Cardiovascular magnetic resonance imaging and computed tomography in patients with suspected coronary artery disease

Groothuis, J.G.J.

2013

document version
Publisher's PDF, also known as Version of record

Chapter 6

Clinical outcome of patients with suspected coronary artery disease after evaluation with computed tomography coronary angiography and magnetic resonance myocardial perfusion imaging

Jan G.J. Groothuis, Aernout M. Beek, Stijn L. Brinckman, Martijn R. Meijerink, Mijntje L.P. van den Oever, Martijn W. Heymans, Mark B.M. Hofman, Cornelis van Kuijk, Albert C. van Rossum

Submitted

ABSTRACT

Purpose: Computed tomography coronary angiography (CTCA) and cardiovascular magnetic resonance (CMR) myocardial perfusion imaging are increasingly used in clinical cardiology practice for the non-invasive evaluation of patients with suspected coronary artery disease (CAD). CTCA detects or excludes any coronary artery disease and CMR subsequently determines its hemodynamic significance. In the present study we explored clinical outcome of patients who underwent both CTCA and CMR myocardial perfusion imaging as a combined protocol for the evaluation of CAD.

Methods: Symptomatic patients with low or intermediate probability of CAD underwent both 64-slice cardiac computed tomography (coronary calcium scoring and CTCA) and CMR (assessment of left ventricular function, adenosine stress and rest first pass myocardial perfusion and late gadolinium enhancement imaging). Subsequently, they were followed-up for cardiac events after 1 year. Uni- and multivariable survival analysis was performed including pre-test probability of CAD, coronary calcium scoring, CTCA and CMR findings.

Results: A total of 203 patients successfully underwent both CTCA and CMR within 1 month. During a mean follow-up interval of 18 ± 5 months, 25 patients experienced an event: 23 revascularizations, 1 myocardial infarction and 1 death. Multivariable Cox regression analysis showed a significant improvement in predictive value by the combination of CTCA and CMR versus CTCA or CMR alone (chi-square change 17.06, $p<0.001$ or 8.06, $p=0.005$).

Conclusions: The combination of CTCA and CMR had incremental value for prediction of cardiac events over their use as a single technique in patients with suspected CAD.

INTRODUCTION

Computed tomography coronary angiography (CTCA) and cardiovascular magnetic resonance (CMR) myocardial perfusion imaging are increasingly used in clinical cardiology practice for the non-invasive evaluation of patients with suspected coronary artery disease (CAD). CTCA is an anatomical imaging technique that accurately visualizes coronary anatomy and atherosclerosis. CTCA has excellent diagnostic accuracy for detection of significant CAD (1-3) and it is particularly useful to exclude significant CAD in patients at low or intermediate risk (4). Recently, several studies have shown its value for prediction of mortality and major acute cardiovascular events (5-7).

CMR myocardial perfusion imaging is a rapidly expanding technique for the detection of myocardial ischemia that has at least similar diagnostic accuracy as single photon emission computed tomography myocardial perfusion imaging (SPECT-MPI) (8;9). Recently, several studies have reported the prognostic value of CMR perfusion imaging for the prediction of future cardiac events (10-13).

Previously, we have shown that CTCA and CMR myocardial perfusion imaging provide complementary information in the diagnostic evaluation of patients with suspected CAD (14). The combined use of CTCA and CMR enables the clinician to non-invasively assess coronary morphology and function in these patients. CTCA detects or excludes any coronary artery disease and CMR subsequently determines its hemodynamic significance. In the present study we explored whether the combination of CTCA and CMR had incremental prognostic value compared to their use as a single technique in patients with suspected CAD.

MATERIALS AND METHODS

Patients and study protocol

Patients were prospectively recruited from the outpatient cardiology clinic in our hospital. Inclusion criteria were chest pain and low to intermediate pre-test probability CAD according to the previously described Diamond/Forrester and CASS scale (15-17). Exclusion criteria were any prior history of CAD (prior documented myocardial ischemia, myocardial infarction, percutaneous coronary intervention or cardiac surgery), significant arrhythmia, pregnancy, renal insufficiency (serum creatinine> 110μmol/L), known allergy to iodinated contrast material, any absolute contra-indication for magnetic resonance imaging (e.g. cerebral clips), claustrophobia and asthma.

All patients underwent cardiac computed tomography and CMR within 1 month. Patients were referred for further evaluation by invasive coronary angiography when non-invasive imaging was suggestive of obstructive CAD (CTCA: > 50% diameter stenosis and/or CMR: reversible perfusion defect and/or regional late enhancement suggestive of ischemic heart disease), or on clinical grounds, at the discretion of the treating physician. All patients were followed-up by standardized telephone interview and review of their medical charts after 1

year. The study protocol was approved by the local ethics committee and written informed consent was obtained in all patients.

