2 (0.2%)	4 (0.4%)	6 (0.6%)	0.3%	19 (2.0%)	0.9%
Right dominant	856	12 (1.4%)	2 (0.2%)	3 (0.4%)	5 (0.6%)	0.3%	15 (1.8%)	0.8%
Left dominant	96	3 (3.1%)	0 (0.0%)	1 (1.0%)	1 (1.0%)	1.1%	4 (4.2%)	2.1%
Log-rank p value		0.151	0.445	0.301	0.563		0.106	
Significant CAD	435	23 (5.3%)	7 (1.6%)	14 (3.2%)	21 (4.8%)	2.2%	37 (8.5%)	3.8%
Right dominant	400	15 (3.8%)	2 (0.5%)	11 (2.8%)	13 (3.3%)	2.0 %	26 (6.5%)	3.2%
Left dominant	35	8 (23%)	5 (14%)	3 (8.6%)	8 (23%)	7.9 %	11 (31%)	9.9%
Log-rank p value		<0.001	0.010	0.059	<0.001		<0.001	

Annual event rates were calculated by dividing the Kaplan-Meier event rates by mean number of years follow-up. Patient with balanced coronary artery system were excluded from the analysis. *One patient with balanced coronary artery system without significant CAD on CTA died because of non-cardiac death, accordingly in the total population of 1425 patients 39 patients died.
CAD: coronary artery disease; CTA: computed tomography coronary angiography; MI: myocardial infarction.

after 3 years of follow-up for right and left dominant coronary artery system, respectively (log-rank p=0.106; Figure 2A).

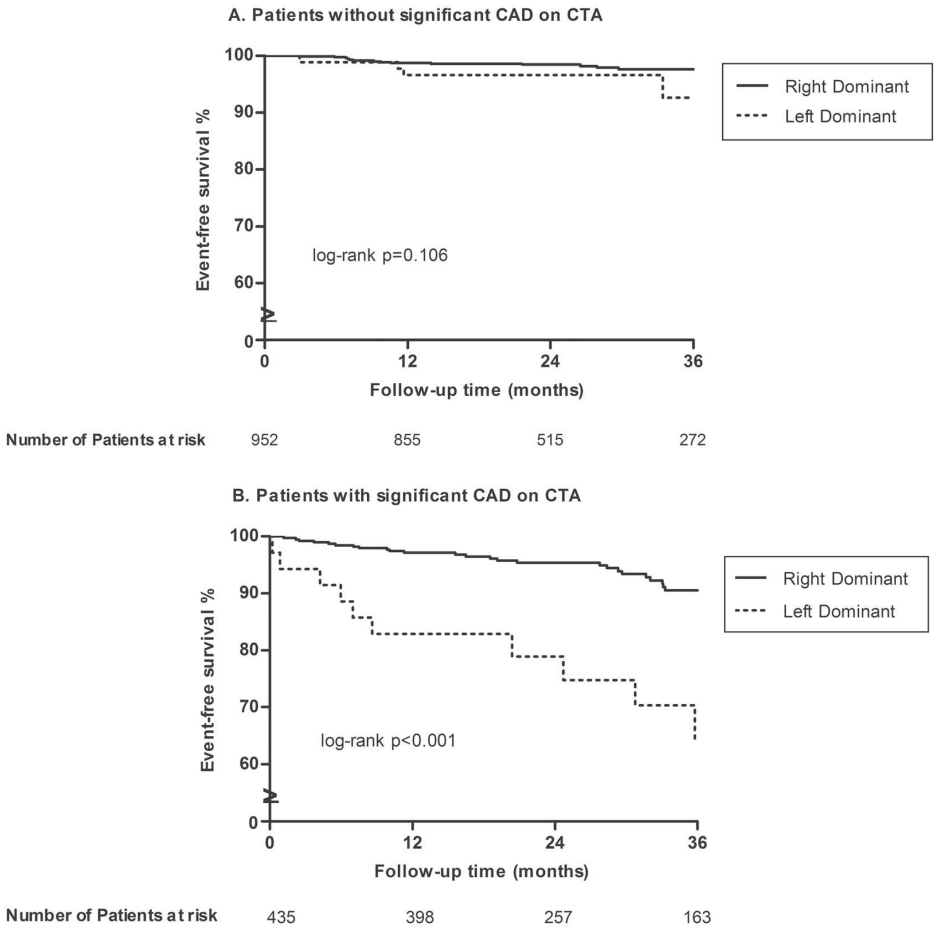

Figure 2. Kaplan Meier curve for non-fatal myocardial infarction and all-cause mortality in patients with right dominant and left dominant coronary artery system, stratified for the presence of significant CAD on CTA.

