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Design and rationale for the treatment effects of provisional side branch stenting and DK crush stenting techniques in patients with unprotected distal left main coronary artery bifurcation lesions (DKCRUSH V) Trial

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ABSTRACT

Background: Provisional stenting (PS) is effective for great majority of patients with coronary bifurcation lesions. Double kissing (DK) crush approach demonstrated significant reduction of target lesion revascularization (TLR) for patients with more complex bifurcation lesion when compared with PS. Furthermore, DK crush technique was associated with lower rate of composite major adverse cardiac event (MACE), revascularization and stent thrombosis (ST) for patients with unprotected distal left main coronary artery bifurcation lesions (ULMb), compared to culotte stenting approach. The DKCRUSH V trial is designed to elucidate the benefits of DK crush over PS in patients with ULMb.

Study design: DKCRUSH V is a randomized, prospective, multinational clinical trial designed to evaluate the efficacy and safety of DK crush over PS for patients with ULMb. Subjects with Medina 1,1,1 or 0,1,1 ULMb will be randomized in a 1:1 fashion to PS or DK crush. The primary endpoint is target lesion failure (TLF) including target

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vessel myocardial infarction, cardiac death and TLR. Other endpoints address individual event of primary endpoint, and target vessel revascularization. The safety objective is the ST. Recruitment began in January 2012 and was completed in December 2015; 484 patients were randomized. The trial will continue until at least 56 adjudicated primary endpoints occur.

Conclusions: The DKCRUSH V study is investigating if DK crush approach versus PS will reduce the incidence of TLF in patients with symptomatic ULMb.

Percutaneous coronary intervention (PCI) using DES dramatically reduces the requirement of revascularization for patients with obstructive coronary artery stenosis, as compared to bare metal stents [1,2]. However, stenting coronary artery bifurcation lesions is technically challenging and associated with less acceptable results mainly due to higher rate of in-stent restenosis (ISR) particularly at ostial side branch (SB). Furthermore, previous studies demonstrated that systematical two stents techniques did not put any advantages over provisional stenting (PS) approach, and PS was effective for great majority of bifurcation lesions [3–6]. When NORDIC stent technique study [7] showed the reduced rate of ISR by culotte technique compared to classical crush stenting, our group reported the benefits by double kissing (DK) crush over either PS [8] for overall of bifurcated stenosis or over culotte stenting [9] for left main distal bifurcation lesions (ULMb). Left main coronary artery is featured by a larger SB, decreased left ventricular function, more frequent multi-vessel disease and chronic total occlusion (CTO) in right coronary artery (RCA). However, there is a lack of data showing the advantage of PS versus DK crush stenting for ULMb.

1. Provisional stenting for ULMb

J-cypher Registry using cypher stent [10] showed a 7.6% TLR for distal left main disease (rather than ULMb), similarly to the results by Palmerini et al. [11]. French Registry [12] is divided into three arms, the first TAXUS 2004 registry had a 5.9% TLR, the FRIEND and LEMAX using sirolimus-eluting stent had 2.7% and 2.3% TLR, respectively. However, these three registry studies did not provide stronger evidences because of no consistent stenting techniques and lesions classifications. Price et al. [13] reported a 38% TLR in a smaller study ($n = 50$) for distal left main disease. The shortcomings of these studies are the lack of non-randomization, lack of using propensity score to compare patients in pair, and all distal lesions (bifurcation and non-bifurcation lesions) were included.

2. DK crush stenting for ULMb

Even the fact that PS has been effective for great majority of entire coronary bifurcation lesions, lesions' complexity has been thought to influence the clinical outcomes when previous studies [3–6] are analyzed. CACTUS [5], BBK [6], BBC ONE [4] and NORDIC Bifurcation Study [3] trials compared different two-stent techniques versus PS, and did not report benefits by two-stent techniques over PS. However, a wide discrepancy in study design existed among these studies. For example, SB lesions length in NORDIC study [3] was only 2.8 mm in PS group, significantly different to 10.3 mm in two-stent group. Also, baseline SB and main vessel (MV) diameter stenosis was around 40%, tremendously less severe than other studies [8–10]. Our DKCRUSH I [14], DKCRUSH II [8] and DKCRUSH III [9] trials showed the baseline SB lesion length longer than 10 mm, with more complex lesions or more patients at high-risk (MI, chronic total occlusion, multi-vessel disease) included, compared to others [3–6].

