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Incremental prognostic value of hybrid [^{15}O]H_2O positron emission tomography–computed tomography: combining myocardial blood flow, coronary stenosis severity, and high-risk plaque morphology

Roel S. Driessen [1†], Michiel J. Bom[1†], Pepijn A. van Diemen[1], Stefan P. Schumacher[1], Remi M. Leonora[1], Henk Everaars[1], Albert C. van Rossum[1], Pieter G. Raijmakers[2], Peter M. van de Ven[3], Cornelis C. van Kuijk[2], Adriaan A. Lammertsma[2], Juhani Knuuti[4], Amir Ahmadi[5], James K. Min[6], Jonathon A. Leipsic[7], Jagat Narula[5], Ibrahim Danad[1], and Paul Knaapen[1]*

[1]Department of Cardiology, Amsterdam UMC, Vrije Universiteit Amsterdam, De Boelelaan 1117, 1081 HV Amsterdam, The Netherlands; [2]Department of Radiology & Nuclear Medicine, Amsterdam UMC, Vrije Universiteit Amsterdam, Amsterdam, The Netherlands; [3]Department of Epidemiology and Biostatistics, Amsterdam UMC, Vrije Universiteit Amsterdam, Amsterdam, The Netherlands; [4]Turku PET Centre, Turku University Hospital and University of Turku, Kiinamyllynkatu 4-8, 20520 Turku, Finland; [5]Division of Cardiology, Department of Medicine, Icahn School of Medicine at Mount Sinai, Mount Sinai Heart, Zena and Michael A. Wiener Cardiovascular Institute, and Marie-Josée and Henry R. Kravis Center for Cardiovascular Health, One Gustave L Levy Place, Box 1030, New York, NY 10029, USA; [6]Department of Radiology, New York-Presbyterian Hospital, Weill Cornell Medicine, 413 E 69th Street, Suite 108, New York, NY 10021, USA; and [7]Department of Medicine and Radiology, University of British Columbia, 2775 Laurel St. Vancouver, BC V5Z 1M9, Canada

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Aims This study sought to determine the prognostic value of combined functional testing using positron emission tomography (PET) perfusion imaging and anatomical testing using coronary computed tomography angiography (CCTA)-derived stenosis severity and plaque morphology in patients with suspected coronary artery disease (CAD).

Methods and results In this retrospective study, 539 patients referred for hybrid [^{15}O]H_2O PET-CT imaging because of suspected CAD were investigated. PET was used to determine myocardial blood flow (MBF), whereas CCTA images were evaluated for obstructive stenoses and high-risk plaque (HRP) morphology. Patients were followed up for the occurrence of all-cause death and non-fatal myocardial infarction (MI). During a median follow-up of 6.8 (interquartile range 4.8–7.8) years, 42 (7.8%) patients experienced events, including 23 (4.3%) deaths, and 19 (3.5%) MIs. Annualized event rates for normal vs. abnormal results of PET MBF, CCTA-derived stenosis, and HRP morphology were 0.6 vs. 2.1%, 0.4 vs. 2.1%, and 0.8 vs. 2.8%, respectively ($P < 0.001$ for all). Cox regression analysis demonstrated prognostic values of PET perfusion imaging [hazard ratio (HR) 3.75 (1.84–7.63), $P < 0.001$], CCTA-derived stenosis [HR 5.61 (2.36–13.34), $P < 0.001$], and HRPs [HR 3.37 (1.83–6.18), $P < 0.001$] for the occurrence of death or MI. However, only stenosis severity [HR 3.01 (1.06–8.54), $P = 0.039$] and HRPs [HR 1.93 (1.00–3.71), $P = 0.049$] remained independently associated.

Conclusion PET-derived MBF, CCTA-derived stenosis severity, and HRP morphology were univariably associated with death and MI, whereas only stenosis severity and HRP morphology provided independent prognostic value.

* Corresponding author. Tel: +31 (20) 444 2441; Fax: +31 (20) 444 2446. E-mail: p.knaapen@amsterdamumc.nl
† These authors contributed equally to this work.
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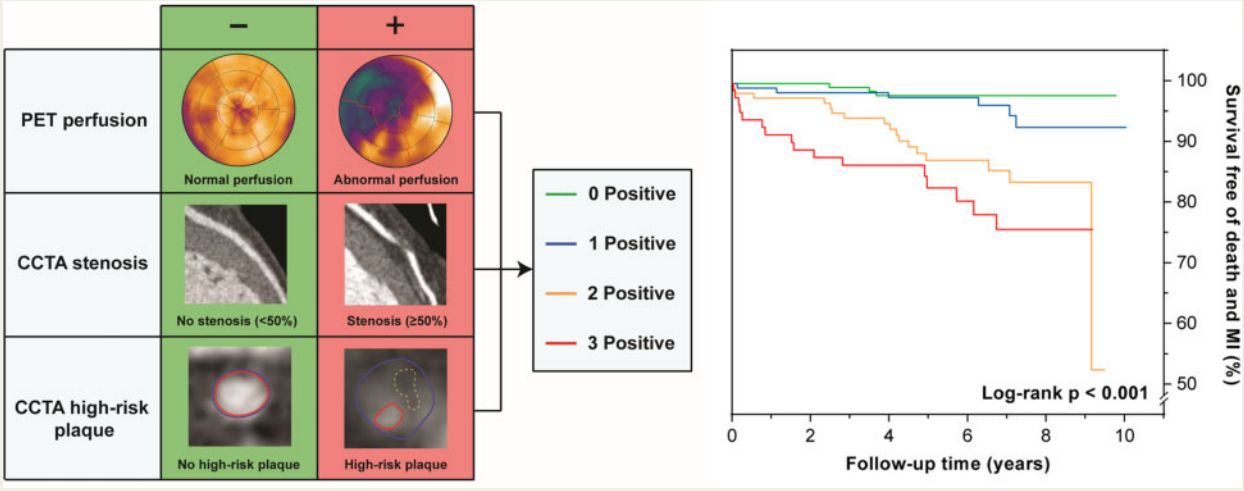
Graphical Abstract



