Coronary computed tomography angiography investigation of the association between left main coronary artery bifurcation angle and risk factors of coronary artery disease

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Abstract To explore the association between the left main coronary artery bifurcation angle and common atherosclerotic risk factors with regard to the development of coronary artery disease (CAD) using coronary computed tomography angiography (CCTA). A retrospective review of 196 CCTA cases (129 males, 67 females, mean age 58 ± 10.5 years) was conducted. The bifurcation angle between the left anterior descending (LAD) and left circumflex (LCx) was measured on two-dimensional (2D) and three-dimensional (3D) reconstructed images and the type of plaque and degree of lumen stenosis was assessed to determine the disease severity. An association between bifurcation angle and patient risk factors (gender, body mass index [BMI], hypertension, cholesterol, diabetes, smoking and family history) of CAD was also assessed to demonstrate the relationship between these variables. The mean bifurcation angle between the LAD and LCx was 79.40º ± 22.97, ranging from 35.5 to 178º. Gender and BMI were found to have significant associations with bifurcation angle. Males were at 2.07-fold greater risk of having a > 80º bifurcation angle and developing CAD than females (P = 0.003), and patients with high BMI (> 25 kg/m^2) were 2.54-fold more likely to have a > 80º bifurcation angle than patients with a normal BMI (P = 0.001) and thus were at greater risk of developing CAD. There is a direct relationship between the left main coronary artery bifurcation angle and patient gender and BMI. Measurement of the bifurcation angle should be incorporated into clinical practice to identify patients at high risk of developing CAD.

Keywords Anatomy · Atherosclerosis · Coronary artery disease · Coronary angiography

Introduction

In recent years, coronary computed tomography angiography (CCTA) has become a highly reliable, non-invasive imaging modality with excellent diagnostic accuracy for coronary artery disease (CAD) [1]. In addition to the direct assessment of lumen stenosis enabled by CCTA, this imaging technique has a unique ability to assess and characterize the type and composition of coronary artery plaque, which has been reported to have a direct link to plaque vulnerability [2, 3]. Understanding plaque vulnerability is very important in the prediction of future cardiac events; however, prevention of CAD is the key solution [4, 5]. Recently, correlation between hemodynamic changes in the blood and development of CAD has attracted attention since it improves our understanding of the pathogenesis of coronary atherosclerosis [4-9].

Studies investigating blood flow conditions in coronary arteries have suggested that the tension/force acting against the vessel wall (known as wall shear stress) can lead to complex local characteristics (plaque formation) at areas of flow separation due to the turbulence in the flow [4-7]. This theory was again tested in recent studies looking at the bifurcation angle of the left coronary artery, with findings showing that the larger the angle of bifurcation, the greater the severity of atherosclerotic plaque formation caused by a low wall shear stress [4, 7]. The bifurcation angle has been shown to influence hemodynamic parameters in bifurcation regions, with a larger angle associated with decreased wall shear stress and an increased oscillatory shear index, thus inducing proliferation in the bifurcation regions [8-12]. In addition, a large bifurcation angle has been found to be significantly associated with high-risk and non-calcified plaque at proximal coronary segments [13, 14]. Therefore, areas of bifurcation or great curvature could be an independent risk factor for coronary artery disease

development, and if so should be assessed in clinical practice for early detection of high-risk patients with suspected CAD.

Many studies of CCTA focus on lumen assessment and degree of stenosis; however, only a few have reported correlation of the bifurcation angle with development of CAD and degree of stenosis [5, 15-19]. Some of these studies reported the natural distribution of the left coronary bifurcation angle based on autopsy and CCTA results as an average value of 80º [15, 16], while others demonstrated the relationship between normal and diseased coronary arteries and CAD, with left coronary artery disease associated with a large bifurcation angle (more than 80º) [17, 18]. Furthermore, these studies were based on small sample sizes without addressing the relationship between bifurcation angle and other risk factors related to CAD. Therefore, the aim of this study was to assess whether there is a direct relationship between the bifurcation angle of the left main coronary artery and the development of atherosclerotic plaque. The main hypothesis was that patients with a larger bifurcation angle will be at greater risk of developing CAD than patients with a smaller bifurcation angle. Also, patients with a larger angle will be more likely to exhibit common risk factors related CAD such as age, gender, body mass index (BMI), diabetes, cholesterol, smoking status, blood pressure (BP) levels and family history of CAD in comparison to patients with a smaller bifurcation angle.

