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Prognostic Value of Coronary CT Angiography With Selective PET Perfusion Imaging in Coronary Artery Disease

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ABSTRACT

OBJECTIVES The purpose of this study was to evaluate the prognostic value of sequential hybrid imaging strategy in which positron emission tomography (PET) perfusion imaging is performed selectively in patients with suspected obstructive coronary artery disease (CAD) on coronary computed tomography angiography (CTA).

BACKGROUND Coronary CTA is an accurate diagnostic test for excluding obstructive CAD. However, the positive predictive value is suboptimal.

METHODS We investigated 864 consecutive symptomatic patients with intermediate probability of CAD who adhered to the sequential imaging approach. PET myocardial perfusion imaging using ^{15}O-labeled water during adenosine stress was performed when suspected obstructive stenosis was present on coronary CTA. The major adverse events (AEs) including all-cause mortality, myocardial infarction (MI), and unstable angina pectoris (UAP) were recorded.

RESULTS During a median follow-up of 3.6 years, 16 deaths, 10 MIs, and 5 UAPs occurred. Obstructive CAD was excluded by coronary CTA in 462 (53%) patients who had significantly lower annual AE rate than did patients with suspected obstructive stenosis on coronary CTA (0.4% vs. 1.5%; $p = 0.003$). The latter underwent PET study, on which 195 (49%) had normal and 207 had abnormal perfusion. The annual rate of AEs was 5 times higher in those with abnormal perfusion than with normal perfusion (2.5% vs. 0.5%; $p = 0.004$). Patients with normal perfusion had AE rate comparable to patients without obstructive CAD on coronary CTA ($p = 0.77$).

CONCLUSIONS In patients with suspected CAD obstructive disease can be excluded in 53% of patients by coronary CTA, and these patients have good outcome. About one-half (49%) of the remaining patients have normal perfusion and event rate comparable to patients without obstructive CAD on coronary CTA while patients with ischemia have clearly worse outcome. Sequential approach utilizing anatomical imaging by coronary CTA followed by selective functional perfusion imaging is a feasible strategy to diagnose and risk-stratify patients with suspected CAD. (J Am Coll Cardiol Img 2017;10:1361–70) © 2017 by the American College of Cardiology Foundation.

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ABBREVIATIONS AND ACRONYMS

AE = adverse event(s)

CAD = coronary artery disease

CT = computed tomography

CTA = computed tomography angiography

ICA = invasive coronary angiography

MI = myocardial infarction

MPI = myocardial perfusion imaging

PCI = percutaneous coronary intervention

PET = positron emission tomography

SPECT = single-photon emission computed tomography

UAP = unstable angina pectoris

Coronary computed tomography angiography (CTA) enables noninvasive detection of coronary atherosclerosis and obstructive coronary artery disease (CAD). Having high negative predictive value, coronary CTA has rapidly become a widely used method for ruling out obstructive CAD in patients with intermediate pretest probability of CAD (1). However, coronary CTA cannot directly assess the hemodynamic significance of the detected stenoses (1,2), which may result in increased utilization of downstream diagnostic testing, particularly invasive coronary angiography (3).

Previous studies have suggested superior diagnostic accuracy of coronary CTA combined with myocardial perfusion imaging (MPI) to detect obstructive CAD as compared to either technique alone (4–6). Consequently, a Class IIa indication for the detection of obstructive CAD was granted for combined or hybrid imaging approach in the recent revascularization guidelines of the European Society of Cardiology (7). However, the evidence about the optimal use of multimodality and hybrid imaging in routine clinical practice is currently limited.

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Prognosis with a normal coronary CTA scan is excellent while the presence of extensive obstructive or nonobstructive coronary atherosclerosis on coronary CTA predicts increased risk of death and adverse cardiovascular events (8–12). Similarly, patients with normal myocardial perfusion have good prognosis while myocardial ischemia is associated with cardiovascular events (13–17). Previous studies have also demonstrated the incremental prognostic value of the combined assessment of anatomy by coronary CTA and function by single-photon emission computed tomography (SPECT) MPI, with the highest event risk related to the presence of both anatomical stenosis and abnormal perfusion (18,19). However, the prognostic value of the hybrid imaging in routine clinical practice, where MPI is only selectively applied to patients with suspected obstructive CAD on coronary CTA, is currently unknown.

