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Clinical utility of circulating interleukin-6 concentrations in the detection of functionally relevant coronary artery disease☆

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ABSTRACT

Background: Inflammation plays a major role in the pathogenesis of coronary artery disease (CAD).
Methods: We hypothesized, that quantifying inflammation by measuring circulating interleukin-6 concentrations help in the diagnosis and/or prediction of functionally relevant CAD. Among consecutive patients with symptoms suggestive of CAD, functionally relevant CAD was adjudicated in two domains: first, diagnosis according to myocardial perfusion single photon emission tomography (MPI-SPECT) and coronary angiography; second, cardiovascular death and all-cause death during 2-years follow-up. Adjudication was done blinded to the interleukin-6 concentrations.
Results: Among 1553 patients, symptoms were adjudicated to be causally related to CAD in 43% (665/1553). Interleukin-6 concentrations were higher in patients with functionally relevant CAD as compared to those without (1.56 pg/mL versus 1.30 pg/mL, $p < 0.001$), but overall had only low-to-modest diagnostic accuracy (area under the curve [AUC]: 0.57, 95%CI 0.55–0.61) and were no independent predictor of functionally relevant CAD after multivariable adjustment ($p = 0.068$). Interleukin-6 concentrations had moderate-to-high accuracy in the prediction of cardiovascular death (AUC 0.75, 95%CI 0.69–0.82) and all-cause death (AUC 0.72, 95%CI 0.66–0.78) at 2-years, and remained a significant predictor after multivariable adjustment ($p < 0.001$). Compared to patients with interleukin-6 concentrations below the median (1.41 pg/mL), patients with concentrations above the median had a significantly higher cumulative incidence of cardiovascular death (1% vs. 4%, log-rank $p < 0.001$) and all-cause death (2% vs. 8%, log-rank $p < 0.001$) at 2 years.
Conclusion: Interleukin-6 concentrations are strong and independent predictors of cardiovascular death and all-cause death.

1. Introduction

Coronary artery disease (CAD) is the leading cause of death in developed countries [1,2], even though effective treatment modalities including life-style modification, optimal medical therapy and revascularization are available [3–6]. The clinical course of CAD is highly variable and CAD extremely common when applying the conventional anatomical definition with up to 50% of all persons developing CAD during their life-time [7,8]. Hence, the differentiation between the benign and clinically silent phenotype from the malignant phenotype associated with functionally relevant myocardial ischemia resulting in

Abbreviations: CAD, coronary artery disease; MPI-SPECT/CT, myocardial perfusion single-photon emission tomography imaging/computer tomography; VAS, visual analogue scale; ECG, electrocardiogram; LoD, limit of detection; LoQ, limit of quantification; AUC, area under the receiver-operating-characteristics curve; NPV, negative predictive value; PPV, positive predictive value; CI, confidence interval; IQR, interquartile range.

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symptoms interfering with everyday activities or clinical events such as nonfatal acute myocardial infarction or cardiovascular death within the next years is a major unmet clinical need.

Increasingly, patients with low pre-test probability for functionally relevant CAD are referred for work-up [9]. This is underlined by the finding that cardiac imaging tests are possibly inappropriate in one third of referred patients, causing annual costs of more than $500 million in the United States alone [9]. Further, while being central to diagnosing functionally relevant CAD, cardiac imaging techniques have important limitations such as radiation and its associated risk with cancer [9].

Preclinical and clinical studies have highlighted that inflammation plays a key role in the pathogenesis of CAD [10–17]. It is thought that T-cell cytokines generated during plaque development stimulate the production of quantifiable amounts of circulating interleukin-6 downstream [12]. Pilot studies suggested that elevated interleukin-6 concentrations might correlate with a patient's CAD burden and angiographic severity [14,18–23]. Furthermore, anti-inflammatory therapy with canakinumab has recently been shown to reduce the rate of acute myocardial infarction and coronary revascularization [24].

Therefore, the aim of this study was to prospectively assess the clinical utility of interleukin-6 concentrations in patients with suspected functionally relevant CAD.

2. Methods

2.1. Study design and oversight

This analysis is part of a large ongoing prospective diagnostic study (NCT01838148, clinicaltrials.gov) designed to advance the early detection of functionally relevant CAD [25–28]. The study was approved by the local ethics committee and carried out according to the principles of the Declaration of Helsinki. All patients provided written informed consent. The authors designed the study, gathered, analyzed and reported the data according to the STARD guidelines for studies of diagnostic accuracy [29], vouched for the data and analysis, wrote the paper, and made the decision to submit it for publication.

