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Short title: Coronary Bifurcation Intervention in Asia Pacific

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Abbreviation

APAC	**Asia Pacific**
EBC	**European Bifurcation Club**
DES	**Drug-eluting stent**
JBT	**Jailed balloon technique**
JWT	**Jailed wire technique**
KBT	**Kissing balloon technique**
LAD	**Left anterior descending artery**
LCx	**Left circumflex artery**
LM	**Left main stem**
M-JBT	**Modified jailed balloon technique**
MACE	**Major adverse cardiovascular event**
MV	**Main vessel**
RCT	**Randomised controlled trial**
PCI	**Percutaneous coronary intervention**
SB	**Side branch**
ST	**Stent thrombosis**
TLF	**Target lesion failure**
TVR	**Target vessel revascularization**

Abstract

Coronary bifurcation intervention is common but complex. Progress in this field has been made in recent years with much contribution from the Asia Pacific (APAC) region. However, the standard of practice varies across the APAC due to differences in culture, socioeconomic state and healthcare set-up. Practice may also differ from the rest of the world. Hence, a panel of experts was invited to discuss topics relevant to bifurcation intervention in order to make a concerted effort in achieving consensus that is applicable within the region and in line with available evidence.

Introduction

Asia Pacific (APAC) is the most populous region with over 60% of the world population living in 76 Asian and Oceanic countries. The differences in culture, tradition and socioeconomy across the region is vast with great heterogeneity in the healthcare infrastructure, clinical practice and progress in medical knowledge. This provides an excellent platform for mutual support, learning and collaboration in order to improve the standard of healthcare and facilitate the advance in clinical practice and research.

Understanding the challenges of coronary bifurcation intervention[1], 22 regional leaders in percutaneous coronary intervention (PCI) met in a 2-day forum to discuss regional commonalities in treatment and best-practice. This is also a concerted effort to achieve an APAC consensus. Two international experts were invited to share their experience and facilitate the discussion.

Aims

Although the European Bifurcation Club (EBC) consensus documents are comprehensive and applicable to the APAC, differences between the APAC and Europe may affect practices (Figure 1). There are also techniques and original data within the region which can complement the EBC consensus. Hence, the panel agreed that an APAC consensus document should be developed. This document is based on the 12th and 13th (Left main (LM) intervention) EBC consensus

documents[2, 3] and the 14th EBC consensus document which was only published during the preparation of this manuscript.[4] Special consideration is given to practices, data and techniques developed within the region.

This document is intended to be a reference promoting systematic and evidence-based best-practice relevant to APAC. It serves as platform to identify challenges, share knowledge and skills, and foster research collaboration. It also aims to facilitate reimbursement for useful adjuvant technologies including intravascular imaging and physiology assessment in countries across the region. The panel intends to hold regular forum with update to the document.

Special considerations for Asia Pacific Region

The panel discussion was mostly qualitative or based on consensus opinion. In many developing APAC countries, access of patients to healthcare remains unsatisfactory. The availability of PCI infrastructure including physicians and devices are limited or financially unaffordable. The treatment options for patients would differ from those in the West. Further, many patients would opt for PCI over coronary artery bypass graft surgery regardless of the prognostic implication due to cultural background, religious belief and lack of social welfare support. A Heart Team approach is becoming a common practice in many APAC countries to encourage appropriate treatment.

Cardiovascular risk factors are more prevalent within the APAC but health awareness among the general public and screening for cardiovascular risk factors is lacking. Western Pacific is home to 37.4% of the world's diabetics. The age-adjusted prevalence of diabetes mellitus among adults in the Western Pacific and Southern Asia are 8.6% and 10.1% respectively, compared to 6.8% in the Europe.[5] Alarmingly, half of these diabetics are undiagnosed. Hence, many cardiovascular risk factors only become apparent when the patients present with end organ complications such as myocardial infarction (MI) or advanced diffuse multivessel coronary artery disease with the consequence of technically more challenging PCI and less favourable outcome.

The perception of coronary artery calibre for the people of Asian descent being smaller than that of the Caucasians is unsupported by evidence and should not affect the definition or interventional strategies for coronary bifurcation. Few available studies found that the calibre of major epicardial coronary artery was related to body surface area but not ethnic descent.[6] Coronary artery calibre is also affected by age, the dominance of coronary system, gender, vasomotor tone and left ventricular size or mass.[6, 7] However, smaller 2.0 mm diameter stents are not available in some non-APAC countries presumably due to commercial or local regulatory reasons but larger diameter stents are generally available within the APAC.

Further, recent development of knowledge and techniques in bifurcation intervention within the APAC including intravascular imaging, invasive functional assessment, side branch (SB) protection methods and bifurcation stenting strategies should be given careful consideration as most are relevant to the clinical practice and future research.

Recommendation:

The fundamentals of bifurcation PCI in APAC, including coronary artery calibre, are similar to the rest of the world with consideration given to more extensive or diffuse disease. The Heart Team approach is essential as patient's treatment choice may be determined by factors beyond clinical evidence .

Patient and lesion consideration

Bifurcation intervention strategy should not be based solely on anatomical characteristics. Consideration should be given to patient factors, significance of the SB involved and risk of SB compromise. Patient's comorbidities, functional status, ability to complete dual antiplatelet regimen, renal function or occupation and recreational pursuit may affect the decision on bifurcation treatment strategy.

The significance of a SB comprises four aspects: anatomical, physiological, clinical and prognostic. A SB could be considered anatomically important by its

diameter and length. Importantly, there is discordance between angiographic severity of a stenosis and its functional significance.[8, 9] This could be one limitation of bifurcation intervention trials in which lesion selection was based on anatomical criteria. Whether a SB lesion is physiologically important requires functional assessment by non-invasive imaging and/or invasive evaluation. Further, the clinical relevance of a SB has to be established. The burden of ischaemia or amount of ischaemic myocardium and completeness of revascularization should also be taken into consideration.