Cardiac computed tomography

Cardiac computed tomography was performed using a 64-slice computed tomography scanner (Sensation 64, Siemens, Erlangen, Germany). When resting heart rate was > 65 beats per minute, 50 mg metoprolol was administered orally one hour before start of CT. In case of persistent heart rate above 65 beats per minute, metoprolol (5-15 mg) was administered intravenously immediately before image acquisition. All patients received 0.4 mg nitroglycerin sublingual before start of the scan.

First a non-contrast scan was performed at 150 mAs and 120 kV. Using dedicated software (Syngo Calcium scoring, Siemens, Germany) the Agatston calcium score was calculated semi-automatically by an experienced observer, blinded to CTCA and CMR data. The coronary angiography scan was performed using a scan collimation of 64x0.6 using a flying z-focus at 900mAs and 120 kV. The CTCA scan was started automatically after injection of 100 ml non-ionic contrast agent (Ultravist300, Bayer, Germany) using automated bolus tracking. Using retrospective ECG triggering, data were reconstructed at 65% of the RR interval (slice thickness 0.75 mm, increment 0.4 mm).

CTCA data were analysed in consensus by a radiologist and a cardiologist, blinded to the CMR data. Analysis was performed on the original axial dataset and on curved multiplanar reconstructions. The coronary tree was evaluated according to a 16-segment coronary artery model modified from the American Heart Association (18). Each segment was graded by visual assessment on a 4 point scale: normal (no stenosis); mild CAD (0-50% diameter stenosis); obstructive CAD (>50% diameter stenosis) and non-diagnostic (severe motion artifacts that impaired adequate image interpretation). Non-diagnostic segments were excluded from the analysis. Subsequently, all segments with obstructive CAD were divided in the following categories: calcified plaque (defined as plaque with a higher attenuation than the contrast enhanced lumen), non-calcified plaque (defined as plaque with a higher attenuation than the epicardial fat and connective tissue surrounding the vessel wall, but a lower attenuation than the contrast enhanced lumen) and mixed plaque (plaque consisting of both non-calcified and calcified plaque).

Cardiovascular magnetic resonance imaging

All imaging was performed on a 1.5 Tesla whole body MRI scanner (Sonata/Avanto, Siemens, Erlangen, Germany). Patients were instructed to refrain from caffeinated drinks and other competitive antagonists of adenosine 24 hours before the examination. Left ventricular volumes and function were assessed with cine imaging using a retro-triggered, balanced steady-state free precession sequence. Image parameters were: slice thickness 5 mm, slice gap 5 mm, temporal resolution 35-50ms, repetition time/echo time 3.2/1.5 ms, flip angle 60^{o} and matrix 256 *156. Cine images were acquired in 2-, 3- and 4- chamber long axis orientations and in short axis orientations covering the entire left ventricle. First

pass myocardial perfusion was assessed using a dynamic single shot saturation recovery gradient-echo planar pulse sequence (repetition time/echo time 5.6/1.1 ms, saturation time 110 ms, flip angle 18^{o}, echo-planar factor 4, matrix-size 160 x 144 and voxel size 2.5 x 2.5 x 10 mm^{3}), accelerated by parallel imaging with a factor two using time-adaptive sensitivity encoding, during the administration of 0.1 mmol/kg body weight of a gadolinium-based contrast agent (Magnevist, Schering AG, Berlin, Germany). To suppress signal of epicardial fat, a frequency selective fat saturation RF pulse was applied before imaging. Every heartbeat 3 left ventricle short axis slices (basal, mid and apical) were acquired during 50 heartbeats. After 3 minutes of continuous intravenous infusion of adenosine (140 µg/kg/min) the stress scan was started and simultaneously the contrast agent was injected and flushed with saline; the adenosine was stopped immediately after completion of the scan. Blood pressure and heart rate were monitored during adenosine infusion. The rest scan was acquired at least ten minutes after the stress scan, with identical scan parameter setting, contrast dose and slice positions. After the rest perfusion scan late gadolinium enhancement (LGE) images were obtained in identical orientations as the cine images using a 2D segmented inversion recovery gradient echo pulse sequence. Image parameters were: slice thickness 5 mm, slice gap 5 mm, repetition time/echo time 9.6/4.4 ms, flip angle 25^{o} and a matrix 256*166 mm.