Keywords coronary artery disease • prognosis • positron emission tomography • coronary computed tomography angiography • myocardial blood flow • high-risk plaque morphology

Introduction

Traditionally, angiographic severity of coronary artery disease (CAD) has been used to guide patient management with either revascularization or optimal medical treatment. Stenosis severity is now increasingly assessed non-invasively with coronary computed tomography angiography (CCTA), which was shown to be a powerful prognostic tool.[1,2] Next to luminal stenosis severity, CCTA allows for non-invasive evaluation of atherosclerotic plaque morphology, including adverse plaque characteristics (APCs), such as positive remodelling and low attenuation. The presence of these characteristics has been described to represent an elevated risk for future cardiac events.[3,4] CCTA's moderate specificity, however, might cause increased downstream diagnostic and treatment costs.[5] Moreover, in recent years, the clinical arena has shifted from anatomically to physiologically guided management as a result of various trials[6] which is reflected by recommendations in current revascularization guidelines.[7] In this regard, positron emission tomography (PET) is considered the non-invasive reference standard for quantitative myocardial perfusion analysis and showed incremental prognostic value over traditional clinical predictors.[8,9] Combining PET with CCTA (the so-called hybrid PET-CT) allows for functional and anatomical evaluation of CAD, which is suggested to enhance prognostic value over either one modality alone.[10] While PET-derived myocardial perfusion as well as CCTA-derived stenosis severity and plaque morphology all have their established individual value, the incremental prognostic value of these combined entities derived from hybrid PET-CT is currently unknown. Therefore, this study investigated the prognostic value of comprehensive hybrid PET-CT imaging in patients with suspected CAD.

Methods

Patient population

A total of 650 consecutive patients, who underwent PET-CT imaging because of suspected stable CAD at the VU University Medical Center in Amsterdam between 2008 and 2014, were initially evaluated for inclusion. In all patients, PET and CT imaging was performed, regardless of the result of either one of the imaging tests. Exclusion criteria for PET-CT imaging performance were atrial fibrillation, high degree atrioventricular block, impaired renal function, symptomatic asthma, and pregnancy. No cardiovascular events occurred between the two tests. Post-imaging treatment strategy was left to the discretion of the referring physician. Among these patients, 32 (5%) were excluded because of a documented history of CAD [myocardial infarction (MI), percutaneous coronary intervention, or coronary artery bypass grafting], whereas 25 (4%) patients were excluded due to uninterpretable imaging results. Of the remaining 593 patients, 54 (10%) were lost to follow-up, resulting in a final study population of 539 patients. This study complied with the Declaration of Helsinki and was approved by the Medical Ethics Review Committee of the VU University Medical Center with waiver of informed consent.

Positron emission tomography and coronary computed tomography angiography assessment

All patients underwent hybrid PET-CT imaging. PET perfusion images were acquired on a Gemini TF 64 PET-CT scanner (Philips Healthcare, Best, The Netherlands). CCTA images were acquired on the same Gemini TF 64 PET-CT scanner in 352 patients and on a 256-slice Brilliance iCT scanner (Philips Healthcare, Best, The Netherlands) in the

remaining 187 patients. The hybrid PET-CT imaging procedures have been described in detail previously.[11,12]

With regard to the PET imaging protocol, a dynamic perfusion scan was performed using 370 MBq of [^{15}O]H_2O both during resting and adenosine (140 μg·kg^{-1}·min^{-1}) induced hyperaemic conditions. Low-dose CT scans were used for attenuation correction. Quantitative parametric myocardial blood flow (MBF) images were generated using in-house developed software.[13] Hyperaemic MBF, expressed in mL·min^{-1}·g^{-1} of perfusable myocardial tissue, was calculated for all three vascular territories derived from standard segmentation: left anterior descending, left circumflex, and right coronary artery. Hyperaemic MBF ≤ 2.30 mL·min^{-1}·g^{-1} in any of the vascular territories was defined as abnormal.[14] PET and CCTA images were evaluated separately.