2.2. Patient population

Consecutive patients with suspected functionally relevant CAD and referred for rest/stress myocardial perfusion single-photon emission tomography/computer tomography (MPI-SPECT) to the University Hospital Basel, Switzerland were recruited. At this institution, MPI-SPECT/CT is the preferred imaging modality in patients with a wide range of pre-test probabilities for functionally relevant CAD. This study was conducted in a real-world setting and did not employ specific exclusion criteria concerning inter-current infectious/inflammatory diseases and/or hematologic disorders or malignancy. While the patients' systemic inflammatory status was not routinely screened, it is important to highlight that in clinical practice myocardial perfusion imaging is only performed in stable patients without clinically apparent infection or active inflammation. For this analysis, patients with terminal kidney failure requiring chronic dialysis were excluded.

2.3. Evaluation of clinical assessment

The treating cardiologist recorded a subjective clinical assessment regarding the presence of functionally relevant CAD on a visual analogue scale (VAS) with values between 0% and 100%. Clinical assessment VAS was obtained before stress testing based on the clinical integration of all medical information available at this time point, including patient age, sex, previous cardiac history, the number and extent of cardiovascular risk factors, detailed assessment of symptoms, and baseline ECG data. A second clinical assessment VAS was recorded after stress testing when the cardiologist was able to add symptoms during exercise/stress, the workload achieved, and ECG changes recorded during exercise/stress. The cardiologist was blinded to results of biomarker measurements and MPI-SPECT images at the time of the assessment.

2.4. Blood sampling and laboratory methods

Venous blood samples for biomarker testing were taken before stress-testing. Blood was immediately processed and frozen at −80 °C, until it was assayed. Interleukin-6 concentrations were measured using the ultrasensitive Erenna® immunoassay system (Singulex, CA), which uses a micro-particle immunoassay and single-molecule counting in a capillary flow system [30]. The assay's limit of detection is 0.01 pg/mL with a lower limit of quantification at 0.4 pg/mL [31]. The laboratory technicians who measured interleukin-6 were blinded to patient, stress-test and imaging data.

2.5. Adjudication of the presence of functionally relevant CAD

Adjudication of functionally relevant CAD was based on expert interpretation of MPI-SPECT/CT images combined with information obtained from invasive coronary angiography and fractional flow reserve measurements whenever available.

All patients underwent a routine rest/stress dual isotope (^{201}Tl for rest, ^{99m}Tc sestamibi for stress) or single isotope (^{99m}Tc sestamibi for stress and rest) MPI-SPECT protocol as described previously [26,28,32]. MPI-SPECT images were scored semi-quantitatively using a 17-segment model with a 5-point scale (0 = normal, 1 = mildly reduced tracer uptake, 2 = moderately reduced uptake, 3 = severely reduced uptake and 4 = no uptake). Summed stress score (SSS) and summed rest score (SRS) were calculated by adding the scores of the 17 segments in the stress and rest images. Summed difference score (SDS) was the difference between SSS and SRS scores. SDS of at least 2 or positive transient ischemic dilation ratio (TID) was considered as inducible myocardial ischemia. SSS and SRS were derived by visual assessment (two readers) and compared with the software (QGS) result. Differences in the visual assessment by the two readers were resolved by finding consensus. In case of equivocal findings from MPI-SPECT and coronary angiography, two independent cardiologists (one interventional cardiologist, one general cardiologist) that were blinded to biomarker results reviewed the case. A positive perfusion scan was overruled when coronary angiography showed normal coronary arteries and a negative perfusion scan was overruled (except in the case of acute myocardial infarction) if coronary angiography within three months A) revealed a high-grade coronary lesion (>75%) or B) revealed a 50–75% stenosis followed by a percutaneous coronary intervention or a coronary artery bypass or if there was fractional flow reserve lower than 0.80. Of the 1605 eligible patients that provided informed consent, 414 (25%) patients underwent coronary angiography within three months, with 13 (<1%) of the 1605 patients being reclassified to the functionally relevant CAD group and 52 (3%) patients being reclassified to the non-ischemic group. Myocardial perfusion MPI-SPECT images and coronary angiography findings were evaluated blinded to interleukin-6 levels.

2.6. Prognostic outcome definition

Primary endpoints for the prognostic analyses were all-cause death, cardiovascular death and acute myocardial infarction. Patients were contacted either in written form or by telephone interview performed by trained researchers. In case of an event, further information was obtained from the hospital records, general practitioner/cardiologists records, or the national death registry.