Recently, we have reported a new stratification for classifying the bifurcation lesions' complexity, DEFINITION criteria [15], which demonstrated that PS was associated with lower rate of composite major adverse cardiac event (MACE) for overall bifurcations or simple bifurcated lesions. In contrast, two-stent technique reduced in-hospital MACE and 1-year cardiac death for complex bifurcation lesions when compared with PS. As patients with ULMb have more complex lesions, and complete revascularization could not be achieved for most of these patients, the comparison of treatment effects by PS or two-stent techniques is critical.

Although previous studies did not show any difference in MACE between two-stent techniques, NORDIC stent technique study [7] reported less frequent in-stent restenosis (ISR) at ostial SB by culotte over classical crush approach. Furthermore, our DKCRUSH III study [9], a first RCT comparing DK crush with culotte for ULMb, revealed that patients were benefited from DK crush, compared to culotte stenting through 3-year follow-up [16]. Taking together, insight analysis from subgroup of patients with ULMb in our DKCRUSH I [14] and DKCRUSH II [8] studies, a five-times reduction in TLR was achieved by DK crush (3.9%), compared to 20.7% by provisional T stenting, a finding was supported by the only one RCT, DKCRUSH III trial [9], for ULMb. As a result, the significant improvement of clinical outcomes by DK crush over PS for patients with ULMb is critically to be tested in a RCT, which will simultaneously elucidate the reason why PS cannot win in the population with ULMb.

3. Study design and population

DKCRUSH V is an international, multicenter, randomized, endpoint-driven study to evaluate the benefits by DK crush compared with PS for patients with ULMb. The study is shown in Figure (Chictr.org, no ChiCTR-TRC-11001213).

The inclusion criteria for DKCRUSH V are designed to enroll a representative sample of subjects with ULMb. Study patients must be 18–80 years of age with objective evidences of ischemia, defined by 2 of the following: (1) Medina 1,1,1 and 0,1,1, and (2) both ostial left anterior descending artery (LAD) and left circumflex (LCX) diameter stenosis ≥50% by visual estimation.

Key exclusion criteria included Severe calcification needing rotational atherectomy, restenotic lesions, and acute myocardial infarction <24 h. All patients must provide written informed consent for participation. A complete listing of the inclusion/exclusion criteria is provided in Table 1.

DKCRUSH V patients were being randomized in a 1:1 ratio to receive either PS or DK crush stenting technique. Everolimus eluting stents, biolimus eluting stents, or sirolimus eluting stents will be implanted during the procedures duo to the discretion of the operators. Recruitment began in January 2012 and was completed in December 2015, and 484 patients were randomized. Two patients were excluded due to double enrolled and randomized (i.e., same patient enrolled and randomized at 2 separate sites), therefore, the total number of randomized subjects was 482. The baseline characteristics of patients enrolled in DKCRUSH V are shown in Table 2. There were 4 patients suffered previous Aorta-RCA CABG with occluded saphenous graft. Randomized subjects are being followed for all clinical endpoints and serious adverse events (SAEs) until the end of the study, with the primary and several secondary endpoints events confirmed by Independent Committee. The trial will continue until January 2017.

The study is being performed in accordance with ethical principles consistent with the Declaration of Helsinki, International Conference