After the initial validation study we have provided hybrid positron emission tomography-computed tomography (PET-CT) imaging as a routine clinical service in our hospital in symptomatic patients with intermediate probability of CAD (4). Given the high negative predictive value and low cardiovascular risk associated with normal coronary CTA or MPI, we hypothesized that a strategy of selective use of PET perfusion imaging in patients with abnormal coronary CTA findings would be a safe and cost-effective way to apply hybrid imaging. In this strategy coronary CTA is first performed to exclude obstructive CAD. If suspected obstructive stenosis is present on the initial analysis of coronary CTA images, the hemodynamic significance of the stenosis is evaluated with PET perfusion study in the same imaging session.

The aim of the present study was to investigate the prognostic value and safety of our selective hybrid imaging strategy in symptomatic patients who had been referred to noninvasive testing for suspected CAD.

METHODS

PATIENTS AND COMBINED PET-CT STRATEGY. We studied 957 consecutive patients referred to PET-CT imaging due to suspected CAD at the Turku University Hospital during 2007 to 2011. The coronary CTA scan was performed using a hybrid PET-CT scanner. Immediately after coronary CTA, the attending physician performed an initial evaluation of the scan to decide whether a PET perfusion study was needed. If obstructive CAD was excluded by coronary CTA, no further testing was performed. In the presence of suspected obstructive CAD by coronary CTA, a PET myocardial perfusion study with ^{15}O-labeled water was performed during adenosine stress.

Patients with previous coronary revascularization or obstructive CAD documented as >50% diameter stenosis by invasive angiography, as well as the patients who underwent PET-CT to study the etiology of cardiomyopathy or heart failure, were not included. Fifty-two patients of 957 were excluded due to nondiagnostic imaging results and 41 patients due to failure to adhere to the imaging protocol (i.e., PET study was not performed despite abnormal coronary CTA). Thus, the final study population consisted of 864 patients.

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 written informed consent.

DATA COLLECTION AND PATIENT FOLLOW-UP. Data on risk factors for CAD, symptoms (chest pain or dyspnea on exertion), exercise electrocardiography findings, laboratory tests and medication use, were retrospectively collected from electronic medical records. Coronary CTA and PET imaging data and findings were obtained from the imaging database and electronic medical records.

Comprehensive data on all-cause death, myocardial infarction (MI), and unstable angina pectoris

(UAP) were recorded using the registries of the Finnish National Institute for Health and Welfare and the Centre for Clinical Informatics of the Turku University Hospital. The events identified from the registries were confirmed by investigators using electronic medical records, according to the criteria of the European Society of Cardiology guidelines (20). The individual follow-up time ranged from the initial coronary CTA until the end of 2013. Information on possible early (i.e., within 6 months after coronary CTA) invasive angiography or revascularization was collected, but these were not included as AEs.

CORONARY CTA AND PET PROCEDURES. The coronary CTA and PET imaging procedures have been previously described in detail (4). Coronary CTA scans were performed with a 64-row hybrid PET-CT scanner (GE Discovery VCT or GE D690, General Electric Medical Systems, Waukesha, Wisconsin). Before coronary CTA, metoprolol (0 to 30 mg) was intravenously administered to achieve target heart rate of <60 beats/min. Isosorbide dinitrate aerosol (1.25 mg) or sublingual nitrate (800 μg) was also administered. Agatston coronary calcium score was measured prior to coronary CTA (in 78% of the patients). Coronary CTA was performed using intravenously administered low-osmolal iodine contrast agent (48 to 155 ml; 320 to 400 mg iodine/ml). Prospectively triggered acquisition was applied whenever feasible.

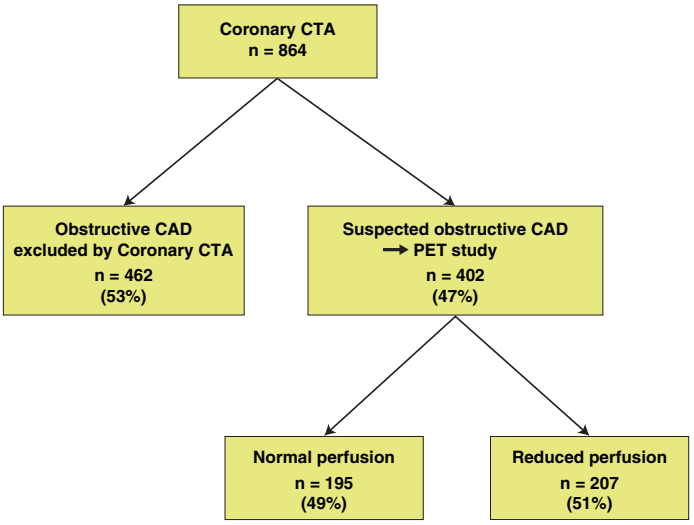
Based on the initial interpretation of the coronary CTA findings, dynamic quantitative PET perfusion scan during adenosine stress was carried out using a hybrid PET-CT device in the same imaging session, as previously described (4). ^{15}O-labeled water was used as a radiotracer (mean injected activity 1,042 ± 117 MBq) and adenosine infusion (140 μg/kg/min) was used for vasodilator stress (4). The patients were instructed to abstain from caffeine for 24 h before the PET study. In some patients, perfusion imaging was performed in the following days or weeks due to logistic reasons or caffeine use.

