EuroIntervention

Is there a higher risk of stent thrombosis in bifurcation lesions, or is this related to the technique?

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The authors have no conflicts of interest to declare.

Abstract

Bifurcation lesions and bifurcation stenting have been reported to be risk factors of stent thrombosis (ST). ST is a complex process that may be the culmination of device, patient, lesion and procedural factors. The strategy of provisional SB stenting is widely accepted for suitable bifurcation lesions, and is accompanied by low rates of ST. However, it is not applicable to all patients, and in these clinical scenarios (approx. 10%), there is no consensus on the best option for elective stenting with two stents regarding the incidence of ST. Excessive metal scaffolding, such as in the classical crush technique, should be avoided. Further accumulation of long-term data from larger clinical registries and randomised studies will be needed to elucidate the best technique regarding the avoidance of ST in bifurcation treatment. Dedicated bifurcation stents tailored for each type of lesion could resolve this issue, especially the excess of metal protruding in the vessel lumen or crushed onto the wall. However, they need to be tested in upcoming and ongoing trials.

Stent thrombosis (ST) is the sudden occlusion of a stented coronary artery due to thrombus formation. Despite major improvements of antiplatelet therapy, thrombotic events remain the primary cause of death after percutaneous coronary interventions (PCI).[1,2] The clinical consequences of ST are frequently catastrophic and include death in 20% to 48% or major myocardial infarction (MI) in 60% to 70% of the cases.[1-3] In the drug-eluting stent era, ST and especially very late ST remains a concern of coronary intervention. Bifurcation lesions and bifurcation stenting have been reported to be the risk factors for ST.[3] ST is a complex process that may be a culmination of device, patient, lesion, and procedural factors.[4] The exact cause of the higher risk of ST in bifurcation lesions is unknown although pathologic studies have suggested that the arterial branch points are predisposed to development of atherosclerotic plaque, thrombus, and inflammation because they are foci of low shear stress.[5-8]

One versus two-stent techniques

There is consensus in the interventional community that the best treatment strategy in bifurcational lesions, in the majority of cases, is provisional stenting which consists of provisional side-branch (SB) stenting where the main branch (MB) is stented, and the SB is stented only if necessary.[9,10] However, if the SB is large and has disease extending beyond the vessel ostium, two stents are usually needed, but there is no consensus on the best technique.[10,11] However, the impact of the stenting strategy for bifurcation lesion on ST remains unclear. Initial studies with two-stent techniques had high rates of ST.[12,13] However, recent randomised studies comparing single- and two-stent techniques did not show any clear advantage of one versus the other regarding the incidence of ST.[14-18] These findings were verified by subsequent meta-analyses of the above studies which could not show any difference in the incidence of ST.[19,20] These results may be due to the refinement of two-stent technique, such as high pressure ballooning, final kissing

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technique, and intravascular ultrasound (IVUS)-guided optimal stenting at main and side branches.[21-23] From another point of view, these results could be due to certain limitations of these randomised studies. First, the number of subjects in the previous studies was too small to evaluate rare events such as ST. Second, their data components were not enough to show the real-world percutaneous coronary intervention (PCI) experience because acute MI cases were excluded. Finally, the follow-up period of all randomised studies (six to 14 months) was too short to evaluate late and very late ST adequately. Thus, important complementary data are being provided by well conducted registries. Of the 607 patients (2,160 lesions) in the ARTS II study, 324 patients underwent revascularisation procedures involving treatment of at least one bifurcation (465 lesions).[24,25] Three-year outcomes of the patients of the bifurcation group were compared to the patients without bifurcations. Despite more diffuse and complex disease in the bifurcation group, survival free of adverse events was equivalent in the two groups. At 3-years, there was no difference in rate of overall major adverse cardiac events (20.2% vs. 18.5%, p=NS) or any of the component events between the bifurcation and the non-bifurcation group. There was a trend towards a higher rate of definite ST in the bifurcation group (4.6 vs. 2.1%, p=0.1); however in the multivariate analysis the CK value post procedure was the only independent predictor of definite ST (p=0.015), with the presence of a bifurcation lesion of borderline significance (p=0.056).[24] Similar rates of ST have been shown after DES implantation in bifurcation lesions by Iakovou et al. The incidence of ST according to selected patient characteristics in this study is shown in Figure 1.[26] It is of note that while bifurcational treatment was accompanied with a higher than expected incidence of ST, there were no significant differences between the one versus the two-stent techniques.