2.7. Statistical analysis

The normality assumption was tested using the Kolmogorov–Smirnov test and visual assessment. Continuous variables are presented as median and respective inter quartile range (IQR) and categorical variables are presented as frequencies and respective percentages. Confidence intervals of proportions were calculated using the Agresti-Coull method. Using logistic regression with functionally relevant CAD as outcome, interleukin-6 concentrations were adjusted for patient characteristics, risk-factors and treatment, and combined with the clinical assessment of the treating physician before and after stress testing. Diagnostic accuracy of the clinical assessment, interleukin-6, and their combination for functionally relevant CAD was quantified by the area under the receiver operating curve (AUC) and compared with the method described by DeLong et al. [33]. Interleukin-6 cutoffs for pre-defined target sensitivities and specificities for functionally relevant CAD were derived and the incidence of criteria calculated.

Cox regression analysis was used to evaluate whether interleukin-6 was a predictor of all-cause death, cardiovascular death and acute myocardial infarction independent of patient characteristics, risk-factors and elective revascularization within 90 days after MPI-SPECT examination. To adjust for possibly uncontrolled other inflammatory systemic disorders, the equivalent Cox regression analysis was performed while excluding the 5% of patients with the highest interleukin-6 concentrations. Time dependent AUCs were used to quantify the predictive accuracy (discriminative ability) of the biomarkers for all-cause death within 2 years, cardiovascular death within 2 years and acute myocardial infarction within 2 years, while accounting for censoring and competing risks [34].

Kaplan-Meier curves for interleukin-6 concentrations below and above the median were constructed for 2-year all-cause death as well as 2-year cardiovascular death and compared by log rank testing. Statistical analyses were performed with SPSS version 25.0 and R version 3.4.2. All hypothesis testing was two-tailed, and a p-value < 0.05 was considered statistically significant.

3. Results

Overall, 1553 patients with suspected functionally relevant CAD were included (Supplemental Fig. 1). The median age was 67 years (IQR 59–75 years), 32% (493/1553) were female. Patient characteristics stratified by the presence or absence of functionally relevant CAD are presented in Table 1.

Table 1
Patient characteristics stratified by presence or absence of functionally relevant CAD.

	All patients N = 1553 (100%)	Functionally relevant CAD		*p* value
		No N = 888 (57%)	Yes N = 665 (43%)	
Female (%)	493 (32)	352 (40)	141 (21)	<0.001
Age [IQR], years	67 [59, 75]	67 [58, 74]	69 [61, 76]	<0.001
BMI [IQR]	27.1 [24.5, 30.4]	26.7 [24.1, 30.3]	27.4 [24.9, 30.4]	0.009
Ever smoker (%)	937 (60)	505 (57)	432 (65)	0.002
Family history of CAD (%)	440 (28)	232 (26)	208 (31)	0.030
Medical History (%)				
Hypertension	1259 (81)	667 (75)	592 (89)	<0.001
Hypercholesterinemia	1111 (72)	557 (63)	554 (83)	<0.001
CAD	755 (49)	283 (32)	472 (71)	<0.001
AMI	501 (32)	175 (20)	326 (49)	<0.001
Prior PCI	569 (37)	222 (25)	347 (52)	<0.001
Prior CABG	212 (14)	53 (6)	159 (24)	<0.001
Heart failure	30 (2)	10 (1)	20 (3)	0.013
Aortic valve disease				0.020
Mild stenosis	27 (2)	11 (1)	16 (2)	
Moderate stenosis	11 (1)	3 (<1)	8 (1)	
Severe stenosis	10 (1)	3 (<1)	7 (1)	
Mild insufficiency	76 (5)	43 (5)	33 (5)	
Moderate insufficiency	14 (1)	7 (1)	7 (1)	
Severe insufficiency	11 (1)	3 (<1)	8 (1)	
Mitral valve disease				<0.001
Mild stenosis	0	0	0	
Moderate stenosis	3 (<1)	2 (<1)	1 (<1)	
Severe stenosis	1 (<1)	0 (<1)	1 (<1)	
Mild insufficiency	202 (13)	87 (10)	115 (17)	
Moderate insufficiency	54 (3)	22 (2)	32 (5)	
Severe insufficiency	9 (1)	3 (<1)	6 (1)	
Stroke or TIA	130 (8)	72 (8)	58 (9)	0.734
COPD	128 (8)	72 (8)	56 (8)	0.898
Diabetes	369 (24)	178 (20)	191 (29)	<0.001
Insulin-dependent	112 (7)	51 (6)	61 (9)	0.013
Malignancy	196 (13)	119 (13)	77 (12)	0.321
Medication (%)				
Aspirin	979 (63)	457 (51)	522 (78)	<0.001
Thienopyridine	246 (16)	91 (10)	155 (23)	<0.001
Nitroglycerin	170 (11)	66 (7)	104 (16)	<0.001
Betablocker	934 (60)	445 (50)	489 (74)	<0.001
Calcium channel blocker	344 (22)	165 (19)	179 (27)	<0.001
Amiodarone	32 (2)	17 (2)	15 (2)	0.773
Diuretic	572 (37)	301 (34)	271 (41)	0.007
ACE inhibitor	523 (34)	242 (27)	281 (42)	<0.001
ARB	459 (30)	252 (28)	207 (31)	0.263
Statin	927 (60)	435 (49)	492 (74)	<0.001
Phenprocoumon	182 (12)	103 (12)	79 (12)	0.928
Proton pump inhibitor	393 (25)	225 (25)	168 (25)	0.999
VAS before stress testing [IQR], %	40 [20, 60]	30 [20, 50]	50 [30, 70]	<0.001
VAS after stress testing [IQR], %	40 [20, 70]	30 [10, 60]	50 [30, 80]	<0.001
Left ventricular ejection fraction [IQR][a]	55 [47, 63]	58 [50, 66]	51 [42, 59]	<0.001

