Clinical Investigation Plan

Randomized comparison of Culotte Technique versus “Double Kissing” – Crush technique (DK-Crush) for the percutaneous treatment of de novo non-left main coronary bifurcation lesions with modern everolimus-eluting stents (EES) –

The BBK 3 Study

Study Type:	Open, multi-center, randomized trial
Study Registration:	NCT04192760
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SIGNATURE PAGES

Study Number NCT04192760

Study Title Randomized comparison of Culotte technique versus “Double Kissing” – Crush technique (DK-Crush) for the percutaneous treatment of de novo non-left main coronary bifurcation lesions with modern everolimus-eluting stents (EES) –multicenter study – The BBK-3 study

Principal Investigator

The Principal Investigator has approved the investigation plan version 4.0 dated 01 Dec 2020 and confirms hereby to conduct the study according to the investigation plan, current version of the World Medical Declaration of Helsinki, ISO 14155 norm and the local legally applicable requirements.

Miroslaw Ferenc

Principal Investigator

_____ _____

Place / Date Signature

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Local Principal Investigator Signature

I have read and fully understand the amended protocol version and agree hereby to conduct the study according to the investigation plan version 4.0 dated 01 Dec 2020, the current version of the World Medical Declaration of Helsinki, ISO 14155 norm and the local legally applicable requirements.

_____	_____	_____
Investigator	Signature	Date

Center name and address:

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STUDY SUMMARY

Background: In percutaneous coronary intervention (PCI) of bifurcation lesions, the need for stenting of both, the main and side branch (double stenting), depends on lesion complexity. With high complexity (Medina classification 1,1,1 or 0,1,1), double stenting may be the treatment of choice. When double stenting is required, there are three major technical approaches: T-stenting (T- and Protrusion = TAP) technique, Culotte-stenting or “double kissing” Crush – technique (DK-Crush). Thus far, there is only limited evidence on the optimal double stenting technique. In the BBK 2 study, Culotte stenting demonstrated benefit over TAP stenting [1]. The DK-Crush 3 study [2] showed superiority for DK-crush technique as compared to Culotte technique, however only patients with distal left main stenosis were treated in this study. Thus, no randomized study directly compared the Culotte with the DK crush technique in non-left main coronary bifurcation lesions.

Aim: This prospective randomized multicenter study will compare the long-term safety and efficacy of Culotte stenting versus DK-Crush stenting in the treatment of the de-novo non-left main coronary bifurcation lesions with new generation everolimus-eluting stents.

Methods: Four-hundred patients, in whom a double-stenting technique is intended for the treatment of a non-left main de-novo coronary bifurcation lesion will be randomly assigned to Culotte stenting or to DK-crush stenting with an approved contemporary everolimus-eluting stent. As a part of usual care, patients will undergo 9-month angiographic follow-up with quantitative coronary angiography. Clinical follow-up is planned at 9-12 months. The primary study endpoint is the maximal percent diameter stenosis in the bifurcation lesion at 9 months. Secondary endpoints include binary restenosis (estimated by Quantitative Coronary Angiography (QCA) analysis), Target Lesion Revascularization (TLR), Freedom from Major Adverse Cardiac Events (MACE) and the rate of stent thrombosis according to the definition of the Academic Research Consortium (ARC definition). The study will have 80% power to detect a 25% decrease in the primary endpoint at $p < 0.05$ by Culotte stenting as compared with DK-Crush.

1. STUDY BACKGROUND

Provisional side branch stenting is the most frequently used type of treatment in coronary bifurcation lesions. When stenting of both the side branch and the main branch (double stenting) is needed - because of complex anatomy, dissection occurring during lesion preparation, TIMI flow < 2 or high residual stenosis > 75% - there is a variety of established technical approaches. The most common double stenting techniques in daily routine are TAP stenting, Culotte stenting and “double kissing “-Crush stenting.

Our recently published BBK 2 - study [1] demonstrated a benefit of the Culotte technique as compared to TAP technique during PCI of de-novo coronary bifurcation lesions, with a significant reduction in in-stent restenosis (primary study endpoint). Moreover, the BBK 2 - study showed a trend to better clinical outcomes after Culotte stenting during the first year of the clinical follow-up (secondary study endpoints). The difference was mainly driven by significant reduction for in-stent restenosis of the side branch stent.

In China, Dr. Chen and his colleagues [2] modified the initially introduced classic crush technique to the “double kissing“-crush technique. The DK-Crush technique is technically more challenging due to more procedural steps. The use of the DK-crush technique was assessed in several randomized trials: comparison with classic crush technique [3], with provisional T-stenting [4] and with Culotte [2] (only for patients treated for distal left main stenosis). The DK-Crush technique was associated with a lower angiographic restenosis rate and as well as with lower reintervention rates during long-term clinical follow-up.

