Clinical outcomes of the proximal optimisation technique (POT) in bifurcation stenting

Bernard Chevalier[1]*, MD; Mamas A. Mamas[2,3], MD; Thomas Hovasse[1], MD; Muhammad Rashid[2,3], MD; Joan Antoni Gomez[4], MD; Manuel Pan[5], MD; Adam Witkowski[6], MD; James Crowley[7], MD; Adel Aminian[8], MD; John McDonald[9], MD; Farzin Beygui[10], MD; Javier Fernández Portales[11], MD; Ariel Roguin[12], MD; Goran Stankovic[13], MD; on behalf of the e-ULTIMASTER investigators

1. Ramsay Générale de Santé, ICPS, Hôpital Jacques Cartier, Massy, France; 2. Department of Cardiology, University Hospital of North Midlands, Stoke-on-Trent, United Kingdom; 3. Keele Cardiovascular Research Group, Centre of Prognosis Research, Institute of Primary Care Sciences, Keele University, Stoke-on-Trent, United Kingdom; 4. Heart Disease Institute, Bellvitge University Hospital (IDIBELL), University of Barcelona, Barcelona, Spain; 5. Reina Sofia Hospital, Department of Cardiology, University of Córdoba (IMIBIC), Cordoba, Spain; 6. Department of Interventional Cardiology and Angiology, Institute of Cardiology, Warsaw, Poland; 7. Department of Cardiology, University Hospital Galway, Galway, Ireland; 8. Centre Hospitalier Universitaire de Charleroi, Department of Cardiology, Charleroi, Belgium; 9. Department of Cardiology, Royal Blackburn Hospital, Blackburn, United Kingdom; 10. Department of Interventional Cardiology and Cardiology Research Units, CHU Caen, Caen, France; 11. Department of Cardiology, Complejo Universitario Hospital de Caceres, Caceres, Spain; 12. Department of Cardiology, Hillel Yafe Medical Center, Hadera, Israel; 13. Department of Cardiology, Clinical Center of Serbia, University of Belgrade, Belgrade, Serbia

This paper also includes supplementary data published online at: https://eurointervention.pcronline.com/doi/10.4244/EIJ-D-20-01393

KEYWORDS

- bifurcation
- drug-eluting stent
- miscellaneous

Abstract

Background: Optimal deployment of coronary stents in a bifurcation lesion remains a matter of debate.

Aims: We sought to capture the daily practice of bifurcation stenting by means of a worldwide registry and to investigate how post-implantation deployment techniques influence clinical outcomes.

Methods: Data from the e-ULTIMASTER registry were used to perform an analysis of 4,395 patients undergoing percutaneous coronary intervention for bifurcation lesions. Inverse probability of treatment weights (IPTW) propensity score methodology was used to adjust for any baseline differences. The primary outcome of interest was target lesion failure (TLF) at one year (follow-up rate 96.2%).

Results: The global one-year TLF rate was low (5.1%). The proximal optimisation technique (POT) was used in 33.9% of cases and was associated with a reduction in the adjusted TLF rate (4.0% [95% confidence interval: 3.0-5.1%] vs 6.0% [5.1-6.9%], p<0.01) due to a reduction of all components of this composite endpoint, except for cardiac death. Stent thrombosis was also positively impacted (0.4% [0.04-0.7%] vs 1.3% [0.8-1.7%], p<0.01). POT benefit was uniform across subgroups. Conversely, the use of the kissing balloon technique (36.5%) did not influence the adjusted TLF rate.

Conclusions: Despite a low one-year failure rate in this large bifurcation stenting cohort, POT was associated with a further reduction in the event rate and a uniform benefit across subgroups, suggesting systematic use of this deployment technique regardless of the bifurcation anatomy and stenting technique.

**Corresponding author: ICPS, Hôpital Privé Jacques Cartier, 6 Avenue du Noyer Lambert, 91300 Massy, France. E-mail: b.chevalier@angio-icps.com*

SUBMITTED ON 14/12/2020 - REVISION RECEIVED ON 1st 25/03/2021 / 2nd 21/04/2021 - ACCEPTED ON 06/05/2021

Abbreviations

AHA/ACC American Heart Association/American College of Cardiology
CABG coronary artery bypass graft
CD clinically driven
DES drug-eluting stent
KBT kissing balloon technique
LAD left anterior descending coronary artery
LCX left circumflex coronary artery
MI myocardial infarction
PCI percutaneous coronary intervention
POCE patient-oriented composite endpoint
POT proximal optimisation technique
RCA right coronary artery
SS simple strategy (one stent)
ST stent thrombosis
STEMI ST-segment elevation myocardial infarction
TLF target lesion failure
TLR target lesion revascularisation
TS two-stent
TVF target vessel failure
TVMI target vessel myocardial infarction
TVR target vessel revascularisation

Introduction

Bifurcation lesions remain a challenge in terms of both procedural success and long-term cardiovascular outcomes[1]. Many stenting techniques have been proposed to overcome these limitations from the early days of the bare metal stent era until the advent of new-generation drug-eluting stents (DES)[2]. Most of them aim at restoring the natural bifurcation anatomy whilst conforming to a wide range of configurations in terms of diameters and angulation. Early results of the two-stent approach prompted the European Bifurcation Club to strongly promote the provisional strategy as a one-stent strategy when acceptable, which was associated with a better or neutral outcome in several randomised clinical trials and most meta-analyses[3].

The one-stent technique and two-stent techniques were developed in combination with two major post-dilatation methods to adjust a regular stent to the dedicated anatomy of a bifurcation - the kissing balloon technique (KBT)[4] and the proximal optimisation technique (POT)[5]. Expert consensus has progressively established their respective roles, emphasising the need to respect the fractal geometry of the coronary vasculature[6]. Although the KBT was evaluated in randomised trials[7], recommendations regarding POT have been based mainly on bench testing and small size cohort clinical studies by means of intravascular imaging[8-12].

On the basis of the e-ULTIMASTER study[13], we sought to evaluate post-stent implantation deployment techniques, with specific focus on POT and KBT, and their impact on the one-year clinical outcome of a large pre-specified bifurcation subgroup of this worldwide prospective mega-registry.

Editorial, see page 869

Methods

STUDY DESIGN

e-ULTIMASTER (NCT02188355) is an all-comer, single-arm, prospective, multicentre registry with clinical follow-up at three months and one year. The study was conducted worldwide and enrolled patients between October 2014 and June 2018 from 378 hospitals **(Supplementary Appendix 1)** in 50 countries across Europe, Asia, Africa, South America and Mexico[13]. The primary objective of the registry was to evaluate further the safety and performance of the Ultimaster® DES system (Terumo Corporation, Tokyo, Japan) in daily practice.

STUDY POPULATION

Inclusion criteria were broad and involved all patients ≥18 years old, with coronary artery disease eligible for percutaneous coronary intervention (PCI) using DES according to local hospital practice and intended to be treated with the Ultimaster DES (with reference vessel diameter matching available Ultimaster DES sizes). Dual antiplatelet regimen was left to the operators' discretion. The registry was conducted in accordance with the Declaration of Helsinki and country-specific regulatory requirements. All patients signed the informed consent form reviewed and approved by the Institutional Review Board/Ethics Committee of each participating centre. A bifurcation lesion is defined as a significant stenosis in a coronary artery adjacent to and/or involving the origin of a side branch (SB) that is clinically significant. Selection of patients in the bifurcation cohort was at the operator's discretion.

The study population used to analyse clinical outcomes during follow-up comprised all patients who received an Ultimaster DES upon enrolment in the e-ULTIMASTER study and (i) completed one-year follow-up, or (ii) who reached the primary endpoint target lesion failure (TLF: cardiac death, target vessel myocardial infarction [TVMI] or clinically driven target lesion revascularisation [TLR]), or (iii) who died during follow-up **(Figure 1)**.

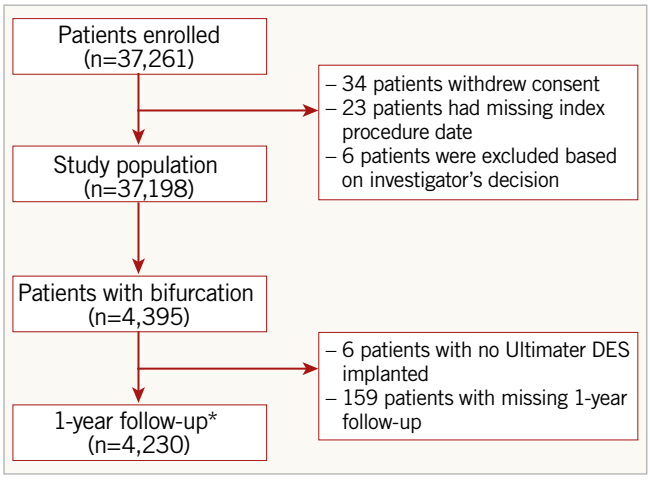


Figure 1. *Flow chart of the study population. *The one-year follow-up population includes patients who had an event that contributed to the primary endpoint, died during follow-up or completed one-year follow-up.*

STUDY DEVICE

The Ultimaster coronary stent system is a new-generation open-cell cobalt-chromium thin-strut (80 µm) sirolimus-eluting stent with an abluminal biodegradable polymer coating (poly-D,L-lactic acid polycaprolactone)[14]. Sirolimus is released over a 3- to 4-month period after which the polymer coating is fully degraded.

FOLLOW-UP

Follow-up was performed either via direct phone contact with the patient or during a visit of the patient to the outpatient clinic of the hospital. Measures to ensure data quality included remote and on-site monitoring with a risk-based approach as well as close communication with the sites to reinforce the importance of complete and accurate data entry. All events composing the primary endpoint were independently adjudicated by a clinical events committee.

OUTCOMES AND DEFINITIONS

The primary outcome was TLF, defined as a composite of cardiac death, myocardial infarction that could not be clearly attributed to a vessel other than the target vessel (TVMI) and clinically driven target lesion revascularisation (CD-TLR). Secondary outcomes included any death, cardiac death, MI, TLR, target vessel revascularisation (TVR), target vessel failure (TVF, a composite of cardiac death, TVMI and TVR), stent thrombosis (ST) and major vascular and bleeding complications.

STATISTICAL ANALYSIS

Baseline patient, lesion and procedural characteristics are summarised using mean±standard deviation (SD) for continuous variables and frequencies and percentages for categorical variables. Continuous variables were compared using the Wilcoxon test and categorical variables with the chi-square test. To account for differences in baseline demographics, the POT versus no POT and KBT versus no KBT comparisons were adjusted by weighting the subject by inverse propensity weights. These propensity scores were calculated using a logistic regression model, predicting the probability of belonging to the POT or KBT group, with the baseline demographic variables as independent variables (age, gender, smoking status, renal impairment, previous MI, previous PCI, previous coronary artery bypass grafting [CABG], acute coronary syndrome, ST-elevation myocardial infarction [STEMI], multivessel disease, number of lesions identified and treated, treated vessel location, small vessels, long lesions, lesion type B2 or C, ostial lesions, chronic total occlusion [CTO], calcification, Medina classification, one- versus two-stent technique, number of stents implanted, total stent length, radial access, balloon predilatation, balloon post-dilatation, imaging). Propensity scores for POT versus no POT additionally included KBT, while propensity scores for KBT versus no KBT additionally included POT. The inverse weights were investigated for extreme values **(Supplementary Figure 1)**. Due to the large overlap in populations and the large sample sizes, neither the POT nor the KBT propensity score matching resulted in extreme weights (maximum weights <4).

In the propensity score weighted analyses, categorical variables were compared with a weighted chi-square test. For time-to-event analysis, an inverse propensity score weighted Kaplan-Meier method was applied. Logistic regression was used to test the interaction effect for POT or KBT separately versus a list of predictor variables on one-year TLF, by modelling, per predictor variable, the one-year TLF as binary outcome, while using POT or KBT and the predictor variable as independent variables, and the interaction between POT or KBT and the predictor variable as interaction effect. Statistical analyses were performed using SAS software, version 9.4 (SAS Institute, Inc., Cary, NC, USA).

Results

At least one bifurcation lesion was treated in 4,395 patients, 11.8% of the 37,198 patients enrolled in the e-ULTIMASTER registry, among whom 4,230 patients (96.2%) were followed up to one year. Baseline and procedural characteristics of this bifurcation cohort are shown in **Table 1**. More than half of the patients were treated on a true bifurcation lesion (Medina x,x,1: 52.2%), mainly in the left anterior descending coronary artery (LAD) (68.4%) via radial access in 80.2% of cases. A double (main and side branches) vessel treatment was carried out in 51.8% and a double stenting was performed in 22.8%, reflecting a high incidence of adoption of a provisional strategy. Details of techniques are presented in **Supplementary Figure 2**. At the one-year endpoint, the TLF rate was 5.1%; each component of the composite endpoint is described in **Figure 2**.

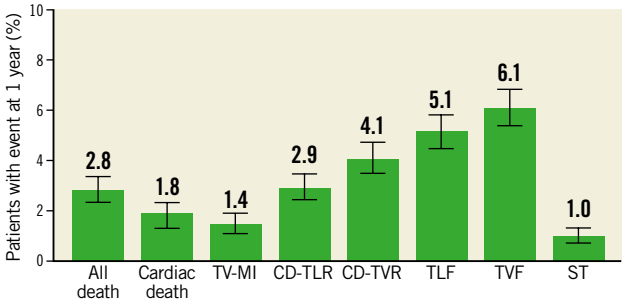


Figure 2. *Unadjusted one-year clinical outcomes of all bifurcation patients (N=4,230). CD-TLR clinically driven target lesion revascularisation; CD-TVR clinically driven target vessel revascularisation; ST: stent thrombosis; TLF: target lesion failure; TVF: target vessel failure; TV-MI target vessel myocardial infarction*

POT was performed in 33.9% of cases. Its use was more prevalent in left main (LM) and LAD lesions as well as in long lesions, true bifurcations, and when a two-stent technique was used **(Table 2)**. KBT was performed in 36.5% of cases; its use was heterogeneous regarding the main baseline characteristics **(Supplementary Table 1)**. Unadjusted and adjusted (inverse propensity score weighted) outcomes according to POT and KBT use are presented in **Table 3** and **Supplementary Table 2**.