Prior to the CCTA scanning protocol, sublingual nitroglycerine spray was administered to all patients and metoprolol when necessary, aiming for a heart rate of < 65 bpm. Coronary artery calcium scoring (CACS) was obtained during a single breath-hold on a non-contrast CT and expressed in Agatston units. Electrocardiogram-gated prospective acquisition was then applied when feasible, triggered at 75% of the R-R interval. For visualization of the coronary artery lumen, a bolus of 100 mL iobitidol (Xenetix 350) was injected intravenously. Scans were triggered using an automatic bolus tracking technique, with a region of interest in the descending thoracic aorta. All coronary segments with a diameter of ≥2 mm were assessed for stenosis severity and plaque morphology as previously described.[15] The coronary tree was evaluated according to a 17-segment coronary artery model using axial, multiplanar reformation, maximum intensity projection, and cross-sectional images. Stenosis severity was graded visually and a diameter stenosis ≥ 50% was considered significantly obstructive. In addition, coronary lesions were analysed for APCs. The remodelling index was computed as the ratio of vessel area at the site of the maximal lesion to that of a proximal reference point, with an index > 1.1 representing positive remodelling (PR).[16] Low-attenuation plaque (LAP) was defined as a plaque containing any voxel < 30 HU.[16] Spotty calcification (SC) was characterized by a calcified plaque comprising < 90° of the vessel circumference and < 3 mm in length.[16] The napkin ring sign (NRS) was defined by a plaque core with low-CT attenuation surrounded by a rim-like area of higher CT attenuation.[17] A high-risk plaque (HRP) was defined by the presence of at least two plaque characteristics.[16]

Follow-up

Patients were retrospectively followed-up by observers blinded to the imaging results using national registry databases, electronic medical records, and standardized telephone interviews. Individual follow-up intervals ranged from the imaging acquisition until April 2018. Follow-up was censored at the time of the endpoint or at the time patients were last contacted. The study endpoint was a composite of all-cause death and non-fatal MI. Identified events were scored in accordance with the criteria provided in the European Society of Cardiology guidelines.[7]

Statistical analysis

Continuous variables are shown as mean ± standard deviation or median [interquartile range (IQR; 25th–75th percentile)]. Categorical variables are presented as percentages. Continuous variables were tested for normal distribution and compared using the Student's *t*-test or Mann–Whitney *U* test where applicable. Categorical variables were compared using the χ^2 test. Annualized event rates were expressed as a proportion of the number of patients experiencing events divided by the number of patient-years follow-up and compared between groups using Poisson regression analysis. The cumulative event-free survival in subgroups of patients defined by results of PET, CCTA stenosis, and presence of HRPs were visualized with Kaplan–Meier curves and compared using the log-rank test. Univariable Cox regression was used to assess associations of patient and imaging characteristics with death and MI. Significant covariates on univariable regression analysis were included in a multivariable analysis. The assumption of proportional hazard was tested by obtaining and reviewing the log-minus-log plots and deemed appropriate in all categories. A two-sided $P < 0.05$ was considered statistically significant. Statistical analyses were conducted with IBM SPSS Statistics version 22.0 (IBM Corporation, Armonk, NY, USA).

Results

Study population

Detailed baseline and imaging characteristics of the 539 study patients, with and without adverse events, are presented in *Table 1*. Mean age was 58.6 ± 9.2 years and 297 (55%) were male. Patients who suffered from an event were older, featured a higher coronary risk profile and were taking more medications.

Imaging findings

PET showed abnormal quantitative myocardial perfusion in 259 (48.1%) patients. According to CCTA, atherosclerotic plaques were present in 422 (78.1%) patients, whereas 302 (56.0%) patients showed obstructive stenosis (≥50%). In patients with a significant stenosis on CCTA, abnormal perfusion on PET was found in 202 (66.9%) cases. Among patients with abnormal PET perfusion, 21 (9%) showed normal coronary arteries on CCTA. CCTA-derived APCs were present in 303 (56.2%) patients. Among these characteristics, PR ($n = 270$, 50.1%) and LAP ($n = 131$, 24.3%) were most prevalent, followed by SC ($n = 53$, 9.8%) and NRS ($n = 47$, 8.7%). HRPs (defined by presence of ≥2 APCs) were present in 127 (23.6%) of patients. APCs were most commonly present in patients with significant stenosis ($n = 230$, 76.2%) as opposed to non-significant stenosis ($n = 72$, 23.8%). Ninety-four (74%) patients with HRPs also showed abnormal PET. Median CACS was 52.9 (0–312.0), whereas high levels (>1000) were observed in 52 (9.6%) patients. An overview of the distribution of the imaging findings within groups is provided in *Figure 1*.

Follow-up results

During the median follow-up period of 6.8 years (IQR 4.8–7.8 years), an event occurred in 42 (7.8%) patients, including 23 (4.3%) deaths, 19 (3.5%) MIs. A total of 109 (20.2%) early, 38 (7.1%) late non-urgent, and 20 (3.7%) urgent revascularizations were performed during follow-up. These revascularizations were not regarded as adverse events. Annual rates of all-cause mortality and MI were 0.68% and 0.60%, respectively.

Survival analysis

Figure 2 depicts the Kaplan–Meier survival curves of individual PET perfusion, CCTA stenosis severity, and CT HRP for the combined endpoint of death and MI (log-rank $P < 0.001$ for all). Annualized event rates were 2.1 and 0.6% ($P < 0.001$) for patients with and without abnormal PET perfusion, respectively. Similarly, for patients with and without an obstructive stenosis on CCTA, the annual rates of death or MI were 2.1% and 0.4% ($P < 0.001$), respectively. Respective