On the contrary, in a sub-analysis of the j-Cypher registry for left main disease, the prevalence of definite ST in the two-stent technique group was higher than the single-stent technique group (2.8% vs. 0.4%, p=0.050).[27] However, the prevalence of ST was not different between single- and two-stent techniques in the non-left main subset. At three years, there were only nine cases of ST after two-stent technique in all cohorts (five in the left main and four in the non-left main subset), which was inadequate for a definitive conclusion.[28] The incidence of ST in the j-Cypher registry was lower than that in the Bern-Rotterdam data or ESTROFA registry.[29,30] Routlege et al showed that uniform provisional T stenting with DES is applicable to over 90% of patients in the real world, with a 10% need for repeat revascularisation in the first two years and a low incidence of late ST (2.52%).[31]

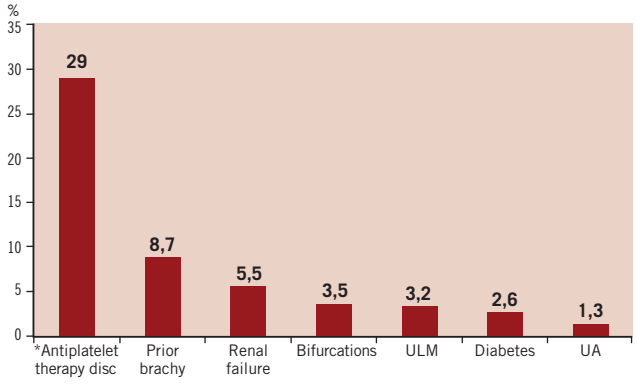

Figure 1. Rates of stent thrombosis according to selected patient characteristics. Adapted from Iakovou et al.[26]

Are there any differences regarding ST between 2-stent techniques?

Although the strategy of provisional SB stenting is widely accepted for suitable bifurcation lesions, there is no consensus on the best option for elective stenting with two stents. The crush technique has the potential to scaffold and apply the drug to the side-branch ostium where restenosis is most common. However, ST by 9-month follow-up is more frequent after classical crush stenting than after simple stenting, and the incidence was not reduced with 1-step kissing post-dilation.[32] Classical crush stenting may also be predisposed to ST because of the multiple layering of stent struts. Overlapping of DES is associated with reduced endothelialisation of struts in preclinical studies and reduced tissue coverage in humans.[33] Ormiston et al showed by his trademark bench deployments that mini-crush variations of classical crush, limit multiple layering of stent struts and may be associated with more complete endothelialisation.[34] Side-branch ostial stenosis after crush stenting was minimised by mini-crush deployment, 2-step kissing post-dilation, and the use of stents with larger cell size. These results have been verified in clinical studies which showed that optimising stent deployment at bifurcation lesions with these variations will reduce clinical ST and restenosis.[35-37]

Interesting information regarding the comparison between two stent techniques comes from large registries, such as the Kurashiki Central Hospital registry which compared the incidence of ST after DES implantation for bifurcation treatment with the culotte and the T stent technique (modified T or provisional T). Culotte stent technique was used for 283 patients (follow-up period: 2.44±1.46 years) and T stent for 285 (follow-up period: 3.30±1.79 years). The cumulative incidence curves of ST at follow-up are shown in the Figure 2. Although no statistical difference was seen, there seemed to be different time courses of ST between the two techniques.

Similar with the above are the results of several published studies which showed no significant differences in ST between various stent techniques (Table 1). The PRECISE-SKS trial (n=100) comparing simultaneous kissing stent with conventional technique, showed lower SB restenosis rate using the SKS method, higher procedural success of SB and no ST in both arms after 9-12 months on dual antiplatelet therapy.[38] In the CACTUS trial (n=350) the incidence of ST was 1.7% in the "crush" arm (versus 1.1% for the provisional stenting technique) with no significant difference in target lesion revascularisation (TLR), or angiographic restenosis.[14] In the BBC ONE trial (7) (n=500) the crush and the culotte techniques were compared to provisional stenting with a significant raise in ST (2% vs. 0.4%) and MACE (15.2% vs. 8%) after a 9-month average

Table 1. Rates of stent thrombosis in studies of bifurcation lesions treated with DES.

