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Dual quantitative coronary angiography accurately quantifies intracoronary thrombotic burden in patients with acute coronary syndrome: Comparison with optical coherence tomography imaging

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ABSTRACT

Background: Dual quantitative coronary angiography (QCA) has been recently tested for assessment of intracoronary thrombus volume in experimental models. The present study aimed to validate dual QCA in vivo for the assessment of thrombus burden by exploring the correlations between dual QCA-thrombus volume and optical coherence tomography (OCT)-derived indices of thrombotic burden.

Methods and results: Fifty-one patients with ACS and angiographic evidence of thrombus undergoing OCT of the culprit lesion before stenting were included. Dual QCA-thrombus volume was calculated as difference between edge-detection and video-densitometry area functions along the target segment. Culprit lesion was categorized using the Ambrose's and AHA/ACC angiographic classifications. Thrombus volume (mean thrombus area × thrombus length), thrombus burden [(mean thrombus area/mean lumen area) x100] and Prati thrombus score (number of quadrants with thrombus) were measured by OCT, and the presence of plaque rupture (PR) or intact fibrous cap (IFC) was assessed. Dual QCA-thrombus volume correlated significantly with OCT-thrombus volume ($R = 0.791$), thrombus burden ($R = 0.767$) and Prati thrombus score ($R = 0.600$) (all $p < 0.001$). Dual-QCA thrombus volume was significantly higher in patients with PR compared with those with IFC (3.48 mm^3 [1.45–11.26] vs. 1.69 mm^3 [0.09–5.02], $p = 0.013$). Compared with IFC, PR showed higher prevalence of eccentric type II Ambrose lesion (41.7% vs. 7.4%, $p = 0.004$), complex B2/C lesion (87.5% vs. 55.6%, $p = 0.012$), and heavy calcification (29.2% vs. 3.7%, $p = 0.013$).

Conclusions: Dual QCA analysis appears to be a promising tool for quantification of intracoronary thrombus in vivo. This novel methodology may be useful to guide intracoronary thrombus removal during percutaneous coronary intervention and to aid prognostic stratification in patients with ACS.

1. Introduction

Coronary thrombosis caused by plaque rupture (PR) or erosion is the most frequent underlying mechanism of acute coronary syndromes (ACS) and sudden cardiac death [1,2]. A large coronary thrombus burden (TB) is associated with higher rates of distal embolization, stent thrombosis, and long-term adverse cardiac events [3,4]. Pharmacological and mechanical strategies are routinely used with the aim of reducing TB and minimizing its adverse effects [5–9]. An accurate quantification of the TB is therefore pivotal for understanding the pathophysiology, predicting prognosis, and optimizing coronary interventions in patients with ACS. Angiographic thrombus grading scales,

Abbreviations: QCA, quantitative coronary angiography; OCT, optical coherence tomography; ACS, acute coronary syndrome; STEMI, ST-segment elevation myocardial infarction; TB, thrombus burden; PR, plaque rupture; IFC, intact fibrous cap.

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such as the Thrombolysis In Myocardial Infarction (TIMI) thrombus grading [10] and its simplified version proposed by Sianos et al. [4], are commonly used to estimate coronary TB. However, these analyses are notoriously subjective and have poor sensitivity. A novel method of quantitative coronary angiographic (QCA) analysis, based on both edge-detection and video-densitometry techniques (i.e., dual QCA), has been recently developed for enhanced quantitative assessment of intracoronary TB [11]. This technique provides high intra- and inter-observer agreements, and shows higher sensitivity for the detection of thrombus volume changes in response to pharmacological treatment as compared with the TIMI thrombus grading [11]. However, this methodology has never been validated for thrombus quantification in vivo, thus precluding its clinical use in patients with ACS undergoing percutaneous coronary intervention, as well as its potential role for assessment of thrombus volume as surrogate endpoint in clinical trials.

The aim of the present study was to validate dual QCA in vivo, by exploring the correlations between dual QCA-thrombus volume and multiple indices of TB measured by optical coherence tomography (OCT) in patients with ACS, which is considered to be the modality of choice for the identification and quantification of intracoronary thrombus [12].

