

Culotte stenting for coronary bifurcation lesions with 2nd and 3rd generation everolimus-eluting stents: the CELTIC Bifurcation Study



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KEYWORDS

- bifurcation
- drug-eluting stent
- radial

Abstract

Aims: The aim of this study was to provide contemporary outcome data for patients with *de novo* coronary disease and Medina 1,1,1 lesions who were treated with a culotte two-stent technique, and to compare the performance of two modern-generation drug-eluting stent (DES) platforms, the 3-connector XIENCE and the 2-connector SYNERGY.

Methods and results: Patients with Medina 1,1,1 bifurcation lesions who had disease that was amenable to culotte stenting were randomised 1:1 to treatment with XIENCE or SYNERGY DES. A total of 170 patients were included. Technical success and final kissing balloon inflation occurred in >96% of cases. Major adverse cardiovascular or cerebrovascular events (MACCE: a composite of death, myocardial infarction [MI], cerebrovascular accident [CVA] and target vessel revascularisation [TVR]) occurred in 5.9% of patients by nine months. The primary endpoint was a composite of death, MI, CVA, target vessel failure (TVF), stent thrombosis and binary angiographic restenosis. At nine months, the primary endpoint occurred in 19% of XIENCE patients and 16% of SYNERGY patients ($p=0.003$ for non-inferiority for platform performance).

Conclusions: MACCE rates for culotte stenting using contemporary everolimus-eluting DES are low at nine months. The XIENCE and SYNERGY stents demonstrated comparable performance for the primary endpoint.

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Abbreviations

BBK	Bifurcations Bad Krozingen
CERC	European Cardiovascular Research Center
CVA	cerebrovascular accident
DES	drug-eluting stent
DK	double kissing
EBC	European Bifurcation Club
IVUS	intravascular ultrasound
LMS	left main stem
MACE	major adverse cardiovascular events
MACCE	major adverse cardiovascular or cerebrovascular events
MI	myocardial infarction
OCT	optical coherence tomography
PCI	percutaneous coronary intervention
POT	proximal optimisation technique
TAP	T-and-protrusion
TVF	target vessel failure
TVI	target vessel inadequacy
TVR	target vessel revascularisation

Introduction

Percutaneous coronary intervention (PCI) for bifurcation lesions is still viewed as a complex procedure. Bifurcations show substantial variation in their anatomical presentation, either by Medina classification¹, by angulation from the main vessel to the daughter branches or by discrepancy in the diameter of the parent and daughter branches. Historically, randomised controlled trials have tended to favour a less complex strategy to treat these lesions²⁻⁵. Lower rates of major adverse cardiovascular events (MACE) were reported with a provisional (preferred single-stent) strategy at the bifurcation. Whilst this concept may be attractive for a number of bifurcation lesions, many Medina 1,1,1 lesions create a significant burden of ischaemia in both branches and an initial provisional approach is not always appropriate for the patient. Under these circumstances, up-front two-stent strategies may be necessary for complete and durable resolution of ischaemia. Numerous different two-stent strategies are described⁶, with the strategic approach best dictated by the specific anatomy that is encountered during the case, whether this is a bail-out manoeuvre after a provisional approach, or as an up-front strategy where clinically indicated.

Culotte stenting has been evaluated against other techniques in randomised trials⁷⁻¹¹. Results have been mixed, with some favourable outcomes compared to crush or T-and-protrusion (TAP)^{7,9,10} and some unfavourable compared with double kissing (DK) crush in the left main⁸. The European Bifurcation Club (EBC) 2 study found improved outcomes with a provisional approach versus culotte, although in a variety of Medina classified lesions with $\geq 50\%$ stenosis¹¹. Furthermore, none of these trials exclusively evaluated contemporary everolimus-eluting stents that have the broadest evidence base for both use and outcomes. One aim of the current study was to assess outcomes for patients who were exclusively treated with these devices.

There are also a number of mechanical features of modern DES platforms that have the potential to influence mechanical and ultimately patient outcomes in bifurcation lesions. These include the overexpansion capability that dictates the ability to appose the device in a larger proximal main vessel. The number of connectors through the body of the stent affects the stiffness of the device, bending moments and fracture risk. These are important considerations at areas of significant vasomotion or hinge potential, including at a bifurcation. Finally, the number of connectors and their construction also influence guidewire access as well as the maximum area that can be achieved at the ostium of the side branch. Therefore, a second aim of the study was to explore whether the type of stent used during culotte stenting would potentially influence the procedural or clinical outcome.

Methods

This was an investigator-led, prospective, randomised, multicentre trial that was undertaken in nine centres in Ireland and the United Kingdom. The trial was administered and overseen by a clinical research organisation (European Cardiovascular Research Center [CERC]) and the data were overseen, assessed, and adjudicated by a clinical events committee, angiographic core laboratory (CERC core laboratory using CASS QCA V7.3 software by Pie Medical Imaging BV, Maastricht, the Netherlands) and data and safety monitoring board. The study protocol was approved by the relevant authorities in each country/centre and there was compliance with the Declaration of Helsinki. All patients provided written, informed consent prior to trial participation. The research was funded by an unrestricted educational grant from Boston Scientific. The trial was registered on clinicaltrials.gov (NCT02232815). Procedural technique as well as inclusion and exclusion criteria are shown in **Supplementary Appendix 1**.