Materials and methods

Data collection

Medical records of patients with suspected CAD (presenting with symptoms of angina pectoris) over a period of 12 months (June 2014-June 2015) at a major private clinical center were retrospectively reviewed. The inclusion criterion was CCTA showing coronary artery tree and coronary plaque with good image quality. Patients were excluded if they met any of

the following conditions: those with metallic implants in situ (stents, heart valves, pacemakers etc.), a prior history of coronary artery bypass surgery, and absence of a risk factor checklist. A total of 200 patients were found to be eligible for inclusion in this study and the CCTA images were de-identified for analysis. Patient risk factor checklists were obtained for this study from the clinical center and included patient age, gender, BMI (low risk: < 25 or high risk: > 25 kg/m^2), BP (low risk: < 140/90 or high risk: > 140/90 mmHg), cholesterol level (low risk: < 0.0018 mol/L or high risk: > 0.0018 mol/L), diabetic (Yes or No), smoking (Yes or No) and family history (immediate family members with a history of CAD at < 55 years vs. no history). Ethical approval was obtained from the Curtin Human Research Ethics Committee, and data access to CCTA images was granted by the clinical center.

All procedures performed in this study were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. No informed consent was obtained from the patients, given the retrospective nature of the study.

CCTA scanning protocol

CCTA scans were performed on a Toshiba 320-slice Aquilion ONE CT scanner (Toshiba Aquilion ONE, Toshiba, Otawara, Japan). The scanning protocol was as follows: beam collimation 320 × 0.5 mm, reconstruction interval 0.25 mm, pitch 1.0, tube voltage 120 kVp and tube current modulation was applied to determine the tube current (mA) in each patient. A beta-blocker, metroprolol, was given to all patients with a heart rate above 60 bpm to reduce motion artifacts. Prospective ECG gating was also used to initiate scans to reduce radiation dose. A non-ionic contrast agent was administered intravenously using a bolus tracking technique with a CT attenuation-triggering threshold of 200 to 220 Hounsfield units

(HU) at the descending aorta to initiate the scan. The axial images were then post-processed and reconstructed with a slice thickness of 0.5 mm at 0.25-mm increments. This resulted in an isotropic voxel size of $0.5 \times 0.5 \times 0.5$ mm^3.

Image reconstruction and measurement of the left main coronary bifurcation angle

The original data in digital imaging and communication in medicine (DICOM) format was uploaded onto a workstation equipped with Tera Recon 8.0 (TeraRecon, Inc, Foster City, CA, USA) for generation of two-dimensional (2D) and three-dimensional (3D) volume reconstructions. Left main bifurcation angle was defined as the angle between the centerline of the left anterior descending (LAD) and left circumflex (LCx) on 3D volume rendering images with surrounding anatomical structures removed. This angle was measured three times at varying coronal rotations and the mean value was used to avoid intra-observer disagreement (Fig. 1).

Characterization of coronary plaque type and degree of stenosis

The 2D reconstructed images were used to assess plaque type and degree of stenosis. First, coronary plaque was characterized into three main types: non-calcified, calcified and mixed plaque, which was based on CT attenuation, with a calcified plaque having a CT attenuation of > 220 HU, non-calcified having a CT attenuation less than the contrast-filled lumen, and mixed plaques with a CT attenuation of 130 HU with less than 50% calcium within the lesion [20]. 2D axial images at the site of each plaque were used to determine the degree of luminal stenosis, which was then categorized into four groups: 0% stenosis representing no development of CAD, < 30% stenosis representing low risk, 30-50% stenosis representing intermediate risk and > 50% stenosis representing high-risk patients.