The coronary CTA data were analyzed according to the 17-segment vessel system (21). The PET data were quantitatively analyzed using the Carimas software version 1.1.0 (developed at Turku PET Centre, Turku, Finland) in standardized 17 segments according to American Heart Association recommendations (4,22). PET-CT fusion images were created using GE IQfusion software (GE ADW 4.4 Workstation, General Electric Medical Systems, Waukesha, Wisconsin). The analysis was performed by an experienced physician and recorded in a standardized reporting system.

IMAGE INTERPRETATION. The presence, extent, and severity of coronary atherosclerosis and stenoses on coronary CTA were evaluated in all patients. According to the most severe vessel abnormality in each individual coronary CTA, the patients were first classified into those without significant CAD by coronary CTA and those with suspected obstructive CAD requiring further PET perfusion imaging (**Figure 1**). In the initial interpretation of coronary CTA ≥50% diameter stenosis by visual analysis was used as a criterion for suspected obstructive stenosis. On the PET perfusion study, absolute myocardial stress perfusion ≤2.4 ml/g/min at least in 1 of the 17 myocardial segments was considered abnormally low (4).

STATISTICAL ANALYSIS. Continuous variables are shown as mean ± SD or median (interquartile range [25th to 75th percentile]). Categorical variables are shown as percentages. Independent-samples Mann-Whitney *U* test or Kruskal-Wallis test was used to compare continuous variables and 2-sided Pearson chi-square test or Fisher exact test was used for categorical variables. Annual event rates (all-cause mortality, and the composite of mortality, MI, or UAP) were compared using Poisson regression analysis. A p value <0.05 was considered statistically significant. Kaplan-Meier curves were created and pooled log-rank tests conducted (Mantel-Cox).

FIGURE 1 Imaging Findings According to a Sequential Hybrid PET-CT Imaging Strategy



In one-half of the patients (53%) coronary computed tomography angiography (CTA) alone was considered sufficient to exclude obstructive coronary artery disease (CAD). The remaining patients had suspected obstructive CAD based on the initial interpretation of coronary CTA, and therefore underwent quantitative positron emission tomography (PET) perfusion imaging, which revealed abnormally low myocardial perfusion in one-half (51%) of these patients. PET-CT = positron emission tomography–computed tomography.

TABLE 1 Patient Characteristics

	Total (N = 864)	Normal Coronary CTA (n = 260)	Nonobstructive Coronary CTA (n = 202)	Suspected Stenosis, Normal Perfusion (n = 195)	Suspected Stenosis, Reduced Perfusion (n = 207)	p Value
Age, yrs	61 ± 9	57 ± 10	62 ± 9	64 ± 8	64 ± 9	<0.001
Male	45	27	44	40	72	<0.001
Risk factors for CAD						
Current smoking	13	12	16	12	14	0.57
Previous smoking	20	14	18	21	29	0.001
Pre-diabetes	17	12	15	19	22	0.025
Diabetes	14	8	12	14	25	<0.001
Hypertension	54	33	56	66	68	<0.001
Dyslipidemia	62	47	66	65	74	<0.001
Family history of CAD	46	48	43	45	46	0.69
Primary symptom						
Typical AP	23	15	18	26	34	<0.001
Atypical AP, nonanginal chest pain or dyspnea on exertion	65	70	65	63	59	0.085
Other	13	15	16	11	7	0.022
Positive exercise ECG (n = 604)	58	54	46	63	68	0.001
Agatston CCS (n = 675)	26 (0–255)	0 (0–0)	25 (4–84)	157 (35–328)	422 (117–1,047)	<0.001
Medication						
Beta-blocker	48	38	42	53	62	<0.001
Lipid-lowering drug	43	27	41	48	60	<0.001
Antiplatelet drug	55	42	50	58	72	<0.001
Anticoagulant	6	6	6	5	6	0.93
Long-acting nitrate	9	3	10	11	15	<0.001
Diuretic	18	11	21	21	22	0.004
ACE inhibitor	19	11	22	20	27	<0.001
Angiotensin receptor blocker	15	7	15	18	19	0.001
Calcium-channel blocker	14	7	14	17	18	0.003
Antiarrhythmic agent	2	4	0	2	1	0.080

Values are mean ± SD, %, or median (25th to 75th percentile).