Study	Technique	Number (n)	Mean follow-up months	Stent thrombosis (%)
NORDIC[18]	MV+SB stent vs. MV stenting	413	6	0 vs. 0.5
CACTUS[14]	crush vs. provisional stenting	350	6	1.7 vs. 1.1
BBC ONE[39]	crush/culotte vs. provisional stenting	500	9	2.0 vs. 0.4
BBK[17]	T stent vs. provisional stenting	202	9	3 vs. 3

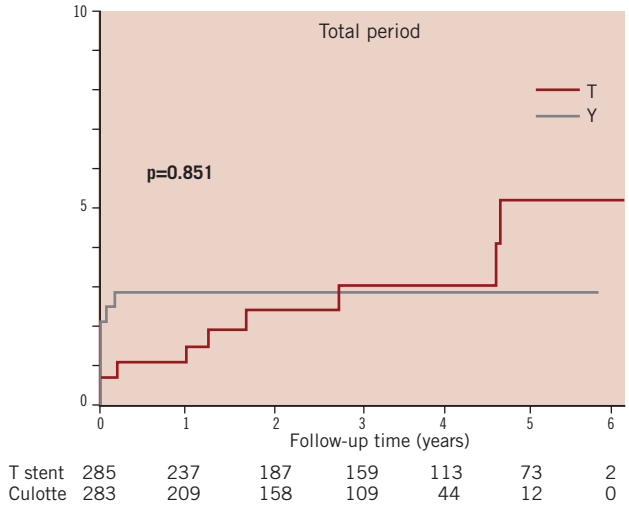

Figure 2. Cumulative incidence of definite stent thrombosis in Kurashiki Central Hospital registry (unpublished data) in patients treated with T-stenting vs. culotte.

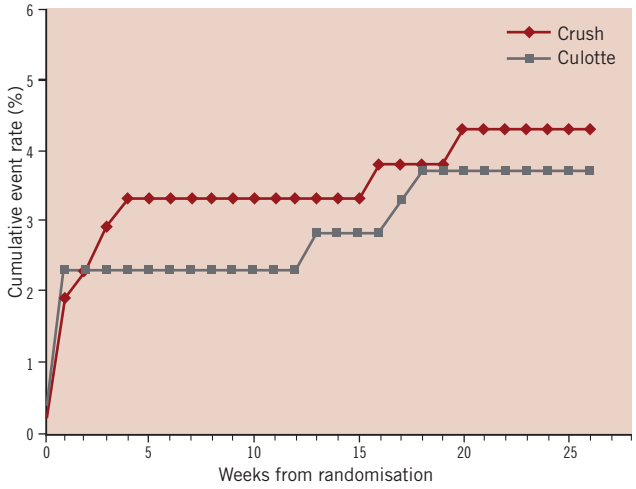

Figure 3. Cumulated MACE rate (cardiac death, MI, target vessel revascularisation, stent thrombosis) during 6 months follow-up. MACE rates after six months; crush 4.3%, culotte 3.7% (p=0.87). The log-rank test was used. Taken from Ergils et al.[1] (With kind permission from Wolters Kluwer Health)

follow-up period.[39] In the BBK trial (n=202) T-stenting was compared to provisional stenting. ST was similar in both groups (3%), but there was a markedly higher angiographic restenosis in the T-stenting arm.[17] In the NORDIC II trial (n=424) culottes technique was compared to Crush and ST occurred in 1.9% versus 1.4% respectively (P=NS).[16] In addition, there were no statistically significant differences regarding major adverse cardiac event (cardiac death, MI, target vessel revascularisation, ST) rates during six months follow-up (crush 4.3%, culotte 3.7%, P=0.87) (Figure 3).