Statistical analysis

Statistical tests were performed using SPSS V 22.0 (SPSS, Inc., Chicago, IL, USA). Continuous variables were expressed as the mean value ± standard deviation, while categorical variables were displayed as frequencies and percentages. Initially, variations in response proportions were examined with generalized linear models, testing for possible factor interaction effects as well as factor main effects. However, adequately fitting multi-factorial models could not be found, which was mostly due to several cells defined by the factorial structures having no corresponding observations. Consequently, factors were assumed to operate independently of one another, and analyses were limited to a series of separate responses in factor contingency tables, each employing the likelihood ratio χ^2test statistic. A *P*-value of less than 0.05 was considered statistically significant.

Results

Of the 200 CCTA cases, bifurcation angles were measured in 196 patients (129 males, 67 females, mean age 58 ± 10.5 years), while in the remaining 4 cases, measurements could not be performed due to difficulty identifying the angulation. The mean bifurcation angle between the LAD and LCx was 79.40˚± 22.97, ranging from 35.5˚ to 178˚. An 80˚ angle was used as the cut-off value to determine significant coronary stenosis according to previous studies, which assessed hemodynamic changes in the left coronary artery at various bifurcation angles [17, 18]. Our study identified 90 cases (45.9%) to have a bifurcation angle > 80˚ and 106 (54.1%) with a bifurcation angle < 80˚.

Fifty cases were randomly selected for inter-observer variability testing and comparison of measurements on CCTA. The two readers blindly measured bifurcation angles on multiplanar reformatted and volume rendering images with high correlation achieved in these angulation values between the two observers ($r = 0.954$, $P < 0.001$).

Table 1 shows the association between bifurcation angle and characteristics and distribution of plaque in the left main stem coronary artery (LM) and its associated branches. As shown in the table, for all coronary arteries and branches that showed development of CAD, the most common type of plaque detected was calcified (LM = 60%, LAD = 44%, LCx = 39%) and the most common degree of coronary lumen stenosis was < 30% stenosis (LM = 85%, LAD = 67%, LCx = 78%). Of the 196 LAD branches assessed, 76 (39%) coronary arteries had no findings of CAD. Assessment of the 194 LM and 194 LCx branches showed no development of CAD in 149 (77%) and 124 (64%) cases, respectively.

Association between bifurcation angle, plaque type and degree of stenosis was not highly correlated, with no significant difference reached between each coronary artery and the associated branches ($P > 0.05$) (Table 1).

Analysis of risk factors, as demonstrated in Table 2, revealed two risk factors, gender and BMI, to have a statistically significant association with bifurcation angle and the development of CAD. The results showed that the probability of a male patient having a bifurcation angle > 80˚ was 2.072-fold ($P = 0.003$) that of a female patient. The probability of a patient with high-risk BMI having a bifurcation angle > 80˚ was 2.537-fold ($P = 0.001$) that of a patient with low-risk BMI. Figures 2 and 3 demonstrate the association between males and bifurcation angles > 80˚ and high-risk BMI (> 25) and bifurcation angles > 80˚. The highest peaks were seen at bifurcation angles of 80-90˚, whereas the histograms representing females and low-risk BMI with bifurcation angle were seen at the lower end of the scale, with a small variation in the frequency of patients in each bifurcation group.

Table 2 shows the distribution of risk factors between the > 80˚ and < 80˚ bifurcation groups. Analysis of risk factors shows that BMI was associated with the greatest ratio of positive to negative findings in this study population with a ratio of 131:65, followed by

blood pressure and cholesterol at 41:63 and 84:40, respectively. The risk factors that showed minimal positive presentation in the cohort were diabetes, smoking and family history at 21:175, 16:180 and 65:131, respectively. However, no significant association was found between age, cholesterol level, blood pressure, diabetes, smoking and family history and bifurcation angle ($P > 0.05$).

