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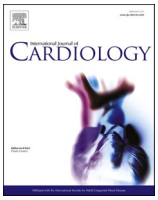

Prognostic utility of hybrid coronary computed tomography angiography and myocardial perfusion imaging in elderly patients with suspected coronary artery disease

Wail Nammas [a,b,*,1], Iina Ajosenpää [b,1], Teemu Maaniitty [a,c,1], Iida Stenström [a,1], Jeroen J. Bax [b,d,1], Juhani Knuuti [a,c,1], Antti Saraste [a,b,1]

[a] Turku PET Centre, Turku University Hospital and University of Turku, Turku, Finland
[b] Heart Center, Turku University Hospital, Turku, Finland
[c] Department of Clinical Physiology, Nuclear Medicine and PET, Turku University Hospital, Turku, Finland
[d] Department of Cardiology, Leiden University Medical Center, Leiden, the Netherlands

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ABSTRACT

Background: The prognostic utility of sequential hybrid imaging strategy (coronary computed tomography angiography (CCTA) followed by positron emission tomography (PET) myocardial perfusion imaging in those with obstruction) in the elderly remains unclear. We explored the predictors of adverse outcome in patients ≥65, versus those <65 years, who underwent hybrid CCTA-PET for evaluation of coronary artery disease (CAD).

Methods: Retrospectively, we evaluated 1948 patients (43.8 % ≥65 years) referred for CCTA due to suspected CAD from 2008 through 2016. Patients with obstructive CAD by CCTA (n = 657) underwent ^{15}O-water PET under adenosine stress.

Results: Mean age was 61.9 ± 9.9 years, 58.9 % were females. Elderly patients had more often obstructive CAD by CCTA, and ischemia by PET. During a median follow-up of 6.7 years, the composite adverse outcome (all-cause death, myocardial infarction, or unstable angina) occurred more often in patients ≥65, versus those <65 years (14.2 % vs. 5.6 %, $p < 0.001$). Ischemic CAD assessed by hybrid imaging predicted events with a hazard ratio of 5.65 (95 % CI 2.35–13.57) in older patients, and 7.01 (95 % CI 3.08–15.94) in younger patients, compared with patients without CAD. The c-statistic of a multivariable model including the hybrid CCTA-PET finding (adjusted for clinical risk predictors) for predicting the composite outcome was similar between patients ≥65, versus those <65 years ($p = 0.1$). There was no interaction between age category and the hybrid CCTA-PET finding for prediction of events ($p = 0.9$).

Conclusion: The prognostic utility of hybrid CCTA-PET for predicting adverse events at long-term follow-up was similar between patients ≥65 and those <65 years.

1. Introduction

Old age is an independent risk factor for atherosclerotic coronary artery disease (CAD), and is associated with increased CAD-related morbidity and mortality [1]. Yet, diagnosis and management of CAD in elderly population may be associated with challenges caused by atypical symptoms, frailty and comorbidities [1].

Coronary computed tomography angiography (CCTA) and functional imaging of myocardial ischemia by positron emission tomography (PET) are recommended by the current European guidelines for the management of chronic coronary syndromes as the initial diagnostic work-up in symptomatic patients with suspected obstructive CAD [1]. CCTA is associated with clinical outcomes similar to those of functional imaging [2,3]. The feasibility of CCTA in elderly population was previously demonstrated [4]. However, the prevalence and extent of coronary calcification increase with age [5] which may decrease the likelihood of obtaining a CCTA scan of diagnostic quality [4].When CCTA is not diagnostic or functional significance of CAD remains uncertain, guidelines recommend sequential use of functional testing to establish an accurate diagnosis of obstructive, ischemia-inducing CAD

* Corresponding author at: Heart Center, Turku University Hospital, Hämeentie 11, 20520 Turku, Finland.
E-mail address: wail.elnammas@tyks.fi (W. Nammas).
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[1].

In our center, we adopted a sequential hybrid imaging strategy for patients presenting with symptoms of obstructive CAD. Patients initially undergo CCTA, and only those with suspected obstructive CAD by CCTA are triaged for ^{15}O-water PET myocardial perfusion imaging (MPI), whereas those with no or non-obstructive atherosclerotic plaques by CCTA undergo no further imaging [6,7]. We observed that normal MPI is associated with favorable prognosis, even in the presence of obstructive CAD by CCTA [6]. Nevertheless, the prognostic utility of sequential hybrid-imaging in older vs. younger patients remains unclear. We hypothesized that the prognostic value of this strategy is similar among older vs. younger, with potentially pronounced benefits over CCTA alone in the elderly. Therefore, we evaluated whether the PET imaging results are predictive of adverse clinical outcomes in patients <65 versus ≥65 years of age, who underwent sequential CTA and PET for evaluation of suspected CAD.