Prevention of ST in bifurcation lesions

Prevention of ST in PCI of bifurcation lesions is pivotal and must include appropriate duration of dual antiplatelet therapy, meticulous attention to stent deployment techniques, and, possibly, the use of intravascular imaging in order to better guide the procedure.[8,21,40,41] Kim et al evaluated 758 patients with *de novo* non-left main coronary bifurcation lesions who underwent IVUS-guided stenting and showed that IVUS guidance significantly reduced the long-term all-cause mortality (hazard ratio [HR] 0.31, 95% confidence interval [CI] 0.13 to 0.74, p=0.008) in the total population and in the patients receiving DES (HR 0.24, 95% CI 0.06 to 0.86, p =0.03), but not in the patients receiving bare metal stents. IVUS-guided stenting had no effect on the rate of ST or target lesion revascularisation. In patients receiving DES, however, IVUS guidance reduced the development of very late ST (0.4% vs. 2.8%, p=0.03).[42]

Future directions and conclusions

The strategy of provisional SB stenting is widely accepted for suitable bifurcation lesions and is accompanied by low rates of ST. However it is not applicable to all patients and in these clinical scenarios (approx. 10%), there is no consensus on the best option for elective stenting with two stents regarding the incidence of ST. Excessive metal scaffolding, such as in the classical crush technique should be avoided. Further accumulation of long-term data from larger clinical registries and randomised studies will be needed to elucidate the best technique regarding the avoidance of ST in bifurcation treatment.

Dedicated bifurcation stents tailored for each type of lesion could resolve this issue, especially the excess of metal protruding in the vessel lumen or crushed onto the wall. Some of these stents are tested in a number of trials but have yet to establish a stable place in the interventional cardiology arsenal.[43-45]

In the meantime, vigilance in maintenance of dual antiplatelet therapy is mandatory. It is necessary for physicians and patients to be aware not only of the risk of thrombosis, but also of the most important contributing factor: interruption of antiplatelet therapy. For this reason, it is imperative to avoid stopping prematurely antiplatelet therapy. It is well known that according to the present guidelines, the optimal duration of dual antiplatelet therapy is at least 12 months for the use of DES. Whether there should be a modification to these guidelines according to the level of endothelisation-strut coverage is not determined and remains to be answered in the near future with the upcoming and ongoing trials.

References

1. Costa MA, Sabate M, van der Giessen WJ, Kay IP, Cervinka P, Ligthart JM, Serrano P, Coen VL, Levendag PC, Serruys PW. Late coronary occlusion after intracoronary brachytherapy. *Circulation.* 1999;100:789-792.

2. Moussa I, Di Mario C, Reimers B, Akiyama T, Tobis J, Colombo A. Subacute stent thrombosis in the era of intravascular ultrasound-guided coronary stenting without anticoagulation: frequency, predictors and clinical outcome. *J Am Coll Cardiol.* 1997;29:6-12.

3. Iakovou I. Thrombosis after stent implantation: how much of a problem is there? *Future Cardiol.* 2008;4:261-267.

4. Honda Y, Fitzgerald PJ. Stent thrombosis: an issue revisited in a changing world. *Circulation.* 2003;108:2-5.

5. Farb A, Burke AP, Kolodgie FD, Virmani R. Pathological mechanisms of fatal late coronary stent thrombosis in humans. *Circulation.* 2003;108:1701-1706.

6. Papafaklis MI, Bourantas CV, Theodorakis PE, Katsouras CS, Fotiadis DI, Michalis LK. Association of endothelial shear stress with plaque thickness in a real three-dimensional left main coronary artery bifurcation model. *Int J Cardiol.* 2007;115:276-278.

7. Virmani R, Guagliumi G, Farb A, Musumeci G, Grieco N, Motta T, Mihalcsik L, Tespili M, Valsecchi O, Kolodgie FD. Localized hypersensitivity and late coronary thrombosis secondary to a sirolimus-eluting stent: should we be cautious? *Circulation.* 2004;109:701-705.

8. Tan HC. Stent thrombosis after percutaneous coronary intervention for bifurcation lesions. *J Interv Cardiol.* 2009;22:114-116.

9. Hildick-Smith D, Lassen JF, Albiero R, Lefevre T, Darremont O, Pan M, Ferenc M, Stankovic G, Louvard Y. Consensus from the 5th European Bifurcation Club meeting. *EuroIntervention.* 2010;6:34-38.

10. Stankovic G, Darremont O, Ferenc M, Hildick-Smith D, Louvard Y, Albiero R, Pan M, Lassen JF, Lefevre T. Percutaneous coronary intervention for bifurcation lesions: 2008 consensus document from the fourth meeting of the European Bifurcation Club. *EuroIntervention.* 2009;5:39-49.

11. Iakovou I, Ge L, Colombo A. Contemporary stent treatment of coronary bifurcations. *J Am Coll Cardiol.* 2005;46:1446-1455.