Discussion

This study was performed to determine the relationship between the left main coronary bifurcation angle and the development of CAD. Comprehensive analysis explored the relationship between the associated risk factors of CAD and the left bifurcation angle. Assessing the left main coronary bifurcation angle in relation to the development of CAD is a research topic that deserves further investigation because previous studies have only looked at small numbers of patients without exploring the link between bifurcation angle and other risk factors. This study provides insight into the association between the left bifurcation angle and external risk factors of CAD. The main findings in this study suggest that males are at 2.07-fold greater risk of having a bifurcation angle >80˚ compared to females, and patients with high-risk BMI are at higher risk of developing CAD compared to those with a low-risk BMI due to an association between BMI and larger bifurcation angle.

The results of this study are in accordance with reports released by the Australian and American Heart Associations on the prevalence of CAD [21, 22]. This study also revealed a significant correlation between left main coronary bifurcation angle and BMI. An international multicenter study of 13,874 patients with known CAD showed that a high-risk BMI was positively associated with the prevalence of CAD, obstructive stenosis of > 50% and an increased number of segments with coronary plaque ($P < 0.001$). At a mean follow-up of 2.4 years, patients in the larger BMI category were at an increased risk of mortality (P =

0.004) and myocardial infarction ($P < 0.001$) [23]. Although no follow-up was performed in this study, our results show a direct link between BMI, a bifurcation angle > 80˚ and the development of CAD, which further strengthens previous findings of BMI as a reliable risk factor for CAD.

Plaque vulnerability has been widely investigated and is known to be a factor in future cardiac event depending on plaque composition. According to the Providing Regional Observations to Study Predictors of Events in the Coronary Tree (PROSPECT) trial, vulnerable plaques were those with large plaque burden (volume), a small luminal area, the presence of a thin fibrous cap of < 65µm, a large lipid core, signs of spotty calcification and positive remodeling [24]. A CCTA-based study using semi-automated plaque quantification, followed 1059 patients for acute coronary syndrome (ACS) over a mean time frame of 27 ± 10 months [25]. Their study proved that patients diagnosed with ACS on follow-up examination had a higher total plaque volume of 134.9 ± 14.1 mm^3 vs. 57.8 ± 5.6 mm^3, as well as a higher total low-attenuation plaque volume of 20.4 ± 3.4 mm^3 vs. 1.1 ± 1.4 mm^3 compared to those patients that did not develop ACS. The present study found that calcified plaque was the most common plaque type; however, the difference between the presence of the 3 plaque types did not differ significantly in the LAD and LCx (Table 1). Therefore, further studies need to be performed in a multi-center trial that includes patients with low-, intermediate- and high-risk of CAD groups and analyzes plaque burden.

This study presented consistent findings regarding plaque distribution in the coronary arteries [10, 19, 26]. The LAD, particularly just proximal to the site of bifurcation, had the greatest amount of atherosclerotic plaque formation. In this study 61% of the LAD branches showed plaque formation in comparison to the LCx and LM, which only showed development of CAD in 36% and 23% of the branches, respectively. Another single center

study that sought to understand which artery segments are at greatest risk of plaque development at bifurcation regions presented the following results: Of the 41 patients with 46 bifurcation lesions, 37% of plaque was located in the LM, 48% in the LAD, 13% in the LCx and only 2% in the right coronary artery and side branches [27]. Their results highlighted the predominance of coronary plaques in the left coronary arteries, mainly in the LAD. This will provide insight for further studies looking at the difference in hemodynamic changes between the LAD and LCx, which could yield in-depth comparative data on local characteristics of the coronary vessels.