2. Methods

2.1. Patient cohort

Retrospectively, we identified all consecutive patients referred for CCTA in Turku PET Centre for suspected CAD during the period from 1 January 2006 to 31 December 2016. The patients had predominantly intermediate pre-test probability of obstructive CAD.

We excluded patients with previously known CAD (previous coronary revascularization or ≥ 50 % diameter stenosis by invasive coronary angiography), and those referred for reasons other than suspected obstructive CAD, including cardiomyopathy, heart failure, and preoperative evaluation. In patients with repeat PET MPI scans during the study period, only the earliest scan was considered for the current analysis.

The study complies with the Declaration of Helsinki. The Ethics Committee of the Hospital District of Southwest Finland approved the study protocol, and waived the need for informed consent for this observational study.

2.2. CCTA and PET data acquisition and interpretation

The details of CCTA and PET image acquisition and interpretation were described earlier [6] (summarized in the supplemental data file). We defined obstructive CAD on CCTA as ≥50 % diameter stenosis on clinical assessment by the attending physician. Abnormal PET MPI scan was defined as sMBF ≤2.3 mL/g/min in ≥1 segment within the territory supplied by a stenotic coronary artery or an adjacent territory [7]. For description purposes, CCTA findings were classified as 1: no CAD (normal CCTA), 2: non-obstructive CAD, and 3: obstructive CAD. Similarly, hybrid CCTA-PET findings were classified as 1: no CAD, 2: non-ischemic CAD (non-obstructive or obstructive CAD on CCTA with normal PET MPI), and 3: ischemic CAD (obstructive CAD on CCTA with abnormal PET MPI).

2.3. Data collection and follow-up

Data on cardiovascular risk factors and symptoms were retrospectively collected from electronic medical records. CCTA and PET MPI scan data were obtained from the institutional imaging database and electronic medical records. Clinical and imaging data were collected blinded to outcomes. Comprehensive data on the occurrence of the primary endpoint including all-cause death, myocardial infarction (MI), and unstable angina [6] until May 2020 were obtained from the registries of the Finnish Institute for Health and Welfare and the Centre for Clinical Informatics of Turku University Hospital. In case of occurrence of multiple adverse events, the first event was counted. The clinical events identified from these registries were validated by the investigators using electronic medical records. Data of early revascularization within 6 months after CCTA (percutaneous coronary intervention or coronary bypass surgery), were also collected, but not used as endpoints. The Finnish Institute for Health and Welfare gave permission to retrospective data collection.

2.4. Statistical analysis

Continuous variables were reported as mean ± standard deviation or median [interquartile range], as appropriate. Categorical variables were shown as count (percentage). The χ^2 test, Fisher Exact test, student *t*-test, and Mann–Whitney *U* test were used to compare descriptive data as appropriate. The cumulative incidence of the primary endpoint was based on Kaplan–Meier estimates, and was compared between patients <65 years and those ≥65 years, using the log-rank test. Cox proportional hazards models were used to identify the univariable and multivariable predictors of the primary endpoint in the whole cohort, in patients <65 years, and in those ≥65 years. The clinical variables bearing significant association with the primary endpoint in the univariable analysis were added to the clinical multivariable model as covariates. Those covariates bearing significant association with the primary endpoint in the clinical multivariable model were then transferred as covariates to multivariable models including CCTA finding or hybrid CCTA-PET finding. Hazard ratios and 95 % confidence intervals (CI) were presented. The interaction between age ≥ 65 years on one hand and either the CCTA finding or hybrid CCTA-PET finding, on the other hand, for predicting the primary endpoint was tested using Cox regression models. Harrel's C indices (with 95 %CI) were estimated and compared to assess the discriminatory ability of Cox proportional hazards models. C-indices of the Cox proportional hazards models were compared between patients <65 years and those ≥65 years using *Z*-test. Furthermore, receiver operating characteristics curves were constructed comparing the prognostic value of the CCTA finding and hybrid CCTA-PET finding (unadjusted and adjusted for the clinical risk predictors) for predicting the primary endpoint between patients <65 years and those ≥65 years. Statistical significance was set at $P < 0.05$. Statistical analyses were performed using SPSS v. 25.0 (IBM Corporation New York, USA) statistical software and R version 4.3.2 (package survcomp).

3. Results

Out of 2212 scans available, we excluded 122 patients with non-diagnostic CCTA scan, 100 with obstructive CAD on CCTA scan but PET scan was not performed, 28 with failed PET scan, and 14 with normal or non-obstructive CAD by CCTA in whom PET scan was performed (Fig. 1). The proportion of non-diagnostic CCTA was similar between patients ≥65 years and those <65 years (6.0 % vs. 5.1 %, $p = 0.3$). The final analysis included 1948 patients (43.8 % ≥65 years), of whom 662 (34.0 %) had normal CCTA, 954 (49.0 %) had non-ischemic CAD (either non-obstructive CAD by CCTA and PET MPI not performed or obstructive CAD by CCTA but normal PET MPI scan), and 332 (17.0 %) had ischemic CAD (obstructive CAD by CCTA and ischemia by PET MPI).