A: Patients without significant CAD on CTA. **B:** Patients with significant CAD on CTA. Patients with balanced coronary artery system were excluded from the analysis, because of the low number of patients in this group. Patients without significant CAD on CTA (A) had good event-free survival, showing no statistically significant difference in event-free survival between patients with a left dominant and a right dominant coronary artery system in this patient category (log-rank p=0.106). In the subgroup patients with significant CAD on CTA (B), patients with a left dominant coronary artery system had statistically significant worse outcome compared to patients with a right dominant coronary artery system (log-rank p<0.001).

CAD coronary artery disease; CTA computed tomography coronary angiography.

However, in patients with significant CAD higher annual event rates were observed for adverse cardiac events and the composite of non-fatal MI and all-cause death of 2.2% and 3.8%, respectively (Table 3). In addition, in the subgroup of patients with significant CAD differences in prognosis were observed between patients with right dominant and left dominant coronary artery system, because patients with a left dominant coronary artery system showed a significantly worse outcome with a cumulative incidence of non-fatal MI and all-cause mortality of 35% compared to 9.5% in patients with a right dominant coronary artery system within a follow-up period of 3 years (log–rank p<0.001; Figure 2B).

Incremental prognostic value

The incremental value of coronary vessel dominance and CAD on CTA was assessed for non-fatal MI and all-cause mortality (Table 4). Left dominant coronary artery system was identified as a significant predictor of the primary endpoint and remained a significant predictor after correction for baseline risk factors and CAD on CTA, with a HR of 3.20 (95% CI 1.67-6.13, p<0.001). Balanced coronary artery system did not predict for events (HR 0.82; 95%CI 0.11-6.05, p=0.842). In addition, significant CAD in 1 vessel was also identified as a predictor for non-fatal MI and all-cause mortality, with a HR of 2.79 (95%CI 1.03-7.60, p=0.045). Subsequently, the risk was increased when more vessels were diseased,

Table 4. Multivariate Cox regression analysis for the composite endpoint of non-fatal myocardial infarction and all-cause mortality including clinical risk factors, CTA results and coronary vessel dominance

	HR (95%-CI)	p-value
Clinical risk factors		
Age	1.06 (1.03-1.08)	<0.001
Gender (male)	1.33 (0.76-2.33)	0.320
Known CAD	1.25 (0.65-2.40)	0.506
Smoking	3.03 (1.79-5.12)	<0.001
Diabetes	1.53 (0.86-2.72)	0.146
CTA results		
Normal CTA or minor wall irregularities (<30%)	1.0 (reference)	
Non-significant CAD (30-50%)	1.44 (0.53-3.88)	0.473
1-vessel disease (>50%)	2.79 (1.03-7.60)	0.045
2-vessel disease (>50%)	3.59 (1.24-10.40)	0.019
3-vessel disease (>50%)	4.14 (1.31-13.06)	0.016
Coronary vessel dominance		
Right dominant coronary artery system	1.0 (reference)	
Left dominant coronary artery system	3.20 (1.67-6.13)	<0.001
Balanced coronary artery system	0.82 (0.11-6.05)	0.842

CAD: coronary artery disease; CI: confidence interval; CTA: computed tomography coronary angiography; HR: hazard ratio.

with a HR of 3.59 (95%CI 1.24-10.40, p=0.019) and a HR of 4.14 (95%CI 1.31-13.06, p=0.016) for 2- and 3-vessel disease, respectively. No interaction was observed for the effect of right dominant versus left dominant coronary artery system and the absence versus the presence of significant CAD on CTA for non-fatal MI and all-cause mortality (p-value for interaction=0.227). Furthermore, a significant increase in global chi-square values confirmed that CAD on CTA had incremental value over clinical risk factors (53.05 vs. 36.32, p=0.025) and that coronary vessel dominance had incremental value over CAD and clinical risk factors (65.53 vs. 52.05, p=0.006) (Figure 3). Additionally, in reduced Cox regression models left dominant coronary artery system remained a significant predictor for non-fatal MI and all-cause mortality with comparable risk estimates, when correcting for overall plaque burden (model 1), proximally located CAD (model 2) and the number of vessels with significant stenosis on CTA (Table 5). Subsequently, overall plaque burden, proximally located CAD and the number of vessels affected were identified as predictors of non-fatal MI and all-cause mortality with the highest HR of 1.68 (95% CI 1.32-2.14, p<0.001) for the number of vessels affected.