The cut-off bifurcation angle between the LAD and LCx for this study was 80˚, which determined whether the patient was at high risk (> 80˚ angle) or low risk (< 80˚ angle) of developing CAD. This value was derived from previous studies of a similar nature assessing the bifurcation angle between the LAD and LCx. A study by Reig and Petit [15] reported an average bifurcation angle between LAD and LCx of 86.7 ± 28.8˚ in 100 autopsies of human hearts. Another study by Sun and Cao [17] reported the use of an 80˚ cut off value assessing 30 patients with the development of CAD, and their results showed a larger bifurcation angle measured in the diseased left coronary arteries compared to the normal ones. Similarly, another study by Pflederer et al. [16] found an average bifurcation angle of 80 ± 27˚ in 100 patients assessed for suspected CAD, and, lastly, a study by Kawasaki et al. [28] reported an average bifurcation angle of 72 ± 22˚ in 209 patients. Our study showed an average bifurcation of 79.40 ± 22.97˚, which correlates well with previous findings. These previous studies and the current study provide evidence that CCTA imaging can be used as a reliable source for measuring the bifurcation angle, and thus should be recommended as part of the CAD assessment in clinical practice.

Risk factor analysis of this study shows a statistically significant association of BMI and gender with a > 80˚ bifurcation angle, leading to an increased risk of developing CAD. However, other risk factors (blood pressure, cholesterol, diabetes, smoking and family history) showed no association with a greater bifurcation angle and consequent CAD risk. This is due to the small number of patients with such external risk factors in the cohort of patients included in this study. These common risk factors are closely related to the development of CAD; however, in this study, these risk factors were analyzed solely with regard to their association with bifurcation angle. Thus, our results should be interpreted carefully as the study focus is bifurcation angle in relation to other risk factors. Further studies including a large number of patients with different risk factors are needed to verify our findings.

Some limitations in this study should be acknowledged. First, because our study included a large percentage of coronary arteries that were normal in all 3 coronary branches, the results need to be interpreted with caution. This limitation could be overcome by including patients at intermediate and high-risk of CAD to allow for a more comprehensive analysis of risk groups. Second, this is a retrospective study using data obtained after patient imaging. This limits the ability to follow patient treatment and outcomes. Further studies that are conducted over a longer time period to allow for comprehensive analysis of CCTA results and the development of major adverse cardiac events are needed. Third, previous studies have tested blood flow changes in the coronary arteries, with the results confirming that larger bifurcation angles are associated with increased turbulence in the flow, leading to areas with increased risk of atherosclerotic development. This study used this theory as a basis; however, due to its retrospective nature, blood flow analysis was not part of our assessments. Further research should focus on measuring blood flow changes in the bifurcation area using the latest CCTA-derived computational fluid dynamics to allow robust conclusions to be

drawn [29, 30]. Fourth, only plaque distribution, plaque type and degree of lumen stenosis were analyzed in this study, while other parameters contributing to plaque vulnerability, such as plaque burden, plaque volume and lesion length were not assessed [31, 32]. These variables should be included in CCTA analysis of coronary plaques in future studies. Finally, there is no correlation between CCTA and invasive coronary angiography findings. In addition, measurement of the bifurcation angle is not a standard approach in daily clinical practice. Therefore, the exact position of measurement may not be standardized. This leads to potential inter-observer and intra-observer variance. Systematic measurement of bifurcation angles should be performed at end systole and end diastole to achieve more accurate and reproducible results [33]. Despite these limitations, a recent study has shown good correlation between CCTA and invasive coronary angiography using bifurcation angle measurements as a criterion to determine coronary stenosis [34]. Further studies need to be performed to assess the most effective method of measuring the angle to minimize inter- and intra-observer variance and bias.

In conclusion, this study suggests a strong association between patient gender and BMI and bifurcation angle. The high risk of developing CAD in males and high BMI patients with large bifurcation angles should not be ignored. The left main coronary bifurcation angle should be further assessed as a part of routine clinical practice to identify high-risk patients and to prevent CAD-related events.

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Conflict of interest Authors declare that they have no conflict of interest.

