# Comparison of Computed Tomography Angiography Versus Invasive Angiography to Assess Medina Classification in Coronary Bifurcations

Kajetan Grodecki, MD[a,b], Maksymilian P. Opolski, MD[a,*], Adam D. Staruch, MD[a], Anna M. Michalowska, MS[a,b], Cezary Kepka, MD[c], Rafal Wolny, MD[a], Jerzy Pregowski, MD[a], Mariusz Kruk, MD[c], Mariusz Debski, MD[c], Artur Debski, MD[a], Ilona Michalowska, MD[d], and Adam Witkowski, MD[a]

**The Medina classification is used to determine the presence of significant stenosis (≥50%) within each of the 3 arterial segments of coronary bifurcation in invasive coronary angiography (ICA). The utility of coronary computed tomography angiography (coronary CTA) for assessment of Medina classification is unknown. We aimed to compare the agreement and reproducibility of Medina classification between ICA and coronary CTA, and evaluate its ability to predict side branch (SB) occlusion following percutaneous coronary intervention (PCI). In total 363 patients with 400 bifurcations were included, and 28 (7%) SB occlusions among 26 patients were noted. Total agreement between CTA and ICA for assessment of Medina class was poor (kappa = 0.189), and discordance between both modalities was noted in 253 (63.3%) lesions. Larger diameter ratio between main vessel and SB in CTA, and larger bifurcation angle in ICA were independently associated with discordant Medina assessment. Whereas the interobserver agreement on Medina classification in CTA was moderate (kappa = 0.557), only fair agreement (kappa = 0.346) was observed for ICA. Finally, Medina class with any proximal involvement of main vessel and SB (1.X.1) on CTA or ICA was the most predictive of SB occlusion following PCI with no significant differences between both modalities (area under the curve 0.686 vs 0.663, p = 0.693, respectively). In conclusion, Medina classification was significantly affected by the imaging modality, and coronary CTA improved reproducibility of Medina classification compared with ICA. Both CTA and ICA-derived Medina class with any involvement of the proximal main vessel and SB was predictive of SB occlusion following PCI.**  **(Am J Cardiol 2020;125:1479−1485)**

The wide variety of schemes has been introduced to characterize coronary bifurcation lesions throughout the years, but none has earned the more widespread clinical adoption than the angiography-based Medina classification system.[1−3] The Medina classification describes the presence of significant stenosis in a binary fashion within each of 3 segments of coronary bifurcation and remains the sole classification system recommended by the European Bifurcation Club.[4,5] Recently, noninvasive coronary computed tomography angiography (coronary CTA) has gained recognition as the first-line diagnostic test in subjects with suspected coronary artery disease.[6,7] Whereas the number of patients undergoing CTA before invasive coronary angiography (ICA) is expected to increase, it seems reasonable to utilize all information embedded within a CTA scan for planning and guiding percutaneous coronary intervention (PCI).[8−11] Till now, the utility of coronary CTA for assessment of Medina classification is unknown. We, thus, sought to: (1) compare agreement and variability between coronary CTA and ICA for assessment of Medina classification, and (2) evaluate the utility of Medina classification derived from coronary CTA and ICA for prediction of side branch (SB) occlusion following PCI.

## Methods

From January 2010 to July 2018, 15,918 consecutive patients underwent PCI at a single high-volume center. Inclusion criteria were: (1) PCI of a bifurcation lesion with a significant SB using a provisional approach with initial stenting of the main vessel (MV), and (2) performance of coronary CTA within 30 days before attempted PCI. Coronary bifurcation lesion was defined as a coronary artery narrowing occurring adjacent to or involving the origin of a significant SB. Significant SB was defined according to the 11th consensus document from the European Bifurcation Club as a branch that the operator would not want to lose in the global context of an individual

[a]Department of Interventional Cardiology and Angiology, National Institute of Cardiology, Warsaw, Poland; [b]Medical University of Warsaw, Warsaw, Poland; [c]Department of Coronary and Structural Heart Diseases, National Institute of Cardiology, Warsaw, Poland; and [d]Department of Radiology, National Institute of Cardiology, Warsaw, Poland. Manuscript received January 9, 2020; revised manuscript received and accepted February 14, 2020.

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*Corresponding author: Tel: +48 501444303; fax: +48 (22) 6133819.