ACE inhibitor - angiotensin-converting-enzyme inhibitor; AMI - acute myocardial infarction; ARB - angiotensin II receptor blockers; BMI - body mass index; CAD - coronary artery disease; COPD - chronic obstructive pulmonary disease; TIA - transient ischemic attack; VAS - clinical assessment of cardiologist for presence of functionally relevant CAD before and after cardiac stress testing but prior to imaging.

[a] Left ventricular ejection fraction as measured during myocardial perfusion single-photon emission tomography imaging/computer tomography.

3.1. Diagnostic performance of interleukin-6

Functionally relevant CAD was adjudicated to be present in 43% (665/1553) of patients. Interleukin-6 concentrations were significantly higher in patients with functionally relevant CAD (1.56 pg/mL, IQR: 1.00–2.65 pg/mL) than in patients without functionally relevant CAD (1.30 pg/mL, IQR: 0.82–2.12 pg/mL, $p < 0.001$, Fig. 1). There only was a weak correlation between interleukin-6 concentrations and the area of inducible ischemia as quantified by the SDS (spearman correlation $r = 0.091$, $p = 0.001$). While interleukin-6 remained a significant predictor ($p = 0.013$) when adjusted for age, sex, prior CAD history, hypertension, body mass index, diabetes, hyperlipidemia and tobacco use, it lost its independent association during further multivariable adjustment (Supplemental Table 1). The overall diagnostic accuracy of interleukin-6 as quantified by the AUC was only low-to-modest (0.57, 95%CI 0.55–0.61), lower than clinical assessment of the treating physician before stress testing (0.65, 95%CI 0.63–0.68) and after stress testing (AUC: 0.67, 95%CI 0.65–0.70), and did not provide a significant incremental value on top of clinical judgment (Table 2). Cutoff values of interleukin-6 for rule-out and rule-in of functionally relevant CAD are presented in Supplemental Table 2.

3.2. Prognostic performance of Interleukin-6

Median follow-up duration was 1023 days (IQR 748–1925 days). Overall, in 14% (216/1553) of patients elective revascularization was performed within 90 days after the MPI-SPECT examination. The 2-year cumulative incidence of cardiovascular death was 2.6% (39 events), of all-cause death 4.8% (72 events) and of acute myocardial infarction 4.6% (69 events). In Cox regression, interleukin-6 remained a significant predictor for cardiovascular death (hazard ratio: 1.95, 95%CI 1.56–2.42, $p < 0.001$), all-cause death (hazard ratio: 1.84, 95%CI