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Figures and figure legends

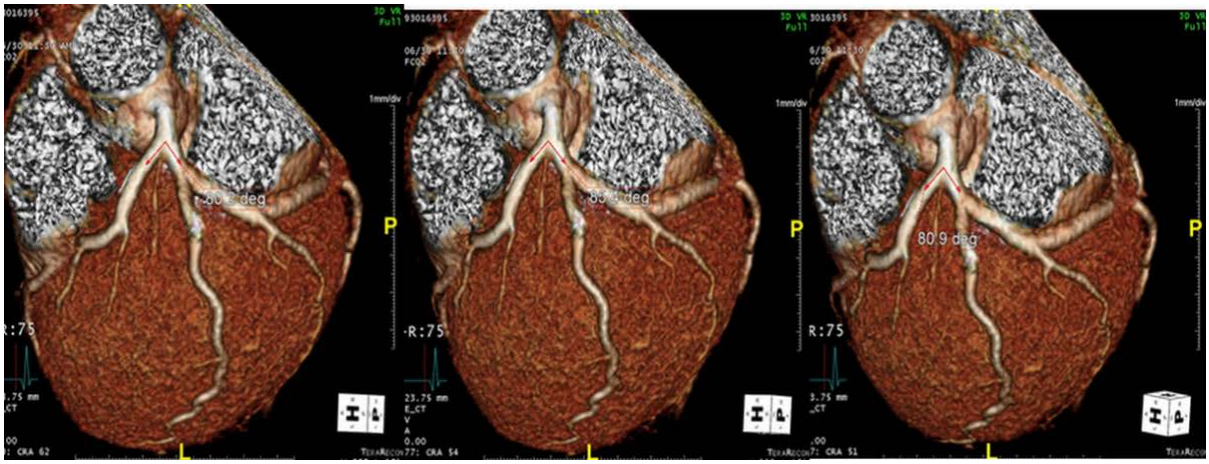

Fig. 1 Three-dimensional (3D) reconstructed images showing the bifurcation angle of the left main coronary artery as it branches into the left anterior descending and left circumflex. Measurement of the angle was performed three times on 3D volume rendered images at different positions

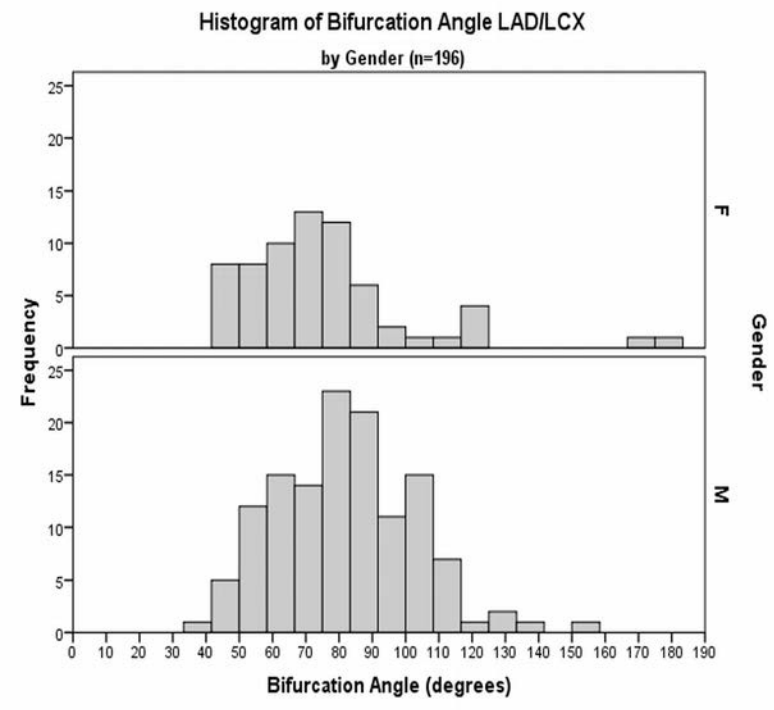

Fig. 2 Histogram of the distribution of patients with regard to gender and bifurcation angle, with male gender associated with a bifurcation angle > 80º