The baseline characteristics of the study population after propensity weighting are shown in **Supplementary Table 3** (POT vs no POT) and **Supplementary Table 4** (KBT vs no KBT). After

Table 1. Baseline patient and procedural characteristics.

	Bifurcation n=4,395
Patient characteristics	
Age, years	65.6±11.1 (4,395)
Gender, male	76.5% (3,364/4,395)
Body mass index, kg/m²	27.7±4.6 (3,849)
Diabetes mellitus	27.2% (1,189/4,366)
Current smoking	20.5% (860/4,190)
Hypertension	68.8% (2,886/4,193)
Hypercholesterolaemia	62.1% (2,550/4,105)
Renal impairment	9.1% (397/4,368)
Previous MI	23.9% (1,019/4,265)
Previous PCI	30.1% (1,300/4,326)
Previous CABG	4.5% (194/4,304)
Clinical presentation	
Silent ischaemia	12.3% (539/4,395)
Stable angina	39.3% (1,726/4,395)
Unstable angina	12.7% (556/4,395)
NSTEMI	23.0% (1,012/4,395)
STEMI	12.7% (559/4,395)
Procedural characteristics	
Radial access	80.2% (3,523/4,395)
Imaging use	9.3% (407/4,395)
Vessel treated	
RCA	17.3% (761/4,395)
Left main	12.4% (546/4,395)
LAD	68.4% (3,008/4,395)
LCX	31.4% (1,381/4,395)
Graft (arterial or venous)	0.2% (9/4,395)
Bifurcation type per patient	
True bifurcation	52.2% (2,266/4,334)
Non true bifurcation	46.2% (2,004/4,334)
Both	1.5% (64/4,334)
Medina classification per lesion	
0,0,1	3.7% (171/4,681)
0,1,0	9.1% (426/4,681)
0,1,1	8.4% (394/4,681)
1,0,0	8.1% (378/4,681)
1,0,1	8.6% (403/4,681)
1,1,0	24.9% (1,165/4,681)
1,1,1	37.3% (1,744/4,681)
Lesion characteristics	
No. of lesions identified, per patient	2.1±1.1 (4,395)
No. of lesions treated, per patient	1.5±0.8 (4,394)
CTO	3.8% (165/4,395)
Long lesions	42.6% (1871/4,395)
Procedure characteristics	
No. of study stents implanted per patient	1.9±1.1 (4,393)
Length of implanted study stents per patient, mm	36.1±22.5 (4,385)

Data are reported for all lesions of 4,395 patients with at least 1 bifurcation lesion and are mean±standard deviation for continuous variables or % (n) for categorical variables. The number of patients with available data is indicated in brackets. Renal impairment: defined as estimated glomerular filtration rate <60 ml/min/1.73 m². Lesion characteristics at index procedure are reported. CABG: coronary artery bypass graft; CTO: chronic total occlusion; LAD: left anterior descending artery; LCX: left circumflex; MI: myocardial infarction; (N)STEMI: (non-) ST-elevation myocardial infarction; PCI: percutaneous coronary intervention; RCA: right coronary artery

propensity weighting, POT was associated with a reduction of TVMI (0.7% [0.2-1.1%] vs 2.0% [1.5-2.6%], p=0.001), CD-TLR (1.9% [1.2-2.6%] vs 3.6% [2.9-4.3%], p<0.01), ST (0.4% vs 1.3%, p<0.01) with a strong impact on TLF (4.0% [3.0-5.1%] vs 6.0% [5.1-6.9%], p<0.01). POT benefit was consistent across the subgroups (p for interaction=NS) with regard to major angiographic and procedural features **(Figure 3)**. The difference was established early, during the first month, and maintained during the first year **(Central illustration)**.

KBT had a limited clinical impact on clinical outcomes with a reduction in TVMI after propensity weighting (1.0% [0.5-1.5%] vs 1.9% [1.4-2.4%], p=0.02) with no effect on the one-year composite endpoint TLF (4.5% [3.5-5.6%] vs 4.7% [3.9-5.5%], p=0.77) or on ST rates (0.9% [0.4-1.4%] vs 0.8% [0.5-1.2%], p=0.76). There was an interaction between KBT effect and some procedural characteristics: LM location, Medina type, stent size and persistent dual antiplatelet therapy (DAPT) at one year **(Supplementary Figure 3)**. Details of this analysis are presented in **Supplementary Table 2**.

Discussion

To the best of our knowledge, this is the largest bifurcation study aiming at assessing the respective impact of post-stent implantation deployment techniques, namely POT and KBT. Our study shows, first, a low one-year event rate in this large registry capturing the real-world practice in bifurcation stenting when using a latest-generation DES despite a surprisingly low rate of POT, second, a strong impact of POT on one-year clinical outcomes which is consistent across subgroups, and third, a minimal effect of KBT on outcomes.

FROM FRACTAL GEOMETRY TO POT

The law of conservation of mass, also known as Murray's law, established the fractal geometry[15] of artery bifurcations. A simplification of this rule, suggested by Finet et al[16], was validated by means of quantitative angiography and intravascular ultrasound (IVUS) and allows the quantification of the step-up of proximal main branch reference diameter according to the distal main branch and side branch reference diameters. In order to minimise the risk of carina shift after main branch stent implantation, and

Table 2. Baseline patient characteristics according to use of POT - unadjusted.

		POT n=1,453	No POT n=2,828	*p*-value
Patient characteristics				
Age, years		65.9±11.1 (1,453)	65.4±11.1 (2,828)	0.18
Gender, male		76.1% (1,105/1,453)	76.3% (2,157/2,828)	0.87
Geographical region	Europe	80.9% (1,176/1,453)	73.9% (2,089/2,828)	<0.001
	Asia	8.1% (117/1,453)	14.0% (396/2,828)	
	Africa/Middle East	5.6% (81/1,453)	7.2% (203/2,828)	
	South America/Mexico	5.4% (79/1,453)	5.0% (140/2,828)	
Body mass index, kg/m²		27.8±4.6 (1,280)	27.6±4.6 (2,462)	0.38
Diabetes mellitus		26.2% (378/1,443)	28.0% (786/2,810)	0.22
Current smoking		21.0% (257/1,224)	24.5% (590/2,407)	0.02
Hypertension		71.2% (988/1,387)	67.5% (1,822/2,699)	0.01
Hypercholesterolaemia		63.3% (862/1,362)	61.5% (1,622/2,639)	0.26
Renal impairment		9.1% (132/1,444)	9.2% (258/2,814)	0.98
Previous MI		25.0% (349/1,397)	23.6% (652/2,760)	0.33
Previous PCI		32.7% (467/1,429)	28.8% (803/2,789)	0.01
Previous CABG		4.7% (67/1,417)	4.1% (114/2,778)	0.35
Clinical presentation				
Silent ischaemia		32.7% (467/1,429)	28.8% (803/2,789)	0.01
Stable angina		4.7% (67/1,417)	4.1% (114/2,778)	0.35
Unstable angina		12.5% (182/1,453)	12.2% (344/2,826)	0.74
NSTEMI		41.8% (608/1,453)	38.0% (1,073/2,826)	0.01
STEMI		13.2% (192/1,453)	12.4% (349/2,826)	0.42
Vessel treated				
RCA		14.5% (211/1,453)	18.6% (525/2,828)	0.001
Left main		16.2% (236/1,453)	10.2% (287/2,828)	<0.001
LAD		70.3% (1,021/1,453)	67.3% (1,904/2,828)	0.05
LCX		26.4% (384/1,453)	33.1% (935/2,828)	<0.001
Graft (arterial or venous)		0.1% (1/1,453)	0.3% (8/2,828)	0.15
Lesion characteristics				
No. of lesions identified, per patient		2.0±1.1 (1,453)	2.1±1.1 (2,828)	0.91
No. of lesions treated, per patient		1.4±0.7 (1,452)	1.5±0.8 (2,828)	0.04
Long lesions		47.2% (685/1,451)	40.3% (1,140/2,826)	<0.001
True bifurcation		58.8% (854/1,453)	50.3% (1,421/2,828)	<0.001
Two-stent technique		28.0% (407/1,453)	19.7% (556/2,828)	<0.001
Type of two-stent technique	T-stenting	6.5% (95/1,453)	5.0% (140/2,828)	0.03
	V-stenting	0.4% (7/1,453)	2.3% (66/2,828)	<0.001
	Kissing stents	1.4% (20/1,453)	2.2% (62/2,828)	0.07
	Crush	4.8% (70/1,453)	2.8% (79/2,828)	<0.001
	Culotte	4.2% (61/1,453)	1.9% (55/2,828)	<0.001
	TAP or other	10.5% (153/1,453)	5.4% (152/2,828)	<0.001
KBT		45.2% (657/1,453)	32.6% (923/2,828)	<0.001
Procedure characteristics				
No. of study stents implanted per patient		1.9±1.03 (1,452)	1.9±1.1 (2,828)	0.58
Length of implanted study stents per patient, mm		29.4±15.62 (1,887)	26.5±14.5 (3,693)	<0.001

Data are reported for 4,281 patients with at least 1 bifurcation lesion (114 patients were excluded from this comparison because of lack of information on POT). Data are mean±standard deviation for continuous variables or % (n) for categorical variables. The number of patients with available data is indicated in brackets. Renal impairment: defined as estimated glomerular filtration rate <60 ml/min/1.73 m². Lesion characteristics at index procedure are reported. CABG: coronary artery bypass graft; KBT: kissing balloon technique; LAD: left anterior descending artery; LCX: left circumflex; MI: myocardial infarction; (N)STEMI: (non-) ST-elevation myocardial infarction; PCI: percutaneous coronary intervention; POT: proximal optimisation technique; RCA: right coronary artery

Table 3. One-year clinical outcomes according to use of the proximal optimisation technique (POT).

		Unadjusted			Adjusted by inverse propensity score weighting		
		POT n=1,398	No POT n=2,729	*p*-value	POT n=1,398	No POT n=2,729	*p*-value
Primary outcome							
Target lesion failure		3.9% (3.0-5.1) (55/1,398)	5.7% (4.9-6.7) (156/2,729)	0.01	4.0% (3.0-5.1) (56/1,398)	6.0% (5.1-6.9) (164/2,729)	0.01
Cardiac death		1.9% (1.2-2.7) (26/1,398)	1.9% (1.4-2.5) (51/2,729)	0.98	1.9% (1.2-2.6) (26/1,398)	2.0% (1.5-2.6) (55/2,729)	0.72
Target vessel MI		0.6% (0.3-1.2) (9/1,398)	1.9% (1.4-2.5) (51/2,729)	<0.01	0.7% (0.2-1.1) (9/1,398)	2.0% (1.5-2.6) (55/2,729)	0.001
Clinically driven TLR		1.8% (1.2-2.6) (25/1,398)	3.4% (2.8-4.2) (94/2,729)	<0.01	1.9% (1.2-2.6) (26/1,398)	3.6% (2.9-4.3) (97/2,729)	<0.01
Secondary outcomes							
All-cause death		2.9% (2.1-3.9) (40/1,398)	2.8% (2.2-3.5) (77/2,729)	0.94	2.9% (2.4-3.8) (41/1,398)	3.2% (2.6-3.9) (88/2,729)	0.60
All MI		1.0% (0.6-1.7) (14/1,398)	2.3% (1.8-2.9) (63/2,729)	<0.01	1.0% (0.5-1.5) (14/1,398)	2.5% (1.9-3.1) (67/2,729)	<0.01
Revascularisations	TVR	3.1% (2.2-4.1) (43/1,398)	4.8% (4.1-5.7) (132/2,729)	<0.01	3.2% (2.3-4.1) (45/1,398)	5.1% (4.2-5.9) (138/2,729)	0.01
	TV non-TLR	1.4% (0.8-2.1) (19/1,398)	1.5% (1.1-2.0) (41/2,729)	0.72	1.4% (0.8-2.0) (19/1,398)	1.5% (1.0-1.9) (40/2,729)	0.79
	TLR	1.9% (1.2-2.7) (26/1,398)	3.6% (3.0-4.4) (99/2,729)	<0.01	2.0% (1.2-2.7) (27/1,398)	3.8% (3.1-4.5) (103/2,729)	<0.01
Clinically driven revascularisations	TVR	3.0% (2.2-4.0) (42/1,398)	4.6% (3.9-5.5) (126/2,729)	0.01	3.1% (2.2-4.1) (44/1,398)	4.8% (4.0-5.6) (131/2,729)	0.01
	TV non-TLR	1.4% (0.8-2.1) (19/1,398)	1.4% (1.0-2.0) (39/2,729)	0.86	1.4% (0.8-2.0) (19/1,398)	1.4% (1.0-1.9) (38/2,729)	0.93
Target vessel failure		5.2% (4.1-6.4) (72/1,398)	6.6% (5.7-7.6) (181/2,729)	0.06	5.3% (4.1-6.5) (74/1,398)	6.9% (6.0-7.9) (189/2,729)	0.04
Stent thrombosis	Definite	0.3% (0.08-0.7) (4/1,398)	0.8% (0.5-1.2) (21/2,729)	0.06	0.3% (0.02-0.6) (4/1,398)	0.7% (0.4-1.1) (20/2,729)	0.09
	Probable	0.1% (0.0-0.4) (1/1,398)	0.4% (0.2-0.8) (12/2,729)	0.05	0.04% (0.0-0.1) (1/1,398)	0.5% (0.3-0.8) (14/2,729)	0.01
	Definite/probable	0.4% (0.1-0.8) (5/1,398)	1.2% (0.8-1.7) (33/2,729)	0.01	0.4% (0.04-0.7) (5/1,398)	1.3% (0.8-1.7) (34/2,729)	<0.01
	Possible	0.9% (0.4-1.5) (12/1,398)	0.8% (0.5-1.3) (23/2,729)	0.96	1.0% (0.4-1.5) (13/1,398)	0.8% (0.5-1.2) (23/2,729)	0.74
All bleedings		3.0% (2.2-4.0) (42/1,398)	2.2% (1.7-2.9) (61/2,729)	0.13	3.0% (2.1 to 3.9) (42/1,398)	2.3% (1.7-2.8) (62/2,729)	0.14
Bleeding BARC type 1 to 2		2.1% (1.4-3.0) (29/1,398)	1.4% (1.0-1.9) (38/2,729)	0.10	2.2% (1.4-2.9) (30/1,398)	1.4% (1.0-1.9) (39/2,729)	0.08
Bleeding BARC type 3 to 5		0.8% (0.4-1.4) (11/1,398)	1.0% (0.6-1.4) (26/2,729)	0.59	0.7% (0.3-1.1) (10/1,398)	1.0% (0.6-1.4) (27/2,729)	0.35

