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Research Article

Validation of regional wall motion abnormality assessment methods based on coronary CT-angiography with left ventricular function regarding prediction of hemodynamically relevant stenoses with instantaneous wave-free ratio

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Abstract

Purpose: To evaluate the concordance of different CT-based regional wall motion abnormality (RWMA) assessment methods with the presence of a hemodynamically relevant instantaneous wave-free ratio (iwFR) in the supplying coronary artery in patients who underwent both coronary CT-angiography (cCTA) and invasive coronary angiography (ICA).

Materials and Methods: All patients included in the study underwent a retrospective coronary cCTA protocol on a 2x192 slice dual-source-CT scanner system and one or more iwFR measurements during ICA. The myocardial segments were evaluated according to American Heart Association 17-segment bulls-eye diagram with three different RWMA assessment methods 1. semiquantitatively: visual (normokinetic/hypokinetic/akinetic) 2. quantitatively: Wall Thickness (15-11/10-6/5-1 mm) 3. quantitatively: Wall Motion (10-6,7/6,6-3,4/3,3-0 mm).

Results: 24 patients were included in this analysis. Stenoses in 35 coronary segments were examined with iwFR. 6 stenoses revealed hemodynamically relevant iwFR values. The quantitative assessment method demonstrated the highest sensitivity for the detection of hemodynamically relevant stenosis (83%), followed by the semiquantitative (visual) assessment method (67%). The semiquantitative (visual) assessment method showed the highest specificity (76%), followed by the ventricle wall thickness measurement (48%). The semiquantitative (visual) assessment method showed the highest negative predictive value for the presence of hemodynamically relevant stenosis (92%), followed by the quantitative wall motion assessment method (80%).

Conclusions: The semiquantitative (visual) assessment method performed best in exclusion of hemodynamically relevant stenosis. Retrospectively ECG-gated cCTA can be a valuable diagnostic method for evaluation of left ventricular regional and global function and help patients to avoid unnecessary invasive diagnostics.

Keywords: Acute lymphoblastic leukemia; relapse; polyradiculoneuritis; modified Hyper-CVAD.

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Introduction

Invasive coronary angiography (ICA) is the gold standard for diagnostic and treatment of CAD in high-risk patients [1]. Patients with stable angina or silent ischaemia undergo revascularization therapy when ischaemia or a hemodynamically relevant stenosis are detected [2]. The DEFINE-FLAIR and iFR-SWEDEHEART randomized trials demonstrated similar outcomes in FFR (fractional flow reserve) and iwFR (instantaneous wave-free ratio) guided revascularizations in patients with intermediate-grade stenosis [3, 4]. ICA combined with iwFR measurement is a reliable test for detection of hemodynamically relevant coronary stenosis [5]. It is safe, fast, more cost-effective, and does not require medication-induced hyperaemia compared to ICA combined with FFR measurement [5]. However, a significant proportion of patients undergoing ICA do not have hemodynamically rel-

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evant coronary stenosis and do not need revascularization in the end [6]. Meanwhile, the number of non-invasive assessment techniques of hemodynamic relevance of a stenosis increases rapidly and their role in detection and management of CAD becomes more significant [7]. According to the recent updates of the European Society of Cardiology (ESC) guidelines, along with non-invasive functional imaging methods (MRI, SPECT, PET-CT), coronary computed tomography angiography (cCTA) is recommended to be the initial diagnostic examination in patients with suspected CAD where CAD cannot be excluded by clinical examination [1]. cCTA is an accurate and reliable diagnostic method for CAD assessment. Today, its role according to the recent guidelines lies especially in the CAD assessment of symptomatic low- and intermediate-risk patients [1].

However, a meta-analysis performed by Knuuti et al (2018) showed that coronary CTA demonstrates high sensitivity and specificity in detection of anatomical stenosis, while exclusion accuracy of hemodynamically relevant stenosis compared to ICA combined with FFR measurement remains unsatisfactory [8].