3.1. Baseline characteristics

Mean age was 61.9 ± 9.9 years (median 63 [interquartile range 13], 25th–75th percentile 56–69 years). Age distribution in the cohort is shown in Supplementary Fig. 1A. Of the cohort, 58.9 % were females; 14.8 % diabetic; 22.1 % presented with typical angina, and 38.8 % with dyspnea. Baseline characteristics of the cohort, as well as of patients <65 years and those ≥65 years, are shown in Table 1. Older patients were more often women, and more likely to have diabetes, hypertension, and dyslipidemia. They presented more often with typical angina and dyspnea. They had a higher CAC score and were more likely to have suspected obstructive CAD on CCTA. They were also more likely to have ischemic CAD based on PET MPI. However, among 657 patients (44.4 %

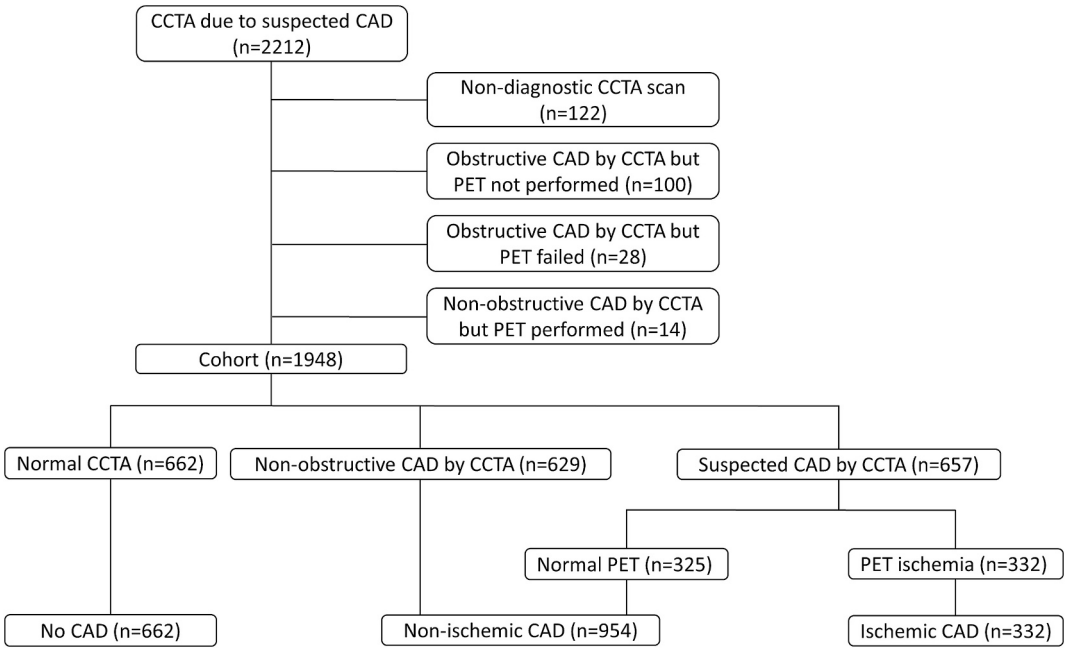

Fig. 1. Study flow chart.
CAD = coronary artery disease, CCTA = coronary computed tomography angiography, PET = positron emission tomography.

of older vs. 25.4 % of younger patients) who underwent PET MPI based on obstructive CAD on CCTA, ischemia was found in equal proportion of older and younger patients (48.5 % versus 53.2 %, $p = 0.2$).

Of 217 patients who underwent early invasive angiography, 190 (87.6 %) had ischemia by PET MPI, and 27 (12.4 %) had obstructive CAD by CCTA but no ischemia by PET MPI. Of these, 127 patients underwent early revascularization, of whom 123 (96.9 %) had ischemia by PET MPI. In 332 patients who had ischemia by PET MPI, the rate of early invasive angiography and that of early revascularization were similar in patients ≥65 years and those <65 years (59.8 % vs. 54.1 %, $p = 0.2$; and 38.0 % vs. 35.8 %, $p = 0.6$; respectively).

3.2. Adverse events at follow-up

Patients were followed up for a mean of 6.8 ± 2.5 years (median 6.7 [interquartile range 4.0] years). During follow-up, 126 (6.5 %) patients died; 45 (2.3 %) developed non-fatal MI; and 21 (1.1 %) unstable angina. The primary endpoint of death, MI, or unstable angina occurred in 182 (9.4 %) patients. The cumulative incidence of the primary endpoint increased progressively with increasing age category (Supplementary Fig. 1B), and was higher in patients ≥65 years than in those <65 years (14.2 % vs. 5.6 %, $p < 0.001$, Table 1, Supplementary Fig. 2). Similarly, the event-free survival decreased progressively from no atherosclerosis to non-obstructive atherosclerosis and obstructive atherosclerosis in CCTA, as well as with worsening hybrid CCTA-PET finding in patients <65 years ($p < 0.001$ both, Fig. 2 A and B, respectively) and in those ≥65 years ($p < 0.001$ both, Fig. 2 C and D, respectively).

