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„True“ coronary artery bifurcations in acute coronary syndrome are associated with longer PCI, but do not influence clinical outcome

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Abstract

Introduction: Percutaneous coronary interventions (PCI) in bifurcation lesions with more than 50% stenosis of both main and side branch remain challenging. These “true” bifurcation lesions (TBL) causing acute coronary syndrome (ACS) could pose an additional challenge for adequate treatment since there are no recommended strategies. We investigated the influence of the presence of TBLs as culprit lesions for ACS on the clinical outcomes after PCI.

Methods: The study was retrospective and conducted in a high-volume university PCI centre. Study included 256 consecutive patients with native coronary artery bifurcation lesions causing an ACS. Patients with ACS caused by stent thrombosis were not included in the study. All patients underwent PCI of the culprit bifurcation lesion and afterwards were treated according to the appropriate guidelines.

Results: Most of the bifurcations were located in left anterior descending 152/256 (59.3%), then in circumflex 66/256 (25.9%) and right coronary artery 38/256 (14.8%). The initial clinical presentation was STEMI in 144/256 (56.2%), then NSTEMI 59/256 (23.1%) and unstable angina in 53/256 (20.7%) patients. TBLs were present in 146/256 (57.0%) patients. TBLs were associated with longer PCI procedural time 48±24min vs. 31±28min ($p<0.05$) and greater contrast volume 177±73 vs. 149±48 ml ($p=0.01$), but not with larger myocardial infarction in terms of magnitude of troponin I release 47.35±73.73 vs 31.07±38.05 ng/ml ($p=0.164$) and LVEF 40±13 vs 42±13% ($p=0.439$), as compared to other bifurcations. The patients were followed for 405±377 days. MACCE (major adverse cardio-cerebral events: death, myocardial infarction, repeated revascularization and stroke) occurred in 55/256 (21.5%) patients. In univariate regression analysis, provisional PCI strategy was associated with fewer MACCE [OR 0.283 (95 % CI 0.089–0.898)]. However, in the multivariate regression analysis, that included recognized predictors of MACCE (diabetes, LVEF, chronic kidney disease, multivessel disease, provisional PCI strategy, use of ticagrelor, TBLs) only the presence of the multi-vessel coronary artery disease remained an independent predictor of MACCE [OR 5.147 (95 % CI 1.859–14.248)].

Conclusions: TBL in acute coronary syndrome are associated with longer PCI duration, but were not associated with larger myocardial infarction and adverse cardiovascular outcomes. The extent of the CAD at presentation is associated with future cardiovascular events.

Key words true bifurcation lesion, acute coronary syndrome, percutaneous coronary intervention

Introduction

A bifurcation lesion (BL) is an atherosclerotic lesion formed at or near the junction of two significant epicardial coronary arteries[1] ,,True'' coronary bifurcation (TBL) includes stenosis more than 50% of both main branch (MB) and side branch (SB). Medina classification is based on lesion greater than 50% in bifurcation branches, while TBL have a significant narrowing of both MB and SB[2-4]. The complex morphology of TBL is manifested in MB and SB diameters' difference, angle between the arteries and plaque characteristics (calcification, presence of the inflammatory cells and lipid content)[5]. Atherosclerosis frequently develops in areas adjacent to branching points of coronary arteries. Almost 15-20% of patients undergoing a percutaneous coronary intervention (PCI) have BL as a target lesion. PCI procedures involving TBL are complex and challenging for

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interventional cardiologists. They are frequently associated with complications such as restenosis, stent thrombosis and worse clinical outcomes.[6-8]. Data on clinical outcomes of TBLs in the acute coronary syndrome (ACS) are limited. TBLs are usually treated with provisional stenting strategy that includes MB stent implantation across the ostium of the SB. SB should be treated in a case of unfavourable angulation of SB or its significant stenosis leading to critical ischemia after MB stent implantation. These procedures carry potential high risk of residual myocardial ischemia. The clinical success of PCI depends mainly on the optimal treatment of MB, which should be the main goal of PCI in any bifurcation lesion including TBL.[9] Since there are no recommended strategies for TBL causing ACS, they could pose an additional challenge for adequate treatment. In this study we have investigated the influence of TBLs compared to other bifurcation, causing an ACS on the clinical outcomes after PCI.