ACE = angiotensin-converting enzyme; AP = angina pectoris; CAD = coronary artery disease; CCS = coronary calcium score; CTA = computed tomography angiography; ECG = electrocardiography.

Cox's proportional hazards model was applied to identify the predictors of AE and death; covariates with a p value ≤0.10 on univariable regression analysis were included in multivariable analysis. The statistical analyses were conducted with IBM SPSS Statistics for Windows version 22.0 (IBM Corporation, Armonk, New York).

RESULTS

PATIENTS. Total of 864 patients who completed the combined sequential PET-CT protocol for evaluation of suspected CAD were included in the prognostic analysis. The baseline patient characteristics are shown in Table 1.

During the median follow-up of 3.6 years (interquartile range: 2.7 to 4.8 years), 31 AEs occurred including 16 deaths, 10 MIs, and 5 UAPs. Four of 5 UAPs led to percutaneous coronary intervention (PCI). Two additional deaths occurred in patients with an earlier nonfatal event making the total number of deaths 18. Thus, the annual rate of all combined AEs was 0.95% and the annual rate of all-cause mortality was 0.54%. Two of 10 MIs and none of the deaths or UAPs were related to in-stent restenosis. The radiation dose was 8.2 ± 4.0 mSv from coronary CTA and 0.97 ± 0.11 mSv from PET perfusion imaging.

IMAGING FINDINGS. Coronary CTA alone was considered sufficient to exclude obstructive CAD in 462 (53%) patients (Figure 1). In these patients, coronary CTA was either normal (n = 260) or showed nonobstructive atherosclerosis (n = 202). In 402 patients (47%) the coronary CTA was suggestive of obstructive CAD, including 74 (18%) patients with 2-vessel and 55 (14%) patients with 3-vessel obstructive CAD. These 402 patients underwent quantitative stress PET perfusion imaging, which demonstrated reduced myocardial perfusion in 207 (51%) patients, whereas 195 (49%) patients had normal perfusion study.

In patients with reduced myocardial perfusion there were a median of 12 myocardial segments (interquartile range: 6 to 16 myocardial segments) affected per patient. The mean global stress perfusion was 2.2 ± 0.7 ml/g/min in patients with reduced perfusion versus 3.8 ± 0.9 ml/g/min in patients with normal perfusion ($p < 0.001$).

FOLLOW-UP. In patients with normal coronary arteries based on coronary CTA (n = 260), there were 3 deaths, 1 MI, and no UAPs during the follow-up. The combined annual rate of AEs was 0.42% and the annual rate of all-cause mortality was 0.31% (Figures 2A and 2B). In 202 patients with nonobstructive atherosclerosis, there were 3 deaths and no other events. Therefore, the annual rates of AEs and all-cause mortality were both 0.42%. There was no significant difference in the occurrence of AEs or deaths between patients with nonobstructive atherosclerosis and normal coronary arteries (0.42 vs. 0.42%; p = 0.99; and 0.42 vs. 0.31%; p = 0.71, respectively) who underwent coronary CTA alone.

There were 12 deaths, 9 MIs, and 5 UAPs in patients with suspected obstructive CAD by coronary CTA and who thus underwent subsequent PET perfusion (n = 402). In these patients, the annual combined AE rate was significantly higher than in 462 patients in whom obstructive CAD was excluded by coronary CTA alone (1.50% vs. 0.42%; p = 0.003). However, the annual rate of all-cause mortality was statistically nonsignificantly different (0.73% vs. 0.36%; p = 0.15).

Of the 402 patients with suspected CAD on coronary CTA, 207 (51%) patients had myocardial ischemia on the PET study. In these patients there were 9 deaths, 8 MIs, and 5 UAPs, whereas in the patients with a normal PET perfusion (n = 195) there were only 3 deaths and 1 MI. The annual rate of AEs was 5 times higher in patients with abnormal perfusion compared to patients with a normal PET perfusion study (2.5% vs. 0.50%; p = 0.004). The annual rates of all-cause mortality in patients with reduced perfusion and in patients with normal perfusion were 1.07% and 0.38%, respectively. The difference was not statistically significant (p = 0.12).

The rate of AEs, as well as the annual rate of all-cause mortality, were comparable between patients with suspected obstructive coronary stenosis, but normal subsequent PET perfusion and patients in whom obstructive CAD was excluded by negative initial coronary CTA alone (0.50% vs. 0.42%, p = 0.77; and 0.38% vs. 0.36%, p = 0.94, respectively). Survival according to PET-CT findings is depicted in Figures 3A and 3B.

