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Atheroma and coronary bifurcations: before and after stenting

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Abstract

First generation drug-eluting stents (DES) have significantly improved the treatment options for patients with symptomatic coronary artery disease by decreasing rates of restenosis after percutaneous coronary revascularisation procedures. However, early enthusiasm was tempered by reports of late stent thrombosis, primarily in "off-label" use. In particular, the treatment of atherosclerotic plaques at coronary bifurcations has been challenging for interventional cardiologists regardless of the stent choice due to the underlying nature of the atherosclerotic disease and the use of multiple stents. In this article we illustrate the location and severity of plaque and investigate the healing following both bare metal stents (BMS) and drug-eluting stents (DES) at bifurcations using post-mortem specimens. The presented data will demonstrate that neointimal growth following stent implantation correlate to flow conditions, as there is less underlying atherosclerotic disease at high shear regions and subsequently less neointimal growth is observed in these regions versus low shear regions. The occurrence of late stent thrombosis in DES is also shown to be associated with greater presence of uncovered stent struts at the high shear region, which is likely due to local flow mechanics.

Abbreviations

ARC	academic research consortium
CAD	coronary atherosclerotic disease
BMS	bare metal stent (s)
DES	drug eluting stents (s)
PCI	percutaneous coronary intervention

Introduction

Flow in the coronary arteries is inherently complex due to the pulsatile conditions, curvature of the coronary, the contraction and relaxation of the myocardium and the extensive branching that leads to large variations in wall shear stress levels. Coronary atherosclerotic disease (CAD) tends to form at specific regions of the coronary vasculature where flow is disturbed, in particular in areas of low flow-induced shear stress[1,2]. Because dramatic haemodynamic alternations occur at branch points within the arterial tree, coronary bifurcation are extraordinarily susceptible to atherosclerosis. Areas of low shear stress are thought to accelerate atherosclerosis through modulation of gene expression including the promotion of endothelial cell dysfunction which causes increased uptake of lipoproteins, up-regulation of leukocyte adhesion molecules, and leukocyte endothelial transmigration, all of which contribute to the development and progression of atherosclerosis[3].

It is estimated that coronary bifurcation lesions are involved in up to 15-20% of all percutaneous coronary intervention procedures (PCI)[4]. Morphologically, these lesions are complex with variations in severity of atherosclerotic disease in the main artery and side branch, the absolute and relative diameters of these vessels, the amount and distribution of calcium and fibrous tissue in the lesion, and the angle of the bifurcation[5]. The factors that contribute to the higher rates of procedural complications of coronary bifurcation include restenosis and stent thrombosis following percutaneous intervention irrespective of the stent platform used[6,7]. Early results using bare metal stents (BMS) to treat bifurcation lesions resulted in

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a high angiographic acute success rate but were limited by a high rate of restenosis[8]. Even though the use drug eluting stents (DES) has reduced restenosis rates in bifurcation lesions, long-term outcomes are tempered by an increased risk for late thrombosis[9], which raises the possibility that delayed healing seen after DES implantation might be exacerbated at bifurcation sites, perhaps secondary to stent-induced flow disturbances in combination with locally eluted drug.

In this review, we will focus on the distribution of atherosclerotic plaque in human coronaries and compare the pathologic arterial response to bifurcation stenting following implantation of DES or BMS.

Plaque distribution in human coronary bifurcations

Bifurcations vary not only in anatomy (plaque burden, location of plaque, angle between branches, diameter of branches, bifurcation site) but also in the dynamic changes in anatomy during treatment (plaque shift, dissection). As a result, no two bifurcations are identical and no single strategy exists that can be applied to every bifurcation lesion.

Currently there are at least six different classifications of bifurcation lesions, with Medina classification being the most commonly used[10]. Practically, the most important distinction is to divide bifurcation lesions into either: i) "true" bifurcations where MB and SB are both significantly narrowed (>50% diameter stenosis); or ii) "non-true bifurcations," which include all the other lesions involving a bifurcation. Other important elements to consider (that are not inherent in the bifurcation classifications) include the extent and distribution of disease on the side branch and its size and angle[10].