STUDY ENDPOINTS

The primary endpoint of the study was a composite of death, myocardial infarction (MI), cerebrovascular accident (CVA), target vessel failure (TVF), stent thrombosis (definite or probable) and binary angiographic restenosis assessed at nine months. Secondary endpoints included predefined procedural parameters. These included technical success (deployment of stents in both branches with $<20\%$ residual stenosis and kissing balloon inflation at end of procedure), assessment of the equipment used and evidence of longitudinal stent deformation (index implant) or stent fracture at angiographic follow-up. Patients will be followed for 24 months for adverse events.

Major adverse cardiovascular or cerebrovascular events (MACCE) were defined as a composite of death, MI, CVA and target vessel revascularisation (TVR).

Death was considered cardiac unless there was another clear cause. MI was defined according to the third universal definition of MI¹². TVR was defined by any balloon being inflated within the target vessel, or if any new stent was implanted, or if the vessel was treated with a bypass graft. Target vessel inadequacy (TVI)

was defined as complete or sub-total occlusion (<TIMI 3 flow) in the stented vessel at follow-up angiography. TVF was a combination of TVR and TVI. Binary in-stent restenosis was defined as the presence of an angiographic lesion of $\geq 50\%$ of the previously stented segment at nine-month follow-up by core lab assessment.

STATISTICAL ANALYSIS

A primary endpoint rate of 10% was anticipated on the basis of historical trial results^{2,4,13}. This investigation was a pilot study for the comparison of the two study stents, with the potential for a larger subsequent trial based on the results. As such, a perfunctory power calculation was performed. It was calculated that 85 patients per group were required (with α of 5% and $1-\beta$ of 90%) to assess a one-sided non-inferiority limit of 15% for SYNERGY. A more detailed description of statistical methods is available (**Supplementary Appendix 2**).

Results

One hundred and seventy patients were consented for and randomised in the study. The patient flow is outlined in **Figure 1**. A small number did not proceed to culotte stenting for a variety of reasons (presence of previously undiagnosed significant left main disease, presence of stents in both target vessels not apparent on diagnostic angiography, occlusion of the target vessel subsequent to diagnostic angiography, a side branch diameter <2.5 mm at PCI and physiology-based deferment of a two-stent strategy). Patient characteristics are provided in **Supplementary Table 1** and procedural characteristics are described in **Supplementary Table 2**. Patients were allowed to have a non-study vessel treated at the time of the index PCI. In total, 11 patients (six XIENCE [Abbott

Vascular, Santa Clara, CA, USA], five SYNERGY™ [Boston Scientific, Marlborough, MA, USA]) had 12 non-study lesions treated (six XIENCE, six SYNERGY).

Both groups were well matched at inclusion. There was good adherence to the protocol with POT and final kissing inflation rates exceeding 90%. As one might expect with patients who had coronary disease that was amenable to culotte stenting, the diameter of the side branch stent matched the main vessel stent. Procedure-related parameters are presented in **Supplementary Table 3**. These demonstrated very similar results in both groups, inferring that there was little difference in procedural performance between a thin-strut 2-connector and 3-connector DES.

Follow-up rates were high at 98% for clinical follow-up and 84% for angiographic follow-up for the entire study cohort. A Kaplan-Meier curve for MACCE (death, MI, CVA or TVR) is shown for the intention-to-treat population in **Figure 2**. The overall MACCE rate was low for all patients, occurring in 5.9% by nine months. Numerically, more MACCE events occurred in the SYNERGY group (**Figure 2, Table 1**) although this was not statistically significantly different. Detailed analysis of the MACCE events revealed that a number of these were specific neither to the culotte technique, nor to stent type. These included an atheromatous embolic CVA periprocedurally that led to in-patient (non-cardiac) mortality, a traumatic subdural haematoma that also led to a later (non-cardiac) mortality, a CVA one week post procedure and a perforation during post-dilation with a non-compliant balloon that led to in-patient coronary artery bypass grafting.

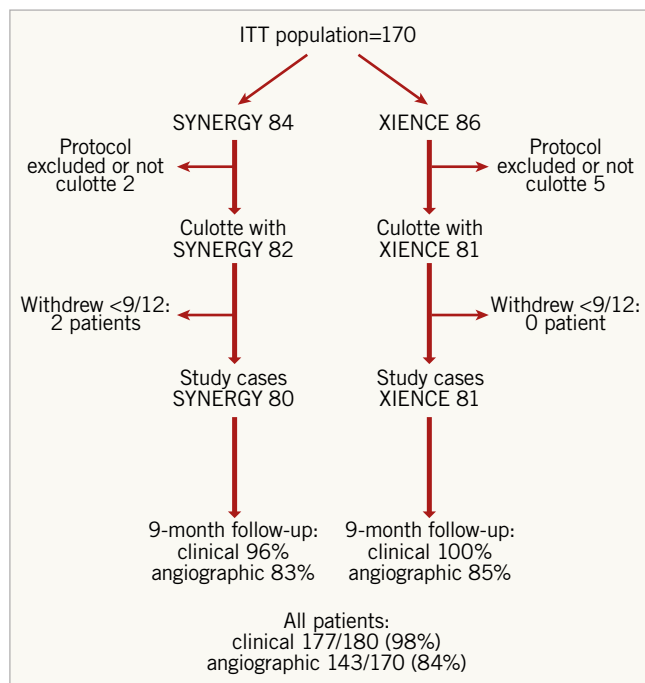


Figure 1. Patient flow through the study. ITT: intention-to-treat

Table 1. Primary endpoint and components at nine months.