Left ventricular (LV) function abnormalities are considered important markers of CAD along with perfusion assessment and anatomical examination of coronary arteries [9]. Several authors have reported high accuracy and reliability of ECG-gated cardiac computed tomography in assessment of LV function [10, 11]. In addition, since impaired regional LV motion is an important sign of myocardial ischemia, the regional LV function also needs to be reported along with the global LV function [12].

The aim of this study is to compare the efficacy of semiquantitative and quantitative regional LV function parameters derived from retrospectively ECG-gated cardiac computed tomography in comparison to the reference standard iwFR performed in the course of ICA in the diagnosis of hemodynamically relevant stenosis.

Materials and Methods

Study population

This was a retrospective method-comparison study. All examinations were clinically indicated. Patients were diagnosed and treated according to national and international guidelines. Local review board approval was waived due to the retrospective character of this study. The patient data were collected from the local database of the University Medical Centre Mannheim. Images acquired from the patients with clinical symptoms of chronic CAD who underwent both retrospectively ECG-gated cCTA examination and ICA combined with iwFR at the University Medical Centre Mannheim in the years 2017 and 2018, and who were diagnosed with one or more coronary artery stenosis with at least one lesion examined by means of iwFR were included in the study. Patients with more than one atherosclerotic plaque within a single coronary artery (tandem coronary stenosis) were excluded, due to known technical limitations associated with the iwFR measurement. Individuals with stenosis within ramus intermedius (RIM) were excluded as well, since RIM and its myocardial supply is highly variable [13].

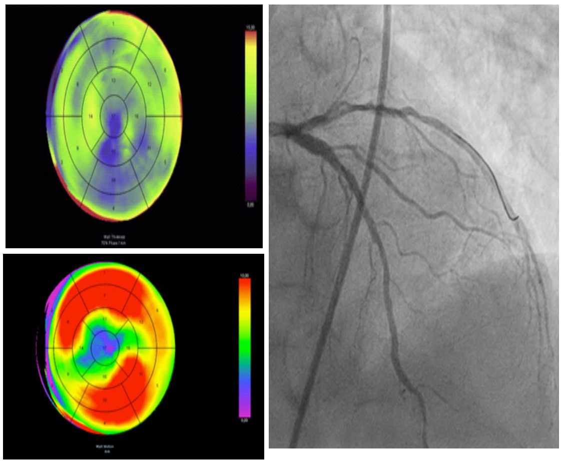
cCTA protocol

All CT examinations were performed with a third generation dual-source CT system (SOMATOM Force; Siemens Healthcare, Forchheim, Germany). Before the cCTA study, a noncontrast ECG-triggered CT scan was performed in all patients to assess the coronary calcium score and the cCTA scan was planned on these reconstructions. The retrospectively ECG-gated cCTA spiral acquisition included the following parameters: 0.25-second gantry rotation time, 2 × 192 × 0.6 mm detector collimation, 555 ± 231 (range, from 119 to 728) reference mAs, 80 ± 16 (range, from 70 to 120)-kV tube voltage, and pitch of 0.15. ECG-controlled tube current modulation was turned off in all patients. However, automated anatomic tube current modulation (CARE Dose4D, Siemens Healthcare) was used per default in all patients. Contrast medium timing was accomplished by using bolus tracking with a region of interest (ROI) placed within the descending aorta. Once a threshold of 100 HU had been exceeded within the ROI in the descending aorta, the scan automatically started after an additional delay of 5 seconds. The contrast agent administered was 400 mg/100 mL of iomeprol (Iomeron 400; Bracco Imaging S.p.A., Milan, Italy) for a total of 80 mL injected at a flow rate of 5 mL/s. This was followed by a pure saline chaser of 50 mL injected at the same flow rate. If no contraindications were present, patients were administered 0.8 mg nitroglycerine sublingually before cCTA. Patients with heart rates over 60 bpm additionally received 5 to 25 mL betablocker Beloc (metoprolol 1mg/ml) intravenously.

