1-Year cardiovascular outcomes of FFR-CT in suspected coronary artery disease

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Abstract

Purpose: Computed tomography fractional flow reserve (FFR-CT) is a non-invasive method to estimate the fractional flow reserve (FFR) using images of coronary computed tomography angiography (CCTA). The aim of this study is to assess whether patients with suspected CAD evaluated with additional FFR-CT have similar or different rates of major adverse cardiac and cerebrovascular events (MACCE) compared to patients receiving no FFR-CT.

Methods: In this single-center retrospective cohort study, patients who received CCTA followed by FFR-CT (FFR-CT group) and patients who received CCTA without FFR-CT before FFR-CT was available (CCTA group) were compared. Included patients had ≥1 anatomically significant stenosis on CCTA. Primary outcome was the rate of MACCE after one year. Secondary outcomes were invasive coronary angiography- (ICA) and revascularization rates. Hazard ratio (HR) for MACCE was calculated. Secondary outcomes were compared using the Pearson chi-square test.

Results: A total of 360 participants (FFR-CT group n=136, CCTA group n=224, mean age 59.4 years, 52.8% men) were analyzed. The rate of MACCE was low (n=11 events in 10 participants(2.8%)) and consisted of myocardial infarctions (n=7) and strokes (n=4). MACCE rate in the FFR-CT group was not significantly different from the CCTA group (2.2% vs 3.1%) (HR 0.71, 95% confidence interval 0.18-2.73, p=0.61). Significantly fewer ICAs as consequence of the CCTA were conducted in the FFR-CT group (19.9% vs 51.3%, p<0.001).

Conclusion: The equal low rate of MACCE suggest that FFR-CT can safely be used for clinical decision making in patients with suspected CAD on CCTA. Additionally, the number of ICAs can be reduced.

Abbreviations and acronyms:

CABG, coronary artery bypass grafting; CAD, coronary artery disease; CCTA, coronary computed tomography angiography; CI, confidence interval; CDM, clinical decision making; ECG, electrocardiogram; FFR, fractional flow reserve; FFR-CT, computed tomography fractional flow reserve; HR, Hazard ratio; ICA, invasive coronary angiography; LAD, left anterior descending artery; LBBB, left bundle branch block; LMCA, left main coronary artery; MACCE, major adverse cardiac and cerebrovascular events; MI, myocardial infarction; MO, obtuse marginal branche; IM, ramus intermedius artery; NSTEMI, non-ST-elevation myocardial infarction; PCI, percutaneous coronary intervention; RCA, right coronary artery; RCx, ramus circumflexus; RDP, ramus descendens posterior; RPL, right posterolateral artery; SD, standard deviation; SPECT, single photon-emission computed tomography; STEMI, ST-elevation myocardial infarction

Introduction

Cardiovascular diseases cause approximately one-third of deaths worldwide. Among cardiovascular diseases, coronary artery disease (CAD) is the most prevalent[1–3]. CAD involves the reduction of blood flow to the heart muscle due to coronary stenoses caused by plaque buildup in the wall of the arteries (atherosclerosis)[4,5]. This could lead to chest pain (angina pectoris), exertional dyspnea, myocardial infarction (MI) and death[5,6]. Most patients with CAD have stable CAD, meaning no signs of acute pathology[7]. In these patients, further investigation using (non-)invasive tests is needed to lower symptom burden and to prevent (recurrent) MI and cardiovascular death[8,9]. The goal of these tests is to clarify the diagnosis of CAD and to direct subsequent care, which could include revascularization and optimal medical therapy[8–10], or a combination, while maximizing patient safety, reducing the risk of cardiovascular events and maximizing the cost-effectiveness.