None of the patients with normal coronary CTA, 3% with nonobstructive coronary CTA, 8% with normal perfusion, and 55% of patients with reduced perfusion underwent early invasive angiography. Finally, 97 (11%) of the total 864 patients underwent revascularization within 6 months, while 42% of the patients with myocardial ischemia on the PET study underwent early revascularization. There was no difference in annual rate of AEs or all-cause mortality between revascularized or nonrevascularized patients (2.1% vs. 2.8%; p = 0.57; and 0.52% vs. 1.5%; p = 0.17, respectively). Hence, the patients with or without early revascularization were pooled together for prognostic analyses; but coronary revascularization was not considered as an endpoint.

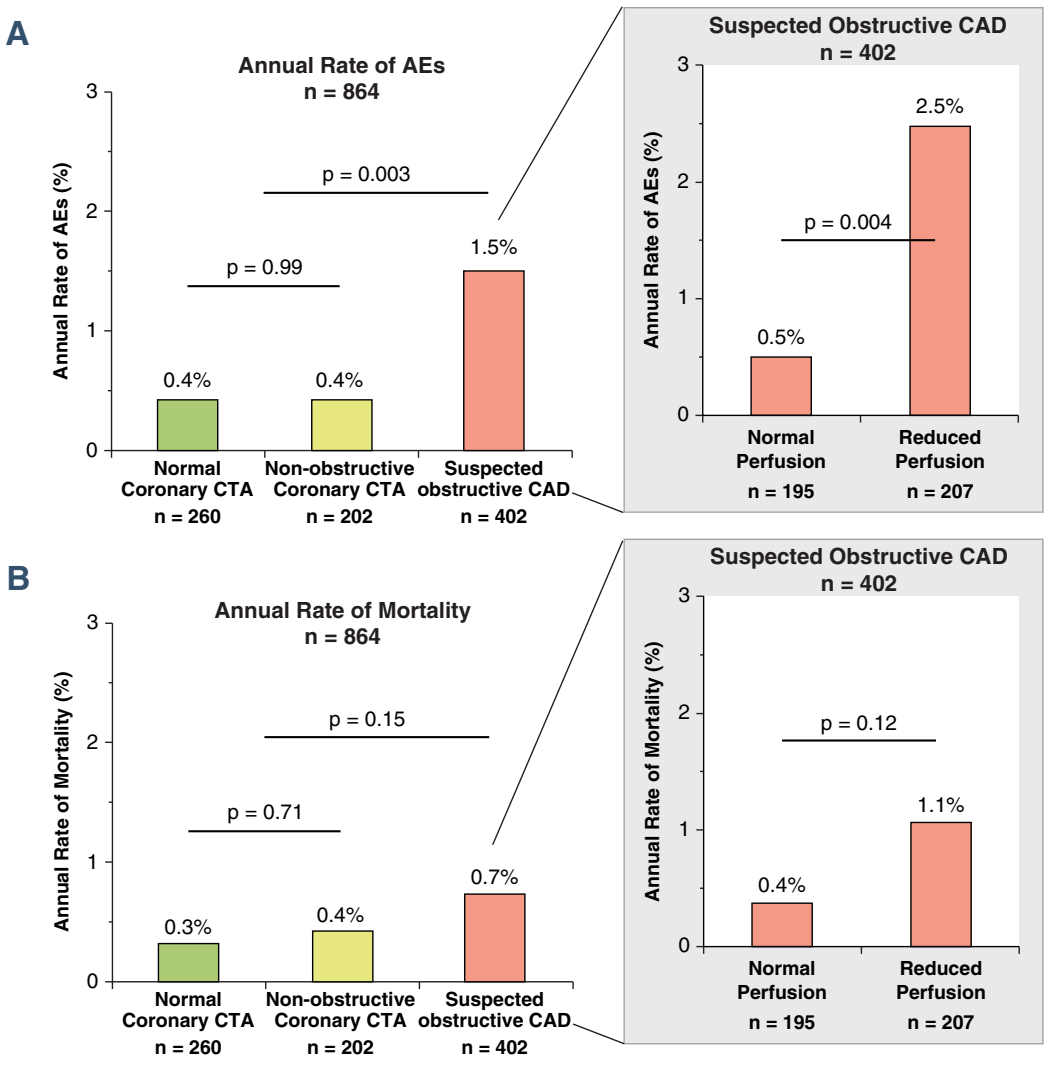
Independent prognostic value of the imaging findings was studied using the Cox proportional hazards model. On univariable analysis, statistically significant predictors of AEs were increasing age and abnormal perfusion by PET (Table 2). In addition, male sex and presence of pre-diabetes or diabetes predicted AEs at significance level of 0.10. These variables were included in the multivariable Cox regression analysis, on which abnormal perfusion and increasing age were found to be independent predictors of AEs (Table 3). However, abnormal perfusion finding was not statistically significant in predicting all-cause death (hazard ratio: 3.03, p = 0.098; on univariable analysis).