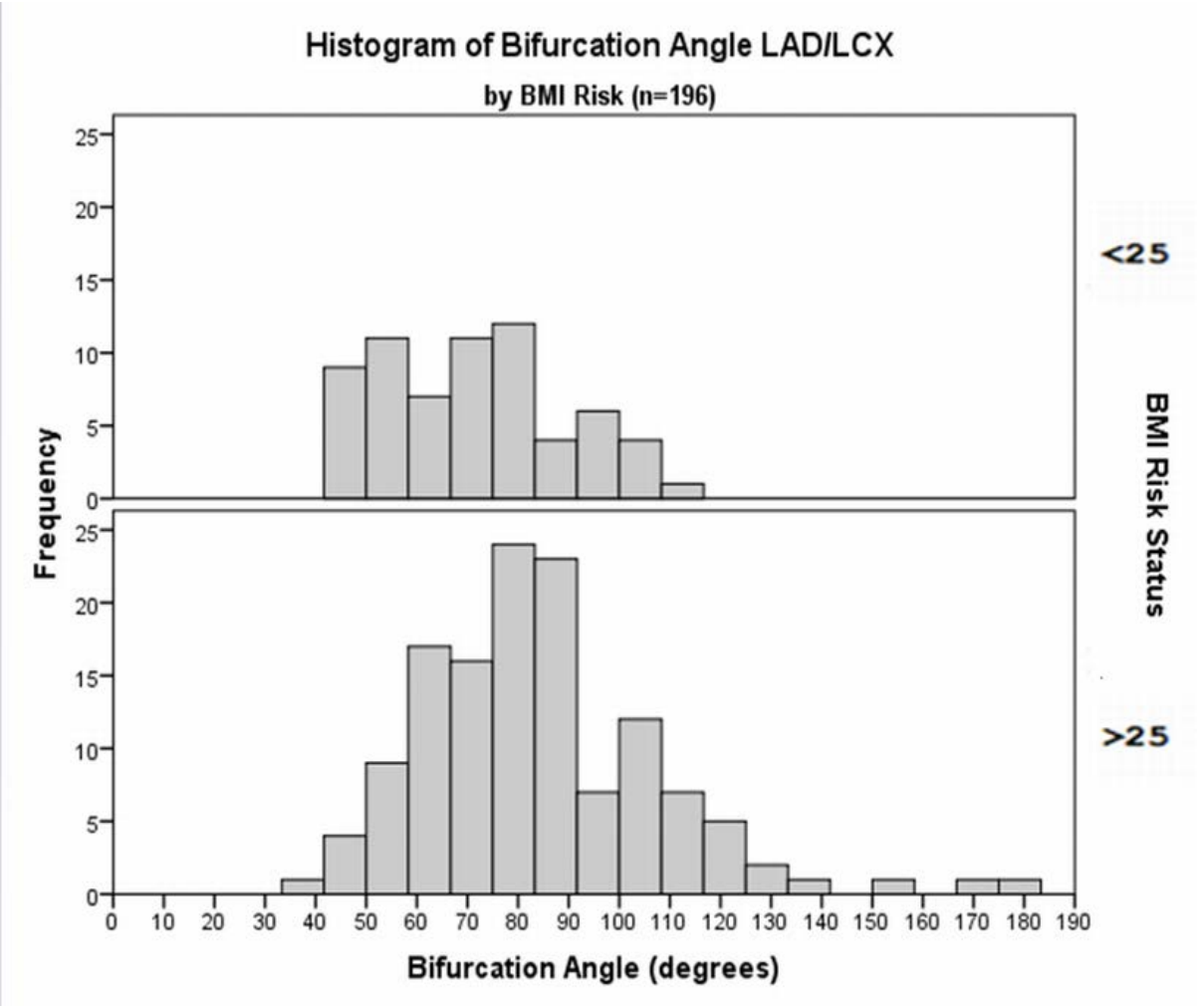

Fig. 3 Histogram of the distribution of patients with regard to body mass index (BMI) and bifurcation angle, with high BMI associated with a bifurcation angle of > 80º