In Europe, the randomized multicenter Nordic II study [7] addressed the question whether classic Crush-stenting or Culotte-stenting achieves better angiographic and clinical outcome after PCI in bifurcation lesions. The results demonstrated no significant difference in respect to the primary study endpoint. Major adverse cardiac events (MACE) as primary study endpoint occurred in 3.7 % in the Culotte study arm as compared to 4.3 % in the Crush study arm ($p = 0.87$).

All previous studies on the DK-Crush technique were performed using first generation drug-eluting stents (DES), which are no longer in use. Currently, no randomized study compared DK-crush with Culotte techniques in patients with non-left main bifurcation lesions using contemporary DES. However, recent data showed that the use of new-generation DES is associated with better clinical outcomes as compared to first-generation DES [5, 6].

2. STUDY DESIGN

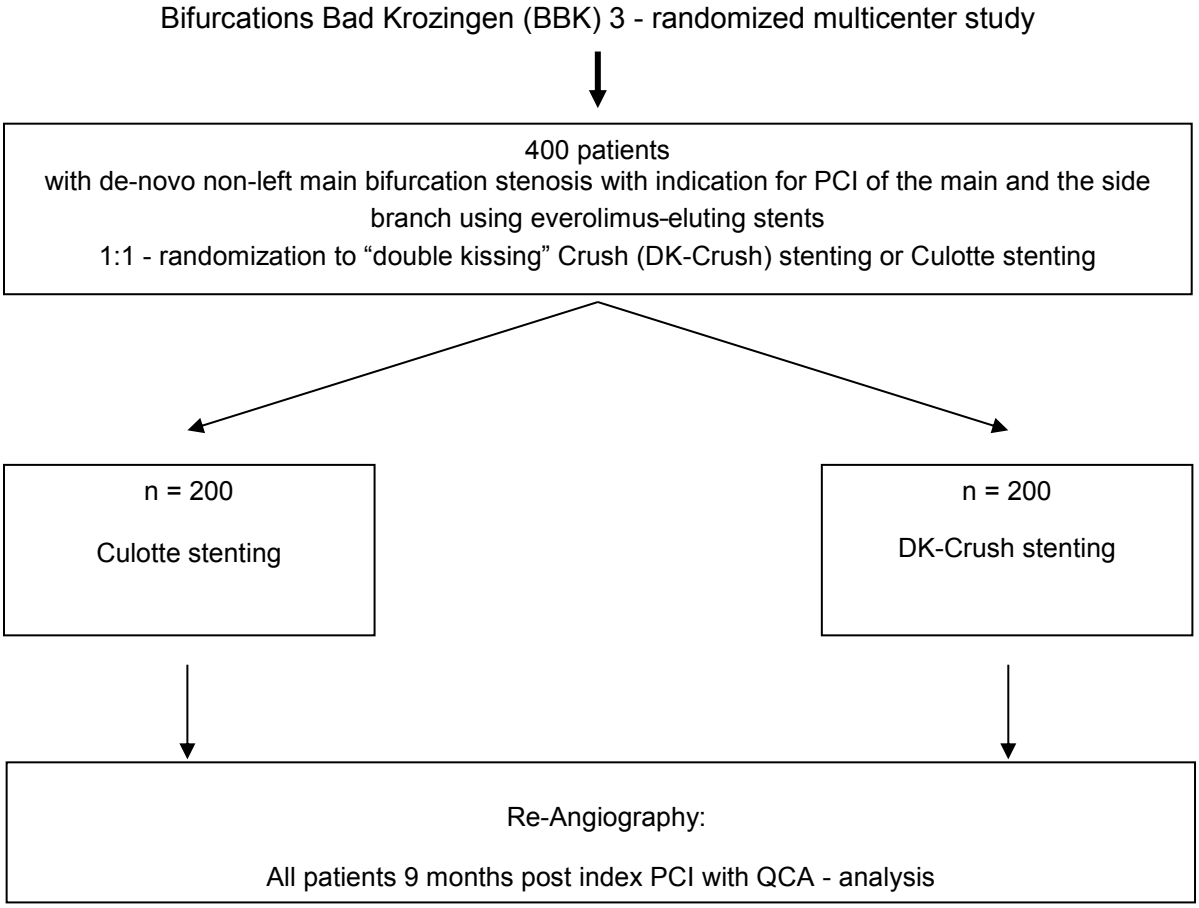
This study is a prospective, randomized, multicenter evaluation of the treatment of de-novo coronary bifurcation lesions comparing DK-crush stenting with Culotte stenting using approved modern third-generation DES.

The primary endpoint of this study is the maximal percent diameter stenosis within the bifurcation at 9 months, assessed by quantitative coronary angiography. In addition, the study will assess various safety parameters.

Four-hundred patients will be enrolled and randomly assigned to DK-crush stenting or to Culotte stenting of non-left main bifurcation lesions. Only CE-certified everolimus-eluting Synergy™ and Synergy Megatron™ stents must be used.