Variable	Statistic	SYNERGY II	XIENCE	p-value	95% CI
Composite of death, MI, CVA, TVF, ST and restenosis*	%	16.3%	18.6%	0.003	(NC;12.7)
Target vessel failure (TVF)	n (%)	1 (1.4)	0	0.472	(-14.8;17.4)
Death	n (%)	3 (3.7)	1 (1.4)	0.404	(-14.0;18.7)
Cardiac	n (%)	2 (2.4)	0	0.252	(-13.6;18.3)
MI	n (%)	4 (4.9)	1 (1.2)	0.201	(-12.3;19.7)
Type 1	n (%)	2 (2.4)	0	0.244	(-13.3;18.0)
Type 2	n (%)	1 (1.2)	0	0.489	(-14.4;16.8)
Type 4a	n (%)	1 (1.3)	1 (1.2)	0.969	(-15.8;16.1)
Q-wave	n (%)	2 (2.5)	0	0.237	(-13.5;18.4)
CVA	n (%)	1 (1.3)	1 (1.2)	0.973	(-16.0;16.2)
ST	n (%)	0	1 (1.2)	0.995	(-17.0;14.9)
Late	n (%)	0	1 (1.2)	0.995	(-17.0;14.9)
Definite	n (%)	0	1 (1.2)	0.995	(-17.0;14.9)
Binary angiographic stenosis	n (%)	5 (7.7%)	10 (13.9%)	0.316	(-25.0;13.5)

*One-sided non-inferiority test with margin of 15% and one-sided confidence interval (CI). All other tests are two-sided exact tests with a two-sided exact CI. Numbers are observed, percentages, differences and CIs come from a multiple imputation analysis with 100 imputations. CVA: cerebrovascular accident; MI: myocardial infarction; NC: not calculated; ST: stent thrombosis

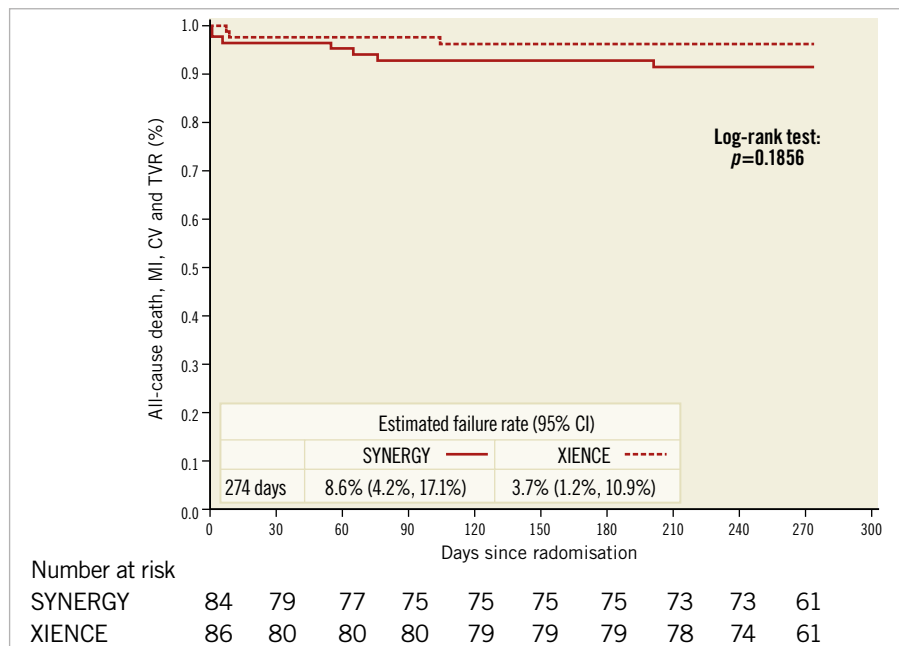


Figure 2. Kaplan-Meier curve for MACCE for the intention-to-treat population.

The primary endpoint and its components are presented in **Table 1**. The non-inferiority test for device performance was met (16.3% vs. 18.6% for SYNERGY vs. XIENCE, $p=0.003$). The components were similar for both groups, although the XIENCE had an in-stent restenosis (ISR) rate almost double that of the SYNERGY stent. This did not achieve statistical significance. For both devices, this occurred almost exclusively in the distal segments, was moderate, was not associated with geographical miss and did not require repeat PCI.

Discussion

There has been considerable evolution in the practice of PCI over the last decade. Many of these changes in practice are reflected in the CELTIC Bifurcation Study. In contrast to the reports of Ferenc⁹, Zheng¹⁰ and Hildick-Smith¹¹, our patients had exclusively Medina 1,1,1 lesions. This higher disease burden led to longer stent lengths in the side branches relative to previous reports. However, irrespective of the higher lesion complexity and disease burden, our cases were performed almost exclusively with transradial access (96%) compared to <2/3 of patients in other recent contemporary series^{10,11}. A transradial approach is viewed by some clinicians as a step that offers less guide catheter support and potentially hampers complex PCI procedures. Our experience demonstrated very high rates of technical success and final kissing balloon inflation. Furthermore, the recorded procedural parameters including procedure time, fluoroscopy time, radiation and contrast doses are comparable to other recent publications that examine culotte stenting⁹⁻¹¹ and more closely mirror those of the provisional stenting group in the EBC-2 study¹¹. These findings may in part reflect more modern X-ray equipment¹⁴, the specific stents that were used in addition to operator experience.