CMR data were analysed visually by 2 cardiologists blinded to the CTCA data. Wall motion was assessed visually per segment and left ventricular volumes and ejection fraction were calculated using Siemens Syngo Argus software. Both stress and rest perfusion images were analysed simultaneously on one workstation. The myocardium of the 3 short axis scans during stress and rest were divided into segments using a 16 segment model as described previously and all segments were scored normal, ischemic or scar (19). A myocardial perfusion defect was defined as hypo-enhancement during > 3 consecutive images after arrival of the contrast agent in the left ventricular cavity. Myocardial ischemia was defined as a stress induced myocardial perfusion defect without hyperenhancement at LGE imaging. Scar was defined as a region of hyperenhancement at LGE imaging. The presence of any hyperenhancement at LGE was scored per segment and subsequently categorized as ischemic (subendocardial, transmural) or non-ischemic. Subsequently, all segments were allocated to their coronary artery territories according to the 16 segment model (18).

Follow-up

All patients were followed-up for cardiovascular events by standardized telephone interview and review of their medical charts after 1 year. Follow-up was performed by a research nurse blinded for CTCA and CMR findings. Events were defined as: all cause death, acute coronary syndrome, myocardial infarction and percutaneous or surgical coronary revascularization.

Statistical analysis

All data were presented as mean ± standard deviation for continuous data. Differences between groups were tested by a t-test, Fisher's exact test and a chi-square test. In 50 randomly selected patients intra- and interobserver agreement for CMR perfusion was tested using Cohen's kappa test.

Kaplan Meier curves were used to determine the time to event for patients with and without obstructive CAD on CTCA, with and without myocardial ischemia on CMR and the combination for CTCA and CMR. The curves were compared using the log rank test.

Cox regression analysis was used for uni- and multivariable analysis. A multivariable model was created consisting of clinical parameters (pre-test probability of CAD, based on age, gender and symptoms) (15-17), calcium scoring, CTCA and CMR, in concordance to clinical practice. The incremental predictive value of CTCA and CMR was investigated by comparing the log likelihood values of the different models. By subtracting log likelihood values, significant differences between models could be obtained by using the likelihood ratio test. This difference in the log likelihood value follows a chi-square distribution with degrees of freedom equal to the number of variables that differ between models.

Additionally, the incremental value of CTCA and CMR was investigated, when applied in two different stepwise strategies (first CTCA, then CMR or first CMR and subsequently CTCA). Therefore, Cox regression analysis was performed in the following patient subgroups: all patients without obstructive CAD on CTCA, all patients with obstructive CAD on CTCA, all patients without ischemia on CMR and all patients with ischemia on CMR.

Statistical analysis was performed using SPSS version 15.0 (SPSS, Chicago, IL, USA).

RESULTS

Baseline characteristics

A total of 203 patients underwent both CTCA and CMR successfully. Mean age was 57 ± 10 years and the majority of patients (169, 83%) had non-anginal or atypical chest pain. Baseline characteristics of patients with and without events are listed in table 1. Differences between groups were statistically significant for gender and pre-test probability of CAD.

Table 1. Clinical characteristics among patients with and without events.

	Patients without events n=178	Patients with events n=25	p-value
Male	81 (46)	22 (88)	<0.001
Mean age (yrs)*	57 ± 10	59 ± 11	0.397
Body mass index (kg/m²)*	27 ± 5	28 ± 4	0.384
Risk factors for CAD			
Diabetes	20 (11)	5 (20)	0.204
Hyperlipidaemia	38 (21)	5 (20)	0.878
Hypertension	72 (40)	9 (36)	0.828
Family history	72 (40)	5 (20)	0.050
Current smoking	43 (24)	6 (24)	1.000
Symptoms			
non-anginal chest pain	77 (43)	6 (24)	0.085
atypical chest pain	75 (42)	11 (44)	1.000
typical chest pain	26 (15)	8 (32)	0.043
Pre-test probability of CAD†			
low-intermediate (<30%)	88 (49)	7 (28)	0.054
intermediate (30-70%)	58 (33)	4 (16)	0.108
intermediate-high (70-90%)	32 (18)	14 (56)	<0.001

Note: unless otherwise stated data are expressed as number of patients with percentages within parentheses.
* Mean ± standard deviation; † According to the combined Diamond/Forrester and CASS scale [15-17];
CAD: coronary artery disease.

Imaging findings

Overall, mean CCS was 152 ± 396 (median 14, interquartile range 0-166). CCS was 0 in 77 (38%) patients, 1-100 in 65 (32%) patients, 101-400 in 41 (20%) and >400 in 20 (10%) patients. Obstructive CAD was detected on CTCA in 83 (41%) patients. In 47 (23%) patients, myocardial ischemia was found on CMR.

Of 83 patients with obstructive CAD on CTCA, 37 (45%) had myocardial ischemia. Of 156 patients with normal myocardial perfusion on CMR, 46 (30%) had obstructive CAD on CTCA. Detailed imaging findings among patients with and without events are listed in table 2.Intra- and interobserver agreement for CMR perfusion results was good: kappa 0.78 ± 0.09 and 0.81 ± 0.09, respectively (both p<0.0001).