2. Material and methods

2.1. Study population and procedures

Study patients were identified from the "A. Gemelli" Hospital (Rome, Italy) OCT database, and from the Oxford Heart Centre (Oxford, United Kingdom) OCT database (recruited as part of the prospective Ox-AMI study – REC number 10/H0408/24) [13]. Inclusion criteria were: i) diagnosis of ACS; ii) OCT imaging of the culprit lesion before stenting; and iii) angiographic evidence of thrombus at the culprit lesion. Exclusion criteria were: i) low angiographic image quality (i.e., absence of at least 2 coronary angiograms with projections separated by >45° and/or poor angiogram quality); or ii) low OCT image quality (e.g., suboptimal blood clearance). The culprit lesion was identified based on angiographic findings, electrocardiographic changes, and/or left ventricular wall motion abnormalities. Angiographically identifiable thrombus was defined as the presence of haziness or filling defect within the coronary lumen, surrounded by contrast dye, seen in multiple projections [14]. STEMI was defined as chest pain lasting at least 30 min, new persistent ST-segment elevation >2 mm in at least two contiguous leads or new left bundle-branch block, cardiac troponin T rise and/or fall, and/or new regional wall motion abnormalities. NSTE-ACS was defined as new-onset angina, progressive crescendo pattern of angina or angina at rest with normal levels [unstable angina pectoris (UAP)] or raise and/or fall [NSTE-myocardial infarction (NSTEMI)] of cardiac troponin T levels. Baseline coronary angiograms were recorded with full contrast injection before the insertion of a guidewire and the OCT catheter. Coronary angiograms acquired after wire passage and thrombus aspiration were used for dual QCA analysis of thrombus volume. Thrombus aspiration and glycoprotein IIb/IIIa (GpIIb/IIIa) inhibitors use were both left to the operator's discretion. OCT pullback of the culprit vessel was performed after intracoronary administration of nitroglycerin (100–200 μg), using an FD-OCT system (C7-XR, St. Jude Medical, St. Paul, MN at "A. Gemelli" Hospital; or ILUMIEN OPTIS, St. Jude Medical, St. Paul, MN at both "A. Gemelli" Hospital and Oxford Heart Center). An automated pullback was initiated at a speed of 20 mm/s (C7-XR, 100 frames/s) or 36 mm/s (ILUMIEN OPTIS, 180 frames/s), in concordance with blood clearance using contrast medium. Institutional review board approval was given by the local ethics committees of "A. Gemelli" Hospital and Oxford Heart Center, and each patient gave written informed consent.

2.2. Angiographic analysis

A validated, automated software with edge contour detection and video-densitometry features (CAAS 5.9, Pie Medical Imaging, Maastricht, The Netherlands) was used for qualitative angiographic and dual QCA analyses. Angiographic analysis was performed by two independent investigators blinded to clinical, laboratory and OCT data. The basic principle on which video-densitometry relies is the existing relationship between the attenuating power of the lumen filled with contrast medium, which is a function of the luminal area, and the X-ray image intensity [11]. Video-densitometry relies on the calibration of the system using a reference densitometric profile, which is assessed in a segment of known dimensions [11]. Based on the densitometric profile of the adjacent, non-stenotic (i.e., reference) segment, in which luminal area was geometrically calculated by edge detection and assuming a circular luminal shape, transformation from density to area units was automatically carried out by the CAAS system for each scan line perpendicular to the vessel centerline along the studied segment. The difference between edge detection and video-densitometry areas for each scanline along the studied segment provides an estimation of the volume of thrombus in the target segment [11]. Angiographic and dual QCA analyses were performed after thrombus aspiration and at the same time points of the OCT analysis. After selection of end-diastolic frames and proper calibration using the tip of the guiding catheter, a vessel segment corresponding to the stenosis *plus* the adjacent reference segments was manually drawn on the target angiogram, and a centerline of the target segment was automatically determined by the CAAS software. The subsequent analysis of the brightness profile of individual scanlines perpendicular to the derived centerline automatically generated the edges of the luminal borders of the target coronary segment. At the site of the thrombotic lesion, the operator manually drew the luminal edges based on the expected contour in the absence of thrombus or stenosis. A densitometric analysis was automatically carried out by the CAAS system, with conversion of the density area units of each scanline to absolute area values, using the densitometric profile of adjacent, non-stenotic segments as reference [11]. Intracoronary *thrombus volume* (i.e., obstructive volume), expressed in mm^3, was automatically calculated as difference between edge detection and video-densitometry area functions along the target segment, as previously described [11]. Dual QCA-thrombus volume measurement was carried out on two different angiographic projections, and the averaged value was calculated. In addition to dual-QCA derived thrombus volume, TIMI flow grade and thrombus grade (TG) were determined, as previously described [4,10,15]. Culprit lesions were morphologically classified as "non-complex" (type A/B1) or "complex lesions" (type B2/C) according to the AHA/ACC coronary lesion classification system [16]. Based on the Ambrose's lesion classification, culprit lesions were further categorized into four types: 1) *concentric lesion*: symmetric stenosis with smooth or only slightly irregular borders; 2) *type I eccentric lesion*: asymmetric stenosis with smooth borders and a broad neck; 3) *type II eccentric lesion*: asymmetric stenosis with irregular borders or scalloped profile; 4) *lesion with multiple irregularities*: three or more serial and severe (>70%) closely spaced obstructions [17]. The presence of heavy calcification was also recorded, defined as persisting opacification of the vessel wall visible in more than one projection at the site of the target lesion [18]. Minimum lumen diameter (MLD), reference diameter (RD), diameter stenosis, and lesion length were finally measured by QCA.