Table 1 Patient baseline and imaging characteristics

	Overall (n = 539)	Death/MI (n = 42)	No death/MI (n = 497)	P-value
Demographics				
Age (years)	58.6 ± 9.2	64.2 ± 8.5	58.1 ± 9.1	<0.001
Male	297 (55%)	27 (64%)	270 (54%)	0.14
Body mass index (kg/m^2)	27.0 ± 4.1	26.6 ± 3.4	27.0 ± 4.2	0.49
CAD risk factors (n = 532)				
Hypertension	251 (47%)	25 (60%)	226 (46%)	0.06
Hyperlipidaemia	196 (37%)	22 (52%)	174 (36%)	0.02
Diabetes	93 (17%)	15 (36%)	78 (16%)	0.002
Smoking	184 (35%)	17 (41%)	167 (34%)	0.24
Family history of CAD	286 (54%)	21 (50%)	265 (54%)	0.36
Medication (n = 534)				
Aspirin	404 (76%)	38 (91%)	366 (74%)	0.01
Statin	356 (67%)	35 (83%)	321 (65%)	0.01
Beta-blocker	325 (61%)	32 (76%)	293 (60%)	0.02
ACE inhibitor/ARB	190 (36%)	23 (55%)	167 (34%)	0.01
Calcium-channel blocker	141 (26%)	17 (41%)	124 (25%)	0.03
Type of chest pain (n = 533)				0.06
Typical angina	165 (31%)	16 (39%)	149 (30%)	–
Atypical angina	188 (35%)	17 (42%)	171 (35%)	–
Non-specific chest pain	180 (34%)	8 (20%)	172 (35%)	–
PET perfusion imaging				
Abnormal hyperaemic MBF	259 (48%)	32 (76%)	227 (46%)	<0.001
CCTA findings				
CACS (n = 535), median (IQR)	52.9 (0–312)	320.9 (87.2–1365.9)	39.0 (0.0–281.4)	<0.001
Normal coronary arteries	118 (22%)	0 (0%)	118 (24%)	<0.001
Non-obstructive CAD	119 (22%)	6 (14%)	113 (23%)	0.14
Obstructive CAD	302 (56%)	36 (86%)	266 (54%)	<0.001
High-risk plaque	127 (24%)	20 (48%)	107 (22%)	<0.001

Values are expressed as mean ± standard deviation or n (%).
ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blocker; CACS, coronary artery calcium score; CAD, coronary artery disease; CCTA, coronary computed tomography angiography; IQR, interquartile range; MBF, myocardial blood flow; MI, myocardial infarction; PET, positron emission tomography.

annual rates for patients with and without HRPs were 2.8% and 0.8% (P < 0.001), respectively.

Furthermore, the combined use of PET and CCTA parameters resulted in a significantly improved prediction of detrimental outcome (log-rank P < 0.001) as shown in the survival curves in*Figure 3*. In patients without positive imaging findings (i.e. normal PET perfusion, CCTA stenosis < 50%, no HRP, n = 169), the annualized event rate was 0.3%. This resulted in a total event-free survival during follow-up (median 6.8 years) of 98.2% in our cohort. Accordingly, for patients with one (n = 144), two (n = 134), and three (n = 92) positive PET-CT findings, the annualized event rate was 0.7%, 2.2%, and 3.3%, respectively, with a total event-free survival of 95.8%, 87.3%, and 82.6%, respectively, during follow-up in our cohort.

Among patients who reached the combined endpoint of death or MI, patients with HRPs showed the shortest median time to event of 566 days (IQR 79–1810 days), as compared with obstructive stenosis 1037 days (IQR 224–1814 days) and abnormal perfusion 1231 (IQR 290–1806 days). Accordingly, landmark analysis with pairwise log-rank comparisons showed very low risk of events for patients without HRPs at 4 years and no significant differences, regardless of obstructive stenosis (P = 0.21) or impaired MBF (P = 0.11) (*Figure 4*).

Univariable and multivariable analyses

Baseline univariable and multivariable prognostic factors and corresponding hazard ratios (HRs) are listed in *Table 2*. Among baseline patient characteristics, age and presence of diabetes and dyslipidaemia were univariably associated with death and MI. Accordingly, all imaging results (PET-derived MBF, CT-derived CACS, stenosis, and HRP) were univariably associated with future events. Among the univariable parameters, the largest HR was observed for a significant CCTA stenosis (≥50%) (HR: 5.61, P < 0.001). Univariably significant prognostic factors were included in a subsequent multivariable Cox regression analysis, on which only age, CCTA stenosis, and HRPs remained independently associated. Abnormal PET perfusion and higher CACS did not reach independent prognostic value. Regarding