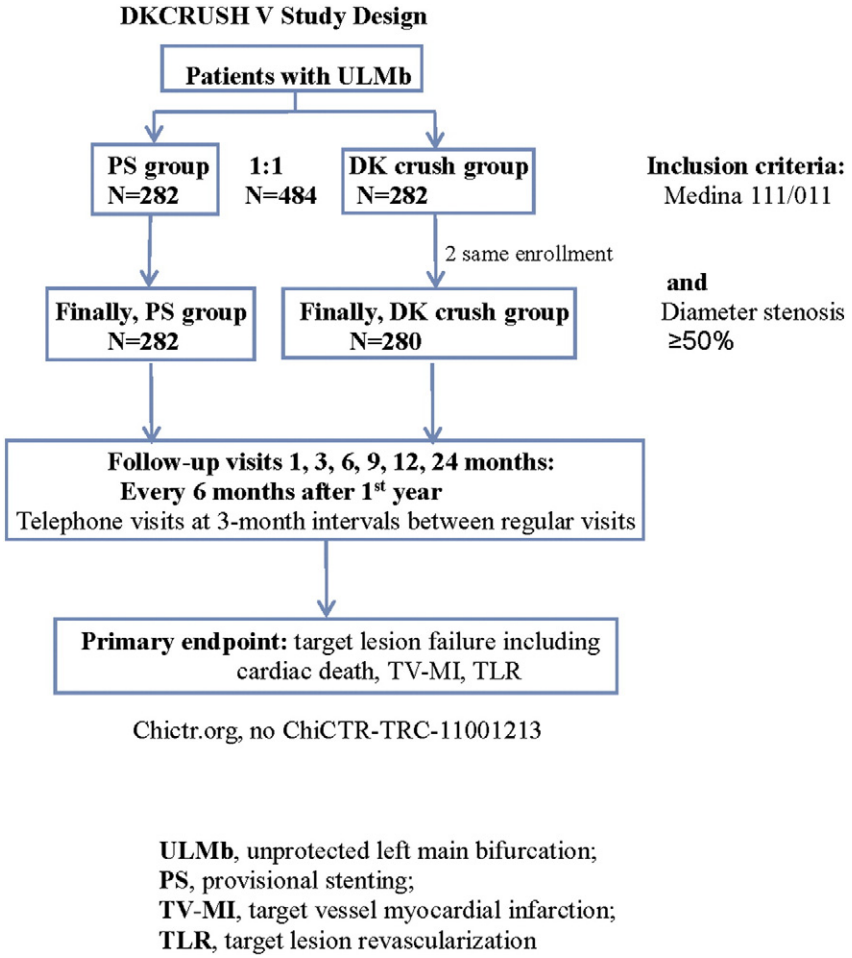

Figure. DKCRUSH V study flowchart.

Table 1
Inclusion and exclusion criteria.

Inclusion
Patient must be at least ≥18, ≤80 years of age.
Lesions are eligible for percutaneous coronary intervention (PCI).
Patient has stable/unstable angina or myocardial infarction (MI).
ULMb (Medina 0,1,1/1,1,1) with/without left main ostial/shaft lesions.
Downstream lesions in LAD or LCX could be covered by two stents.
ULMb with chronic total occlusion (CTO) lesion in LAD, or LCX or RCA after recanalization.
Diameter stenosis in LAD/LM and LCX ≥ 50% by visual estimation.
Exclusion
Patient with MI < 24-h from the onset of chest pain to admission).
Patient was allergic to the study stent or protocol-required concomitant medications.
Patient is intolerable to dual anti-platelet therapy.
Patient has any other serious medical illness that may reduce life expectancy to <12 months.
Patient is a woman who is pregnant or nursing.
Patient has a planned procedure that may cause non-compliance with the protocol or confound data interpretation.
Patient is participating in another clinical trial that has not reached its primary endpoint within 24 months after the index procedure.
CTO lesion in either LAD, or LCX or RCA not re-canalized.
Severe calcification needing rotational atherectomy.
Distal left main coronary restenosis.

Table 2
Baseline characteristics of patients included in DKCRUSH V at study entry.

	All patients (N = 482)[a]
Age, y	64.44 ± 9.6
Male sex	387(80.3)
Medical history	
Hypertension	322(66.8)
Hyperlipidemia	231(47.9)
Diabetes mellitus	127(26.3)
Acute myocardial infarction < 24 h	53(11.0)
Previous PCI	58(12.0)
Previous CABG	4(0.8)
Medina classification	
Medinal 1,1,1	406(84.2)
Medina 0,1,1	76(15.8)
Renal dysfunction	20(4.1)

Data presented as number (percentage), unless otherwise indicated.
PCI, percutaneous coronary intervention; CABG, coronary artery bypass graft.
[a] N represented final total number of patients, not randomizations. Two patients were determined to be double enrolled.

on Harmonisation Good Clinical Practice guidelines, and applicable regulatory requirements. The final study protocol and informed consent have been reviewed and approved by the corresponding health authorities and ethics boards/institutional review boards for all participating study sites. Enrolled patients gave written informed consent for participation in the trial.

4. Study protocol and follow-up procedure

4.1. Periprocedural medication

A loading dose of aspirin (300 mg) and clopidogrel (300 mg) is recommended for all patients if not used before admission, at least 6 h before PCI procedure.

During the index procedure, the patients are treated according to contemporary guidelines and local practice. Per-procedural medical treatment in all patients include: unfractioned heparin (100-120 U/kg i.v.), low molecular heparin (0.7 mg/kg s.c.) or bivalirudin.

Following PCI, lifelong aspirin in a dose of 100 mg/d will be prescribed. Duration of clopidogrel treatment is 12-month (75 mg/d). Lifelong clopidogrel treatment may be used in individual patients at the discretion of the operator. A loading dose of aspirin (300 mg) and clopidogrel (300 mg) is recommended for all patients, at least 6 h before PCI procedure.