The MACCE rate of 5.9% at nine months provides reassurance with regard to outcomes with the two-stent culotte technique for more complex disease subsets. These results are difficult to compare to older studies due to different endpoint definitions, especially of MI. For example, MACE was defined as cardiac death, non-procedure-related MI, stent thrombosis, or TVR (PCI or coronary artery bypass surgery) after six months in the Nordic Stent Technique Study⁷. Despite being almost a decade old, low MACE rates were noted in this study for sirolimus-eluting culotte stents at six months (3.7%). However, using the same definition of MI as in the CELTIC Bifurcation Study, this rose to 12.5% if type 4a MI was added to the composite endpoint⁷. The finding of a 16.3% MACE rate at 12 months in the DKCRUSH-III study in left main stem (LMS) bifurcations is surprising in the context of the CELTIC Bifurcation outcomes⁸. The DKCRUSH-III definition of MACE was MI, cardiac death, and/or TVR. Whilst the majority of implanted stents were XIENCE in this trial (almost 2/3), a significant proportion were not everolimus-eluting stents. It is likely that the high adverse event rate was driven by the small final diameters achieved in the LMS and its branches (only 3 mm in the main vessel, with no description of systematic POT). A mean LMS diameter of ~5 mm would be anticipated on the basis of population-derived IVUS data assessing the LMS bifurcation¹⁵. Indeed, the “side branch” stent diameter (i.e., LAD or LCx) in DKCRUSH-III is comparable to those described for diagonal, marginal and distal RCA branches in our study. Whilst speculative, it is possible that a double layer (culotte) of relatively undersized stent in the LMS would lead to worse outcomes than a comparable single layer (the DK crush group) in suboptimal mechanical circumstances.

The CELTIC Bifurcation outcomes also compare favourably to more contemporary studies. The results of the Bifurcations Bad Krozingen (BBK) 2 study, which used a variety of contemporary DES, demonstrated a “target lesion failure” rate (composite of cardiac death, target vessel MI, and target lesion revascularisation) of 6.7% for culotte stenting at 12 months⁹. Presumably, the same definition of MACCE would have led to a higher adverse event rate. The study of Zheng and colleagues used cardiac death, MI, stent thrombosis, and/or TVR as the composite for MACE¹⁰. Culotte stenting showed a MACE rate of 5.3% at 12 months, although it is not clear which stents were used in the study or whether the universal definition of MI was applied. The EBC-2 primary endpoint (composite of all-cause death, MI, and TVR) more closely reflects our definition of MACCE¹¹. The 12-month event rate of 10.3% and adverse procedural parameters compared to our study are more likely to reflect the specific biolimus-eluting stent that was used in this study, given the similarity of the technical approach to the culotte procedure.

The comparison of the different stents in the CELTIC Bifurcation Study was hypothesis-generating. Whilst the power calculation anticipated a primary endpoint event rate of 10%, this was noted to be 18% overall. Therefore, the trial retained 80% power to test the initial hypothesis despite a lower number of patients having angiographic follow-up. Overall, the finding of comparable performance for the primary endpoint was unsurprising (SYNERGY 16% vs. XIENCE 19%, $p=0.003$ for non-inferiority).

In a relatively small population, it is important to understand the MACCE events in context, where a low number of adverse events occurred. Whilst the MACCE rate was numerically different between the two groups, a number of these events were generic complications of PCI procedures and their relevance to the stent platforms should be interpreted cautiously. The binary angiographic restenosis rate was 11% overall. This is higher for culotte stenting than the 6.6% in-segment restenosis at six months reported in the Nordic Stent Technique Study⁷, 6% in BBK 2⁹ and 6% reported by Zheng and colleagues¹⁰ at 12 months. The latter two investigations did not use an angiographic core laboratory that may in part have contributed to the outcome differences.

The finding of differing rates of in-stent restenosis observed between the two platforms in our study is at most hypothesis-generating. The adverse event rate observed in a large all-comer PCI population was similar when 2-connector and 3-connector durable fluoropolymer everolimus-eluting stents were compared in the PLATINUM PLUS study¹⁶. The 12-month results of the EVOLVE II clinical trial would also suggest that there is unlikely to be a major early influence of a durable versus biodegradable polymer with modern everolimus-eluting stent platforms¹⁷, although the rates of two-stent bifurcation treatment in these all-comer studies were likely to be low and are not specifically reported. It is possible that these features may be of some relevance to longer-term outcomes in more complex lesions. Nevertheless, the importance of a moderate angiographic restenosis that does not lead to TVI or repeat intervention is of questionable clinical relevance.

There was a very low stent thrombosis rate at nine months (0.6% overall) in our patients, with one longitudinal stent deformation noted that did not hamper the technical result after intraprocedural correction. The stent fracture rate of 2.1% overall is similar to that described for a larger population of >1,000 patients with less complex lesions who were treated with 3-connector everolimus-eluting stents and had systematic follow-up angiography at six to nine months (2.9% per lesion fracture rate)¹⁸. A similar study of 2-connector everolimus-eluting stents in >800 patients found a per lesion fracture rate of 1.7%¹⁹. Both registries reported low rates of two-stent bifurcation treatments. This finding would suggest that two-stent culotte bifurcation stenting is not an added risk factor for stent fracture.

Limitations

This study did not directly compare culotte stenting to a provisional approach for the patients who were enrolled in the trial. Therefore, implications regarding the results when compared to a provisional approach should be interpreted with caution. The procedures were carried out by high-volume PCI operators with extensive experience of bifurcation stenting; similar results may not be achieved by less experienced operators who are not familiar with this technique.

Conclusions

The CELTIC Bifurcation Study confirms that a transradial approach for a two-stent culotte bifurcation strategy is associated with high rates of technical success and acceptable procedural parameters. The overall MACCE rate is low at nine months and provides reassurance that patients with true bifurcation disease can be safely treated with this two-stent technique. The XIENCE and SYNERGY stents were comparable in performance for the primary endpoint. Contrary to prior conclusions and current dogma that a “provisional approach” is preferable for bifurcation lesions, this randomised multicentre study demonstrates that culotte stenting with either device is safe and effective and may also be considered as the primary strategy in appropriately selected, symptomatic Medina 1,1,1 lesions with large side branches.

