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Tesi di Dottorato

Regional myocardial perfusion evaluation by CZT SPECT imaging in predicting lesion-related outcome in patients with suspected or known CAD

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INTRODUCTION

Myocardial perfusion imaging (MPI) by novel cadmium-zinc-telluride (CZT) camera has been largely validated in diagnosis and risk stratification of patients with suspected or known coronary artery disease (CAD) [1-3]. Non-invasive assessment of stress-induced ischemia, along with the severity of symptoms and presence of significant epicardial coronary stenosis on angiography, are powerful tools in both risk estimation and patient management [4]. Prognostic value of CZT cameras has been demonstrated to be similar as compared to conventional cameras [5-6]. In particular, patients with normal scans have a trend to a low prevalence of hard cardiovascular events at mid-term follow-up, leading to the possibility of a prognosis even better than that of conventional stress SPECT [7]. Moreover, the greater extension of myocardial hypoperfusion by CZT cameras is associated to higher risk of major cardiac events and all-cause mortality [8-9]. Some authors [10–11] have investigated the role of global ischemic total perfusion defect (ITPD) assessed by traditional SPECT cameras. As well, different studies have analysed the power of semiquantitative regional assessment by PET/CT in the identification of obstructive CAD [12-13]. To our knowledge, no data are available on the prognostic value of regional myocardial perfusion evaluated by CZT cameras.

Therefore, the aim of our study was to evaluate the prognostic value of regional myocardial perfusion assessed by CZT camera in predicting lesion-related outcome in patients with suspected or known CAD.

MATERIAL AND METHODS

Study population

Between February 2016 and June 2020, we studied 840 patients referred to stress/rest MPI for clinical evaluation. For the purpose of the present study, 250 (30%) patients with no available angiographic data were excluded. The final study population was composed by 590 subjects with suspected or known CAD who were referred by a clinical physician to coronary angiography within 90 days from MPI. Demographic information, as well as clinical history, cardiovascular risk factors, such as diabetes, hypertension, dyslipidemia, smoking history, family history of CAD, chest pain symptoms, electrocardiographic abnormalities, previous history of myocardial infarction or coronary revascularization, were collected. Patients were considered as diabetic in case of a previous diagnosis of diabetes mellitus or treatment with oral hypoglycemic drugs or insulin. Hypertension was defined as a known history of systolic blood pressure >140 mmHg or treatment with antihypertensive medication. Dyslipidemia was defined as a known history of dyslipidemia or the use of cholesterol-lowering medication. A positive family history of CAD was defined as the presence of CAD in first-degree relatives. All the data were verified and complemented with demographic and clinical

information collected from medical records. The review committee of our institution approved this study and all patients gave informed consent (‘‘Comitato Etico, Università Federico II’’, protocol number 110/17).

MPI

All patients underwent gated stress/rest MPI after intravenous injection of 99mTc-sestamibi (185 MBq for stress and 370 MBq for rest images) using a cardio-dedicated SPECT camera (D-SPECT, Spectrum Dynamics, Caesarea, Israel). Stress testing was performed using physical exercise by treadmill or dipyridamole (0.142 mg kg^{-1} x $minute^{-1}$ intravenous over 4 minutes). All patients were instructed to withheld beta-blocking medications, calcium antagonists for 48 hours and nitrates for 12 hours before examination. For patients undergoing pharmacological stress test, consuming caffeine was not allowed for 24 hours before testing. Rest and peak stress heart rate and blood pressure were recorded; monitoring of heart rate, rhythm and ECG were performed all along the stress protocol. Physical test endpoints were achievement of 85% maximal predicted heart rate, horizontal or down-sloping ST-segment depression >2 mm, ST-segment elevation >1 mm, moderate to severe angina, systolic blood pressure decrease >20 mm Hg, blood pressure >230/120 mmHg, dizziness, or clinically important cardiac arrhythmia. At

peak exercise or 4 minutes after dipyridamole infusion, a bolus of 99mTc-sestamibi was intravenously injected. In case of chest pain or other symptoms, as well as significant ST depression, 100 mg of aminophylline were administered intravenously. Total perfusion deficit (TPD), incorporating the extent and severity of perfusion defects and expressed as a percentage of the LV myocardium, was calculated by an automated software program (e-soft 2.5, QGS/QPS, Cedars-Sinai Medical Center, Los Angeles, CA), using standardized segmentation of 17 myocardial regions; moreover, left ventricular (LV) volumes and ejection fraction (EF) were automatically computed. Ischemic TPD (ITPD) was defined as stress TPD - rest TPD. Both per-vessel TPD and ITPD were calculated separately for each vascular territory (left anterior descending, left circumflex, and right coronary artery) [12]. A value of stress TPD $\geq$5% was considered abnormal [14].