It has been reported that the occurrence of atherosclerosis at bifurcations is closely related to local haemodynamic forces such as shear stress[1,11]. Patterns of early intimal thickening in several arteries coincide with locations of low and oscillating wall shear stresses[1,12]. Moreover, autopsy studies have also demonstrated a higher prevalence of atherosclerotic plaques in the low shear regions in coronary bifurcation lesions[13,14]. In our laboratory, we investigated the axial distribution of coronary plaques in bifurcation lesions utilising longitudinal sectioning method[15] (Figure 1). Twenty-six bifurcation lesions in 18 patients dying with severe coronary artery disease were examined. The lateral wall (i.e., low shear areas) showed significantly greater prevalence of coronary plaque formation as compared to the flow divider sites (i.e., high shear areas) consistent with previous studies[13,14] (Figure 2). In addition to the plaque distribution, progressive atherosclerosis such as necrotic core formation was significantly more frequent in the lateral wall (low shear regions).

Plaque progression has been shown to be initiated by endothelial dysfunction followed by increased permeability to lipoproteins, up-regulation of adhesion molecules such as ICAM-1 (intercellular adhesion molecules) and VCAM (vascular cell adhesion molecules), and leukocyte transmigration[3]. It is well known that there is a strong correlation between endothelial dysfunction and low shear stress and oscillatory flow which is observed at sites of bifurcations or in severe curvatures. Cheng et al reported up-regulation of eNOS (endothelial nitric oxide synthase) at high shear regions utilising cast-induced increased shear stress model, as a cylinder with a tapered lumen was placed around a mouse carotid artery[16]. In a later study, they also showed elevated gene expressions of

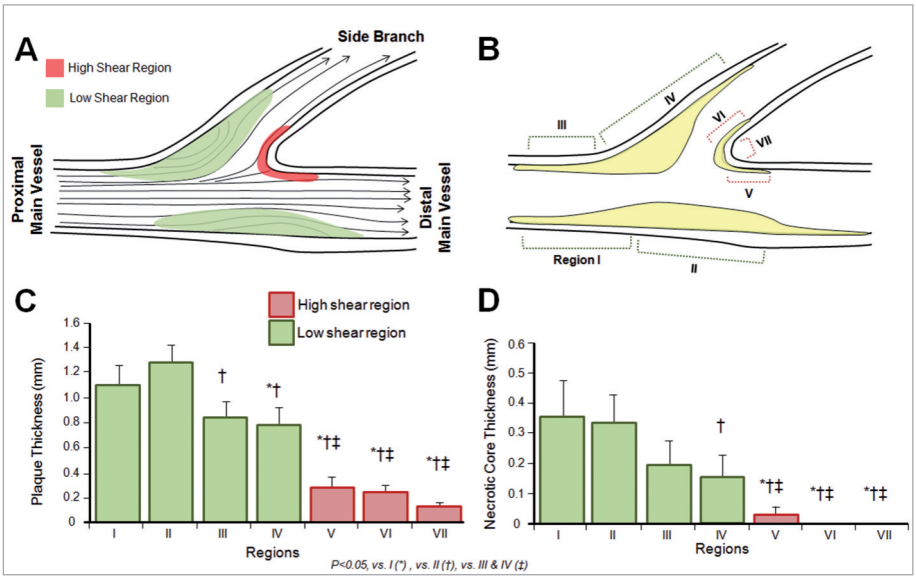

Figure 1. Morphometric analysis of native coronary bifurcations. (A) Schematic diagram illustrating flow behaviour within a coronary branch with low shear regions observed in the lateral walls and high shear regions observed at the carinal region. (B) For non-stented atherosclerotic lesions, sections were assessed based on the longitudinal location; Region I - Proximal main vessel, Region II - Distal main vessel on the lateral wall, Region III - Proximal main vessel on the side branch, Region IV - Distal side branch on the lateral wall, Region V - Distal main vessel on the flow divider side, Region VI - Distal side branch on the flow divider side, and Region VII - Carinal region. (C) Plaque thickness was greater in regions of low shear as compared to high shear. (D) Similarly, necrotic core thickness was significantly greater in low shear regions as compared to high shear. Note the absent of necrotic core at the carinal region (VII).