Coronary computed tomography angiography (CCTA) is a non-invasive test, which is used to determine the presence of CAD and its anatomic severity in patients with stable CAD[8,9]. CCTA has a high sensitivity, which makes it a reliable test to rule-out CAD, but not to identify hemodynamically significant coronary stenosis due to the low specificity[11–13]. This is because the correlation between anatomic significance and functional significance is poor, with the majority of the anatomically significant stenoses causing no functional impairment of the coronary artery[12,14]. For this reason, invasive coronary angiography (ICA) with fractional flow reserve (FFR) measurement remains the reference standard in the diagnosis of CAD. FFR is the ratio between the coronary pressure distal to a coronary artery stenosis and the aortic pressure, and is measured during ICA by using a pressure wire to determine the quality of blood flow[13,15].

Since 2014, a non-invasive method to estimate FFR using CT-images, called computed tomography FFR (FFR-CT), by HeartFlow (HeartFlow, Redwood City, CA, USA) has become available. FFR-CT evaluates the hemodynamic significance of coronary stenoses visible on CCTA using an algorithm based on computational fluid dynamics and simulated coronary hyperemia to estimate the FFR-value[16,17]. The addition of FFR-CT to CCTA increases the diagnostic performance of CCTA and might lead to a decrease in the number of diagnostic ICAs and invasive FFR procedures in patients without obstructive CAD[12,18,19].

FFR-CT has been available for clinical use in the Maasstad Hospital, Rotterdam, The Netherlands since October 2018. However, the impact of the use of FFR-CT on patient safety and clinical decision making in patients with possible functional significant CAD in this center has not been formally analyzed. The present aim of this study is to assess whether patients with suspected CAD evaluated with additional FFR-CT have similar or different rates of major adverse cardiac and cerebrovascular

events (MACCE) compared to patients receiving no additional FFR-CT.

Methods

Design and study population

This was a retrospective single-center cohort study in which patients who received CCTA with additional FFR-CT (FFR-CT group) between October 2018 and December 2020 in the Maasstad Hospital were compared with an historical cohort of patients (CCTA group) who received CCTA between January 2015 and September 2018, before FFR-CT was introduced in this hospital. The local Institutional Review Board approved the study protocol. Informed consent was waived by the ethics committee.

Patients were eligible for inclusion if they had any symptoms of possible stable CAD (i.e. chest pain, exertional dyspnea, cardiac arrhythmia, left bundle branch block, etc.) for which they had undergone CCTA. Additionally, CCTA should show at least one anatomically significant stenosis (≥50% stenosis), for which patients in the FFR-CT group received additional FFR-CT. Patients were excluded if they had a history of coronary artery imaging (i.e. CCTA, ICA) or revascularization (i.e. percutaneous coronary intervention (PCI) or coronary artery bypass grafting (CABG)), one or more total occlusions on CCTA or non-interpretable CCTA image quality. Additionally, patients were excluded if the FFR-CT was not used for clinical decision making after CCTA.

Outcome measures and definitions

The primary outcome measure was the rate of major adverse cardiac and cerebrovascular events (MACCE) within a follow-up duration of one year after CCTA acquisition. MACCE was defined as a composite of MI, stroke and cardiovascular death. MI included non-ST-elevation MI and ST-elevation MI. Stroke included ischemic stroke, hemorrhagic stroke and transient ischaemic attack. Cardiovascular death included death as result of MI, sudden cardiac arrest, heart failure and stroke.

Secondary outcome measures were ICA- and revascularization rates, both as direct consequence of CCTA or FFR-CT and during one-year follow-up. Revascularization included PCI and CABG. If patients were discharged from cardiological follow-up before the one-year mark and no additional information was available regarding the outcomes in the medical records, outcomes were considered negative.