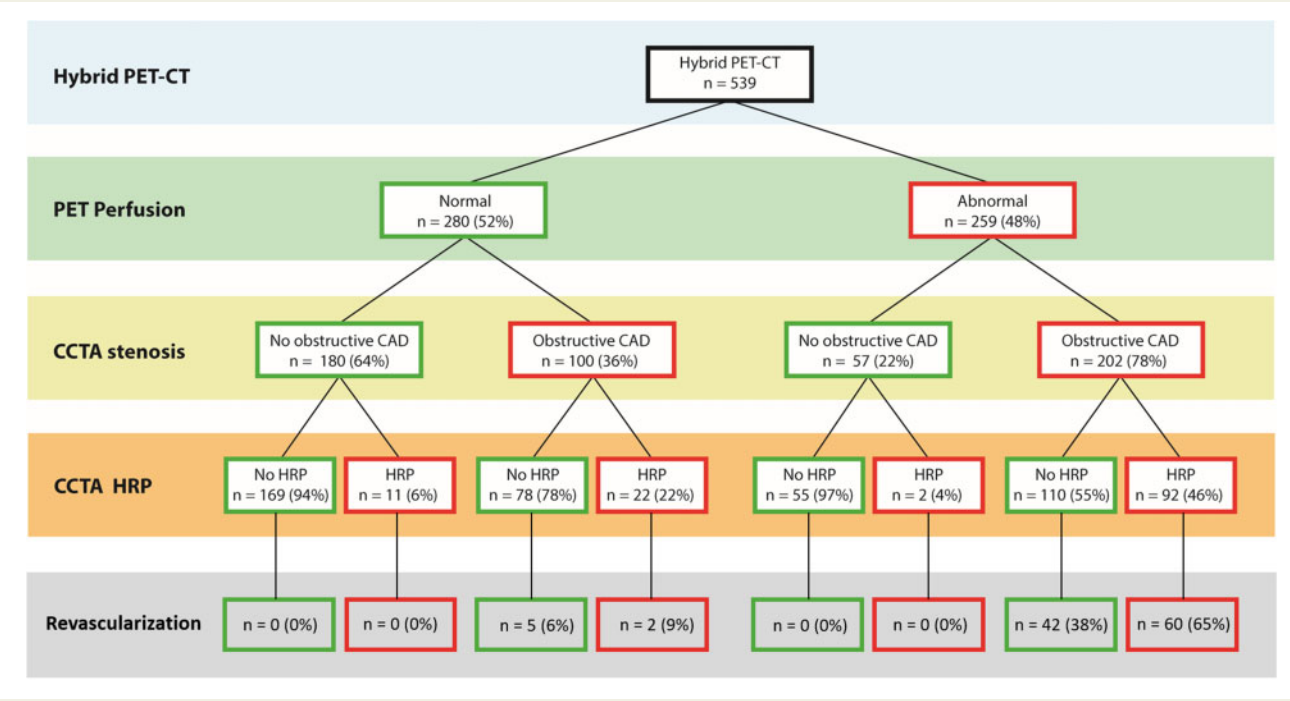


Figure 1 Distribution of hybrid PET-CT findings. Flowchart demonstrating the distribution of the hybrid PET-CT findings and revascularization performance among the three imaging parameters, i.e. PET perfusion abnormalities, CCTA-derived obstructive CAD, and CCTA-derived HRP. CAD, coronary artery disease; CCTA, coronary computed tomography angiography; CT, computed tomography; HRP, high-risk plaque; PET, positron emission tomography.

the prognostic value of the PET-CT imaging measures, the largest HR was again observed for CCTA obstructive stenosis (3.01, $P = 0.039$).

Discussion

This study of hybrid PET-CT imaging in patients with suspected stable CAD explored the prognostic value of PET-derived MBF, CCTA-derived stenosis severity, and plaque morphology. All three imaging parameters were associated with the combined endpoint death and MI. Moreover, an incremental prognostic value of comprehensive hybrid PET-CT assessment was found (*Graphical abstract*). In this cohort, CCTA stenosis severity showed an independent and the strongest prognostic value among all parameters. Also, adverse plaque morphology provided independent prognostic value. PET-derived MBF, which is strongly related to stenosis severity and plaque morphology, did not. Still, the current findings also suggest that comprehensive imaging assessment could result in an improved risk stratification as compared to any of the separate assessments alone.

Previous studies have described the prognostic value of both myocardial perfusion imaging with PET as well as stenosis severity assessment with CCTA and seem to improve risk stratification and patient management.[1,8,9,11] Both a normal perfusion with myocardial perfusion imaging[8] and no luminal stenosis on CCTA[18] confer a favourable prognosis. This is in line with this study, which revealed a good long-term prognosis with very limited adverse events in case of normal PET MBF or no obstructive stenosis on CCTA. In recent years, attention grew on combining functional and anatomical assessment with hybrid devices like PET-CT. Although this promising technique was of incremental diagnostic value in some studies, others found only limited additional value.[11,19,20] Only few studies, however, assessed the prognostic value of hybrid single-photon-emission computed tomography-CT, while prognostic data of PET-CT is even more scarce.[10,21–23] The present findings add to these previous studies that hybrid imaging has indeed some incremental prognostic value as compared to one of the stand-alone imaging techniques.

Apart from traditional stenosis severity, CCTA also allows for a non-invasive evaluation of atherosclerotic plaque morphology. Previous studies identified specific morphological features that could be linked to the so-called vulnerable plaques with pathology studies.[24] These CCTA-derived HRP features have been associated with a poorer clinical outcome, even independent of stenosis severity[3,4] and CACS.[25] A recent substudy of the SCOT-HEART trial, however, reported that HRPs did not provide independent prognostic value when CACS was taken into account as a measure of total atherosclerotic plaque burden.[26] Our results differ from these findings, as HRP morphology in the present analysis did clearly improve prognostic value over quantitative CACS. Interestingly, patients with HRPs who suffered from an event had the shortest median time-to-event as compared to obstructive stenosis and abnormal myocardial perfusion (566 vs. 1037 vs. 1231 days, respectively). This is underlined by the finding that absence of HRPs conferred a very low risk of death and MI at short-term follow-up, regardless of CT stenosis or abnormal perfusion (*Figure 4*). This suggests that patients with such plaques may be more vulnerable for plaque progression or rupture resulting

