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Anatomical and functional coronary imaging to predict long-term outcome in patients with suspected coronary artery disease: the EVINCI-outcome study

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Aims To investigate the prognostic relevance of coronary anatomy, coronary function, and early revascularization in patients with stable coronary artery disease (CAD).

Methods and results From March 2009 to June 2012, 430 patients with suspected CAD (61 ± 9 years, 62% men) underwent coronary anatomical imaging by computed tomography coronary angiography (CTCA) and coronary functional imaging followed by invasive coronary angiography (ICA) if at least one non-invasive test was abnormal. Obstructive CAD was documented by ICA in 119 patients and 90 were revascularized within 90 days of enrolment. Core laboratory analysis showed that 134 patients had obstructive CAD by CTCA (>50% stenosis in major coronary vessels) and 79 significant ischaemia by functional imaging [>10% left ventricular (LV) myocardium]. Over mean follow-up of 4.4 years, major adverse events (AEs) (all-cause death, non-fatal myocardial infarction, or hospital admission for unstable angina or heart failure) or AEs plus late revascularization (LR) occurred in 40 (9.3%) and 58 (13.5%) patients, respectively. Obstructive CAD at CTCA was the only independent imaging predictor of AEs [hazard ratio (HR) 3.2, 95% confidence interval (CI) 1.10–9.30; $P = 0.033$] and AEs plus LR (HR 4.3, 95% CI 1.56–11.81; $P = 0.005$). Patients with CAD in whom early revascularization was performed in the presence of ischaemia and deferred in its absence had fewer AEs, similar to patients without CAD (HR 2.0, 95% CI 0.71–5.51; $P = 0.195$).

Conclusion Obstructive CAD imaged by CTCA is an independent predictor of clinical outcome. Early management of CAD targeted to the combined anatomical and functional disease phenotype improves clinical outcome.

Keywords stable coronary artery disease • computed tomography coronary angiography • coronary functional imaging • coronary anatomical imaging • coronary revascularization • prognosis • clinical outcome

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Introduction

The 2019 guidelines of the European Society of Cardiology for the diagnosis and management of chronic coronary syndromes recommend non-invasive cardiac imaging in patients with suspected coronary artery disease (CAD) at intermediate pre-test clinical likelihood.[1] Functional imaging is suggested in the higher range of intermediate likelihood of CAD, while in lower range categories coronary anatomical imaging using computed tomography coronary angiography (CTCA) is the preferred alternative.

While the prognostic role of CTCA,[2,3] functional imaging,[4–6] and the combination of anatomical and functional imaging[7–9] is well established, the impact of non-invasive imaging strategies to guide patient management and modify long-term prognosis is unclear.[10,11] This may be because of the relatively low prevalence of severe CAD and the intermediate-low risk of populations submitted to cardiac imaging limit the ability of studies to show a prognostic advantage of one strategy over another. Moreover, available randomized trials involve mainly a single imaging technique with clinical management not clearly guided by non-invasive imaging results. Thus, the combined relevance of anatomical and functional coronary imaging has not been fully assessed.[11–13]

In the 'Evaluation of Integrated Cardiac Imaging for the Detection and Characterization of Ischemic Heart Disease' (EVINCI) study, patients with suspected stable CAD enrolled from a contemporary European population were characterized by both coronary anatomical and functional imaging before invasive coronary angiography (ICA).[14] Further patient management was decided by the attending clinicians who were aware of clinical data and local imaging reports. Data from the EVINCI core-labs for each imaging technique were included in this EVINCI-Outcome study, whose aim was to assess the impact on clinical outcome of different disease phenotypes, described by combined coronary anatomical and functional imaging.

Methods

Study design

In the EVINCI study, 697 patients with symptoms of suspected stable CAD were enrolled prospectively from 14 European centres between March 2009 and June 2012.[14] Briefly, patients underwent CTCA and at least one coronary functional imaging test, including stress perfusion imaging by either single-photon emission computed tomography (SPECT) or positron emission tomography (PET) and stress wall motion imaging by either cardiac magnetic resonance (CMR) or echocardiography (Echo). If at least one test was reported locally as abnormal, patients were advised to undergo ICA. Further clinical management, including early revascularization (within 90 days from enrolment or 30 days from ICA), was at the discretion of the managing clinician. Optimal medical therapy was encouraged in all patients.

Patients who completed the protocol and for whom imaging studies were submitted to core-lab, and were considered of sufficient quality to be interpretable, entered the EVINCI Outcome study. Core-lab analysis was blinded to the clinical data, local imaging interpretation, management decisions, and to the results of other tests. Long-term clinical follow-up was by clinical visits and/or structured phone interviews at 3–6 months and each year after enrolment until February 2016. Ethical approval was provided by each participating centre and all subjects gave written informed consent.