Events are reported as % with 95% confidence interval (number of patients with event/total number of patients) in the patient population that reached 1-year follow-up, died during follow-up or who had an event that contributed to the primary endpoint (n=4,230 patients with at least 1 bifurcation lesion). Out of 4,230 patients, 103 patients were excluded from this comparison because of lack of information on POT. Target lesion failure: composite of cardiac death, TVMI or clinically driven TLR. Target vessel failure: composite of cardiac death, TVMI or clinically driven TVR. BARC: Bleeding Academic Research Consortium; MI: myocardial infarction; POT: proximal optimisation technique; TLR: target lesion revascularisation; TV non-TLR: target vessel, non-target lesion revascularisation; TVR: target vessel revascularisation

the subsequent risk of side branch occlusion inducing a periprocedural MI, a 1:1 stent diameter/distal reference diameter ratio was proposed by Darremont at the 5th European Bifurcation Club meeting[5] in combination with a 1:1 balloon post-dilatation just proximal to the carina, sized on the basis of a simplified Murray's law, to eliminate undersizing, and subsequent malapposition in the proximal segment of the bifurcation and to facilitate access to the side branch by reducing strut obstruction. This concept of two diameters with a single stent allows the transformation of a regular stent in order to comply with the fractal nature of the coronary tree.

POT VALIDATION

Despite this strong rationale and the intuitive benefit, few studies have been performed to validate this strategy. This could be the reason why the POT was used only in one third of our bifurcation registry despite strong recommendations by the various

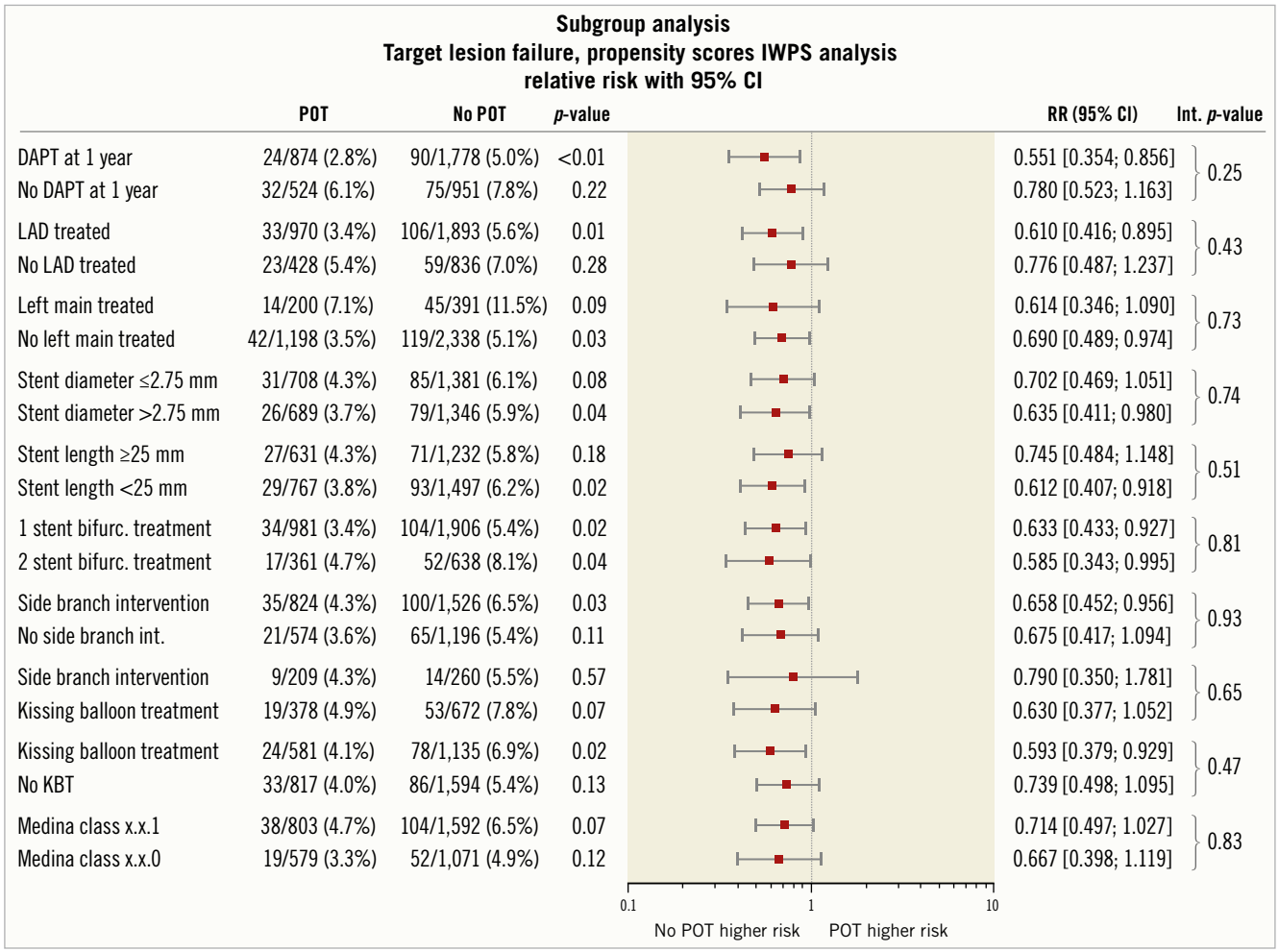
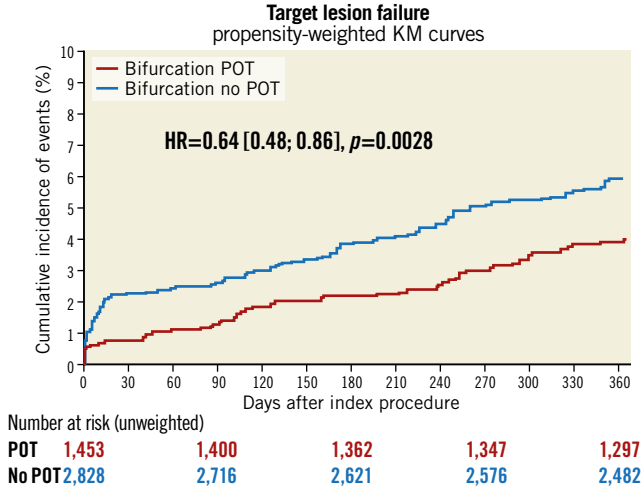


Figure 3. *Impact of POT in major angiographic and procedural subgroups - inverse propensity score weighted analysis. DAPT: duel anti platelet therapy; KBT: kissing balloon technique; LAD: left anterior descending coronary artery; POT: proximal optimisation technique*



Central illustration. *POT versus no POT: inverse propensity score weighted Kaplan-Meier curve of target lesion failure. KM: Kaplan Meier; POT: proximal optimisation technique*

bifurcation clubs. Rigatelli et al[17] showed a significant improvement in terms of flow dynamics when POT is used on bench models with some two-stent techniques. Derimay et al emphasised the impact of balloon position to obtain the expected effect on bench testing[10] and highlighted differences between balloon brands in terms of marker to shoulder distances.

Some studies used intravascular imaging to evaluate the potential benefit with contradictory results. Hakim et al[8] showed that POT increased proximal stent area, as assessed by IVUS, while Murasato et al did not obtain the expected benefit on incomplete stent apposition as assessed by optical coherence tomography (OCT)[9]. Few clinical studies have been conducted so far. Mylotte et al evaluated the role of POT among other modifications of the provisional strategy to improve clinical outcome[18]. Takagi et al studied a series of 586 patients treated on LM bifurcation lesions, showing a strong trend towards major adverse cardiac events (MACE) and TLR reductions (hazard ratio [HR] 0.73 and 0.69, p=0.05 and 0.06) when POT was performed[19]. More recently, Yang et al[12], in a series of 1,191 bifurcation lesions with a 21.1% POT rate, showed a benefit in terms of MACE and TLR when no KBT was performed (p for interaction=0.03). Our results in a much larger cohort found an early and sustained benefit in terms of safety - ST and TVMI – and efficacy – TVR with no interaction with major angiographic and procedural characteristics.

ROLE OF THE KISSING BALLOON TECHNIQUE

In our study, KBT was not associated with a TLF benefit after propensity weighting, a result which is consistent with data from NORDIC III[7] in which KBT failed to prove an impact on a provisional stenting strategy. However, the KBT subgroup, despite worse baseline characteristics, experienced less TVMI without any difference in terms of ST, a finding which could be related to less side branch periprocedural obstruction with no further effect on the TLR rate. Conversely, registry data have shown a late revascularisation benefit, as shown in COBIS II[20] and RAIN[21]. However, guidelines[22] recommend using KBT in two-stent techniques. A significant interaction was present with some baseline angiographic characteristics and DAPT duration but the KBT effect was similar regardless of the number of stents and the deployment technique.

The question as to whether KBT and POT are complementary techniques is still a matter of debate as both techniques are implemented to reduce proximal malapposition and to facilitate further access to the side branch. In our study, POT and KBT practices were more frequently associated than dissociated.

Given the low event rates, it is important to remove as much of the variability induced by the confounding factors as possible. For this purpose, we performed propensity-matched POT and KBT analyses. In order to identify the combined effects of POT and KBT in our study population more clearly, we used logistic regression models where we included both POT and KBT as predictive factors of one-year TLF **(Supplementary Table 5)**, together with their interaction effect and the covariates we used in propensity score weighting. From the multivariate model, it seems that POT only (p=0.046), rather than KBT (p=0.81) or their interaction effect (p=0.76), is the protective factor for TLF in our study. Additionally, we performed 2 by 2 propensity-matched analyses, classifying patients by their POT and KBT status into four groups: (1) using POT and KBT, (2) using POT but no KBT, (3) using KBT but no POT, and (4) neither POT nor KBT used **(Supplementary Table 6)**. These results corroborate the results from the logistic regression models: POT is the protective factor for TLF, while KBT or the POT-KBT interaction does not seem to play a major role. These data suggest that KBT cannot be a substitute for the POT technique.

Limitations

First, due to the registry design, there is a potential for selection bias and under-reporting of events despite the prospective nature of the study and the specific measures undertaken to improve data quality using on- and off-site monitoring. In particular, an underestimation of periprocedural MI cannot be excluded as periprocedural biomarker collection was per hospital practice. Second, vessel and lesion characteristics were assessed by operators, most commonly through visual estimation, and not measured centrally by a core lab. Third, deployment technique details are limited in terms of size selection and inflation technique. Sequence description data with regard to POT and KBT are missing, even though the latter was always performed after stenting; moreover, a small number of patients were treated under intravascular imaging guidance, limiting the extrapolation of these results to intravascular imaging-guided interventions. Fourth, the outcomes reported are based on the use of a single new-generation stent platform for all patients; these may potentially differ with the use of different DES. Fifth, as the antiplatelet regimen nature and duration was left to the operator's discretion, interaction with deployment techniques is unknown. Finally, although we report a follow-up of one year, coronary stents are lifelong implants; it is possible that further differences between our study groups could be observed at longer follow-up.

Conclusions

In this large prospective single-arm study with an already low one-year failure rate in the bifurcation stenting cohort, the proximal optimisation technique was associated with a further reduction in the event rate and a uniform benefit across subgroups, reinforcing the recommendation for a systematic use of this deployment technique regardless of the bifurcation anatomy and stenting technique.

Impact on daily practice

This large bifurcation subgroup from a global registry using a latest-generation DES shows a low one-year event rate with significant clinical improvement when the proximal optimisation technique was performed. The kissing balloon technique has a more limited influence on the outcome. The current findings suggest a benefit of the proximal optimisation technique irrespective of the lesion anatomy and the stenting technique, promoting its systematic use.

Funding

The e-Ultimaster registry was funded and sponsored by Terumo Europe NV (Leuven, Belgium).

Conflict of interest statement

B. Chevalier reports grants from Terumo during the conduct of the study, personal fees from Terumo, outside the submitted work, and being a minor shareholder of CERC (CRO). M. Mamas has the following interests to declare: unrestricted educational grants from Terumo, Abbott, Medtronic and Biosensors, and speaker fees from Terumo, Daiichi Sankyo and Biosensors. M. Pan reports minor lecture fees from Abbott, Terumo and Volcano. F.F. Beygui reports grants from Terumo during the conduct of the study, grants and personal fees from Medtronic and Biosensor, and personal fees from Bristol Myers Squibb, outside the submitted work. The other authors have no conflicts of interest to declare.

References

1. Sawaya FJ, Lefèvre T, Chevalier B, Garot P, Hovasse T, Morice MC, Rab T, Louvard Y. Contemporary Approach to Coronary Bifurcation Lesion Treatment. *JACC Cardiovasc Interv.* 2016;9:1861-78.