*E-mail addresses:* opolski.mp@gmail.com; mopolski@ikard.pl (M.P. Opolski).


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patient.[12] The SB occlusion was represented by any decrease in thrombolysis in myocardial infarction flow grade after MV stenting.[13]

Among 15,918 patients, 1,006 underwent both CTA and PCI within an interval of 30 days. After the exclusion of 62 patients undergoing PCI for chronic total occlusion, 526 patients without bifurcation lesions, and 21 patients with elective SB stenting, the total of 397 patients were eligible for the study. Due to insufficient diagnostic quality of CT scans, 34 patients were excluded, and the final cohort included 363 patients with 400 bifurcation lesions. The study protocol was derived from the CT-PRECISION registry (NCT03709836), and was approved by the Institutional Review Board and complied with the declaration of Helsinki.

The CT imaging protocol is provided in the Data Supplement. CT analysis was performed on a dedicated workstation (Syngo, Siemens Healthcare, Forchheim, Germany) by an independent reader (K.G.) blinded to the results of coronary angiography and PCI. Analysis of the first 80 patients (20%) was discarded and repeated at the end of the study to minimize the effect of the learning curve. Coronary bifurcation was divided into: the proximal MV, the distal MV, and the SB. The beginning of the distal MV was defined at the carinal level as previously described.[4] To determine Medina classification, presence of a significant stenosis (defined as diameter reduction of ≥50%) within each of the 3 segments of coronary bifurcation (proximal MV, distal MV, and SB) was visually determined by careful axial scrolling on curved multiplanar reformations in the diastolic phase. The sites with the largest lumen proximal/distal to the carinal level but within the same segment (usually within 10 mm of the stenosis with no major intervening branches) were used as reference to assess diameter stenosis within respective MV segments.[14] Diameter stenosis of the SB was assessed in relation to the distal reference segment of the SB within its first 10 mm. All diameter evaluations were performed using a prespecified mediastinal window (width: 400 Hounsfield units; level: 40 Hounsfield units) and adjusted when necessary. To determine the position of the plaque in relation to SB, cross-sectional luminal area was divided into quarters and both proximal and distal MV were analyzed within 5 mm from the SB carina.[15,16] Severe tortuosity was defined as one or more bends ≥90°, or three or more bends of 45° to 90° proximal to the diseased segment.[17] Bifurcation angles were visually estimated with high-resolution thin slab multiplanar reconstruction (reconstructed slice thickness of 1.5 mm) using the view in which the angulation between the proximal parts of the MV and SB was maximal.[18] Moderate calcification was defined as cross-sectional arc calcium of 90° to 180°, whereas severe calcification was defined as cross-sectional arc calcium ≥180°.[19]

Coronary angiography evaluation was performed offline using a commercially available software on a Leonardo workstation (Quant, Siemens Healthcare Diagnostics GmbH, Eschborn, Germany) by an independent experienced reader (A.S.) blinded to the incidence of SB occlusion and CTA analysis. To determine Medina classification, presence of the significant stenoses (diameter reduction of ≥50%) within respective bifurcation segments was visually evaluated by reviewing coronary angiograms in multiple projections. Severe tortuosity was defined as one or more bends ≥90°, or three or more bends of 45° to 90° proximal to the diseased segment.[17] Moderate calcification was defined as readily visible but mild degree opacification, whereas severe calcification as multiple persisting opacifications of the coronary wall visible in more than one projection surrounding the complete lumen of the coronary artery at the site of the lesion.[20] All measurements were determined using end-diastolic frames.

For both CTA and ICA, a true bifurcation was defined as a Medina classification of 0.1.1, 1.0.1, or 1.1.1.[21] Medina classification with any involvement of the proximal MV and SB included classes of 1.0.1 or 1.1.1 (1.X.1), whereas Medina classification with any proximal plaque represented classes of 1.0.0, 1.1.0, 1.0.1, or 1.1.1 (1.X.X). Medina classification with any plaque in the distal MV was described as 0.1.0, 1.1.0, 0.1.1, or 1.1.1 (X.1.X).