This study is an investigator-initiated trial, designed and conducted by the University Heart Center Freiburg · Bad Krozingen. Partial financial support is obtained by a scientific grant from Boston Scientific (BSI). Data from patients enrolled at participating study sites will be transferred after pseudonymization to a central database at the University Heart Center Freiburg • Bad Krozingen to perform final data analysis and to publish the results of the study.

Trial randomisation scheme:



Primary study endpoint:	Maximal % diameter stenosis in the bifurcation lesion (QCA)
Secondary study endpoints:	Binary restenosis; TLR; MACE/ Death/ MI / Stent-Thrombosis
Clinical Follow-up:	9 - 12 months

Assessment Schedule

Assessment	Screening	PCI	Pre-discharge	9 months ± 30 days	If no Re – Angiography: 12 months ± 30 days
Inclusion/Exclusion criteria	X				
Informed consent signed	X				
Medical History	X				
Angina pectoris and NYHA status	X			X	X
Creatine kinase (CK) and hs-troponin	X		X		
12 lead ECG	X		X		
Medication History	X	X		X	X
Adverse Event Monitoring		X	X	X	X
Index Procedure		X			
Re – Angiography				X	

3. HYPOTHESIS

The hypothesis of this study is as follows:

In non left-main coronary bifurcation lesions (main vessel > 2.5mm, side branch > 2.25mm) including significant ostial side branch disease, Culotte stenting compared with DK-crush stenting reduces maximal percent diameter stenosis at the bifurcation at 9-month follow-up by 25 %.

4. STUDY ENDPOINTS

4.1 Primary study endpoint

The primary study endpoint is:

- Maximal percent diameter stenosis at the bifurcation at 9 months.

4.2 Secondary endpoints

The following secondary endpoints will be evaluated in this study:

- Binary restenosis (≥ 50% diameter stenosis) rate at any segment of the bifurcation at 9 months post procedure

- Binary restenosis (≥ 50% diameter stenosis) in the main and side branch at 9 months post procedure.

- TLR of the main and side branch at 9-12 months post procedure. Intervening target-lesion revascularization is defined as any repeated percutaneous revascularization of the stented segment, including the 5-mm proximal and distal margins.

- MACE defined as death, myocardial infarction (according to the fourth universal definition of myocardial infarction, 2018), emergent cardiac bypass surgery, or TLR at 9-12 months.

- Device success defined as attainment of < 30% residual stenosis of the target lesion using drug-eluting stent (DES) in the main and side branch

- Procedure time, radiation time and volume of used contrast medium

- Post-procedure thrombotic stent occlusion at 9-12 months according to the Academic Research Consortium-criteria: Stent thrombosis is classified by the ARC definition as definite, probable, or possible and as early (0 to 30 days), late (31 to 360 days), or very late (>360 days). The definition of definite stent thrombosis requires the presence of an acute coronary syndrome with angiographic or autopsy evidence of thrombus or occlusion. Probable stent thrombosis includes unexplained deaths within 30 days after the procedure or acute myocardial infarction involving the target-vessel territory without angiographic confirmation. Possible stent thrombosis includes all unexplained deaths occurring at least 30 days after the procedure.

- Disabling stroke defined as stroke requiring inpatient rehabilitation or skilled nursing care.

- Bleeding classified as type 3-5 according to the BARC classification as follows:

Type 0: No bleeding

Type 1: Bleeding that is not actionable and does not cause the patient to seek unscheduled performance of studies, hospitalization, or treatment by a health-care professional; may include episodes leading to self-discontinuation of medical therapy by the patient without consulting a health-care professional.

Type 2: Any overt, actionable sign of hemorrhage (e.g., more bleeding than would be expected for a clinical circumstance, including bleeding found by imaging alone) that does not fit the criteria for type 3, 4, or 5 but does meet at least one of the following criteria: requiring nonsurgical, medical intervention by a health-care professional, leading to hospitalization or increased level of care, or prompting evaluation

Type 3:
Type 3a: Overt bleeding plus hemoglobin drop of 3 to < 5 g/dL* (provided hemoglobin drop is related to bleed), any transfusion with overt bleeding
Type 3b: Overt bleeding plus hemoglobin drop ≥5 g/dL* (provided hemoglobin drop is related to bleed), Cardiac tamponade, Bleeding requiring surgical intervention for control (excluding dental/nasal/skin/hemorrhoid), Bleeding requiring intravenous vasoactive agents
Type 3c: Intracranial hemorrhage (does not include microbleeds or hemorrhagic transformation, does include intraspinal), subcategories confirmed by autopsy or imaging or lumbar puncture, intraocular bleed compromising vision

Type 4:
CABG-related bleeding, perioperative intracranial bleeding within 48 h, reoperation after closure of sternotomy for the purpose of controlling bleeding, transfusion of ≥ 5 U whole blood or packed red blood cells within a 48-h period, chest tube output more than or equal to 2L within a 24-h period

Type 5:
Fatal bleeding
Type 5a:
Probable fatal bleeding; no autopsy or imaging confirmation but clinically suspicious
Type 5b:
Definite fatal bleeding; overt bleeding or autopsy or imaging confirmation

5. PATIENT SELECTION

This trial will include 400 symptomatic patients with a de novo bifurcation lesion of a native coronary artery who meet eligibility criteria and provide written informed consent for participation in the study.
Eligible subjects will be informed about the scope and potential risks of the study verbally and in written form (ICF) the day before PCI. Informed consent will be obtained at the subsequent day before any study-related procedure and before start of the PCI.