2.3. OCT analysis

OCT image acquisition was achieved after thrombus aspiration (when performed) and prior to stenting. The number of passes with the thrombectomy catheter was at the operator's discretion, and multiple passes were allowed before imaging. OCT analysis was performed at the same time points chosen for the measurement of thrombus volume by dual QCA. Analysis was performed at 0.2 mm intervals (i.e., every frame) by two independent investigators blinded to angiographic, clinical and laboratory data, using a proprietary software for offline analysis (LightLab Imaging, Westford, Massachusetts). *Thrombus* was defined as an irregular mass protruding into the lumen attached to the vessel wall or discontinuous from its surface [19,20], and categorized as either red thrombus, defined as a highly backscattering mass with high attenuation, or white thrombus, appearing as a less backscattering, homogeneous mass with low attenuation, according to the predominant pattern [19,20]. In each frame, the *number of quadrants* encroached by thrombus was determined [7,19]. Each frame was additionally analyzed for the assessment of *thrombus area (TA)*, calculated as *lumen area* (LA) – *flow area* (FA) [21]. Flow area represented the residual coronary lumen not occupied by thrombus [21]. *Thrombus length* was measured as distance between the first and last frames containing thrombus [21,22]. Based on the above mentioned measurements, the following indices of TB were derived:

1) *Prati thrombus score*: sum of the number of quadrants containing thrombus in each cross-section along the lesion length [7,19];
2) *Thrombus volume* (mm^3): mean TA (mm^2) × thrombus length (mm) [21,22];
3) *Thrombus burden* (%): [mean TA (mm^2) / mean LA (mm^2)] × 100 [21].

The culprit lesion was classified into OCT-PR or OCT-IFC, as previously described [23–25]. *OCT-PR* was defined as a discontinuity of the fibrous cap leading to a communication between inner plaque core and coronary lumen [25]. *OCT-IFC* included both plaque erosion, defined as the presence of thrombus overlying a plaque without signs of disruption, and smooth plaques without overlying thrombus [23,24]. Representative images of dual QCA and OCT analyses in patients with OCT-PR and OCT-IFC are shown in Fig. 1 and Supplementary Fig. 1, respectively.

2.4. Statistical analysis

Categorical data were expressed as counts and percentages, and compared using the Chi-square or Fisher's exact test. After assessing data distribution using the Kolmogorov-Smirnov test, continuous data were presented as mean ± standard deviation or median (interquartile range) as appropriate, and compared using Student's *t*-test or Mann–Whitney *U* test. Logarithmic transformation of thrombus volume, thrombus score and thrombus burden data was performed to achieve normal distribution. Then, correlation between log-transformed values of dual QCA-thrombus volume and OCT-derived thrombus measurements was assessed using linear regression analysis. To enable log-transformation of zero values (i.e., cases with no detection of thrombus) a neutral constant (i.e., value 1) was added to all measurements before transformation. Bland-Altman plot was used to evaluate the consistency between dual QCA and OCT-derived thrombus volume. Intra- and inter-observer agreement of dual QCA-thrombus volume measurements was assessed by intraclass correlation coefficient (ICC) based on the random effects analysis of variance model. A p value <0.05 was considered statistically significant. Statistical analyses were performed by SPSS (v. 24.0, Inc., Chicago, IL) and MedCalc (v. 14.10.2, Mariakerke, Belgium).