Continuous variables are expressed as the mean ± standard deviation or median with interquartile range, and were compared with Student's t-test or Mann−Whitney U test as appropriate. Chi-square or Fisher's exact tests were used for comparison of categorical variables expressed as counts and percentages. Kappa statistic was used to evaluate agreement between CTA and ICA as well as intra- and interobserver variability for Medina classification of bifurcation lesions. The degree of agreement was considered excellent for kappa >0.80; substantial for kappa 0.61 to 0.80; moderate for kappa 0.41 to 0.60; fair for kappa 0.21 to 0.40; and poor for kappa ≤0.20. Univariate and multivariate logistic regression was utilized to determine features associated with discordant Medina classification between imaging modalities. Multivariable model was created only with variables associated with the outcome on univariate analysis ($p < 0.1$) and adjusted for baseline covariates presented in Table 1. Separate models were created for variables derived

Table 1
Baseline characteristics

| Variable | Side branch occlusion | | *p* value |
|---|---|---|---|
| | No (n = 337) | Yes (n = 26) | |
| Age (years) | 64.3 ± 9.9 | 63.6 ± 11.0 | 0.745 |
| Men | 247 (73%) | 19 (73%) | 1.000 |
| Body mass index (kg/m$^2$) | 28.1 ± 4.2 | 28.9 ± 5.1 | 0.612 |
| Diabetes mellitus | 81 (24%) | 6 (23%) | 1.000 |
| Hyperlipidemia | 266 (79%) | 21 (81%) | 1.000 |
| Hypertension | 268 (80%) | 22 (85%) | 0.799 |
| Smoking history | 65 (19%) | 7 (27%) | 0.319 |
| Current smoker | 36 (11%) | 3 (12%) | 0.750 |
| Previous myocardial infarction | 77 (23%) | 9 (35%) | 0.229 |
| Previous coronary artery bypass grafting | 33 (10%) | 3 (12%) | 0.733 |
| Previous PCI | 80 (24%) | 8 (31%) | 0.476 |
| Previous stroke | 14 (4%) | 0 | 0.611 |
| Stable coronary artery disease | 262 (78%) | 24 (92%) | 0.223 |
| Unstable angina pectoris | 53 (16%) | 2 (8%) | 0.271 |
| Non-ST-elevation myocardial infarction | 18 (5%) | 0 | 0.629 |
| ST-elevation myocardial infarction | 4 (1%) | 0 | 1.000 |
| Left ventricular ejection fraction | 56.4 ± 12.0 | 54.7 ± 12.6 | 0.585 |

PCI = percutaneous coronary intervention from CTA and ICA. Discriminatory performance of Medina classification for prediction of SB occlusion, as assessed with CTA and ICA, was determined by the C-statistic and compared using the method of DeLong et al.[22] All probability values were 2-tailed, and a p value of <0.05 was considered statistically significant. Data were processed using the SPSS software, version 23 (IBM SPSS Statistics, New York, USA) and SAS 9.4 (SAS Institute, Cary, USA).

## Results

In total 363 patients with 400 bifurcation were included, and 28 (7%) SB occlusions among 26 patients were observed. The absence of flow occurred in 12 (43%) of lesions, whereas a decrease in thrombolysis in myocardial infarction flow was recognized in 16 (57%) lesions. No significant differences in neither clinical nor procedural characteristics were observed between patients and lesions with versus without SB occlusion (Table 1 and Supplementary Table 1).

Overall Medina classification differed significantly between coronary CTA and ICA (p < 0.001) (Figure 1A). The difference between both scales was primarily driven by the lower prevalence of significant SB disease in CTA than ICA. While true bifurcations were significantly less frequent in CTA than in ICA (44.8% vs 61.3%, p < 0.001), no discrepancies were observed for identification of Medina classifications containing proximal (1.X.X) (77.8% vs 75.6%, p = 0.452) or distal (X.1.X) (82.3% vs 80.5%, p = 0.524) MV plaques (Figure 1B).

Total agreement between CTA and ICA for assessment of Medina class was poor (kappa = 0.189). Similarly, poor agreement was observed between modalities for identification of true bifurcations (kappa = 0.199) (Figure 2A), and bifurcations with any lesions involving proximal MV and SB (1.X.1) (kappa = 0.172) (Figure 2B). Fair agreement was noted for recognition of bifurcations with any proximal MV plaque (1.X.X) (kappa = 0.393) (Figure 2C), and moderate agreement for bifurcations with any distal MV plaques (X.1.X) (kappa = 0.415) (Figure 2D). Out of 400 bifurcations, discordant classification was noted in 253 (63.3%) lesions. Reclassification patterns for respective Medina classes of bifurcation lesions are presented in Figure 3.