Image reconstruction and analysis

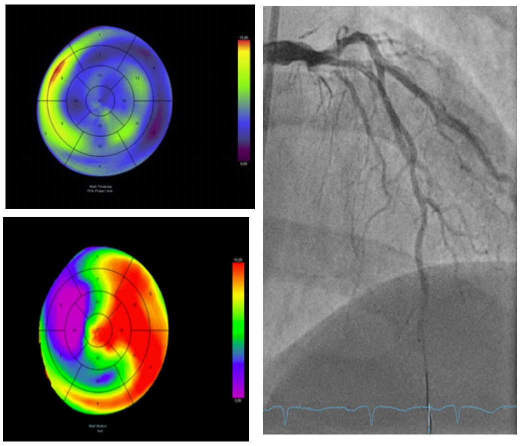
All contrast-enhanced cCTA data were reconstructed with a section thickness of 0.6 mm and an increment of 0.3 in the transverse plane and analysed on a multi-modality 3D-enabled workstation Cardio (Syngo VE36A; Siemens). Functional images were reconstructed with a matrix of 256x256 with a slice thickness of 1.5 mm and increment of 1.3 mm, of the full 0-100% heart cycle with either 11 (n= 16) or 21 (n= 8) phases. Epicardial and endocardial LV contours were automatically determined and manually corrected in all phases 0-100% of the heart cycle by one board-certified radiologist (S.J.) with over 6 years of expertise in cardiac CT imaging. Quantitative automated assessment of LV ejection fraction, myocardial mass ED, ED volume, ES volume, and cardiac output was calculated. End-systole and end-diastole were automatically determined (**Table 2**).

For quantitative assessment of regional wall motion abnormalities (RWMA) polar maps were automatically generated (**Figure 1** and **2**): regional myocardial wall motion, and wall thickness were depicted in the form of two polar maps.



A B

Figure 1: Case of a 78-year-old patient without hemodynamically relevant stenoses. A: the polar maps generated with syngo.via workflow Cardiac (Syngo VE36A; Siemens) demonstrate normal myocardial wall thickness and motion B: invasive coronary angiography without significant stenoses.



A B

Figure 2: Case of a 48-year-old patient with symptoms of angina pectoris and a significant stenosis in the LAD (iwFR = 0.42). A: the polar maps generated with syngo.via workflow Cardiac (Syngo VE36A; Siemens) show myocardial wall thickening and hypokinesia in the LAD territory. B: invasive coronary angiography with iwFR measurement in the LAD.

Radiological assessment of RWMA

For the evaluation of regional wall motion (RWM), the myocardium was separated into 17 segments (basal segments 1-6; mid-cavity segments 7-12; apical segments13-16; apex 17) according to American Heart Association (AHA) bulls-eye diagram [14] (**Figure 3**). RWMA were evaluated with one semiquantitative (visual) and two quantitative assessment methods. RWM was visually assessed for each segment with a 3-point Likert scale from 1 to 3: 3 for normal wall motion, 2 for hypokinetic segments, and 1 for akinetic segments. The quantitatively assessed parameters evaluated in this study were the parameters LV wall thickness and wall motion. All quantitative values corresponded to the colors on the polar maps. The color that covered more than 50% of the segment determined the quantitative value. Wall thickness was uniformly assessed at 70% of RR. Ranges between 6 and 10 mm were considered as normal and were green on the polar map. Myocardial segments with a wall thickness of 11-15 mm and 1-5 mm we evaluated as hypercontractile and hypocontractile, respectively. On the polar map the maximal values were yellow and red, and the minimal values were purple and blue. Cardiac wall motion was depicted as total movement in mm between 0-100% RR of each myocardial segment: values between maximal contraction and maximal relaxation from 6.7 to 10 mm we classified as normal. The normal values were yellow and red on the polar map. Wall motions measured 3.4-6.6 mm and 0-3.3 mm we estimated as hypokinesia and akinesia conditions, respectively (between purple and green on the polar map).