In patients who had ischemia by PET MPI, the cumulative incidence of the primary endpoint was similar between those who underwent early revascularization and those who were treated conservatively (17.9 % vs. 22.5 %, $p = 0.3$); however, such proportions were different for patients ≥65 years (24.3 % vs. 26.3 %, $p = 0.8$) and those <65 years (9.4 % vs. 17.9 %, $p = 0.2$).

3.3. Predictors of the primary endpoint

Univariable and multivariable predictors of the primary endpoint are summarized in supplemental table 1 and Table 2, respectively. In multivariable models including the clinical predictors of events, age was an independent predictor of adverse events in the whole cohort, as well as in both age categories ($p < 0.05$ for all). The clinical predictors of adverse events differed between patients ≥65 years and those <65 years: in older patients, male sex, diabetes and dyspnea ($p < 0.05$ for all), whereas in younger patients, typical angina predicted events ($p = 0.01$).

In multivariable models including the CCTA finding, age remained independent predictor of events in the whole cohort, as well as in patients ≥65 years ($p < 0.01$ both), but not in those <65 years. The presence of obstructive CAD by CCTA predicted events with a HR of 4.47 (95 % CI 1.92–10.44) in older patients, and 5.09 (95 % CI 2.29–11.27) in younger patients, compared with normal coronaries. Likewise, in multivariable models including the hybrid CCTA-PET finding, age remained independent predictor of events in the whole cohort, as well as in patients ≥65 years ($p < 0.01$ both), but not in those <65 years. Myocardial ischemia by PET predicted events with a HR of 5.65 (95 % CI 2.35–13.57) in older patients, and 7.01 (95 % CI 3.08–15.94) in younger patients, compared with normal coronaries. There was no interaction between age category (≥65 versus <65 years) and the CCTA findings for prediction of adverse events ($p = 0.8$). Similarly, there was no interaction between age and the hybrid CCTA-PET findings for prediction of events ($p = 0.9$).

In the entire cohort, the c-statistic for the clinical risk prediction model was 0.713 (95 % CI 0.674–0.752). Adding the CCTA results to the clinical model increased the c-statistic to 0.746 (95 % CI 0.711–0.782; $p < 0.001$ versus the clinical model), and adding the hybrid CCTA-PET findings to the clinical model increased the c-statistic to 0.752 (95 % CI 0.717–0.787; $p < 0.001$ versus the clinical model; $p = 0.04$ versus "clinical + CTA" model). In older patients, the c-statistic for the clinical risk prediction model was 0.670 (95 % CI 0.614–0.726). Adding the CCTA results to the clinical model increased the c-statistic to 0.712 (95 % CI 0.663–0.760; $p = 0.008$ versus the clinical model), and adding the hybrid CCTA-PET findings to the clinical model increased the c-statistic to 0.713 (95 % CI 0.663–0.763; $p = 0.009$ versus clinical model; $p = 0.4$ versus "clinical + CTA" model). In younger patients, the c-statistic for the clinical risk prediction model was 0.676 (95 % CI 0.611–0.741).

Table 1
Baseline characteristics, imaging findings, invasive procedures and follow-up events.