2. Louvard Y, Thomas M, Dzavik V, Hildick-Smith D, Galassi AR, Pan M, Burzotta F, Zelizko M, Dudek D, Ludman P, Sheiban I, Lassen JF, Darremont O, Kastrati A,

Ludwig J, Iakovou I, Brunel P, Lansky A, Meerkin D, Legrand V, Medina A, Lefèvre T. Classification of coronary artery bifurcation lesions and treatments: time for a consensus! *Catheter Cardiovasc Interv.* 2008;71:175-83.

3. Lassen JF, Holm NR, Stankovic G, Lefèvre T, Chieffo A, Hildick-Smith D, Pan M, Darremont O, Albiero R, Ferenc M, 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.

4. Sgueglia GA, Chevalier B. Kissing balloon inflation in percutaneous coronary interventions. *JACC Cardiovasc Interv.* 2012;5:803-11.

5. Hildick-Smith D, Lassen JF, Albiero R, Lefèvre T, Darremont O, Pan M, Ferenc M, Stankovic G, Louvard Y; European Bifurcation Club. Consensus from the 5th European Bifurcation Club meeting. *EuroIntervention.* 2010;1:34-8.

6. Darremont O, Leymarie JL, Lefèvre T, Albiero R, Mortier P, Louvard Y. Technical aspects of the provisional side branch stenting strategy. *EuroIntervention.* 2015;11 Suppl V:V86-90.

7. Niemelä 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, Mäkikallio T, Hansen KN, Thayssen P, Aberge L, Jensen LO, Hervold A, Airaksinen J, Pietilä M, Frobert O, Kellerth T, Ravkilde J, Aarøe J, Jensen JS, Helqvist S, Sjögren I, James S, Miettinen H, Lassen JF, Thuesen L; Nordic-Baltic PCI Study Group. 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.

8. Hakim D, Chatterjee A, Alli O, Turner J, Sattar A, Foin N, Leesar MA. Role of Proximal Optimization Technique Guided by Intravascular Ultrasound on Stent Expansion, Stent Symmetry Index, and Side-Branch Hemodynamics in Patients With Coronary Bifurcation Lesions. *Circ Cardiovasc Interv.* 2017;10:e005535.

9. Murasato Y, Mori T, Okamura T, Nagoshi R, Fujimura T, Yamawaki M, Ono S, Serikawa T, Nakao F, Shite J; 3D-OCT Bifurcation Registry Investigators. Efficacy of the proximal optimization technique on crossover stenting in coronary bifurcation lesions in the 3D-OCT bifurcation registry. *Int J Cardiovasc Imaging.* 2019;35:981-90.

10. Dérimay F, Rioufol G, Nishi T, Kobayashi Y, Fearon WF, Veziers J, Guérin P, Finet G. Optimal balloon positioning for the proximal optimization technique? An experimental bench study. *Int J Cardiol.* 2019;292:95-7.

11. Andreasen LN, Holm NR, Webber B, Ormiston JA. Critical aspects of balloon position during final proximal optimization technique (POT) in coronary bifurcation stenting. *Catheter Cardiovasc Interv.* 2020;96:31-9.

12. Yang JH, Lee JM, Park TK, Song YB, Hahn JY, Choi JH, Choi SH, Yu CW, Chun WJ, Oh JH, Koo BK, Jeong JO, Kim HS, Gwon HC. The Proximal Optimization Technique Improves Clinical Outcomes When Treated without Kissing Ballooning in Patients with a Bifurcation Lesion. *Korean Circ J.* 2019;49:485-94.

13. Mohamed MO, Polad J, Hildick-Smith D, Bizeau O, Baisebenov RK, Roffi M, Íñiguez-Romo A, Chevalier B, von Birgelen C, Roguin A, Aminian A, Angioi M, Mamas MA. Impact of coronary lesion complexity in percutaneous coronary intervention: one-year outcomes from the large, multicentre e-Ultimaster registry. *EuroIntervention.* 2020;16:603-12.

14. Chisari A, Pistritto AM, Piccolo R, La Manna A, Danzi GB. The Ultimaster Biodegradable-Polymer Sirolimus-Eluting Stent: An Updated Review of Clinical Evidence. *Int J Mol Sci.* 2016;17:1490.

15. Murray CD. THE PHYSIOLOGICAL PRINCIPLE OF MINIMUM WORK APPLIED TO THE ANGLE OF BRANCHING OF ARTERIES. *J Gen Physiol.* 1926;9:835-41.

16. Finet G, Gilard M, Perrenot B, Rioufol G, Motreff P, Gavit L, Prost R. Fractal geometry of arterial coronary bifurcations: a quantitative coronary angiography and intravascular ultrasound analysis. *EuroIntervention.* 2008;3:490-8.

17. Rigatelli G, Zuin M, Dell'Avvocata F, Vassilev D, Daggubati R, Nguyen T, Van Viet Thang N, Foin N. Evaluation of coronary flow conditions in complex coronary artery bifurcations stenting using computational fluid dynamics: Impact of final proximal optimization technique on different double-stent techniques. *Cardiovasc Revasc Med.* 2017;18:233-40.

18. Mylotte D, Routledge H, Harb T, Garot P, Hovasse T, Benamer H, Unterseeh T, Chevalier B, Morice MC, Louvard Y, Lefèvre T. Provisional side branch-stenting for coronary bifurcation lesions: evidence of improving procedural and clinical outcomes with contemporary techniques. *Catheter Cardiovasc Interv.* 2013;82:E437-45.

19. Takagi K, Fujino Y, Naganuma T, Watanabe Y, Yabushita H, Mitomo S, Kawamoto H, Tahara S, Kobayashi T, Warisawa T, Karube K, Matsumoto T, Sato T, Ishiguro H, Kurita N, Nakamura S, Hozawa K, Nakamura S. Impact of a combination of full coverage stenting and proximal optimization technique on long term outcome for unprotected distal left main disease. *Cardiovasc Revasc Med.* 2016;17:515-21.

20. Yu CW, Yang JH, Song YB, Hahn JY, Choi SH, Choi JH, Lee HJ, Oh JH, Koo BK, Rha SW, Jeong JO, Jeong MH, Yoon JH, Jang Y, Tahk SJ, Kim HS, Gwon HC. Long-Term Clinical Outcomes of Final Kissing Ballooning in Coronary Bifurcation Lesions Treated With the 1-Stent Technique: Results From the COBIS II Registry (Korean Coronary Bifurcation Stenting Registry). *JACC Cardiovasc Interv.* 2015;8:1297-307.

21. Gaido L, D'Ascenzo F, Imori Y, Wojakowski W, Saglietto A, Figini F, Mattesini A, Trabattoni D, Rognoni A, Tomassini F, Bernardi A, Ryan N, Muscoli S, Helft G, De Filippo O, Parma R, De Luca L, Ugo F, Cerrato E, Montefusco A, Pennacchi M, Wańha W, Smolka G, de Lio G, Bruno F, Huczek Z, Boccuzzi G, Cortese B, Capodanno D, Omedè P, Mancone M, Nuñez-Gil I, Romeo F, Varbella F, Rinaldi M, Escaned J, Conrotto F, Burzotta F, Chieffo A, Perl L, D'Amico M, di Mario C, Sheiban I, Gagnor A, Giammaria M, De Ferrari GM. Impact of Kissing Balloon in Patients Treated With Ultrathin Stents for Left Main Lesions and Bifurcations: An Analysis From the RAIN-CARDIOGROUP VII Study. *Circ Cardiovasc Interv.* 2020;13:e008325.

22. Neumann FJ, Sousa-Uva M, Ahlsson A, Alfonso F, Banning AP, Benedetto U, Byrne RA, Collet JP, Falk V, Head SJ, Jüni P, Kastrati A, Koller A, Kristensen SD, Niebauer J, Richter DJ, Seferovic PM, Sibbing D, Stefanini GG, Windecker S, Yadav R, Zembala MO; ESC Scientific Document Group. 2018 ESC/EACTS Guidelines on myocardial revascularization. *Eur Heart J.* 2019;40:87-165.

Supplementary data

Supplementary Appendix 1. List of participating sites and local principal investigators.

Supplementary Appendix 2. Clinical Event Committee members.

Supplementary Table 1. Baseline patient characteristics according to use of KBT – unadjusted.

Supplementary Table 2. One-year clinical outcomes according to use of KBT.

Supplementary Table 3. Baseline patient characteristics according to use of POT – inverse propensity score weighted.

Supplementary Table 4. Baseline patient characteristics according to use of KBT – inverse propensity score weighted.

Supplementary Table 5. Multivariate logistic regression of one-year TLF.

Supplementary Table 6. One-year clinical outcomes according to use of POT and KBT – inverse propensity score weighted.

Supplementary Figure 1. Distribution of the inverse weights for POT versus no POT and KBT versus no KBT.

Supplementary Figure 2. Overview of bifurcation subgroups.

Supplementary Figure 3. Impact of KBT in major angiographic and procedural subgroups.

The supplementary data are published online at: https://eurointervention.pcronline.com/doi/10.4244/EIJ-D-20-01393

Supplementary data

Supplementary Appendix 1. List of participating sites and local principal investigators.

Country	Participating sites and investigators
Argentina	Fundación Favaloro: **Oscar Mendiz**; Hospital Universitario Austral: **Juan Manuel Telayna**; Clinica Centro Médico Privado Junin: **José Magni**; Instituto Cardiovascular de Buenos Aires: **Fernando Cura**; Sanatorio San Miguel: **Juan Lloberas**
Armenia	Astghik Medical Center (Natali Farm): **Mikayel Adamyan**; Medical Center Gyumri CJSC: **Davit Minasyan**; Qancor Cardiovascular MC LLC: **Shahen Khachatryan**; Republican Medical Center Armenia CJSC: **Boghos Sarkissian**; Yerevan State Medical University Hospital: **Hamayak Sisakian**
Austria	AKH Linz: **Clemens Steinwender**; Medical University Vienna (AKH): **Irene Lang**; Medizinische Universität Graz: **Gabor Toth-Mayor**
Bangladesh	National Heart Foundation Hospital and Research Institute: **Fazila Tun-Nesa Malik**
Belarus	City Clinical Emergency Hospital: **Alexander Beimanov**; RSPC: **Oleg Polonetsky**
Belgium	AZ Sint Lucas: **Jan Nimmegeers**; CHR de La Citadelle: **Suzanne Pourbaix**; Hôpital Ambroise Paré de Mons: **Stéphane Carlier**; CHU Charleroi: **Adel Aminian**; CHU UCL Mont Godinne Namur: **Antoine Guédès**; Epicura Hornu: **Philippe Decroly**; Imelda Ziekenhuis: **Willem De Wilde**; Jan Yperman Ziekenhuis: **Dries De Cock**; OLVZ Aalst: **Bernard De Bruyne**; UCL Saint Luc: **Joelle Kefer**
Brazil	Eurolatino Natal Pesquisas Medicas (Eurolatino Natal Medical Research): **Maria Sanali Paiva**; Hospital E Maternidade Dr. Christóvão Da Gama: **Bruno Palmieri Bernardi**; Hospital Felicio Rocho: **Jamil Abdalla Saad**; Hospital Moinhos de Vento: **Marco Vugman Waistein**; Hospital Monte Sinai: **Gustavo De Moraes Ramalho**; Hospital Santa Cruz: **Roberto Otsubo**; Hospital São Vicente de Paulo: **Rogério Tumelero**, **Alexandre Tognon**; Paraná Medical Research Center: **Marcos Franchetti**; Unicor: **João Eduardo Tinoco De Paula**; Unimed Joinville: **Bruno Cupertino Migueletto**
Bulgaria	Mbal Haskovo: **Sevdalin Topalov**; Mbal Montana City Clinic Sveti Georgi: **Krasimir Pandev**; Mbal Sveta Karidad, Plovdiv: **Dimitar Karageorgiev**; Mbal Sveta Petka Vidin: **Diana Trendafilova-Lazaroba**; Specialized Cardiology Hospital For Active Treatment: **Angel Mitov**; Trakiya Hospital, Stara Zagora: **Borislov Borisov**; Umhat Alexandrovska: **Dobrin Vassilev**; Umhat St.Ekaterina: **Julia Jorgova-Makedonska**
Chile	Clinica Bicentenario: **Carlos Romero**; Clinica Santa Maria: **Pablo Pedreros**; Hospital Clínico San Borja Arriaran: **Gabriel Maluenda**; Hospital Guillermo Grant Benavente: **Luis Perez**; Hospital Regional de Antofagasta: **Bernhard Westerberg**; Hospital Regional Puerto Montt: **Victor David Assef**; Hospital San Juan de Dios: **Angel Puentes**
Colombia	Centro Cardiovascular de Caldas: **Hugo Castaño**; Clinica Shaio: Pablo Castro; Fundación Cardiovascular de Colombia (Bucaramanga): **Tamara Gorgadze**; Instituto del Corazon Bucaramanga: **Boris Eduardo Vesga**, **Hector Hernandez**
Czech Republic	St Anne's University Hospital Brno: **Ladislav Groch**; Kardiologie na Bulovce: **Miroslav Erbrt**; Karlovarská Krajská Nemocnice: **Alexandr Schee**; FNKV Hospital: **Viktor KočKa**; Krajska Nemocnice T. Bati: **Zdenek Coufal**