Coronary angiography

Coronary angiography was performed using the standard Judkins method. Results of CTA were visually interpreted by experienced cardiologists and significant CAD was considered in presence of luminal diameter stenosis ≥50% in at least one of the three major vascular territories [15-16].

Follow-up

Patient follow-up was prospectively obtained by use of a questionnaire assessed by a phone call to all patients and general practitioners or cardiologists and by review of hospital or physicians' records by individuals blinded to the patient's test results. The outcome was a composite end point of cardiac death, target vessel-related myocardial infarction, or late coronary revascularization, whichever occurred first. The cause of death was confirmed by review of death certificate, hospital chart, or physician's records. Death was considered of cardiac origin if caused by acute myocardial infarction, congestive heart failure, valvular heart disease, sudden cardiac death, cardiac interventional/surgical procedure related. Myocardial infarction was defined when more than 2 of the following 3 criteria were met: chest pain or equivalent symptom complex, positive cardiac biomarkers, or typical electrocardiographic changes [17]. Data of patients with event at follow-up were blindly reviewed and the event was unequivocally assigned to the culprit vessel in case of acute myocardial infarction and target-vessel revascularization. In case the identification of the culprit vessel was not possible or feasible (i.e., cardiac death, no coronary angiography performed, or non-ST segment elevation myocardial infarction in patients with multivessel disease), the event was referred to all the

stenotic vessels of those patients [18]. The date of the last examination or consultation was used to determine the length of follow-up.

Statistical analysis

Continuous data are expressed as mean ± standard deviation and categorical data as percentage. A Student two-sample t-test and chi-square test were used to compare the differences in continuous and categorical variables, as appropriate. A P value <0.05 (two-sided) was considered statistically significant. Receiver operating characteristics (ROC) area under curve (AUC) was applied to evaluate the diagnostic ability of regional ITPD in identifying vessel-related event and to establish the best trade-off between sensitivity and specificity for different cut-off points of regional ITPD. Hazard ratios with 95% confidence intervals (CI) were calculated by univariable and multivariable Cox regression analysis. Variables showing a P value <0.05 at univariable analysis were considered for multivariable analysis. Annualized event rate (AER), expressed as % person-years or as % vessel-years, was calculated as the cumulative number of events divided by person-time or vessel-time. Event-free survival curves were obtained by the Kaplan-Meier method and compared with the log-rank test. Statistical analysis was performed using STATA software (ver. 12, College station, TX).

RESULTS

Among the overall population of 590 patients, follow-up was 92% complete, leaving 541 subjects for the analysis. Coronary angiography showed significant CAD in 296 patients; among them, 190 (64%) had single-vessel disease, 78 (26%) two-vessels disease and 28 (10%) three-vessels disease. During a median follow-up of 27 months (range 7-56 months) 31 cardiac events occurred (6% cumulative event rate with an annual event rate of 2.2% person-years). The events were cardiac deaths in 4 (13%) patients, non-fatal myocardial infarctions in 7 (23%), and late coronary revascularizations in 20 (64%) subjects. Clinical characteristics of patients with and without events are summed in Table 1. Patients with events had similar clinical features and cardiovascular risk factors as compared to patients without events. However, a higher prevalence of significant CAD at coronary angiography was observed in patients with events ($P<0.001$). Imaging findings of patients with and without events are summed in Table 2. As shown, patients with events had significantly higher values of stress TPD ($P=0.04$), ITPD ($P<0.001$) and left ventricular (LV) volumes (all $P<0.05$) as compared to patients without events.