	Cohort (N = 1948)	Age < 65 years (N = 1095)	Age ≥ 65 years (N = 853)	p value
Female sex	1147 (58.9)	584 (53.3)	563 (66.0)	<0.001
Age (years)	62.9 ± 9.6	55.1 ± 7.3	70.8 ± 4.5	<0.001
Body mass index	27.9 ± 6.6	28.1 ± 7.2	27.8 ± 5.8	0.5
Current or ex-smoking	625 (32.1)	394 (36.0)	231 (27.1)	<0.001
Diabetes	288 (14.8)	144 (13.2)	144 (16.9)	0.02
Hypertension	1083 (55.6)	541 (49.4)	542 (63.5)	<0.001
Dyslipidemia	1221 (62.7)	659 (60.2)	562 (65.9)	0.01
Family history of ischemic heart disease	918 (47.1)	586 (53.5)	332 (38.9)	<0.001
Typical angina	411 (22.1)	213 (20.3)	198 (24.4)	0.03
Any angina	1374 (73.9)	786 (75.1)	588 (72.3)	0.1
Dyspnea	755 (38.8)	366 (33.4)	389 (45.6)	<0.001
Coronary artery calcium score	246.6 ± 597.6	138.8 ± 404.3	381.4 ± 735.2	<0.001
Coronary artery calcium category				<0.001
0	578 (36.3)	418 (47.2)	160 (22.6)	
1–99	467 (29.3)	259 (29.2)	208 (29.4)	
100–399	304 (19.1)	128 (14.4)	176 (24.9)	
>400	245 (15.4)	81 (9.1)	164 (23.2)	
CCTA finding				<0.001
No CAD	662 (34.0)	488 (44.6)	174 (20.4)	
Non-obstructive CAD	629 (32.3)	329 (30.0)	300 (35.2)	
Obstructive CAD	657 (33.7)	278 (25.4)	379 (44.4)	
Hybrid CCTA-PET finding				<0.001
No CAD	662 (34.0)	488 (44.6)	174 (20.4)	
Non-ischemic CAD	954 (49.0)	459 (41.9)	495 (58.0)	
Ischemic CAD	332 (17.0)	148 (13.5)	184 (21.6)	
Early invasive procedures (≤6 months of imaging)				
Coronary angiography	217 (11.1 %)	93 (8.5)	124 (14.5)	<0.001
Coronary angioplasty	112 (5.7 %)	50 (4.6)	62 (7.3)	0.01
Coronary bypass surgery	18 (0.3 %)	7 (0.6)	11 (1.3)	0.1
Follow-up events				
Death	126 (6.5)	37 (3.5)	89 (10.4)	<0.001
Myocardial infarction	45 (2.3)	20 (1.8)	25 (2.9)	0.1
UAP	21 (1.1)	6 (0.5)	15 (1.8)	0.01
Death/myocardial infarction	164 (8.4)	55 (5.0)	109 (12.8)	<0.001
Death/myocardial infarction/UAP	182 (9.4)	61 (5.6)	121 (14.2)	<0.001

CAD = coronary artery disease, CCTA = coronary computed tomography angiography, PET = positron emission tomography, UAP = unstable angina pectoris.

Adding the CCTA findings to the clinical model increased the c-statistic to 0.724 (95 % CI 0.664–0.784; $p = 0.04$ versus the clinical model), and adding the hybrid CCTA-PET finding to the clinical model increased the c-statistic to 0.739 (95 % CI 0.676–0.803; $p = 0.01$ versus clinical model; $p = 0.02$ versus "clinical + CTA" model). The c-statistic was similar between patients ≥65 years and those <65 years for the clinical risk prediction model ($p = 0.8$), for the "clinical + CTA" model ($p = 0.7$), as well as for the "clinical + hybrid imaging" model ($p = 0.5$). The ROC curves comparing prognostic utility of the CCTA and CCTA-PET findings (unadjusted and adjusted for the clinical risk predictors) to predict the primary endpoint are shown in Supplementary Fig. 3.

4. Discussion

The current study demonstrated that in patients who underwent sequential hybrid-imaging (CCTA followed by PET MPI in those with anatomical coronary obstruction), the prognostic utility of CCTA, and the hybrid imaging approach was similar in patients ≥65 years versus those <65 years for prediction of adverse events at long-term follow-up. Furthermore, the hybrid imaging approach added to the prognostic utility of CCTA in patients <65 years, but not in patients ≥65 years. Age independently predicted events in patients ≥65 years, but not in patients <65 years.

In the current study, CCTA was feasible with interpretable results in 94.5 % of the patients. However, a considerably larger proportion of patients ≥65 years versus patients <65 year (44.4 % versus 25.4 %, $p < 0.001$) were referred for functional imaging of myocardial ischemia consistent with larger proportion of patients with obstructive CAD on CCTA. Still, the yield of functional imaging in detecting ischemia was similar in the older and younger subgroups (48.5 % versus 53.2 %, $p = 0.2$) indicating similar positive predictive value in selected patients in both age groups. Previously, Laggoune et al. [4] reported CCTA feasibility of 68 % in low to intermediate-risk patients ≥75 years of age [4]. In their study, the main cause (80 %) of non-interpretable CCTA was extensive coronary calcifications, which precluded ruling out obstructive CAD [4]. Other predictors of non-interpretability were age > 78 years, male gender, and diabetes [4]. In our study, 23.2 % of patients ≥65 years had a coronary artery calcium score > 400, as compared with only 9.1 % in patients <65 years, which may partly explain higher rate of referral to ischemia testing in the elderly.

Age is a non-modifiable risk factor for the progression of atherosclerotic CAD and advancing age is associated with higher prevalence of obstructive CAD [8,9]. In our study, the prevalence of obstructive CAD on CCTA (anatomical imaging) and the presence of ischemia by PET MPI (functional imaging) were higher in older versus younger patients. This observation is in line with a post-hoc analysis from the PROMISE trial [10], where a positive test (obstructive CAD by CCTA or ischemia by functional imaging) was significantly more frequent in the higher age groups, compared with patients <65 years [10]. Furthermore, in the PROMISE trial, interaction was observed between age and test type (anatomical versus functional test) for the composite of cardiovascular death or MI, such that positive CCTA result was associated with adverse events in younger (<65 years) but not in older (≥65 years) patients; whereas positive functional imaging result was associated with events in older rather than younger ones [10]. These observations indicate that the clinical value of CCTA results was most significant in patients <65 years. Nevertheless, such interaction was not found for the composite of all-cause death, MI or unstable angina [10]. In our study, the predictive performance of either the anatomical (CCTA) or the combined anatomical and functional (hybrid) imaging was statistically similar between these 2 age groups, although the AUC was slightly bigger in younger versus older patients. Due to the small number of individual end-points, the predictive value of imaging for the composite of death or MI could not be analyzed. These results indicate that the use of hybrid imaging effectively risk-stratifies patients in the elderly (≥65 years) population.