Approach to bifurcation intervention should be systematic and adoption of complex bifurcation PCI strategy should be weighed against its potential drawbacks. Intravascular imaging would be helpful in better defining the anatomy and evaluate the likelihood of SB compromise. If the risk of SB compromise is high but there are factors precluding complex treatment strategy, a 'keep-it-open' approach can be adopted with a more elaborate SB protection technique, appropriate stent sizing and meticulous approach to main vessel (MV) treatment. If the SB is compromised, bail-out SB intervention should be kept simple and care taken to avoid disruption to the MV stent integrity. In the absence of any factor precluding PCI to a complex bifurcation with high risk of compromising SB, elective two-stent approach could be considered. (Figure 2)

Recommendation:

Patient factors should be considered for the holistic approach. Selection of bifurcation strategy should be systematic and the significance of a SB should be based on anatomical, physiological, clinical and prognostic aspects.

Technical and procedural consideration

Most technical and procedural aspects of bifurcation intervention have been well described in the EBC documents[2] including LM intervention[3] and use of intravascular imaging.[10, 11] However, there are areas with data and techniques relevant to the practice within APAC.

Vascular access

Most bifurcation lesions can be effectively treated transradially using a 6Fr guide catheter but to accommodate more devices, 7 Fr guide catheter system is feasible among patients within APAC. The trend to miniaturise transradial PCI initiated by the Slender Club Japan is gradually extending beyond the APAC. This has helped facilitate the distal radial artery approach which is also feasible for patients within APAC.

Side branch protection techniques

Some SB protection techniques that are more elaborate than the conventional jailed wire technique (JWT) have been developed since SB occlusion can occur in up to 9% of bifurcation PCI cases despite JWT and recanalization can be unsuccessful.[12, 13] JWT does not reduce the incidence of SB occlusion which increases the risk of stent thrombosis (ST) by 6 folds and cardiac death by 4 folds.[13] The risk of cardiac death remains higher even after re-establishing blood flow.

Besides techniques such as the jailed balloon (JBT) and modified jailed semi-inflated balloon, the modified jailed balloon technique (M-JBT) by Dr. Saito has a lower eccentricity index than conventional JBT.[14] The initial study showed that few cases with M-JBT required SB stenting without any SB loss and severe dissection acutely or unexpected intervention after 6 months.

Although there is no randomized controlled trial (RCT), these techniques could be considered especially when it is imperative to preserve the patency of a significant SB. Care should be taken to ensure that the stent segment proximal to the SB is well expanded and apposed when using these techniques.

Provisional stenting

Provisional stenting is the default strategy for bifurcation intervention[2] but some aspects remain unclear including SB intervention, the effects of evolving drug-eluting stent (DES) technology and newer provisional or 2-stent techniques.

Treatment of SB in provisional stenting

Provisional stenting may cause carina or plaque shift leading to SB ostial stenosis in 10 – 40% of the cases but the treatment remains uncertain due to the discordance between angiographic appearance and functional significance of SB disease.[8, 9]

Using balloon inflation to open the stent cell over the SB can cause stent distortion, carina shift into the MV and malapposition of struts opposite the SB ostium. However, unapposed stent struts at the SB ostium is common without SB treatment and might lead to uncovered struts, fibrin deposition, thrombus formation and late ST.[15] Kissing balloon technique (KBT) can reduces the amount of uncovered struts and incidence of thrombus formation.[15]

Although SB FFR < 0.75 or myocardial ischaemia is more common in provisional stenting without KBT, the incidence of significant ischaemia >10% of left ventricular myocardium is not more frequent and routine KBT does not improve clinical outcome.[16] SB treatment with KBT and stenting or routine KBT in non-diseased SB could lead to higher incidence of target lesion failure (TLF) in the MV .[17, 18] KBT can increase the incidence of MV restenosis by 3 folds[19] due to elliptical deformation of the stent, over-sizing of the proximal stent segment that increases wall stress with intimal hyperplasia or edge dissection, increased strut malapposition proximal to the KBT segment and disruption of strut configuration and polymer coatings.

Proximal optimisation technique (POT)[2, 3] can correct stent deformation, eccentricity and malapposition following KBT but not abolishing stent over-expansion or reversing stent edge dissection. POT does not require high pressure balloon inflation but it is essential to achieve appropriate stent expansion and

apposition.[2] Hence, a semi-complaint balloon with larger expansion range is preferred over non-compliant balloon.[20]

The re-POT technique can optimize the result of provisional stenting by reducing SB ostium strut obstruction and global strut malapposition whilst maintaining stent circular geometry without arterial over-stretch.[21] The rePOT technique is effective and technically less demanding with early experience showing satisfactory short-term outcomes.

Recommendation:

More elaborate SB protection strategies can be considered to preserve vessel patency in provisional stenting. SB treatment and KBT should be performed only when clinically important SB is functionally compromised following provisional stenting.