Country	Participating sites and investigators
Egypt	Al Hayat Hospital: **Hany Ragy**; Al Nakheel Hospital: **Yasser Sadek**; Dr Ahmed Abdel Aziz Multicenter: **Mohamed Abdel Aziz**; Dr Hussien Heshmat – As Salam International Hospital: **Hussien Heshmat**; El Marwa Hospital: **Mounir Asman**; Italian Hospital: **Ihab Daoud**; L-Fouad Cardiac Center: **Ahmed Emara**; Dr Hisham Ammar Multicenter: **Hisham Ammar**; Police Hospital: **Mohamed Helal**; Tarek Rasid: **Tarek Rashid**; Um El Korra M Setiha Hospital: **Mohamed Setiha**; Nile Badrawy Hospital: **Sameh Ahmed Salama**; Wadi El Neel: **Hazem Khamis**
Estonia	North-Estonia Medical Center: **Peep Laanmets**;
France	Centre D'exploration-Chirurgie Cardio-Vasculaire: **Jean-Louis Leymarie**; CH Bretagne Atlantique: **Emmanuelle Filippi**; CH de Marne La Vallée: **Simon Elhadad**; CH de Montreuil: **Chaib Aures**; CH Haguenau: **Fabien De Poli**; Groupe Hospitalier de la Rochelle Ré Aunis: **Charlotte Trouillet**; CH La Timone Marseille: **Jean-Louis Bonnet**; CH Louis Pasteur-Le Coudray: **Grégoire Rangé**; CH de Pau: **Nicolas Delarche**; CH René Dubos Pontoise: **Francois Funck**; CH St Joseph St Luc Lyon: **Olivier Dubreuil**; CH Sud Francilien: **Pascal Goube**; CH Valence: **Stanislas Champin**; CH Yves Le Foll - Saint Brieuc: **Denis Amer Zabalawi**; CHD Vendée La Roche Sur Yon: **Emmanuel Boiffard**; CH Général de Saint Quentin: **Pierre Henon, Florent Chevalier**; CHIC Quimper: **Thierry Joseph**; CHR Orleans Cardiologie: **Olivier Bizeau**; CHU Angers: **Alain Furber**; CHU Caen: **Farzin Beygui**; CHU Clermont-Ferrand: **Pascal Motreff**; CHU de Poitiers: **Sebastien Levesque**; Clinique Ambroise Paré: **Julien Rosencher**; Clinique Diaconat Fonderie Mulhouse: **Pradip Kumar Sewoke**; Clinique du Millénaire Montpellier: **Christophe Piot**; Clinique Du Pont de Chaume Montauban: **Laurent Delorme**; Clinique Louis Pasteur Essey les Nancy: **Max Amor, Michael Angioi**; Clinique Rhône Durance: **Gilles Bayet**; Clinique Saint-Laurent: **Yves Biron**; Clinique St Hilaire Rouen: **Matthieu Godin;** Clinique St Joseph: **Julien Jeanneteau**; GCS Cardiologique de Bayonne: **Jean Luc Banos**; Groupe Hopitalier Paris Saint Joseph: **Romain Cador**; Groupement Mutualiste de Grenoble: **Jacques Monsegu;** Hopital Privé Claude Galien Quincy: **Stéphane Champagne**; Hopital Albert Schweitzer GHCA Colmar: **Plastaras Philoktimon**; Hôpital Europøen de Paris la Roseraie: **Hakim Benamer**; Hopital Privé Dijon Bourgogne: **Philippe Brunel**; Hopital Privé Jacques Cartier Massy: **Thomas Hovasse**, **Bernard Chevalier**; Hopital Privé La Louviere-Lille: **Fabrice Leroy**; Hopital Privé Saint Martin: **Guillaume Lecoq**; Hôpital Privé St Martin de Pessac: **Levy Raphy**; Hôpital Privé St Martin de Pessac: **Bernard Karsenty**; Institut Arnault Tzanck St Laurent du Var: **Alexandre Avran**; Le Confluent Nouvelles Cliniques Nantaises: **Ashok Tirouvanziam**; Nouvel Hopital Civil de Strasbourg: **Olivier Morel**; Pôle Santé République Clermont Ferrand: **Pascal Barraud**; Polyclinique Les Fleurs: **Philippe Commeau**
Georgia	Joann Medical Center (JAMC): **Lasha Chantladze**
Hungary	Pándy Kálmán Hospital: **Jambrik Zoltan**; Markusovszky University Teaching Hospital: **Lajos Nagy**; Moritz Kaposi General Hospital: **Andras Vorobcsuk**; PECS University: **Ivan Horvath**; Semmelweis University: **Bela Merkely**; Szabolcs - Szatmar - Bereg County Hospital and University Teaching Hospital: **Kôszegi Zsolt**
Iceland	Landspitali National University Hospital of Iceland: **Ingibjörg Jóna Guðmundsdóttir**;

Country	Participating sites and investigators
India	Dayanand Medical College: **Gurpreet Singh Wander**; Fortis Hospital: **R. Keshava**; G. Kuppuswamy Naidu Memorial Hospital: **Rajpal Abhaichand**; H .J. Doshi Ghatkopar Hindusabha Hospital: **Anil Potdar**; Heart & General Hospital: **Prakash Chandwani**; Kamalnayan Bajaj Hospital, Aurangabad: **Ajit Bhagwat**; Krishna Institute of Medical Sciences: **Rajendra Kumar Premchand**; Madras Medical Mission: **Ajit Mullasari**; Maharaja Agrasen Hospital: **B B Chanana**; Max Super Specialty Hospital: **Viveka Kumar**; Medanta Hospital: **Praveen Chandra**; BM Birla Heart Research Cente: **Ashwani Mehta**; Sree Chitra Tirunal Institute of Medical Sciences & Technology: **Bijulal Sasidharan**; Wockhardt Hospital: **Prashant Jagtap**
Indonesia	Awal Bros Hospital: **Bambang Budiono**; Binawaluya Cardiac Center: **Muhammad Munawar**; RSUPN Dr. Cipto Mangunkusumo Hospital: **Muhammad Yamin**; Dr. Soetomo General Hospital: **Yudi Her Oktaviono**; Dr. Wahidin Sudirohusodo General Hospital- Awal Bros Hospital: **Abdul Hakim Alkatiri**; Medistra Hospital: **Teguh Santoso**; National Cardiovascular Center Harapan Kita Hospital: **Doni Firman**; Saiful Anwar General Hospital: **Sasmojo Widito**
Ireland	Cork University Hospital: **Eugene McFadden**; University Hospital Galway: **Jim Crowley**; University Hospital Limerick: **Thomas Kiernan**
Israel	Assaf Harofeh Medical Center: **Minha Saar**; Galilee Medical Center: **Marc Brezins**; Rambam Medical Center: **Ariel Roguin**; Ziv Medical Center: **Majdi Halabi**
Japan	Gunma Prefectural Cardiovascular Center: **Ren Kawaguchi**; Higashi Takarazuka Satoh Hospital: **Satoru Otsuji**; Iwaki Kyoritsu General Hospital: **Yoshito Yamamoto**; Kakogawa Central City Hospital: **Makoto Kadotani**; Kansai Rosai Hospital: **Takayuki Ishihara**; Kokura Memorial Hospital: **Kenji Ando**; Komaki City Hospital: **Katsuhiro Kawaguchi**; Kouseikai Takai Hospital: **Yasunori Nishida**; Mie Heart Center: **Hideo Nishikawa**; Mimihara General Hospital: **Shozo Ishihara**; Okamura Memorial Hospital: **Yasuhiro Tarutani**; Osaka General Medical Center: **Takashi Morita**; Osaka Rosai Hospital: **Masami Nishino**; Saiseikai Senri Hospital: **Keiji Hirooka**; Saiseikai Yamaguchi General Hospital: **Shiro Ono**; Saiseikai Yokohama City Eastern Hospital: **Yoshiaki Ito**; Saitama Cardiovascular And Respiratory Center: **Makoto Muto**; Sakurabashi Watanabe Hospital: **Kenshi Fujii**; Sapporo Higashi Tokushukai Hospital: **Seiji Yamazaki**; Seirei Hamamatsu General Hospital: **Hisayuki Okada**; Seirei Yokohama Hospital: **Kazuhiro Ashida**; Shonan Kamakura General Hospital: **Shigeru Saito**; Showa University Fujigaoka Hospital: **Hiroshi Suzuki**; Tokai University Hachiouji Hospital: **Takashi Matsukage**
Jordan	Jordan Hospital: **Imad Alhaddad**
Kazakhstan	Aktobe Regional Hospital: Aidos Taumov; Cardiology Center Petropavl: **Maxat Kudratullayev**; City Hospital #2: **Marat Alikhanov**; Clinical Center of Cardiac Surgery and Transplantation: **Vadim Seisembekov**; Jsc Nat. Scient. Cardiosurgery Ctr.: **Marat Aripov**; Medical University Clinic West Kazakhstan: **Dauren Teleuov**; National Surgery Center Almaty: **Bauyrzhan Ormanov**; Pavlodar Regional Cardiologic Center: **Ruslan Baisebenov**; Regional Cardiosurgery Center: **Azamat Kenzhinovich Zhashkeyev**; Rudnyi City Hospital: **Azamat Yerzhanov**; The Almaty City Heart Center: **Orazbek Sakhov**; Semey State Medical University, Interventional Cardiology Dpt: **Ersin Sabitov**
Kuwait	Sabah Al Ahmad Cardiac Center: **Vladimir Kotevski**

Country	Participating sites and investigators
Lebanon	Hôpital Abou Jaoudé: **Daou Abdo**; Labib Medical Center: **Ahmad Serhal**
Lithuania	Hospital Of Lithuanian University Of Health Sciences Kauno klinikos: **Ramunas Unikas**; Klaipeda Seamen's Hospital: **Aurimas Knokneris**
Macedonia	City General Hospital: **Vladimir Ristovski**; University Clinic Of Cardiology: **Sasko Kedev**
Malaysia	Desa Park City: **Chong Yoon Sin**; Hospital Serdang: **Abdul Kahar Ghapar**; Hospital Sultanah Bahiyah: **Abd Syukur Bin Abdullah**; Hospital Tengku Ampuan Afzan: **Siti Khairani bt Zainal Abidin**; HSC Medical Center: **Tee Chee Hian**; UiTM Sg. Buloh Campus: **Nicholas Chua Yul Chye**
Mexico	Clinica Hospital San Jose de Navojoa: **Santiago Sandoval Navarrete**; Hospital Fray Juan de San Miguel de Uruapan: **Juan Jorge Beltran Ochoa**; Hospital Star Medica Merida: **Sergio Alonso Villareal Umaña**; Casa del Corazon de la Peninsula de Yucatan SCP: **Carlos Ramon Rodas Caceres**
Morocco	Cherradi_Clinique Agdal: **Rhizlan Cherradi**; Clinique Achifaa de Casablanca: **Anass Assaidi**; Clinique Grant Atlas: **Dounia Benzaroual**; Clinique Internationale de Marrakech: **Fahd Chaara**
Netherlands	Albert Schweitzer Ziekenhuis: **Martijn Scholte**; Amphia Ziekenhuis: Al**exander J.J. Ijsselmuiden**; Catharina Ziekenhuis: W.A.L. **Pim Tonino**; Jeroen Bosch Ziekenhuis: **Jawed Polad; Jacob van Eck**; Maasstad Ziekenhuis: **Pieter Cornelis Smits**; Meander MC: **Fabrizio Spano**; Medisch Centrum Haaglanden: **Lucas H. Savalle**; Medisch Spectrum Twente, Enschede: **Clemens Von Birgelen**; Rijnstate Ziekenhuis: **Peter W. Danse**; Scheper Hospital: **Gillian Jessurun**; Zorgsaam Ziekenhuis Zeeuws-Vlaanderen: **Pieter Bisschops**
Oman	Muscat Private Hospital: **Amr Hassan**
Poland	Insytut Kardiologii im. Prymasa Tys ąclecia Stefana Kardynała Wyszyńskiego: **Adam Witkowski**; Miedziowe Centrum Zdrowia: **Adrian Wlodarczak**; Szpital Kliniczny Przemienienia Panskiego Um Im. K. Marcinkowskiego W Poznaniu: **Maciej Lesiak**;
Portugal	CHLN Norte Hospital Santa María: **Pedro Canas Da Silva**
Romania	Centrele de Excelenta Ares: **Alexandru Voican**; Clinicile Icco S.R.L.: **Mihai Ursu**; Cordismed Timisoara: **Milovan Slovenski**; Spitalul Judetean de Urgenta Sibiu: **Ioan Bitea Cornel**
Saudi Arabia	Dallah Hospital, Riyadh: **Samih Lawand**; King Fahad Cardiac Center: **Tarek Kashour**; Prince Abdullah Bin Abdul Aziz Musad Cardiac Center: **Muhammad Aurangzaib Mughal**
Serbia	Cardiovascular Institute Dedinje: **Dragan Sagic**; Clinical Center Kragujevac: **Nikola Jagic**; Cardiology Clinic, Clinical Centre of Serbia: **Vladan Vukcevic**; Kbc Zvezdara: **Alexandar Davidovic**; CHC Bezanijska Kosa: **Sasa Hinic**
Slovakia	Stredodlovensky Ustav Srdcovych A Cievnych Chorob: **Martin Hudec**
South Africa	Ethekwini Hospital & Heart Centre: **Shiraz Gafoor**; **Ismail Soosiwala**; Milpark Hospital: **Graham Cassel**; Netcare Greenacres Hospital: **Martin Tawanda Butau**; Netcare Union Hospital: **Jean-Paul Theron**; Netcare Unitas Hospital: **Jean Vorster**; Netcare Unitas Hospital: **Pieter Blomerus**; Netcare Unitas Hospital: **Iftikar Osman Ebrahim**; Netcare Unitas Hospital: **Jacobus Badenhorst**
Spain	Bellvitge University Hospital: **Joan Antonio Gomez**; Complexo Hospitalario Universitario A Coruña (CHUAC): **Nicolás Vázquez Gonzalez**; Hospital 12 Octubre: **Fernando Sarnago**; Hospital Cabueñes: **Iñigo Lozano**; Hospital Clínico Lozano Blesa de Zaragoza: **José Ramón Ruiz Arroyo**; Hospital Clínico

