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Antithrombotic therapy after percutaneous coronary intervention of bifurcation lesions

Marco Zimarino[1,2]*, MD, PhD; Dominick J. Angiolillo[3], MD, PhD; George Dangas[4], MD, PhD; Davide Capodanno[5], MD, PhD; Emanuele Barbato[6], MD, PhD; Joo-Yong Hahn[7], MD, PhD; Gennaro Giustino[4], MD; Hirotoshi Watanabe[8], MD, PhD; Francesco Costa[9], MD, PhD; Thomas Cuisset[10], MD, PhD; Roberta Rossini[11], MD, PhD; Dirk Sibbing[12], MD; Francesco Burzotta[13], MD; Yves Louvard[14], MD; Abdulla Shehab[15], MD, PhD; Giulia Renda[1], MD, PhD; Takeshi Kimura[8], MD, PhD; Hyeon-Cheol Gwon[7], MD; Shao-Liang Chen[16], MD, PhD; Ricardo Costa[17], MD, PhD; Bon-Kwon Koo[18], MD, PhD; Robert F. Storey[19], MD, DM; Marco Valgimigli[20], MD, PhD; Roxana Mehran[4], MD; Goran Stankovic[21], MD, PhD

The authors' affiliations can be found in the Appendix paragraph.

GUEST EDITOR: Franz-Josef Neumann, MD; *University Heart Centre Freiburg Bad Krozingen, Division of Cardiology and Angiology II, Bad Krozingen, Germany*

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KEYWORDS

- adjunctive pharmacotherapy
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Abstract

Coronary bifurcations exhibit localised turbulent flow and an enhanced propensity for atherothrombosis, platelet deposition and plaque rupture. Percutaneous coronary intervention (PCI) of bifurcation lesions is associated with an increased risk of thrombotic events. Such risk is modulated by anatomical complexity, intraprocedural factors and pharmacological therapy. There is no consensus on the appropriate PCI strategy or the optimal regimen and duration of antithrombotic treatment in order to decrease the risk of ischaemic and bleeding complications in the setting of coronary bifurcation. A uniform therapeutic approach meets a clinical need. The present initiative, promoted by the European Bifurcation Club (EBC), involves opinion leaders from Europe, America, and Asia with the aim of analysing the currently available evidence. Although mainly derived from small dedicated studies, substudies of large trials or from authors' opinions, an algorithm for the optimal management of patients undergoing bifurcation PCI, developed on the basis of clinical presentation, bleeding risk, and intraprocedural strategy, is proposed here.

*Corresponding author: Institute of Cardiology, "G. d'Annunzio" University – Chieti, c/o Ospedale SS. Annunziata, Via dei Vestini, 66013 Chieti, Italy. E-mail: m.zimarino@unich.it

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Abbreviations

ACS	acute coronary syndrome
CAD	coronary artery disease
DAPT	dual antiplatelet therapy
DAT	dual antithrombotic therapy
DES	drug-eluting stent(s)
DK	double kissing
EBC	European Bifurcation Club
HBR	high bleeding risk
IVUS	intravascular ultrasound
LM	left main
LOE	level of evidence
MI	myocardial infarction
MV	main vessel
OAC	oral anticoagulant
OCT	optical coherence tomography
PCI	percutaneous coronary intervention
SB	side branch
ST	stent thrombosis
TAT	triple antithrombotic therapy
TVR	target vessel revascularisation

Introduction

Dual antiplatelet therapy (DAPT) with aspirin and a $P2Y_{12}$ receptor inhibitor (clopidogrel, prasugrel, or ticagrelor) is the standard of care for patients undergoing percutaneous coronary intervention (PCI) with drug-eluting stents (DES)[1,2]. However, the optimal duration of DAPT remains a topic of debate[3], particularly in complex lesions.

Patients with a coronary bifurcation account for 15-20% of candidates to PCI and are at higher risk of both periprocedural and long-term adverse events[4]. Coronary artery bifurcation lesions exhibit localised turbulent flow and an enhanced propensity for platelet aggregation, plaque rupture, and atherothrombosis. Anatomical factors, including the fractal geometry of vascular bifurcations, increase the incidence of strut malapposition and stent underexpansion. Definite or probable stent thrombosis (ST) occurs more frequently early (within the first 30 days) rather than late. The overall incidence of ST in bifurcation PCI is in the range of 1.5-2%, almost double as compared to non-bifurcation PCI (<1%)[4]. The risk varies according to bifurcation complexity, as ST occurs in about 2% when side branch (SB) lesion length is >10 mm, and 1% for SB lesion length <10 mm[5], and procedural technique, with two stents showing a doubled risk of ST as compared to a single-stent technique[6].

The term "bifurcation lesion" encompasses a large variety of anatomic subsets and clinical scenarios, from left main (LM) bifurcation with a significant amount of myocardium at risk to a small branching lateral branch with negligible myocardium at risk. Such anatomic subsets, both listed in the "complex bifurcation lesion" classification of the DEFINITION II study[7] **(Supplementary Table 1)**, show thrombotic and ischaemic risks pointing in different directions, therefore hindering the identification of the optimal antithrombotic therapy.

The European Bifurcation Club (EBC) recommends single stenting with the "provisional" side branch (SB) stenting strategy for the treatment of the vast majority of bifurcation lesions[6], while European Society of Cardiology (ESC) guidelines "suggest considering" the use of double stenting with the double kissing (DK-) crush technique in the treatment of LM bifurcation lesions (class IIb, level of evidence [LOE] B), following the results of the DKCRUSH-V trial[8].