Provisional versus two-stent strategy

Older RCTs that favour provisional versus 2-stent strategy mainly involved the first generation DES using crush, T-stenting or Culotte techniques. Two-stent strategy has higher major adverse cardiovascular events (MACE) but medium-term events were mainly related to peri-procedural MI.[22]

The Nordic-Baltic Bifurcation Study IV reported in EuroPCR 2015 showed that provisional stenting trended to have higher MACE than 2-stent strategy especially with the first generation DES. A Korean patient-level pooled analysis found higher 3-year MACE rate with 2-stent strategy than provisional stenting only among those who received first generation DES.[23] The EBC TWO Study also found similar outcome between provisional T stenting and Culotte technique using Biolimus-eluting stent.[24]

The DKCRUSH II involved patients with true bifurcation lesions (Medina 1,1,1 and 0,1,1) across 7 APAC countries found similar 1-year composite cardiac death, MI and target vessel revascularization (TVR) rates between provisional

stenting and double-kissing double crush (DK crush) technique.[25] Importantly, DK crush had sustained lower restenosis and TVR rates over 5 years.[26] Further, DKCRUSH V found that DK crush had lower 1-year TLF rate than provisional stenting in true LM bifurcation lesions.[27] Another RCT comparing DK Crush, Culotte or T-stenting also found higher short-term restenosis and MACE rates with provisional stenting.[28]

Therefore, 2-stent strategy especially with DK crush technique and current generation DES may confer similar outcome to provisional stenting when optimally performed.

Techniques in two-stent strategy

Two-stent strategy is thought to be more commonly adopted across the APAC. Among the panel, only 39% adopt a 2-stent strategy in < 10% of their bifurcation cases. The remaining perform 2-stent strategy in 11 to 50% of their bifurcation cases. In the COBIS II registry, 2-stent strategy was adopted in 20.8% of non-LM and 40.3% of the LM cases.[29]

DK crush technique devised by Dr. Chen[30] is the first 2-stent technique proven to show superior clinical outcomes. The DKCRUSH-I trial[31] found lower MACE with DK crush than classical crush technique. Although DK crush was technically more demanding, KBT was successfully performed in all of the cases which might explain its improved efficacy. DK crush can also be performed regardless of the bifurcation angle.

The DKCRUSH-III trial[32] exclusively involved unprotected true distal LM bifurcation lesions using second generation everolimus or sirolimus DES. The 8-month SB in-stent restenosis was less frequent with DK crush than Culotte, and mainly involved the ostium of left circumflex artery (LCx). The 12-month MACE was also higher in the Culotte group.

Although longer term and more data are needed, it may be reasonable to consider DK crush as the preferred 2-stent technique. Some experts have recommended sticking with technique most familiar to the operator as this is most likely to achieve an optimal result. It is important to note that proximal cell

crossing is required for classical or DK crush techniques. It is also imperative to optimize 2-stent techniques with KBT followed by POT.[2]

Elective two-stent strategy

Elective 2-stent strategy may be needed to secure the SB in complex bifurcation lesions.[2] A few clinical,[13] angiographical[12, 13, 33, 34] and intravascular imaging[35, 36] features associated with SB compromise have been described. (Figure 3) Risk prediction models such as DEFINITION[34], RESOLVE[12] and baseline V-RESOLVE[33] have also been validated and can guide interventional strategy.

An elective 2-stent strategy could be considered in SBs that are functionally significance, clinically relevant and prognostically important. A thoughtful approach should be adopted in the planning and execution of treatment strategy. (Figure 2)

Recommendation:

Elective 2-stent strategy could be adopted in selected true bifurcation cases where DK crush technique can be considered although physician's familiarity with a certain technique should also be taken into consideration.

Fractional flow reserve (FFR) in bifurcation lesions

Functional assessment of SB following MV stenting can be affected by vessel wall oedema, hematoma, thrombus or plaque shift which can remodel with time.[2] Tracking of pressure wire through MV stent struts can be unsuccessful in 10% of the cases although this can be improved by KBT.[37] SB can also be dissected by pressure wire and, although not recommended, some avoid pressure wire tracking by placing it in the SB as JWT.

There is discordance between angiographic appearance and functional significance of the SB disease. Following provisional stenting, only 27% of SBs with stenosis of > 75% have FFR < 0.75, and none of the SBs with stenosis < 75%

were functionally significant.[9] In contrast, approximately 13% of jailed SBs with angiographically insignificant stenosis have FFR < 0.80.[38] The DKCRUSH-VI study showed that FFR-guided strategy reduced the need for SB stenting and had similar clinical outcome to angiography-guided treatment following provisional stenting.[37]

Clinical outcome can be affected by the burden of ischemia and not only functional abnormality demonstrated by FFR. In LAD/Diagonal bifurcation intervention, diagonal artery occlusion leads to less angina, electrocardiographic changes and arrhythmogenic potential than LAD occlusion.[39] A recent study has established that 97% of LM SBs but only 21% of non-LM SBs supply myocardium with percentage fractional myocardial mass (%FMM) ≥10%.[40] The SBs that supply myocardium with %FMM ≥ 10% can be identified by vessel length ≥ 73 mm. Further, a LCx FFR of ≤ 0.80 following LM provisional stenting was found to be associated with higher 5-year TLF.[41]

Hence, functional assessment of SB should include the presence of ischaemia, ischaemic burden, and perhaps anatomic burden. In the absence of definitive prognostic benefit from SB intervention, a more conservative FFR of ≤0.75 is considered by some to be a reasonable treatment threshold. Recent data suggest that non-hyperaemic pressure ratio can be used to assess SB stenosis but further studies are needed for their prognostic validation.

Intracoronary imaging

Intravascular ultrasound (IVUS)[11] and optical coherent tomography (OCT)[10] have been well appraised by the EBC to optimise bifurcation PCI.

IVUS-guided bifurcation intervention reduces MACE in unprotected LM or bifurcation intervention for up to 7 years.[42, 43] RCTs on OCT-guided bifurcation intervention are ongoing. OPINION trial included a large proportion of bifurcation lesions and found OCT-guided PCI conferred similar 1-year outcome to IVUS-guided PCI. The result might be further optimised by three-dimensional OCT.[10]

The use of intravascular imaging is often limited by cost especially in APAC. Regional consensus can facilitate and align the practice and reimbursement criteria especially for complex PCI including bifurcation intervention.