The presence of obstructive CAD and ischemia on hybrid CCTA-PET was associated with the highest risk of adverse events in our study, which is in line with previous findings of incremental prognostic value of combined functional and CCTA parameters [11,12]. In the study of Pazhenkottil et al. combination of obstructive CAD and ischemia in a matching location predicted the risk of death or MI with a hazard ratio of 3.78 after adjustment for clinical risk factors and left ventricular function during median follow-up of 6.8 years [11].

As expected, the cumulative incidence of adverse events was higher in patients ≥65 years than in those <65 years. The presence of dyspnea independently predicted adverse events in both age groups. Likewise, in the study by Magna et al. dyspnea predicted major cardiac events

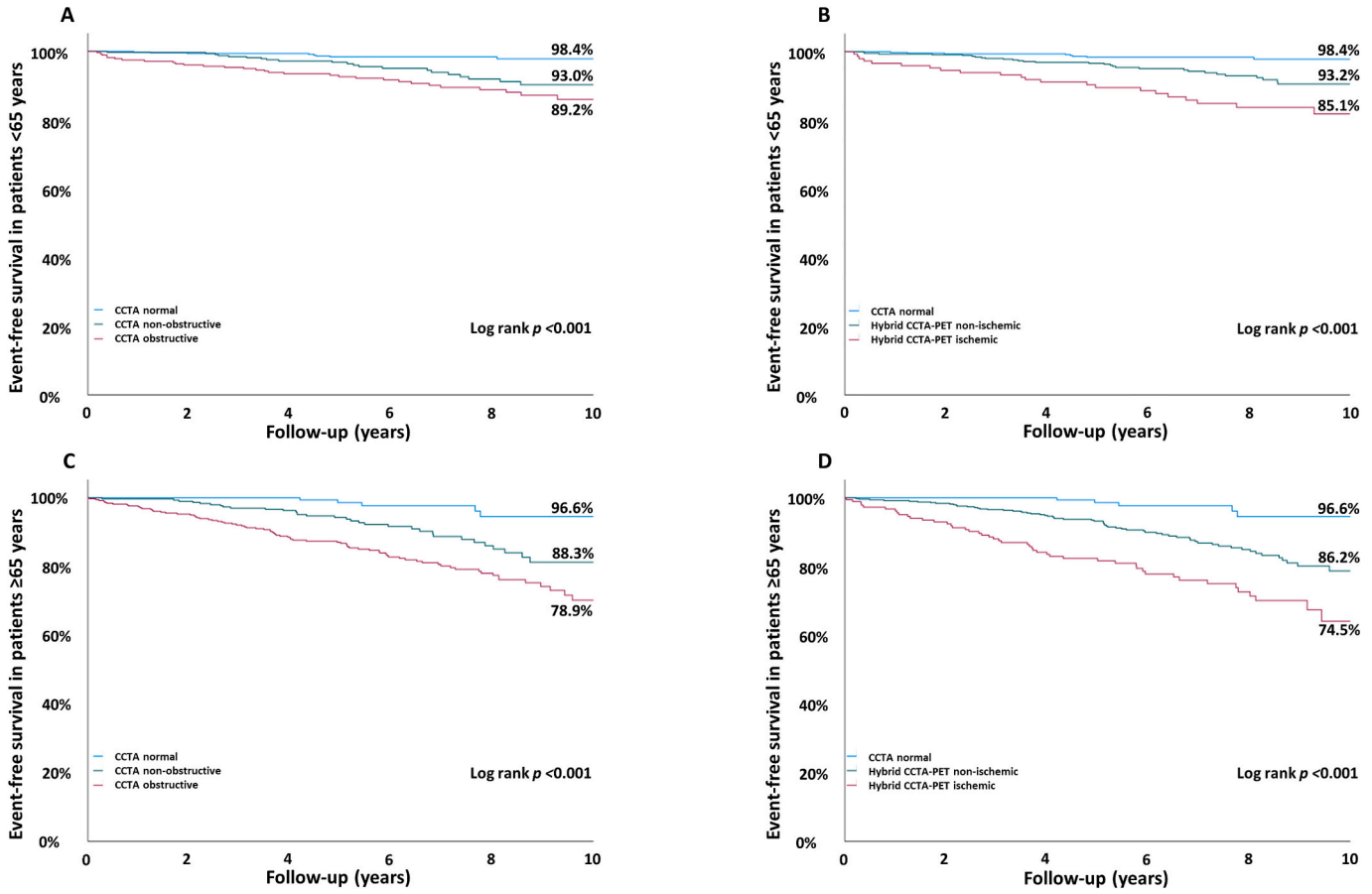

Fig. 2. Event-free survival per CCTA finding and per hybrid CCTA-PET finding in patients <65 years (A and B, respectively), as well as in those ≥65 years (C and D, respectively).
CCTA = coronary computed tomography angiography, PET = positron emission tomography.