In any event, careful planning is absolutely mandatory in bifurcation PCI, as a "bail-out" placement of a second stent has been associated with higher risk of ST than planned double stenting[9,10].

In the two-stent strategy, the EBC recommends final kissing balloon inflation followed by the proximal optimisation technique (POT) in order to minimise strut malapposition and subsequent ST risk[6]. Intravascular guidance represents a valuable strategy in bifurcation PCI: ESC guidelines recommend intravascular ultrasound (IVUS) guidance only for the treatment of unprotected LM lesions (class IIa, LOE B)[11], while the EBC underlines the benefit of intravascular imaging for any bifurcation[6] **(Figure 1)**.

Therefore, the implementation of individualised antithrombotic management to mitigate the risk of ST and spontaneous myocardial infarction (MI) without a concurrent increased risk of bleeding according to the procedural complexity in PCI bifurcation answers a clinical need.

The EBC suggested a state-of-the-art paper on antithrombotic therapy after bifurcation PCI. The document chairs (M. Zimarino and D.J. Angiolillo) identified key opinion leaders from Europe, America, and Asia with expertise in basic, translational, and clinical sciences in the field of antiplatelet therapy and interventional cardiology.

In this manuscript, specific issues related to antithrombotic therapy after PCI of bifurcation lesions are presented. For further details please refer to **Supplementary Appendix 1**.

CHOICE OF ANTITHROMBOTIC DRUGS AND TIMING OF INITIATION

In acute coronary syndrome (ACS) patients, potent oral $P2Y_{12}$ inhibitors (prasugrel and ticagrelor) are recommended in the light of their superior efficacy when compared to clopidogrel[2]. As compared to clopidogrel, ticagrelor[12] and prasugrel[13] were associated with a similar (1.0% and 1.2%, respectively) absolute reduction of ST in ACS patients, which was higher (3.2% after prasugrel) in the cohort of patients with a bifurcation stent[13]. Following the results of the ISAR-REACT 5 trial[14], ESC guidelines[15] now give a preference to prasugrel over ticagrelor in patients who proceed to PCI (class IIa).

Although the efficacy of newer $P2Y_{12}$ inhibitors over clopidogrel has never been documented in stable coronary artery disease (CAD), the authors agree with the ESC guidelines, where prasugrel and ticagrelor may be considered (class IIb) in patients with stable CAD and a high risk of thrombosis, such as complex LM cases, based on expert consensus (LOE C)[16].

With ST occurring mostly in the acute and early phase, rapid and effective i.v. inhibition of the platelet $P2Y_{12}$ receptor may be

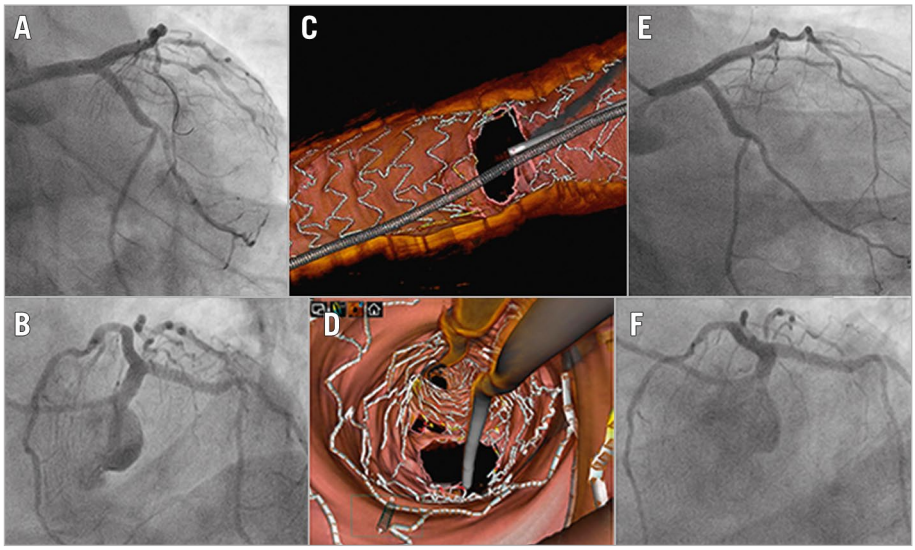


Figure 1. *OCT assessment of LM bifurcation stenting. After double stenting of the left main (LM) with the culotte technique (A & B), 3D optical coherence tomography (OCT) documented adequate stent expansion without strut protrusion (C & D). The patient remained asymptomatic and, 12 months later, the stents were widely patent at control angiography (E & F).*

adopted in patients undergoing bifurcation PCI without adequate pretreatment. A substudy of the CHAMPION-PHOENIX trial reported that the number of high-risk lesions (a coronary bifurcation was present in almost 50% of cases) was strongly predictive of periprocedural MI and ST and cangrelor significantly reduced such adverse events, with a greater absolute effect proportional to the number of high-risk lesions, irrespective of clinical presentation[17].

DAPT DURATION AND RISK STRATIFICATION

International guidelines list coronary bifurcation as a risk factor for ST (among other characteristics of PCI complexity), suggesting that a longer duration of DAPT for both stable CAD and ACS may be considered in this setting (class IIb, LOE B)[1,2].