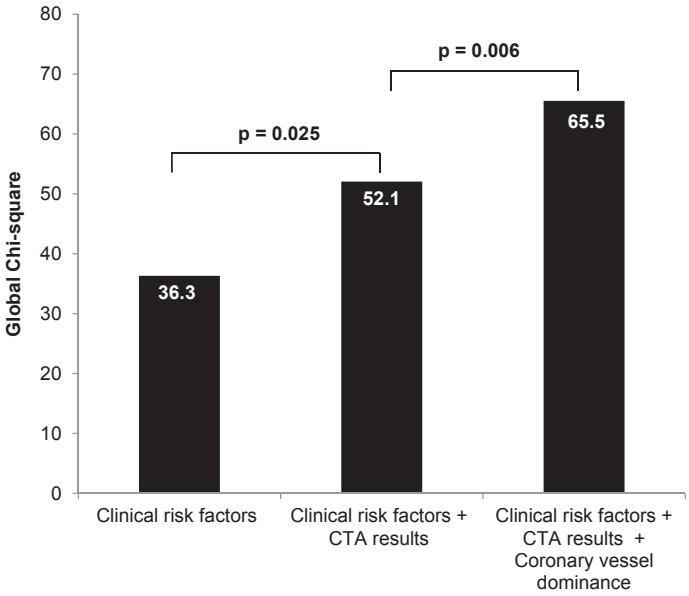

Figure 3. Bar graph illustrating the incremental prognostic value (depicted by χ^2 values on the y-axis) of clinical risk factors, CTA results and coronary vessel dominance.
The presence of significant CAD on CTA had a significant incremental prognostic value over the clinical risk factors age, gender, known CAD, smoking and diabetes (p=0.025). A further incremental prognostic value over clinical risk factors and significant CAD on CTA was observed with the addition of coronary vessel dominance (p=0.006). The CTA results included in the model consisted of the 5 categories: normal coronaries or minimal wall irregularities (< 30%), non-obstructive CAD (30-50%) and 1-, 2-, and 3-vessel disease (>50%).
CAD: Coronary artery disease; CTA: computed tomography coronary angiography.

Table 5. Reduced cox regression models of age and gender, CTA results and coronary vessel dominance for the composite endpoint of non-fatal myocardial infarction and all-cause mortality

	HR (95%-CI)	p-value
Model 1 : Overall Plaque burden on CTA		
Age	1.05 (1.02-1.08)	<0.001
Gender	1.28 (0.71-2.30)	0.406
Number of segments diseased (>30%)	1.14 (1.06-1.23)	<0.001
Left dominant coronary artery system	3.97 (2.11-7.50)	<0.001
Model 2: Proximally located CAD on CTA		
Age	1.04 (1.01-1.07)	0.004
Gender	1.32 (0.74-2.36)	0.341
Proximal diseased segments (>30%)	1.48 (1.20-1.83)	<0.001
Left dominant coronary artery system	3.77 (2.00-7.10)	<0.001
Model 3: Extent of significant CAD on CTA		
Age	1.04 (1.02-1.07)	0.002
Gender	1.45 (0.82-2.56)	0.199
Number of vessels with significant stenosis (>50%)	1.68 (1.32-2.14)	<0.001
Left dominant coronary artery system	3.72 (1.98-6.99)	<0.001

Overall plaque burden was assessed by the number of diseased segments including all plaques causing >30% luminal narrowing (model 1). Proximally located CAD was defined as non-significant and significant stenosis in all proximally located segments (model 2). The number of vessels with significant stenosis (>50%) included 1-, 2- and 3-vessle disease and was entered into the models as a continuous variable (model 3).

CAD: coronary artery disease; CI: confidence interval; CTA: computed tomography coronary angiography; HR: hazard ratio.