Table 1 Association between left main coronary bifurcation angle, plaque type and degree of stenosis

		Bifurcation angle < 80º	Bifurcation angle > 80º	*P* value	Likelihood ratio	Total
Left anterior descending						
Plaque type	No plaque	41 (53.9%)	35 (46.1%)	0.935	0.936	76 (100%)
	Calcified	27 (50.9%)	26 (49.1%)			53 (100%)
	Non-calcified	15 (55.6%)	12 (44.4%)			27 (100%)
	Mixed	23 (57.5%)	17 (42.5%)			40 (100%)
Degree of stenosis	0%	48 (54.5%)	40 (45.5%)	0.435	0.442	88 (100%)
	< 30%	38 (54.3%)	32 (45.7%)			70 (100%)
	30-50%	15 (60%)	10 (40%)			25 (100%)
	> 50%	3 (30%)	7 (70%)			10 (100%)
Left circumflex						
Plaque type	No plaque	69 (55.6%)	55 (44.4%)	0.912	0.912	124 (100%)
	Calcified	14 (51.9%)	13 (48.1%)			27 (100%)
	Non-calcified	12 (54.5%)	10 (45.5%)			22 (100%)
	Mixed	10 (47.6%)	11 (52.4%)			21 (100%)
Degree of stenosis	0%	78 (55.3%)	63 (44.7%)	0.846	0.846	141 (100%)
	< 30%	21 (51.2%)	20 (48.8%)			41 (100%)
	30-50%	6 (60%)	4 (40%)			10 (100%)
Left main stem						
Plaque type	No plaque	83 (55.7%)	66 (44.3%)	0.909	0.909	149 (100%)
	Calcified	14 (51.9%)	13 (48.1%)			27 (100%)
	Non-calcified	6 (54.5%)	5 (45.5%)			11 (100%)
	Mixed	3 (42.9%)	4 (57.1%)			7 (100%)
Degree of stenosis	0%	92 (53.8%)	79 (46.2%)	0.711	0.713	171 (100%)
	< 30%	10 (58.8%)	7 (41.2%)			17 (100%)
	30-50%	1 (33.3%)	2 (66.7)			3 (100%)

Table 2 Association between left main coronary bifurcation angle and risk factors of coronary artery disease

Risk factors		Bifurcation angle <80º	Bifurcation angle >80º	P value	Likelihood ratio	Total
Gender	Male	60 (46.5%)	69 (53.5%)	0.003	0.003	129 (100%)
	Female	46 (68.7%)	21 (31.3%)			67 (100%)
Age	≤ 50	26 (60.5%)	17 (39.5%)	0.265	0.273	43 (100%)
	51-60	36 (51.4%)	34 (48.6%)			70 (100%)
	61-70	28 (48.3%)	30 (51.7%)			58 (100%)
	≥ 71	16 (69.6%)	7 (30.4%)			23 (100%)
Body mass index	High risk	60 (45.8%)	71 (54.2%)	0.001	0.001	131 (100%)
	Low risk	46 (70.8%)	19 (29.2%)			65 (100%)
Cholesterol	High risk	49 (58.3%)	35 (41.7%)	0.860	0.860	84 (100%)
	Low risk	24 (60%)	16 (40%)			40 (100%)
Blood pressure	High risk	23 (56.1%)	18 (43.9%)	0.359	0.358	41 (100%)
	Low risk	41 (65.1%)	22 (34.9)			63 (100%)
Diabetes	Yes	9 (42.9%)	12 (57.1%)	0.275	0.275	21 (100%)
	No	97 (55.4%)	78 (44.6%)			175 (100%)
Smoking history	Yes	8 (50%)	8 (50%)	0.733	0.732	16 (100%)
	No	98 (54.4%)	82 (45.6%)			180 (100%)
Family history	Yes	38 (58.5%)	27 (41.5%)	0.385	0.386	65 (100%)
	No	68 (51.9%)	63 (48.1%)			131 (100%)