Table 2 displays comparison between concordant and discordant Medina classifications as assessed by CTA and ICA. Diameter ratio between MV/SB was the only tomographic variable associated with discordance of Medina classification between modalities on univariate analysis. After adjusting for baseline clinical characteristics, it remained independently associated with discordant Medina classification (OR 1.338 per 0.585 [1-standard deviation] increase, 95% confidence interval [CI]: 1.043 to 1.716, p = 0.022).

Univariate factors derived from ICA and associated with discordant Medina classification were diameter ratio between MV/SB and bifurcation angle. After adjusting for baseline clinical characteristics, only bifurcation angle remained associated with discordance of Medina classification (OR 1.301 per 25.5° [1-standard deviation] increase, 95% CI: 1.013 to 1.672, p = 0.041).

Sensitivity analysis showed no disparities between CT scanners of different generations in prevalence of discordant Medina classification (58% [SOMATOM Definition] vs 65% [SOMATOM Definition Flash] vs 69% [SOMATOM Force], p = 0.266).

Reproducibility of Medina classification was assessed in a subset of 100 lesions by the second reader (A.M.). There was moderate interobserver agreement on Medina classification (kappa = 0.557) as well as identification of true bifurcations (kappa = 0.536) on CTA. For ICA, only fair interobserver agreement on Medina classification (kappa = 0.346) and identification of true bifurcations (kappa = 0.323) was observed.

Rates of SB occlusion following PCI were distributed similarly across respective Medina classes as assessed by CTA and ICA (p = 0.351) (Figure 4A). In both CTA and ICA, the majority of SB occlusion occurred in Medina class with any proximal MV and SB plaque (1.X.1), and the incidence was comparable between both modalities (13.6% vs 11.4%, p = 0.540) (Figure 4B). Consequently, this type of bifurcations yielded the highest diagnostic accuracy for predicting SB occlusion after PCI on CTA (area under the curve [AUC] 0.686, 95% CI: 0.586 to 0.787, p = 0.001) and ICA (AUC 0.663, 95% CI: 0.566 to 0.760, p = 0.004) (Table 3).

## Discussion

This study presents the first comprehensive comparison between coronary CTA and ICA for evaluation of Medina classification in bifurcation lesions. The main findings can be summarized as follows: (1) the agreement between CTA

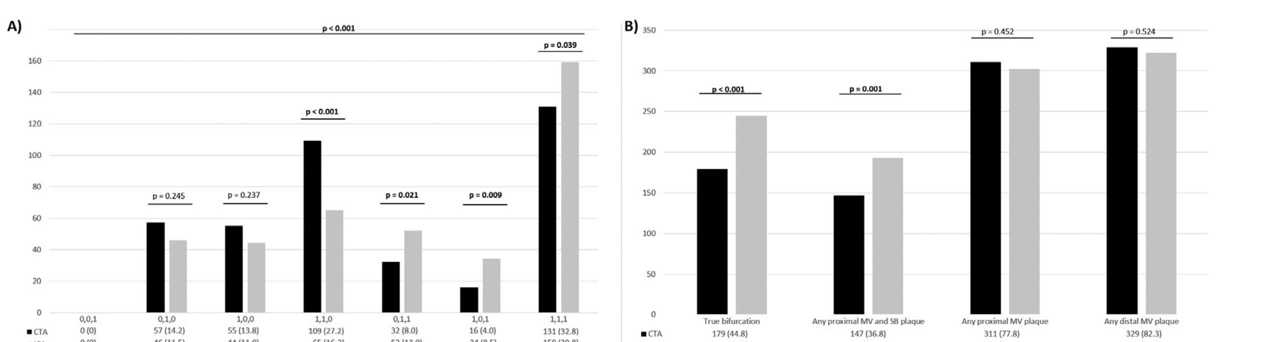


Figure 1. Comparison of computed tomography angiography (CTA) and invasive coronary angiography (ICA) on: (A) distribution of Medina categories; (B) prevalence of different bifurcation lesions.