5.1 Inclusion Criteria

Patients will be enrolled only, if all the following conditions are met:

1. Clinical indication, evidenced by angina/angina-equivalent symptoms or documented ischemia (non-invasive imaging such as scintigraphy, stress-MRI or stress-echo; FFR or iwFR) or patients with acute coronary syndromes (NST-ACS).

2. Clinical indication to perform double stenting only with Synergy™ stents for a clinically significant bifurcation stenosis as judged by the operator.

3. De-novo non-left main coronary bifurcation lesions - 1,1,1 or 0,1,1 according to the Medina classification - of a native coronary artery with the following reference vessel diameters: main branch > 2,5 mm; side branch > 2,25 mm. The difference between vessel diameter of the main and side branch is ≤ 1 mm.

4. The target lesion has not been previously treated with any interventional procedure.

5. The target vessel (main branch and side branch) must appear feasible for stent implantation.

6. Patient has no other coronary intervention planned within 30 days of the procedure.

7. Patient has been informed of the nature of the study and agrees to its provisions and has written informed consent as approved by the Ethics Committee.

8. Patient is willing to comply with all required post-procedure follow-up.

5.2 Exclusion Criteria

Patients are not eligible for enrollment into the study if any of the following conditions apply:

1. Patient had an acute ST-elevation myocardial infarction or target vessel contains intraluminal thrombus.

2. Use of any other coronary stent than Synergy™ and Synergy Megatron™ except for bail-out situations.

3. Patient with a known hypersensitivity or contraindication to the needed antithrombotic therapy, stent type or contrast media that cannot be adequately pre-medicated.

4. Non successful treatment of other lesion during the same procedure.

5. Patient with a severe bleeding diathesis, history of recent major bleeding or stroke (≤ 6 months), coagulopathy or severe liver disease.

6. Patient has a co-morbidity (i.e. cancer) that may cause the patient to be non-compliant with the protocol, or is associated with limited life-expectancy (less than 1 year).

7. Patient is participating in any other clinical study with an investigational product.

8. Patient is known to be pregnant or lactating at time of inclusion.

5.3 Randomization

Patients who fulfill inclusion and have no exclusion criteria and provided written informed consent to the study will be randomized to DK-Crush stenting or to Culotte-stenting using computer-generated random sequences stratified by investigation sites. The random sequence and block sizes per site will be selected by the statistician and will be unknown to the investigators and medical staff caring for the patients. Randomization will be performed immediately before catheter treatment of the bifurcation lesion.

6. STUDY ASSESSMENTS

6.1 Patient Enrollment

All potential subjects must be consented prior to performing any study related procedures. The investigator or representative will explain the nature and scope of the study, potential risks and benefits of participation, and answer questions for the patient. If the patient agrees to participate, informed consent must be signed and dated; a copy must be provided to the patient

Baseline data to be collected will include demographics, angiographic and clinical parameters.

6.2 Laboratory Assessments

- 12-lead ECG prior to procedure and between 12 hours and 24 hours post-procedure or before hospital discharge
- CK and CKMB and Troponin T prior to procedure and at least once prior to discharge. If several pre- and post-procedure assessments are available, highest levels are reported.

6.3 Concomitant Medications

All subjects receive the medication regimen listed below. All medications administered should be recorded in the subject`s medical record.

Prior to Procedure	Aspirin	At least 400 mg per os
	Clopidogrel	600 mg loading dose or
	Prasugrel	60 mg loading dose or

	Ticagrelor	180 mg loading dose
	for all: if not on chronic treatment	
During Procedure	IV Heparin	For angioplasty bolus 100 I.U./ kg/ KG
	IC Glyceryl trinitrate	100 – 200 mcg prior to baseline and post intervention angiograms
Post-Procedure	Aspirin	At least 100 mg per day indefinitely
	Clopidogrel	75 mg per day for at least 6 months or
	Prasugrel	10 mg or 5 mg/day for at least 6 months as per drug label
	Ticagrelor	2 x 90 mg /day for at least 6 months as per drug label

Glycoprotein IIb/IIIa inhibitors can be used for bail out.