This recommendation is based mainly on a meta-analysis[18] **(Table 1)** where, as compared with 3-6 months, ≥12 months DAPT duration was associated with a significant reduction in the composite endpoint among patients who underwent "complex" PCI – defined according to the so-called "Giustino criteria" – but not in the non-complex PCI group ($p_{interaction}$ = 0.01). The presence of a bifurcation treated with double stenting was the strongest risk factor for the composite of cardiac death, MI or ST, and its individual components. Long-term DAPT was associated with an increased risk for major bleeding, regardless of PCI complexity.

Given the trade-off between ischaemic and bleeding risks for any DAPT duration, three scoring systems have been developed **(Supplementary Table 2)**.

A substudy of the DAPT trial[19] **(Table 1)** documented that, among subjects with anatomic complexity (19% double stenting for bifurcation), those with a DAPT score ≥2 receiving 30-month DAPT experienced a significantly lower rate of MI or ST (3.0%) than those receiving only 12-month DAPT (6.1%, p<0.001), while no difference was detected among patients with a score <2.

In a sub-analysis of the PRECISE-DAPT pooled data set[20] **(Table 1)**, patients who underwent a complex PCI, based on the Giustino criteria[18], experienced a risk reduction (-4%) in the composite net adverse clinical events from long-term DAPT only if the bleeding risk at baseline was low (PRECISE-DAPT score <25). When receiving long-term DAPT, patients at high baseline bleeding risk (PRECISE-DAPT score ≥25) experienced no significant risk reduction for ischaemic events regardless of the complexity of PCI and suffered a significant excess of bleeding complications (p_{int}=0.89).

The greatest benefit of prolonged DAPT is accrued in bifurcation PCI with a larger thrombogenic milieu (ACS, double stenting, no imaging) and higher ischaemic risk (large myocardium at risk, as for unprotected LM); in this setting, a thorough evaluation of the bleeding risk becomes crucial.

THE IDENTIFICATION OF PATIENTS AT HIGH BLEEDING RISK

The concept of "high bleeding risk" (HBR) has recently been emphasised to guide DAPT duration in patients undergoing PCI[2].

The Academic Research Consortium (ARC)-HBR initiative recently issued a consensus[21] identifying HBR patients as those with a one-year risk of a Bleeding Academic Research Consortium (BARC)-defined type 3 or 5 bleeding of ≥4% and of intracranial haemorrhage of ≥1%. According to twenty clinical major or minor criteria **(Supplementary Table 3)**, patients are identified as being at HBR if at least one major criterion or two minor criteria are met.

In the context of bifurcation PCI, the identification of HBR should be an argument to favour a procedural strategy – single "provisional" stenting, intravascular guidance – that allows a shorter DAPT duration.

Table 1. Studies assessing the impact of DAPT duration after PCI of bifurcation lesions.

	Giustino et al[18]	Yeh et al[19]	Jang et al[32]	Rhee et al[33]	Zimarino et al[10]	Kogame et al[22]	Costa et al[20]	Dangas et al[23]
Year	2016	2017	2018	2018	2019	2019	2019	2020
Type of study	Pooled analysis from 6 RCTs	Substudy of an RCT	nROS	Pooled analysis from 5 nROS	nROS	Substudy of an RCT	Pooled analysis from RCTs	Substudy of an RCT
Name of the original study	–	DAPT	COBIS II	–	EBC registry	GLOBAL LEADERS	PRECISE-DAPT	TWILIGHT COMPLEX
Study population	n=9,577	n=11,554	n=2,082	n=700	n=5,036	n=15,845	n=14,963	n=2,342
Bifurcation lesions	6.8%	6.2%	100%	100%	100%	15.8%	8%	10.7%
2-stent	100%	100%	26%	19%	10%	20%	100%	100%
DAPT duration Short-term Long-term	3-6 months ≥12 months	12 months 30 months	<12 months ≥12 months	<12 months ≥12 months	<6 months SCAD, <12 months ACS ≥6 months SCAD ≥12 months ACS	1 month (then ticagrelor) 12 months (then aspirin)	3-6 months 12-24 months	3 months 15 months
Follow-up	13 months	30 months	4 years	3 years	18 months	2 years	2 years	18 months
Efficacy endpoint	MACE (cardiac death, MI, or ST)	MI or ST	Death or MI	MACE (cardiac death, MI, or ST)	MACE (cardiac death, MI, or ST)	Death or MI	MI, ST, stroke, TVR	Death, MI, stroke
Safety endpoint	Major bleeding	Moderate/severe bleeding	NA	NA	NA	Major bleeding	Major and minor bleeding	BARC 3 or 5 bleeding
Main findings	Long-term DAPT reduces the risk of MACE in the complex PCI group, increases the risk of major bleeding	Long-term DAPT increases the risk of bleeding and reduces MI or ST, most evident among complex PCI with DAPT score ≥2	After PS matching, the risk of death or MI was lower in the long- vs short-term DAPT group	After PS matching, the risk of MACE in the 2-stent group was lower with long- vs short-term DAPT	Long-term DAPT was associated with a lower risk of MACE	No differences in death or MI. No differences in bleeding risk	Long-term DAPT reduces the risk of ischaemic events in complex PCI only if PRECISE-DAPT score <25.	Long-term DAPT increased the risk of bleeding and is associated with a trend towards a reduction in risk of death, MI or stroke

MACE: major adverse cardiac events; NA: not available; nROS: non-randomised observational study; PS: propensity score; RCT: randomised clinical trial; TVR: target vessel revascularisation

ROLE OF $P2Y_{12}$-RECEPTOR INHIBITOR MONOTHERAPY

Against the tenet of $P2Y_{12}$ inhibitor discontinuation on a background of continued aspirin, there has been growing interest in the concept of discontinuing aspirin in favour of monotherapy with a sole $P2Y_{12}$ inhibitor, aiming to contain the bleeding risk.