In addition, sub-analysis assessing the independent prognostic value of coronary vessel dominance for the occurrence of non-fatal MI and cardiac death (extensive analysis is not shown) revealed that a left dominant coronary artery system remained a significant predictor of cardiac events (hazard ratio between 5.13 and 5.66 when corrected for significant CAD, overall plaque burden or proximally located CAD, all analyses p<0.001).

Prognostic value of significant stenosis location

A stenosis in the left coronary system was observed in 222 patients and was associated with an increased risk of non-fatal myocardial infarction and all-cause mortality, with a HR of 2.79 (95%CI 1.46-5.31, p=0.002) (Table 6). In case of a stenosis in both (right and left) coronary systems, as was present in 150 patients, a HR of 3.05 (95%CI 1.47-6.31, p=0.003) was observed. A significant stenosis in the right coronary system, as observed in 63 patients, was not significantly associated with the composite endpoint. Furthermore, in patients with a right dominant coronary artery system, a stenosis in the left coronary system and a stenosis in both (right and left) coronary systems were associated with an increased

risk of events with a HR of 2.41 (95%CI 1.14-5.12, p=0.022) and a HR of 3.12 (95%CI 1.40-6.98, p=0.006), respectively. Subsequently, in patients with a left dominant coronary artery system, a stenosis in the left coronary system was associated with an increased risk of non-fatal MI and all-cause death, with a HR of 5.00 (95%CI 1.35-18.43, p=0.016). The difference in the risk-estimate of a stenosis in the left coronary system in patients with a right dominant and patients with a left dominant coronary artery system was statistically non-significant (HR of 2.4 and HR of 5.0, respectively, p-value for interaction=0.351).

Table 6. Cox Regression analysis of significant stenosis location for non-fatal myocardial infarction and all-cause mortality in all patients, patients with right dominant and patients with left dominant coronary artery system

		Univariate		Multivariate	
Variable	**n**	**HR (95%-CI)**	**p-value**	**HR (95%-CI)**	**p-value**
All patients	**1387**				
No significant CAD (<50%)	952	1.0 (reference)		1.0 (reference)	
Significant stenosis in the right coronary system[a]	63	3.11 (1.07-9.08)	0.037	2.25 (0.76-6.65)	0.142
Significant stenosis in the left coronary system[b]	222	3.54 (1.90-6.59)	< 0.001	2.79 (1.46-5.31)	0.002
Significant stenosis in both coronary systems[c]	150	4.20 (2.10-8.39)	< 0.001	3.05 (1.47-6.31)	0.003
Patients with right dominant coronary artery system	**1256**				
No significant CAD (<50%)	856	1.0 (reference)		1.0 (reference)	
Significant stenosis in the right coronary system	61	1.94 (0.45-6.65)	0.376	1.48 (0.34-5.12)	0.602
Significant stenosis in the left coronary system	196	3.20 (1.54-6.65)	0.002	2.41 (1.14-5.12)	0.022
Significant stenosis in both coronary systems	143	4.44 (2.06-9.57)	< 0.001	3.12 (1.40-6.98)	0.006
Patients with left dominant coronary artery system	**131**				
No significant CAD (<50%)	96	1.0 (reference)		1.0 (reference)	
Significant stenosis in the right coronary system[†]	2	-		-	
Significant stenosis in the left coronary system	26	5.30 (1.49-18.82)	0.010	5.00 (1.35-18.43)	0.016
Significant stenosis in both coronary systems	7	5.68 (1.03-31.42)	0.046	4.81 (0.85-27.16)	0.075

Patients with balanced coronary artery system were excluded from the analysis. Multivariate analysis correcting for age and gender was performed. Patients without significant CAD on CTA were considered the reference group. [a]Stenosis in the right coronary system = at least one significant stenosis in the RCA. [b]Stenosis in the left coronary system = at least one significant stenosis in the LM, LAD and/or LCX. [c]Stenosis in both coronary systems = at least one significant stenosis in the RCA and the LM, LAD and/or LCX. [†]Hazard ratio's could not be calculated for patients with left dominant coronary artery system and a stenosis in the right coronary system, due to the very small number of patients within this group. *CAD: coronary artery disease; CI: confidence interval; HR: hazard ratio; LAD: left anterior descending artery; LCX: left circumflex artery; LM: left main artery; RCA: right coronary artery.*

DISCUSSION

This study demonstrated that coronary vessel dominance assessed by CTA has incremental prognostic value and extends the predictive value of CTA. The main findings of the study were that the presence of a left dominant coronary artery system is associated with an increased risk of non-fatal myocardial infarction and all-cause mortality as compared to a right dominant coronary artery system. Moreover, the presence of significant CAD on CTA in patients with a left dominant coronary artery system was associated with worse outcome than significant CAD on CTA in patients with a right dominant coronary artery system. These findings suggest that the assessment of coronary vessel dominance using CTA may further enhance the risk stratification beyond the assessment of degree of stenosis in patients referred for CTA.