In 41 patients (4%) excluded from the analysis due to nonadherence to the imaging strategy, there were 3 deaths, 2 MIs, and 1 UAP. Of these patients, 3 had very severe CAD on coronary CTA and were referred directly to invasive angiography. In the other patients (n = 38) the PET perfusion study was not performed for various reasons such as contraindication to adenosine, earlier performed functional testing or noncompliance of the patient. Among the 52 patients (5%) excluded due to nondiagnostic coronary CTA (n = 35) or PET (n = 17), 1 death and 1 UAP occurred during follow-up.

DISCUSSION

The results of the current study show that the hybrid imaging approach with sequential use of coronary CTA followed by selective application of PET perfusion imaging is able to accurately identify patients with low and high risk of death, MI, or UAP. Obstructive CAD was excluded by coronary CTA alone in about one-half of the patients with suspected CAD, and these patients had a good outcome. In the patients with suspected obstructive CAD on coronary

FIGURE 2 Annual Rates of AEs and All-Cause Mortality According to Hybrid Imaging Findings

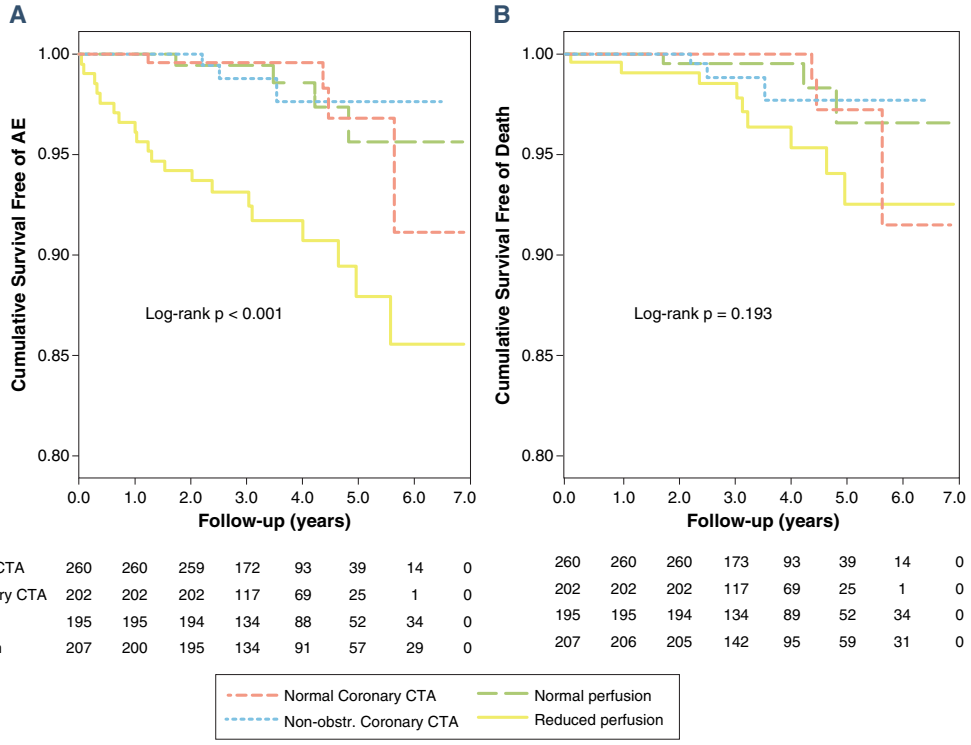


(A) Patients with obstructive CAD excluded by coronary CTA alone and patients with suspected obstructive CAD but normal perfusion had low and comparable ($p = 0.77$) annual rates of adverse events (AEs). In contrast, patients with reduced myocardial perfusion on PET perfusion imaging had significantly worse outcome. **(B)** The differences between imaging finding groups were not statistically significant in terms of all-cause mortality. Abbreviations as in Figure 1.

CTA, about one-half of the patients had normal PET MPI. In these patients the event rate was low and comparable to those without significant CAD on coronary CTA. The outcome of the patients with significant CAD on coronary CTA and abnormal PET perfusion was 5-fold higher as compared to those with normal perfusion. The presence, extent, and severity of myocardial ischemia have been shown also in previous studies to predict poor prognosis in CAD while normal MPI findings are associated with a low rate of MI and death (13-17).