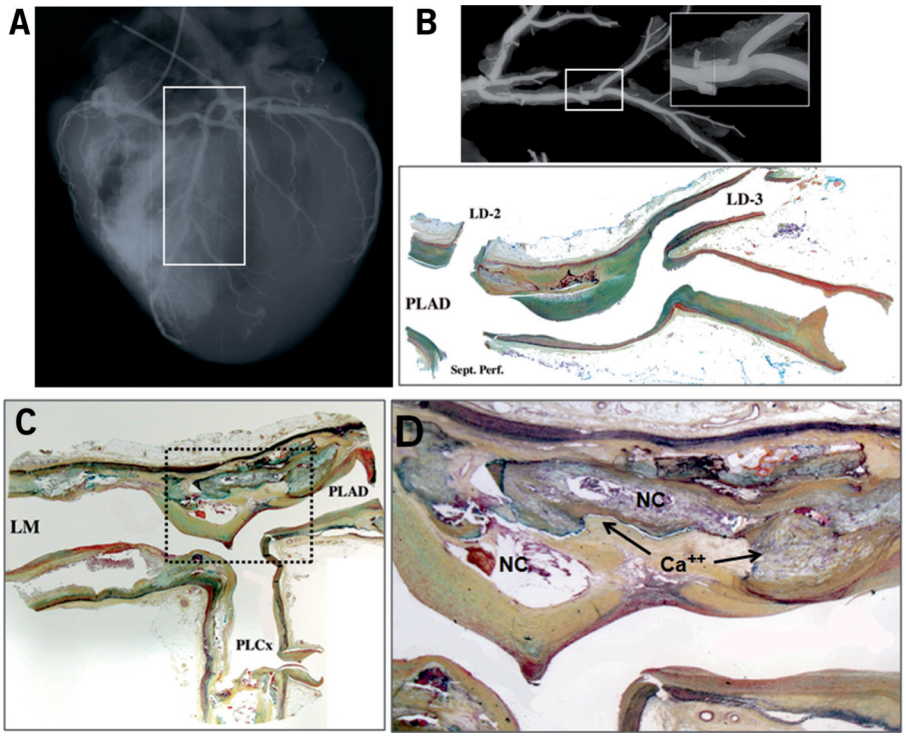

Figure 2. Representative histologic images of coronary plaque in bifurcation lesion. (A-B). Photograph of an angiogram following high contrast x-ray of the bifurcation lesion (LAD / left diagonal). Note presence of atherosclerotic plaques in the lateral wall, while the flow divider regions are spared. (C-D) Longitudinal section taken in the region of LM/PLAD/PLCx bifurcation. Note, severe luminal narrowing proximal to the bifurcation. Necrotic core (NC) accompanied with heavy calcification (Ca++) is observed within the plaque at the low shear (lateral wall) region, whereas the high shear (the carina) has minimal intimal thickening. (LM - Left main, PLAD - proximal left anterior descending coronary artery, PLCx - proximal left circumflex).

interleukins-6, C-reactive protein, ICAM, VCAM, and vascular endothelial growth factor in low shear regions using the same model[17]. Thus, shear stress play an important role not only in early plaque formation but also its progression.

In addition, bifurcation angle variation also has an influences as shown by Perktold et al that the larger the angle of bifurcation the greater the turbulence in flow[18]. Moreover, ratio of the vessel diameter, i.e., from proximal to distal and similarly side branch size also influences flow turbulence[19]. Obtaining a 3-D structure of the bifurcation along with post mortem angiography followed by digital reconstruction may be useful to further understand how atherosclerotic plaque develops in its spatial relationship, which was not employed in our post mortem vessel morphology study.

Healing of stented coronary bifurcations: bare metal vs. drug eluting stents

Polymer-based DES have dramatically reduced rates of restenosis and late lumen loss as compared to BMS in randomised clinical trials in de novo short non-complex lesions[20,21]. Subsequently, DES have been used for the treatment of a wider range of lesion morphologies such as bifurcation/ostial, left main coronary artery, and long lesions, which have been reported to have a high incidence of restenosis and revascularisation following BMS implantation[7,22,23]. Recent clinical trials showed similar rate of stent thrombosis between BMS and DES based on the Academic Research Consortium (ARC) definition of definite and/or probable thrombosis[24], whereas several other studies have revealed steady increase in late stent thrombosis rate in DES[25,26], especially for "off-label" indications[27].

Many techniques have been used to treat coronary bifurcation lesions, including deployment of a single stent in the main vessel with balloon angioplasty of the side branch alone, or more complex stenting utilising two stents in various configurations which, including T-stenting with or without crush, V-stenting, simultaneous kissing stents, the culotte technique, and more recently, a variation called balloon alignment T-stenting[5]. Nevertheless, the clinical outcome remains far from ideal as shown in a recent larger multicentre registry of bifurcation stenting from Italy with higher major adverse event rate of 17.7 % at median follow-up of 24 month[28]. Moreover, to date, no consensus technique has been accepted primarily due to variation of disease severity and geometry.