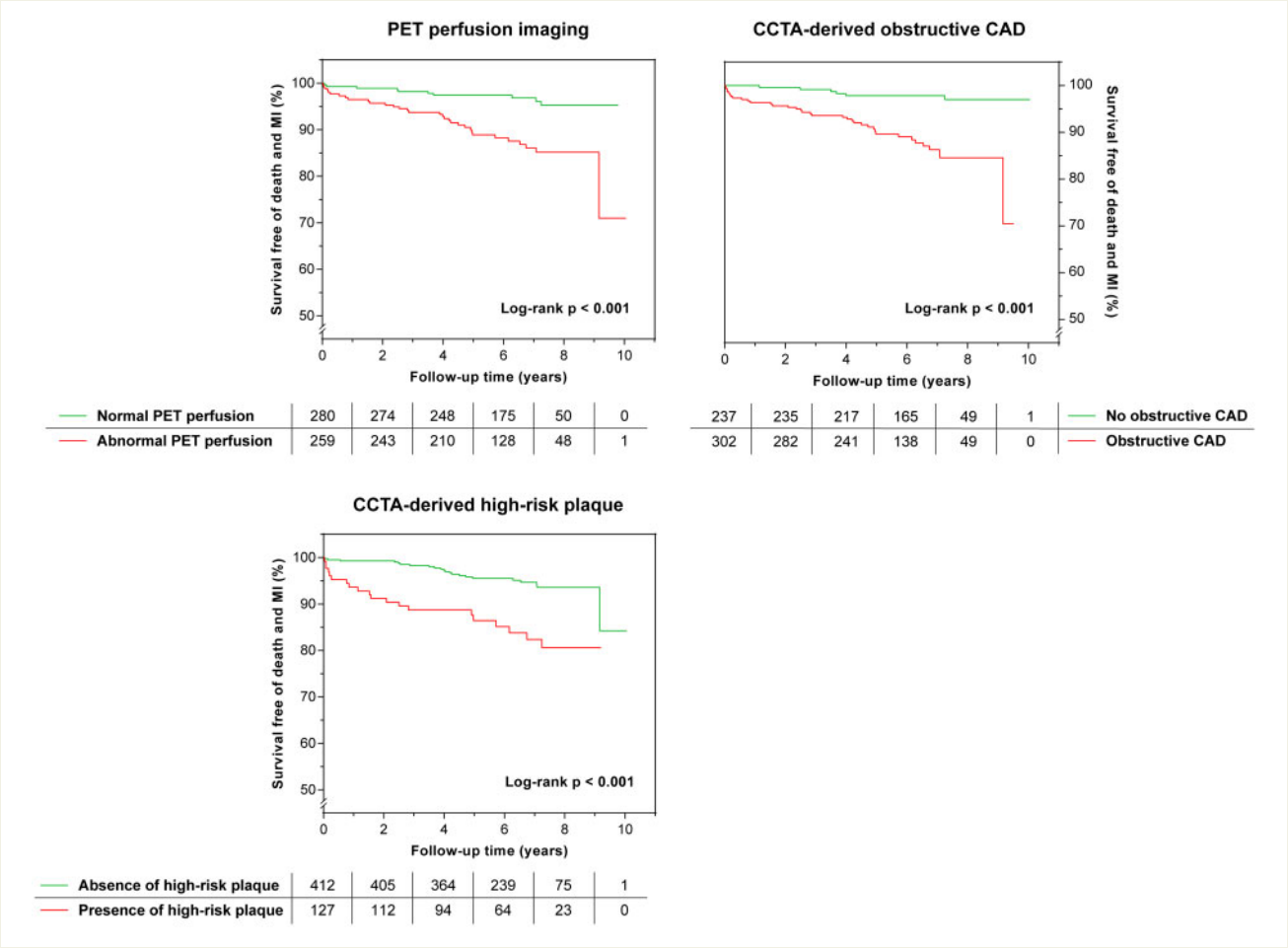


Figure 2 Survival analyses for death and MI according to imaging findings. Kaplan–Meier curves for survival free from myocardial infarction and all-cause death according to PET perfusion, CCTA-derived stenosis grade, and CCTA-derived high-risk plaque. CAD, coronary artery disease; CCTA, coronary computed tomography angiography; CT, computed tomography; HRP, high-risk plaque; MI, myocardial infarction; PET, positron emission tomography.

in adverse events in a relative short term. Our findings represent the first evaluation of the prognostic value of HRPs in a comprehensive assessment with myocardial perfusion and coronary stenosis severity and evidently demonstrated incremental value of plaque morphology over clinical variables, perfusion, CACS, and stenosis severity. A possible explanation could be that patients having such plaques benefit from statin therapy which might slow plaque progression and induce phenotypic plaque transformation into more calcified and less vulnerable plaques.[27]

There has been a long debate about the comparative prognostic value of anatomical versus physiological findings, but until recently most argued for an advantage of physiology over anatomy. Some recent studies, however, reported a superior prognostic value of anatomical testing, such as a substudy from the PROMISE trial showing a significantly better discriminatory ability of CCTA in predicting events than functional testing and also the EVINCI trial hinted in that direction.[2,28] Furthermore, the SCOT-HEART trial showed a lower rate of MI when using CCTA as compared to standard care.[1,2] Considering the largest HRs in our multivariable analysis (*Table 2*), more diverging