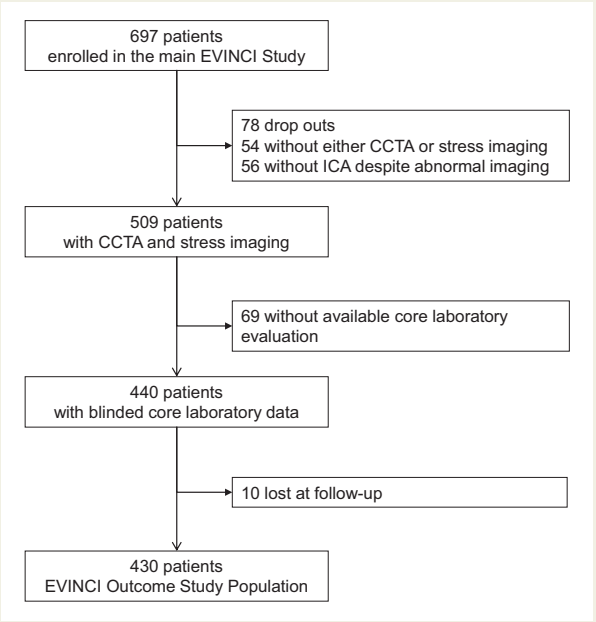

Figure 1 Patient flowchart. CTCA, computed tomography coronary angiography.

Image analysis

Only the findings of the EVINCI core laboratories were used. CTCA findings were categorized as no CAD, non-obstructive CAD (≤50% stenosis), and obstructive CAD (>50% stenosis in at least one major coronary vessel). Coronary functional imaging findings were categorized as no ischaemia, mild ischaemia [involving <10% of left ventricular (LV) myocardium by SPECT or PET and <3 newly dysfunctional segments by Echo or CMR], and significant ischaemia (involving ≥10% of the LV myocardium by SPECT or PET and ≥3 newly dysfunctional segments by Echo or CMR).[15] Ischaemia was defined by the positivity of at least one functional test and in case of positivity of multiple tests the severity of the most abnormal was considered.

Endpoints

The primary endpoint was a major adverse event (AE) including all-cause death, non-fatal myocardial infarction, and hospital admission for unstable angina or heart failure. The secondary endpoint was a composite of major AEs and late revascularization (LR; performed more than 90 days after enrolment or 30 days after ICA). Follow-up was censored at the time of the endpoint if any.

Statistical analysis

Baseline characteristics were described as numbers and frequencies for categorical variables and as mean ± standard deviation (SD) for continuous variables. Variables were compared between groups using χ^2 and analysis of variance with Bonferroni's correction. The relationship between imaging phenotype, clinical management, and AEs was evaluated by Kaplan–Meier analysis and the log-rank test.

Univariate Cox-regression analysis was used to assess the association between baseline clinical, imaging and treatment covariates, and risk of AEs. Variables with $P < 0.10$ at univariate analysis were included as

Table 1 Baseline characteristics

Parameter	Overall population ($n = 430$)
Demographics	
Age (years), mean ± SD	61 ± 9
Male gender	266 (62)
Clinical characteristics	
Typical angina	109 (25)
Atypical angina	257 (60)
Non-anginal chest pain	64 (15)
Pre-test probability of CAD (%), mean ± SD	49 ± 19
Left ventricular ejection fraction (%), mean ± SD	60 ± 8
Cardiovascular risk factors	
Family history of CAD	146 (34)
Diabetes mellitus	131 (30)
Hypercholesterolaemia	321 (75)
Hypertension	289 (67)
Smoking	56 (13)
Obesity	136 (32)
Euro Risk SCORE (%), mean ± SD	4 ± 3
Pharmacological therapies	
Beta-blockers	173 (40)
Calcium channel blockers	92 (21)
Nitrates	49 (11)
Anti-hypertensive	207 (48)
Anti-diabetic	110 (26)
Statins	260 (60)
Anti-platelets	234 (54)
Anti-coagulants	18 (4)
Non-invasive imaging	
CCTA abnormal	156 (36)
Functional imaging abnormal	178 (41)
Invasive coronary angiography (291 patients)	
>50% coronary stenosis and/or FFR <0.8	128 (30)
Early coronary revascularizations	
Percutaneous coronary intervention	77 (18)
Coronary artery bypass graft	13 (3)

Invasive coronary angiography results are derived from local reports (visual analysis); data are given in absolute numbers and % of the whole population, unless otherwise stated.
FFR, fractional flow reserve.

covariates in the multivariate models. For both the primary and secondary endpoints, two multivariate models were developed. In the first, the presence of CAD, myocardial ischaemia and early revascularization were considered separate variables. In patients with CAD, early management was defined 'appropriate' if early revascularization was performed in the presence of significant inducible ischaemia or deferred in its absence and 'inappropriate' if it was performed in the absence of significant inducible ischaemia or deferred in its presence. Accordingly, a three levels variable (no CAD, CAD with 'appropriate' early management, and CAD with 'inappropriate' early management) was considered to assess whether an early management targeted to the combined anatomical and functional imaging phenotype could affect outcome. In all multivariable analyses, the final model was developed taking into account clinical and statistical considerations. In detail, age and gender were forced to enter in all the models. Other independent predictors were selected using a step by step approach in which all variables with $P < 0.1$ at univariate analysis were entered into the model, checking at each step for collinearity, confounding, and model improvement. The comparison with results obtained by a stepwise selection procedure (using both the forward and backward approach) was also considered for the final model development.