Table 2. Imaging findings among patients with and without events.

	Patients without n=178	Patients with events n=25	p-value events
CCS:			
Mean CCS*	32 ± 25	60 ± 31	< 0.001
CCS > 0	102 (57)	24 (96)	< 0.001
CCS > 100	46 (26)	15 (60)	0.001
CCS > 400	12 (7)	8 (32)	0.001
CTCA:			
Any CAD	99 (56)	24 (96)	< 0.001
Only non-obstructive CAD	40 (23)	0 (0)	NA
Obstructive CAD	59 (33)	24 (96)	< 0.001
Multivessel CAD	23 (13)	15 (60)	< 0.001
Obstructive calcified plaque	30 (17)	10 (40)	0.013
Obstructive mixed plaque	40 (22)	16 (64)	< 0.001
Obstructive non-calcified plaque	6 (3)	8 (32)	< 0.001
CMR :			
Ischemia	27 (15)	20 (80)	< 0.001
Multivessel-ischemia	12 (7)	16 (64)	< 0.001
HE at LGE (any)	20 (10)	8 (32)	0.010
HE at LGE†	2 (1)	5 (20)	< 0.001
LV EDV (ml/ m2)*	77.2 ±15.6	78.4 ± 19.7	0.772
LV ESV (ml/ m2)*	30.0 ± 11.0	33.3 ± 15.3	0.255
LV EF (%)*	61.7 ± 7.3	58.8 ± 8.14	0.104

Note: unless otherwise stated data are expressed as number of patients with percentages within parentheses.

* Mean ± standard deviation; † transmural or subendocardial HE on LGE; CAD: coronary artery disease; CCS: coronary calcium scoring; CMR: cardiovascular magnetic resonance imaging; CTCA: computed tomography coronary angiography; EDV: end-diastolic volume; EF: ejection fraction; ESV: end-systolic volume; HE: hyperenhancement; LGE: late gadolinium enhancement; LV: left ventricular

Follow-up results

During a mean follow-up interval of 18 ± 5 months, 25 patients (12.3%) experienced an event. No patients were lost to follow-up. One patient experienced an acute myocardial infarction and one patient died. A total of 23 patients underwent coronary revascularization (20 percutaneous coronary intervention, 3 coronary artery bypass grafting). The decision to perform revascularization was performed on the basis of clinical data, findings on invasive coronary angiography and fractional flow reserve measurements. Of patients with events, 96% had obstructive CAD on CTCA and 80% had myocardial ischemia on CMR.

Event rates

Of 110 patients without obstructive CAD on CTCA and normal myocardial perfusion 1 (0.9%) patient experienced an event. No events were recorded in 10 patients with myocardial ischemia on CMR but without obstructive CAD on CTCA. In 46 patients with obstructive CAD on CTCA but normal myocardial perfusion, 4 (8.7%) experienced an event. Of 37 patients with obstructive CAD on CTCA and myocardial ischemia on CMR, 20 (54%) experienced an event. Figure 1, 2 and 3 represent Kaplan Meier curves of CTCA, CMR and combined findings of CTCA and CMR, respectively.

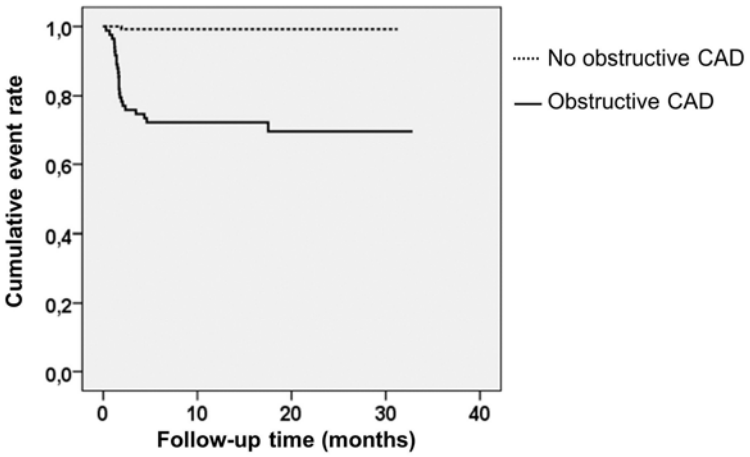

Figure 1. Kaplan-Meier event curves in patients with and without obstructive coronary artery disease on computed tomography coronary angiography. Log rank test: $p<0.001$.