In the GLOBAL LEADERS trial, among patients who underwent bifurcation PCI (16%) with a biolimus-eluting stent **(Table 1)**, one month of DAPT followed by ticagrelor monotherapy for 23 months was associated with a similar risk of two-year all-cause death or MI, without any significant reduction in the bleeding risk when compared with 12-month DAPT followed by aspirin[22].

In the TWILIGHT-COMPLEX substudy[23] **(Table 1)**, this approach was specifically evaluated among patients who underwent "complex" PCI, with two-stent bifurcation being used in 10.7% of cases. Ticagrelor monotherapy was associated with a similar and consistent reduction in the BARC 2, 3 or 5 bleeding risk in both the "complex" and "non-complex" PCI groups, without increasing the risk of ischaemic events.

A recent meta-analysis documented that ST was infrequent, and aspirin discontinuation was not associated with a statistically significant increase in the risk[24]. However, such an appealing strategy still needs confirmation in the bifurcation setting.

SWITCHING OR DISCONTINUATION OF $P2Y_{12}$ INHIBITORS

In general, escalation – an increase in platelet inhibition – may be indicated in the early phase after a complex PCI[25]. The presence of high-risk angiographic characteristics, namely thrombotic, long, and bifurcating lesions, has been identified as the major determinant of escalation from clopidogrel to prasugrel in clinical practice[26].

De-escalation – the transition from a more potent $P2Y_{12}$ inhibitor – is the most common of the switching strategies, given that thrombotic events are more likely to occur early and the prolonged use of potent $P2Y_{12}$ inhibition is associated with an increased risk of bleeding with less enhanced antithrombotic benefit[25]. It comes into the clinical field when you have, for example, a high-risk lesion such as in bifurcation stenting but at the same time an HBR on ticagrelor or prasugrel.

Premature discontinuation of oral antiplatelet therapy after PCI is associated with a significant increase in the risk of ischaemic events and ST[27], with non-cardiac surgery representing one of the most common causes.

Following the Surgery After Stenting 2 document[28], bridging with an intravenous antiplatelet agent, such as cangrelor at a dose regimen of 0.75 mcg/kg/min, may be recommended in patients deemed to be at high thrombotic risk, such as those with bifurcation lesions treated with double stenting, who cannot safely interrupt oral antiplatelet therapy.

MANAGEMENT OF CANDIDATES FOR ORAL ANTICOAGULATION

A recent meta-analysis[29] underlined that, in candidates for oral anticoagulant (OAC) therapy after PCI, a dual antithrombotic

therapy (DAT) with OAC and a single antiplatelet agent is associated with a reduction of bleeding as compared with triple antithrombotic therapy (TAT, i.e., OAC in combination with DAPT) (risk ratio [RR] 0.66, 95% CI: 0.56-0.78; p<0.0001); non-vitamin K (N)OAC-based DAT versus vitamin K antagonist TAT yielded consistent results and a significant reduction of intracranial haemorrhage (RR 0.33, 95% CI: 0.17-0.65; p=0.001). Such benefit is, however, counterbalanced by a significant increase of ST (RR 1.59, 95% CI: 1.01-2.50; p=0.04) and a trend towards higher risk of MI with DAT as compared with TAT.

Substudies on complex lesions from both the PIONEER AF-PCI trial[30] and the REDUAL PCI trial[31] showed that NOAC-based DAT following PCI was associated with a reduced bleeding and a similar thrombotic risk compared with warfarin-based TAT, irrespective of the complexity of PCI.