12. Al Suwaidi J, Yeh W, Cohen HA, Detre KM, Williams DO, Holmes DR, Jr. Immediate and one-year outcome in patients with coronary bifurcation lesions in the modern era (NHLBI dynamic registry). *Am J Cardiol.* 2001;87:1139-1144.

13. Di Mario C, Airoldi F, Reimers B, Anzuini A, Vilas Dharmadhikari A, Colombo A. Bifurcational stenting. *Semin Interv Cardiol.* 1998;3:65-76.

14. Colombo A, Bramucci E, Sacca S, Violini R, Lettieri C, Zanini R, Sheiban I, Paloscia L, Grube E, Schofer J, Bolognese L, Orlandi M, Niccoli G, Latib A, Airoldi F. Randomized study of the crush technique versus provisional side-branch stenting in true coronary bifurcations: the CACTUS (Coronary Bifurcations: Application of the Crushing Technique Using Sirolimus-Eluting Stents) Study. *Circulation.* 2009;119:71-78.

15. Colombo A, Moses JW, Morice MC, Ludwig J, Holmes DR, Jr., Spanos V, Louvard Y, Desmedt B, Di Mario C, Leon MB. Randomized study to evaluate sirolimus-eluting stents implanted at coronary bifurcation lesions. *Circulation.* 2004;109:1244-1249.

16. Erglis A, Kumsars I, Niemela M, Kervinen K, Maeng M, Lassen JF, Gunnes P, Stavnes S, Jensen JS, Galloe A, Narbute I, Sondore D, Makikallio T, Ylitalo K, Christiansen EH, Ravkilde J, Steigen TK, Mannsverk J, Thayssen P, Hansen KN, Syvanne M, Helqvist S, Kjell N, Wiseth R, Aaroe J, Puhakka M, Thuesen L. Randomized comparison of coronary bifurcation stenting with the crush versus the culotte technique using sirolimus eluting stents: the Nordic stent technique study. *Circ Cardiovasc Interv.* 2009;2:27-34.

17. Ferenc M, Gick M, Kienzle RP, Bestehorn HP, Werner KD, Comberg T, Kuebler P, Buttner HJ, Neumann FJ. Randomized trial on routine vs. provisional T-stenting in the treatment of de novo coronary bifurcation lesions. *Eur Heart J.* 2008;29:2859-2867.

18. Steigen TK, Maeng M, Wiseth R, Erglis A, Kumsars I, Narbute I, Gunnes P, Mannsverk J, Meyerdierks O, Rotevatn S, Niemela M, Kervinen K, Jensen JS, Galloe A, Nikus K, Vikman S, Ravkilde J, James S, Aaroe J, Ylitalo A, Helqvist S, Sjogren I, Thayssen P, Virtanen K, Puhakka M, Airaksinen J, Lassen JF, Thuesen L. Randomized study on simple versus complex stenting of coronary artery bifurcation lesions: the Nordic bifurcation study. *Circulation.* 2006;114:1955-1961.

19. Brar SS, Gray WA, Dangas G, Leon MB, Aharonian VJ, Brar SK, Moses JW. Bifurcation stenting with drug-eluting stents: a systematic review and meta-analysis of randomised trials. *EuroIntervention.* 2009;5:475-484.

20. Katritsis DG, Siontis GC, Ioannidis JP. Double versus single stenting for coronary bifurcation lesions: a meta-analysis. *Circ Cardiovasc Interv.* 2009;2:409-415.

21. Colombo A, Al-Lamee R. Bifurcation lesions: an inside view. *Circ Cardiovasc Interv.* 2010;3:94-96.

22. Fujii K, Carlier SG, Mintz GS, Yang YM, Moussa I, Weisz G, Dangas G, Mehran R, Lansky AJ, Kreps EM, Collins M, Stone GW, Moses JW, Leon MB. Stent underexpansion and residual reference segment stenosis are related to stent thrombosis after sirolimus-eluting stent implantation: an intravascular ultrasound study. *J Am Coll Cardiol.* 2005;45:995-998.

23. Latib A, Airoldi F. Comments on the article by Routledge et al "Three-year clinical outcome of percutaneous treatment of bifurcation lesions in multivessel coronary artery disease with the sirolimus-eluting stent: insights from the Arterial Revascularisation Therapies Study, part II (ARTS II)". *EuroIntervention.* 2010;5:875-876; author reply 876.