Country	Participating sites and investigators
	Universitario de Santiago de Compostela: **Ramiro Trillo Nouche**; Clinico Universitario Valencia: **Juan Sanchís**; Hospital de Cruces-Barakaldo: **Juan Alcibar**; Hospital Universitario Donostia: **Mariano Larman**; Hospital de Galdakao: **José Ramón Rumoroso**; Hospital de La Cruz Roja de Córdoba: **José Suárez de Lezo**; Hospital de León: **Maria López Benito**; Hospital de Mérida: **Pablo Cerrato Garcia**; Hospital de Navarra: **Baltasar Lainez**; Hospital del Mar: **Beatriz Vaquerizo**; Hospital Fundacion Alcorcon: **Javier Botas**; Hospital G. Trias I Pujol: **Eduard Fernández Nofrerias**; Hospital General Castellón: **Pascual Baello Monge**; Hospital General Ciudad Real: **Fernando Lozano Ruiz-Poveda**; Hospital General de Albacete: **Jesus Maria Jimenez Mazuecos**; Hospital General Universitario de Burgos: **Javier Robles**; Hospital Infanta Cristina: **José Ramon Lopez Minguez**; Hospital Juan Ramón Jiménez: **Pepi Garcia**; Clinica La Luz: **Jorge Palazuelos**; Hospital Manises: **Gema Miñana**; Hospital Marqués de Valdecilla: **Jose Javier Zueco**; Hospital Meixoeiro-Medtec: **Andrés Iñiguez Romo**; Hospital Moncloa: **Eulogio Garcia Fernandez**; Hospital Puerta de Hierro: **Javier Goicolea**; Hospital Reina Sofia de Córdoba: **Manuel Pan**; Clínica San Fransisco de Asis: **Arturo García Touchard**; Hospital San Pedro: **Javier Fernández**; Hospital San Pedro de Alcantara-Caceres: **Javier Fernandez Portales**; Hospital San Rafael: **Gonzalo Peña**; Hospital Sant Pau: **Antonio Peñaranda Serra**; Hospital Santa Lucía de Cartagena Hospital Nostra Señora Rossell: **José Domingo Cascón**; Hospital Txagorritxu: **Alfonso Torres**; Hospital Universitario de Gran Canaria Dr Negrin: **Pedro Martin Lorenzo**; Hospital Universitario de Guadalajara: **Javier Balaguer Requena**; Hospital Universitario Lucus Augusti (HULA): **Raymundo Ocaranza Sanchez**; Hospital Universitario Miguel Servet (H.U.M.S.): **Jose Antonio Diarte de Miguel**; Hospital Vall d'Hebron: **Bruno García Del Blanco**; Hospital Virgen Arrixaca: **Eduardo Pinar**; Hospital Virgen de La Salud: **P. José Moreu Burgos**; Instituto Cardiologico Hospital Campo Grande: **Juan Manuel Duran**; San Juan de Alicante: **Ramón López Palop**; Universitario Central de Asturias: **César Moris-De La Tassa**
Sweden	Gävle Sjukhus: **Robert Kastberg**; Mälarsjukshuet: **Finn Hjortevang**; Skaraborgs Sjukhus v Skövde: **Jason Stewart**; Sundvalls Sjukhus: **Espen Haugen**; Universitets Sjukhuset I Örebro: **Ole Fröbert**; Västmanlads Sjukhus Västerås: ;
Switzerland	Cardiocentro Lugano, Ticino: Giovanni Pedrazzini; Herz Gefäss Zentrum Zürich: **Peter Wenaweser**; Hôpital de La Tour: **Edoardo De Benedetti**; Hôpitaux Universitaires de Genève: **Maro Roffi**; Kantonsspital Baselland: **Gregor Leibundgut**; Kantonsspital Frauenfeld Spital Thurgau AG: **Michael Neuhaus**; Kantonsspital Luzern: **Florim Cuculi**
Thailand	Central Chest Institute Of Thailand: **Wirash Kehasukcharoen**; HRH Princess Maha Chakri Sirindhorn Medical Center (Nakornayok): **Arthit Wongsoasup**; Paolo Memorial Hospital Phaholyothin: **Niphonth Srisuwanunt**
Tunisia	Dr. Mohamed Drissa Clinique Hannibal Lac 2: **Mohamed Akram Drissa**; Dr. Ben Chedli Tarek - Soukra Medical: **Ben Chedli Tarek**; Dr. Bouziri - Clinique Générale Et Cardiovasculaire de Tunis: **Sami Bouziri**; Dr. Elyes Kharrat - Bassatine Clinic: **Elyes Kharrat**; Polyclinique El bassatine_Dr. Mohamed Najeh Abid: **Mohamed Najeh Abid**; Clinique Générale et Cardiovasculaire de Tunis _Dr. Saloua Trabelsi: **Saloua Trabelsi**; Polyclinique El Bassatine: **Rridha Ennouri**
Ukraine	Heart Institute: **Andriy Khohlov**; NAMS Amosov | Emergency Endovascular Surgery Department: **Sergii Salo**; NAMS Amosov | X-Ray Diagnostics And

Country	Participating sites and investigators
	Invasive Cardiology Department: **Yevhenii Aksonov**; S.P.M.C. of Pediatric Cardiology and Cardiac Surgery: **Georgiy Mankovskiy**
United Arab Emirates	Al Noor Hospital - Airport: **Mohammad Andron**; Al Qassimi Hospital: **Arif Al Nooryani**; Al Zahra Private Hospital, Dubai: **Syed Nazir**; Belhoul Speciality Hospital, Dubai: **Muhammad Adnan Raufi**; Dr. Sulaiman Al Habib: **Albert Alahmar**; Dubai Hospital: **Hesham Ahmed Osman**; Iranian Hospital, Dubai: **Seyed Bagher Tabatabaei**; Lifecare Hospital: **Khaled Galal**; Prime Hospital, Dubai: **Murali Krishna**; Rashid Hospital: **Fahad Omar Baslaib**
United Kingdom	Essex Cardiothoracic Centre, Basildon: **Rohan Jagathesan**; Bedford Hospital: **Ramesh de Silva**; Blackpool Victoria Hospital: **Jonas Eichhofer**; Bradford Teaching Hospitals: **John Kurian**; Croydon University Hospital: **Sanjay Kumar**; Dorset County Hospital: **Javed Iqbal**; Eastbourne District General Hospital: **David Walker**; Freeman Hospital: **Rajiv Das**; GBS Re Bucks Healthcare NHS Trust (Buckinghamshire, Wycombe): **Piers Clifford**; James Cook University Hospital: **David Austin**; Kettering General Hospital: **Javed Ehtisham**; Kings Mill Hospital: **Ifti Fazal**; Lincoln County Hospital: **Kelvin Lee**; Lister Hospital, Stevenage: **Paul Kotwinski**; The Royal Wolverhampton Hospitals: **Shahzad Munir**; Norfolk And Norwich University Hospital: **Alisdair Ryding**; Northwick Park Hospital: **Ahmed Elghamaz**; Plymouth Hospital: **Girish Viswanathan**; Queen Elizabeth Hospital, Birmingham: **Sagar Doshi**; Queens Medical Center Nottingham: **Sachin Jadhav**; Royal Berkshire Hospital: **Nicos Spyrou**; Royal Blackburn Hospital: **John Mcdonald**; Royal Bournemouth And Christchurch Hospitals NHS Foundation Trust: **Suneel Talwar**; Royal Brompton And Harefield: **Robert Smith**; Royal Cornwall Hospitals: **Sen Devadathan**; Derby Teaching Hospitals: **Kamal Chitkara**; The Royal Free Hospital: **Sundeep Kalra**; Royal Gwent Hospital, Newport: **James Cullen**; Royal Stoke University Hospital: **Mamas Mamas**; Royal Sussex Hospital, Brighton: **David Hildick-Smith**; Royal United Hospital, Bath**: Kevin Carson**; Salisbury District Hospital: **Tim Wells**; Sandwell And West Birmingham Hospitals: **Chetan Varma**; Sheffield Teaching Hospital: **James Richardson**; Tunbridge Wells Hospital: **Clive Lawson**; UH Coventry and Warwickshire: **Rajathurai Thirumaran**; University Hospital South Manchester: **Hussain Contractor**; University Hospital Of Wales: **Rito Mitra**; University Hospitals Of Leicester: **Ian Hudson**; West Middlesex Hospital: **Sukhinder Nijjer**; Western Sussex Hospitals - Worthing Hospital: **Nicholas Pegge**; Worcestershire Acute Hospitals NHS Trust: **Helen Routledge**; Wrightington Hospital: **V J Karthikeyan**
Uzbekistan	Republic Specialized Center of Surgery: **Mirjamol Mirumarovich Zufarov**
Vietnam	Thong Nhat Hospital: **Nguyen Van Tan**

Supplementary Appendix 2. Clinical Event Committee members.

Name	Affiliated hospital
Taku Asano	St Luke's International Hospital, Tokyo, Japan
Claude Hanet	Catholic University Hospital Mont-Godinne, Belgium
Hara Hironori	Academic Medical Center (AMC), Amsterdam, the Netherlands
Yuki Katagiri	Academic Medical Center (AMC), Amsterdam, the Netherlands
Hideyuki Kawashima	Academic Medical Center (AMC), Amsterdam, the Netherlands
Norihiro Kogame	Academic Medical Center (AMC), Amsterdam, the Netherlands
Hidenori Komiyama	Nippon Medical school, Tokyo, Japan
Yosuke Miyazaki	Erasmus Medical Center Rotterdam, the Netherlands
Masafumi Ono	Academic Medical Center (AMC), Amsterdam, the Netherlands
Bastiaan Schölzel	Amphia Ziekenhuis Breda, the Netherlands
Kuniaki Takahashi	Academic Medical Center (AMC), Amsterdam, the Netherlands
George Vlachojannis	Maasstad Ziekenhuis Rotterdam, the Netherlands

Supplementary Table 1. Baseline patient characteristics according to use of KBT – unadjusted.

	KBT n=1,583	No KBT n=2,757	*p*-value
Patient characteristics			
Age, years	65.7±11.1 (1,583)	65.5±11.1 (2,757)	0.88
Gender, male	75.2% (1,191/1,583)	77.2% (2,127/2,757)	0.15
Geographical region			<0.001
Europe	65.1% (1,031/1,583)	83.2% (2,294/2,757)	
Asia	18.2% (288/1,583)	8.1% (224/2,757)	
Africa/Middle East	8.5% (135/1,583)	5.4% (148/2,757)	
South America/Mexico	8.2% (129/1,583)	3.3% (91/2,757)	
Body mass index, kg/m²	27.3±4.6 (1,349)	27.9±4.6 (2,456)	<0.001
Diabetes mellitus	28.0% (442/1,577)	26.7% (730/2,734)	0.35
Current smoking	18.1% (273/1,512)	22.1% (579/2,625)	0.24
Hypertension	71.9% (1,089/1,515)	67.2% (1,765/2,627)	<0.01
Hypercholesterolaemia	63.5% (942/1,484)	61.5% (1,584/2,575)	0.21
Renal impairment	10.6% (166/1,574)	8.2% (225/2,740)	0.01
Previous MI	25.5% (388/1,521)	23.1% (621/2,691)	0.08
Previous PCI	34.1% (531/1,556)	27.8% (755/2,716)	<0.001
Previous CABG	3.8% (59/1,544)	4.9% (132/2,707)	0.11
Clinical presentation			
Silent ischaemia	11.9% (188/1,583)	12.4% (341/2,757)	0.63
Stable angina	43.9% (695/1,583)	36.6% (1,010/2,757)	<0.001
Unstable angina	12.8% (203/1,583)	12.6% (348/2,757)	0.85
NSTEMI	20.5% (325/1,583)	24.4% (672/2,757)	<0.01
STEMI	10.8% (171/1,583)	13.9% (384/2,757)	<0.01
Vessel treated			
RCA	14.0% (221/1,583)	19.1% (526/2,757)	<0.001
Left main	19.3% (306/1,583)	8.20% (226/2,757)	<0.001
LAD	67.9% (1,075/1,583)	68.5% (1,889/2,757)	0.68
LCX	29.1% (461/1,583)	32.2% (887/2,757)	0.04
Graft (arterial or venous)	0.1% (1/1,583)	0.3% (8/2,757)	0.11
Lesion characteristics			
No. of lesions identified, per patient	2.1±1.1 (1,583)	2.1±1.15 (2,757)	0.59
No. of lesions treated, per patient	1.5±0.8 (1,583)	1.5±0.7 (2,756)	<0.01
Long lesions	47.5% (752/1,583)	39.6% (1,093/2,757)	<0.001
True bifurcation	68.8% (1,089/1,583)	43.7% (1,206/2,757)	<0.001
Two-stent technique	43.8% (693/1,583)	10.3% (284/2,757)	<0.001
Type of two-stent technique			
T-stenting	9.0% (143/1,583)	3.4% (94/2,757)	<0.001

	KBT n=1,583	No KBT n=2,757	*p*-value
V-stenting	2.5%(40/1,583)	1.1%(31/2,757)	<0.001
Kissing stents	4.6%(72/1,583)	0.4%(11/2,757)	<0.001
Crush	7.5%(119/1,583)	1.7%(32/2,757)	<0.001
Culotte	7.1%(111/1,583)	0.3%(9/2,757)	<0.001
TAP or other	13.2% (209/1,583)	3.6%(100/2,757)	<0.001
POT	42.0% (664/1,583)	29.9% (825/2,757)	<0.001
Procedure characteristics			
No. of study stents implanted per patient	2.1±1.1 (1,583)	1.8±1.0 (2,756)	<0.001
Length of implanted study stents per patient, mm	40.5±24.8 (1,578)	33.4±20.5 (,2754)	<0.001

Data are reported for 4,340 patients with at least 1 bifurcation lesion (55 patients were excluded from this comparison because of lack of information on KBT).

Data are mean±standard deviation for continuous variables or % (n) for categorical variables. The number of patients with available data is indicated in brackets.

Renal impairment: defined as estimated glomerular filtration rate <60 ml/min/1.73 m². Lesion characteristics at index procedure are reported.

CABG: coronary artery bypass graft; KBT: kissing balloon technique; LAD: left anterior descending artery; LCX: left circumflex; MI: myocardial infarction; (N)STEMI: (non-) ST-elevation myocardial infarction; PCI: percutaneous coronary intervention; POT: proximal optimisation technique; RCA: right coronary artery

Supplementary Table 2. One-year clinical outcomes according to use of KBT.