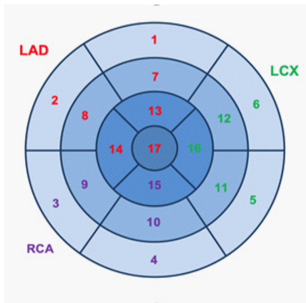


Figure 3: Myocardial segments according to American Heart Association (AHA) 17-segment bulls-eye diagram. LAD: left anterior descending; LCX: left circumflex; RCA: right coronary artery.

ICA

All participants underwent ICA at the University Medical Centre Mannheim. First, each coronary vessel was evaluated visually by an experienced interventional cardiologist. If required, pathological findings or stenoses with unclear hemodynamic relevance were assessed by iwFR measurements. Unclear hemodynamic relevance was defined as a coronary artery in which the stenosis of questionable physiology with a 40–70% stenosis of the diameter on visual assessment. iwFR measurements were obtained using a coronary-pressure guidewire (Verrata™pressure wire, Volcano Corporation, Koninklijke Philips N.V. Amsterdam, The Netherlands). The pressure sensor was positioned distal to the stenosis. The optimal diastolic interval with minimized and constant microvascular resistance for pressure measurement was calculated by a dedicated software (Volcano Corporation, Koninklijke Philips N.V. Amsterdam, The Netherlands). Stenosis with iwFR equal or less than 0.89 units considered to be hemodynamically relevant [5]. Coronary arteries with stenotic plaques and iwFR equal or less than 0.89 units underwent percutaneous coronary intervention (PCI) with implantation of a drug-elution stent.

Statistics

Statistical analyses were performed using MedCalc for Windows, version 19.1 (MedCalc Software, Ostend, Belgium). For the descriptive analysis mean, standard deviation, range, PPV, NPV, PLR, NLR, prevalence, AUC as well as sensitivity and specificity have been assessed. Differences between the modalities are described by the inter-rater agreement and its 95% confidence interval (CI) The Kappa (k) index was calculated as well for this purpose.

Results

Patient population

Twenty-four patients met the selection criteria. Nine of them were females and 15 males. The age of participants was equal to 68 ± 13 (range, from 46 to 89) years at the time of ICA. Demographic data of the study population are shown in (Table 1).

Table 1: Demographic data, findings of coronary computed tomography (cCTA) and invasive coronary angiography (ICA).

Parameter	
Patients (n)	24
Age (years ±SD; range)	68 ± 13; 46 - 89
Men (n (%))`	15 males (62.5%)
iwFR ≤0.89 (n (%))	6 (17%)
CT-FFR ≤0.8 (n (%))	7 (20%)
Grade 5 (severe) stenosis in cCTA (SCCT guidelines) (n (%))	15 (43%)
Agatston score (mean ± SD; range)	864 ± 871; 109 - 3246
Patients with Agatston score >400	13 (72%)
Interprocedural time between cCTA and ICA (days mean ± SD; range)	11.9 ± 22,59; 0 - 89

Data are mean ± standard deviation (SD). iwFR: instantaneous wave-free ratio. FFR: fractional flow reserve

Diagnostic procedures

cCTA and ICA combined with iwFR measurement

The patients underwent cCTA and ICA combined with iwFR measurement in our radiology and cardiology department between November of 2017 and December of 2018. Twenty patients out of 24 underwent cCTA followed by ICA. In four patients cCTA was performed after diagnostic ICA without coronary angioplasty. The average time between cCTA and ICA was 11.9 (range, from 0 to 89) days. The findings of cCTA are demonstrated in (**Table 1**).

During the ICA procedure iwFR measurement was performed in 35 coronary segments with luminal narrowing. iwFR was performed mostly within LAD (49%), followed by LCX (29%), RCA (20%), and LM (3%). (Table 2 and Figure 4). Six out of 35 stenoses (17%) revealed pathologic iwFR values (≤0.89), indicating hemodynamically relevant stenosis. According to the Society of Cardiovascular Computed Tomography (SCCT) guidelines, the detected stenoses were graded moderate (grade 4) or severe (grade 5)[15]. Twenty grade 4 and 15 grade 5 stenoses were evaluated.