The prognostic value of significant CAD using CTA is well established, and an increased risk of cardiovascular events in patients with significant CAD on CTA has been previously demonstrated[4-6,18,19]. These findings are confirmed in the present study, showing a higher risk of events in patients with significant CAD on CTA, regardless of coronary vessel dominance. While coronary vessel dominance is routinely assessed using CTA, limited information is available about the prognostic value of coronary vessel dominance in patients referred for CTA. A previous study by Goldberg et al. showed that in a large cohort of patients (n=27,289) who underwent cardiac catheterization due to acute coronary syndrome the presence of a left dominant coronary artery system was a predictor of death at a mean follow-up duration of 3.5 years (HR 1.18, 95%CI 1.05-1.34)[20]. The prognostic value of coronary vessel dominance was most pronounced in patients with acute ST-segment elevation myocardial infarction. Remarkable is that the hazard of the presence of a left dominant coronary artery system was less pronounced in the study by Goldberg et al. compared to the hazard observed in the current study (HR 3.20, 95%CI 1.67-6.13). However, the study population may have differed substantially between our investigation and the one by Goldberg et al. The event rate in the study population of Goldberg et al. was higher in all coronary vessel dominance groups since their population consisted of high risk patients, as compared to low to intermediate risk patients in our population. Because of the overall worse prognosis in all patients, the difference between groups could be less pronounced. Furthermore, the outcome measure of Goldberg et al. was all-cause mortality, whereas in the present study also non-fatal MI was included as a primary endpoint in addition to all-cause mortality. These differences in study population and outcome are expected to account for the difference in findings between studies. Importantly, the prognostic value of coronary vessel dominance in patients with and without significant CAD was evaluated in the present study. Patients without significant CAD on CTA showed to have a good prognosis irrespective of coronary vessel dominance. These findings confirm the excellent prognostic value of a CTA examination without significant

CAD[21]. In addition, this study showed that in patients with significant CAD on CTA the presence of a left dominant coronary artery system significantly increased the risk of non-fatal MI and all-cause mortality as well as for adverse cardiac events including cardiac death as confirmed by sub-analysis.

The extent of atherosclerosis in relation to coronary vessel dominance

Although limited information is currently available regarding the prognostic value of coronary vessel dominance, the relationship between coronary vessel dominance and anatomical variance of the coronary arteries was investigated in several different studies. A study by Dodge et al., evaluating 83 invasive coronary angiograms, demonstrated a smaller RCA diameter and a larger LCX diameter in patients with a left dominant coronary artery system[22]. In addition, Ilia et al. found that a long LAD (defined as a LAD wrapped around the apex of the heart) was present in 87% of patients with left dominant coronary artery system compared to 47% of patients with a right dominant coronary artery system[23].

Furthermore, the relation between coronary vessel dominance and the extent of CAD remains uncertain as different studies showed opposing results. The aforementioned study by Goldberg et al. showed more extensive CAD in patients with a right dominant coronary artery system as compared to patients with a left dominant coronary artery system[20]. Similar findings were shown in the study by Vasheghani-Farahani et al., identifying a higher prevalance of three-vessel disease in patients with right dominant coronary artery system[24]. However, Balci et al. did not find a significant difference in the extent of significant CAD between patients with a right and left dominant coronary artery system[25]. Though the current study did not reveal significant differences in the distribution of significant CAD on CTA, normal CTA results or wall irregularities causing less than 30% luminal narrowing were observed less frequently in patients with right dominant coronary artery system compared to patients with left dominant and balanced coronary artery systems. Still, for the determination of the relationship between the extent of significant CAD and coronary vessel dominance, more extensive research is required in larger patient populations.