	Unadjusted			Adjusted by inverse propensity score weighting		
	KBT n=1,517	No KBT n=2,663	*p*-value	KBT n=1,517	No KBT n=2,663	*p*-value
Primary outcome						
Target lesion failure	5.5% (4.4-6.7) (83/1,517)	4.7% (4.0-5.6) (126/2,663)	0.29	4.5% (3.5-5.6) (69/1,517)	4.7% (3.9-5.5) (126/2,663)	0.77
Cardiac death	2.2% (1.6-3.1) (34/1,517)	1.6% (1.2-2.2) (43/2,663)	0.15	1.8% (1.1-2.5) (27/1,517)	1.6% (1.1-2.1) (42/2,663)	0.60
Target vessel MI	1.1% (0.6-1.7) (16/1,517)	1.6% (1.1-2.1) (42/2,663)	0.17	1.0% (0.5-1.5) (15/1,517)	1.9% (1.4-2.4) (50/2,663)	0.02
Clinically driven TLR	2.8% (2.1-3.8) (43/1,517)	2.8% (2.2-3.5) (74/2,663)	0.92	2.4% (1.7-3.2) (37/1,517)	2.7% (2.1-3.3) (71/2,663)	0.62
Secondary outcomes						
All-cause death	3.4% (2.5-4.4) (51/1,517)	2.4% (1.9-3.1) (65/2,663)	0.08	2.7% (1.9-3.5) (41/1,517)	2.7% (2.1-3.3) (71/2,663)	0.92
All MI	1.7% (1.1-2.4) (25/1,517)	2.0% (1.5-2.6) (52/2,663)	0.48	1.6% (0.9-2.2) (23/1,517)	2.2% (1.7-2.8) (59/2,663)	0.14
Revascularisations						
TVR	4.2% (3.3-5.4) (64/1,517)	4.1% (3.4-5.0) (110/2,663)	0.89	3.7% (2.7-4.6) (56/1,517)	4.0% (3.3-4.8) (107/2,663)	0.60
TV non-TLR	1.3% (0.8-2.0) (19/1,517)	1.5% (1.1-2.0) (40/2,663)	0.51	1.2% (0.7-1.8) (18/1,517)	1.4% (1.0-1.9) (38/2,663)	0.53
TLR	3.0% (2.2-4.0) (46/1,517)	2.9% (2.3-3.6) (78/2,663)	0.85	2.6% (1.8-3.4) (39/1,517)	2.8% (2.2-3.4) (75/2,663)	0.64

	Unadjusted			Adjusted by inverse propensity score weighting		
	KBT n=1,517	No KBT n=2,663	*p*-value	KBT n=1,517	No KBT n=2,663	*p*-value
Clinically driven revascularisations						
TVR	4.0% (3.1-5.1) (61/1,517)	3.9% (3.2-4.8) (105/2,663)	0.90	3.6% (2.6-4.5) (54/1,517)	3.9% (3.2-4.6) (104/2,663)	0.60
TV non-TLR	1.3% (0.8-2.0) (19/1,517)	1.4% (1.0-2.0) (38/2,663)	0.64	1.2% (0.7-1.8) (18/1,517)	1.4% (1.0-1.9) (38/2,663)	0.57
Target vessel failure	6.4% (5.2-7.7) (97/1,517)	5.8% (4.9-6.7) (154/2,663)	0.42	5.5% (4.4-6.7) (84/1,517)	5.9% (5.0-6.7) (156/2,663)	0.66
Stent thrombosis						
Definite	0.7% (0.3-1.2) (10/1,517)	0.6% (0.3-0.9) (15/2,663)	0.70	0.7% (0.3-1.1) (11/1,517)	0.6% (0.3-0.9) (16/2,663)	0.65
Probable	0.3% (0.1-0.8) (5/1,517)	0.3% (0.1-0.6) (8/2,663)	0.87	0.2% (0.0-0.5) (3/1,517)	0.3% (0.1-0.4) (7/2,663)	0.89
Definite/probable	1.0% (0.6-1.6) (15/1,517)	0.9% (0.6-1.3) (23/2,663)	0.68	0.9% (0.4-1.4) (14/1,517)	0.8% (0.5-1.2) (22/2,663)	0.76
Possible	1.1% (0.6-1.7) (16/1,517)	0.7% (0.4-1.1) (19/2,663)	0.24	0.8% (0.4-1.3) (13/1,517)	0.6% (0.3-0.9) (16/2,663)	0.37
All bleedings	2.4% (1.7-3.3) (36/1,517)	2.6% (2.0-3.3) (69/2,663)	0.67	2.4% (1.7-3.2) (37/1,517)	2.3% (1.7-2.9) (61/2,663)	0.78
Bleeding BARC type 1 to 2	1.5% (0.9-2.2) (22/1,517)	1.8% (1.3-2.3) (47/2,663)	0.44	1.7% (1.1-2.3) (26/1,517)	1.5% (1.1-2.0) (41/2,663)	0.69
Bleeding BARC type 3 to 5	0.9% (0.5-1.5) (14/1,517)	0.9% (0.6-1.3) (23/2,663)	0.84	0.8% (0.3-1.2) (11/1,517)	0.8% (0.4-1.1) (20/2,663)	0.96

Events are reported as % with 95% confidence interval (number of patients with event/total number of patients) in the patient population that reached 1-year follow-up, died during follow-up or who had an event that contributed to the primary endpoint (n=4,230 patients with at least 1 bifurcation lesion). Out of 4,230 patients, 50 patients were excluded from this comparison because of lack of information on KBT).

Target lesion failure: a composite of cardiac death, TVMI or clinically driven TLR. Target vessel failure: a composite of cardiac death, TVMI or clinically driven TVR.

BARC: Bleeding Academic Research Consortium; MI: myocardial infarction; TLR: target lesion revascularisation; TV non-TLR: target vessel, non-target lesion revascularisation; TVR: target vessel revascularisation

Supplementary Table 3. **Baseline patient characteristics according to use of POT - inverse propensity score weighted.**

	POT n=1,398	No POT n=2,729	*p*-value
Patient characteristics			
Age, years	65.9±11.1 (1,398)	65.9±11.1 (2,729)	0.99
Gender, male	75.7% (1,058/1,398)	75.7% (2,065/2,729)	0.99
Body mass index, kg/m²	27.8±4.56 (1,233)	27.8±4.7 (2,378)	0.80
Diabetes mellitus	26.2% (364/1,388)	28.4% (770/2,711)	0.14
Current smoking	19.5% (260/1,331)	19.4% (508/2,620)	0.90
Hypertension	71.1% (947/1,333)	69.0% (1,796/2,602)	0.18
Hypercholesterolaemia	63.0% (824/1,308)	62.0% (1,577/2,544)	0.54
Renal impairment	8.9% (124/1,389)	8.9% (242/2,720)	0.98
Previous MI	24.9% (335/1,345)	24.7% (654/2,650)	0.88
Previous PCI	31.3% (429/1,373)	31.2% (838/2,691)	0.93
Previous CABG	4.6% (63/1,361)	4.6% (122/2,681)	0.95
Clinical presentation			
Silent ischaemia	12.6% (175/1,398)	13.0% (354/2,729)	0.71
Stable angina	40.3% (563/1,398)	39.8% (1,085/2,729)	0.75
Unstable angina	13.4% (187/1,398)	12.1% (330/2,729)	0.24
NSTEMI	22.4% (308/1,398)	23.3% (636/2,729)	0.36
STEMI	11.8% (165/1,398)	11.8% (321/2,729)	0.99
Vessel treated			
RCA	15.1% (211/1,398)	17.4% (474/2,729)	0.06
Left main	14.3% (200/1,398)	14.3% (391/2,729)	0.14
LAD	69.4% (970/1,398)	69.4% (1,893/2,729)	0.99
LCX	27.5% (385/1,398)	30.4% (830/2,729)	0.05
Graft (arterial or venous)	0.06% (1/1,398)	0.3% (8/2,729)	0.14
Lesion characteristics			
No. of lesions identified, per patient	2.1±1.15 (1,398)	2.1±1.1 (2,729)	0.99
No. of lesions treated, per patient	1.4±0.7 (1,398)	1.5±0.8 (2,729)	0.04
Long lesions	45.1% (631/1,398)	45.1% (1,232/2,729)	0.99
True bifurcation	56.6% (791/1,398)	54.9% (1,499/2,729)	0.31
Two-stent technique	26.1% (365/1,398)	24.0% (656/2,729)	0.14
KBT	41.6% (581/1,398)	41.6% (1,135/2,729)	0.99
Procedure characteristics			
No. of study stents implanted per patient	1.9±1.0 (1,398)	2.0±1.1 (2,729)	0.04
Length of implanted study stents per patient, mm	37.3±22.8 (1,397)	37.3±23.0 (2,728)	0.99

Data are mean±standard deviation for continuous variables or % (n) for categorical variables. The number of patients with available data is indicated in brackets.

Renal impairment: defined as estimated glomerular filtration rate <60 ml/min/1.73 m². Lesion characteristics at index procedure are reported.
CABG: coronary artery bypass graft; KBT: kissing balloon technique; LAD: left anterior descending artery; LCX: left circumflex; MI: myocardial infarction; (N)STEMI: (non-) ST-elevation myocardial infarction; PCI: percutaneous coronary intervention; POT: proximal optimisation technique; RCA: right coronary artery

Supplementary Table 4. Baseline patient characteristics according to use of KBT - inverse propensity score weighted.

	KBT n=1,517	No KBT n=2,663	*p*-value
Patient characteristics			
Age, years	65.5±10.9 (1,517)	65.5±11.1 (2,663)	0.99
Gender, male	76.5% (1,160/1,517)	76.5% (2,037/2,663)	0.99
Body mass index, kg/m²	27.4±4.5 (1,297)	27.9±4.56 (2,371)	<0.001
Diabetes mellitus	28.0% (423/1,513)	28.2% (745/2,643)	0.89
Current smoking	19.6% (283/1,445)	19.7% (496/2,522)	0.93
Hypertension	70.2% (1,019/1,452)	67.9% (1,729/2,546)	0.13
Hypercholesterolaemia	63.4% (897/1,414)	61.6% (1,535/2,494)	0.25
Renal impairment	8.7% (131/1,506)	8.7% (230/2,650)	0.98
Previous MI	24.0% (353/1,468)	23.9% (619/2,592)	0.92
Previous PCI	30.5% (456/1,494)	30.5% (800/2,626)	0.98
Previous CABG	4.3% (64/1,483)	4.3% (112/2,620)	0.97
Clinical presentation			
Silent ischaemia	13.5% (205/1,517)	12.2% (325/2,663)	0.21
Stable angina	39.4% (598/1,517)	40.7% (1,084/2,663)	0.41
Unstable angina	13.0% (198/1,517)	11.9% (316/2,663)	0.28
NSTEMI	21.9% (332/1,517)	23.1% (614/2,663)	0.40
STEMI	12.1% (183/1,517)	12.1% (322/2,663)	0.99
Vessel treated			
RCA	14.6% (221/1,517)	17.9% (475/2,663)	0.006
Left main	13.6% (206/1,517)	13.6% (362/2,663)	0.99
LAD	69.6% (1,056/1,517)	69.6% (1,854/2,663)	0.99
LCX	29.4% (446/1,517)	31.6% (841/2,663)	0.14
Graft (arterial or venous)	0.05% (1/1,517)	0.3% (8/2,663)	0.08
Lesion characteristics			
No. of lesions identified, per patient	2.1±1.1 (1,517)	2.1±1.1 (2,663)	0.99
No. of lesions treated, per patient	1.5±0.8 (1,517)	1.5±0.8 (2,663)	0.39
Long lesions	43.6% (661/1,517)	43.6% (1,160/2,663)	0.99
True bifurcation	61.2% (929/1,517)	53.2% (1,418/2,663)	<0.001
Two-stent technique	27.5% (417/1,517)	20.9% (557/2,663)	<0.001
POT	37.7% (572/1,517)	37.7% (1,004/2,663)	0.99
Procedure characteristics			
No. of study stents implanted per patient	1.9±1.1 (1,517)	1.9±1.1 (2,663)	0.82
Length of implanted study stents per patient, mm	36.6±22.4 (1,515)	36.6±23.4 (2,663)	0.99

Data are mean±standard deviation for continuous variables or % (n) for categorical variables. The number of patients with available data is indicated in brackets.

Renal impairment: defined as estimated glomerular filtration rate <60 ml/min/1.73 m². Lesion characteristics at index procedure are reported.

CABG: coronary artery bypass graft; KBT: kissing balloon technique; LAD: left anterior descending artery; LCX: left circumflex; MI: myocardial infarction; (N)STEMI: (non-) ST-elevation myocardial infarction; PCI: percutaneous coronary intervention; POT: proximal optimisation technique; RCA: right coronary artery

Supplementary Table 5. Multivariate logistic regression of one-year TLF.

	Odds ratio	95% confidence interval	*p*-value
Use of POT	0.65	0.43 to 0.99	0.046
Use of KBT	0.96	0.68 to 1.36	0.81
Use of POT and KBT (interaction effect)	1.11	0.59 to 2.07	0.76
Age	1.02	1.17 to 2.07	0.003
Current smoker	1.42	0.99 to 2.21	0.053
Renal impairment	1.77	1.02 to 2.12	0.038
Previous PCI	1.56	1.23 to 2.56	0.002
History of MI	1.48	1.07 to 2.29	0.021
Number of lesions identified	1.25	1.006 to 1.03	0.005
Left main treated	1.47	0.99 to 2.02	0.055
Imaging	1.57	0.98 to 2.29	0.064

Supplementary Table 6. One-year clinical outcomes according to use of POT and KBT - inverse propensity score weighted.