24. Routledge HC, Lefevre T, Colombo A, Oldroyd KG, Hamm CW, Guagliumi G, von Scheidt W, Guetta V, Ruzyllo W, Wittebols K, Goedhart DM, Serruys PW. Three-year clinical outcome of percutaneous treatment of bifurcation lesions in multivessel coronary artery disease with the sirolimus-eluting stent: insights from the Arterial Revascularisation Therapies Study, part II (ARTS II). *EuroIntervention.* 2009;5:190-196.

25. Tsuchida K, Colombo A, Lefevre T, Oldroyd KG, Guetta V, Guagliumi G, von Scheidt W, Ruzyllo W, Hamm CW, Bressers M, Stoll HP, Wittebols K, Donohoe DJ, Serruys PW. The clinical outcome of percutaneous treatment of bifurcation lesions in multivessel coronary artery disease with the sirolimus-eluting stent: insights from the Arterial Revascularization Therapies Study part II (ARTS II). *Eur Heart J.* 2007;28:433-442.

26. Iakovou I, Schmidt T, Bonizzoni E, Ge L, Sangiorgi GM, Stankovic G, Airoldi F, Chieffo A, Montorfano M, Carlino M, Michev I, Corvaja N, Briguori C, Gerckens U, Grube E, Colombo A. Incidence, predictors, and outcome of thrombosis after successful implantation of drug-eluting stents. *JAMA.* 2005;293:2126-2130.

27. Kimura T, Morimoto T, Nakagawa Y, Tamura T, Kadota K, Yasumoto H, Nishikawa H, Hiasa Y, Muramatsu T, Meguro T, Inoue N, Honda H, Hayashi Y, Miyazaki S, Oshima S, Honda T, Shiode N, Namura M, Sone T, Nobuyoshi M, Kita T, Mitsudo K. Antiplatelet therapy and stent thrombosis after sirolimus-eluting stent implantation. *Circulation.* 2009;119:987-995.

28. Toyofuku M, Kimura T, Morimoto T, Hayashi Y, Ueda H, Kawai K, Nozaki Y, Hiramatsu S, Miura A, Yokoi Y, Toyoshima S, Nakashima H,

Haze K, Tanaka M, Take S, Saito S, Isshiki T, Mitsudo K. Three-year outcomes after sirolimus-eluting stent implantation for unprotected left main coronary artery disease: insights from the j-Cypher registry. *Circulation.* 2009;120:1866-1874.

29. Alfonso F. The "vulnerable" stent why so dreadful? *J Am Coll Cardiol.* 2008;51:2403-2406.

30. de la Torre-Hernandez JM, Alfonso F, Hernandez F, Elizaga J, Sanmartin M, Pinar E, Lozano I, Vazquez JM, Botas J, Perez de Prado A, Hernandez JM, Sanchis J, Nodar JM, Gomez-Jaume A, Larman M, Diarte JA, Rodriguez-Collado J, Rumoroso JR, Lopez-Minguez JR, Mauri J. Drug-eluting stent thrombosis: results from the multicenter Spanish registry ESTROFA (Estudio ESpanol sobre TROmbosis de stents FArmacoactivos). *J Am Coll Cardiol.* 2008;51:986-990.

31. Routledge HC, Morice MC, Lefevre T, Garot P, De Marco F, Vaquerizo B, Louvard Y. 2-year outcome of patients treated for bifurcation coronary disease with provisional side branch T-stenting using drug-eluting stents. *JACC Cardiovasc Interv.* 2008;1:358-365.

32. Hoye A, Iakovou I, Ge L, van Mieghem CA, Ong AT, Cosgrave J, Sangiorgi GM, Airoldi F, Montorfano M, Michev I, Chieffo A, Carlino M, Corvaja N, Aoki J, Rodriguez Granillo GA, Valgimigli M, Sianos G, van der Giessen WJ, de Feyter PJ, van Domburg RT, Serruys PW, Colombo A. Long-term outcomes after stenting of bifurcation lesions with the "crush" technique: predictors of an adverse outcome. *J Am Coll Cardiol.* 2006;47:1949-1958.