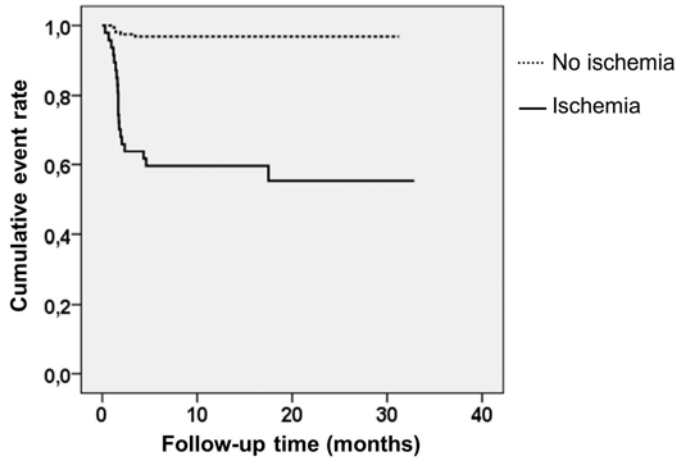

Figure 2. Kaplan-Meier event curves in patients with and without myocardial ischemia on cardiovascular magnetic resonance imaging (CMR). Log rank test: p<0.001

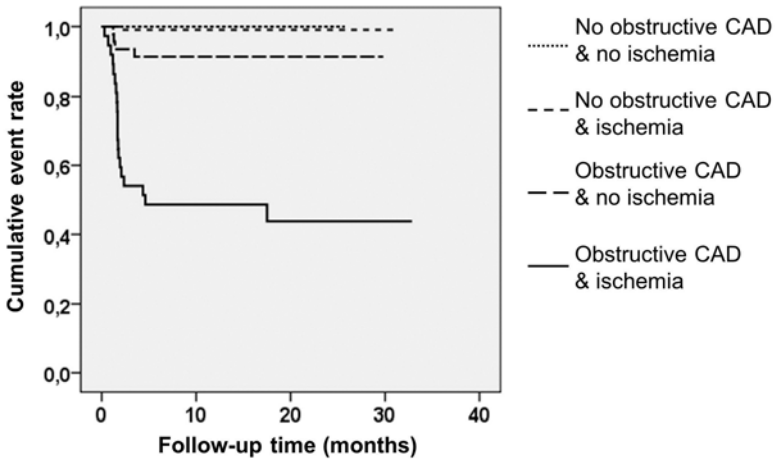

Figure 3. Kaplan-Meier event curves in patients with different combinations of findings on computed tomography coronary angiography (CTCA) and cardiovascular magnetic resonance imaging (CMR). Log rank test: 89.02, p<0.001

Predictors of events

Table 3 shows univariable analysis of all relevant clinical and imaging results. Baseline risk factors for CAD and left ventricular volumes and function were no predictors of events. In contrast, CTCA findings (the presence, severity and extent of CAD) as well as presence and extent of myocardial ischemia on CMR were associated with events.

Table 4 shows multivariable analysis of a clinical practice based model consisting of pre-test probability of CAD (Clinical), CCS, CTCA and CMR. The addition of either CTCA or CMR to a model consisting of Clinical and CCS improved the prediction of events ($p<0.001$). Moreover, CMR improved the predictive value of a model with Clinical, CCS and CTCA ($p<0.001$). Similarly, CTCA significantly improved the predictive value when added to a model with Clinical, CCS and CMR ($p=0.005$).

Table 3. Univariable analysis.

variable		HR	95% CI	p-value
Gender		7.831	2.34-26.17	0.001
Age		1.02	0.98-1.05	0.42
Body mass index		1.04	0.96-1.12	0.366
Risk factors for CAD				
	Diabetes	1.81	0.68-4.82	0.238
	Hyperlipidaemia	0.93	0.35-2.48	0.887
	Hypertension	0.84	0.37-1.90	0.68
	Family history	0.39	0.15-1.03	0.058
	Current smoking	1.00	0.40-2.51	0.995
Symptoms		1.94	1.14-3.31	0.015
Pre-test probability of CAD*		2.40	1.45-3.96	0.001
CCS				
	CCS > 0	16.22	2.19-119.89	0.006
	CCS > 100	3.886	1.75-8.65	0.001
	CCS > 400	4.906	2.12-11.38	< 0.001
CTCA				
	Any CAD (compared to no CAD)	17.291	2.34-127.83	0.005
	Non-obstructive CAD	0.033	0.00-254.88	0.456
	Obstructive CAD	40.74	5.51-301.27	< 0.001
	Multivessel obstructive CAD	7.864	3.53-17.53	< 0.001
	Calcified obstructive plaque	2.891	1.30-6.44	0.009
	Mixed obstructive plaque	5.415	2.39-12.27	< 0.001
	Non-calcified obstructive plaque	7.507	3.23-17.47	< 0.001
CMR				
	Myocardial ischemia	16.53	6.19-44.10	< 0.001
	Multivessel ischemia	14.85	6.45-33.72	< 0.001
	Number of ischemic segments	1.36	1.24-1.50	< 0.001
	HE at LGE (any)	3.28	1.42-7.61	0.006
	HE at LGE†	9.951	3.72-26.63	<0.001
	LV EDV	1.00	0.98-1.03	0.806
	LV ESV	1.016	0.99-1.05	0.284
	LV EF	0.965	0.92-1.01	0.115