4.2. Biomarker assessment

Creatine Kinase Myocardial-Band Isoenzyme and TNT/TNI will be assessed before the procedure and 6–9(optional) and 12–24 h after the index procedure.

4.3. Angiography assessment

The index angiograms will be assessed by the QCA-laboratories at China Cardiovascular Research Fundation (CCRF, Beijing, China). All the lesions will be described and classified by SYNTAX [12], and NERS [17] scores.

Basic angiograms for all lesions should consist of at least injections after intracoronary injection of 100-200 μg nitroglycerin (documented on angiogram). Bifurcation-view must be gained for all patients; there should be an angulation difference between the two baseline angiograms of at least 30°. The diagnostic/guiding catheter should be well visible, near the center of the angiogram and filled with dye. The index lesions should be well visible, near the center of the angiogram and shown without foreshorting. Between the pre- and post-angiograms all balloon inflations and stent implantations should be documented by short cine-runs.

5. Intravascular ultrasound analysis

After intra-coronary administration of nitroglycerin(100–200 μg), the imaging catheter was advanced by at least 10 mm beyond the distal edge of the stent under fluoroscopic guidance, and IVUS images were obtained with automated pullback (0.5 mm/s) using a commercially available imaging system with a 40-MHz mechanical transducer (Boston Scientific Corporation, Natick, MA, USA). The 12 images were recorded on a DVD for subsequent off-line analysis. The IVUS images were analyzed by two technicians who were blind to the study design. The inter- and intra-observer variability was under 5%, determined using the Kappa test. All IVUS analysis was performed using dedicated software (EchoPlaque, IndecSystems, Mountainview, CA, USA). IVUS measurements included the minimum stent cross-sectional area (MSA), the minimum lumen area (MLA), the stent expansion index, the stent symmetry index and stent opposition at the minimum stent area. The stent expansion index was defined as the ratio of the minimum stent cross-sectional area (CSA) divided by the distal reference lumen area. The stent symmetry index was defined as the ratio of the minimum stent diameter divided by the maximum stent diameter. The incomplete crush was defined as the incomplete apposition of the SB or the MV stent struts against the MV wall proximal to the carina. The late luminal loss was defined as the difference between the lumen CSA post-procedure and at follow-up. The chronic stent recoil was defined as the difference between the minimal stent CSA post-procedure and at follow-up. Neointimal hyperplasia (NIH) was defined as the difference between the stent CSA and the lumen CSA at follow-up. The Core Lab for QCA and IVUS analysis is, Nanjing, China.

Table 3
Secondary endpoints.

Combined endpoint of all-cause death, MI, TVR at 1-year
Individual endpoints of all-cause death, cardiac death, MI, TLR, TVR at 1-year
Definite and probable stent thrombosis
NYHA functional class
Angina CCS class
Braunwald class
ISR
Net gain of lumen diameter
Procedure related biomarker release
Stroke
Outer diameter of guiding catheter
Devices consumed during indexed procedure
Contrast volume
Procedural time
X-ray exposure time
X-ray dose, DAP-total, DAP-record, DAP-fluoro

6. Randomization procedure

The patients will be randomized after angiography to either DK or PS group. The randomization serial number for patients will be performed by Interactive Web Randomization System (IWRS). The randomization serial number for each participating center will be undergone by the same system.

6.1. Patient follow-up

All patients will be seen at the outpatient clinic of the participating centers after 1-, 6-, and 12-month. The outpatient visit may be substituted with a telephone contact and subsequent investigational documentation forms. Angiographic follow-up would be undergone at 13-month after index procedure, and would be encouraged for 80% of all patients, with IVUS & FFR for 50% of all patients. Earlier re-angiography will not be suggested unless clinically indicated earlier.

7. Study endpoints

The primary endpoint in this trial is the composite of cardiac death, target vessel MI and target lesion revascularization at 1-year after indexed procedure. The major secondary endpoints include stent thrombosis (safety endpoint), in-stent restenosis, target vessel revascularization (TVR), MI, and each individual component of the primary endpoint (Table 2). Definition of study endpoints are described in Appendix A.

All endpoints are site-reported in an electronic Web-based capture system with additional submission of supporting medical documents where applicable. Adjudication for each event is performed according to definitions in the DKCRUSH V Clinical Endpoints Charter by 3 members in Independent Committee (see Organization).