Coronary Computed Tomography Angiography

Standard coronary CT angiography was performed by using a 128-section dual-source CT-scanner (Siemens Somatom Flash from 2015 until August 2020 and Siemens Somatom Drive from August to December 2020). The CCTA acquisition was performed in accordance with the Society of Cardiovascular Computed Tomography-guidelines for the performance and acquisition of CCTA[20], and the local protocol of Maasstad Hospital, Rotterdam. In brief, ß-blockers and/or ivabradine was administered if needed to obtain a heart rate ≤65 beats per minute. Sublingual nitroglycerin was given immediately before image acquisition. If possible, CCTA-examinations were performed using a prospectively (step and shoot) electrocardiographically triggered axial scan mode. If this was not possible, high-pitch (FLASH) or retrospective scan protocol was used. Image acquisition included the coronary arteries, left ventricle and proximal ascending aorta. The scans were reviewed by the treating cardiologist and the radiologist, independently. A coronary stenosis was considered anatomically significant if the lumen of the coronary was ≥50% reduced.

Computed Tomography Fractional Flow Reserve

CT-images were transmitted to the HeartFlow core laboratory for FFR-CT-analysis using the latest FFR-CT analysis software. This software uses highly advanced algorithms incorporating artificial intelligence to generate a digital 3-dimensional anatomic model of the aortic root and epicardial coronary arteries out of standard CCTA-images. Once the model is complete, the software computes coronary flow and FFR-CT values at every point in the model by using computational fluid dynamics (CFD). CFD are based on the conservation law of physical properties of fluid. The Navier-Stokes equations are the governing equations that are used in CFD[16,17,21] . The completed Heartflow Analysis is a personalized color-coded digital 3-dimensional model of the heart, reflecting the impact that stenoses have on the coronary blood flow. The cut-off value for hemodynamically significant stenosis is defined as FFR-CT value ≤0.80.

Data collection

All data was collected from medical records. For patient characteristics, demographics and CAD risk factors at the time of CCTA acquisition were collected. For clinical presentation, the presence of exertional dyspnea and classification of angina symptoms using the Diamond and Forrester Chest Pain Prediction Rule[22] was assessed from clinical notes. Moreover, functional limitation of symptoms, for both angina pectoris and dyspnea, was determined using the Canadian Cardiovascular Society grading of angina pectoris score (CCS)[23] to summarize the symptom burden. To assess the impact of FFR-CT, clinical outcomes and all cardiovascular diagnostic and therapeutic steps taken after the CCTA were recorded. Follow-up was collected until one year after the initial CCTA.

Study data was collected and managed in REDCap electronic data capture tools[24,25]. All data was collected from medical records by two researchers independently. Discrepancies in data were assessed and adapted by mutual agreement.

Statistical analysis

Normally distributed continuous variables were reported as means and standard deviations. The Shapiro-Wilk and Kolmogorov-Smirnov test of normality was used to check if the data was normally distributed. If the continuous variable was not normally distributed, medians with ranges were reported instead. Categorical variables were reported as total patients and percentages.

For the primary outcome and its individual composites the hazard ratio (HR) with the corresponding 95% confidence interval (95%CI) was calculated. Survival curves for time-to-event analysis for the primary outcome and its individual composites were constructed based on all available follow-up data until one year with the use of Kaplan-Meier estimates and were compared with the log-rank test. The secondary outcomes were compared between groups using the Pearson chi-square test.

For all statistical tests, significance level was set at P-values of <0.05. All statistical analyses were performed using IBM SPSS Statistics 26 (IBM Corp. Released 2019. IBM SPSS Statistics for Windows, Version 26.0. Armonk, NY: IBM Corp).

Results

Participants

A total of 210 patients who underwent CCTA with FFR-CT and a total of 1877 patients who underwent CCTA without FFR-CT were assessed for eligibility (Figure 1). After assessment 136 participants were included in the FFR-CT group and 224 participants were included in the CCTA group (N=360). The mean age of participants was 59.4 years ± 8.7. A little more than half was male (52.8%) and mean body mass index was 28.6 kg/m^2 ± 4.9. Hypertension, hyperlipidemia, diabetes mellitus and history of smoking were present in 62.2%, 50.3%, 17.8% and 51.1% of the participants, respectively. Only 10.8% had typical angina symptoms and the majority (64.7%) had non- or only slightly restrictive symptoms. An overview of the baseline characteristics can be found in Table 1.