Recommendation:

Intravascular imaging should be advocated and functional assessment can be considered in both LM and non-LM bifurcation intervention.

Left main stem (LM) bifurcation

The EBC Consensus documents provide comprehensive guidance for optimal LM intervention.[2, 3] Intravascular imaging is mandatory to ensure optimal outcome. During functional assessment, consideration should be given to downstream lesions and a significant lesion in one branch could spuriously increase the FFR in the other.

Most distal LM lesions are true bifurcation lesion since distal LM plaque extends into the LAD and LCx in 90% and 66% of the cases respectively.[44] Only 9% of LAD and 17% of LCx ostial lesions are without LM involvement. The discrepancy between diameter of LM and that of LAD or LCx is often substantial and will influence the stent choice. Resistance of stent to compression is also important in order to minimize guide catheter-related stent deformity. Following LM PCI, restenosis is more likely to occur at the LCx ostium especially with 2-stent techniques and remains susceptible to recurrence even after repeat intervention.[27, 32] Importantly, almost all LAD and LCx supply blood to myocardium with %FMM ≥10% which can be prognostically relevant.[40]

Since KBT in provisional stenting does not alter the clinical outcome[16], it is only recommended for selected cases.[3] Compared to provisional stenting or Culotte, DK crush has lower MACE rate.[27, 32] However, physicians' familiarity with stenting techniques and ensuring optimal minimal stent area are paramount for better outcome.

Physicians in the APAC may be faced with more patients with LM disease opting for PCI. Selection of patients should be based on current clinical evidence and multi-disciplinary Heart Team approach. The New Risk Stratification Score II (NERS II), incorporating clinical and anatomical variables, is more sensitive and specific than SYNTAX score in predicting MACE which may help to guide patient selection.[45]

Recommendation:

A heart team approach guided by clinical criteria should be adopted when counselling patients for LM disease treatment. Intravascular imaging should be mandated during PCI while DK crush technique could be considered for true bifurcation lesions.

Stent choice consideration

There are differences in biomechanical properties and performance among the different stent platforms depending on the stenting technique but their impact on clinical outcome is uncertain. Although most metallic platforms can be expanded within predefined threshold in cases where there is a large discrepancy in the vessel size proximal and distal to the SB, their structure, durability and polymer integrity for bifurcation lesion is unknown. In addition, dedicated bifurcation stent technologies are also evolving.

Present and Future

In understanding the challenges within APAC, the current consensus focuses on areas relevant to regional practices. The heart team approach to patient management and counselling using established criteria is advocated especially when tradition or cultural beliefs are in conflict with evidence-based practice. Challenging and complex bifurcation lesions should be approached systematically by establishing the significance of SB and its risk of being compromised based on

known factors with consideration given to protection techniques and, in some cases, an elective 2-stent strategy.

Much research is needed in most of the areas discussed. Development of standardised and robust lesion classification that would influence clinical outcome and allow selection of bifurcation treatment technique will help guide treatment and facilitate research. Intravascular imaging criteria to define optimal bifurcation intervention are also lacking. The optimal dual antiplatelet regimen after bifurcation intervention remains uncertain. A region-wide survey would help to identify the differences among the countries and focus effort relevant to individual countries and within APAC.

Conclusion

Although the sentiment and clinical practice within APAC for bifurcation intervention are largely similar to the rest of the world, there remains differences due to culture, socioeconomy and healthcare provision. Consideration should be given to anatomical, functional, clinical and prognostic relevance of the lesion, adopting a systematically thought-through interventional strategy. Clinical data, expertise and research efforts within APAC could contribute to the progress in bifurcation intervention. This first concerted effort sets the scene for continuing development of future regional consensus, building the network for research collaboration and establishing partnership beyond APAC.

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Legends

Figure 1. Challenges faced by APAC countries.

Figure 2. Systematic approach to bifurcation intervention.

Figure 3. Features associated with SB compromise.

Reference

1. Lassen JF, Holm NR, Stankovic G, Lefevre T, Chieffo A, Hildick-Smith D, Pan M, Darremont O, Albiero R, Ferenc M and Louvard Y. Percutaneous coronary intervention for coronary bifurcation disease: consensus from the first 10 years of the European Bifurcation Club meetings. *EuroIntervention*. 2014;10:545-60.

2. Lassen JF, Burzotta F, Banning AP, Lefevre T, Darremont O, Hildick-Smith D, Chieffo A, Pan M, Holm NR, Louvard Y and Stankovic G. Percutaneous coronary intervention for the left main stem and other bifurcation lesions: 12th consensus document from the European Bifurcation Club. *EuroIntervention*. 2018;13:1540-1553.

3. Burzotta F, Lassen JF, Banning AP, Lefevre T, Hildick-Smith D, Chieffo A, Darremont O, Pan M, Chatzizisis YS, Albiero R, Louvard Y and Stankovic G. Percutaneous coronary intervention in left main coronary artery disease: the 13th consensus document from the European Bifurcation Club. *EuroIntervention*. 2018;14:112-120.

4. Banning AP, Lassen JF, Burzotta F, Lefevre T, Darremont O, Hildick-Smith D, Louvard Y and Stankovic G. Percutaneous coronary intervention for obstructive bifurcation lesions: the 14th consensus document from the European Bifurcation Club. *EuroIntervention*. 2019;15:90-98.

5. Cho N, Kirigia J, Mbanya J, Ogurstova K, Guariguata L, Rathmann W, Roglic G, Forouhi N, Dajani R, Esteghamati A, Boyko E, Hambleton I, de Morais Neto O, Montoya P, Joshi S, Chan J, Shaw J, Samuels T, Pavkov M and Reja A. IDF Diabetes Atlas - Eighth edition 2017. 2017.