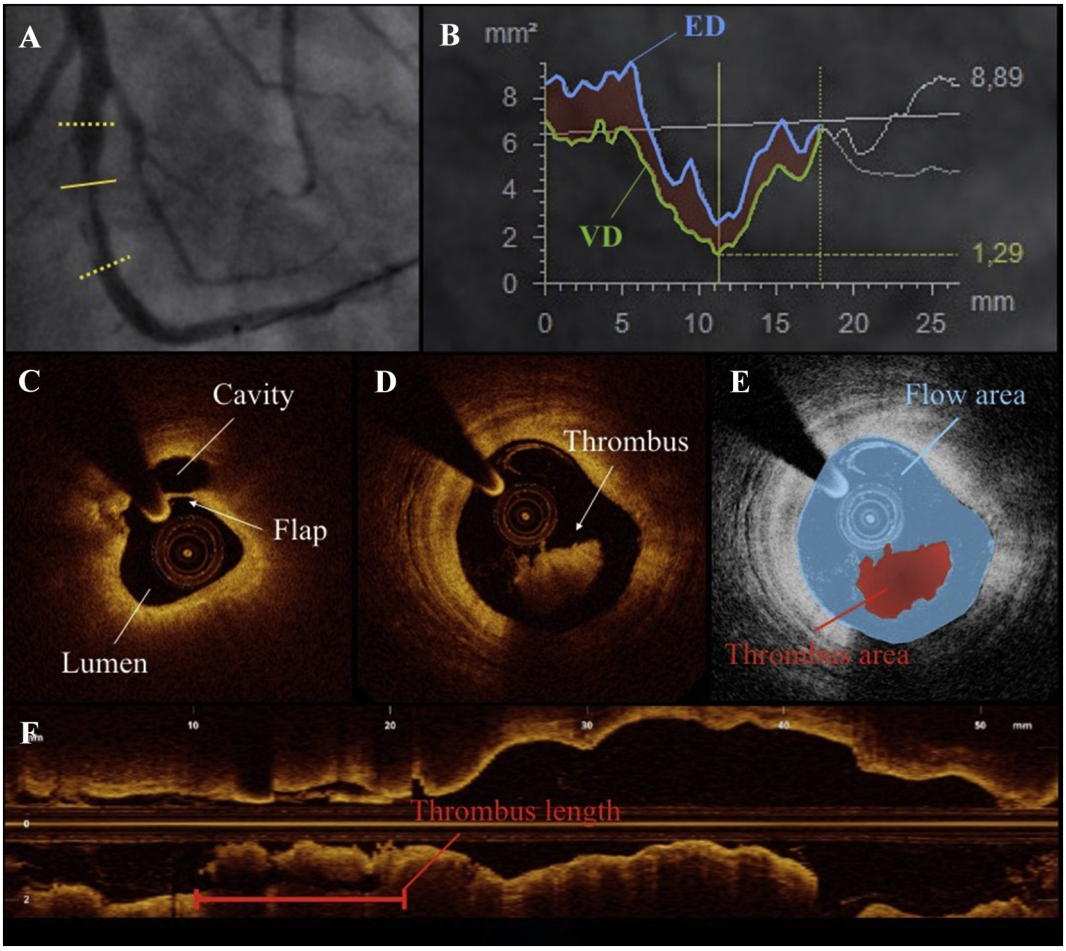

Fig. 1. Representative images of dual QCA and OCT analyses in a patient with STEMI caused by PR. A. Coronary angiogram obtained after aspiration thrombectomy showing an irregularly eccentric, complex, thrombotic lesion of the distal left circumflex (LCx). B. Dual QCA analysis of the culprit lesion in the distal LCx, with the corresponding area plots, where thrombus borders are defined by the dashed yellow lines. The large shaded red area corresponds to the mismatch between edge detection (blue line) and video-densitometry (green line) areas caused by a substantial amount of intracoronary thrombus. C. Cross-sectional OCT image showing PR, appearing as a communication between the coronary lumen and an emptied cavity through a disrupted fibrous cap (flap). D–E. Cross-sectional OCT image, distal to the previous one in panel C, showing intraluminal thrombus (D), with a corresponding illustration detailing measurements of thrombus area and flow area (E). F. Longitudinal OCT image exhibiting a large amount of intracoronary thrombus (red line). ED, edge detection; VD, video-densitometry.

3. Results

3.1. Patient population and procedural findings

From January to July 2014, a total of 66 patients with ACS who underwent OCT imaging before stenting were identified from the Oxford Heart Center ($n = 32$, recruited as part of the prospective Ox-AMI Study – REC number 10/H0408/24) and from the "A. Gemelli" Hospital OCT database ($n = 34$). Of these, 62 patients had angiographic evidence of thrombus and were enrolled in the study. After exclusion of cases with low angiographic ($n = 4$) or OCT ($n = 7$) image quality, a total of 51 patients were included in the final analysis. Baseline patient characteristics are summarized in Table 1. All patients were loaded with dual antiplatelet therapy (DAPT) at the time of the procedure: aspirin 250 mg i.v. or 300 mg orally, plus clopidogrel 600 mg orally (86.3% of patients) or ticagrelor 180 mg orally (13.7% of patients). Of note, all patients enrolled from the Oxford Heart Center were loaded with clopidogrel 600 mg and aspirin 300 mg orally in the ambulance. Door-to-balloon time was 20 min (IQR: 15–30 min) in patients with STEMI, and 1080 min (IQR: 105–2880 min) in patients with NSTE-ACS ($p < 0.001$). DAPT-to-OCT time was 50 min (IQR: 45–60 min) in patients with STEMI, and 975 min (IQR: 105–2800 min) in patients with NSTE-ACS ($p < 0.001$). Supplementary Table 1 and 2 summarize the baseline clinical characteristics and procedural and angiographic findings stratified according to the presence of OCT-PR and OCT-IFC. Thrombus aspiration was performed in more than half patients (28/51, 55%), almost all patients were treated with stenting (49/51, 96%), and drug-eluting stent (DES) was the treatment of choice in the vast majority of cases (45/51, 88%) (Supplementary Table 2).

At OCT analysis, the prevalence of thrombus was significantly higher in patients with OCT-PR than in those with OCT-IFC (100% vs. 81.5%, $p = 0.026$), and thrombus volume was greater in patients with OCT-PR than in those with OCT-IFC [4.14 mm^3 (1.38–16.20) vs. 1.01 mm^3 (0.02–10.37), $p = 0.048$]. White thrombus was more frequently observed in OCT-IFC than OCT-PR (77.3% vs. 45.8%), while red thrombus was more frequent in OCT-PR than in OCT-IFC (54.2% vs. 22.7%) ($p = 0.029$) (Supplementary Table 3).