All analyses were stratified for centre and the proportional hazard assumption was verified using the Schoenfeld test. All tests were two-tailed, and $P < 0.05$ was considered statistically significant. Analyses were performed using STATA-14 (Stata Corp., College Station, TX, USA).

Results

Patient's characteristics and early management

Among the patients enrolled in the initial EVINCI study, 78 dropped out and a further 110 were excluded for protocol violations, including 54 who did not perform either CTCA or stress imaging, and 56 who did not undergo ICA despite an abnormal imaging study. Of the remaining 509 patients, 430 had available core laboratory evaluation and complete follow-up and were the population considered in this study (*Figure 1*).

The population characteristics are shown in *Table 1*. All had both CTCA and at least one functional imaging test. More specifically, 347 underwent either SPECT (267) or PET (80), and 327 either Echo (222) or CMR (105). At least one non-invasive test was reported locally as abnormal in 291 patients (68%). According to the protocol, these patients underwent ICA, which was reported as abnormal in 128 (30%). The agreement between local imaging reports and core laboratory analysis is shown in Supplementary data online, *Table SA*. It was good for CTCA (80%) and ICA (91%) and lower for functional imaging (74%).

Early revascularization was performed in 90 patients (21%), either by percutaneous coronary intervention (PCI) in 77 or coronary artery bypass grafting (CABG) in 13 (*Table 1*). No serious AEs occurred during non-invasive imaging. One patient had a stroke during early PCI and one other patient had a peri-procedural myocardial infarction.

Follow-up

Median follow-up was 52 months (interquartile range 46–61 months). Medical treatment was changed between enrolment and follow-up in 265 patients (62%), mainly with the addition of a statin (78), antiplatelet agent (53), and anti-ischaemic therapy (beta-blockers in 52, nitrates in 11).

During follow-up, 40 patients (9.3%) experienced a major AE including 12 deaths (2.8%), 25 admissions for non-fatal myocardial infarction or unstable angina (5.8%), and three admissions for heart failure (0.7%). There were 31 LR procedures (PCI 22, PCI and CABG 3, and CABG 6).

Imaging findings

CTCA showed no CAD in 117 patients (27%), non-obstructive CAD in 179 (42%), and obstructive CAD in 134 (31%) (*Table 2*). Significant

Table 2 Patients characteristics and outcome according to CTCA core-lab results

Number of patients	No CAD 117 patients	Non-obstructive CAD (≤50%) 179 patients	Obstructive CAD (>50%) 134 patients	*P*-value among groups	Any CAD 313 patients
Clinical information					
Pre-test probability of CAD (%)	40 ± 17	50 ± 18**	54 ± 18**	<0.001	52 ± 18**
European risk SCORE, 10 years fatal CVD risk (%)	2 ± 3	4 ± 3**	5 ± 4**,#	<0.001	4 ± 4**
Functional imaging results					
No ischaemia, *n* (%)	100 (87)	140 (77)	78 (58)**,##	<0.001	218 (69)**
Mild ischaemia (≥5 and <10%), *n* (%)	6 (5)	16 (9)	11 (8)		27 (9)
Significant ischaemia (>10%), *n* (%)	11 (9)	23 (13)	45 (34)**,##		68 (22)**
Quantitative coronary angiography (291 patients)					
>50% coronary stenosis, *n* (%)	3 (2)	31 (17)**	85 (63)**,##	<0.001	116 (37)**
Early coronary revascularizations					
Any revascularization	2 (2)	26 (15)**	62 (46)**,##	<0.001	88 (28)**
Percutaneous coronary intervention, *n* (%)	1 (1)	25 (14)**	51 (38)**,##	<0.001	76 (24)**
Coronary by-pass graft, *n* (%)	1 (1)	1 (1)	11 (8) ##		12 (4)
Clinical outcome endpoint					
Primary composite endpoint, *n* (%)	5 (4)	15 (8)	20 (15)*	0.012	35 (11)*
Death from any cause, *n* (%)	2 (2)	7 (4)	3 (2)	0.477	10 (3)
Non-fatal myocardial infarction or unstable angina, *n* (%)	2 (2)	8 (4)	15 (11)*	0.004	23 (7)*
Hospitalization for heart failure, *n* (%)	1 (1)	0 (0)	2 (2)	0.284	2 (1)
Primary composite endpoint plus late coronary revascularizations, *n* (%)	5 (4)	22 (12)	31 (23)**	<0.001	53 (17)**

Invasive and non-invasive imaging results are derived from core laboratories analysis; data are given in absolute numbers and % of each disease group, unless otherwise stated. *<0.05 and **<0.01 vs. 'no CAD'; #<0.05 and ##<0.01 'obstructive CAD' vs. 'non-obstructive CAD'.