Overall, there were no major differences between groups in baseline characteristics. However, small differences were observed. The CCTA group had more participants with hypertension (64.3%) compared to the FFR-CT group (58.8%). History of smoking was present in 54.0% of the participants in the CCTA group and 46.3% in the FFR-CT group. Further, modified-CCS scores between groups differed, whereby the FFR-CT group had more non- to slightly restrictive symptoms (71.3%)

compared to the CCTA group (60.7%).

Coronary CT Angiography results

Table 2 shows a summary of the CCTA results of the participants. The median Agatston calcium score was 121.5 [range 0-2189]. Eighty-five percent of the CCTAs were of good quality. Most CCTAs were performed using a prospective scan protocol (93.6%). The average heart rate during CT acquisition was 59.4 beats per minute. However, for two-thirds of the participants the heart rate was not reported. A number of 267 (74.2%) participants had at least one anatomically significant left anterior descending artery (LAD) stenosis. At least one anatomically right coronary artery (RCA) stenosis was found in 38.3% of participants and an anatomically significant ramus circumflex stenosis in 24.4%. Only 3.3% of the participants had an anatomically significant stenosis in the left main coronary artery.

No major differences between groups in CCTA results were observed. However, the number of LAD and RCA stenoses was slightly different between the FFR-CT group and CCTA group. In the FFR-CT group, 79.4% of the participants had an anatomically significant LAD stenosis, whereas 71.0% in the CCTA group. Anatomically significant RCA stenoses were found in 33.8% of the participants in the FFR-CT group and 41.1% of the participants in the CCTA group.

Major adverse cardiac and cerebrovascular events

The event rate one-year follow-up was low in both groups. Hazard ratios for the primary outcome and all its individual composites were not significant and had broad confidence intervals (Table 2).

MACCE occurred in ten participants of the total study population (event rate = 2.8%). One patient in the CCTA group had two events (MI and stroke). MACCE occurred in three participants in the FFR-CT group and in seven participants in the CCTA group (2.2% versus 3.1%) (HR MACCE for FFR-CT group: 0.71, 95%CI 0.18 to 2.73, p=0.61). The FFR-CT group had one MI and whereas the CCTA group had six MIs (0.7% versus 2.7%) (HR MI for FFR-CT group: 0.27, 95%CI 0.033 to 2.27, p=0.23). A stroke arose twice in both groups (1.5% versus 0.9%) (HR stroke for FFR-CT group: 1.62, 95%CI 0.23 to 11.72, p=0.61). Three patients died during follow-up and were all in the CCTA group, however these deaths were not related to cardiovascular causes.

The Kaplan-Meier event-free survival curves of MACCE, MI and stroke are presented in Figure 2. Event-free survival rates of MACCE for the FFR-CT group and CCTA group were 97.8% and 96.9%, respectively (log-rank p=0.61). For MI the event-free survival rates were 99.3% for the FFR-CT group and 97.3% for the CCTA group (log-rank p=0.20). Event-free survival rates for stroke were 98.5% for

the FFR-CT group and 99.1% for the CCTA group (log-rank p=0.61).

Invasive Coronary Angiography and revascularization

Participants underwent significantly less ICAs after CCTA with additional FFR-CT compared to CCTA without additional FFR-CT (19.9% versus 55.4%, p<0.001). Moreover, significantly fewer revascularizations were performed in the FFR-CT group compared to the CCTA group (11.0% versus 22.3%, p=0.007). The rate of revascularizations after ICA in the FFR-CT group was higher, but not significantly different from the rate of revascularizations after ICA in the CCTA group (55.6% versus 40.3%, p=0.15). During the one-year follow-up, an additional eight ICAs were performed in the FFR-CT group (5.9% of FFR-CT group) and twenty-seven (12.1% of CCTA group, p=0.055) in the CCTA group. Revascularization was performed in 50.0% and 25.9% of these ICAs respectively (p=0.20).