Our results are consistent with the previous studies that have repeatedly shown that the patients with normal coronary arteries on coronary CTA have an excellent prognosis, while the presence of anatomically obstructive CAD on coronary CTA is associated with an increased rate of major adverse cardiac events (10,11,23). Studies in large populations have also shown that the presence of nonobstructive atherosclerosis has prognostic significance (10,12,23). However, in the present study we could not observe this. In our study, this group of patients may

FIGURE 3 Kaplan-Meier Cumulative Survival Curves According to Hybrid Imaging Findings With Corresponding Log-Rank Tests



(A) Reduced perfusion finding on PET study predicted future adverse events. **(B)** The differences in all-cause mortality were not statistically significant. Abbreviations as in Figures 1 and 2.

represent those with mild atherosclerosis because the patients with suspected coronary stenosis entered to further PET perfusion imaging. Also the number of events was generally relatively small.

Hybrid imaging combining coronary CTA and PET perfusion has a high diagnostic accuracy for obstructive CAD (4,6). In the present study, adding perfusion information over coronary CTA, provided clear additional prognostic value and was able to identify patients with low risk. The abnormal perfusion remained an independent predictor for AEs on the multivariable analysis. These findings are in agreement with the previous prognostic studies combining data from coronary CTA and SPECT perfusion (18,19). Our findings provide real-life evidence of the prognostic value of hybrid PET-CT imaging in a reasonably large patient population, using absolute perfusion quantitation (24).

The optimal strategy for using cardiac hybrid imaging in clinical practice remains unknown. In most of the earlier studies all patients underwent both anatomical and functional imaging. Due to the high negative predictive value of coronary CTA, a hybrid imaging strategy in which coronary CTA is used as a gatekeeper to functional testing is attractive (1,25). Since 2005 we have utilized this approach in clinical routine. Our hybrid PET-CT imaging protocol is fast (<30 min), is associated with low about 1 mSv additional radiation dose from PET imaging (26), and has costs comparable to SPECT perfusion imaging in our hospital. The current study extends the evidence of prognostic power of hybrid imaging to the stepwise application of imaging tests, which can be suggested to be more cost-effective compared to unselected performance of both tests to all patients. Based on the results, our strategy of performing coronary CTA first reduced the need to do the PET perfusion study without compromising patient safety. As anatomical data are acquired from every patient, this information can be used to guide the pharmacological therapy. The potential drawback of this coronary CTA-first approach is that patients with coronary microvascular dysfunction without epicardial CAD could be missed. However, according to our recent analysis, such patients are rare in this kind of patient population (27) and the therapeutic options are limited.

TABLE 2 Univariable Analysis of Predictors of Adverse Events (n = 864)

	Hazard Ratio	95% CI	p Value
Clinical risk factors of CAD			
Age*	1.06	1.01–1.10	0.01
Male†	1.84	0.89–3.79	0.10
Smoking (current or previous)	0.81	0.37–1.75	0.59
Pre-diabetes or diabetes†	2.02	1.00–4.08	0.05
Dyslipidemia	0.66	0.32–1.34	0.25
Hypertension	1.35	0.65–2.78	0.42
Family history of CAD	1.24	0.61–2.51	0.55
Number of clinical risk factors‡			
≥1	1.56	0.37–6.56	0.54
≥2	1.62	0.66–3.95	0.29
≥3	1.11	0.55–2.25	0.77
≥4	1.08	0.44–2.63	0.87
PET-CT finding			
Normal coronary CTA (reference)			
Nonobstructive coronary CTA	1.03	0.23–4.59	0.97
Suspected stenosis, normal perfusion	1.15	0.29–4.62	0.84
Suspected stenosis, reduced perfusion*	5.63	1.92–16.53	0.002

*Statistically significant ($p < 0.05$) predictor of adverse events. †Nearly significant ($p \leq 0.10$) predictor of adverse events. ‡Smoking, pre-diabetes or diabetes, dyslipidemia, hypertension, family history of CAD.

CI = confidence interval; PET-CT = positron emission tomography-computed tomography; other abbreviations as in Table 1.

Another option would be to start with perfusion imaging, as in a recent study by Engbers et al. (28), because functional information is currently used as the main criterion for the revascularization decisions. The drawback of this approach is that some nonobstructive atherosclerosis will be missed, which may have impact on medical therapy for secondary prevention.