Table 2: LV functional parameters.

Parameter	Mean ±standard deviation	Largest values	Lowest values	Normal values given
EF (% ±SD)	64 ±19	83	19	56-78
Myocardial Mass ED (g± SD)	120 ±42	197.7	54.5	118-238
Stroke Volume (ml± SD)	102 ±33	173.2	52	51-133
ED Volume (ml ±SD)	175 ±80	342.6	74.5	77-195
ES Volume (ml ±SD)	73 ±76	278.9	20.9	19-72
Cursor Volume (ml ±SD)	135 ±71	301.6	49.7	-
Cardiac Output (l/min± SD)	6 ±1	9.9	3.8	2.82-8.82

EF: ejection fraction; ED: end-diastolic; ES: end-systolic

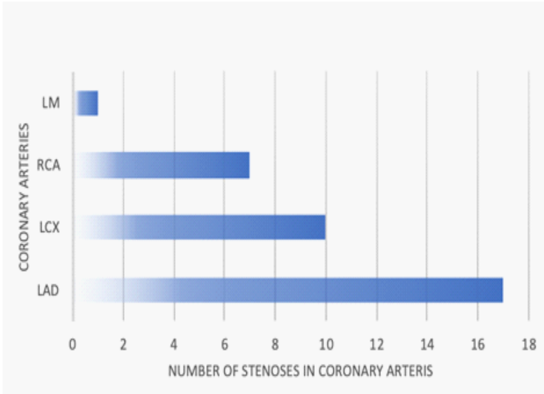


Figure 4: Number of stenoses in coronary arteries and segments. LAD: left anterior descending; LCX: left circumflex; RCA: right coronary artery; LM: left main.

CT-based RWMA assessment: semiquantitative and quantitative methods

The quantitative assessment method of ventricle wall motion demonstrated the highest sensitivity for the detection of hemodynamically relevant stenosis (83.3%) followed by the semiquantitative (visual) assessment method (66.6%). However, the specificity of the quantitative method was low (13.7%). The semiquantitative (visual) assessment method showed the highest specificity for the detection of hemodynamically relevant stenosis (75.8%) followed by the ventricle wall thickness measurement (48%). It was shown that the wall thickness quantitative assessment was the method with the lowest sensitivity (16.6%).

The predictive ability of the CT-based RWMA assessment to identify the presence as well as the absence of hemodynamically relevant stenosis was evaluated too. Meanwhile, both, the highest positive and the lowest negative likelihood ratios was gained using the visual assessment method (2.7 and 0.4, respectively), followed by the quantitative methods (wall thickness measurement 0.97 and 1.7, wall motion assessment 0.3 and 1.2, consecutively). The semiquantitative (visual) assessment method showed the highest positive and negative predictive values for the presence of hemodynamically relevant stenosis (36% and 91.7 %, respectively), followed by the quantitative wall motion assessment method (16.5% and 80%, respectively). The lowest positive and negative predictive values were seen with the left ventricle wall thickness measurement (6% and 48%, consequently). The inter-rater agreement between the ICA combined with iwFR and the CT-based RWMA assessment for the detection of hemodynamically relevant stenosis was calculated using the Kappa (k) index. The agreement between ICA combined with iwFR and the CT-based RWMA visual assessment method was low (K-value of 0.32). There was no correlation between the results of the ICA combined with iwFR and the quantitative assessment of wall thickness and wall motion (K-values of -0.21 and -0.01, respectively).

See Table3 for detailed results.

Table 3: Diagnostic accuracy of cCTA-based semiquantitative and quantitative RMWA assessment methods compared to invasive iwFR.