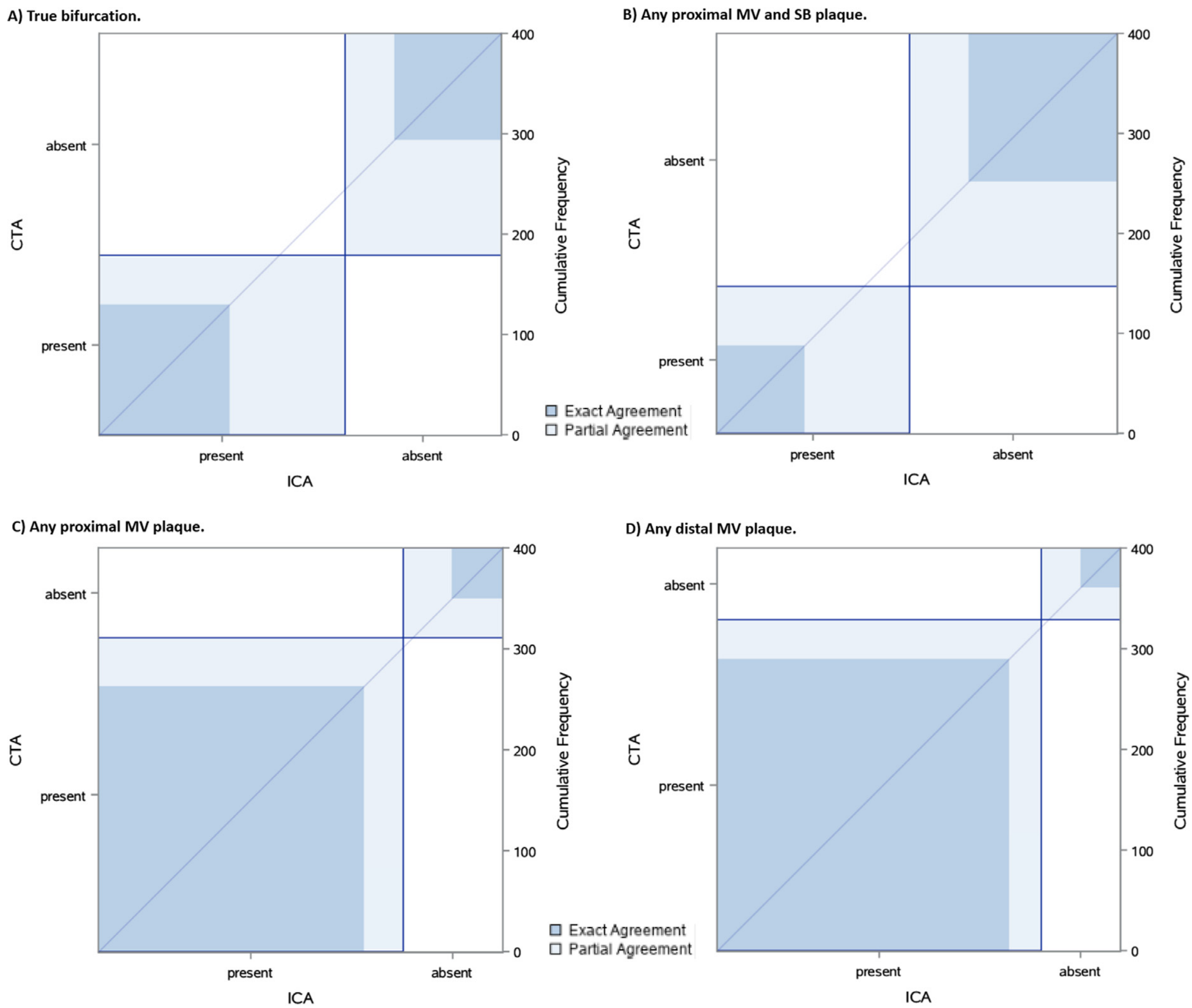


Figure 2. Agreement between computed tomography angiography (CTA) and invasive coronary angiography (ICA) on identification of: (A) true bifurcations (kappa = 0.199); (B) bifurcations with any proximal MV and SB plaque (kappa=0.172); (C) bifurcations with any proximal MV plaque (kappa = 0.393); (D) bifurcations with any distal MV plaque (kappa = 0.415).