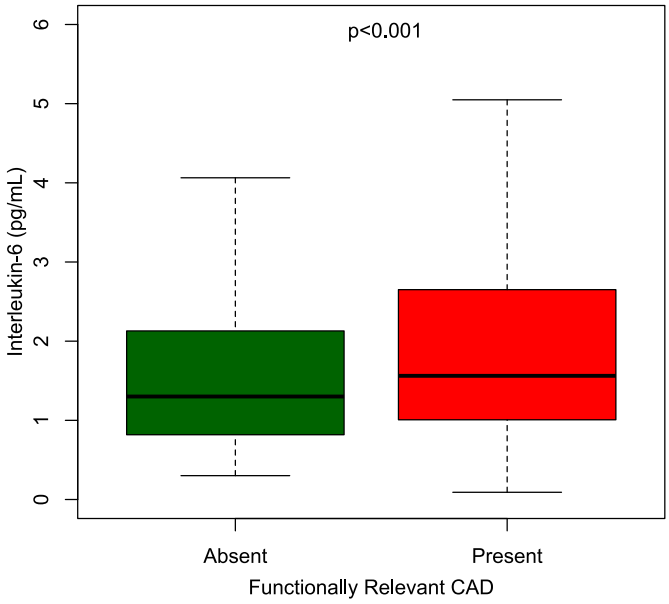

Fig. 1. Boxplots of interleukin-6 concentrations stratified by presence of functionally relevant CAD. The boxes are delimited by the interquartile range and whiskers represent ±1.5 * inter quartile range.

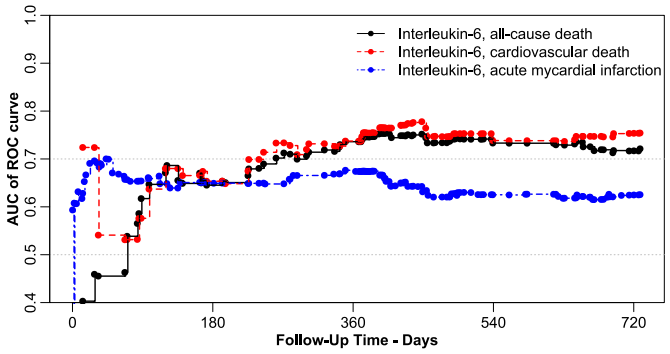

Fig. 2. Time-dependent areas under receiver operating characteristics curve (AUC of ROC) of interleukin-6 plotted over 2 years for all-cause death (72 events), cardiovascular death (39 events) and acute myocardial infarction (69 events). Each dot represents a change in AUC due to death or censoring.

1.58–2.14, $p < 0.001$) and acute myocardial infarction (hazard ratio: 1.45, 95%CI 1.14–1.84, $p = 0.003$) after adjustment for age, sex, prior CAD history, hypertension, body mass index, diabetes, hyperlipidemia and tobacco use. While interleukin-6 also remained a significant prognostic predictor in further multivariable analysis, it lost its independent predictive association with acute myocardial infarction ($p = 0.063$) when excluding the 5% of patients with the highest interleukin-6 concentrations (Supplemental Table 3). Time-dependent ROC curve analysis showed moderate-to-good discriminative performance of interleukin-6 concentrations for the prediction of cardiovascular death and all-cause death, with consistently equivalent or superior predictive performance for cardiovascular death (Fig. 2). At 2 years, interleukin-6 concentrations provided a time dependent AUC of 0.75 (95%CI 0.69–0.82) for cardiovascular death, 0.72 (95%CI 0.66–0.78) for all-cause death and 0.63 (95%CI 0.57–0.69) for acute myocardial infarction. Compared to patients with interleukin-6 concentrations below the median (1.41 pg/mL), patients with concentrations above the median had a significantly higher cumulative incidence of cardiovascular death (1% vs. 4%, $p < 0.001$), all-cause death (2% vs. 8%, $p < 0.001$) and acute myocardial infarction (3% vs. 6%, $p < 0.001$) at 2-years (Supplemental Fig. 2–4).

Table 2
Comparison of receiver operating characteristic curves.

	AUC	95%CI	*p* value (vs. reference)
All patients (N = 1553)			
IL-6	0.57	0.55–0.61	–
Clinical assessment before stress testing	0.65	0.63–0.68	Reference
Clinical assessment before stress testing + IL-6	0.67	0.64–0.69	0.051
Clinical assessment after stress testing	0.67	0.65–0.70	Reference
Clinical assessment after stress testing + IL-6	0.68	0.66–0.71	0.182
Patients without known CAD (N = 798)			
IL-6	0.60	0.55–0.65	–
Clinical assessment before stress testing	0.65	0.61–0.70	Reference
Clinical assessment before stress testing + IL-6	0.67	0.63–0.72	0.094
Clinical assessment after stress testing	0.69	0.65–0.73	Reference
Clinical assessment after stress testing + IL-6	0.70	0.66–0.74	0.154
Patients with known CAD (N = 755)			
IL-6	0.54	0.49–0.58	–
Clinical assessment before stress testing	0.60	0.56–0.64	Reference
Clinical assessment before stress testing + IL-6	0.61	0.57–0.65	0.429
Clinical assessment after stress testing	0.61	0.57–0.65	Reference
Clinical assessment after stress testing + IL-6	0.62	0.57–0.66	0.836

AUC - area under the receiver operating characteristics curve; CAD - coronary artery disease; CI - confidence interval; IL-6 - interleukin 6; VAS - clinical assessment of cardiologist for presence of functionally relevant CAD prior to imaging.