Per-vessels imaging findings

Of the overall 1623 vessels analysed, 430 (27%) showed CAD ≥50% on coronary angiography while 1193 (73%) did not. In the vessels with CAD ≥50% as compared to those without, significantly higher regional stress TPD and ITPD (3.96±6.60 vs 2.72±4.91, and 1.62±2.29 vs 1.29±1.60, respectively, both P <0.001) were observed. Moreover, lesion-related events were observed in 39 (2%) vessels. Regional imaging findings according to vessels-related events are reported in Table 3. As shown, the prevalence of significant CAD was higher in vessels with events as compared to those without. Moreover, regional stress TPD and regional ITPD resulted significantly higher in vessels with lesion-related events as compared to those without (both P <0.001).

At ROC analysis, the AUC for the identification of vessel-related event was 0.81 (95% confidence interval, CI, 0.75-0.86) for regional ITPD. An ITPD value of 2 provided the best trade-off between sensitivity and specificity for identifying vessel-related event (Figure 1). Using this cut-off value, sensitivity and specificity for vessel-related event identification were 72% (95% CI 0.55-0.85) and 74% (95% CI 0.70-0.76).

Predictors of lesion-related outcome events

The results of Cox regression univariable and multivariable analysis are depicted in Table 4. CAD ≥50%, stress TPD ≥5% and ITPD ≥2% were significant predictors of target-related event. At multivariable analysis, only the presence of CAD ≥50% and ITPD ≥2% resulted as independent predictors of events. The AER according to CAD and ITPD are reported in Figure 2. As depicted, although the vessels with CAD ≥50% and ITPD ≥2% showed the highest AER, those with CAD <50% and ITPD ≥2% showed significantly higher AER as compared to those with ITPD <2% ($P < 0.05$).

Finally, event-free survival analysis by Kaplan-Meier method was performed according to CAD and ITPD as shown in Figure 3. The worst prognosis was observed in vessels with CAD ≥50% and ITPD ≥2% (log-rank $P<0.001$).

DISCUSSION

To our knowledge, this is the first study analysing the prognostic value of regional perfusion assessed by CZT camera in predicting vessel-related events, in patients with suspected or known CAD. Our data highlight that regional ITPD is a significant predictor of target-related events, also in vessels with no obstructive CAD. The prognostic significance of stress perfusion abnormalities assessed by CZT camera in the prediction of adverse cardiac events have been extensively addressed. All published data confirmed that the presence of a normal scan is associated with good outcome, whereas the degree of myocardial perfusion defect is a good predictor of cardiovascular events [8-11]. Engbers et al. [19] in 2017 demonstrated, in a very large cohort of 4057 patients with suspected CAD undergoing MPI with a CZT SPECT camera, that cardiovascular events occurred more in patients with abnormal than in those with normal MPI. Moreover, the events were more frequent along with increasing of the extension of reversible defects, as well as differences in terms of AER were observed between small and large total perfusion defects. In a recent prospective registry of patients with suspected or known CAD [20] it has been demonstrated that the extent of stress perfusion abnormalities detected by CZT SPECT had the best accuracy in

predicting cardiovascular death and myocardial infarction; in addition, the presence of ischemia involving >10% of the myocardium was also associated with all-cause death and late revascularization. Similarly, in our study population, patients experiencing cardiovascular events during follow-up showed a greater extent of perfusion abnormalities, as demonstrated by higher values of global stress TPD and ITPD observed in patients with event. Accordingly with our observations, Lima et al. [9] demonstrated that in 2930 patients with known or suspected CAD, the event rates were higher in patients showing greater extension of perfusion defects and ischemia, and lower values of LVEF. Of note, in our population LVEF was not associated with events, which may be explained by the overall normal values of LVEF in the whole study cohort. Despite these previous data suggest the prognostic value of ischemia assessed by CZT cameras, no studies have performed a regional analysis and analysed the potential interplay between perfusion results and angiographic findings. Our results showed that regional TPD and ITPD values were higher in vessels with significant CAD on coronary angiography, suggesting that there was a relationship between regional perfusion data and the presence of angiographically demonstrated CAD. Moreover, both regional stress TPD and ITPD resulted significantly higher in vessels with lesion-related events as compared to those without. In particular we found that an ITPD value of 2 provided

the best trade-off between sensitivity and specificity for identifying vessel-related event.