Impact on daily practice

This study demonstrates that culotte stenting can be performed safely and efficiently from a transradial approach. Cardiologists can be reassured that, if two-stent techniques are indicated for either bail-out after a provisional approach or as an up-front technique, outcomes are favourable when modern everolimus-eluting stents are used with culotte stenting. The SYNERGY and XIENCE stents both perform well under these circumstances.

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Conflict of interest statement

S. Walsh is a consultant to and has received research funding from Abbott Vascular and Boston Scientific. C. Hanratty is a consultant to Abbott Vascular and Boston Scientific. J. Spratt is a consultant to Abbott Vascular and Boston Scientific. M-C. Morice is the CEO of the clinical research organisation that conducted the trial. The other authors have no conflicts of interest to declare.

References

1. Medina A, Suarez de Lezo J, Pan M. [A new classification of coronary bifurcation lesions]. *Rev Esp Cardiol*. 2006;59:183.
2. Steigen TK, Maeng M, Wiseth R, Erglis A, Kumsars I, Narbutė I, Gunnes P, Mannsverk J, Meyerdierks O, Rotevatn S, Niemelä M, Kervinen K, Jensen JS, Galløe A, Nikus K, Vikman S, Ravkilde J, James S, Aarøe J, Ylitalo A, Helqvist S, Sjögren I, Thayssen P, Virtanen K, Puhakka M, Airaksinen J, Lassen JF, Thuesen L; Nordic PCI Study Group. Randomized study on simple versus complex stenting of coronary artery bifurcation lesions: the Nordic bifurcation study. *Circulation*. 2006;114:1955-61.
3. Colombo A, Bramucci E, Saccà S, Violini R, Lettieri C, Zanini R, Sheiban I, Paloscia L, Grube E, Schofer J, Bolognese L, Orlandi M, Niccoli G, Latib A, Airolidi F. Randomized study of the crush technique versus provisional side-branch stenting in true coronary bifurcations: the CACTUS (Coronary Bifurcations: Application of the Crushing Technique Using Sirolimus-Eluting Stents) Study. *Circulation*. 2009;119:71-8.
4. Hildick-Smith D, de Belder AJ, Cooter N, Curzen NP, Clayton TC, Oldroyd KG, Bennett L, Holmberg S, Cotton JM, Glennon PE, Thomas MR, McCarthy PA, Baumbach A, Mulvihill NT, Henderson RA, Redwood SR, Starkey IR, Stables RH. Randomized trial of simple versus complex drug-eluting stenting for bifurcation lesions: the British Bifurcation Coronary Study: old, new, and evolving strategies. *Circulation*. 2010;121:1235-43.
5. 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, Mäkilallio 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.
6. Lassen JF, Burzotta F, Banning AP, Lefèvre T, Darremont O, Hildick-Smith D, Chieffo A, Pan M, Holm NR, Louvard Y, Stankovic G. Percutaneous coronary intervention for the left main stem and other bifurcation lesions: 12th consensus document from the European Bifurcation Club. *EuroIntervention*. 2018;13:1540-53.
7. Erglis A, Kumsars I, Niemelä M, Kervinen K, Maeng M, Lassen JF, Gunnes P, Stavnes S, Jensen JS, Galløe A, Narbutė I, Sondore D, Mäkilallio T, Ylitalo K, Christiansen EH, Ravkilde J, Steigen TK, Mannsverk J, Thayssen P, Hansen KN, Syvånne M, Helqvist S, Kjell N, Wiseth R, Aarøe J, Puhakka M, Thuesen L; Nordic PCI Study Group. Randomized comparison of coronary bifurcation stenting with the crush versus the culotte technique using sirolimus eluting stents: the Nordic stent technique study. *Circ Cardiovasc Interv*. 2009;2:27-34.
8. Chen SL, Xu B, Han YL, Sheiban I, Zhang JJ, Ye F, Kwan TW, Paiboon C, Zhou YJ, Lv SZ, Dangas GD, Xu YW, Wen SY, Hong L, Zhang RY, Wang HC, Jiang TM, Wang Y, Chen F, Yuan ZY, Li WM, Leon MB. Comparison of double kissing crush versus Culotte stenting for unprotected distal left main bifurcation lesions: results from a multicenter, randomized, prospective DKCRUSH-III study. *J Am Coll Cardiol*. 2013;61:1482-8.
9. Ferenc M, Gick M, Comberg T, Rothe J, Valina C, Toma A, Löffelhardt N, Hochholzer W, Riede F, Kienzle RP, Achartari A, Neumann FJ. Culotte stenting vs. TAP stenting for treatment of de-novo coronary bifurcation lesions with the need for side-branch stenting: the Bifurcations Bad Krozingen (BBK) II angiographic trial. *Eur Heart J*. 2016;37:3399-405.
10. Zheng XW, Zhao DH, Peng HY, Fan Q, Ma Q, Xu ZY, Fan C, Liu LY, Liu JH. Randomized Comparison of the Crush Versus the Culotte Stenting for Coronary Artery Bifurcation Lesions. *Chin Med J (Engl)*. 2016;129:505-10.
11. Hildick-Smith D, Behan MW, Lassen JF, Chieffo A, Lefèvre T, Stankovic G, Burzotta F, Pan M, Ferenc M, Bennett L, Hovasse T, Spence MJ, Oldroyd K, Brunel P, Carrie D, Baumbach A, Maeng M, Skipper N, Louvard Y. The EBC TWO Study (European Bifurcation Coronary TWO): A Randomized Comparison of Provisional T-Stenting Versus a Systematic 2 Stent Culotte Strategy in Large Caliber True Bifurcations. *Circ Cardiovasc Interv*. 2016 Sep;9(9).
12. Thygesen K, Alpert JS, Jaffe AS, Simoons ML, Chaitman BR, White HD; Joint ESC/ACCF/AHA/WHF Task Force for Universal Definition of Myocardial Infarction; Authors/Task Force Members Chairpersons, Thygesen K, Alpert JS, White HD; Biomarker Subcommittee, Jaffe AS, Katus HA, Apple FS, Lindahl B, Morrow DA; ECG Subcommittee, Chaitman BR, Clemmensen PM, Johanson P, Hod H; Imaging Subcommittee, Underwood R, Bax JJ, Bonow JJ, Pinto F, Gibbons RJ; Classification Subcommittee, Fox KA, Atar D, Newby LK, Galvani M, Hamm CW; Intervention Subcommittee, Uretsky BF, Steg PG, Wijns W, Bassand JP, Menasche P, Ravkilde J; Trials & Registries Subcommittee, Ohman EM, Antman EM, Wallentin LC, Armstrong PW, Simoons ML; Trials & Registries Subcommittee, Januzzi JL, Nieminen MS, Gheorghiade M, Filippatos G; Trials & Registries Subcommittee, Luepker RV, Fortmann SP, Rosamond WD, Levy D, Wood D; Trials & Registries Subcommittee, Smith SC, Hu D, Lopez-Sendon JL, Robertson RM, Weaver D, Tendera M, Bove AA, Parkhomenko AN, Vasilieva EJ, Mendis S; ESC Committee for Practice Guidelines (CPG), Bax JJ, Baumgartner H, Ceconi C, Dean V, Deaton C, Fagard R, Funck-Brentano C, Hasdai D, Hoes A, Kirchhof P, Knuuti J, Kolh P, McDonagh T, Moulin C, Popescu BA, Reiner Z, Sechtem U, Sirnes PA, Tendera M, Torbicki A,