Table 2
Comparison of bifurcation characteristics between concordant and discordant results in different imaging modalities

| Variable | Medina class | | *p* value |
|---|---|---|---|
| | Concordant (n = 147) | Discordant (n = 253) | |
| **Computed tomography angiography** | | | |
| Main vessel tortuosity | 5 (3%) | 11 (4%) | 0.794 |
| Bifurcation angle (°) | 50.0 (45.0 to 70.0) | 55.0 (37.5 to 80.0) | 0.846 |
| Diameter ratio between main vessel and side branch | 1.9 (1.6 to 2.5) | 2.1 (1.8 to 2.5) | **0.004** |
| Plaque at the side of side branch | 130 (88%) | 218 (86%) | 0.542 |
| Main vessel severe/moderate calcium | 77 (52%) | 137 (54%) | 0.756 |
| Side branch severe/moderate calcium | 22 (15%) | 40 (16%) | 0.887 |
| **Invasive coronary angiography** | | | |
| Main vessel tortuosity | 3 (2%) | 6 (2%) | 1.000 |
| Bifurcation angle (°) | 50.0 (40.0 to 80.0) | 60.0 (45.0 to 85.0) | **0.008** |
| Diameter ratio between main vessel and side branch | 1.6 (1.3 to 2.1) | 1.8 (1.4 to 2.1) | 0.057 |
| Plaque at the side of side branch | 122 (83%) | 206 (81%) | 0.787 |
| Main vessel severe/moderate calcium | 13 (9%) | 16 (6%) | 0.424 |
| Side branch severe/moderate calcium | 4 (3%) | 7 (3%) | 1.000 |

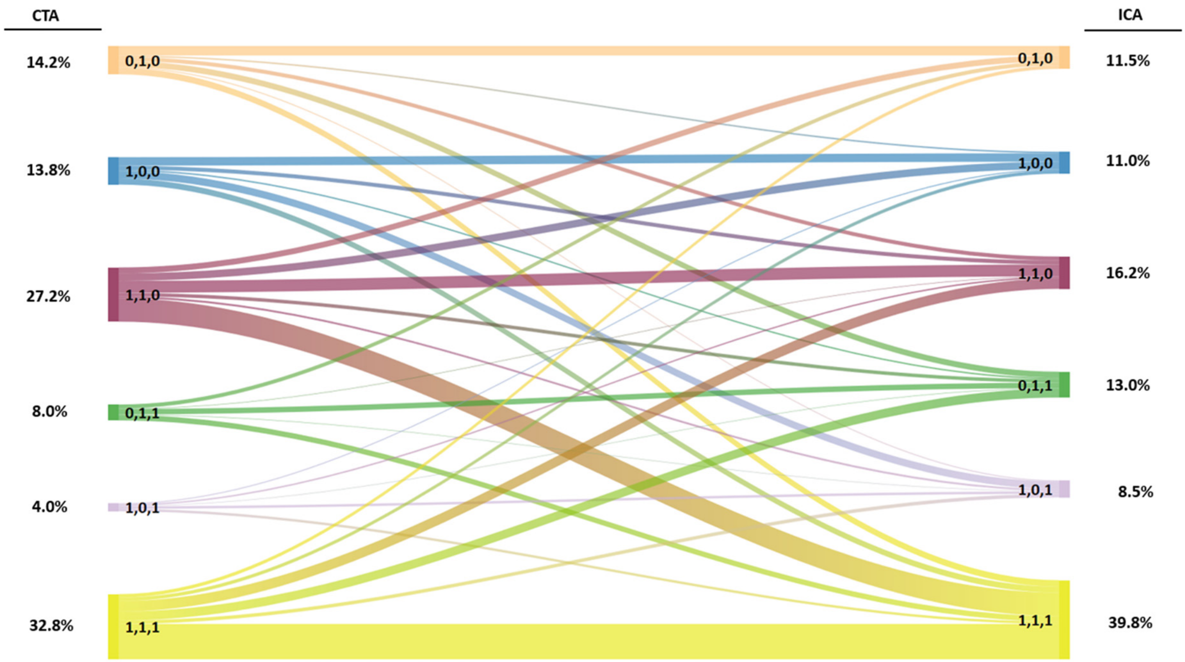


Figure 3. Reclassification patterns between computed tomography angiography (CTA) and invasive coronary angiography (ICA) for Medina classification of bifurcation lesions. The width of the lines between Medina class in CTA and ICA is proportional to the number of reclassified lesions.