Interestingly, we found no difference in prognosis between patients who underwent revascularization and those who did not. However, simple comparison of these quite small groups is subject to bias, since revascularization is typically triggered by ischemia, and the general burden of CAD and existence of ischemia are closely correlated. Furthermore, the risk could have been even higher without revascularizations. Most revascularizations were PCIs, which may have limited impact on prognosis in patients with diffuse CAD.

TABLE 3 Multivariable Analysis of Predictors of Adverse Events (n = 864)

	Hazard Ratio	95% CI	p Value
Clinical risk factors of CAD			
Age	1.05	1.00–1.10	0.04
Male	1.21	0.54–2.75	0.64
Pre-diabetes or diabetes	1.31	0.63–2.71	0.47
PET-CT finding			
Normal coronary CTA (reference)			
Nonobstructive coronary CTA	0.79	0.17–3.61	0.76
Suspected stenosis, normal perfusion	0.79	0.19–3.30	0.74
Suspected stenosis, reduced perfusion	3.62	1.08–12.15	0.04

Abbreviations as in Tables 1 and 2.

STUDY LIMITATIONS. In the present population the prognosis was generally good, and the limited sample size may decrease the statistical power of the study. However, our study population represents well the target population of noninvasive cardiac imaging with intermediate pretest probability of CAD. About 4% (n = 35) of the total patient population had a nondiagnostic coronary CTA scan. A majority (n = 26) of these patients underwent further PET perfusion study to exclude hemodynamically significant CAD. There were 41 patients (4%) who did not adhere to the sequential imaging protocol. A variety of reasons existed for this nonadherence, such as contraindication to pharmacological stress or direct referral to invasive angiography.

This study was retrospective and some information was not available. The registries in Finland, however, are highly reliable and complete (29). All-cause mortality, rather than cardiovascular mortality, was used and can be considered a reliable measure as verification bias is avoided. We can hypothesize that cardiovascular mortality would even better correlate with the imaging findings. We do not have data whether imaging triggered other secondary prevention measures than revascularizations.

As the studies were performed in years 2007 to 2011, the radiation dose from coronary CTA was relatively high as compared to current state-of-the-art systems and also at our hospital today. Adding a PET study after coronary CTA naturally increased the dose further and in the current study leaded to total average dose of 8.7 mSv per patient. However, as PET perfusion was abnormal only in about one-half of the patients with abnormal coronary CTA, the downstream invasive coronary angiography (ICA) with 7 mSv dose was avoided in significant fraction of the patients. Furthermore, only 55% of patients with abnormal coronary CTA and PET perfusion underwent early ICA. This is likely because the optimal medical therapy was considered a good alternative based on combined coronary CTA and PET findings. The total radiation dose from coronary CTA, PET, and early ICA was 9.8 mSv on average. For comparison, coronary CTA followed by ICA in all patients with abnormal coronary CTA findings (47%) would result in an average dose of 11.5 mSv. As PET perfusion imaging was selectively performed only in about

one-half of the patients after coronary CTA, we cannot extrapolate our data to a protocol that utilizes only PET first and then ICA in patients with abnormal perfusion.

CONCLUSIONS

In patients referred for imaging due to suspected CAD, coronary CTA alone is sufficient for exclusion of significant CAD in about one-half of the patients and these patients have good outcome. Even in the presence of suspected obstructive CAD on coronary CTA, about one-half had normal perfusion associated with low risk of AEs, while patients with ischemia had clearly worse outcome. A hybrid imaging approach applying PET perfusion imaging selectively to those patients with coronary CTA imaging suggestive of obstructive CAD is a safe strategy to identify patients without significant ischemic CAD.

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PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE: Normal or nonobstructive coronary CTA finding is associated with good outcome, but coronary CTA alone is not sufficient for assessing hemodynamic significance of a suspected obstructive stenosis. Combined coronary CTA and stress PET MPI with ^{15}O-labeled water is able to identify patients without myocardial ischemia and with low AE risk.

COMPETENCY IN PATIENT CARE AND PROCEDURAL SKILLS: Sequential utilization of coronary CTA with selective application of MPI is a feasible and safe approach to diagnose and risk-stratify patients with suspected CAD of intermediate pre-test probability.

TRANSLATIONAL OUTLOOK 1: In the future, studies with larger patient population and longer follow-up time are warranted to confirm the results of the current study and to assess the prognostic value of the sequential hybrid imaging strategy in a long run. Also the effect of this imaging strategy on downstream referral and the associated costs should be investigated.

TRANSLATIONAL OUTLOOK 2: What is the optimal treatment strategy in different patient subgroups, such as patients with nonobstructive atherosclerosis detected on coronary CTA, is a target for further research.

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