Methods

This was a retrospective, observational study conducted at Department of Cardiology, University Clinical Hospital Centre Zemun, Belgrade, Serbia. A total of 256 consecutive patients with native coronary artery BL causing an ACS, admitted to our hospital between December 2016 and September 2018, were included in the study. Patients with ACS caused by stent thrombosis, previously revascularized and patients in cardiogenic shock were excluded from the study. Coronary angiograms were visually assessed for coronary lesions in two orthogonal planes by an experienced interventional cardiologist blinded to all other data. TBL were assessed by a Medina classification and based on the presence of a lesion> 50% on both MB and SB. All patients underwent PCI procedure of the BL using a technique selected according to the operator's preference, and afterwards were treated in accordance with current recommendations. The choice of a vascular approach, guiding catheters, coronary guidewires, balloons and stents was left to the interventional cardiologist who performed the intervention. Second generation drug eluting stents were implanted according to the catheterization laboratory shelf availability. Puncture site haemostasis was done manually or using a haemostatic device. Patients were followed using telephone interview or an office visit and the clinical status, occurrence of major adverse cardiovascular and cerebral events (MACCE) and use of dual antiplatelet therapy (DAPT) were recorded. The study was approved by the Institutional Ethics Committee.

Statistical analysis

Continuous data were expressed as means with standard deviations and compared between groups using unpaired and paired T-test. Categorical data were summarized by proportions and compared by using a Chi square and Fisher's exact test. Univariable and multivariable logistic regression analyses were performed to determine patient's and procedural characteristics associated with outcomes – cardiovascular events. The multivariable regression model was done using "stepwise selection model". The stepwise selection iteratively selected the most significant variable with multivariate p-value <0.25, to start the model. At each step, another significant variable is added and after running the model, a check was performed to remove the variable with a multivariate p-value >0.10. This was repeated with the complete set of variables until no more variables could be entered and no variables could be dropped. All statistical tests were two-tailed, and p value <0.05 was considered significant. Statistical analysis was performed using PASW Statistics software version 19 (SPSS, Inc., Chicago, IL).

Results

The study included 256 consecutive patients with ACS caused by a bifurcation coronary artery lesion, of which 146 were TBL (57.0%). Characteristics of the study population are summarized in **Table 1.** Patients with TBL were more frequently male, had a higher body mass index (BMI) and more frequently underwent previous PCI. Traditional risk factors for cardiovascular disease were present in both groups at similar rates. Most of the bifurcations were in left anterior descending 152/256 (59.3%), then in circumflex 66/256 (25.9%) and right coronary artery 38/256 (14.8%), while the most common clinical presentation was ST elevation myocardial infarction in both groups (**Table 2**). TBLs were associated with longer PCI duration 48±24min vs. 31±28min (p<0.05) and contrast agent consumption 177±73 vs. 149±48 ml (p=0.01), but not with greater myocardial infarction in terms of magnitude of troponin I release 47.35±73.73 vs 31.07±38.05 ng/ml (p=0.164) and LVEF 40±13 vs 42±13% (p=0.439), as compared to other bifurcation lesions. Patients were followed for 405±377 days by either office visit or telephone contact. MACCE (Major adverse cardiocerebral events: death, myocardial infarction, repeated revascularization and stroke) were noted in 58/256

Table 1. Clinical characteristics of patients

Variable	,,True bifurcation'' n = 146	Other bifurcation n = 110	p
Age (years)	61±10	57±16	0.070
Male sex (%)	73.9	85.4	0.050
Family history of CAD (%)	46.6	49.1	0.750
Smoking (%)	59.6	60.9	0.878
Hypertension (%)	88.3	77.2	0.049
Dyslipidemia (%)	75.3	71.8	0.605
Diabetes mellitus (%)	25.3	29.1	0.605
PAD (%)	4.8	0.0	0.193
Previous IM	26.1	14.5	0.129
Previous CVI (%)	4.1	1.8	0.676
Previous PCI (%)	34.2	16.3	0.005
BMI (kg/m^2)	27±4	26±3	0.028
CKD (%)	7.5	16.3	0.170

BMI - body mass index; CVA - cerebrovascular event; CKD – chronic kidney disease IM - myocardial infarction; PAD - peripheral arterial disease; PCI - percutaneous coronary intervention