4. Discussion

The beneficial effect of anti-inflammatory therapy with canakinumab on the incidence of acute myocardial infarction and coronary revascularization has reignited the interest in exploring the possible clinical utility of interleukin-6 as a quantitative marker of systemic inflammation in patients with suspected functionally relevant CAD [24].

We report three major findings. First, patients adjudicated with functionally relevant CAD had significantly higher interleukin-6 concentrations as compared to patients without functionally relevant CAD. These data corroborate and extend previous findings from pilot studies concerning the association of circulating interleukin-6 concentrations with CAD burden [18–20,35]. Second, however, overall circulating interleukin-6 concentrations had only low-to-modest diagnostic accuracy, did not provide incremental value on top of the clinical assessment of the treating cardiologist and lost their independent predictive association with functionally relevant CAD after multivariable adjustment ($p = 0.068$). Accordingly, in contrast to an organ-specific biomarker such as high-sensitivity cardiac troponin [26,28,32], interleukin-6 as an unspecific biomarker of systemic inflammation does not seem to provide equivalent clinical utility in the detection of functionally relevant CAD. Third, interleukin-6 concentrations were powerful and independent predictors for 2-year cardiovascular death, the second domain in which functionally relevant CAD was defined. Overall, interleukin-6 had moderate-to-high accuracy in the prediction of cardiovascular death. Interleukin-6 also had moderate-to-high accuracy in the prediction of all-cause death These data corroborate and extend previous findings concerning the association of circulating interleukin-6 concentrations with progressive atherosclerosis and plaque rupture/erosion leading to cardiovascular death [21,36–40]. Interleukin-6 only had low-to-moderate accuracy in the prediction of acute myocardial infarction and even lost its independent predictive association ($p = 0.063$) in a sensitivity analysis excluding patients with very high interleukin-6 values and thereby possibly systemic inflammation due to uncontrolled other inflammatory disorders. Consequently, the general association and potentially causal contribution of inflammation to plaque rupture and plaque fissure leading to cardiovascular death seems to be stronger than the association with coronary atherosclerosis in particular. However, although interleukin-6 concentrations

do not seem to improve the diagnosis of functionally relevant CAD, the findings of this study support previous data concerning the significant role of inflammation in cardiovascular outcome and mortality [23,40]. One of the strengths of this study is that it enrolled patients with a need for clinical decision-making regarding further diagnostic and therapeutic management. Therefore, our findings seem suitable for generalization to patients with similar open clinical questions and clearly complement and extend observations made in population-based studies as well as disease cohorts without apparent need for clinical decision making [21,36–40].

Several limitations should be considered when interpreting the findings of this study. First, although we have used the most stringent methodology to adjudicate the presence or absence of functionally relevant CAD, we still may have misclassified a small number of patients, which potentially led to an underestimation of the true accuracy of interleukin-6. Second, patients of African or Asian descent were underrepresented in this European cohort and potential differences between these groups cannot be addressed. Third, these data were generated in a large single-center diagnostic study using central adjudication. However, the fact that MPI-SPECT/CT was the standard non-invasive imaging modality and was applied to patients with a wide range of pretest probability for CAD should have counterbalanced the inherent possibility of referral bias in a single-center study. Fifth, next to interleukin-6 concentrations, there was no additional data concerning the patients' systemic inflammatory status. Sixth, the prognostic analysis is based on 5546 patient-years of follow-up. Additional long-term follow-up is ongoing and will be able to provide even more precise estimates of the prognostic performance.

In conclusion, interleukin-6 concentrations are associated with functionally relevant CAD, but the clinical utility is limited due to low-to-modest diagnostic accuracy. Patients suspected with functionally relevant CAD and elevated interleukin-6 concentrations are at substantially increased risk of cardiovascular death and all-cause death during long-term follow-up.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ijcard.2018.10.029.

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