(cardiac death, non-fatal MI, late coronary revascularization and heart failure hospitalization) in all age tertiles [13]. The importance of dyspnea as a modifier of the pre-test probability of obstructive CAD is highlighted in the latest practice guidelines for the management of chronic coronary syndromes [1]. Apart from age and dyspnea, the clinical predictors of adverse outcome differed between older and younger patients. Similarly, it was previously reported that the clinical risk predictors varied among the tertiles of age [13]. When the imaging test result (either obstructive CAD by CCTA or ischemia by PET MPI) was added to the multivariable model, age was no longer predictive of events in younger patients, although it remained predictive in older patients. Apparently, the significance of age as a risk predictor increases with rising age, since it still predicts adverse outcome independent of the imaging test result.

Both the CCTA and PET MPI results improved the prediction of adverse outcomes compared with the clinical risk model. Such improvement was evident in the whole cohort, as well as in older and younger patients discretely. Previously, in a substudy of the CONFIRM trial, adding CCTA findings to a model including the Framingham risk score and CAC score improved the c-statistics as well as the net reclassification index (for predicting all-cause death or non-fatal MI) in the older age tertiles, but not in younger patients [14]. In the latter report, however, the cohort consisted of asymptomatic patients with a lower risk profile than our cohort and was followed up for a relatively short period (26 months); the index adverse outcome was also different. Likewise, in a smaller study of asymptomatic elderly Korean patients (≥65 years), the CCTA finding improved the c-statistics and the net reclassification index (for predicting cardiac death or non-fatal MI) beyond a model including Framingham risk score and CAC score [15]. In a recent study, myocardial flow reserve <2 in ^{82}rubidium PET MPI identified patients likely to benefit from revascularization; the results were consistent in a subgroup of patients ≥70 years [16]. Yet, the prognostic value of MPI in octogenarians is controversial; whereas one study reported similar prognostic accuracy of MPI in patients ≥80 years and those <80 years [17], in another study, the PET MPI findings (%left ventricular stress defect and %left ventricular ischemia) were not predictive of outcome in patients ≥85 years of age [18].

Employing the hybrid CCTA-PET result improved the prognostic performance versus a model including both the clinical risk predictors and the CCTA finding in the whole cohort, in patients <65 years, but not in those older than 65 years. The specificity of the PET MPI diagnostic cutoff value declines in patients >70 years [7]. This might be attributed to rising prevalence of diffuse non-obstructive coronary disease in old age, which impacts MBF. Additionally, greater competing mortality risk in the elderly from causes other than myocardial ischemia may contribute to higher all-cause death rates independent of ischemia finding.

4.1. Study limitations

The current report has all the inherent limitations of the retrospective study design. Some potentially relevant prognostic factors, such as anemia or renal dysfunction could not be explored in the analysis. In real-life patients referred to CCTA due to suspected CAD, selection bias is introduced by referring physicians being aware of factors associated with low likelihood of obtaining diagnostic image quality, such as extensive coronary calcification [1]. Indeed, the current study included relatively low-risk patients with preserved left ventricular function, only

Table 2
Multivariable predictors of the composite endpoint (death/myocardial infarction/unstable angina) in the cohort, in patients <65 years, and in those ≥65 years.