Table 3 Patients characteristics and outcome according to functional imaging core-lab results

Parameter Number of patients	No ischaemia 318	Mild ischaemia 33	Significant ischaemia 79	*P*-value among groups	Any ischaemia 112
Clinical information					
Pre-test probability of CAD (%)	46 ± 18	58 ± 19**	53 ± 21**	<0.001	54 ± 20**
European risk Score, 10 years fatal CVD risk, %	3 ± 3	3 ± 3	4 ± 4*	0.127	4 ± 4
Quantitative coronary angiography (291 patients)					
>50% coronary stenosis, *n* (%)	51 (16)	14 (42)**	54 (68)**	<0.001	68 (61)**
Early coronary revascularizations					
Any revascularization	44 (14)	5 (15)	41 (52)**,##	<0.001	46 (41)**
Percutaneous coronary interventions, *n* (%)	38 (12)	5 (15)	34 (43)**,##	<0.001	39 (35)**
Coronary by-pass graft, *n* (%)	6 (2)	0 (0)	7 (9)		7 (6)
Clinical outcome endpoint					
Primary composite endpoint, *n* (%)	29 (9)	1 (3)	10 (13)	0.222	11 (10)
Death from any cause, *n* (%)	8 (3)	1 (3)	3 (4)	0.834	4 (4)
Non-fatal myocardial infarction or unstable angina, *n* (%)	19 (6)	0 (0)	6 (8)	0.285	6 (5)
Hospitalization for heart failure, *n* (%)	2 (1)	0 (0)	1 (1)	0.733	1 (1)
Primary composite endpoint plus late coronary revascularizations, *n* (%)	38 (12)	6 (18)	14 (18)	0.176	20 (18)

Invasive and non-invasive imaging results are derived from core laboratories analysis; data are given in absolute numbers and % of each disease group, unless otherwise stated. *<0.05 and **<0.01 vs. 'no ischaemia'; ##<0.01 'severe ischaemia' vs. 'mild ischaemia'.