A previous report [21] investigated the relationship between prognostic value of MPI and the presence of obstructive CAD on coronary angiography, demonstrating that patients with abnormal CZT MPI and no obstructive CAD showed similar prognosis to patients with obstructive CAD and normal MPI. These results are quite consistent with our per-vessel analysis in which vessels with CAD <50% and ITPD ≥2% had not significant differences in terms of AER as compared to vessels with CAD ≥50% and ITPD <2%. However, in our study the presence of ITPD ≥2% even in absence of significant CAD is associated with higher AER and lower event-free survival as compared to vessels with ITPD <2%. Similar results were found in a recent study by Zampella et al. [22] in which the prognostic role of ITPD in predicting lesion-related outcome was investigated using PET/CT. Employing PET/CT, additional information about coronary artery calcium and myocardial blood flow can be derived and it suggests that the combined evaluation of multiple parameters derived from MPI such as regional coronary atherosclerosis and vascular function is useful has incremental value in predicting the occurrence of lesion-related events in the presence of significant CAD.

The advantages of using the new cardio-dedicated CZT camera are correlated to the possibility to reduce the dose of radiotracer administered to the patient, minimizing radiation exposure with a comparable or better efficiency than conventional camera [23]. Moreover, the introduction of cardio-dedicated CZT camera in routine clinical practice compared to conventional cameras has led to a great improvement in terms of image quality, due to higher spatial, temporal, and energy resolution, translating into higher diagnostic accuracy [24]. This is an important issue because, until the introduction of these cameras, reducing tracer dose would cause a dramatic reduction in image quality which could be balanced by increasing acquisition time. Different studies demonstrated that new advantages given by the technical evolution of the CZT machines are the lower dose tracer, shorten time of examination and high efficiency in quality images [25]. In addition, it has already been demonstrated the feasibility of dynamic acquisition by CZT cameras and its good diagnostic accuracy in identifying obstructive CAD [26]. Considering that new machines can be equipped with SPECT/CT, this may be a suggestion to potentially integrate multiple parameters in order to optimize risk stratification of patients with non-invasive techniques, increasing the usefulness of regional assessment.

CONCLUSION

Regional myocardial perfusion assessed by CZT camera demonstrated good reliability in predicting lesion-related events in patients with suspected or known CAD. In particular, an ITPD $\geq$2% showed high sensitivity and specificity in identifying high-risk vessels. These findings suggest that using regional evaluation of myocardial perfusion may help in refining risk stratification and in particular in identifying high risk coronary stenosis at higher risk of events, in which a change of patient's management can be hypothesized.

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FIGURE LEGEND

Fig. 1. Receiver operating characteristic area under the curve (AUC) for the identification of obstructive CAD using regional ischemic total perfusion defect (ITPD). A regional value of 2 provided the best trade-off between sensitivity (72%) and specificity (74%).

Fig. 2. Annualized event rates (AER) in vessels categorized according to the presence of significant CAD and ITPD cut-offs.

Fig. 3. Kaplan-Meier event-free survival curves according to the presence of significant CAD and ITPD cut-offs.

Table 1. Patients' characteristics according to events

	All patients (n=541)	With events (n=31)	Without events (n=510)	P value
Age (years)	64±10	64±9	64±10	0.93
Male gender	431 (80)	26 (84)	405 (79)	0.65
Diabetes mellitus	177 (33)	12 (39)	165 (32)	0.55
Hypertension	503 (93)	29 (93)	474 (93)	1.00
Dyslipidemia	469 (87)	24 (77)	445 (87)	0.17
Smoking history	346 (64)	24 (77)	322 (63)	0.05
Family history of CAD	317 (59)	17 (55)	300 (59)	0.71
Angina	175 (32)	12 (39)	163 (32)	0.44
Known CAD	472 (87)	29 (93)	443 (87)	0.41
CAD ≥50%	296 (55)	28 (90)	268 (53)	<0.001
1-vessel	190 (35)	13 (42)	177 (35)	
2-vessels	78 (14)	10 (32)	68 (13)	
3-vessels	28 (5)	5 (16)	23 (5)	

Values are expressed as mean value ± standard deviation or as number (percentage) of subjects