Table 2. Clinical and angiographic characteristics

Variable	,,True'' bifurcation	Other bifurcation	p
	n = 146	n = 110	
Location (%)			
LAD–D	83 (56.8)	67 (61.0)	0.645
Cx–OM	38 (26.0)	26 (23.6)	0.862
RCA PD–PL	25 (17.2)	17 (15.4)	1.000
Medina class. n (%)			
1.0.1	19 (13.1)	0 (0)	-----
0.1.1	25 (17.1)	0 (0)	-----
1.1.1	102 (69.8)	0 (0)	-----
0.0.1	0 (0)	6 (5.5)	-----
1.0.0	0 (0)	49 (44.5)	-----
0.1.0	0 (0)	55 (50)	-----
STEMI (%)	79 (54.1)	71 (64.5)	0.368
NSTEMI (%)	39 (26.7)	14 (12.7)	0.086
Unstable angina (%)	28 (19.2)	25 (22.8)	0.700

LAD – left anterior descending artery; D - diagonal artery; Cx - circumflex coronary artery; OM - obtuse marginal artery; RCA - right coronary artery; PD – posterior descending artery; PL – posterior olateral artery; STEMI - ST elevation myocardial infarction; NSTEMI – non ST elevation myocardial infarction

(22.6%) patients. Patients with TBL had a higher incidence of angina symptoms and recurrent percutaneous revascularization, but the overall incidence of MACCE was similar in the study groups (**Table 3**). In univariate regression analysis, only ,,provisional'' PCI strategy was associated with lower MACCE [OR 0.283 (95% CI 0.089–0.898)], while in the multivariate regression analysis, including recognized predictors of MACCE (diabetes, LVEF, chronic kidney disease, multivessel disease, ,,provisional'' PCI strategy, use of ticagrelor, TBLs), only presence of multivessel coronary artery disease remained an independent predictor of cardiovascular events [OR 5.147 (95 % CI 1.859–14.248)]. (**Table 4**)

Discussion

In this study, we have investigated the association of true bifurcation lesion causing an acute coronary syndrome with PCI complications and significant adverse cardiovascular events. Our study demonstrated that the presence

Table 3. Incidence of outcomes

Variable	"True" bifurcations n = 146	Other bifurcations n = 110	p
Death n (%)	11 (7.5)	8 (7.2)	1.000
Myocardial infarction n (%)	3 (2.1)	1 (0.9)	0.561
Repeated PCI n (%)	21 (14.3)	6 (5.4)	0.862
CABG n (%)	0 (0)	0 (0)	-----
CVA n (%)	5 (3.4)	2 (1.8)	1.000
Angina pectoris n (%)	32 (21.9)	12 (10.9)	0.146
MACCE n (%)	41 (28.1)	17 (15.4)	0.238

CABG- coronary artery bypass grafting; CVA – cerebrovascular event; MACCE - major adverse cardiovascular and cerebral events; PCI – percutaneous coronary intervention

of TBL responsible for ACS, has been associated with a longer duration of the PCI procedure, as well as an increased amount of contrast given during the intervention. However, the presence of TBL was not associated with a decrease in left ventricular systolic function (LVEF) and the size of the myocardial infarction measured as troponin I release compared to uncomplicated BL responsible for the development of ACS. After approximately one year follow-up period, association between the presence of TBL and the occurrence of adverse cardiovascular events was not found in by a multivariate regression analysis. On the other hand, multivessel coronary artery disease has been shown to be strongly associated with adverse cardiovascular events. [7]

The presence of TBL involving significant lesions of both MB and SB is associated with the higher occurrence of PCI complications, especially if more than one stent was implanted or complex interventional strategy was employed[4,10,11]. At the same time, the interventional treatment of a BL in ACS presents an additional challenge[12]. In our study, the presence of diabetes and decreased LVEF were not associated with the occurrence of adverse cardiovascular events. On the other hand, large registries of BL, as well as acute myocardial infarction, identified these clinical features as significant predictors of adverse clinical outcomes[11,13,14]. The potential reason for this finding could be a small sample size in our study. A favourable signal could be the univariate association