33. Finn AV, Kolodgie FD, Harnek J, Guerrero LJ, Acampado E, Tefera K, Skorija K, Weber DK, Gold HK, Virmani R. Differential response of delayed healing and persistent inflammation at sites of overlapping sirolimus- or paclitaxel-eluting stents. *Circulation.* 2005;112:270-278.

34. Ormiston JA, Webster MW, Webber B, Stewart JT, Ruygrok PN, Hatrick RI. The "crush" technique for coronary artery bifurcation stenting: insights from micro-computed tomographic imaging of bench deployments. *JACC Cardiovasc Interv.* 2008;1:351-357.

35. Chen S, Zhang J, Ye F, Chen Y, Fang W, Wei M, He B, Sun X, Yang S, Kwan TW. Final kissing balloon inflation by classic crush stenting did not improve the clinical outcomes for the treatment of unprotected left main bifurcation lesions: the importance of double-kissing crush technique. *Catheter Cardiovasc Interv.* 2008;71:166-172.

36. Chen S, Zhang J, Ye F, Zhu Z, Lin S, Shan S, Kwan TW. DK crush (double-kissing and double-crush) technique for treatment of true coronary bifurcation lesions: illustration and comparison with classic crush. *J Invasive Cardiol.* 2007;19:189-193.

37. Yang HM, Tahk SJ, Woo SI, Lim HS, Choi BJ, Choi SY, Yoon MH, Park JS, Zheng M, Hwang GS, Kang SJ, Shin JH. Long-term clinical and angiographic outcomes after implantation of sirolimus-eluting stents with a "modified mini-crush" technique in coronary bifurcation lesions. *Catheter Cardiovasc Interv.* 2009;74:76-84.

38. Sharma SK, Sweeny J, Kini AS. Coronary bifurcation lesions: a current update. *Cardiol Clin.* 2010;28:55-70.

39. Hildick-Smith D, de Belder AJ, Cooter N, Curzen NP, Clayton TC, Oldroyd KG, Bennett L, Holmberg S, Cotton JM, Glennon PE, Thomas MR, Maccarthy PA, Baumbach A, Mulvihill NT, Henderson RA, Redwood SR, Starkey IR, Stables RH. Randomized trial of simple versus complex drug-eluting stenting for bifurcation lesions: the British Bifurcation Coronary Study: old, new, and evolving strategies. *Circulation.* 2010;121:1235-1243.

40. Costa RA, Moussa ID. Percutaneous treatment of coronary bifurcation lesions in the era of drug-eluting stents. *Minerva Cardioangiol.* 2006;54:577-589.

41. Fujii K, Mintz GS, Kobayashi Y, Carlier SG, Takebayashi H, Yasuda T, Moussa I, Dangas G, Mehran R, Lansky AJ, Reyes A, Kreps E, Collins M, Colombo A, Stone GW, Teirstein PS, Leon MB, Moses JW. Contribution of stent underexpansion to recurrence after sirolimus-eluting stent implantation for in-stent restenosis. *Circulation.* 2004;109:1085-1088.

42. Kim SH, Kim YH, Kang SJ, Park DW, Lee SW, Lee CW, Hong MK, Cheong SS, Kim JJ, Park SW, Park SJ. Long-term outcomes of intravascular ultrasound-guided stenting in coronary bifurcation lesions. *Am J Cardiol.* 2010;106:612-618.

43. Dibie A, Chevalier B, Guyon P, Fajadet J, Lefevre T, Slama MS, Royer T, Glatt B, Philippe F, Laborde F, Larrazet F. First-in-human feasibility and safety study of a true bifurcated stent for the treatment of bifurcation coronary artery lesions (DBS stent): six month angiographic results and five year clinical follow-up. *EuroIntervention.* 2008;3:558-565.

44. Onuma Y, Muller R, Ramcharitar S, van Geuns RJ, Louvard Y, Morel MA, Morice MC, Davis R, Kaplan AV, Lefevre T, Grube E, Serruys PW. Tryton I, First-In-Man (FIM) study: six month clinical and angiographic outcome, analysis with new quantitative coronary angiography dedicated for bifurcation lesions. *EuroIntervention.* 2008;3:546-552.

45. Rizik DG, Klassen KJ, Hermiller JB. Bifurcation coronary artery disease: current techniques and future directions (part 1). *J Invasive Cardiol.* 2008;20:82-90.