BMI, body mass index; CAD, coronary artery disease

Table 2. Imaging findings results according to events

	All patients (n=541)	With events (n=31)	Without events (n=510)	P value
TPD stress	9.06±12.74	13.55±13.36	8.78±12.67	0.04
TPD rest	6.61±13.23	7.58±12.26	6.55±13.29	0.67
ITPD	2.74±4.35	5.94±5.60	2.54±4.19	<0.001
EDV stress	101.26±52.51	130.10±91.89	99.45±48.60	0.002
ESV stress	52.18±46.23	73.43±79.37	50.84±43.11	0.009
EF stress	53.54±13.89	50.20±13.04	53.74±13.93	0.18
EDV rest	101.38±55.40	126.87±81.42	99.78±53.06	0.009
ESV rest	53.56±50.34	72.70±72.45	52.36±48.47	0.032
EF rest	52.55±14.08	49.53±13.44	52.74±14.11	0.23

Values are expressed as mean value ± standard deviation

TPD, total perfusion defect; ITPD, ischemic TPD; EDV, end diastolic volume;

ESV, end systolic volume; EF, ejection fraction

Table 3. Vessel-related imaging findings according to events

	All vessels (n=1623)	With events (n=39)	Without events (n=1584)	P value
CAD ≥50%	430 (26)	34 (87)	396 (25)	<0.001
Stress TPD, %	3.06±5.51	6.33±6.49	2.98±5.46	<0.001
ITPD, %	1.36±1.80	3.42±2.74	1.30±1.74	<0.001

Values are expressed as mean value ± standard deviation

CAD, coronary artery disease; TPD, total perfusion defect; ITPD, ischemic TPD

Table 4. Univariable and multivariable predictors of events

	Univariable Analysis		Multivariable Analysis	
	Odds ratio (95%CI)	P value	Odds ratio (95%CI)	P value
CAD≥50%	19.371 (7.575-49.538)	<0.001	16.610 (6.469- 42.643)	<0.001
Stress TPD ≥5%	4.275 (2.278-8.023)	<0.001	1.674 (0.824- 3.401)	0.15
ITPD ≥2%	5.341 (2.776-10.275)	<0.001	3.512 (1.684- 7.321)	0.001

CI, confidence interval, CAD, coronary artery disease; TPD, total perfusion defect; ITPD, ischemic TPD