Table 4. Univariable and multivariable predictors of MACCE

	Univariable		Multivariable	
	OR [95% CI]	P value	OR [95% CI]	P value
Diabetes mellitus	1.287 [0.596 – 2.782]	0.521	- - -	- - -
LVEF	0.965 [0.940 – 0.992]	0.010	0.977 [0.948 – 1.007]	0.139
Multivessel disease	6.821 [2.536 – 18.346]	<0.001	5.551 [2.004 – 15.376]	0.001
„Provisional" PCI strategy	0.283 [0.089 – 0.898]	0.032	2.543 [0.736 – 8.778]	0.140
CKD	2.333 [0.854 – 6.375]	0.098	0.556 [0.183 – 1.692]	0.556
„True" bifurcation	1.745 [0.747 – 4.079]	0.199	- - -	- - -
Ticagrelor in DAPT	1.893 [0.897 – 3.994]	0.094	1.865 [0.825 – 4.218]	0.134

CI – confidence interval; CKD - chronic kidney disease; DAPT – dual antiplatelet therapy; LVEF – left ventricular ejection fraction; OR – probability ratio; PCI – percutaneus coronary intervention.

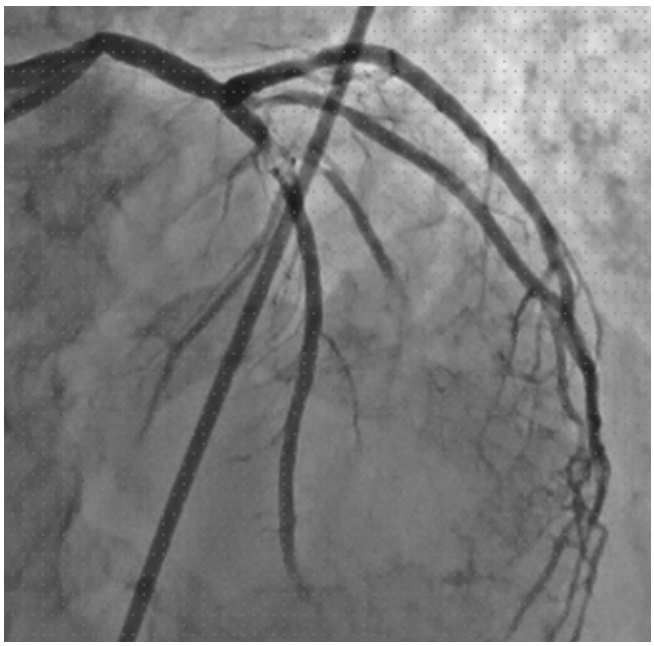

Figure 1. True coronary artery bifurcation in LAD-D territory with large thrombus burden causing an acute coronary syndrome is presented.

of LVEF with adverse cardiovascular outcomes, which did not stand comparison to multivessel coronary artery disease in multivariable analysis. On the other hand, our study included only patients with ACS, in contrast to previously mentioned registries of BL, which may also affect clinical outcomes.

The presence of a TBL was not significantly associated with adverse cardiovascular outcomes, and this is in accordance with a study by Zimarino et al. which included more than 5,000 treated BL[14]. The reason for this finding could be sought primarily in the presence of strong clinical predictors of outcomes like multivessel coronary artery disease, LVEF, diabetes and ACS that might obscure the potential effect of TBL on cardiovascular events. Importantly, most patients, regardless of the presence of TB, were treated with a "provisional" strategy - implantation of stent in the bifurcation's MB - which "equalizes" the treatment of TBL and other bifurcations, thus bringing them into similar position in relation to outcomes. This conclusion stems from studies that have shown that complex strategies with implantation of two stents were associated with increased incidence of adverse cardiovascular events[14,15]. Our study showed that the "provisional" stent implantation strategy was associated with better outcomes in univariate analysis, but this was not maintained in multivariable model. We've demonstrated that TBLs are associated with a longer PCI duration and greater contrast consumption, which pointed towards the complexity of the procedure. The reason for this should be sought in several features of a bifurcation lesion with significant disease of the SB where an operator could experience difficulty to pass the coronary gudewire into the SB. Also, a suboptimal result in the SB after stent implantation in the MB could be the reason to perform additional procedures like SB ostial angioplasty, stent implantation and/or repeated postdilatation of the stent implanted in the MB (proximal optimization - POT). All this could lead to increased procedural time and use of contrast[16]. Multivessel coronary artery disease is a relatively common finding in patients with ACS and is associated with greater cardiovascular events rate in the first year after initial hospitalization[17]. Large registry of BL showed that the multivessel disease was an important clinical predictor of adverse cardiovascular events[14,17]. Our study also showed that the presence of multivessel disease was associated with adverse cardiovascular events. The reasons for this finding should be sought in the prevalence of coronary artery disease, which is growing despite interventions and drug therapy[17,18,19]. On the other hand, complex interventional treatment which includes BL, carries the risk of specific manifestations of coronary artery disease like stent thrombosis and in-stent restenosis[15].