6.4 Coronary Angiography and Intervention

6.4.1 Angiography

Using standard procedures for angioplasty, an introducer sheath of at least 6 French will be introduced and the heparin bolus will be administered. After introduction of the guiding catheter and following intra-coronary injection of nitroglycerin, baseline angiography of the vessel will be performed in at least two best views that show the target lesion free of foreshortening or vessel overlap.

6.4.2 Lesion / Vessel Pre-treatment

For any patients with multiple lesions requiring treatment at the time of the index procedure, lesions outside the target vessel must be treated first successfully.

The target lesion in the main branch will be crossed with an intracoronary guide wire of 0.014 inch diameter and a second guide wire is passed into the side branch to protect the access. The choice of the appropriate guide wires is up to the discretion of the operator. After

successful passage with the guide wires the lesion in the main branch should be pre-dilated with an appropriately sized balloon. Pre-dilatation of the side branch before stenting of the main branch is up to the discretion of the operator.

6.4.3 Stenting Procedure and Stenting Technique

Both the DK-Crush as well the Culotte technique provide complete coverage of the side branch ostium, avoiding non-stented gaps at the orifice of the side branch with minimal stent distortion or stent overlap in the carina region or the proximal segment of the main branch.

Stents should be selected long enough to cover the lesions completely. If more than one stent is needed to cover the lesion in the main or side branch completely, it is recommended to overlap the stents 1 – 2 mm. The aim should be to reach a diameter stenosis < 10% without proximal and distal dissections. Post dilatation may be performed at the discretion of the operator. Pre or post dilatation technique should avoid balloon injury to any segment of the vessel that will not be entirely covered by the drug-eluting stent. Further treatment to proximal or distal aspects of the main vessel or side branch can be continued at the discretion of the operator. At any stage, proximal or distal dissections may be treated as required with further stent implantations. At any stage, post-dilatations may be undertaken to optimize stent expansion.

Irrespective of the assigned treatment, glyceryl trinitrate is injected intra-coronary at the completion of the procedure and final angiography of the vessel is performed in the two optimal views that were chosen at baseline.
The additional use of intracoronary imaging techniques is up to the discretion of the operator.

Final ‘kissing balloon’ dilatation must be performed in all patients irrespective of whether they were assigned to DK-Crush or Culotte-stenting.

DK-Crush stenting technique:
Lesion preparation in the main vessel and side branch may be undertaken according to operator preference (including rotablation). After lesion preparation, the side branch is stented first. Side branch stent should have a small protrusion into the main branch. Before stent implantation in the side branch, an adequately sized balloon should be placed in the main branch, just opposite to the side branch ostium. After stent implantation in the side

branch, stent balloon and wire are removed and the balloon in the main branch must be inflated, to crush the struts into the vessel wall. In next step, the new wire should be crossed into the ostium of the side branch and first kissing balloon dilatation will follow. The next step is to implant the second stent into the main branch, followed by second re-wiring, a second kissing balloon-dilatation and final proximal optimization (POT) procedure (single short balloon inflation in proximal segment).

Culotte stent technique:
Lesion preparation in the main vessel and side branch may be undertaken according to operator preference. After lesion preparation, the side branch has to be stented first. The first stent is placed from main branch into the side branch, covering the entire diseased segment with a wire jailed in the main vessel. The main vessel is rewired through the stent struts, and after removal of the jailed wire, is dilated with a balloon to separate stent struts. The side branch wire is then removed (to prevent metal-to-metal jail) and the main vessel is stented covering the proximal and distal segment. The side-branch is re-wired and high pressure (e.g. 20 atm) individual inflations are made in each vessel at the bifurcation point to ensure good stent strut separation. Afterwards, a lower pressure kissing inflation is made. For both the high pressure individual and lower pressure kissing inflations, balloon sizing should be in accordance with the diameter of the vessel itself. Finally, a proximal optimization (POT) procedure (single short balloon inflation in proximal segment) is performed.

6.4.4 Stent type

Approved modern everolimus-eluting stents will be used as study stents: Only use of Synergy™ and Synergy Megatron™ stents from Boston Scientific is allowed.

6.5 Follow-up

All patients enrolled in the study will be required to complete the follow-up to evaluate long-term results.

6.5.1 Angiographic Follow-Up

Irrespective of symptoms, current guidelines recommend considering routine follow-up angiography after treatment of complex lesions (such as bifurcation lesions). This is routine

practice at our institution. Thus, as part of our clinical routine, all patients will undergo repeat angiography at 9 months (± 30 days) after the index procedure. Angiographies will be performed as described in Section *6.4.1.*

All angiographies, including unscheduled angiograms, will be analyzed by the angiographic core laboratory:

Dr. med. Ulrich Beschorner
coreLab Black Forest GmbH
Bad Krozingen, Germany
Phone: +49 7633 4024975
Fax: +49 7633 4024999

For quantitative coronary angiography, angiograms obtained at baseline, at completion of the intervention and at 9 months follow-up or in case of an unplanned coronary angiography before 9 month will be analyzed using a computer based system dedicated to bifurcation analysis (Qangio XA, version7.0, Medis, Leiden, Netherlands), according to the standard operating procedure of the angiographic core laboratory.
Quantitative angiographic measurements will be obtained of the three segments of the bifurcation lesion: the proximal and distal segment of the main branch and the side branch. Measurements in the stented portion of the vessel (in-stent) and in the distal or proximal 5 mm margin (edge) will be performed. In-segment analyses will comprise the in-stent and the edge area. In addition, the bifurcation angle from the analysis system will be estimated.