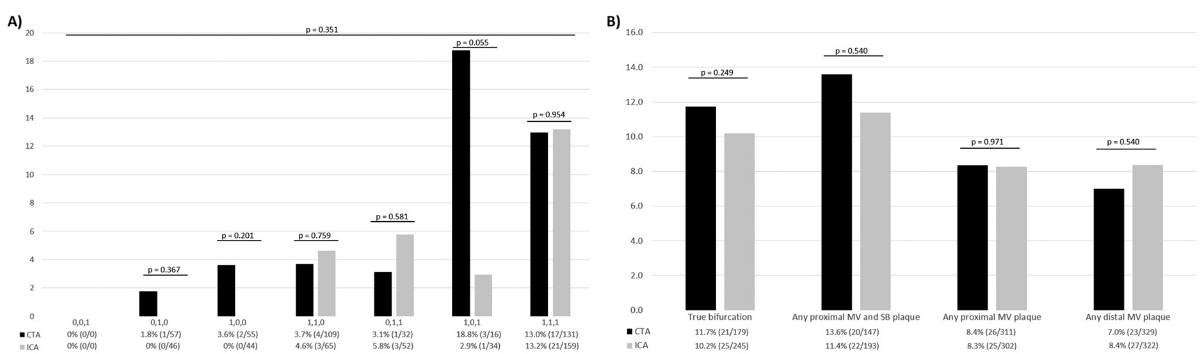


Figure 4. Prevalence of side branch occlusions in: (A) respective Medina categories; (B) different bifurcation lesions as assessed by computed tomography angiography (CTA) and invasive coronary angiography (ICA).

and ICA for characterization of Medina classification is poor resulting from less frequent identification of obstructive SB lesions on noninvasive CTA as compared with ICA; (2) Medina classification is more reproducible with CTA than ICA; (3) Medina class with any proximal involvement of MV and SB (1.X.1) on CTA or ICA is most predictive of SB occlusion following PCI with no significant differences between both modalities.

Visual interpretation of coronary angiograms has been shown to systematically overestimate diameter stenosis compared with quantitative coronary analysis.[23−25] For coronary bifurcations, the extent of inaccuracies arising from

Table 3
Predictive value of side branch occlusion of different bifurcation lesions as assessed by computed tomography angiography and invasive coronary angiography

| | Computed tomography angiography | | | Invasive coronary angiography | | | DeLong P* |
|---|---|---|---|---|---|---|---|
| | AUC | 95% CI | *p* value | AUC | 95% CI | *p* value | |
| True bifurcation | 0.663 | 0.564 to 0.762 | 0.004 | 0.651 | 0.561 to 0.741 | 0.008 | 0.838 |
| Any proximal main vessel and side branch plaque | 0.686 | 0.586 to 0.787 | 0.001 | 0.663 | 0.566 to 0.760 | 0.004 | 0.693 |
| Any proximal main vessel plaque | 0.581 | 0.483 to 0.679 | 0.152 | 0.574 | 0.474 to 0.674 | 0.191 | 0.744 |
| Any distal main vessel plaque | 0.499 | 0.388 to 0.611 | 0.992 | 0.586 | 0.490 to 0.682 | 0.131 | 0.049 |

AUC = area under the curve; CI = confidence interval

* DeLong p to compare AUC between computed tomography angiography and invasive coronary angiography

qualitative visual analysis becomes amplified by the vessel foreshortening and overlap observed in 2-dimensional ICA.[10,11] Aforementioned observations are in line with our results on poor agreement between visual ICA and coronary CTA for grading Medina classification. Specifically, the difference between both modalities was primarily driven by the lower prevalence of significant SB disease in CTA than visual angiography. Indeed, similar observations were encountered in the recent head-to-head comparison between qualitative and quantitative ICA, whereby nearly 3 out of 4 visually estimated true bifurcations were downclassified with quantitative coronary analysis.[26] Furthermore, we believe that the discrepancy between ICA and noninvasive CTA for assessment of Medina classification might represent a function of 3-dimenstional and cross-sectional nature of coronary CTA that is lacking in invasive angiograms.[8,9] Moreover, analysis of vessel characteristics associated with discordance of Medina classification between CTA and ICA explains further pitfalls of both modalities. Whereas association of Medina discordance with larger diameter ratio between MV/SB on CTA might reflect inferior spatial resolution of noninvasive CTA, the higher number of discordant results for larger bifurcation angle in ICA emphasizes significant limitations of invasive angiograms (such as vessel overlap and foreshortening) for evaluation of bifurcation lesions.[9,11]