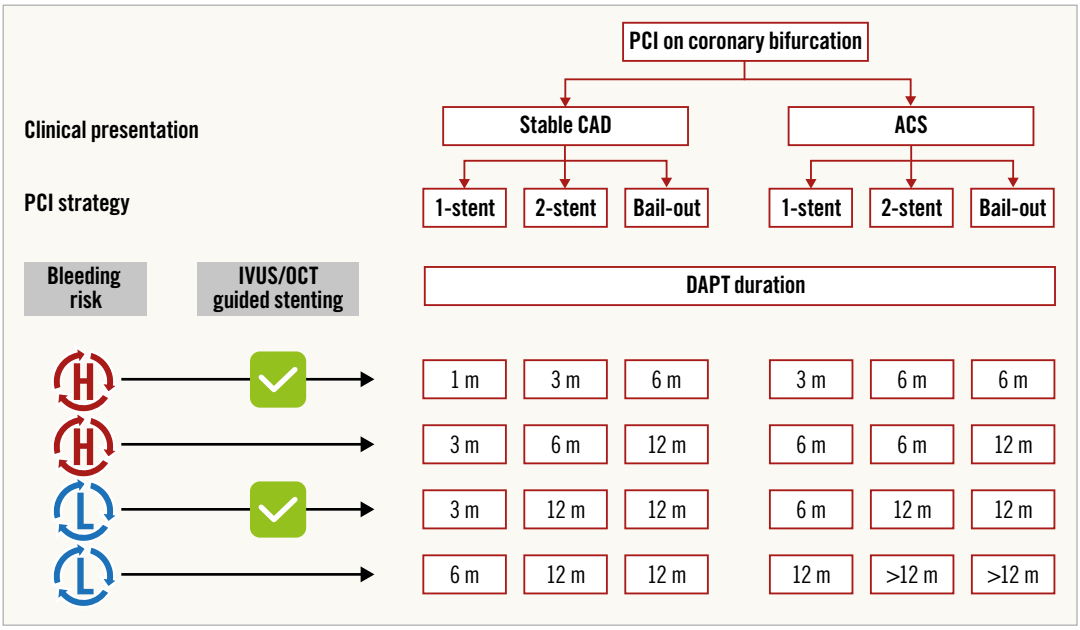
Conclusions

The selection and the duration of antithrombotic therapy after bifurcation PCI should take into account multiple factors. Although we acknowledge that much of the currently available evidence about antithrombotic therapy in bifurcation PCI is not derived from major dedicated studies, we here propose a decision-making algorithm for DAPT duration based primarily on the clinical presentation, the baseline bleeding risk, the stenting strategy, and the possible use of intracoronary imaging in patients not candidates to anticoagulant therapy **(Central illustration)**.

Strategy trials are keenly awaited to refine further the optimal antithrombotic regimen in patients undergoing bifurcation PCI.

Appendix. Authors' affiliations

1. Institute of Cardiology, University "G. d'Annunzio" of Chieti-Pescara, Chieti, Italy; 2. Cath Lab, SS. Annunziata Hospital, ASL2 Abruzzo, Chieti, Italy; 3. Division of Cardiology, University of Florida College of Medicine, Jacksonville, FL, USA; 4. The Zena and Michael A. Wiener Cardiovascular Institute, Icahn School of Medicine at Mount Sinai, New York, NY, USA; 5. Cardio-Thoracic-Vascular Department, Centro Alte Specialità e Trapianti, Catania, and Azienda Ospedaliero Universitario "Vittorio Emanuele-Policlinico", University of Catania, Catania, Italy; 6. Department of Advanced Biomedical Sciences, Federico II University of Naples, Naples, Italy; 7. Heart Vascular Stroke Institute, Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, Republic of Korea; 8. Department of Cardiovascular Medicine, Graduate School of Medicine, Kyoto University, Kyoto, Japan; 9. Department of Clinical and Experimental Medicine, Policlinic "G Martino", University of Messina, Messina, Italy; 10. Department of Cardiology, CHU Timone, Marseille, France; 11. Cardiology, Ospedale Santa Croce e Carle, Cuneo, Italy; 12. Privatklinik Lauterbacher Mühle am Ostersee, Iffeldorf, and Department of Cardiology, Ludwig-Maximilians-University (LMU) München, Munich, Germany; 13. Department of Cardiovascular Sciences, Fondazione Policlinico Universitario A. Gemelli IRCCS, Università Cattolica del Sacro Cuore, Rome, Italy; 14. Ramsay Générale de Santé - Institut Cardiovasculaire Paris Sud, Hopital Privé Jacques Cartier, Massy, France; 15. Department of Internal Medicine, College of Medicine and Health Sciences, UAE University, Al Ain, Abu Dhabi, United Arab Emirates; 16. Nanjing First Hospital, Nanjing Medical University, Nanjing, China; 17. Instituto Dante Pazzanese de Cardiologia,



Central illustration. *Strategy algorithm proposal for DAPT duration after PCI of bifurcation in patients not candidates for oral anticoagulation. ACS: acute coronary syndrome; CAD: coronary artery disease; DS: double stenting; IVUS: intravascular ultrasound; OCT: optical coherence tomography; PCI: percutaneous coronary intervention; SS: single stenting*

Sao Paulo, SP, Brazil; 18. Department of Internal Medicine and Cardiovascular Center, Seoul National University Hospital, Seoul, Republic of Korea; 19. Cardiovascular Research Unit, Department of Infection Immunity and Cardiovascular Disease, University of Sheffield, Sheffield, United Kingdom; 20. Bern University Hospital, Bern, Switzerland; 21. Department of Cardiology, Clinical Center of Serbia, and Medical Faculty, University of Belgrade, Belgrade, Serbia

Guest Editor

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Conflict of interest statement