* According to the combined Diamond/Forrester and CASS scale [15-17]. HR: hazard ratio; † transmural or subendocardial HE on LGE; CI: confidence interval; CAD: coronary artery disease; CCS: coronary calcium scoring; CMR: cardiovascular magnetic resonance imaging; CTCA: computed tomography coronary angiography; EDV: end-diastolic volume; EF: ejection fraction; ESV: end-systolic volume; HE: hyperenhancement; LGE: late gadolinium enhancement; LV: left ventricular

Table 4. Multivariable analysis

Model	$\chi 2$	p-value
Model 1: Clinical*	19.98	<0.001
Model 2: Clinical + CCS†	27.77	<0.001
Incremental value over Model 1	12.36	<0.001
Model 3A: Clinical + CCS† + CTCA‡	47.58	<0.001
Incremental value over Model 2	19.17	<0.001
Model 3B: Clinical + CCS† + CMR§	72.63	<0.001
Incremental value over Model 2	29.39	<0.001
Model 4: Clinical + CCS† + CTCA‡ + CMR§	79.69	<0.001
Incremental value over Model 3A	17.06	<0.001
Incremental value over Model 3B	8.06	0.005

* Pre-test probability of CAD according to the combined Diamond/Forrester and CASS scale [15-17]. † Coronary calcium score > 0; ‡ obstructive CAD on CTCA; § Myocardial ischemia on CMR. CAD: coronary artery disease; CTCA: computed tomography coronary angiography; CMR: cardiovascular magnetic resonance imaging;

Incremental predictive value of stepwise strategies

Table 5 shows multivariable analysis of different stepwise strategies. CTCA significantly improved the predictive value when performed in patients with or without myocardial ischemia on CMR (p=0.001 and p=0.019). Furthermore, CMR significantly improved the predictive value when performed in patients with obstructive CAD on CTCA (p<0.001). However, CMR had no incremental predictive value in patients without obstructive CAD on CTCA (p=0.74).

Table 5. Multivariable analysis for stepwise strategies

Model	n	$\chi 2$	p-value
No obstructive CAD on CTCA	120		
Model 1: Clinical*		0.83	0.36
Model 2: Clinical + CMR‡		0.87	0.65
Incremental value over Model 1		0.11	0.74
Obstructive CAD on CTCA	83		
Model 1: Clinical		7.56	0.006
Model 2: Clinical + CMR‡		23.74	<0.001
Incremental value over Model 1		16.50	<0.001
No myocardial ischemia on CMR	156		
Model 1: Clinical		0.13	0.72
Model 2: Clinical + CTCA†		6.43	0.040
Incremental value over Model 1		5.53	0.019
Myocardial ischemia on CMR	47		
Model 1: Clinical		6.05	0.014
Model 2: Clinical + CTCA†		11.51	0.003
Incremental value over Model 1		10.39	0.001

* Pre-test probability of CAD according to the combined Diamond/Forrester and CASS scale [15-17]; † Obstructive CAD on CTCA; ‡ Myocardial ischemia on CMR. CAD: coronary artery disease; CTCA: computed tomography coronary angiography; CMR: cardiovascular magnetic resonance imaging;

DISCUSSION

The present study explored clinical outcome of patients with suspected CAD in relation to CCS, CTCA and CMR, each as a single technique, and as part of a stepwise protocol. As a main result, we found that the combined use of CTCA and CMR had incremental value for the prediction of events over their use as a single technique in patients with obstructive CAD on CTCA. In patients without obstructive CAD on CTCA, adding CMR results did not improve the prediction of clinical events.

Patient management in cardiology practice depends on the clinical condition of patients and the estimation of the risk for future events. Risk stratification is a continuous process which, in a patient with suspected CAD, involves several steps (17). First, a clinical risk profile based on risk factors such as age, gender and symptoms is assessed. Second, further risk stratification can be performed by detection or exclusion of myocardial ischemia, using exercise electrocardiography or myocardial perfusion imaging. Finally, conventional invasive coronary angiography can be used to visualize coronary morphology and further optimize risk stratification.