FIGURE 1

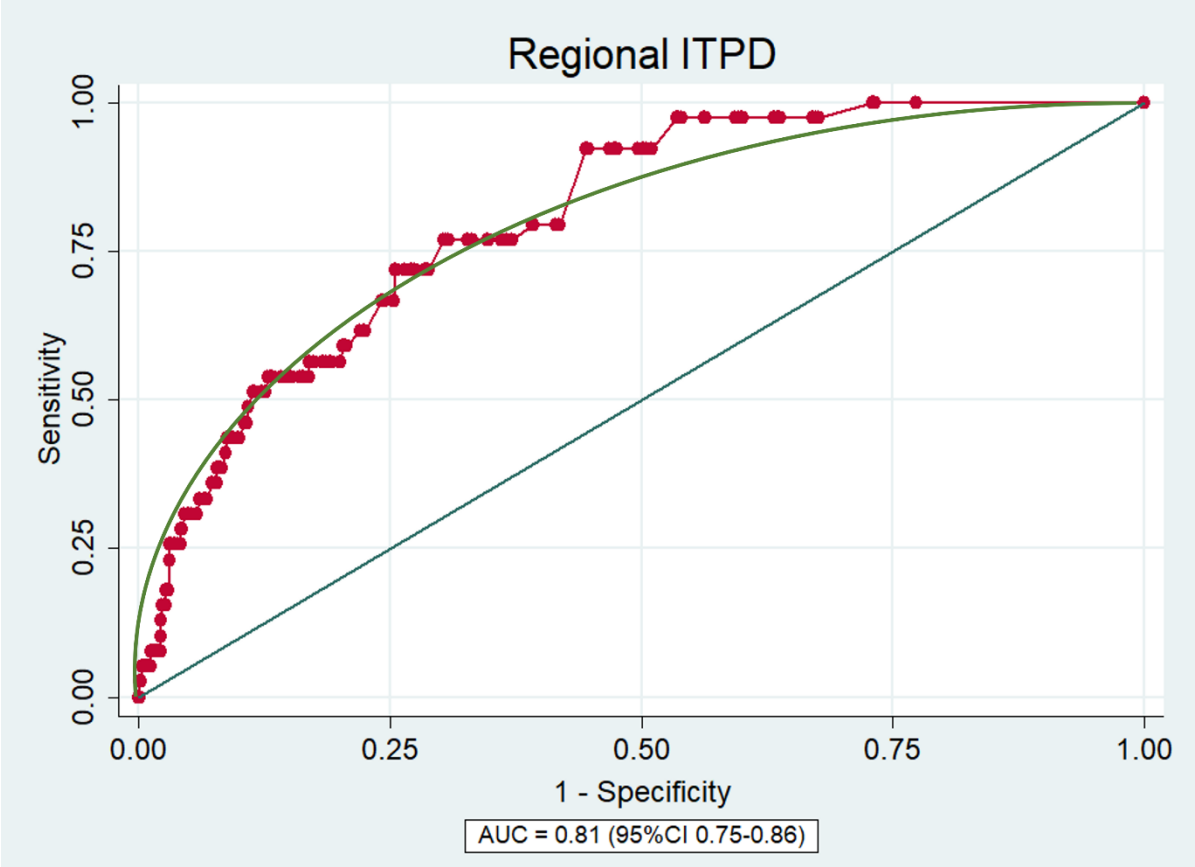

Fig. 1. Receiver operating characteristic area under the curve (AUC) for the identification of obstructive CAD using regional ischemic total perfusion defect (ITPD). A regional value of 2 provided the best trade-off between sensitivity (72%) and specificity (74%).

FIGURE 2

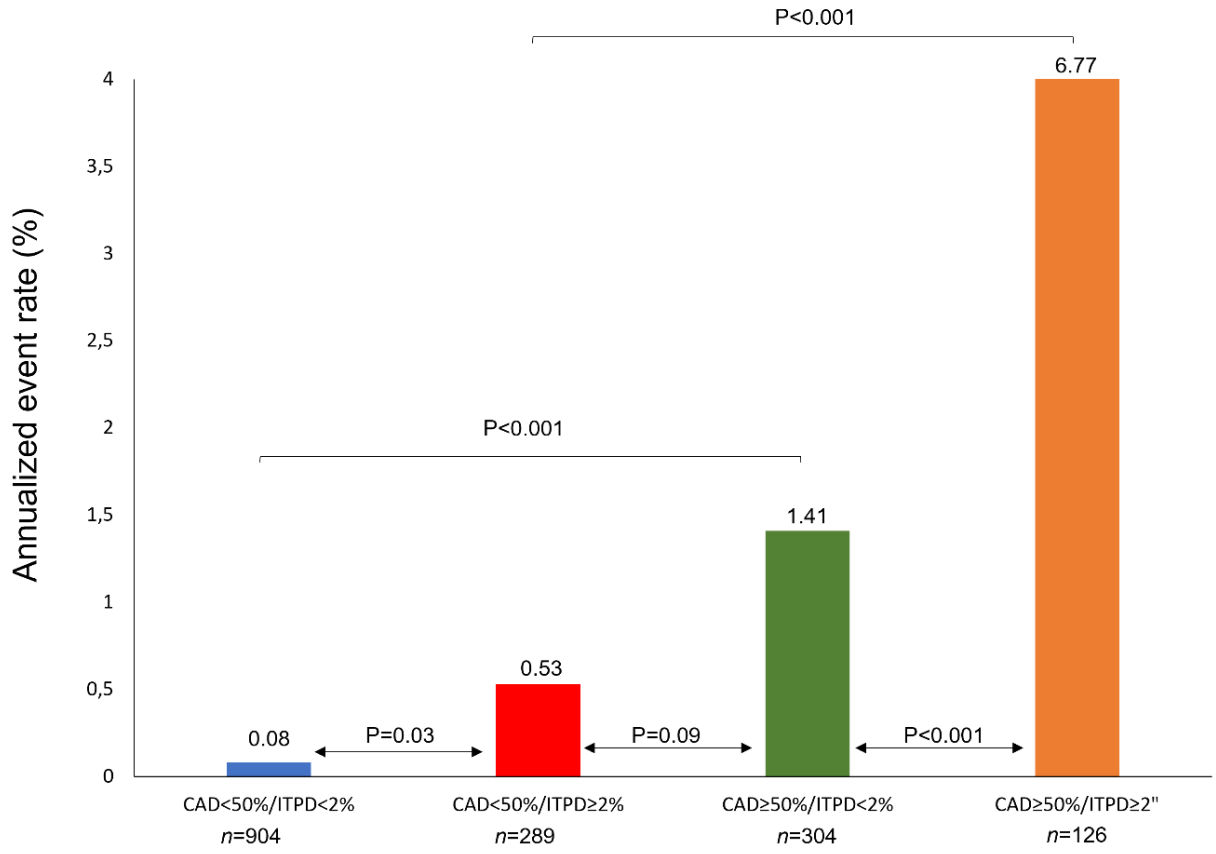

Fig. 2. Annualized event rates (AER) in vessels categorized according to the presence of significant CAD and ITPD cut-offs**.**