6.5.2 Clinical Follow-up

At 9-12 months post procedure (at time of angiographic follow-up or telephone contact or contact with general practitioner).

The assessment will include angina status (according to the Canadian Cardiovascular Society Classification of angina), all adverse events, all concomitant medications and any interventional treatment that occurred since the index procedure.

7. DATA COLLECTION AND DATA MANAGEMENT

Study data will be entered in pseudonymized form in a study database by authorized and trained members of the study team via electronic case report forms (eCRF). The electronic data capture system REDCap™ is used for data acquisition. This system uses built-in security features to prevent unauthorized access to patient data, including an encrypted transport protocol for data transmission from the participating sites to the study database. An audit trail provides a history of the data entered, changed or deleted, indicating the processor and date.

Employees of the Clinical Trials Unit charged with hosting the eCRF and the study database are obliged to maintain data confidentiality and to comply with data protection regulation. Before any data entry is performed, the trial eCRF will be validated. The technical specifications of the database will be described in the codebook delivered automatically by the REDCap™ system.

Access will be granted to authorized personnel only, and only if they have received appropriate training. The study database is located on a server of the IT facility (Klinikrechenzentrum, KRZ) of Medical Center - University of Freiburg.

8. SAFETY

Adverse Events are any untoward occurrence in the patient, which does not necessarily have a causal relationship with study treatment. A Serious Adverse Event is defined as any untoward medical occurrence that meets at least 1 of the following serious criteria:

- led to a death
- led to a serious deterioration in the health of the patient that either resulted in:
  a. life-threatening illness or injury, or
  b. a permanent impairment of a body structure or a body function, or
  c. in-patient or prolonged hospitalization, or
  d. medical or surgical intervention to prevent life threatening illness or injury or permanent impairment to a body structure or a body function.
- led to fetal distress, fetal death or a congenital abnormality or birth defect.

For the BBK3 clinical investigation, the following Serious Adverse Events are considered Serious Adverse Events of Special Interest (SAESI) and will be reported as outcome. SAESI include myocardial infarction, all forms of revascularization, stent thrombosis, disabling stroke as well as bleeding as defined by BARC criteria 3-5. For all these events, the causal relationship with the investigational procedure should be established as detailed as follows:

- Unrelated: the event is definitely not related associated with the procedure

- Possible: the temporal sequence between the procedure and the event is such that the relationship is likely or patient's condition or concomitant therapy could have caused the SAESI.

- Probable: the temporal sequence between the procedure and the event is relevant or the event subsides upon procedure completion (dechallenge) or the event cannot be reasonably explained by the patient`s condition.

- Definite: the temporal sequence is relevant and the event subsides upon procedure completion (dechallenge).

During the complete duration of the study, all SAESIs are collected, examined by the use of source documents and documented in the CRF. Study duration comprises the time from when the informed consent is signed until the last study assessment has been completed. No specific safety assessment is planned. All follow-up visits are part of routine clinical practice. SAESI's will be assessed at 9 months or at latest at 1 year (in accordance with study assessments). SAESI information will be obtained from the treating physician and a copy of the reports will be sent to the representative of the sponsor of the study within 5 working days: University Heart Center Freiburg – Bad Krozingen (PD Dr. M. Ferenc; PI of the BBK 3 study).

9. SAMPLE SIZE ESTIMATION

The study is designed to have a 80% power to detect a 25% relative reduction of the primary endpoint by Culotte technique as compared with DK-crush stenting at a significance level of 0.05.

Based on our previous study we assume a maximum percent diameter stenosis of 20 % in the Culotte arm and a common standard deviation of 22%. We, thus, obtain a sample size of 172 patients in each arm to have an 80 % power to detect a reduction in maximum percent

diameter stenosis from 26.7 % to 20 % by Culotte stenting as compared with DK- Crush stenting. The study will include 200 patients in each study arm, to allow for losses to angiographic follow-up.

10. QUALITIY ASSURANCE

The sponsor is responsible for implementing and maintaining quality assurance to ensure that trials are conducted, data are generated, documented, and reported in compliance with the protocol, ICH-GCP, and the applicable regulatory requirement(s).