Parameter	Sensitivity (%)	Specificity (%)	PPV	NPV	PLR	NLR	AUC	K-value	Disease Prevalence (%)
			(%)	(%)					
Visual assessment	67	76	36	92	2.8	0.4	0.7	0.32	17
Wall thickness	17	48	6	74	0.3	1.7	0.3	-0.21	17
Wall motion	83	14	17	80	1	1	0.5	-0.01	17

PPV: positive predictive value; NPV: negative predictive value; PLR: positive likelihood ratio; NLR: negative likelihood ratio; AUC: area under the curve

Discussion

Accurate detection and revascularization of functionally relevant coronary lesions improves long-term outcomes and prevents reinterventions [16, 17]. Thus, functionally complete revascularization is the prime goal of PCI [2]. The reference standard is the invasive assessment of stenoses with iwFR or FFR measurement. None of the investigated non-invasive imaging methods for evaluation of hemodynamical relevance are recommended by the 2018 ESC/EACTS Guidelines for functional assessment of coronary stenosis [2].

RWMA targeted in our study as surrogate parameter for hemodynamically relevant stenoses can be caused by stunned or hibernating myocardium and revascularization may significantly improve myocardial perfusion [5]. The purpose of the present study was to evaluate the concordance of three different retrospectively ECG-gated cCTA-based RWMA assessment methods with the presence or absence of a hemodynamically relevant iwFR in the supplying coronary arteries in patients with suspected CAD who underwent both cCTA and iwFR measurement in the course of ICA.

Our study is one of the few investigations comparing noninvasive imaging with functional assessment of coronary plaques for detection of hemodynamically relevant stenosis where cCTA data was correlated with iwFR measurements. Baumann and colleagues (2020) were the first to compare cCTA with iwFR values. They demonstrated that cCTA-based morphological and anatomical plaque analysis can enhance the detection of hemodynamically significant coronary stenosis [18]. In 2017, Danad et al. analyzed 23 scientific publications where authors compared different cardiac imaging methods with FFR values and demonstrated superiority of CMR (cardiovascular magnetic resonance) in detection of ischaemia-causing CAD [19]. According to the meta-analysis, cCTA alone showed poorer diagnostic accuracy than CMR, though CT-FFR showed high sensitivity in detection of hemodynamically relevant stenosis. Baumann et al. (2020) reported non-inferiority of machine learning CT-FFR compared to ICA combined iwFR [20]. However, despite high sensitivity CT-FFR has several limitations and its implementation into routine practice remains challenging [21]. In their recent trial Nagel et al. (2019) demonstrated non-inferiority of myocardial-perfusion CMR to FFR with regard to detection of hemodynamically relevant stenosis [22]. The recent meta-analysis of 28 investigations (Ullah et al. 2020) verified high specificity and sensitivity of stress-CMR compared to FFR and recommends CMR for confirmation and exclusion of CAD in both high-risk and low-risk patients [23]. The results of the above-mentioned publications are not surprising since it is well known that CMR is the reference standard in cardiac imaging for LV function assessment [24]. ESC recommends CMR for assessment of global and regional LV function for its highly accurate diagnostic and prognostic performance in patients with stable CAD [1]. However, investigations where authors evaluate global and regional LV function along with coronary stenosis severity on cCTA ensure adequate quality of CT based RWMA assessment.