Despite the widespread application of Medina classification, data regarding its reproducibility are scarce. A survey-based study of Zlotnick et al. showed moderate interobserver agreement (kappa = 0.49) among senior operators for identification of true bifurcations lesions in a set of 12 different coronary angiograms.[27] Furthermore, in the phantom study by Girasis et al. visual assessment of diameter stenosis by expert readers was less reliable compared with quantitative coronary analysis.[25] Similar findings were encountered in our report, wherein only fair interobserver agreement on Medina classification was observed for ICA (kappa = 0.35). In contrast, the reproducibility of Medina classification on CTA was moderate (kappa = 0.56) and numerically higher as compared with ICA. As such, the present data underscore the higher level of reliability and certainty with regard to noninvasive evaluation of bifurcation lesions as compared with invasive angiography.

Finally, Medina classification with any involvement of the proximal MV and SB (1.X.1) yielded the highest accuracy for prediction of SB occlusion following PCI with similar AUC for CTA and ICA. Of note, the relevance of proximal MV and SB plaque locations for occurrence of SB compromise has been recognized in a recent Korean Coronary Bifurcation Stenting (COBIS II) registry as well as prior intravascular ultrasound study.[21,28] Data from CTA studies on this subject are still limited, and do not warrant the application of Medina classification for predicting SB compromise in coronary bifurcation intervention.[29,30] In this context, our results extent prior angiographic observations and add computed tomographic evidence supporting involvement of plaque shift from proximal MV to SB during bifurcation intervention. Yet, identification of lesions within both proximal MV and SB on noninvasive CTA (associated with higher risk for SB occlusion) could be potentially used as a simple tool for deciding on initial two-stent strategy in bifurcation lesions.

There are several limitations to our work. First, this was a single-center, retrospective, and observational study. Second, only patients treated using provisional approach with initial stenting of the MV were included, thereby potentially influencing complexity of analyzed bifurcation lesions. Third, low incidence of acute coronary syndromes (22%) restricts the applicability of our results primarily to the population with stable coronary artery disease. Finally, relatively low number of SB occlusions might limit statistical power for detection of differences between studied modalities. Nevertheless, our study represents the largest CT database on bifurcation lesions so far, and the percentage of SB occlusions in our report is in accordance with the frequency of SB compromise from the large angiographic analysis.[13]

In conclusion, our study showed poor agreement between ICA and coronary CTA for characterization of Medina classification resulting from different classification of SB lesions. Coronary CTA improved reproducibility of Medina classification compared with ICA. Regardless of imaging modality, Medina classification with any involvement of the proximal MV and SB was predictive of SB occlusions following PCI.

## CRediT author statement

Kajetan Grodecki: Conceptualization, methodology, validation, formal analysis, visualization, investigation, writing—original draft.

Maksymilian P. Opolski: Conceptualization, methodology, investigation, resources, writing—original draft, supervision.

Adam D. Staruch: Conceptualization, methodology, validation, investigation, writing—review and editing.

Anna M. Michalowska: Conceptualization, validation, investigation, writing—review and editing.

Cezary Kepka: Resources, writing—review and editing.

Rafal Wolny: Validation, writing—review and editing.

Jerzy Pregowski: Resources, writing—review and editing, supervision.

Mariusz Kruk: Resources, writing—review and editing, supervision.

Mariusz Debski: Validation, writing—review and editing.

Artur Debski: Resources, writing—review and editing, supervision.

Ilona Michalowska: Resources, writing—review and editing, supervision.

Adam Witkowski: Conceptualization, resources, writing—review and editing, supervision.

## Disclosures

The authors have no conflicts of interest to disclose.

## Supplementary materials

Supplementary material associated with this article can be found in the online version at https://doi.org/10.1016/j.amjcard.2020.02.026.

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