3.2. Comparison between dual QCA and OCT for the assessment of TB

At linear regression analysis, dual QCA-defined thrombus volume correlated significantly with OCT-defined Prati thrombus score (log-transformed; $R = 0.600$, $p < 0.001$, intercept = 2.609, slope = 0.930) (Fig. 2A), thrombus burden (log-transformed; $R = 0.767$, $p < 0.001$, intercept = 0.673, slope = 1.065) (Fig. 2B) and thrombus volume (log-transformed; $R = 0.791$, $p < 0.001$, intercept = 0.178, slope = 1.041) (Fig. 2C). Bland-Altman plot confirmed good concordance between dual QCA and OCT for the assessment of thrombus volume (Fig. 2D).

Table 1
Baseline clinical characteristics.

Variables	All patients ($n = 51$)
Age, yrs	59 (53–68)
Male sex	43 (84.3%)
Hypertension	28 (54.9%)
Hyperlipidemia	23 (45.1%)
Diabetes mellitus	4 (7.8%)
Current smoking	25 (49.0%)
Family history of CAD	18 (35.3%)
Prior myocardial infarction	11 (21.6%)
STEMI presentation	32 (62.7%)
Serum creatinine, mg/dl	0.88 (0.77–1.03)
TnT peak, ng/ml	31.9 (0.15–124.0)
Aspirin	51 (100%)
Clopidogrel	44 (86.3%)
Ticagrelor	7 (13.7%)

Data are presented as absolute number (percentage) or median (interquartile range). CAD, coronary artery disease; STEMI, ST-segment elevation myocardial infarction; Tn T, troponin T.

Dual QCA-derived thrombus volume correlated significantly with other semi-quantitative angiographic indices of TB or flow impairment, as TG and TIMI flow grade. In particular, lesions with TIMI flow grade 0–1 had greater dual QCA-derived thrombus volume than those with TIMI flow grade 2–3 [6.02 mm^3 (3.41–14.87) vs. 0.68 mm^3 (0.06–1.72), $p < 0.001$], as well as lesions with TG 3–5 compared with those with TG 0–2 [4.78 mm^3 (1.92–10.57) vs. 0.67 mm^3 (0.12–1.69), $p < 0.001$]. Dual QCA-thrombus volume in patients who did not show thrombus at OCT imaging was 0 in 3 of 5 cases, and 0.67 mm^3 and 0.57 mm^3 in the remaining 2 cases. The correlation between dual QCA-derived and OCT-derived thrombus volume was significant, independent of the presence of calcification, plaque rupture, and type of thrombus. However, this correlation was relatively better when calcification, plaque rupture, and red thrombus were not present (Supplementary Table 4). The intra- and inter-observer agreement for dual QCA-thrombus volume was excellent (ICC 0.91 and 0.89, respectively), as well as those for Prati thrombus score (ICC 0.97 and 0.94, respectively), thrombus burden (ICC 0.93 and 0.92, respectively), and thrombus volume (ICC 0.93 and 0.91, respectively).

3.3. Differences in dual QCA-thrombus volume and other angiographic findings between OCT-PR and OCT-IFC

Patients with OCT-PR had significantly greater values of dual QCA-thrombus volume compared with those with OCT-IFC (3.48 mm^3 [1.45–11.26] vs. 1.69 mm^3 [0.09–5.02], $p = 0.013$) (Fig. 3A). OCT-PR showed significantly greater values of QCA-measured lesion length compared with OCT-IFC (12.6 mm [10.2–15.3] vs. 9.4 mm [7.4–13.9], $p = 0.011$), but no difference was observed in MLD (0.85 mm [0.71–1.53] vs. 0.94 mm [0.65–1.31], $p = 0.984$), RD (2.61 mm [2.28–3.34] vs. 2.99 mm [2.59–3.35], $p = 0.152$), and diameter stenosis (63% [51–74] vs. 68% [49–78], $p = 0.704$). Based on the ACC/AHA lesion