Vahanian A, Windecker S; Document Reviewers, Morais J, Aguiar C, Almahmeed W, Arnar DO, Barili F, Bloch KD, Bolger AF, Botker HE, Bozkurt B, Bugiardini R, Cannon C, de Lemos J, Eberli FR, Escobar E, Hlatky M, James S, Kern KB, Moliterno DJ, Mueller C, Neskovic AN, Pieske BM, Schulman SP, Storey RF, Taubert KA, Vranckx P, Wagner DR. Third universal definition of myocardial infarction. *J Am Coll Cardiol*. 2012;60:1581-98.

13. Behan MW, Holm NR, Curzen NP, Erglis A, Stables RH, de Belder AJ, Niemelä M, Cooter N, Chew DP, Steigen TK, Oldroyd KG, Jensen JS, Lassen JF, Thuesen L, Hildick-Smith D. Simple or complex stenting for bifurcation coronary lesions: a patient-level pooled-analysis of the Nordic Bifurcation Study and the British Bifurcation Coronary Study. *Circ Cardiovasc Interv*. 2011;4:57-64.

14. McNeice AH, Brooks M, Hanratty CG, Stevenson M, Spratt JC, Walsh SJ. A retrospective study of radiation dose measurements comparing different cath lab X-ray systems in a sample population of patients undergoing percutaneous coronary intervention for chronic total occlusions. *Catheter Cardiovasc Interv*. 2018 Feb 7. [Epub ahead of print].

15. Shand JA, Sharma D, Hanratty C, McClelland A, Menown IB, Spence MS, Richardson G, Herity NA, Walsh SJ. A prospective intravascular ultrasound investigation of the necessity for and efficacy of postdilation beyond nominal diameter of 3 current generation DES platforms for the percutaneous treatment of the left main coronary artery. *Catheter Cardiovasc Interv*. 2014;84:351-8.

16. Fajadet J, Neumann FJ, Hildick-Smith D, Petronio S, Zaman A, Spence M, Wöhrle J, Elhadad S, Roberts D, Hovasse T, Valdés M, Silber S. Twelve-month results of a prospective, multi-centre trial to assess the everolimus-eluting coronary stent system (PROMUS Element): the PLATINUM PLUS all-comers randomised trial. *EuroIntervention*. 2017;12:1595-604.

17. Kereiakes DJ, Meredith IT, Windecker S, Lee Jobe R, Mehta SR, Sarembock IJ, Feldman RL, Stein B, Dubois C, Grady T, Saito S, Kimura T, Christen T, Allocco DJ, Dawkins KD. Efficacy and safety of a novel bioabsorbable polymer-coated, everolimus-eluting coronary stent: the EVOLVE II Randomized Trial. *Circ Cardiovasc Interv*. 2015 Apr;8(4).

18. Kuramitsu S, Iwabuchi M, Haraguchi T, Domei T, Nagae A, Hyodo M, Yamaji K, Soga Y, Arita T, Shirai S, Kondo K, Ando K, Sakai K, Goya M, Takabatake Y, Sonoda S, Yokoi H, Toyota F, Nosaka H, Nobuyoshi M. Incidence and clinical impact of stent fracture after everolimus-eluting stent implantation. *Circ Cardiovasc Interv*. 2012;5:663-71.