6. Lip GY, Rathore VS, Katira R, Watson RD and Singh SP. Do Indo-Asians have smaller coronary arteries? *Postgrad Med J*. 1999;75:463-6.

7. Dodge Jr. J, Brown G, Bolson E and Dogde H. Lumen Diameter of Normal Human Coronary Arteries. Influence of Age, Sex, Anatomic Variation, and Left Ventricular Hypertrophy or Dilation. *Circulation*. 1992;86:232-246.

8. Koo BK, Kang HJ, Youn TJ, Chae IH, Choi DJ, Kim HS, Sohn DW, Oh BH, Lee MM, Park YB, Choi YS and Tahk SJ. Physiologic assessment of jailed side branch lesions using fractional flow reserve. *J Am Coll Cardiol*. 2005;46:633-7.

9. Koo BK, Park KW, Kang HJ, Cho YS, Chung WY, Youn TJ, Chae IH, Choi DJ, Tahk SJ, Oh BH, Park YB and Kim HS. Physiological evaluation of the provisional side-branch intervention strategy for bifurcation lesions using fractional flow reserve. *Eur Heart J*. 2008;29:726-32.

10. Onuma Y, Katagiri Y, Burzotta F, Holm NR, Amabile N, Okamura T, Mintz GS, Darremont O, Lassen JF, Lefevre T, Louvard Y, Stankovic G and Serruys PW. Joint consensus on the use of OCT in coronary bifurcation lesions by European and Japanese bifurcation clubs. *EuroIntervention*. 2018.

11. Mintz GS, Lefevre T, Lassen JF, Testa L, Pan M, Singh J, Stankovic G and Banning AP. Intravascular ultrasound in the evaluation and treatment of left main coronary artery disease: a consensus statement from the European Bifurcation Club. *EuroIntervention*. 2018;14:e467-e474.

12. Dou K, Zhang D, Xu B, Yang Y, Yin D, Qiao S, Wu Y, Yan H, You S, Wang Y, Wu Z, Gao R and Kirtane AJ. An angiographic tool for risk prediction of side branch occlusion in coronary bifurcation intervention: the RESOLVE score system (Risk prEdiction of Side branch OccLusion in coronary bifurcation interVEntion). *JACC Cardiovasc Interv*. 2015;8:39-46.

13. Hahn JY, Chun WJ, Kim JH, Song YB, Oh JH, Koo BK, Rha SW, Yu CW, Park JS, Jeong JO, Choi SH, Choi JH, Jeong MH, Yoon JH, Jang Y, Tahk SJ, Kim HS and Gwon HC. Predictors and outcomes of side branch occlusion after main vessel stenting in coronary bifurcation lesions: results from the COBIS II Registry (COronary BIfurcation Stenting). *J Am Coll Cardiol*. 2013;62:1654-1659.

14. Saito S, Shishido K, Moriyama N, Ochiai T, Mizuno S, Yamanaka F, Sugitatsu K, Tobita K, Matsumi J, Tanaka Y and Murakami M. Modified jailed balloon technique for bifurcation lesions. *Catheter Cardiovasc Interv*. 2018;92:E218-e226.

15. Hariki H, Shinke T, Otake H, Shite J, Nakagawa M, Inoue T, Osue T, Iwasaki M, Taniguchi Y, Nishio R, Hiranuma N, Kinutani H, Konishi A and Hirata K. Potential benefit of final kissing balloon inflation after single stenting for the treatment of bifurcation lesions--insights from optical coherence tomography observations. *Circ J*. 2013;77:1193-201.

16. Niemela M, Kervinen K, Erglis A, Holm NR, Maeng M, Christiansen EH, Kumsars I, Jegere S, Dombrovskis A, Gunnes P, Stavnes S, Steigen TK, Trovik T, Eskola M, Vikman S, Romppanen H, Makikallio T, Hansen KN, Thayssen P, Aberge L, Jensen LO, Hervold A, Airaksinen J, Pietila M, Frobert O, Kellerth T, Ravkilde J, Aaroe J, Jensen JS, Helqvist S, Sjogren I, James S, Miettinen H, Lassen JF, Thuesen L and Nordic-Baltic PCISG. Randomized comparison of final kissing balloon dilatation versus no final kissing balloon dilatation in patients with coronary bifurcation lesions treated with main vessel stenting: the Nordic-Baltic Bifurcation Study III. *Circulation*. 2011;123:79-86.

17. Song YB, Park TK, Hahn JY, Yang JH, Choi JH, Choi SH, Lee SH and Gwon HC. Optimal Strategy for Provisional Side Branch Intervention in Coronary Bifurcation Lesions: 3-Year Outcomes of the SMART-STRATEGY Randomized Trial. *JACC Cardiovasc Interv*. 2016;9:517-26.

18. Kim YH, Lee JH, Roh JH, Ahn JM, Yoon SH, Park DW, Lee JY, Yun SC, Kang SJ, Lee SW, Lee CW, Seung KB, Shin WY, Lee NH, Lee BK, Lee SG, Nam CW, Yoon J, Yang JY, Hyon MS, Lee K, Jang JS, Kim HS, Park SW and Park SJ. Randomized Comparisons Between Different Stenting Approaches for Bifurcation Coronary Lesions With or Without Side Branch Stenosis. *JACC Cardiovasc Interv*. 2015;8:550-60.

19. Zhong M, Tang B, Zhao Q, Cheng J, Jin Q and Fu S. Should kissing balloon inflation after main vessel stenting be routine in the one-stent approach? A systematic review and meta-analysis of randomized trials. *PLoS One*. 2018;13:e0197580.

20. Murasato Y, Finet G and Foin N. Final kissing balloon inflation: the whole story. *EuroIntervention*. 2015;11 Suppl V:V81-5.