There are only a hand full of studies evaluating histological outcomes of DES vs. BMS, nevertheless, we have compared bifurcation stenting utilising both these procedures. We reported that stenting of bifurcation lesions is associated with a higher risk of late stent thrombosis and restenosis with DES and BMS respectively[29].To better understand these differences in outcomes between BMS and DES we determined the pattern of healing between BMS and DES. Forty stented bifurcation lesions (DES 19 and BMS 21) from forty patients were evaluated from the CVPath

stent registry[15]. Parameters such as patients, outcomes, location of bifurcation lesions, techniques of stenting, and number of implanted stent were comparable (Table 1). In the bare metal stent group, nine of 21 (43%) lesions were stented with one stent with similar rates in DES (10 of 19 [53%]). The remaining lesions were all stented with two stents (BMS – 11 of 21 [57%] and DES – 9 of 19 [47%]) with the majority in both groups using T-stenting technique. Restenosis in the main vessel was significantly more frequent in BMS as compared to DES whereas the incidence of late stent thrombosis (>30 days) in the main vessel was significantly greater in DES versus BMS, while acute/subacute stent thrombosis (<30 days) was similar between DES and BMS (Table 1).

To assess the impact of flow disturbance on arterial healing in stented lesions, the differences between high shear (flow divider) and low shear (lateral wall) regions were compared (Figure 3). Neointimal thickness was significantly less at the high shear (flow divider) site as compared to the low shear (lateral wall) in DES (median [interquartile range (IQR)]: 0.07 [0.03 to 0.15] vs. 0.17 [0.09 to 0.23] mm, p=0.001), whereas this difference did not reach statistical significance for BMS cases (0.26 [0.16 to 0.73] vs. 0.44 [0.17 to 0.67] mm, p=0.25). Similarly, the percentage of uncovered struts was significantly greater at high shear as compared to low shear in DES (40 [16 to 76]% vs. 0 [0 to 15]%, p=0.001), while there was no significant difference in BMS (0 [0 to 21]% vs. 0 [0 to 0]%, p=0.09). Fibrin deposition was also frequently seen in high shear (flow divider) sites as compared to low shear and was only observed in DES (60 [21 to 67]% vs. 17 [0 to 55]%, p=0.01). Although difference remained of borderline significance because of a limited sample size, a greater incidence of late stent thrombosis was documented in the DES group as compared with the BMS group at bifurcation sites (main vessel: 75% vs. 36%, p=0.06; side branch: 42% vs. 14%, p=0.19). Interestingly, most of the thrombi originated at the flow divider sites where uncovered struts were frequently observed (Figure 4).

Using in vitro experimental bifurcation models[15], we demonstrated that deployment of stents can alter boundary layer separation of the lateral walls and produce disturbances (vortical structures) at the carina. Regions of boundary layer separation are associated with reduced levels of wall shear stress, poor mass transfer of blood flow and vessel wall, and an increase in residence time of circulating blood elements. Moreover, the development of vortical structures can prolong and alter localised areas of low-flow regions and can influence drug deposition, arterial healing post stenting, and local fibrin and platelet deposition[30].

Table 1. Patient, lesion, and procedural characteristics and pathologic findings.

		DES n=19	BMS n=21	*p* value
Age (yrs)		61±16	58±17	0.61
Male Gender (%)		15 (79)	13 (62)	0.49
Mean duration* (day)		330 [188, 680]	150 [54, 540]	0.14
>30 days (%)		12 (63)	14 (67)	>0.99
Location				
LM/ LAD/ LCX		4	1	0.44
LAD/ LD		10	12	
LCX/ OM		4	7	
RCA/ PDA		1	1	
Technique				
1 stent		10	9	0.38
2 stents: T/V/Crush		5/2/2	9/3/0	
Number of stents*		2 [1,2]	2 [1,2]	0.55
Restenosis	MV (%)	1 (5)	7 (33)	0.046
	SB (%)	3 (16)	6 (29)	0.46
Thrombosis				
≤30days	MV (%)	3/7 (43)	3/7 (43)	>0.99
	SB (%)	3/7 (43)	4/7 (57)	0.59
>30days	MV (%)	9/12 (75)	5/14 (36)	0.06
	SB (%)	5/12 (42)	2/14 (14)	0.19
Timing of thrombus* (>30days)		270 [195, 585]	60 [35, 105]	0.003
Cause of death				
SRD/NSRCD/NCD	≤30days	4/2/1	4/2/1	>0.99
	>30days	9/3/0	5/4/5	0.04

MV: main vessel; SB: side branch; SRD: Stent related death; NSRCD: Non-stent related cardiac death; NCD: Non cardiac death *Expressed as median and interquartile range