Discussion

In this retrospective single-center cohort study the safety of FFR-CT for the functional assessment of anatomically significant CAD on CCTA to make further clinical decisions was examined by comparing the clinical results in patients who received CCTA with additional FFR-CT and patients who received only CCTA. In both groups, the rate of MACCE after one year was low and no significant hazard ratios were observed. Patients who received additional FFR-CT had significantly fewer ICAs as consequence of the CCTA compared to patients who did not receive FFR-CT. Further, significant fewer revascularizations were performed in patients receiving FFR-CT.

Since the rate of MACCE was low and there were no significant differences between the groups, these findings suggest that FFR-CT can safely be used for the functional assessment of anatomically significant CAD and the following clinical decision making. The results in the present study are supported by the PLATFORM Study (2016)[19]. This study found equivalent few MACCE in patients who received CCTA with FFR-CT, empowering the safe use of FFR-CT. Moreover, the ADVANCE Registry Study (2020)[26], which prospectively examined the clinical outcomes in more than five thousand patients who received CCTA with additional FFR-CT found a low rate of MACCE. It is noteworthy, that despite ICA was less frequently performed in patients who received CCTA with FFR-CT, the rate of MACCE remained low. This demonstrates FFR-CT is also safe to defer ICA based on FFR-CT results and is thereby an improvement of patient selection for undergoing ICA.

Finally, the reduction of (unnecessary) ICAs means that the diagnostic performance of CCTA can be improved by FFR-CT and due to not undergoing invasive tests reduce the risk of complications. One complication occurred in the CCTA group, where an ICA was complicated by a dissection of the

coronary artery resulting in a MI. Additionally, an ischemic stroke arose a month later. The stenosis observed on CCTA turned out to be not functionally significant, meaning that the ICA was retrospectively unnecessary. These complications might have been prevented if FFR-CT was used. Besides this, extra hospital costs and additional patient burden could have been avoided.

Strength and limitations

The present study has many strengths, including the use of real world data to measure the impact of FFR-CT in the clinical practice, the comparability of the analyzed groups and the collection of data in duplicate. It is also important to acknowledge the limitations of the present study. The first limitation is inherent to the retrospective single-center study design. The study includes a small number of participants resulting in limited power to detect significant differences in the primary outcome measure. However, Maasstad Hospital is currently the only hospital in the Netherlands using FFR-CT in clinical practice, so no other centers could be included. Additionally, the inclusion time of the FFR-CT group was short, since FFR-CT was only in use for approximately two years, resulting in a small FFR-CT group. The second limitation is the brief follow-up duration of one year. This duration may be insufficient to detect an impact on clinical outcomes, since MACCE might occur more often in the longer term. However, due the fact that all data from patients until December 2021 was collected, additional analyses with a longer follow-up duration (particularly in the CCTA group) were done. These analyses suggests that the majority of MACCE occurs in the first year after CCTA, which could mean that one-year results are reasonably representative. Finally, this study only examined MACCE, while more factors play a role in patient safety, such as exposure to certain elements during and risks associated with additional clinical tests (e.g. radiation exposure and medicine administration). Further research can assess the impact on other factors. It might also be interesting to examine the impact of FFR-CT on other clinical tests, hospital costs and patients' quality-of-life. In October 2021 the iCORONARY study (NCT04939207) was started to prospectively examine the safety of FFR-CT. The number of diagnostic tests, cost-effectiveness and patient burden is also included in this study. Results of this study are expected on April 2025.

Conclusion

The use of FFR-CT after CCTA for the functional assessment of CAD seems a safe alternative. No differences in MACCE after one-year follow-up were observed between the FFR-CT group and CCTA group. This substantiates that FFR-CT can safely be used for clinical decision making in patients who have possible CAD on CCTA. Additionally, the number of ICAs can be reduced.