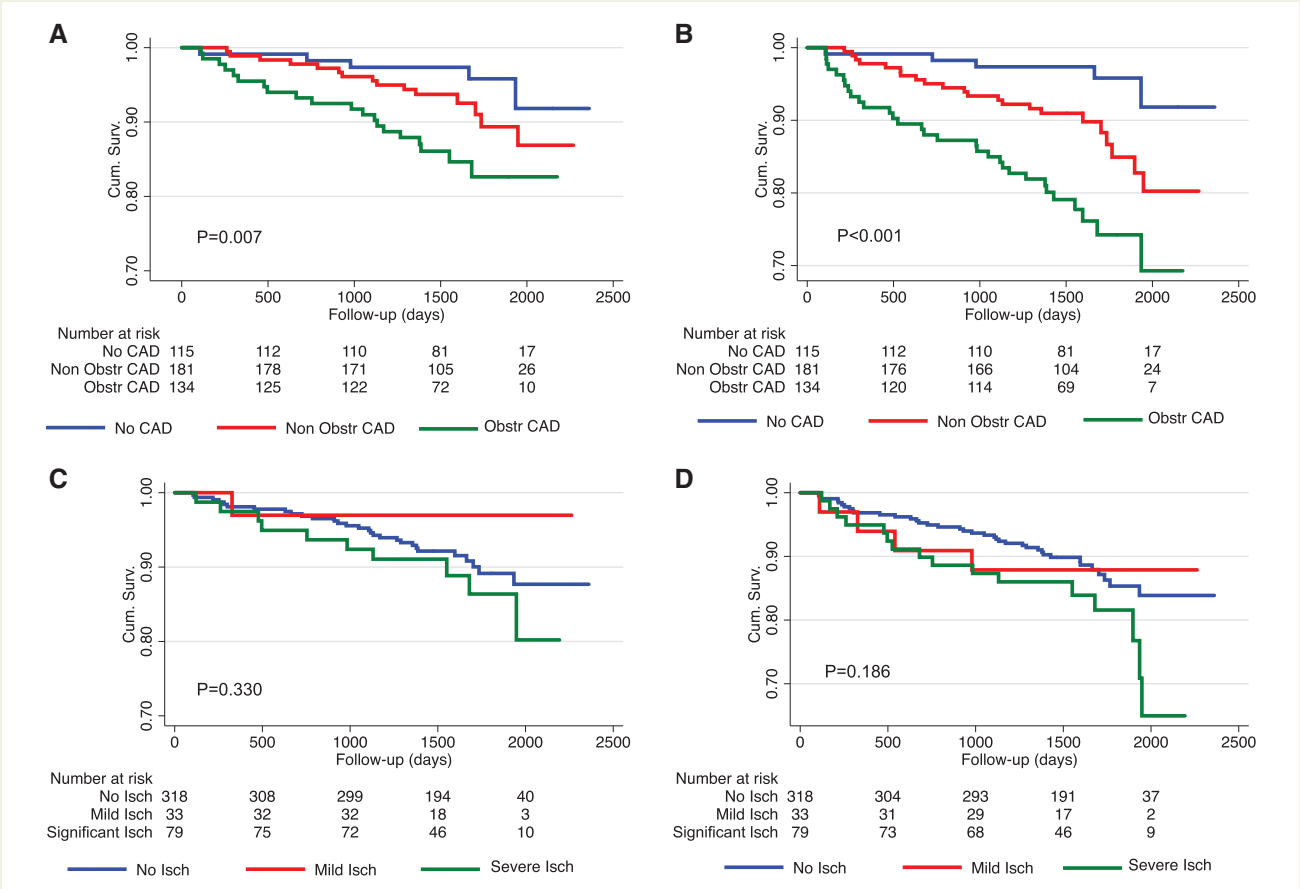

Figure 2 Unadjusted Kaplan–Meier estimates of the primary composite endpoint and secondary endpoint according to CTCA findings (*A* and *B*) and functional imaging (*C* and *D*).

ischaemia was more frequent in patients with obstructive CAD. Abnormal ICA and early revascularization were more frequent in patients with obstructive than non-obstructive disease at CTCA. Both the primary and the secondary endpoints were more frequent in patients with obstructive CAD.

Functional imaging was normal in 318 patients (74%), showed mild inducible ischaemia in 33 (8%) and significant ischaemia in 79 (18%) (*Table 3*). Quantitative ICA was more frequently abnormal in patients with mild or significant ischaemia than in patients with no ischaemia. Early revascularization was more frequent in patients with significant ischaemia (52%) but 15% of patients with mild ischaemia and 14% of patients without ischaemia were revascularized.

Survival analysis

Patients with no CAD at CTCA had a good event-free survival, while the outcome was progressively worse in patients with non-obstructive or obstructive CAD both for the primary and the secondary endpoints (*Figure 2*). Patients without or with inducible ischaemia had similar outcome (*Figure 2*). Obstructive CAD by CTCA was the only independent imaging predictor of AEs and of AEs plus LR (*Tables 4* and *5*).

Imaging phenotype, early management, and outcome

Among the 313 patients with non-obstructive or obstructive CAD at CTCA, 68 (22%) had significant inducible ischaemia at stress testing. Early revascularization was performed in 49 of 245 patients without and in 39 of the 68 patients with significant inducible ischaemia (Supplementary data online, *Table SB*). Early revascularization was associated with an increase in the AEs rate (from 9% to 14%) in the former and a decrease (from 21% to 10%) in the latter group (*Figure 3*).

Patients with CAD at CTCA who received inappropriate early management had more major AEs than those managed appropriately (17% vs. 9%, $P = 0.014$) (Supplementary data online, *Table SC*) and the worst events free survival curve at Kaplan–Meier analysis (*Figure 4*). Moreover, only CAD at CTCA with inappropriate early management remained independently associated with the primary endpoint at

Table 4 Predictors of the primary endpoint by Cox analysis

Variables	Univariate analysis HR (95% CI)	*P*-value	Multivariate analysis HR (95% CI)	*P*-value
Clinical				
Age >60 years	1.90 (0.96–3.79)	0.066	1.64 (0.78–3.42)	0.189
Male sex	2.06 (0.98–4.36)	0.058	1.92 (0.89–4.18)	0.098
Family history of CAD	1.11 (0.56–2.21)	0.762	NA	NA
Diabetes mellitus	1.68 (0.86–3.30)	0.132	NA	NA
Hypercholesterolaemia	0.72 (0.38–1.37)	0.317	NA	NA
Hypertension	0.86 (0.45–1.64)	0.648	NA	NA
Smoking	1.45 (0.72–2.96)	0.301	NA	NA
Obesity	1.14 (0.53–2.46)	0.739	NA	NA
Medical treatment				
Antidiabetics	1.81 (0.92–3.55)	0.086	NS	NS
Antihypertensive	1.07 (0.55–2.06)	0.844	NA	NA
Statins	1.04 (0.52–2.11)	0.904	NA	NA
Antiplatelets	1.84 (0.79–4.29)	0.159	NA	NA
Stress imaging			NA	NA
Mild ischaemia	0.37 (0.05–2.78)	0.333	NA	NA
Significant ischaemia	1.43 (0.65–3.16)	0.376	NA	NA
CCTA				
Non-obstructive CAD	2.16 (0.77–6.06)	0.142	1.71 (0.59–4.96)	0.322
Obstructive CAD	4.50 (1.64–12.33)	0.003	3.21 (1.10–9.38)	0.033
Intervention				
Early coronary revascularization	1.63 (0.79–3.36)	0.186	NA	NA