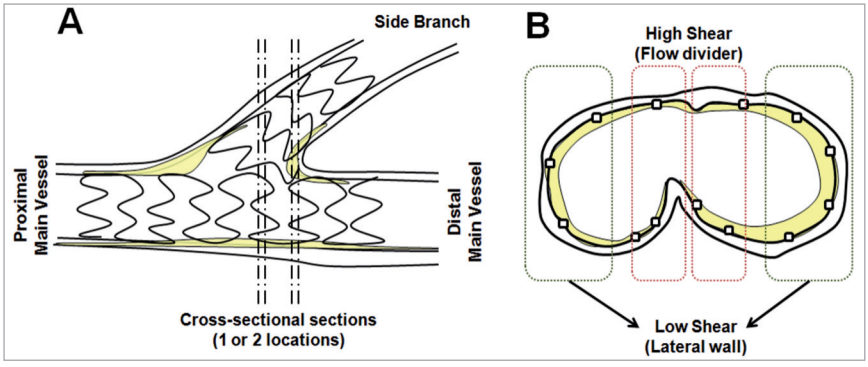

Figure 3. Morphometric analysis of stented coronary bifurcations. (A) Illustration of the method of sectioning of the bare and drug eluting stented coronary bifurcations within the regions of interest. One or two cross-sections (dashed line) were taken from the carinal region and analysed both at the high shear region (flow divider) and low shear regions (lateral walls).

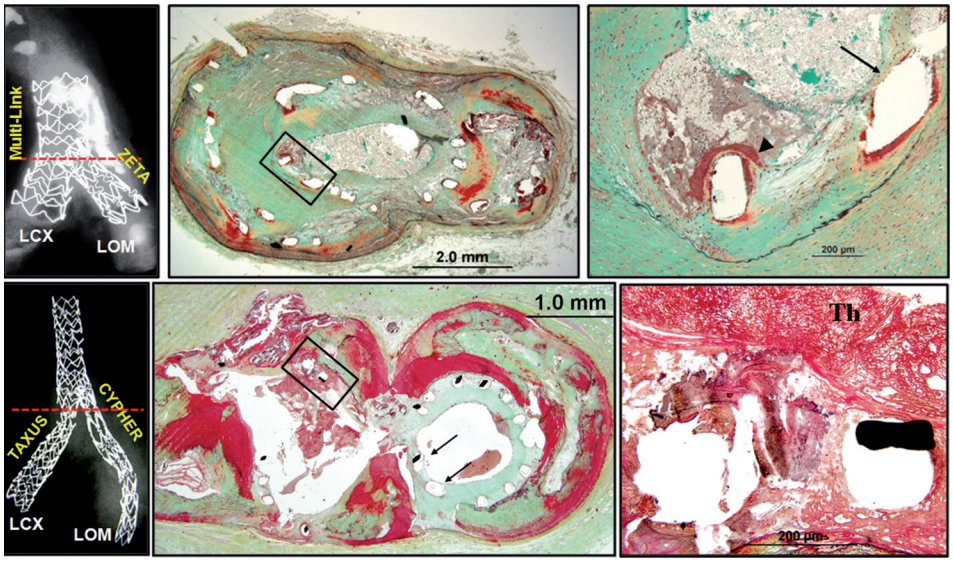

Figure 4. Examples of coronary bifurcations treated with BMS and DES. (Top row) A 77-year-old male with history of severe coronary artery disease received two bare metal stents (4×10mm Multi-Link and 3×9 mm Multi-Link ZETA) in the mid-left circumflex artery (LCX) and first left obtuse marginal branch (LOM). The patient died suddenly 1.5 years after stent implantation. Radiograph show moderate calcification of the coronary arteries. Stents struts show complete coverage except at the carina, where two stent struts are either covered by a thin layer of neointima (black arrow) or there is a platelet-rich surface thrombus (arrow head). (Bottom row) A 69-year-old female with history of hypertension, end-stage renal disease and severe coronary artery disease, she received two overlapping drug eluting stents (3.5×25 mm Taxus and 2.5×20 mm Cypher) in the left circumflex artery (LCX) and left obtuse marginal branch (LOM). The patient died suddenly six months after stent implantation. Stent fractures were observed in both the Cypher and Taxus stents. The stent struts show complete healing in the lateral walls in Cypher (LOM) with a thin layer of neointima in the lateral wall however in the carinal region (black arrow) there are two uncovered struts in Taxus (high magnification image) with overlying adherent thrombus (Th). (red dashed line indicates sampling region)

Richter et al have shown that a greater neointimal formation occurs in the lateral as compared to flow divider walls following stent implantation in porcine iliofemoral bifurcation model[19], which is consistent with our findings. On the other hand, these differences were not significant in BMS which may be due to small number of cases as well as differences in duration and more rapid healing and more uniform neointimal formation after BMS implantation. Thus, a combination of drug effect and flow disturbance both are likely to accelerate the delayed healing in bifurcation lesion.