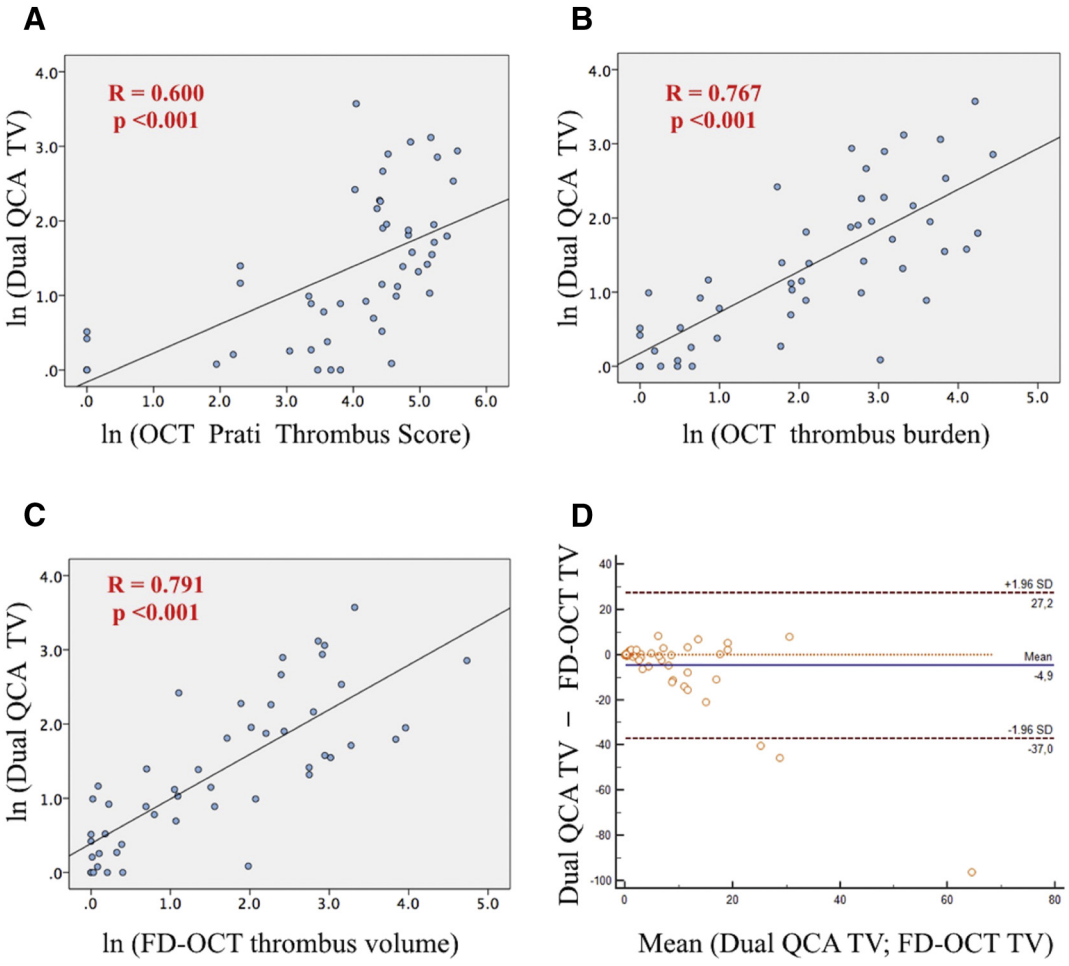

Fig. 2. Correlation between dual QCA-derived thrombus volume and OCT-derived indices of thrombotic burden. Linear regression analyses showing significant correlations between dual QCA-derived thrombus volume and OCT-derived Prati's thrombus score (A), thrombus burden (B), and thrombus volume (C). Data are expressed in natural logarithm units. Bland-Altman plot confirmed good concordance between dual QCA and OCT for the assessment of thrombus volume (D). TV, thrombus volume; QCA, quantitative coronary angiography; OCT, optical coherence tomography; ln, natural logarithm.