Table 5 Predictors of the secondary endpoint by Cox analysis

Variables	Univariate analysis HR (95% CI)	*P*-value	Multivariate analysis HR (95% CI)	*P*-value
Clinical				
Age >60 years	2.50 (1.39–4.52)	0.002	2.21 (1.18–4.13)	0.013
Male sex	2.18 (1.16–4.10)	0.015	2.17 (1.13–4.16)	0.020
Family history of CAD	1.10 (0.62–1.94)	0.749	NA	NA
Diabetes mellitus	1.31 (0.74–2.34)	0.354	NA	NA
Hypercholesterolaemia	0.90 (0.53–1.55)	0.715	NA	NA
Hypertension	0.93 (0.55–1.59)	0.795	NA	NA
Smoking	1.08 (0.58–2.01)	0.809	NA	NA
Obesity	1.25 (0.67–2.34)	0.479	NA	NA
Medical treatment				
Antidiabetics	1.50 (0.85–2.66)	0.160	NA	NA
Antihypertensive	1.20 (0.69–2.10)	0.513	NA	NA
Statins	1.47 (0.78–2.77)	0.235	NA	NA
Antiplatelets	2.88 (1.35–6.12)	0.006	NS	NS
Stress imaging				
Mild ischaemia	1.22 (0.39–3.25)	0.831	NA	NA
Significant ischaemia	1.70 (0.90–3.22)	0.104	NA	NA
CCTA				
Non-obstructive CAD	2.97 (1.11–7.93)	0.030	2.15 (0.78–5.92)	0.139
Obstructive CAD	6.85 (2.60–18.03)	<0.001	4.29 (1.56–11.81)	0.005
Intervention				
Early coronary revascularization	2.03 (1.14–3.61)	0.016	NS	NS

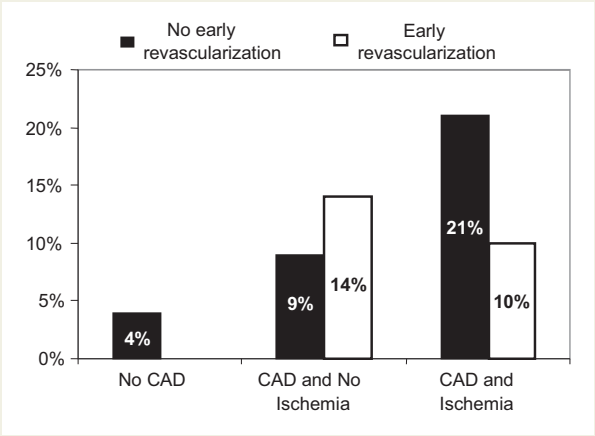

Figure 3 Interaction between imaging phenotype and early patient management on the primary composite endpoint. In patients treated conservatively, the event-rate gradually increased in patients with no CAD, CAD without severe ischaemia, and CAD with severe ischaemia ($P = 0.03$). Interestingly, in patients with CAD treated with early coronary revascularization, the event-rate decreased in the presence of severe ischaemia, while increasing in its absence.

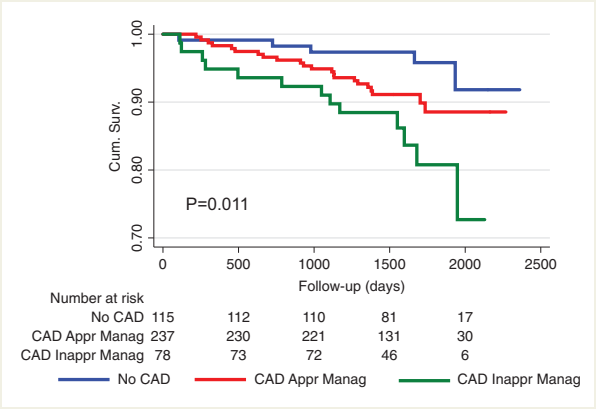

Figure 4 Unadjusted Kaplan–Meier estimates of the primary composite endpoint according to the 'theoretical' appropriateness of early patient management in relation to the combined anatomical and functional imaging findings. The difference between the events-free survival curves for inappropriate and appropriate early management is borderline significant ($P = 0.081$).

multivariate Cox analysis (*Tables* 6 and 7). Similar results were obtained even after restricting the primary endpoint to death and non-fatal myocardial infarction (Supplementary data online, *Table SD*).