Seneviratne et al. demonstrated that regional left ventricular function assessment adds diagnostic value to cCTA examinations [12]. Schlett et al. showed a significant improvement in prediction of major adverse cardiovascular events by addition of RWMA analysis to the cCTA [25]. In their recent investigation Liu et al. (2020) reported that evaluation of RWM during ECG-gated single-photon emission computerized tomography myocardial perfusion imaging has additional diagnostic value in detection of obstructive CAD [26]. Kaniewska et al. demonstrated agreement between CT and MRI in detection of RWMA in their meta-analysis [11]. Moreover, Kaniewska et al. and Kang at el. recommended cCTA as an alternative non-invasive method for LV function assessment [11, 27]. In the present study we compared for the first time cCTA-based RWMA methods with ICA combined with iwFR in assessment of coronary plaques and stenoses in patients with stable CAD. Our results demonstrate superiority of the semi-quantitative (visual) assessment method over the quantitative (wall motion and wall thickness assessment) methods in exclusion of hemodynamically significant coronary stenoses with a negative predictive value of 91.7 % and specificity of 75.8 %. Though the quantitative assessment of wall motion had the higher sensitivity (83.3 %), the specificity of this method was quite low (13.7 %). The statistical analysis demonstrates that inter-rater reliability regarding the semiquantitative visual assessment method was also low (K-value of 0.32), while there was no correlation between the assess quantitative methods and iwFR values. This low correlation values are not surprising, as not all hemodynamically relevant stenosis necessarily lead to regional wall motion abnormalities in rest, without physical or medical stress induction. Our results show that cCTA-based RWMA visual assessment can add diagnostic value in non-invasive exclusion of hemodynamically relevant coronary stenoses and help patients to avoid unnecessary invasive diagnostics. Last but not least, it is well known that CT is a cost-effective and widely available modality [28]. cCTA has greater acceptance among patients than ICA and CMR and can be a valuable diagnostic method for assessing ischaemia-causing CAD especially in patients who have contraindications for cardiac MRI [29].

There are several limitations in this study. The first, and the most important, is the fact that the study was performed retrospectively, and the decision of the diagnostic method was made on an individual basis by cardiologists depending on severity of symptoms and individual preference rather than by randomization. This could be the reason why some patients without hemodynamically relevant stenoses underwent ICA before cCTA. Secondly, the study is limited by a small study cohort. Furthermore, only 17% of stenoses revealed hemodynamically relevant iwFR values (≤0.89). This may be explained by the fact that patients with hemodynamically relevant stenoses had more severe symptoms and directly underwent ICA with stent implantation at the target coronary artery segment. As a rule, these patients do not receive a cCTA examination before ICA. However, it has to be stated, that also patients with stable angina or even silent ischemia do profit with regard to prognosis from functionally-guided revascularization and these patients often undergo cardiac CT instead of invasive coronary angiography in the first place and they would greatly profit from a reliable non-invasive CT parameter correlating well with iwFR results. Thirdly, iwFR has not been validated for patients with LMS stenosis [2]. However, Warisawa and colleagues (2020) reported good long-term outcomes in patients with LM stenosis in whom revascularization was performed or deferred on the basis of iwFR values [30].

In our study myocardial segments were evaluated according to AHA 17-segment bulls-eye diagram without taking into consideration de-facto coronary arterial dominance. What is more, we performed only CT-based RWMA assessment and were not able to correlate RWMA to cardiac MRI (the reference standard for RWMA assessment), since MRI scans were not routinely performed our study cohort. Lastly, we only assessed wall thickness at one single timepoint of the cardiac cycle, namely at RR 70%, which is the default time-point visualized in syngo.via. Assessing more timepoints, especially in systole, might have led to different results, but was out of the scope of this analysis. In conclusion, this is to the best of our knowledge the first study where different RWMA parameters derived from retrospectively ECG-gated cCTA datasets were compared to ICA combined with iwFR measurements in terms of determining hemodynamically relevant stenoses. Our results demonstrate non-inferiority of the cCTA-based semi-quantitative (visual) assessment method to ICA combined with iwFR in exclusion of hemodynamically relevant stenoses in coronary arteries. Furthermore, our results showed that the quantitative assessment methods (wall thickness and wall motion assessment) did not provide any additional diagnostic value. Our findings suggest that cCTA-based semiquantitative (visual) RWMA assessment should be included in radiological reports along with anatomical and morphological plaque characterization in case of coronary CT angiographies being performed with retrospective ECG-gating. We believe that retrospectively ECG-gated cCTA can be a valuable diagnostic method for assessment of the coronary arteries and as a one-stop-shop examination additional assessment of LV regional and global function especially in patients who have contraindications for cardiac MRI.

Statements and Declarations: The authors declare no conflict of interest.

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