19. Kuramitsu S, Hiromasa T, Enomoto S, Shinozaki T, Iwabuchi M, Mazaki T, Domei T, Yamaji K, Soga Y, Hyodo M, Shirai S, Ando K. Incidence and Clinical Impact of Stent Fracture After PROMUS Element Platinum Chromium Everolimus-Eluting Stent Implantation. *JACC Cardiovasc Interv*. 2015;8:1180-8.

Supplementary data

Supplementary Appendix 1. Inclusion, exclusion criteria and procedural technique.

Supplementary Appendix 2. Detailed statistical methods.

Supplementary Table 1. Patient characteristics of intention-to-treat population.

Supplementary Table 2. Procedural characteristics of intention-to-treat population.

Supplementary Table 3. Procedural parameters for both treatment groups.

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Supplementary data

Supplementary Appendix 1. Inclusion, exclusion criteria and procedural technique.

Patients ≥ 18 years old were included if they had a clinical indication for a PCI with evidence of a Medina 1,1,1 bifurcation lesion in the target vessel ($>70\%$ stenosis by visual assessment and diameter ≥ 2.5 mm in both branches), where the operator determined that both branches required stenting and that culotte stenting was indicated. Female patients of childbearing potential required a negative pregnancy test before enrolment.

Exclusion criteria were: acute myocardial infarction with ongoing ST-elevation; cardiogenic shock, target lesion in the left main coronary artery or bypass graft; planned treatment of ≥ 2 other coronary vessels at the time of inclusion; total occlusion of any target vessel; left ventricular ejection fraction $<20\%$; requirement for ongoing haemodialysis; life expectancy limited to <12 months due to comorbid condition; allergy to aspirin or clopidogrel and prasugrel and ticagrelor; known allergy to any component of a study stent; ongoing participation in another investigational device or drug study; inability to provide informed consent.

Once the inclusion and exclusion criteria were fulfilled, the patient was randomised (1:1) to treatment with either the XIENCE (Abbott Vascular, Santa Clara, CA, USA) or SYNERGY (Boston Scientific, Marlborough, MA, USA) everolimus-eluting DES using an online platform provided by CERC.

PCI was performed according to standard techniques. Decisions regarding vascular access site and catheter diameter were left to the discretion of the operator. The culotte stenting procedure was performed on dual antiplatelet therapy (aspirin and one of either clopidogrel, prasugrel or ticagrelor) with unfractionated heparin (70 IU/kg). Predilation of both branches was preferred, with stenting of the side branch first, unless there was extreme and unfavourable angulation into the distal main vessel. The proximal optimisation technique (POT) was carried out after each stent was deployed (mandatory) and as a final step with a balloon that was sized 1:1 with the proximal main vessel. Kissing balloon inflation was also mandatory (nominal pressure) after individual inflations at high pressure at the ostium of both branches with 1:1 sized non-compliant balloons. Adjunctive imaging (by either intravascular ultrasound [IVUS] or optical coherence tomography [OCT]) was encouraged but not mandatory. Dual antiplatelet therapy was planned to continue for 12 months after the PCI.

Supplementary Appendix 2. Detailed statistical methods.

All analyses were based on the intention-to-treat principle. Baseline and procedural characteristics were described with numbers and percentages with respect to the number of subjects with non-missing information for discrete variables or mean, standard deviation, mean and quartiles for continuous variables. Comparisons between treatment groups were performed with a chi-square test or Fisher's exact test and t-test, respectively. To deal with missing data, the primary endpoint and its components were analysed using a multiple imputation analysis with 100 imputations. The imputation models contained age, gender and treatment group. The event rate of the primary endpoint was estimated for each treatment group separately. To assess whether SYNERGY is not inferior to XIENCE, the risk difference (SYNERGY - XIENCE) and its associated one-sided 95% confidence interval was presented using a Z-test. Non-inferiority was concluded if the upper limit of this interval was lower than 15%. All other tests were performed two-sided at a significance level of 0.05 without correction for multiple testing. For discrete endpoints, a Fisher's exact test and the difference between the treatment group with an exact 95% confidence interval was given. For the continuous endpoints, a Wilcoxon rank-sum test and the Hodges-Lehman estimator of the location shift between the two groups with a 95% confidence interval was reported. Finally, as a post hoc analysis, the Kaplan-Meier curve of all-cause mortality, MI, CVA and TVR per treatment group and overall was created and compared between treatment groups by a log-rank test. All analyses were performed with SAS version 9.4 (SAS Institute, Cary, NC, USA).

Supplementary Table 1. Patient characteristics of intention-to-treat population.

Variable	Statistic	SYNERGY	XIENCE	p-value
Total number of patients	N	84	86	
Age (years)	Mean (SD)	64 (10.2)	66 (9.3)	0.169
Male	%	81.0	86.1	0.371
BMI (kg/cm ²)	Mean (SD)	29 (6.4)	29 (4.9)	0.861
LVEF (%)	Mean (SD)	53 (8.9)	53 (6.7)	0.951
Medical history				
Cardiac				
Myocardial infarction	%	21.0	31.3	0.132
CABG	%	3.6	3.6	0.988
PCI	%	37.8	44.1	0.414
Non-cardiac				
Peripheral vascular disease	%	7.7	6.3	0.722
Renal insufficiency	%	12.1	6.0	0.168
Stroke	%	3.6	2.4	0.640
Risk factor				
Current smoker	%	19.0	15.9	0.600
Diabetes mellitus	%	22.8	13.4	0.122
Hypercholesterolaemia	%	73.4	75.6	0.750
Hypertension	%	63.3	61.0	0.762
Family history	%	65.8	69.5	0.617
Indication for PCI				
Silent ischaemia	%	1.2	3.6	0.518
Stable angina	%	65.1	60.7	
Unstable angina	%	8.4	10.7	

Variable	Statistic	SYNERGY	XIENCE	p-value
NSTEMI	%	20.5	16.7	
STEMI (stabilised)	%	1.2	0.0	
Other	%	3.6	8.3	
Extent of CAD				
LAD >70%	%	81.9	88.1	0.264
LCx >70%	%	24.1	19.1	0.428
RCA >70%	%	16.9	13.1	0.495

Renal insufficiency: estimated glomerular filtration rate <60 ml/min.