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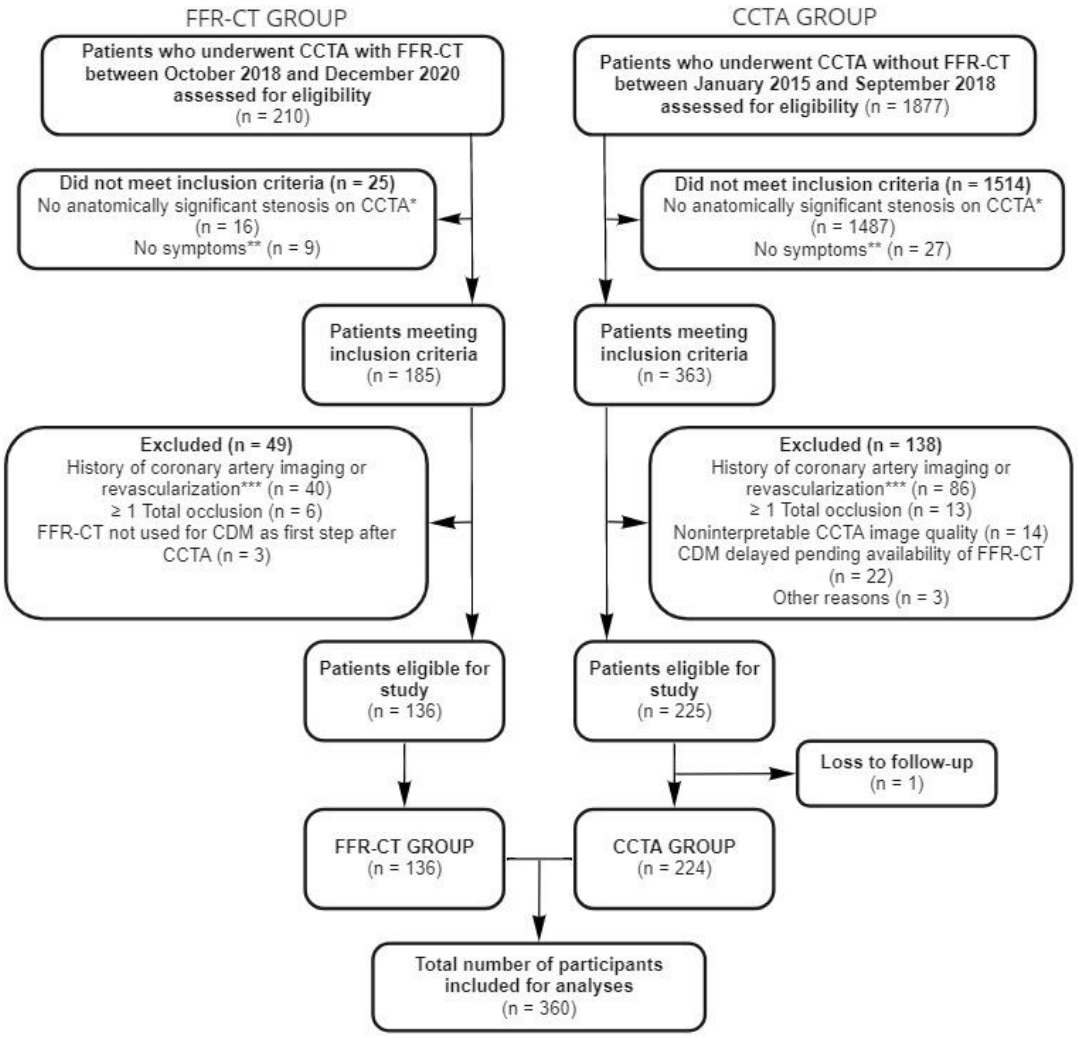

Figure 1. Flowchart of participant selection
FFR-CT group: for the FFR-CT group 210 patients who underwent CCTA with FFR-CT between October 2018 and December 2020 were assessed for eligibility. After checking the inclusion and exclusion criteria 136 cases were eligibile for study. No patients were lost to follow-up. In total 136 patients were included in the FFR-CT group.