21. Derimay F, Finet G, Souteyrand G, Maillard L, Aminian A, Lattuca B, Cayla G, Cellier G, Motreff P and Rioufol G. Benefit of a new provisional stenting strategy, the re-proximal optimisation technique: the rePOT clinical study. *EuroIntervention*. 2018;14:e325-e332.

22. Zhang F, Dong L and Ge J. Simple versus complex stenting strategy for coronary artery bifurcation lesions in the drug-eluting stent era: a meta-analysis of randomised trials. *Heart*. 2009;95:1676-81.

23. Lee JM, Hahn JY, Kang J, Park KW, Chun WJ, Rha SW, Yu CW, Jeong JO, Jeong MH, Yoon JH, Jang Y, Tahk SJ, Gwon HC, Koo BK and Kim HS. Differential Prognostic Effect Between First- and Second-Generation Drug-Eluting Stents in Coronary Bifurcation Lesions: Patient-Level Analysis of the Korean Bifurcation Pooled Cohorts. *JACC Cardiovasc Interv*. 2015;8:1318-31.

24. Hildick-Smith D, Behan MW, Lassen JF, Chieffo A, Lefevre T, Stankovic G, Burzotta F, Pan M, Ferenc M, Bennett L, Hovasse T, Spence MJ, Oldroyd K, Brunel P, Carrie D, Baumbach A, Maeng M, Skipper N and Louvard Y. The EBC TWO Study (European Bifurcation Coronary TWO): A Randomized Comparison of Provisional T-Stenting Versus a Systematic 2 Stent Culotte Strategy in Large Caliber True Bifurcations. *Circ Cardiovasc Interv*. 2016;9.

25. Chen SL, Santoso T, Zhang JJ, Ye F, Xu YW, Fu Q, Kan J, Paiboon C, Zhou Y, Ding SQ and Kwan TW. A randomized clinical study comparing double kissing crush with provisional stenting for treatment of coronary bifurcation lesions: results from the DKCRUSH-II (Double Kissing Crush versus Provisional Stenting Technique for Treatment of Coronary Bifurcation Lesions) trial. *J Am Coll Cardiol*. 2011;57:914-20.

26. Chen SL, Santoso T, Zhang JJ, Ye F, Xu YW, Fu Q, Kan J, Zhang FF, Zhou Y, Xie DJ and Kwan TW. Clinical Outcome of Double Kissing Crush Versus Provisional Stenting of Coronary Artery Bifurcation Lesions: The 5-Year Follow-

Up Results From a Randomized and Multicenter DKCRUSH-II Study (Randomized Study on Double Kissing Crush Technique Versus Provisional Stenting Technique for Coronary Artery Bifurcation Lesions). *Circ Cardiovasc Interv*. 2017;10.

27. Chen SL, Zhang JJ, Han Y, Kan J, Chen L, Qiu C, Jiang T, Tao L, Zeng H, Li L, Xia Y, Gao C, Santoso T, Paiboon C, Wang Y, Kwan TW, Ye F, Tian N, Liu Z, Lin S, Lu C, Wen S, Hong L, Zhang Q, Sheiban I, Xu Y, Wang L, Rab TS, Li Z, Cheng G, Cui L, Leon MB and Stone GW. Double Kissing Crush Versus Provisional Stenting for Left Main Distal Bifurcation Lesions: DKCRUSH-V Randomized Trial. *J Am Coll Cardiol*. 2017;70:2605-2617.

28. Lin QF, Luo YK, Lin CG, Peng YF, Zhen XC and Chen LL. Choice of stenting strategy in true coronary artery bifurcation lesions. *Coron Artery Dis*. 2010;21:345-51.

29. Song YB, Hahn JY, Yang JH, Choi SH, Choi JH, Lee SH, Jeong MH, Kim HS, Lee JH, Yu CW, Rha SW, Jang Y, Yoon JH, Tahk SJ, Seung KB, Oh JH, Park JS and Gwon HC. Differential prognostic impact of treatment strategy among patients with left main versus non-left main bifurcation lesions undergoing percutaneous coronary intervention: results from the COBIS (Coronary Bifurcation Stenting) Registry II. *JACC Cardiovasc Interv*. 2014;7:255-63.

30. Chen SL, Ye F, Zhang JJ, Zhu ZS, Lin S, Shan SJ, Liu ZZ, Liu Y, Duan BX and Ge JB. [DK crush technique: modified treatment of bifurcation lesions in coronary artery]. *Chin Med J (Engl)*. 2005;118:1746-50.

31. Chen SL, Zhang JJ, Ye F, Chen YD, Patel T, Kawajiri K, Lee M, Kwan TW, Mintz G and Tan HC. Study comparing the double kissing (DK) crush with classical crush for the treatment of coronary bifurcation lesions: the DKCRUSH-1 Bifurcation Study with drug-eluting stents. *European journal of clinical investigation*. 2008;38:361-71.

32. Chen SL, Xu B, Han YL, Sheiban I, Zhang JJ, Ye F, Kwan TW, Paiboon C, Zhou YJ, Lv SZ, Dangas GD, Xu YW, Wen SY, Hong L, Zhang RY, Wang HC, Jiang TM, Wang Y, Chen F, Yuan ZY, Li WM and Leon MB. Comparison of double kissing crush versus Culotte stenting for unprotected distal left main bifurcation lesions: results from a multicenter, randomized, prospective DKCRUSH-III study. *J Am Coll Cardiol*. 2013;61:1482-8.

33. He Y, Zhang D, Yin D, Zhu C, Feng L, Song C, Chen C, Feng L and Dou K. Development and validation of a risk scoring system based on baseline angiographic results by visual estimation for risk prEdiction of side-branch OccLusion in coronary bifurcation InterVEntion: The baseline V-RESOLVE score. *Catheter Cardiovasc Interv*. 2019.