D.J. Angiolillo declares that he has received consulting fees or honoraria from Amgen, Aralez, AstraZeneca, Bayer, Biosensors, Boehringer Ingelheim, Bristol-Myers Squibb, Chiesi, Daiichi Sankyo, Eli Lilly, Haemonetics, Janssen, Merck, PhaseBio, PLx Pharma, Pfizer, Sanofi, and The Medicines Company and has received payments for participation in review activities from CeloNova and St. Jude Medical. D.J. Angiolillo also declares that his institution has received research grants from Amgen, AstraZeneca, Bayer, Biosensors, CeloNova, CSL Behring, Daiichi Sankyo, Eisai, Eli Lilly, Gilead, Idorsia, Janssen, Matsutani Chemical Industry Co., Merck, Novartis, Osprey Medical, Renal Guard Solutions, and the Scott R. MacKenzie Foundation. G. Dangas declares that he has received consulting fees from Abbott Vascular, Boston Scientific and Biosensors, reports common stock (entirely divested) from Medtronic and declares that his institution has received institutional payments for research grants from AstraZeneca, Bayer and Daiichi Sankyo. D. Capodanno reports personal fees from Abbott Vascular, Amgen, Bayer, Biosensors, Daiichi Sankyo, Sanofi Aventis, Pfizer, and AstraZeneca. E. Barbato reports speaker's fees from Abbott Vascular, Boston Scientific and GE. G. Renda reports speaker and consulting fees from Bayer, BMS-Pfizer, Boehringer Ingelheim, and Daiichi Sankyo. R.F. Storey declares personal fees and institutional research grants from AstraZeneca, GlyCardial Diagnostics and Thromboserin, and personal fees from Amgen, Bayer, Bristol Myers Squibb/Pfizer, Haemonetics, Medscape, and Portola. M. Valgimigli reports personal fees from AstraZeneca, Alvimedica/CID, Abbott Vascular, Daiichi Sankyo, Opsens, Bayer, CoreFlow, Idorsia Pharmaceuticals Ltd, Universität Basel | Dept. Klinische Forschung, Vifor, Bristol Myers Squibb SA, iVascular and Medscape, and grants and personal fees from Terumo. R. Mehran has received consulting fees from Abbott Vascular, Boston Scientific, Medscape/WebMD, Siemens Medical Solutions, Philips/Volcano/Spectranetics, Roivant Sciences, Sanofi Italy, Bracco Group, Janssen, and AstraZeneca; has received grant support, paid to her institution, from Bayer, CSL Behring, DSI, Medtronic, Novartis Pharmaceuticals, OrbusNeich, Osprey Medical, PLC/RenalGuard, and Abbott Vascular; has received grant support and advisory board fees, paid to her institution, from Bristol-Myers Squibb; has received fees for serving on a data and safety monitoring board from Watermark Research Funding; has received advisory fees and lecture fees from Medintelligence (Janssen); and has received lecture fees from Bayer. The other authors have no conflicts of interest to declare. The Guest Editor reports lecture fees paid to his institution from Amgen, Bayer Healthcare, Biotronik, Boehringer Ingelheim, Boston Scientific, Daiichi Sankyo, Edwards Lifesciences, Ferrer, Pfizer, and Novartis, consultancy fees paid to his institution from Boehringer Ingelheim, and grant support from Bayer Healthcare, Boston Scientific, Biotronik, Edwards Lifesciences, GlaxoSmithKline, Medtronic, and Pfizer.

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Supplementary data

Supplementary Appendix 1. Further insights.

Supplementary Table 1. The DEFINITION[7] criteria of complex bifurcation.

Supplementary Table 2. Risk scores validated to inform dual antiplatelet therapy duration selection.

Supplementary Table 3. Major and minor criteria for high bleeding risk (HBR) at the time of PCI (adapted from Urban et al[21]).

The supplementary data are published online at: https://eurointervention.pcronline.com/doi/10.4244/EIJ-D-20-00648

Supplementary data

Supplementary Appendix 1. Further insights.

Introduction

Patients undergoing bifurcation PCI are at higher risk of both periprocedural and long-term adverse events, mainly related to stent thrombosis (ST) [4]. In a series of patients with ST at a bifurcation site, the main underlying mechanisms were strut malapposition in 33%, stent underexpansion in 19%, and isolated strut non-coverage in 19% of the cases [34].

The European Bifurcation Club (EBC) was established in 2004 to support a continuous exchange of ideas in the field of coronary artery bifurcation interventions. The EBC hosts an annual meeting which brings together physicians, pathologists, engineers, biologists, physicists, mathematicians, epidemiologists and statisticians for multidisciplinary discussions. The EBC has held 12 annual meetings since 2004, published ten general consensus statements, and a number of consensus documents dedicated to specific topics, and has edited two EuroIntervention supplements on bifurcation treatment.

The EBC suggested a state-of-the-art paper on the antithrombotic management of patients undergoing bifurcation PCI. The document chairs (M. Zimarino and D.J. Angiolillo) identified experts with the aim of achieving a balanced composition for the group of authors with varying points of view on the matter under discussion. All invited experts agreed to participate in the development of this document and endorse the advice provided. There was no financial support and no industry involvement for the preparation of this review. Agreement for the various scenarios was reached by discussions of the available evidence. This document summarises expert recommendations for the choice and duration of antithrombotic therapy after bifurcation PCI.

Choice of antithrombotic drugs and timing of initiation

Most of the gain over clopidogrel was obtained with newer $P2Y_{12}$ inhibitors through a reduction in ST.

While both prasugrel and ticagrelor increase spontaneous (i.e., non-procedural) bleeding risk when compared to clopidogrel, their net clinical benefit remains favourable and supports their use instead of clopidogrel in acute coronary syndromes (ACS) [2].

Recently, in 4,018 early invasively managed patients with ACS, the Intracoronary Stenting and Antithrombotic Regimen: Rapid Early Action for Coronary Treatment 5 (ISAR-REACT 5) trial demonstrated a significantly lower one-year combined incidence of death, MI or stroke with a prasugrel-based strategy (6.9%) than with a ticagrelor-based strategy (9.3%), while major bleeding was similar (4.8% vs 5.4%, respectively) in the two groups [14]. Anyway, no information is currently available on whether the treatment of a bifurcation at the time of intervention impacted on the comparative effectiveness of these two treatment strategies.

Procedural strategies to reduce the risk of stent thrombosis

The EBC recommends the “provisional” side branch (SB) stenting strategy for the treatment of the vast majority of bifurcation lesions when feasible [6], but double stenting may be required in cases of extensive SB disease. In patients with extensive SB lesions, the EBC suggests that the choice between

T-stenting, culotte, and double kissing (DK)-crush should be dictated by the anatomy, vessel size, SB take-off angle, and operator experience [6]. In contrast, recently published ESC guidelines "strongly suggest" the use of DK-crush in the treatment of LM bifurcation (class IIb, LOE B) [11], following the results of the DKCRUSH-V trial [8], where provisional stenting was associated with a significantly higher ST rate (3.3%) than DK-crush (0.4%). However, this surprisingly high adverse event rate in the control group was probably driven by a high rate of crossover (47%) to an additional "bail-out" second stent due to a deemed "unsatisfactory" result in the SB. The DEFINITION II study [7] recently documented that the systematic use of two stents was associated with a significant improvement in clinical outcomes compared with provisional stenting in complex bifurcation lesions **(Supplementary Table 1)**.