In the present study, we investigated a new non-invasive strategy for risk stratification of patients with suspected CAD using a combination of CTCA and CMR. In addition to defining the conventional clinical risk profile, coronary morphology was non-invasively assessed by CTCA and presence (and extent) of myocardial ischemia was determined by CMR. Our results showed the complementary prognostic value of CTCA and CMR in patients with low to intermediate risk of having significant CAD. First, CMR was an independent predictor of events in patients with obstructive CAD on CTCA. In these patients, CMR assesses the hemodynamical relevance of their CAD and identifies patients with myocardial ischemia that are at high risk for future cardiac events. Conversely, CTCA was an independent predictor of events in patients with normal myocardial perfusion on CMR. As normal myocardial perfusion does not exclude the presence of any atherosclerotic plaque, CTCA could detect anatomically relevant CAD in these patients and improve risk stratification. Third, CTCA was also of incremental value in patients with myocardial ischemia on CMR. In these patients, CTCA can safely exclude obstructive CAD in the epicardial vessels. Further work is needed to establish whether myocardial ischemia in these patients is truly a ‘false positive’ CMR result or whether it reflects dysfunction of the coronary microcirculation related to conditions like hypertension or (dilated or hypertrophic) cardiomyopathy (20). In our study, most events were related to coronary revascularization, and, as a result, CMR had no incremental prognostic value in patients without obstructive disease on CTCA.

Thus, we found that CTCA can improve risk stratification in patients with or without myocardial ischemia on CMR. Conversely, CMR depicts patients at high risk, among patients with obstructive CAD on CTCA. However, CMR does not have significant incremental predictive value in patients without obstructive CAD on CTCA. Consequently, our findings in this patient group suggest that after defining the clinical risk profile, CTCA

should be performed first. When obstructive CAD is excluded, no additional myocardial perfusion imaging is needed. However, when obstructive CAD is found, additional CMR can improve risk stratification.

To the best of our knowledge, this is the first study that investigated the combined prognostic value of CTCA and CMR. Werkhoven et al. have investigated the prognostic value of the combined use of CTCA and SPECT-MPI (21). Similar to our results, they found that CTCA and SPECT-MPI remained independent predictors of adverse cardiac events, even after correction for baseline clinical risk factors and calcium scoring. Multiple studies have shown the prognostic value of either CTCA or CMR. In concordance with our findings, these studies showed that both presence and extent of CAD on CTCA (5;6;7;22) and myocardial ischemia on CMR (10-13) were predictors of future cardiac events. Our study extends these findings by showing the incremental prognostic value of the combined use of these techniques.

The combined use of CTCA and CMR allows the comprehensive and non-invasive assessment of coronary morphology and myocardial perfusion. Thus, both techniques have complementary value in the diagnostic and prognostic evaluation of patients with suspected CAD. However, further research is needed to investigate the cost-effectiveness of this approach.

In conclusion, the combination of CTCA and CMR had incremental value for prediction of cardiac events over their use as a single technique in patients with low or intermediate probability of having CAD. Based on our results, we propose a stepwise approach in these patients. CTCA can be used as a first discriminator, which, when suggestive of obstructive disease, should be followed by CMR to assess myocardial perfusion.

Limitations

Only a small number of events was observed, most of which were elective coronary revascularization procedures. Although the decision to perform revascularization was made on the basis of clinical parameters, invasive coronary angiography and fractional flow reserve data, bias might have occurred, since referral for invasive coronary angiography was in part based on CTCA and CMR findings.

ACKNOWLEDGEMENTS

This study was supported by a research grant from the Netherlands organization for health research and development (ZonMw), grant number 170991003.

REFERENCES

1. Budoff MJ, Dowe D, Jollis JG, et al. Diagnostic performance of 64-multidetector row coronary computed tomographic angiography for evaluation of coronary artery stenosis in individuals without known coronary artery disease: results from the prospective multicenter ACCURACY (Assessment by Coronary Computed Tomographic Angiography of Individuals Undergoing Invasive Coronary Angiography) trial. J.Am.Coll.Cardiol. 2008 Nov 18;52(21):1724-32.

2. 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 Dec 16;52(25):2135-44.

3. Mollet NR, Cademartiri F, Van Mieghem CA, et al. High-resolution spiral computed tomography coronary angiography in patients referred for diagnostic conventional coronary angiography. Circulation 2005 Oct 11;112(15):2318-23.

4. Hendel RC, Patel MR, Kramer CM, et al. ACCF/ACR/SCCT/SCMR/ASNC/NASCI/SCAI/SIR 2006 appropriateness criteria for cardiac computed tomography and cardiac magnetic resonance imaging: a report of the American College of Cardiology Foundation Quality Strategic Directions Committee Appropriateness Criteria Working Group, American College of Radiology, Society of Cardiovascular Computed Tomography, Society for Cardiovascular Magnetic Resonance, American Society of Nuclear Cardiology, North American Society for Cardiac Imaging, Society for Cardiovascular Angiography and Interventions, and Society of Interventional Radiology. J.Am.Coll.Cardiol. 2006 Oct 3;48(7):1475-97.