Underlying mechanisms

At present, little is known about the prognostic value of significant stenosis location in relation to coronary vessel dominance. This study demonstrated that a stenosis in the left coronary system, meaning the LAD and/or LCX, was associated with an increased risk of events, while a stenosis in the RCA did not statistically significant predict events. The hazard of a stenosis in the left coronary system was comparable between patients with a right dominant and left dominant coronary artery system. Still, coronary vessel dominance has influence on the relative contribution of the different coronary arteries to the total left ventricular blood flow[23,26]. The anatomic importance of a significant stenosis in patients with left dominant coronary artery system might be different than that in patients with

a right dominant or balanced coronary artery system. In risk scores the weight factors for a significant stenosis in the segments of the coronary tree differ for patients with a right and a left dominant coronary artery system, with higher scores for the segments of the LAD and LCX in patients with a left dominant coronary artery system[26]. In patients with a left dominant coronary artery system, the left ventricle receives almost the entire blood supply from the LAD and the LCX, possibly resulting in more extensive myocardial infarction, in case of an significant stenosis in these vessels. Moreover, the possibility to form collaterals might be less in patients with a left dominant coronary artery system. Since the PDA originating from the RCA is lacking, no collaterals can be formed from the right coronary system, when the left coronary system is suffering from a severe stenosis. At present, however, no studies are available investigating the relation between coronary vessel dominance and severity of myocardial infarction or coronary collateral circulation formation. Therefore, further research is needed to identify factors contributing to the inferior prognosis of patients with left dominant coronary artery system.

Clinical implication

In patients referred for CTA, left dominant coronary artery system was identified as a significant risk factor for myocardial infarction and death. Particularly in the subgroup of patients with significant CAD on CTA, those patients with a left dominant coronary artery system had a strongly increased risk of events compared to patients with a right dominant coronary artery system. Therefore, the potential indication for intensive treatment could be more prominent in patients with left dominant coronary artery system. Furthermore, in case of uncertainty about the need for referral for revascularization, subsequent testing for ischemia might reveal important information that may assist in clinical decision making. In current clinical practice no clear distinction is made in the treatment strategies between patients with a right dominant and a left dominant coronary artery system. When other studies will confirm the results of our study, the knowledge of the prognostic impact of coronary vessel dominance might affect choice of treatment. Accordingly, the evaluation of coronary vessel dominance could assist in clinical decision making and prognostication in patients referred for CTA.

Limitations

The current study has several limitations. First, the study was conducted in a relatively small patient population, which results in a comparatively small group of patients with a left dominant coronary artery system, and an even smaller group for patients with a balanced coronary artery system. Of note, the prevalence of right dominant, left dominant and balanced coronary artery system in the present study population is comparable with that described in previous literature[9]. Because of the small patient groups among patients with significant CAD on CTA, statistically significant difference between the risk estimates

for having a significant stenosis in the left coronary system in patients with a right and a left dominant coronary artery system was not observed, presumably due to insufficient power. Larger studies are needed to elucidate the relationship between significant stenosis location and coronary vessel dominance. Second, plaque composition, which may have impact on outcome as well, was not evaluated. In addition, to what extent severely calcified plaques may potentially have influenced the assessment of stenosis severity remains unknown. Third, the multivariate Cox regression model in the current analysis was at the edge of overfitting, due to a relatively low number of clinical events in the present study. However, the confidence intervals observed in the Cox regression analysis were considered reliable and reduced Cox regression models could confirm the prognostic value of coronary vessel dominance. Fourth, 5.5% of patients were lost to follow-up. However, no difference in the distribution of coronary vessel dominance was observed in patients without follow-up. Fifthly, because of the relatively low event rate in the current study, larger studies are needed to evaluate the effect of coronary vessel dominance on cardiac adverse events like the composite of non-fatal MI and cardiac death. Instead, the composite of non-fatal MI and all-cause mortality was the primary endpoint in the current study. Subsequently, future studies in larger patient cohorts are warranted to confirm these findings.

CONCLUSIONS

The presence of a left dominant coronary artery system is associated with an increased risk of non-fatal myocardial infarction and all-cause mortality. Furthermore, coronary vessel dominance has significant incremental prognostic value over clinical risk factors and significant CAD on CTA. In addition, the presence of significant CAD on CTA in patients with a left dominant coronary artery system is associated with worse outcome than the presence of significant CAD in patients with a right dominant coronary artery system. Therefore, the assessment of coronary vessel dominance may further enhance risk stratification beyond the assessment of severity and extent of CAD on CTA. However, the underlying mechanism is unknown and its application therefore remains speculative.

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