In a recent network meta-analysis investigating provisional stenting and two-stent techniques, DK-crush was associated with lower rates of target vessel revascularisation (TVR), whereas no significant differences were observed for cardiac death, MI, and stent thrombosis [35]. Caution should be exercised when translating the results from one clinical trial to another one in terms of comparison of ST rate after different stenting techniques because there are wide discrepancies in the bifurcation complexity, study design, and definitions of clinical outcome.

The concept that the use of intracoronary imaging to optimise stent implantation could impact on the duration of antithrombotic therapies post PCI was introduced more than 20 years ago by Colombo et al [36]. More recently, this concept has also been examined in the Impact of Intravascular Ultrasound Guidance on Outcomes of the XIENCE PRIME Stents in Long Lesions (IVUS-XPL) trial [37]. Among 1,400 patients randomised (2x2 factorial fashion) to intravascular ultrasound (IVUS)-guided versus angiography-guided PCI, followed by 6- versus 12-month DAPT, a significant interaction was observed according to IVUS use, and a greater benefit was documented with prolonged DAPT only in patients who were randomised to angiography-guided PCI. The importance of IVUS guidance with respect to target vessel failure was recently reinforced in the Intravascular Ultrasound-Guided Drug-Eluting Stents Implantation in "All-Comers" Coronary Lesions (ULTIMATE) trial [38], with most of the benefit accrued among patients with "optimal" stent deployment.

Optical coherence tomography (OCT) may document strut coverage with neointima during follow-up, unveiling the substrate for subsequent ST. Interestingly, among patients with a favourable stent strut coverage (<6% uncovered struts) at three months in the Determination of the Duration of the Dual Antiplatelet Therapy by the Degree of the Coverage of The Struts on Optical Coherence Tomography (DETECT-OCT) trial [39], short DAPT (i.e., 3 months) appeared as effective as standard DAPT (i.e., 12 months) for the occurrence of cardiac death, MI, ST, and major bleeding. The feasibility of OCT-guided DAPT discontinuation was also documented in a consecutive series of 40 patients with non-bifurcation lesions who required cancer-related procedures [40].

DAPT duration and risk stratification

A longer DAPT duration for both stable CAD and ACS is encouraged in complex PCI (class IIb, LOE B) [1,2], with coronary bifurcation being listed among other characteristics of higher PCI complexity as a risk factor for stent-related coronary ischaemic events.

Such a recommendation is based mainly on a meta-analysis [18], where "complex" PCI was defined as 3 vessels treated, ≥3 stents implanted, ≥3 lesions treated, bifurcation with 2 stents implanted, total stent length >60 mm, or chronic total occlusion as a target lesion – the so-called "Giustino criteria" **(Table 2)**.

Apart from the stent technology used, the potential benefit of long-term DAPT could mostly be expected in scenarios with high ischaemic risk. Among patients treated for an LM bifurcation lesion, the composite risk for cardiac death, MI and ST in the 2-stent group was significantly higher than in the 1-stent group in those with DAPT interruption <1 year (HR 2.78, 95% CI: 1.25–6.19), while it was similar in those receiving DAPT maintenance ≥1 year (HR 0.51, 95% CI: 0.15–1.69) [33] **(Table 2)**; no heterogeneity was observed for the type of stent implanted.

The three scoring systems [41-43] originally developed to guide DAPT duration in the difficult balance between ischaemic and bleeding risks are listed in **Supplementary Table 2**. However, most of the frequently used risk scores for the assessment of ischaemic and bleeding events were originally developed and validated for the prediction of outcomes limited to the hospital stay or early post discharge.

The only score based on a one-year post-PCI risk assessment is the DAPT (dual antiplatelet therapy) score [41], but it may only be applied in patients with no intervening ischaemic or bleeding event since PCI, as these patients were excluded from the data set used in its inception.

The identification of the patient at high bleeding risk

The concept of "high bleeding risk" (HBR) has recently been emphasised to guide DAPT duration in patients undergoing PCI with modern DES [2]. In elective PCI for stable CAD, whereas the standard DAPT duration remains 6 months (Grade I) in HBR patients, it can be shortened to 3 months (Grade IIa) or even 1 month in selected cases (Grade IIb). Similarly, in patients undergoing PCI for ACS, 12 months is the rule by default (Grade I), but in HBR patients DAPT duration can be reduced to 6 (Grade IIa) or even 1-3 months (Grade IIb).

The Academic Research Consortium (ARC)-HBR initiative recently issued a consensus [21] identifying as being HBR those patients with a one-year risk of a Bleeding Academic Research Consortium (BARC)-defined [44] type 3 or 5 bleeding ≥4% and intracranial haemorrhage ≥1%. According to twenty clinical major or minor criteria **(Supplementary Table 3)**, patients are identified as being at HBR if at least one major criterion or two minor criteria are met.