10.1 Monitoring Procedure

The investigator will accept monitoring visits before, during and after the clinical trial. Prior to patient recruitment, a site initiation visit at each site is conducted in order to train and introduce the investigators and their staff to the trial protocol, related trial specific procedures, ISO 14155 norm and national/local regulatory requirements.
The initiation visit is conducted by the sponsor of this trial.
During the trial, a monitor will visit each site once for the whole study depending on the recruitment rate and quality of data. During these on-site visits, the monitor verifies that the trial is conducted according to the trial protocol, trial specific procedures, ISO 14155 norm and national/local regulatory requirements.
The presence of signed informed consents, eligibility of patients, and documentation/reporting of safety data (SAESIs) will be verified by the monitor.
The monitor performs also source data verification (SDV) and source data review (SDR).The investigator must maintain source documents for each patient in the trial. The investigator must also keep the original signed ICFs. The investigator must give the monitor access to all relevant source documents to confirm their consistency with the eCRF entries.

10.2 Source Data Verification (SDV)

Source data include original documents, data, and records such as hospital records, clinical and office charts, laboratory notes, memoranda, or evaluation checklists, recorded data from automated instruments, copies or transcriptions certified after verification as being accurate

copies, microfilm or magnetic media, X-rays, at the laboratories and at medico-technical departments involved in the clinical trial.
In addition to source data review source data verification will be performed in order to verify the accuracy and completeness of the entries on the case report form (CRF) by comparing them with the source data, and to ensure and increase the quality of the data. All data which are subject to SDV must have been entered in the medical record or, in the case of source documents, enclosed with the medical record. The investigators will afford the CRA access to the medical records for the performance of SDV.

11. ETHICAL AND LEGAL PRINCIPLES

This clinical trial was designed, shall be implemented and reported in accordance with the ICH- GCP, with applicable local regulations (including European Directive 2001/20/EC), and with the ethical principles laid down in the Declaration of Helsinki.
Before initiating the clinical trial, the sponsor/coordinating investigator should submit the CTP and any required application(s) to the appropriate competent authority for review, acceptance, and/or permission, as required by the applicable regulatory requirements.
The protocol and the proposed informed consent form must be reviewed and approved by a properly constituted Independent Ethics Committee (IEC) before trial start. A signed and dated statement that the protocol and informed consent have been approved by the IEC must be available prior to initiation of the trial.

11.1 Regulatory and ethical compliance

Before the start of the trial, the investigator is required to sign a protocol signature page confirming his/her agreement to conduct the trial in accordance with these documents and all of the instructions and procedures found in this protocol and to give access to all relevant data and records to sponsor CRAs, auditors, sponsor Clinical Quality Assurance representatives, designated agents of sponsor, IECs and CA(s) as required.

11.2 Responsibilities of the investigator

Before enrolment in the clinical trial, the patient will be informed that participation in the clinical trial is voluntary and that he/she may withdraw from the clinical trial at any time

without having to give reasons and without penalty or loss of benefits to which the patient is otherwise entitled.

The treating physician will provide the patient with information about the treatment methods to be compared and the possible risks involved. At the same time, the nature, significance, implications, expected benefits and potential risks of the clinical trial and alternative treatment will be explained to the patient. The patient will be given ample time and opportunity to obtain answers to any open questions. All questions relating to the clinical trial should be answered to the satisfaction of the patient.

In addition, the patient will be given a patient information sheet which contains all the important information in writing. The patient's written consent must be obtained before any trial-specific tests/treatments. For this purpose, the written consent form will be personally dated and signed by the trial patient and the investigator conducting the informed consent discussion.

By signing the consent form, the patient agrees to voluntarily participate in the clinical trial and declares his/her intention to comply with the requirements of the clinical trial and the investigator's instructions during the clinical trial. By signing the form, the patient also declares that he/she agrees to the recording of personal data, particularly medical data, for the trial, to their storage and codified ("pseudonymized") transmission to the sponsor, CA(s), and further agrees that authorized representatives of the sponsor, who are bound to confidentiality.

After signing, the patient will be given one copy of the signed and dated written consent form and any other written information to be provided to the patients.

11.3 Confidentiality of trial documents and patient records

The investigator must ensure anonymity of the patients; patients must not be identified by names in any documents submitted to sponsor. Signed informed consent forms and patient enrolment log must be kept strictly confidential to enable patient identification at the site.

All study-related information will be stored securely at the study site. All participant information will be stored in locked file cabinets in areas with limited access. All laboratory specimens, reports, data collection, process, and administrative forms will be identified by a coded identification number only to maintain participant confidentiality.

12. TRIAL DOCUMENTS AND ARCHIVING

12.1 Trial documents/investigator site file

The investigator will be given an investigator site file containing all the necessary essential trial documents for the initiation of the trial at his/her site. The essential documents include a list on which the investigator will enter all appropriately qualified persons to whom he/she has delegated important trial-related tasks.
The investigator, or an individual who is designated by the investigator, will be responsible for the maintenance and completeness of the trial documents during the clinical trial. At the request of the monitor, auditor, IEC the investigator shall make available all the requested trial-related records for direct access. Essential documents must not be removed permanently.