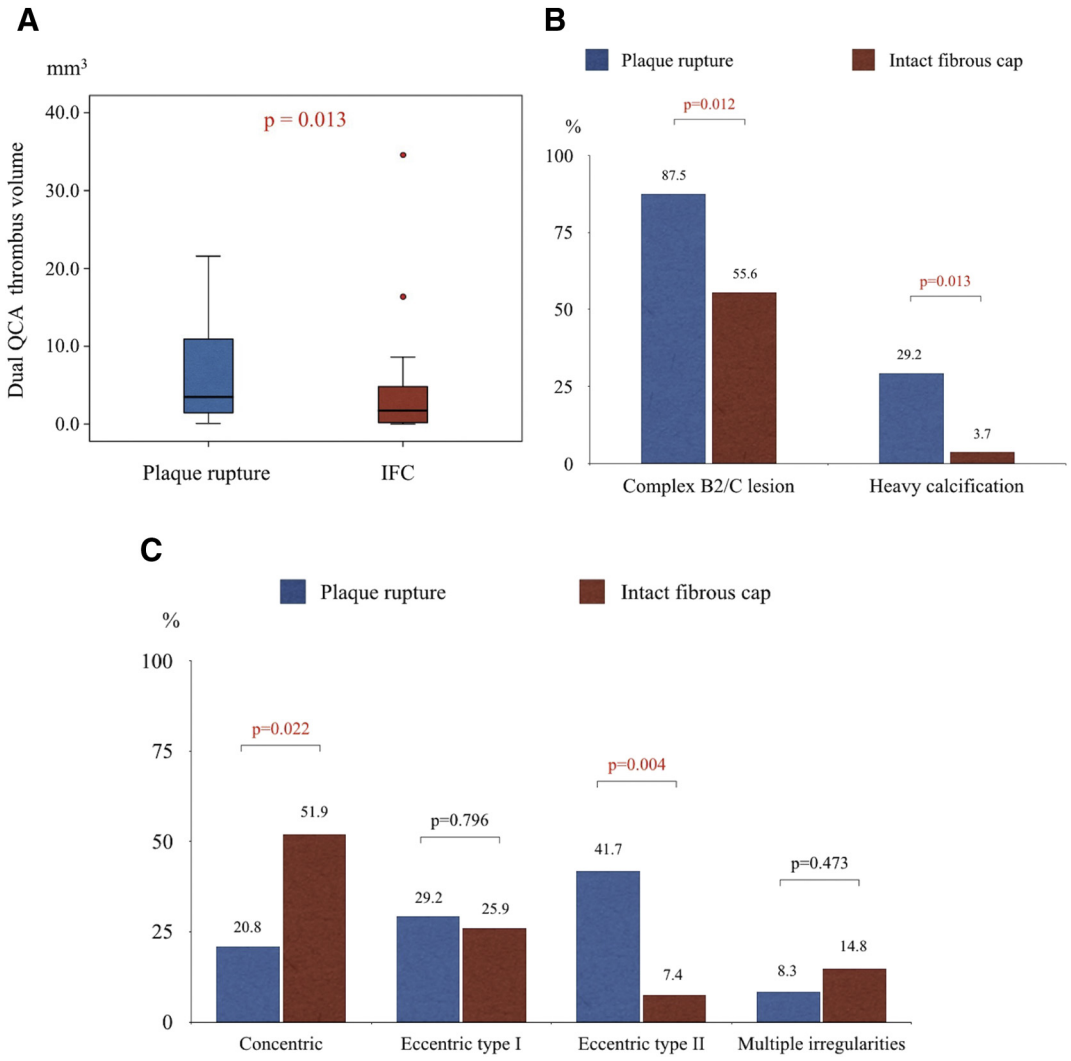

Fig. 3. Dual QCA thrombus volume and angiographic pattern in patients with OCT-PR vs. OCT-IFC. Values of dual QCA-derived thrombus volume were significantly greater in patients with OCT-PR compared with those with OCT-IFC (3.48 mm^3 [1.45–11.26] vs. 1.69 mm^3 [0.09–5.02], $p = 0.013$) (A). Complex B2/C lesions and heavy calcifications were more frequently associated with OCT-PR than OCT-IFC (B). According to the Ambrose's classification, concentric lesions were more frequently associated with OCT-IFC, whereas eccentric type II lesions (irregular/scalloped) were significantly associated with OCT-PR. The prevalence of eccentric type I lesions and lesions with multiple irregularities was not different between patients with OCT-PR and OCT-IFC (**C**). QCA, quantitative coronary angiography; IFC, intact fibrous cap.

classification, complex B2/C lesions were more frequently associated with OCT-PR than OCT-IFC (87.5% vs. 55.6%, $p = 0.012$). In addition, heavy calcifications were significantly related to OCT-PR (29.2% vs. 3.7%, $p = 0.013$) (Fig. 3B). According to the Ambrose lesion classification, concentric lesions were more frequently associated with OCT-IFC than OCT-PR (51.9% vs. 20.8%, $p = 0.022$), whereas eccentric type II lesions (irregular/scalloped) were significantly associated with OCT-PR (41.7% vs. 7.3%, $p = 0.004$) (Fig. 3C). The prevalence of eccentric type I lesions and lesions with multiple irregularities was not different between patients with OCT-PR and OCT-IFC ($p = 0.796$ and $p = 0.473$, respectively) (Fig. 3C).

4. Discussion

In the present study, we validated, for the first time in vivo, a novel advanced angiographic method (i.e., dual QCA) for the assessment of intracoronary thrombus volume as compared with OCT. Dual QCA-derived thrombus volume correlated significantly with OCT-thrombus volume and with other indices of TB, thus appearing to be a promising tool for quantification of intracoronary thrombus in patients with ACS.

Intracoronary thrombus overlying PR or IFC is a frequent substrate in patients with ACS [2]. The response of thrombus to medical therapy or mechanical displacement (e.g., thrombus aspiration) is variable and often unpredictable [5,9], and large evidence relates it to procedural complications and adverse outcome [3,4]. In spite of the clinical relevance of this key finding in patients with ACS, no quantitative method for measurement of intracoronary thrombus volume in vivo has been available so far, that did not require the use of intracoronary imaging techniques, such as OCT. However, these imaging tools are not available in every cath lab, are not always feasible (e.g, patients with hemodynamic instability or unsuitable coronary anatomy) and are costly. An accurate quantification of the TB using an angiographic tool would overcome these issues, and rapidly and safely provide important information, potentially guiding PCI and aiding prognostic stratification. So far, this assessment has been based on qualitative or semi-quantitative scales [4,10,26], such as the modified TIMI thrombus grading scale [15], which have been adopted both in the clinical context and for research purposes. Dual-QCA analysis, based on both edge-detection and video-densitometry techniques has been recently tested for enhanced quantitative assessment of intracoronary thrombus burden by Aleong et al. [11]. In that study, dual QCA was validated against radiological phantoms in an experimental setting, and was then applied to serial coronary angiograms of 19 patients with large intracoronary thrombus to measure their response to anti-thrombotic treatment [11]. The aim of