CCTA group: for the CCTA group 1877 patients who underwent CCTA without FFR-CT between January 2015 and September 2018 were assessed for eligibility. After checking the inclusion and exclusion criteria 225 controls were eligibile for study. One patient was lost to follow-up due to not showing up at the cardiologist after CCTA for CDM. In total 224 patients were included in the CCTA group.

The total number of participants included for analyses were 360.

* ≥50% stenosis on CCTA was anatomically significant
** symptoms included: chest pain, exertional dyspnea, cardiac arrhythmia, left bundle branch block, et cetera.
*** included CCTA, ICA, PCI and CABG

Abbreviations: CABG, coronary artery bypass grafting; CCTA, coronary computed tomography angiography; CDM, clinical decision making; FFR-CT, computed tomography fractional flow reserve; ECG, electrocardiogram; LBBB, left bundle branch block; ICA, invasive coronary angiography; PCI, percutaneous coronary intervention

Table 1. Baseline characteristics

Characteristics*	Total group N=360	FFR-CT group n=136	CCTA group n=224
Demographics			
Age - years, mean ± SD	59.4 ± 8.7	60.9 ± 9.1	58.4 ± 8.3
Male, n (%)	190 (52.8)	72 (52.9)	118 (52.7)
BMI, kg/m², mean ± SD	28.6 ± 4.9	28.1 ± 4.5	29.0 ± 5.1
CAD risk factors, n (%)			
Hypertension[a]	224 (62.2)	80 (58.8)	144 (64.3)
Hyperlipidemia[b]	181 (50.3)	68 (50.0)	113 (50.4)
Diabetes mellitus	64 (17.8)	24 (17.6)	39 (17.4)
History of smoking	184 (51.1)	63 (46.3)	121 (54.0)
Clinical presentation, n (%)			
Classification of angina			
Non-anginal symptoms	191 (53.1)	69 (50.7)	122 (54.5)
Atypical angina	130 (36.1)	53 (39.0)	77 (34.4)
Typical angina	39 (10.8)	14 (10.3)	25 (11.2)
Functional limitation			
Non or slightly restrictive	233 (64.7)	97 (71.3)	136 (60.7)
Mild or severely restrictive	127 (35.3)	39 (28.7)	88 (39.3)
Exertional dyspnea	107 (29.7)	44 (32.4)	63 (28.1)

*As of date of CCTA

[a]Repeated systolic blood pressure >140mmHg/diastolic blood pressure >90mmHg, or use of antihypertensive drugs

[b]Total cholesterol >6,5mmol/l, history of hyperlipidemia, or use of cholesterol-lowering drug for hyperlipidaemia

Abbreviations: BMI, body mass index; CAD, coronary artery disease; CCTA, coronary computed tomography angiography; FFR-CT, computed tomography fractional flow reserve; SD, standard deviation

Table 2. Coronary computed tomography angiography results

CCTA characteristic	Total group N=360	FFR-CT group n=136	CCTA group n=224
Good quality of scan, n (%)	306 (85.0)	123 (90.4)	183 (81.7)
Mediocre quality of scan, n (%)	53 (14.7)	13 (9.6)	40 (17.9)
Prospective scan protocol, n (%)	337 (93.6)	135 (99.3)	202 (90.2)
Agatson calcium score, median [Range]	120.0 [0-2189]	121.5 [0-2189]	118.5 [0-1081]
Heart rate during CCTA† - BPM, mean ± SD	59.4 ± 7.5	58.4 ± 6.4	62.2 ± 9.6
Location of stenosis, n (%)			
≥ 1 anatomically significant RCA stenosis[a]	138 (38.3)	46 (33.8)	92 (41.1)
≥ 1 anatomically significant LAD stenosis[b]	267 (74.2)	108 (79.4)	159 (71.0)
≥ 1 anatomically significant RCx stenosis [c]	88 (24.4)	29 (21.3)	59 (26.3)
Anatomically significant LMCA stenosis	12 (3.3)	4 (2.9)	8 (3.6)
≥ 1 anatomically significant stenosis elsewhere[d]	118 (32.8)	45 (33.1)	73 (32.6)