Discussion

In patients with symptoms of suspected stable CAD, obstructive CAD at CTCA was independently associated with an adverse outcome, while significant inducible ischaemia and early revascularization were not. Any CAD was excluded by CTCA in fewer than one-third of patients, who had a good outcome, while obstructive CAD was present in another third of patients and was associated with 3-to-4-fold higher risk of AEs or AEs plus LR. Patients with non-obstructive CAD had an intermediate risk. Significant inducible ischaemia was present in only 16% of patients and did not predict AEs. Early revascularization was performed in 21% and did not modify outcome. However, only 41 of the 90 (46%) revascularization procedures were performed in patients who had both anatomically and functionally significant disease. Patients with CAD in whom early revascularization was performed in the presence of significant inducible ischaemia and deferred in its absence had an outcome not significantly different from that of patients without CAD. Conversely, patients with CAD who were revascularized despite no evidence of ischaemia or in whom intervention was deferred despite evidence of ischaemia had approximately three-fold higher risk of AEs than patients with no CAD.

Our results are consistent with previous studies demonstrating that patients with symptoms of suspected stable CAD and normal coronary arteries at CTCA have a good outcome, while anatomically non-obstructive and in particular obstructive CAD is associated with a poorer outcome.[2,3,16] In recent studies using combined anatomical and functional imaging, functionally significant CAD identified patients at highest risk.[7–9,17] This study expands these findings, demonstrating that when early coronary revascularization is performed in this higher risk group and deferred in the others the outcome is improved. Conversely, management inconsistent with the combined anatomical and functional findings is associated with a worse outcome.

Comparative studies have not previously demonstrated the superiority of any particular non-invasive technique in terms of prognostication.[11,18] However, the recent 5-year follow-up of the SCOT-HEART trial[12] showed the prognostic benefit of an anatomically based approach over standard care in patients with suspected stable CAD, the better outcome being driven by more aggressive medical treatment in patients with documented CAD. These apparently contradictory findings may be the result of multiple factors. Current populations submitted to imaging as opposed to direct referral to ICA have a relatively low prevalence of severe CAD and an intermediate-low risk.[7,11,14] Moreover, patients are commonly assigned to a single imaging technique and downstream management may not be guided by the imaging results.[12,13] Although the EVINCI-Outcome study was not randomized, it involved a contemporary European population of symptomatic patients in whom both anatomical and functional coronary imaging was performed.[14] Because patient management was at the discretion of the managing physicians, the possible effect of disagreement between imaging phenotype and management choice could be evaluated.

Myocardial ischaemia was not an independent predictor of AEs on multivariate analysis. This conflicts with previous reports,[4,19] even if it is in keeping with results obtained in contemporary multi-centre populations.[20,21] Similar results as in the present study have been reported in the sub-analysis of the COURAGE trial involving a larger population of 621 patients, and demonstrating that coronary anatomical burden predicted outcome while ischaemia of any severity, assessed by SPECT, did not.[22]

Table 6 Predictors of the primary endpoint by Cox analysis

Variables	Univariate analysis HR (95% CI)	*P*-value	Multivariate analysis HR (95% CI)	*P*-value
Clinical				
Age >60 years	1.90 (0.96–3.79)	0.066	1.80 (0.88–3.66)	0.107
Male sex	2.06 (0.98–4.36)	0.058	1.86 (0.85–4.05)	0.121
Family history of CAD	1.11 (0.56–2.21)	0.762	NA	NA
Diabetes mellitus	1.68 (0.86–3.30)	0.132	NA	NA
Hypercholesterolaemia	0.72 (0.38–1.37)	0.317	NA	NA
Hypertension	0.86 (0.45–1.64)	0.648	NA	NA
Smoking	1.45 (0.72–2.96)	0.301	NA	NA
Obesity	1.14 (0.53–2.46)	0.739	NA	NA
Medical treatment				
Antidiabetics	1.81 (0.92–3.55)	0.086	NS	NS
Antihypertensive	1.07 (0.55–2.06)	0.844	NA	NA
Statins	1.04 (0.52–2.11)	0.904	NA	NA
Antiplatelets	1.84 (0.79–4.29)	0.159	NA	NA
Early management choices			NA	NA
Appropriate	2.34 (0.89–6.19)	0.086	1.97 (0.71–5.51)	0.195
Inappropriate	4.28 (1.52–12.01)	0.006	3.16 (1.03–9.64)	0.044