BMI: body mass index; CABG: coronary artery bypass grafts; LVEF: left ventricular ejection fraction; PCI: percutaneous coronary intervention; NSTEMI: non-ST-elevation myocardial infarction; STEMI: ST-elevation myocardial infarction

Supplementary Table 2. Procedural characteristics for intention-to-treat population.

Variable	Statistic	SYNERGY	XIENCE	<i>p</i> -value
Total number of patients	N	84	86	
PCI approach				
Femoral	%	1.2	7.1	0.056
Radial	%	98.8	92.9	
Sheath size				
6 Fr	%	72.3	65.1	0.315
7 Fr	%	27.7	34.9	
Lesion location				
LAD	%	81.9	85.4	0.367
Cx	%	13.3	9.8	
RCA	%	4.8	4.9	
Medina classification				
1, 1, 1	%	100.0	100.0	
Pre procedure				
Proximal main branch reference vessel diameter (visual estimate, mm)	Mean (SD)	3 (0.5)	4 (0.5)	0.067
	Median (Q1-Q3)	4 (3-4)	4 (3-4)	
Proximal main branch stenosis (visual estimate, %)	Mean (SD)	83 (8.5)	84 (8.4)	0.757
Distal main branch reference vessel diameter (visual estimate, mm)	Mean (SD)	3 (0.3)	3 (0.4)	0.170
	Median (Q1-Q3)	3 (3-3)	3 (3-3)	
Distal main branch stenosis (visual estimate, %)	Mean (SD)	84 (9.5)	84 (8.2)	0.969
Side branch reference vessel diameter (visual estimate, mm)	Mean (SD)	2.7 (0.3)	2.8 (0.4)	0.019
	Median (Q1-Q3)	2.5 (2.5-3)	2.8 (2.5-3)	
Side branch stenosis (visual estimate, %)	Mean (SD)	85 (9.0)	84 (8.8)	0.795
Procedure				

Variable	Statistic	SYNERGY	XIENCE	p-value
Number of stents implanted				
2	%	67.1	69.1	0.402
3	%	28.1	29.6	
4	%	4.9	1.2	
1st stent in side branch	%	88.0	85.5	0.647
POT after 1st stent	%	92.8	92.8	1.000
POT after 2nd stent	%	94.0	94.0	1.000
Final kissing inflation	%	98.8	95.2	0.173
IVUS evaluation	%	36.1	28.9	0.320
OCT evaluation	%	8.4	8.4	1.000
Mean stent diameter main branch (mm)	Mean (SD)	3 (0.4)	3 (0.4)	0.155
	Median (Q1-Q3)	3 (3-4)	3 (3-4)	
Mean stent diameter side branch (mm)	Mean (SD)	3 (1.0)	3 (0.5)	0.148
	Median (Q1-Q3)	3 (3-3)	3 (3-3)	
Total stent length main branch (mm)	Mean (SD)	36 (13.4)	38 (13.7)	0.316
Total stent length side branch (mm)	Mean (SD)	26 (10.6)	24 (9.0)	0.155
Maximum pressure in main branch (atm)	Mean (SD)	18 (3.0)	18 (3.6)	0.747
Maximum pressure in side branch (atm)	Mean (SD)	17 (3.3)	17 (3.7)	0.656
Procedure result				
Distal main branch post TIMI flow				
0	%	1.2	1.2	1.000
3	%	98.8	98.8	
Side branch post TIMI flow				
3	%	100.0	100.0	

IVUS: intravascular ultrasound; OCT: optical coherence tomography; POT: proximal optimisation technique; TIMI: Thrombolysis In Myocardial Infarction

Supplementary Table 3. Procedural parameters for both treatment groups.

Variable	Statistic	SYNERGY	XIENCE	p-value	95% CI
Technical success*	%	96.4	96.3	1.000	(-15.3;15.7)
Total procedure time (min)	Mean (SD)	76 (42)	74 (46)	0.706	(-10.0;15.0)
Total radiation dose (cGy.cm ²)	Mean (SD) Median (Q1-Q3)	6601 (6955) 4757 (2342-7441)	6715 (6534) 4983 (3177-7242)	0.424	(-657.9;1718.8)
Total contrast volume (ml)	Mean (SD)	215 (90)	225 (85)	0.314	(-40.0;10.0)
Need of secondary equipment	%	24.1	24.1	1.000	(-15.7;15.7)
Extra support guidewire	%	4.8	8.4	0.535	(-19.2;12.1)
Anchor balloon	%	22.9	20.5	0.851	(-13.3;18.1)
Mother and daughter catheters	%	6.0	4.8	1.000	(-14.5;16.9)
Longitudinal stent compression	%	1.2	0.0	1.000	(-14.5;16.9)
Stent fracture at angiographic follow-up	%	1.5	2.7	1.000	(-17.7;15.3)

*Deployment of stents in both branches with <20% residual stenosis and kissing balloon inflation at end of the procedure.

For the continuous variables: the groups are compared with a Wilcoxon test and the difference shows the Hodges-Lehman estimator.