It has been reported that deploying multiple stents (both in the main vessel and side branch) to treat bifurcation lesion have higher restenosis and thrombosis rates as compared to single stent with balloon angioplasty in the side branch[7]. Koo et al[31] demonstrated that fractional flow reserve (FFR)-guided jailed side branch intervention is useful in determining the functional significance of side branch lesions and results in better clinical outcome as compared to angiography-guided intervention. In their study, functional restenosis (FFR <0.75) rate at follow up was only 8% in FFR-guided side branch intervention strategy. From our autopsy study, we observed borderline differences in the incidence of thrombosis in single versus complex bifurcation stenting, (V-, T-, Crush-, Culotte-stenting) (Table 3). We have shown stent thrombosis in DES to correlate with delayed healing (i.e., uncovered struts)[32], it seems obvious that the multi-stent technique would increase the probability of delayed healing as the polymer and drug is higher at sites of overlap. Furthermore, based on our findings of atherosclerotic plaque formation to occur predominantly in the lateral wall, it may be possible to design a new stent, which may only cover the lateral wall. This would minimise the risk of stent thrombosis by reducing unnecessary metals in the carinal region. Several dedicated bifurcation stent designs are currently undergoing clinical trials with the goal to develop a more safe and effective treatment option. While results have shown good procedural process, the first generation bifurcation stents have

Table 2. Morphometric comparison between high shear vs. low shear regions in DES and BMS.

	DES (12 lesion, 17 stents)		p value	BMS (14 lesion, 18 stents)		p value	P value for DES vs. BMS	
	High shear (flow divider)	Low shear (lateral walls)		High shear (flow divider)	Low shear (lateral walls)		High shear	Low shear
Neointimal thickness (mm)	0.07 [0.03, 0.15]	0.17 [0.09, 0.23]	0.001	0.26 [0.16, 0.73]	0.44 [0.17, 0.67]	0.25	0.0002	0.004
Fibrin deposition (%Struts)	60 [21, 67]	17 [0, 55]	0.01	8 [0, 33]	3 [0, 21]	0.21	0.008	0.19
Uncovered struts (%Struts)	40 [16, 76]	0 [0, 15]	0.001	0 [0, 21]	0 [0, 0]	0.10	0.004	0.38

DES: drug-eluting stent; BMS: bare metal stent; Values are expressed as median and interquartile range

Table 3. DES (SES and PES) outcome at bifurcation sites using different techniques single vs. complex stenting (V-, T-, Crush-, and Culotte-stenting).

Bifurcation stenting	Patent (n=21)	Thrombosis (n=16)	*p* value
Single stent	17	8	
V-stenting	1	2	
T-stenting	2	2	0.1936
Crush-stenting	-	3	
Culotte-stenting	1	1	
Single stent	17 (68%)	8 (32%)	
Complex stenting (V/T/Crush/Culotte)	4 (36%)	8 (67%)	0.046

mostly suffered from technical problems and high rates of restenosis as most designs only included bare metal stents[33]. In the future, with addition of drug eluting platforms on dedicated bifurcation-stents should show superiority over current techniques.

Conclusion

Interventional treatment of coronary bifurcation lesions remains one of the most challenging problems in modern interventional cardiology. Flow in the coronaries is inherently complex due to the pulsatile conditions, curvature of the coronary, the contraction and relaxation of the myocardium and the extensive branching that leads to large variations in wall shear stress levels. Plaque formation in native coronary bifurcations and neointimal growth following DES implantation is substantially different between the high shear (carina) versus low shear regions at the lateral walls. There is a higher incidence of late stent thrombosis in DES compared to BMS, however there is a higher restenosis rate in BMS than DES at autopsy. The higher rate of thrombosis in DES is likely related to an exaggerated delay of arterial healing which may be caused by both flow disturbances as well as higher drug retention. BMS restenosis may be due to greater trauma to the carina that results in greater proliferation of SMC, but may also relate to unique flow disturbances that are observed at bifurcations.

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