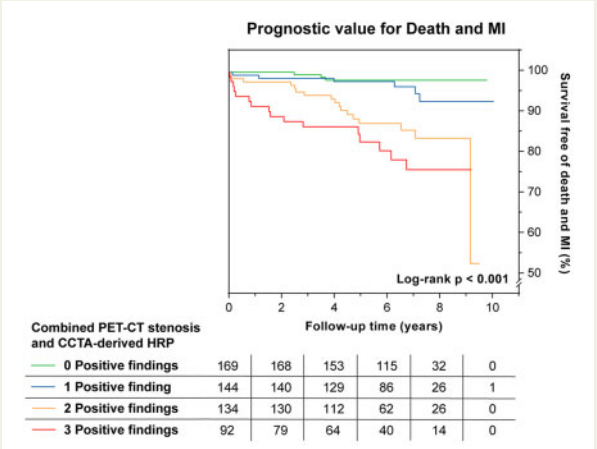


Figure 3 Survival analyses according to combined imaging findings. Kaplan–Meier curves demonstrating cumulative survival for death and MI according to combined hybrid PET-CT imaging findings. CAD, coronary artery disease; CCTA, coronary computed tomography angiography; CT, computed tomography; HRP, high-risk plaque; MI, myocardial infarction; PET, positron emission tomography.

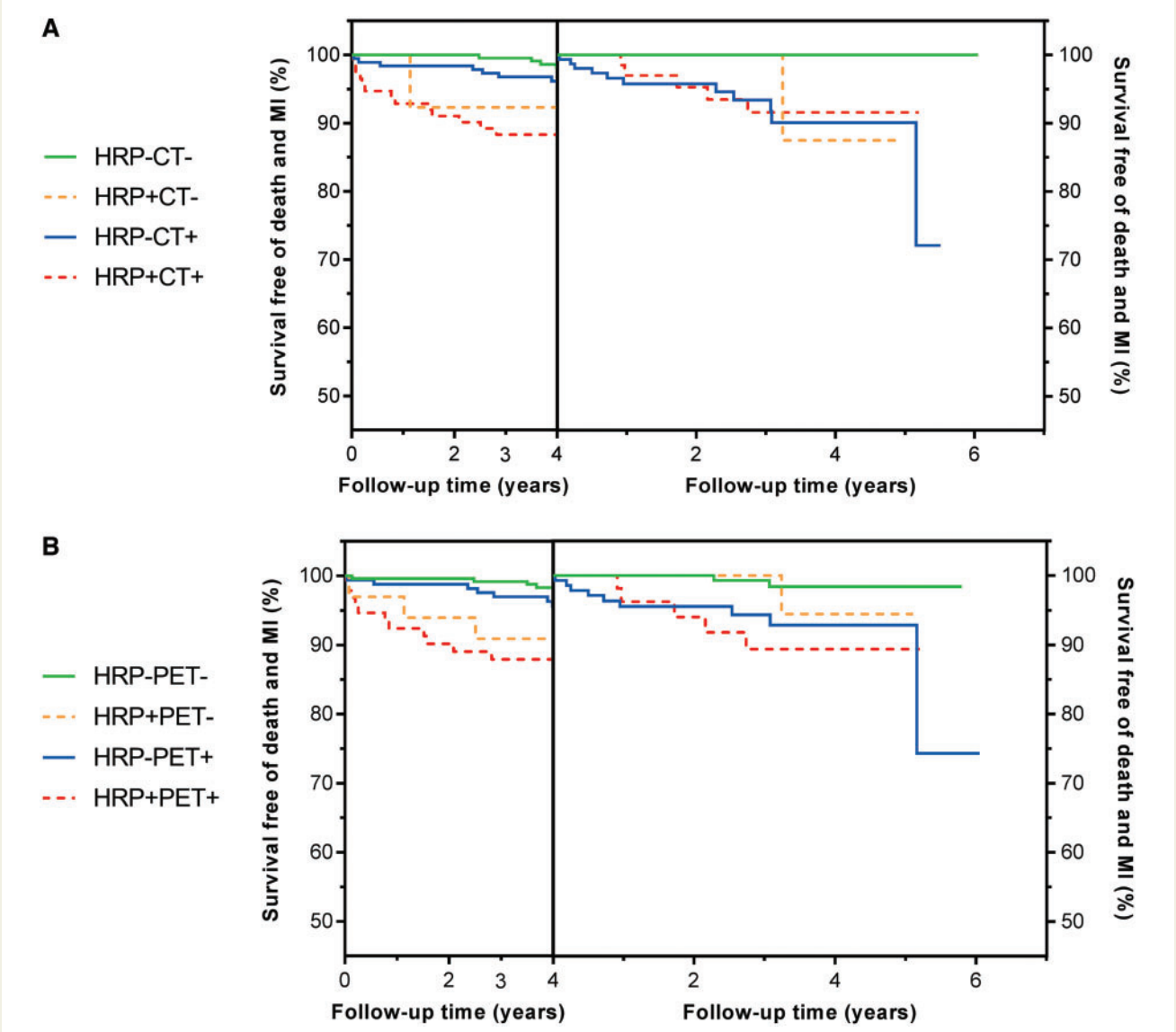


Figure 4 Short-term and long-term survival analyses according to combined imaging stratified by high-risk plaques. Landmark analysis with Kaplan–Meier curves demonstrating cumulative survival of death and MI for short-term (4 years) and long-term follow-up, according to combined high-risk plaque with obstructive stenosis (*A*) and with abnormal flow (*B*). Survival was not significantly different at 4 years for patients without high-risk plaques (HRP), regardless of obstructive stenosis (CT, $P = 0.21$) or impaired myocardial blood flow (PET, $P = 0.11$). CAD, coronary artery disease; CCTA, coronary computed tomography angiography; CT, computed tomography; HRP, high-risk plaque; PET, positron emission tomography.