Table 7 Predictors of the secondary endpoint by Cox analysis

Variables	Univariate analysis HR (95% CI)	*P*-value	Multivariate analysis HR (95% CI)	*P*-value
Clinical				
Age >60 years	2.50 (1.39–4.52)	0.002	2.54 (1.37–4.70)	0.003
Male sex	2.18 (1.16–4.10)	0.015	2.20 (1.14–4.24)	0.018
Family history of CAD	1.10 (0.62–1.94)	0.749	NA	NA
Diabetes mellitus	1.31 (0.74–2.34)	0.354	NA	NA
Hypercholesterolaemia	0.90 (0.53–1.55)	0.715	NA	NA
Hypertension	0.93 (0.55–1.59)	0.795	NA	NA
Smoking	1.08 (0.58–2.01)	0.809	NA	NA
Obesity	1.25 (0.67–2.34)	0.479	NA	NA
Medical treatment				
Antidiabetics	1.50 (0.85–2.66)	0.160	NA	NA
Antihypertensive	1.20 (0.69–2.10)	0.513	NA	NA
Statins	1.47 (0.78–2.77)	0.235	NA	NA
Antiplatelets	2.88 (1.35–6.12)	0.006	NS	NS
Early management choices				
Appropriate	4.19 (1.63–10.79)	0.003	2.92 (1.10–7.73)	0.031
Inappropriate	4.92 (1.75–13.79)	0.002	2.92 (0.99–8.54)	0.051

In populations with low prevalence of obstructive disease, CTCA could be of advantage over ischaemia testing, providing additional information on the coronary atherosclerotic risk beyond the effects of ischaemia. However, the lower prognostic performance of functional imaging could also be explained by the variable effect of patient management. The adverse prognostic impact of ischaemia might be reduced by early revascularization and retained if revascularization is not performed. As a matter of fact, 43% of the patients with CAD and significant ischaemia in the EVINCI population were not revascularized and had the worst outcome (*Figure 3*). On the other hand, in patients with non-significant inducible ischaemia, a possible limited benefit of revascularization could be outweighed by its potential harms. It is not surprising that when early patient's management was defined as inappropriate, on the basis of combined anatomical and

functional non-invasive imaging phenotype, it was associated with the worst prognosis. Thus the present results underline the need for an ischaemia-guided patient management.[23]

The EVINCI-outcome study shares the same limitations of the main EVINCI study,[14] particularly regarding the non-randomized design and the relatively small population. The latter was due to the complexity of the protocol, which required both CTCA and at least one functional test for each patient to be available and interpretable by core-labs, causing a relatively high number of drop-outs and protocol violations. Nevertheless, the same protocol allowed a well-characterized population of patients with stable chest pain and suspected CAD to undergo evaluation by both anatomical and functional coronary imaging, and this has provided unique insights into the relationship between imaging phenotype and clinical outcome.

The main EVINCI study was adequately powered on the basis of the primary diagnostic endpoint.[14] However, due to the relatively small population and low event rate at follow-up, the EVINCI outcome study was relatively underpowered in particular to assess the prognostic role of the modalities that were performed more rarely, such as PET and CMR. Thus, the results of different stress imaging modalities were merged. This, together with the low prevalence of significant inducible ischaemia, could have disadvantaged ischaemia testing as compared to coronary imaging, which was performed in every patient with CTCA.

Only core laboratories imaging results were considered in the main outcome analysis to ensure a more objective and unbiased evaluation of the prognostic role of imaging. This choice may have introduced some limitations but had also some advantages. The core laboratories did not have full clinical information available and hence had neither the benefit nor the possible bias, of integration with clinical features in evaluating imaging studies. This could explain the sub-optimal agreement of imaging interpretation between centres and core laboratories. Core laboratories reclassified to a lower category 43% of patients with CAD and significant ischaemia at centres while upgrading to significant ischaemia 8% of the remaining patients (Supplementary data online, *Figure S1*). Since patient management was at the discretion of the referring physician, it could have been more consistent with the local imaging findings than with core laboratories interpretation.

The specific reasons of management choices, as in most similar studies, were not available. It cannot be excluded, that comorbidities or high interventional risks might have discouraged early revascularization in some patient with significant ischaemia, conditioning *per se* a worse prognosis.

Conclusion

In a population with low prevalence of significant CAD, the high negative predictive value of CTCA and the good prognosis of patients without anatomically significant CAD suggest that a strategy using CTCA as the first test is reasonable. Nevertheless, when anatomical disease is found by CTCA, coronary functional imaging should be encouraged before ICA since this allows patients with significant inducible ischaemia, who have most to gain by revascularization, to be identified.

Results from specific large randomized trials are expected to answer more directly the question of whether revascularization or medical treatment based on anatomical and functional imaging results are able to change outcome.[24]

Supplementary data

Supplementary data are available at *European Heart Journal - Cardiovascular Imaging* online.

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