12.2 Archiving

After completion of the clinical trial, the essential trial documents - as defined by ICH-GCP E6 section - will be retained at the trial site for a sufficient period so that they will be available for audits and inspections by the CA(s).
The investigator will be responsible for the storage. The following retention periods will apply after the completion/termination of the clinical trial:
The above-mentioned essential documents must be retained for at least 10 years (section 13, subsection 10 GCP-V).
The medical records and other source documents must be retained for the longest possible period allowed by the hospital, the institution or the private practice.
The investigator/the institution should take measures to prevent accidental or premature destruction of these documents. The sponsor will notify the investigator in writing when the trial-related essential documents are no longer required.

13. PROTOCOL ADHERENCE AND AMENDMENTS

13.1 Protocol adherence

Investigators ascertain they will apply due diligence to avoid protocol deviations. Under no circumstances should the investigator contact sponsor or its agents, if any, monitoring the trial to request approval of a protocol deviation, as no authorised deviations are permitted. If the investigator feels a protocol deviation would improve the conduct of the trial this must be considered a protocol amendment, and unless such an amendment is agreed upon by sponsor and approved by the IEC it cannot be implemented.

13.2 Amendments to the protocol

Any change or addition to the protocol can only be made in a written protocol amendment that must be approved by sponsor, CA where required, and the IEC.
Only changes of the protocol that are required for patient safety may be implemented prior to IEC approval.
Regardless of the need for approval of formal protocol amendments, the investigator is expected to take immediate action required for the safety of any patient included in this trial, even if this action represents a deviation from the protocol. In such cases, the sponsor has to be notified as soon as possible of this action; the IEC should be informed correspondingly.
Information regarding important protocol modifications will be provided in due time to further relevant parties (e.g. investigators, trial participants, trial registries, journals).

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REFERENCES

1. Ferenc M, Gick M, Comberg T, Rothe J, Valina C, Toma A, Loffelhardt N, Hochholzer W, Riede F, Kienzle RP, Achtari 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**(45):3399-3405.
2. 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, Sansoto T, Chen F, Yuan ZY, Li WM, Leon MB. Clinical Outcome After DK Crush Versus Culotte Stenting of Distal Left Main Bifurcation Lesions: The 3-Year Follow-Up Results of the DKCRUSH-III Study. JACC Cardiovasc Interv 2015;**8**(10):1335-42.
3. Chen SL, Zhang JJ, Ye F, Chen YD, Lu SZ, Tan H, Patel T, Kenji K, Tamari I, Shan SJ, Zhu ZS, Lin S, Tian NL, Li XB, Liu ZZ, Lee M, Wei M, Xu YW, Yuan ZB, Qian J, Sun XW, Yang S, Chen JG, He B, Sumit S. [Comparison of DK crush with classical crush technique with drug-eluting stents for the treatment of coronary bifurcation lesions from DKCRUSH-1 study]. Zhonghua Xin Xue Guan Bing Za Zhi 2008;**36**(2):100-7.
4. Chen SL, Santoso T, Zhang JJ, Ye F, Xu YW, Fu Q, Kan J, Paiboon C, Zhou Y, Ding SQ, Kwan TW. A randomized clinical study comparing double kissing crush with provisional stenting for treatment of coronary bifurcation lesions: results from the DKCRUSH-II (Double Kissing Crush versus Provisional Stenting Technique for Treatment of Coronary Bifurcation Lesions) trial. J Am Coll Cardiol 2011;**57**(8):914-20.
5. Ferenc M, Buettner HJ, Gick M, Comberg T, Rothe J, Khoury F, Valina C, Toma A, Kuebler P, Riede F, Neumann FJ. Clinical outcome after percutaneous treatment of de novo coronary bifurcation lesions using first or second generation of drug-eluting stents. Clin Res Cardiol 2016;**105**(3):230-8.
6. Lee JM, Hahn JY, Kang J, Park KW, Chun WJ, Rha SW, Yu CW, Jeong JO, Jeong MH, Yoon JH, Jang Y, Tahk SJ, Gwon HC, Koo BK, Kim HS. Differential Prognostic Effect Between First- and Second-Generation Drug-Eluting Stents in Coronary Bifurcation Lesions: Patient-Level Analysis of the Korean Bifurcation Pooled Cohorts. JACC Cardiovasc Interv 2015;**8**(10):1318-31.
7. Erglis A, Kumsars I, Niemela M, Kervinen K, Maeng M, Lassen JF, Gunnes P, Stavnes S, Jensen JS, Galloe A, Narbute I, Sondore D, Makikallio T, Ylitalo K, Christiansen EH, Ravkilde J, Steigen TK, Mannsverk J, Thayssen P, Hansen KN, Syvanne M, Helqvist S, Kjell N, Wiseth R, Aaroe J, Puhakka M, Thuesen L, Nordic PCISG. 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**(1):27-34.