5. Min JK, Shaw LJ, Devereux RB, et al. Prognostic value of multidetector coronary computed tomographic angiography for prediction of all-cause mortality. J.Am.Coll.Cardiol. 2007 Sep 18;50(12):1161-70.

6. Chow BJ, Wells GA, Chen L, et al. Prognostic value of 64-slice cardiac computed tomography severity of coronary artery disease, coronary atherosclerosis, and left ventricular ejection fraction. J.Am.Coll.Cardiol. 2010 Mar 9;55(10):1017-28.

7. Pundziute G, Schuijf JD, Jukema JW, et al. Prognostic value of multislice computed tomography coronary angiography in patients with known or suspected coronary artery disease. J.Am.Coll.Cardiol. 2007 Jan 2;49(1):62-70.

8. Greenwood JP, Maredia N, Younger JF, et al. Cardiovascular magnetic resonance and single-photon emission computed tomography for diagnosis of coronary heart disease (CE-MARC): a prospective trial. Lancet. 2012 Feb 4;379(9814):453-60

9. Schwitter J, Wacker CM, van Rossum AC, et al. MR-IMPACT: comparison of perfusion-cardiac magnetic resonance with single-photon emission computed tomography for the detection of coronary artery disease in a multicentre, multivendor, randomized trial. Eur. Heart J. 2008 Jan 21; 29 (4): 480-489.

10. Jahnke C, Nagel E, Gebker R, et al. Prognostic value of cardiac magnetic resonance stress tests: adenosine stress perfusion and dobutamine stress wall motion imaging. Circulation 2007 Apr 3;115(13):1769-76.

11. Steel K, Broderick R, Gandla V, et al. Complementary prognostic values of stress myocardial perfusion and late gadolinium enhancement imaging by cardiac magnetic resonance in patients with known or suspected coronary artery disease. Circulation 2009 Oct 6;120(14):1390-400.

12. Bertaso AG, Richardson JD, Wong DT, et al. Prognostic value of adenosine stress perfusion cardiac MRI with late gadolinium enhancement in an intermediate cardiovascular risk population. Int J Cardiol. 2012 Jun 2. [Epub ahead of print]

13. Buckert D, Dewes P, Walcher T, Rottbauer W, Bernhardt P. Intermediate-term prognostic value of reversible perfusion deficit diagnosed by adenosine CMR: a prospective follow-up study in a consecutive patient population. JACC Cardiovasc Imaging. 2013 Jan;6(1):56-63.

14. Groothuis JG, Beek AM, Brinckman SL, et al. Low to intermediate probability of coronary artery disease: comparison of coronary CT angiography with first-pass MR myocardial perfusion imaging. Radiology 2010 Feb;254(2):384-92.

15. Chaitman BR, Bourassa MG, Davis K, et al. Angiographic prevalence of high-risk coronary artery disease in patient subsets (CASS). Circulation 1981 Aug;64(2):360-7.

16. Diamond GA, Forrester JS. Analysis of probability as an aid in the clinical diagnosis of coronary-artery disease. N.Engl.J.Med. 1979 Jun 14;300(24):1350-8.

17. Gibbons RJ, Abrams J, Chatterjee K, et al. ACC/AHA 2002 guideline update for the management of patients with chronic stable angina--summary article: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Committee on the Management of Patients With Chronic Stable Angina). Circulation 2003 Jan 7;107(1):149-58.
18. Austen WG, Edwards JE, Frye RL, et al. A reporting system on patients evaluated for coronary artery disease. Report of the Ad Hoc Committee for Grading of Coronary Artery Disease, Council on Cardiovascular Surgery, American Heart Association. Circulation 1975 Apr;51(4 Suppl):5-40.
19. Cerqueira MD, Weissman NJ, Dilsizian V, et al. Standardized myocardial segmentation and nomenclature for tomographic imaging of the heart: a statement for healthcare professionals from the Cardiac Imaging Committee of the Council on Clinical Cardiology of the American Heart Association. Circulation 2002 Jan 29;105(4):539-42.
20. Paolo G. Camici and Ornella E. Rimoldi. The Clinical Value of Myocardial Blood Flow Measurement. J Nucl Med 2009 July; 50:1076–1087
21. van Werkhoven JM, Schuijf JD, Gaemperli O, et al. Prognostic value of multislice computed tomography and gated single-photon emission computed tomography in patients with suspected coronary artery disease. J.Am.Coll.Cardiol. 2009 Feb 17;53(7):623-32.
22. Carrigan TP, Nair D, Schoenhagen P, et al. Prognostic utility of 64-slice computed tomography in patients with suspected but no documented coronary artery disease. Eur.Heart J. 2009 Feb;30(3):362-71.