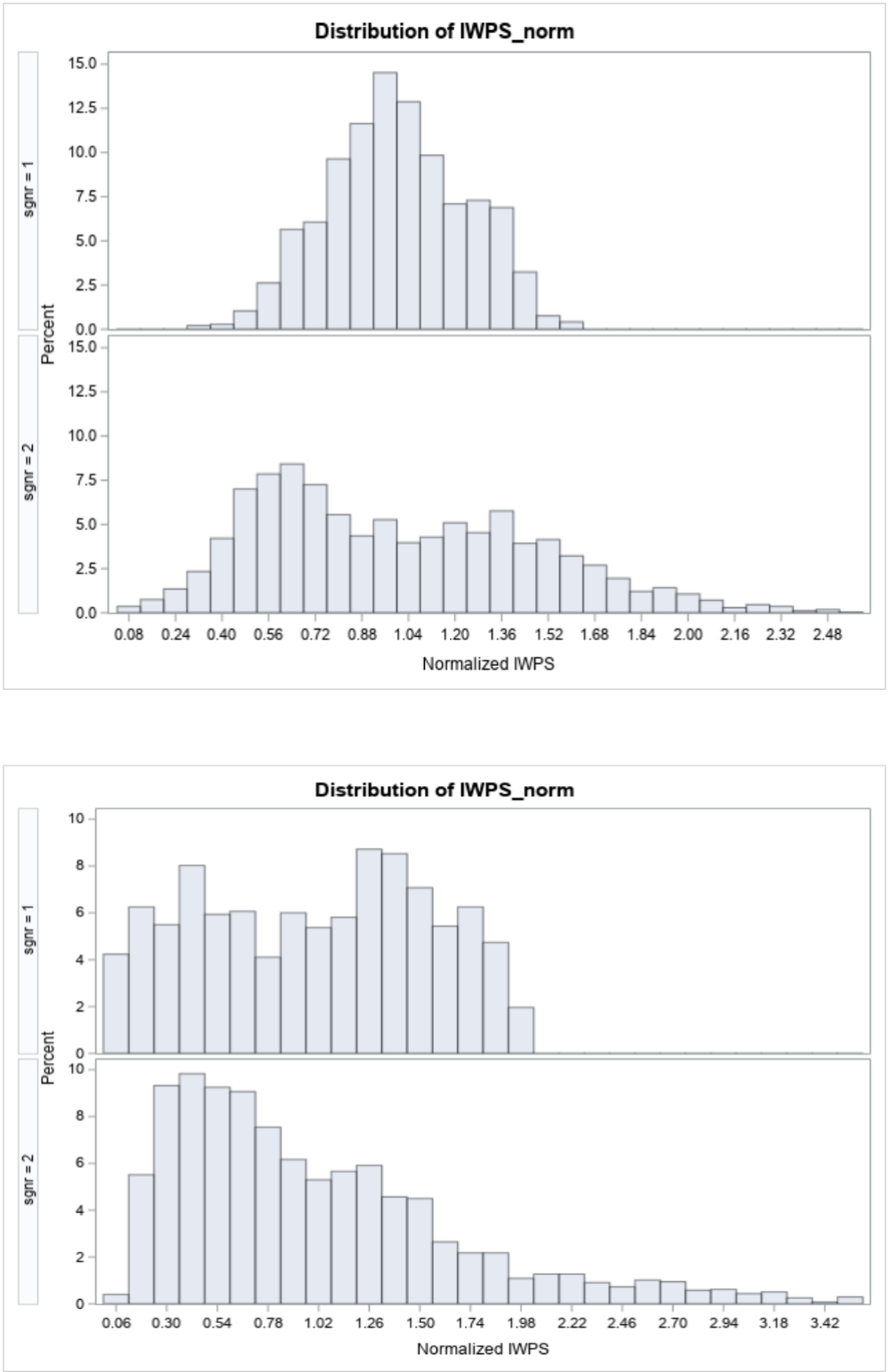
	POT and KBT n=627	POT and no KBT n=762	No POT and KBT n=864	No POT and no KBT n=1,848	*p*-value
Primary outcome					
Target lesion failure	3.6%(22/627)	3.8%(29/762)	5.0%(43/864)	5.7%(105/1,848)	0.09
Cardiac death	2.3%(14/627)	1.6%(12/762)	1.7%(15/864)	2.2% (41/1,848)	0.60
Target vessel MI	0.2%(1/627)	0.9%(7/762)	1.6%(14/864)	2.5%(47/1,848)	<0.001
Clinically driven TLR	1.3%(8/627)	1.6%(13/762)	2.7%(23/864)	3.4%(64/1,848)	0.007
Secondary outcomes					
All-cause death	3.5%(22/627)	2.2%(17/762)	2.7%(23/864)	3.8%(71/1,848)	0.13
All MI	0.4%(3/627)	1.0%(7/762)	2.2%(19/864)	2.89% (53/1,848)	<0.001
Revascularisations					
TVR	2.7%(17/627)	3.4%(26/762)	3.8%(33/864)	4.6%(85/1,848)	0.14
TV non-TLR	1.6%(10/627)	1.8%(14/762)	1.1%(9/864)	1.3%(25/1,848)	0.56
TLR	1.3%(8/627)	1.6%(13/762)	2.8%(24/864)	3.6%(66/1,848)	0.004
Clinically driven revascularisations					
TVR	2.7%(17/627)	3.4%(26/762)	3.7%(32/864)	4.5%(83/1,848)	0.19
TV non-TLR	1.6%(10/627)	1.8%(14/762)	1.1%(9/864)	1.3%(24/1,848)	0.53
Target vessel failure	5.0%(31/627)	5.6%(42/762)	5.8%(50/864)	6.5%(121/1,848)	0.50
Stent thrombosis					
Definite	0.3%(2/627)	0.0%(0/762)	0.8%(7/864)	1.0%(18/1,848)	0.03
Probable	0.0%(0/627)	0.0%(0/762)	0.4%(3/864)	0.4%(6/1,848)	0.16
Definite/probable	0.3%(2/627)	0.0%(0/762)	1.2%(10/864)	1.3%(25/1,848)	0.004
Possible	0.8%(5/627)	0.7%(5/762)	0.9%(8/864)	0.8%(14/1,848)	0.95
All bleedings	3.10% (19/627)	2.88% (22/762)	2.1%(18/864)	2.1% (39/1,848)	0.35
Bleeding BARC type 1 to 2	1.8%(11/627)	2.4%(18/762)	1.6%(14/864)	1.1%(20/1,848)	0.09

	POT and KBT n=627	POT and no KBT n=762	No POT and KBT n=864	No POT and no KBT n=1,848	*p*-value
Bleeding BARC type 3 to 5	1.4% (9/627)	0.2% (2/762)	0.5% (4/864)	1.2% (23/1,848)	0.03

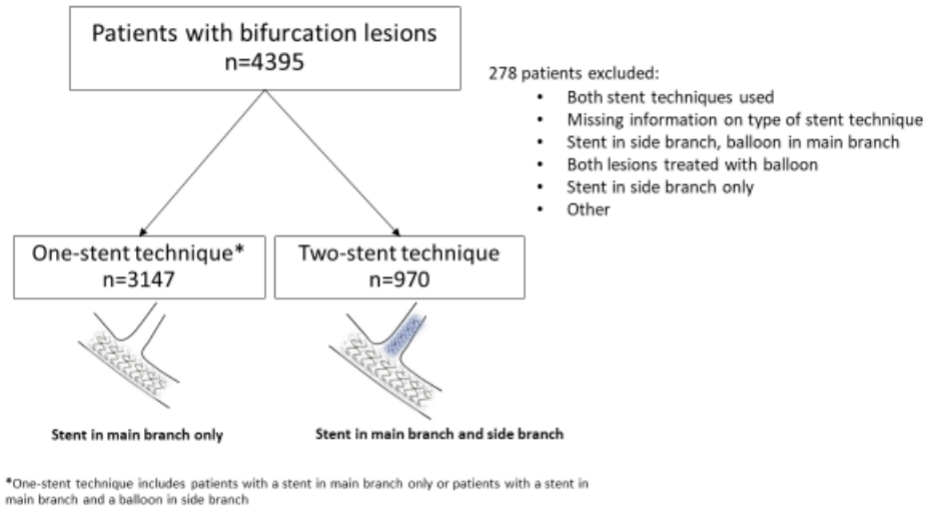
Events are reported as % (n) in the patient population that reached 1-year follow-up, died during follow-up or who had event that contributed to the primary endpoint (n=4,230 patients with at least 1 bifurcation lesion). Out of 4230 patients 129 patients were excluded from this comparison because of lack of information on POT or KBT.

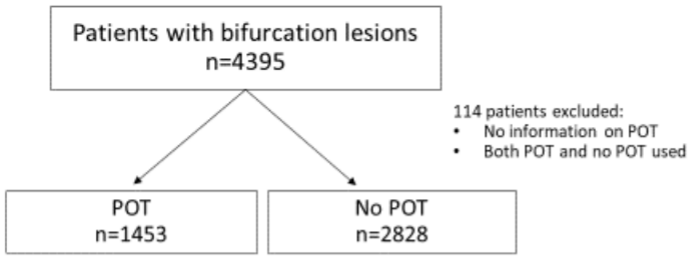
Target lesion failure: composite of cardiac death, TVMI or clinically driven TLR. Target vessel failure: composite of cardiac death, TVMI or clinically driven TVR.

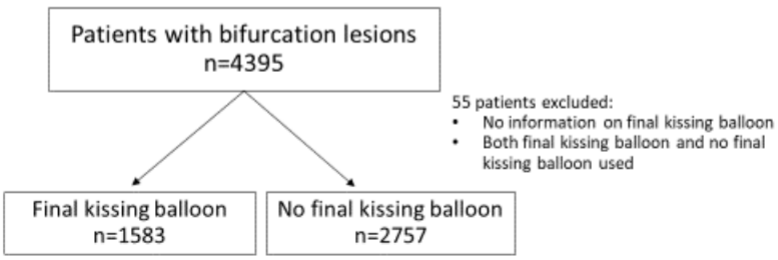
BARC: Bleeding Academic Research Consortium; MI: myocardial infarction; TLR: target lesion revascularisation; TV non-TLR: target vessel, non-target lesion revascularisation; TVR: target vessel revascularisation



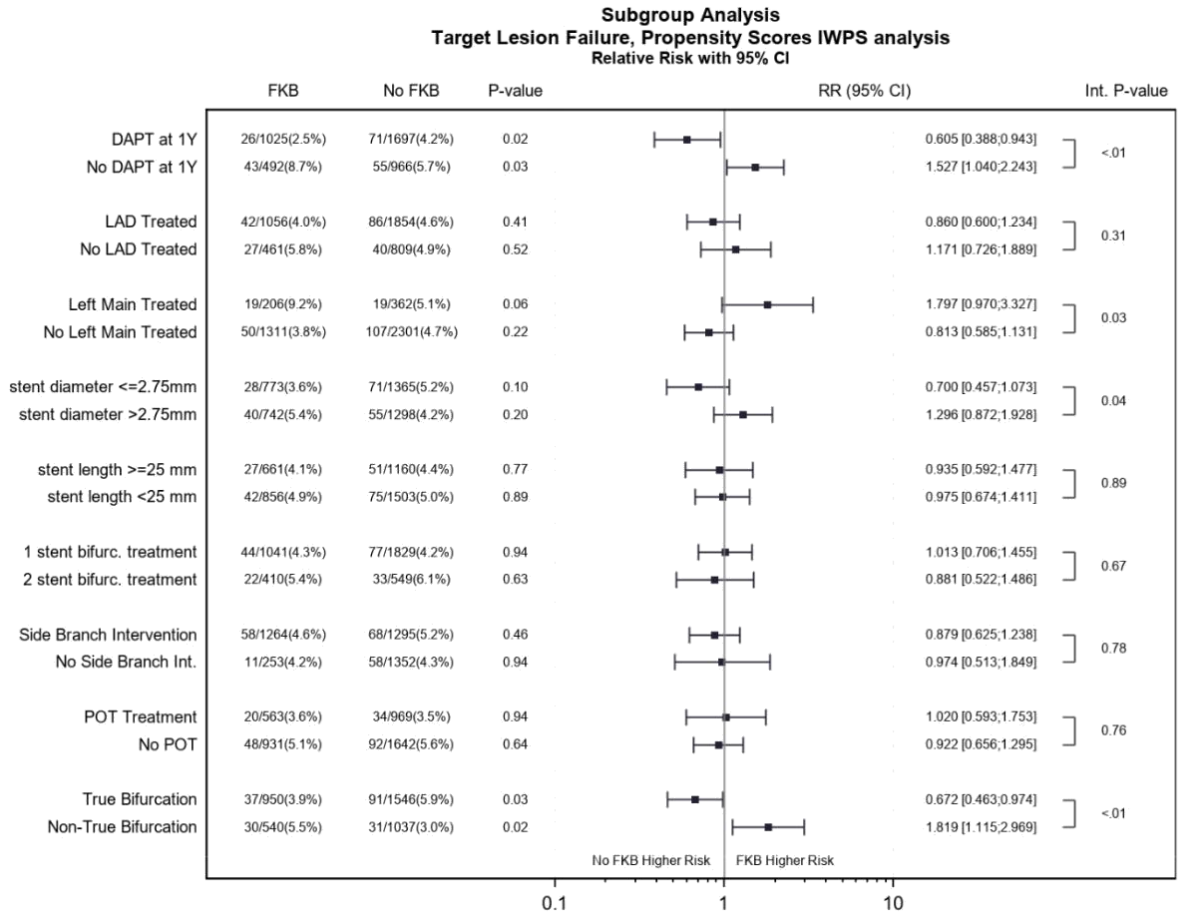
Supplementary Figure 1. Distribution of the inverse weights for POT versus no POT (top) and KBT versus no KBT (bottom).







Supplementary Figure 2. Overview of bifurcation subgroups.



Supplementary Figure 3. Impact of KBT in major angiographic and procedural subgroups.