FIGURE 3

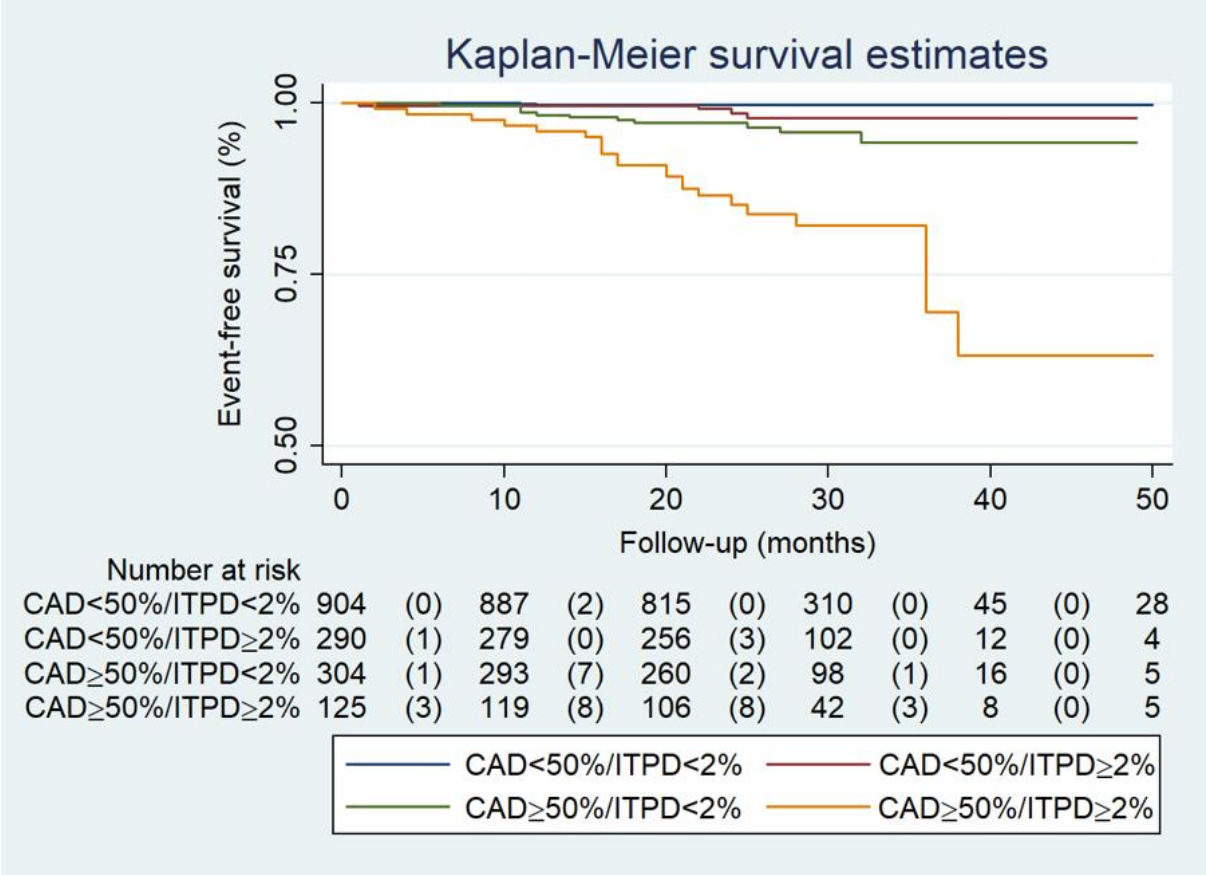

Figure 3. Kaplan-Meier event-free survival curves according to the presence of significant CAD and ITPD cut-offs.