34. Chen SL, Sheiban I, Xu B, Jepson N, Paiboon C, Zhang JJ, Ye F, Sansoto T, Kwan TW, Lee M, Han YL, Lv SZ, Wen SY, Zhang Q, Wang HC, Jiang TM, Wang Y,

Chen LL, Tian NL, Cao F, Qiu CG, Zhang YJ and Leon MB. Impact of the complexity of bifurcation lesions treated with drug-eluting stents: the DEFINITION study (Definitions and impact of complEx biFurcation lesIons on clinical outcomes after percutaNeous coronary IntervenTIOn using drug-eluting steNts). *JACC Cardiovasc Interv*. 2014;7:1266-76.

35. Sakamoto N, Hoshino Y, Mizukami H, Sugimoto K, Yamaki T, Kunii H, Nakazato K, Suzuki H, Saitoh S and Takeishi Y. Intravascular ultrasound predictors of acute side branch occlusion in coronary artery bifurcation lesions just after single stent crossover. *Catheter Cardiovasc Interv*. 2016;87:243-50.

36. Watanabe M, Uemura S, Sugawara Y, Ueda T, Soeda T, Takeda Y, Kawata H, Kawakami R and Saito Y. Side branch complication after a single-stent crossover technique: prediction with frequency domain optical coherence tomography. *Coron Artery Dis*. 2014;25:321-9.

37. Chen SL, Ye F, Zhang JJ, Xu T, Tian NL, Liu ZZ, Lin S, Shan SJ, Ge Z, You W, Liu YQ, Qian XS, Li F, Yang S, Kwan TW, Xu B and Stone GW. Randomized Comparison of FFR-Guided and Angiography-Guided Provisional Stenting of True Coronary Bifurcation Lesions: The DKCRUSH-VI Trial (Double Kissing Crush Versus Provisional Stenting Technique for Treatment of Coronary Bifurcation Lesions VI). *JACC Cardiovasc Interv*. 2015;8:536-46.

38. Ahn JM, Lee JY, Kang SJ, Kim YH, Song HG, Oh JH, Park JS, Kim WJ, Lee SW, Lee CW, Kim JJ, Park SW and Park SJ. Functional assessment of jailed side branches in coronary bifurcation lesions using fractional flow reserve. *JACC Cardiovasc Interv*. 2012;5:155-61.

39. Koo BK, Lee SP, Lee JH, Park KW, Suh JW, Cho YS, Chung WY, Doh JH, Nam CW, Yu CW, Lee BK, Vassilev D, Gil R, Lim HS, Tahk SJ and Kim HS. Assessment of clinical, electrocardiographic, and physiological relevance of diagonal branch in left anterior descending coronary artery bifurcation lesions. *JACC Cardiovasc Interv*. 2012;5:1126-32.

40. Kim HY, Doh JH, Lim HS, Nam CW, Shin ES, Koo BK, Lee JM, Park TK, Yang JH, Song YB, Hahn JY, Choi SH, Gwon HC, Lee SH, Kim SM, Choe Y and Choi JH. Identification of Coronary Artery Side Branch Supplying Myocardial Mass That May Benefit From Revascularization. *JACC Cardiovasc Interv*. 2017;10:571-581.

41. Lee CH, Choi SW, Hwang J, Kim IC, Cho YK, Park HS, Yoon HJ, Kim H, Han S, Kim JY, Lee JM, Doh JH, Shin ES, Koo BK, Hur SH and Nam CW. 5-Year Outcomes According to FFR of Left Circumflex Coronary Artery After Left Main Crossover Stenting. *JACC Cardiovasc Interv*. 2019;12:847-855.

42. Fan ZG, Gao XF, Li XB, Shao MX, Gao YL, Chen SL and Tian NL. The outcomes of intravascular ultrasound-guided drug-eluting stent implantation among patients with complex coronary lesions: a comprehensive meta-analysis