Study limitations

Our study is limited by its single centre, retrospective, observational design. Further, data on angiographic findings and interventions were obtained from the registry instead directly from the angiograms. Finally, in some cases, patient's data were obtained by telephone and patient's self-assessment of their own health and prescribed medications which may cause certain inaccuracy in reporting.

Conclusion

True bifurcation lesions responsible for an acute coronary syndrome are associated with prolonged PCI procedures, but were not associated with larger myocardial infarctions and adverse cardiovascular outcomes compared to uncomplicated ones. The extent of CAD at presentation remains one of the most important clinical factors in prediction of the future cardiovascular events.

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Sažetak

„Prave“ bifurkacije koronarnih arterija u akutnom koronarnom sindromu su povezane sa dužinom trajanja perkutane koronarne intervencije, ali ne utiču na klinički ishod

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Uvod: *Perkutane koronarne intervencije (PKI) na bifurkacionim lezijama (BL) sa suženjem glavne i bočne grane većim od 50 % predstavljaju izazov. Ove ,,prave“ bifurkacione lezije (PBL) predstavljaju dodatni izazov kada su uzrok akutnog koronarnog sindroma (AKS), zato što nema preporuka za njihovo adekvatno lečenje. Cilj studije je ispitati uticaj PBL odgovorne za AKS na klinički ishod nakon PKI.*

Metode: *Studija je retrospektivna, sprovedena u univerzitetskom centru i uključila je 256 konsekutivnih pacijenata sa AKS uzrokovanim BL na nativnoj koronarnoj arteriji. Pacijenti sa AKS usled stent tromboze nisu uključeni u studiju. Svi pacijenti su podvrgnuti PKI odgovorne arterije, a zatim lečeni prema odgovarajućim preporukama.*

Rezultati: *BL su najzastupljenije na prednjoj descedentnoj grani leve koronarne arterije 152/256 (59.3%), zatim na cirkumfleksnoj 66/256 (25.9%) i desnoj koronarnoj arteriji 38/256 (14.8%). Klinička prezentacija bila je STEMI kod 144/256 (56.2%) , zatim NSTEMI 59/256 (23.1%) i nestabilna angina pektoris kod 53/256 (20.7%) pacijenata. PBL su nađene kod 146/256 (57.0%) pacijenata. PBL su povezane sa dužim trajanjem PKI 48±24 min naspram 31±28 min (p<0.05), većom potrošnjom kontrasta 177±73 naspram 149±48 ml (p=0.01), ali ne i većim infarktom prema nivou troponina I 47.35±73.73 naspram 31.07±38.05 ng/ml (p=0.164), i vrednostima ejekcione frakcije leve komore (LVEF) 40±13 naspram 42±13% (p=0.439). Pacijenti su praćeni 405±377 dana. Neželjeni kardiovaskularni događaji (smrt, infarkt miokarda, ponovna revaskularizacija, moždani udar) registrovani su kod 55/256 (21,5%) pacijenata. U univarijantnoj regresionoj analizi, ,,provizorna'' strategija PKI je povezana sa manjom učestalošću kardiovaskularnih događaja [OR 0.283 (95 % CI 0.089–0.898)]. U multivarijantnoj regresionoj analizi koja uključuje poznate prediktora za značajne kardiovaskularne događaje (dijabetes, LVEF, hronična bubrežna insuficijencija, višesudovna koronarna bolest (VKB), ,,provizorna'' strategija PKI, upotreba tikagrelora, prisustvo PBL), utvrđeno je da je samo VKB nezavisni prediktor nastanka kardiovaskularnih događaja [OR 5.551 (95 % CI 2,004–15,376)].*

Zaključak: *,,Prave” bifurkacione lezije u akutnom koronarnom sindromu su povezane sa dužim trajanjem PKI i većom potrošnjom kontrasta, ali ne i sa veličinom infarkta i kardiovaskularnim događajima. Opsežnost koronarne bolesti predstavlja najbolji prediktor budućih kardiovaskularnih događaja.*

Ključne reči: bifurkaciona lezija, akutni koronarni sindrom, perkutana koronarna intervencija