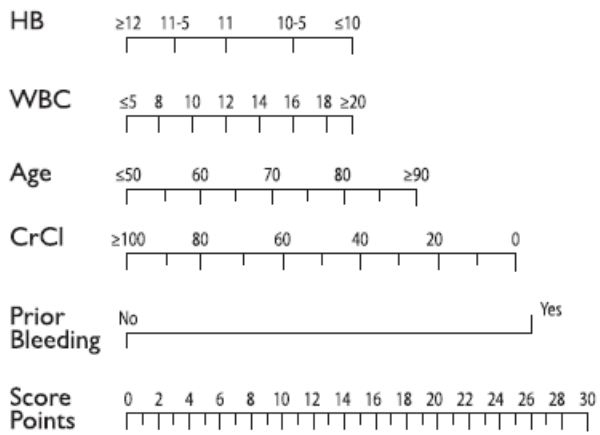
Supplementary Table 1. The DEFINITION [7] criteria of complex bifurcation.

Medina 1,1,1 or 0,1,1 bifurcation lesion	
Major criteria	**Minor criteria**
SB lesion length ≥10 mm with diameter stenosis of SB ≥70% for distal LM bifurcation lesions or diameter stenosis of SB ≥90% for non-LM bifurcation lesions	Moderate-to-severe calcification Multiple lesions Bifurcation angle <45° or >70° MV RVD <2.5 mm Thrombus-containing lesions MV lesion length ≥25 mm

Complex bifurcation lesions were defined as any one major criterion plus any two minor criteria.

LM: left main; RVD: reference vessel diameter; SB: side branch

Supplementary Table 2. Risk scores validated to inform dual antiplatelet therapy duration selection.

	DAPT[41]		PRECISE-DAPT[42]	PARIS[43]	
				Coronary thrombotic event risk	Bleeding risk
Score calculation	Variable Points		Score nomogram	Variable Points	Variable Points
	Age, yrs ≥75 65-74 <65 Smoking Diabetes mellitus Acute MI Prior PCI / MI PES Stent ∅ <3 mm CHF or LVEF <30% Vein graft PCI	 –2 –1 0 1 1 1 1 1 1 2 2		Diabetes mellitus None NID ID ACS No Yes, Tn - Yes, Tn + Current smoking Yes No CrCl <60 ml/min Present Absent Prior PCI Yes No Prior CABG Yes No	 0 1 3 0 1 2 1 0 2 0 2 0 2 0	Age, yrs <50 50–59 60–69 70–79 ≥80 BMI, kg/m² <25 25–34.9 ≥35 Current smoking Yes No Anaemia Present Absent CrCl <60 ml/min Present Absent Triple therapy on discharge Yes No	 0 1 2 3 4 2 0 2 2 0 3 0 2 0 2 0
Total score range	–2 to 10 points		0 to 100 points	0 to 12 points	0 to 15 points
Decision cut-off	<2 ⇒ 12 mos DAPT ≥2 ⇒ 30 mos DAPT		≥25 ⇒ 3-6 mos DAPT <25⇒12-24 mos DAPT	Low risk = 0 - 2 Intermediate risk = 3-4 High risk ≥5	Low risk = 0 - 3 Intermediate risk = 4-7 High risk ≥8

ACS: acute coronary syndrome; BMI: body mass index; CABG: coronary artery bypass grafting; CHF: congestive heart failure; CrCl: creatinine clearance; DAPT: dual antiplatelet therapy; Hb: haemoglobin; ID: insulin-dependent; LVEF: left ventricular ejection fraction; MI: myocardial infarction; mos: months; NID: non-insulin-dependent; PARIS: Patterns of Non-Adherence to Anti-Platelet Regimen in Stented Patients; PCI: percutaneous coronary intervention; PES: paclitaxel-eluting stent; PRECISE-DAPT: PREdicting bleeding Complications In patients undergoing Stent implantation and subsEquent Dual Anti Platelet Therapy; Tn: troponin; yrs: years; WBC: white blood cell count

Supplementary Table 3. Major and minor criteria for high bleeding risk (HBR) at the time of PCI (adapted from Urban et al [21]).

Factors	Major	Minor
Aging		Age ≥75 yrs
Comorbidities - Kidney - Liver - Cancer	Severe or end-stage CKD (eGFR <30 mL/min) Liver cirrhosis with portal hypertension Active malignancy (excluding non-melanoma skin cancer) ≤12 months	Moderate CKD (eGFR 30–59 mL/min)
Blood count - Haemoglobin - Platelet	<11 g/dL Moderate or severe baseline thrombocytopaenia (count $<100x10^9$/L)	11–12.9 g/dL (men) and 11–11.9 g/dL (women)
Central nervous system	Previous spontaneous ICH (at any time) Previous traumatic ICH ≤12 months Presence of a bAVM Moderate or severe ischaemic stroke ≤6 months	Any ischaemic stroke at any time not meeting the major criterion
Bleeding history	Spontaneous bleeding requiring hospitalisation or transfusion ≤6 months or at any time, if recurrent Chronic bleeding diathesis	Spontaneous bleeding requiring hospitalisation or transfusion ≤12 months not meeting the major criterion
Iatrogenic	Anticipated use of long-term oral anticoagulation Non-deferrable major surgery on DAPT Recent major surgery or major trauma ≤30 days before PCI	Long-term use of oral NSAIDs or steroids

bAVM: brain arteriovenous malformation; CKD: chronic kidney disease; DAPT: dual antiplatelet therapy; eGFR: estimated glomerular filtration rate; ICH: intracranial haemorrhage; NSAID: non-steroidal anti-inflammatory drug; PCI: percutaneous coronary intervention