that in vivo substudy, however, was not to validate the technique in patients, but to identify changes in thrombotic burden as compared with other semi-quantitative angiographic indices, without demonstrating or quantifying its efficacy. In our study, we validated for the first time in vivo dual QCA against OCT, which is considered to be the modality of choice for the identification and quantification of intracoronary thrombus in patients with ACS. Dual QCA analysis is performed off-line using the CAAS software, once coronary angiograms are acquired during the procedure. Dual QCA measurement of thrombus volume is rapid (i.e., a total of 1–2 min for selection of the angiographic frame and analysis), and it can therefore be used at the point of care during coronary procedures. As this software is incorporated in the CAAS system, and is available in most of the cath labs, dual QCA assessment of thrombus volume may have a significant clinical impact for decision-making in patients with ACS undergoing cardiac catheterization. We found a significant correlation between dual QCA-derived thrombus volume and OCT-measured thrombus volume, as well as with other OCT-derived indices of thrombotic burden. The two methodologies showed good concordance, and reproducibility of dual-QCA thrombus volume measurements was excellent for both inter- and intra-observer agreement. This novel technique promises to be, therefore, an attractive approach for future assessment of thrombus volume in patients with ACS, for use as surrogate end-point in future clinical trials, and, most importantly, for the evaluation of thrombus response to mechanical displacement (e.g., thrombus aspiration) and/or antithrombotic agents. In the Thrombus Aspiration in ST-Elevation Myocardial Infarction in Scandinavia (TASTE) trial, for instance, routine thrombus aspiration before PCI in patients with STEMI did not reduce major adverse cardiac events (MACE), with consistent results across subgroups of thrombus grade or TIMI flow grade [27]. The use of a more accurate, quantitative angiographic parameter, such as dual QCA-thrombus volume, may aid the selection of patients (likely those with greater thrombus volume) who might benefit from thrombus aspiration [28]. Large, prospective studies are warranted to address these hypotheses. In our study, 21% of patients with NSTE-ACS had no evidence of thrombus at OCT analysis. The most likely explanation for this observation might be the effect of upstream optimal medical therapy [22], as well as use of thrombus aspiration before OCT imaging.

There are several limitations that need to be acknowledged in the present study. First, this was a retrospective study with a relatively small patient population, and was therefore underpowered for assessment of clinical outcomes, as well as potentially exposed to selection bias. However, this was not the aim of our investigation, which was conceived as a validation study. Second, it might be possible that including only ACS patients with angiographic evidence of thrombus might have been responsible of a relative overestimation of the rates of thrombus and PR by OCT in the NSTE-ACS compared with the STEMI subpopulation. However, describing the relative incidence of PR and IFC by OCT in patients with ACS was not the aim of our study, as it has already been investigated extensively in previous studies [2,29,30]. Third, thrombus aspiration was performed prior to OCT in about 50% of patients and, it cannot be potentially excluded that this procedure may have altered the morphology of the underlying plaque. Fourth, deep location of thrombus into the plaque cavity might have affected thrombus measurements in cases of PR [31]. In addition, the presence of large amounts of thrombus, particularly red thrombus, might have limited the assessment of the underlying plaque morphology and lumen delineation by OCT in some cases. Fifth, this angiographic method is suitable only to vessels with at least TIMI flow grade 1, in order to define lumen borders and extension of the thrombotic process; therefore, it did not allow to calculate the change of thrombus volume before and after vessel recanalization. In addition, as for all angiographic techniques, it is sometimes difficult to discriminate protruding atheroma from intraluminal thrombus, thus volume obtained by dual QCA may represent a combination of the two components in some cases. As edge detection of the target segment is subjective, potential operator's bias cannot be excluded, although intra- and inter-observer variability for dual QCA measurement was low in our study. Finally, this method can potentially be influenced by some technical (e.g., angiographic resolution, contrast filling during injections) and morphological factors (e.g., degree of calcifications, lumen dimensions, intimal flaps/dissections, plaque ruptures, thrombus type) [32,33], and these aspects should be considered when using dual QCA analysis for thrombus volume assessment in clinical practice.

5. Conclusions

Dual QCA analysis appears to be a promising tool for the quantification of intracoronary thrombus in patients with ACS. This novel methodology may be useful to guide intracoronary thrombus removal and to predict adverse outcomes. A combination of angiographic morphological features with thrombus volume may help discriminating patients with PR from those with IFC, particularly when intracoronary imaging is not available or feasible, potentially guiding tailored treatments and prognostic stratification.

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Conflicts of interest

Drs. Italo Porto, Cristina Aurigemma, Antonio Maria Leone, Giampaolo Niccoli, Francesco Burzotta, and Carlo Trani received modest speaker's fees from St. Jude Medical. Other authors have nothing to disclose.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ijcard.2019.04.060.

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