†230 missing heart rates (39 in FFR-CT group/191 in CCTA group)
[a]Including: proximal/mid/distal RCA
[b]Including: proximal/mid/distal LAD
[c]Including: proximal/mid/distal RCx
[d]Including: RDP, diagonal branches, MO, RPL, IM

Abbreviations: CCTA, coronary computed tomography angiography; FFR-CT, computed tomography fractional flow reserve; LAD, left anterior descending artery; LMCA, left main coronary artery; MO, obtuse marginal branche; IM, ramus intermedius artery; RCA, right coronary artery; RCx, ramus circumflexus; RDP, ramus descendens posterior; RPL, right posterolateral artery; SD, standard deviation

Table 3. Primary and secondary outcomes after one-year follow-up

Outcome	Total group N=360	FFR-CT group n=136	CCTA group n=224	P-value*	Hazard ratio (95%CI)
Clinical, n (%)					
MACCE[1]	10 (2.8)	3 (2.2)	7 (3.1)		0.71 (0.18-2.73) p=0.61
Myocardial infarction[2]	7 (1.9)	1 (0.7)	6 (2.7)		0.27 (0.033-2.27) p=0.23
Stroke[3]	4 (1.1)	2 (1.5)	2 (0.9)		1.62 (0.23-11.72) p=0.61
Cardiovascular death	0 (0.0)	0 (0.0)	0 (0.0)		-
Overall death	3 (0.8)	0 (0.0)	3[a] (1.3)		-
Diagnostic and therapeutic steps, n (%)					
As direct clinical consequence of CCTA and/or FFR-CT					
ICA	142 (39.4)	27 (19.9)	124[b] (55.4)	**<0.001**	
Revascularization[4]	65 (17.8)	15 (11.0)	50 (22.3)	**0.007**	
% of ICA	45.8	55.6	40.3	0.15	
In 1-year follow-up					
ICA	35 (9.7)	8 (5.9)	27 (12.1)	0.055	
% with prior ICA	22.9	25.0	22.2	0.87	
Revascularization[4]	10 (2.8)	4 (2.9)	6 (2.7)	0.88	
% of ICA	22.9	50.0	25.9	0.20	

*Pearson chi-square test

[1]Patients reached at least one MACCE (MI, stroke or cardiovascular death)

[2]Included STEMI and NSTEMI

[3]Included ischaemic stroke, hemorrhagic stroke and transient ischaemic attack

[4]As consequence of ICA. Included PCI and CABG.

[a]Two patients died due to complications of malignancy, one died of hypovolemia due to ruptured spleen

[b]Nine patients received myocard SPECT before ICA

Abbreviations: CABG, coronary artery bypass grafting; CCTA, coronary computed tomography angiography; CI, confidence interval; FFR-CT, computed tomography fractional flow reserve; ICA, invasive coronary angiography; MACCE, major adverse cardiac and cerebrovascular events; MI, myocardial infarction; NSTEMI, non-ST-elevation myocardial infarction; PCI, percutaneous coronary intervention; SPECT, single photon-emission computed tomography; STEMI, ST-elevation myocardial infarction

Figure 2. Kaplan-Meier Estimates of MACCE-, MI- and Stroke free survival
Abbreviations: CI, confidence interval; MACCE, major adverse cardiac and cerebrovascular events; MI, myocardial infarction