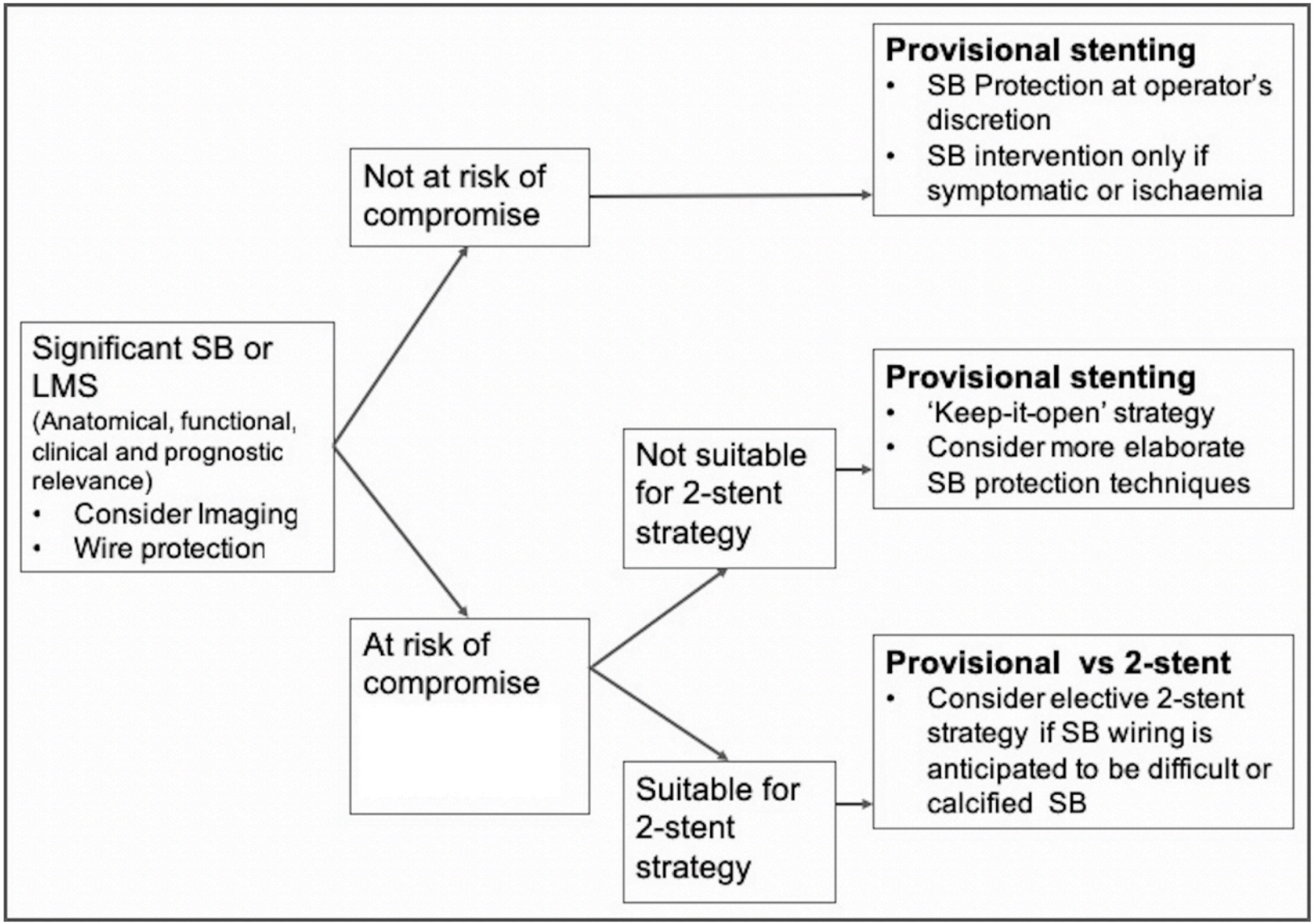
of 15 clinical trials and 8,084 patients. *Anatolian journal of cardiology*. 2017;17:258-268.

43. Chen L, Xu T, Xue XJ, Zhang JJ, Ye F, Tian NL and Chen SL. Intravascular ultrasound-guided drug-eluting stent implantation is associated with improved clinical outcomes in patients with unstable angina and complex coronary artery true bifurcation lesions. *Int J Cardiovasc Imaging*. 2018;34:1685-1696.

44. Oviedo C, Maehara A, Mintz GS, Araki H, Choi SY, Tsujita K, Kubo T, Doi H, Templin B, Lansky AJ, Dangas G, Leon MB, Mehran R, Tahk SJ, Stone GW, Ochiai M and Moses JW. Intravascular ultrasound classification of plaque distribution in left main coronary artery bifurcations: where is the plaque really located? *Circ Cardiovasc Interv*. 2010;3:105-12.

45. Chen SL, Han YL, Zhang YJ, Ye F, Liu HW, Zhang JJ, Xu B, Jiang TM, Zhou YJ and Lv SZ. The anatomic- and clinical-based NERS (new risk stratification) score II to predict clinical outcomes after stenting unprotected left main coronary artery disease: results from a multicenter, prospective, registry study. *JACC Cardiovasc Interv*. 2013;6:1233-41.

APAC	Developed countries
Less well developed or lack of healthcare infrastructure such as availability of physicians or medical services and devices especially in the developing countries.	Generally well developed healthcare infrastructure.
Healthcare reimbursement scheme is not comprehensive in most countries.	Generally well structured and comprehensive.
Tradition, culture, religious and socioeconomic factors: • PCI is often preferred due to cultural or religious reasons. • PCI is often perferred as the long recuperation period following CABG makes it a non-viable option for many due to the lack of social welfare support. • Lack of health awareness, the perception of being elderly and feeling content lead to less invasive treatment options are preferred over prognostically beneficial invasive interventions. • Patient expectation of 'perfect' treatment results may affect decision for 2-stent PCI strategy.	Better health awareness and social welfare support such that treatment options are more often selected based on long-term prognostic benefit.
Lack of health awareness and higher prevalent of diseases such as diabetes mellitus leading to more advanced and complex coronary disease at presentation.	Better health awareness and primary care services.



Clinical	Angiographic	Intravascular imaging
Acute coronary syndrome Low left ventricular ejection fraction	**DEFINITION** Major • Distal LMS: SB-DS ≥70%; SB lesion length ≥10mm • Non-LMS: SB-DS ≥90%; SB lesion length ≥10mm Minor • Moderate to severe calcification • Multiple lesions • Bifurcation angle <45° • MV reference vessel diameter <2.5mm • Thrombus-containing lesions • MV lesion length ≥25mm Complex = 1 major + 2 minor **RESOLVE or Baseline V-RESOLVE** Plaque on same side of SB Low MV TIMI flow grade Bifurcation core >DS 50% Bifurcation angle >70° Diameter ratio MV/SB >1 SB-DS >50% **COBIS II** SB-DS >50% Bifurcation core stenosis >50% SB lesion length	**IVUS** Circumferential plaque at SB ostium MV plaque adjacent to SB ostium >0.9mm in thickness SB ostium media-to-media diameter/intima-to-intima diameter ratio >1.5 LMS • LCx minimal luminal area <3.7mm^2 • Plaque burden >56% • Calcified plaque with calcium arc >60° **OCT** • Carina tip angle <50° • Branching point-to-carina tip length <1.7mm • Lipid plaque with spotty calcification in MV • Calcific Lipid plaque opposite SB ostium • Large lipid plaque arc