Kaplan–Meier curves (*Figure 2*) and annualized event rates, the present study seems to agree that CCTA-derived stenosis might have the greatest prognostic value among the findings which can be derived from a hybrid imaging modality. More specifically, normal coronary arteries on CCTA resulted in no events during follow-up and absence of obstructive lesions showed a greater event-free survival than normal MBF on PET or no HRP morphology on CCTA (*Figure 2*). This is also in line with the recent ISCHEMIA trial, which did not proof that in patients with moderate or severe ischaemia an initial invasive strategy reduced the risk of ischaemic cardiovascular events or death.[29] Possible explanations for those and our results are that obstructive stenoses might act as a more effective surrogate of plaque burden than ischaemia.[30] Alternatively, patients with obstructive disease received more and possibly benefitted the most from revascularization (*Figure 1*).

Altogether, the current study urges for a prospective trial with comprehensive imaging including anatomy, function, and morphology, in order to answer the question whether the present findings could indeed improve patient clinical outcome.

Limitations

The present retrospective study with a moderate sample size and limited number of events, has some limitations. First, current results may not be generalizable due to the single-centre setup of the study, such as inherent-centre specific CCTA scanning techniques and

Table 2 Univariable and multivariable prognostic value for death and MI

Characteristics	Univariable		Multivariable	
	Hazard ratio (95% CI)	*P*-value	Hazard ratio (95% CI)	*P*-value
Baseline characteristics				
Age (years)	**1.07 (1.03–1.10)**	**<0.001**	**1.04 (1.01–1.08)**	**0.022**
Gender (male)	1.57 (0.83–2.95)	0.16		
BMI (kg/m^2)	0.97 (0.89–1.04)	0.36		
Smoking	0.87 (0.47–1.62)	0.67		
Diabetes	**2.49 (1.32–4.71)**	**0.005**	1.85 (0.94–3.66)	0.077
Hypertension	1.65 (0.89–3.05)	0.11		
Dyslipidaemia	**1.88 (1.02–3.45)**	**0.04**	1.22 (0.65–2.30)	0.530
Family history of CAD	0.87 (0.48–1.60)	0.66		
Imaging results				
CACS	**1.00 (1.00–1.00)**	**<0.001**	1.00 (1.00–1.00)	0.778
CCTA stenosis (≥50%)	**5.61 (2.36–13.34)**	**<0.001**	**3.01 (1.06–8.54)**	**0.039**
High-risk plaque (≥2 features)	**3.37 (1.83–6.18)**	**<0.001**	**1.93 (1.00–3.71)**	**0.049**
PET (MBF ≤ 2.30 mL/min/g)	**3.75 (1.84–7.63)**	**<0.001**	1.91 (0.84–4.31)	0.121

CACS, coronary artery calcium score; CAD, coronary artery disease; CCTA, coronary computed tomography angiography; CI, confidence interval; MBF, myocardial blood flow; MI, myocardial infarction; PET, positron emission tomography. Bold values represent significant hazard ratios for p<0.05.

specific PET tracers and thresholds for abnormal perfusion. Accordingly, current results derived from [^{15}O]H_2O PET cannot be extrapolated to the more commonly used tracers [^{13}N]NH_3 and Rubidium-82. As per protocol in our tertiary referral centre, all study patients underwent both PET and CCTA imaging. This might hamper the generalizability of our results to an approach of performing CCTA and PET selectively. Finally, pragmatic dichotomous definitions of abnormal MBF, obstructive CAD, and HRPs were defined based on accepted standards and make current findings most useful for clinical practice. This simplification, however, disregards the potential extent of ischaemia, such as quantitative global and regional absolute hyperaemic flow or flow reserve on a continuous scale, as well as quantitative HRP burden, such as low-attenuation or non-calcified plaque volume, which are of prognostic validity.[8,25,30] A recent study, however, did not find incremental value of (adding) flow reserve over maximal flow.[31] Still, future studies are to be undertaken to examine the anticipated incremental prognostic value of quantification of atherosclerotic disease and myocardial perfusion.

Conclusion

Hybrid PET-CT allowed for an integrated evaluation of MBF, coronary stenosis severity, and atherosclerotic plaque morphology. Such a comprehensive assessment showed an incremental prognostic value in patients suspected of stable CAD for a combined hard endpoint of death and MI. Among these imaging parameters, CCTA-derived stenosis severity might have the greatest independent predictive value for adverse events overall. HRP morphology, specifically, might have the strongest short-term negative predictive value. Future prospective trials are, however, warranted to test whether comprehensive assessment with hybrid PET-CT or CCTA alone could indeed improve patient outcome.

Conflict of interest: J.K.M. serves as a consultant to Abbott Vascular, serves on the scientific advisory board of Arineta, and has an equity interest in MDDX and Cleerly. J.A.L. has received research grants from GE Healthcare; and serves as a consultant and holds stock options in Circle CVI and HeartFlow. J.K. has been a study consultant for GE Healthcare and AstraZeneca. All other authors have reported that they have no relationships relevant to the contents of this paper to disclose.

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