	Cohort		Patients <65 years		Patients ≥65 years	
	HR (95 % CI)	p value	HR (95 % CI)	p value	HR (95 % CI)	p value
	Multivariable model adjusting for clinical risk factors		Multivariable model adjusting for clinical risk factors		Multivariable model adjusting for clinical risk factors	
Age	1.07 (1.05–1.09)	<0.001	1.05 (1.01–1.10)	0.023	1.07 (1.03–1.11)	<0.001
Male sex	1.91 (1.42–2.57)	<0.001	–	–	1.86 (1.29–2.67)	0.001
Diabetes	1.34 (0.93–1.93)	0.11	–	–	1.68 (1.11–2.54)	0.015
Hypertension	1.39 (1.00–1.92)	0.047	1.62 (0.95–2.75)	0.074	–	–
Typical angina	1.52 (1.09–2.13)	0.014	2.03 (1.17–3.53)	0.012	–	–
Dyspnea	1.65 (1.22–2.24)	0.001	1.64 (0.99–2.72)	0.056	1.59 (1.10–2.29)	0.014
	Multivariable model adjusting for clinical risk factors + CCTA findings		Multivariable model adjusting for clinical risk factors + CCTA findings		Multivariable model adjusting for clinical risk factors + CCTA findings	
Age	1.05 (1.03–1.07)	<0.001	1.04 (1.00–1.09)	0.079	1.06 (1.02–1.09)	0.003
Male sex	1.49 (1.09–2.03)	0.012	–	–	1.51 (1.04–2.19)	0.030
Diabetes	–	–	–	–	1.53 (1.01–2.33)	0.046
Hypertension	1.26 (0.91–1.73)	0.17	–	–	–	–
Typical angina	1.37 (0.98–1.93)	0.066	1.66 (0.95–2.90)	0.073	–	–
Dyspnea	1.60 (1.18–2.17)	0.002	–	–	1.48 (1.02–2.15)	0.037
CCTA findings						
No CAD	Reference		Reference		Reference	
Non-obstructive CAD	3.01 (1.66–5.47)	<0.001	3.75 (1.67–8.45)	0.001	2.86 (1.19–6.85)	0.019
Obstructive CAD	4.39 (2.44–7.89)	<0.001	5.09 (2.29–11.27)	<0.001	4.47 (1.92–10.44)	<0.001
	Multivariable model adjusting for clinical risk factors + hybrid CCTA-PET findings		Multivariable model adjusting for clinical risk factors + hybrid CCTA-PET findings		Multivariable model adjusting for clinical risk factors + hybrid CCTA-PET findings	
Age	1.05 (1.04–1.07)	<0.001	1.04 (1.00–1.09)	0.060	1.06 (1.02–1.1)	0.002
Male sex	1.37 (1.00–1.88)	0.052	–	–	1.40 (0.95–2.04)	0.086
Diabetes	–	–	–	–	1.54 (1.02–2.34)	0.042
Hypertension	1.26 (0.92–1.74)	0.15	–	–	–	–
Typical angina	1.34 (0.96–1.88)	0.089	1.61 (0.92–2.80)	0.094	–	–
Dyspnea	1.58 (1.17–2.14)	0.003	–	–	1.46 (1.00–2.12)	0.048
Hybrid-imaging						
No CAD	Reference		Reference		Reference	
Non-ischemic CAD	3.13 (1.76–5.58)	<0.001	3.47 (1.58–7.62)	0.002	3.21 (1.38–7.46)	0.007
Ischemic CAD	5.67 (3.08–10.43)	<0.001	7.01 (3.08–15.94)	<0.001	5.65 (2.35–13.57)	<0.001

CCTA = coronary computed tomography angiography, CI = confidence interval, HR = hazard ratio, PET = positron emission tomography.

9.5 % ageing ≥75 years and 59 % being women. However, consecutive enrollment of the patients is a strength point. The use of PET MPI selectively after CCTA also introduces selection bias, but this reflects common clinical practice supported by guidelines, where ischemia testing is considered only in those with obstructive CAD on CCTA [1]. Our data are derived from a single-center, which implements a sequential hybrid-imaging protocol, and employs stress-only ^{15}O-water PET MPI, which precludes direct comparison with studies reporting myocardial flow reserve, or using other radiotracers of PET MPI. Finally, the lack of data on cardiovascular death is a limitation. Despite these limitations, the current study builds up more evidence in favor of the prognostic utility of the hybrid-imaging approach in elderly patients evaluated for suspected CAD.

5. Conclusion

In patients who underwent sequential hybrid-imaging (CCTA followed by PET MPI in those with obstructive CCTA) for suspected CAD, the prognostic utility of CCTA and the hybrid imaging approach was similar in patients ≥65 years versus those <65 years for prediction of adverse events at long-term follow-up. Furthermore, the hybrid imaging approach added to the prognostic utility of CCTA in patients <65 years, but not in patients ≥65 years. Age independently predicted events in patients older but not in those younger than 65 years.

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ijcard.2025.133493.

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CRediT authorship contribution statement

Wail Nammas: Writing – review & editing, Writing – original draft, Validation, Methodology, Formal analysis, Data curation, Conceptualization. **Iina Ajosenpää:** Investigation, Data curation, Conceptualization. **Teemu Maaniitty:** Writing – review & editing, Formal analysis, Data curation, Conceptualization. **Iida Stenström:** Methodology, Data curation, Conceptualization. **Jeroen J. Bax:** Writing – review & editing, Methodology, Conceptualization. **Juhani Knuuti:** Writing – review & editing, Methodology, Conceptualization. **Antti Saraste:** Writing – review & editing, Supervision, Methodology, Funding acquisition, Formal analysis, Data curation, Conceptualization.

Declaration of competing interest

AS discloses speaker or consultancy fees from Abbott, Astra Zeneca, BMS, Janssen, Novo Nordisk and Pfizer.

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