8. Statistical considerations

The primary efficacy variable is time from randomization to first occurrence of any event from the primary composite of cardiac death, target-vessel MI and TLR. The analysis of all efficacy variables will be based on the intention-to-treatment principle using the Cox-proportional hazards model with a factor for treatment group. The hazard ratio for PS versus DK crush with 95% CIs will be presented. To address the issue of multiple testing, the confirmatory analysis will comprise a hierarchical test sequence with the primary efficacy variable followed by the secondary efficacy variables in the order listed in Table 3. Efficacy analysis will be conducted on an intention-to-treat basis among all subjects randomized. The safety evaluation will include all subjects who received either PS or DK crush treatment and within 7 days after stenting procedures. Subgroup analysis will be performed to evaluate variation of treatment effects, as well as a test of interaction with treatment for each subgroup variable. The P values of the subgroup analyses and interaction tests will not be adjusted for multiple comparisons because the tests are exploratory and will be interpreted descriptively. Subgroup

analyses will be performed on the primary efficacy and safety variables. Subgroup analyses will be based on the set of baseline variables (online Appendix Supplementary Table 1).

Trial sample size estimation required estimates of TLF rates in subjects with ULMb. To detect a true hazard ratio of o.85, randomization of approximately 484 patients with ULMb was expected to yield a primary endpoint event of 14% in provisional stenting group and 6% in DK group, providing 80% power. An independent data monitoring committee (DMC) has responsibility for monitoring safety during the trial and will perform 3 interim analyses of efficacy when approximately half of the projected primary endpoints have been accrued and adjudicated. At its discretion, the independent DMC may perform additional efficacy looks. An alpha spending function will govern interim and final statistical testing to control the overall type I error of 5%.

9. Study organization

All centers with experience and interest in left main stenting techniques and with a potential of randomizing > 15 patients in the study during a 12-month period can participate in the study.

Rules for membership of the steering committee: 1) Writing of protocol and advisory activity concerning the study protocol; 2) Inclusion of >25 patients in the study; one membership; 3) Inclusion of >45 patients; two membership. The steering committee members will be selected on basis of participation in the study.

There will be a country coordinating principal investigator (PI) for each participating country and one PI for each center. The PIs will be responsible for the study in the respective countries. Further, they will be key members of the steering committee of the study (steering committee nucleus), and in charge of the study. The PIs will take care of the study at center level and will be members of the steering committee in actively including centers.

All steering committee members will have full access to the database and will participate in the interpretation of data.

9.1. Independent endpoint committee

Primary and secondary endpoints will be assessed by an independent endpoint committee (IEC)—Treatment Effects Monitoring Committee (TEMC) and Advisory-review Committee. The endpoint committee will consist of experienced cardiologists, trialists, statisticians, and interventionalists.

10. Discussion

Despite the extensive use of PS for coronary bifurcation lesions, the evidence base for therapies aimed at improving clinical outcomes in patients with ULMb is limited. The FRENCH and LEMAX registry for the first time reported the incidence of TLF from a large population of patients with unprotected left main disease. In that two-arm registry study, 75.9% of patients had distal left main disease, of them PS was used in 91.1% of lesions with additional SB stent required in 22% of patients. Notably, Medina 1,1,1 (46.8%) and 0,1,1 (3.2%) only accounted for 50% of overall patients. As such, we postulated that the rate of TLF would be >11.9% if all lesions were classified by Medina 1,1,1 or 0,1,1.

On the other hand, from the first RCT comparing DK crush vs culotte stenting for ULMb defined by Medina 1,1,1 and 0,1,1, we found a dramatic reduction of composite MACE rate by DK crush, with TLF <6%. Therefore, DKCRU V trial will provide evidence to address the role of two-stent technique, particularly in DK crush, for true ULMb lesions.

10.1. Study population

Patients with unprotected left main disease are at their risk of CV events and CABG is recommended to be “gold-standard” for such particular patients. When we are waiting for the results by EXCEL study comparing DES with CABG for patients with left main disease and SYNTAX score < 33, stenting approach for true ULMb is still technically demanding. To address the role of DK crush in ULMb, DKCRUSH V study includes the real true ULMb (Medina 1,1,1 and Medina 0,1,1). When we considered a large trial aimed at ULMb patients, there were several important design consideration in DKCRUH V, including MI > 24 h, CTO lesions in either LAD or LCX or RCA after successful percutaneously recanalization, calcification without requirement of atherectomy. In addition, one of the challenges in DKCRUSH V was that most patients would had have high SYNTAX score (data not included in the Tables).

10.2. Selection of participating centers

Given the fact that DK crush consists of 5 steps including stenting SB, balloon crush, first kissing, stenting MV, final kissing, all participating centers should have yearly PCI number > 500 and the primary operator in each center should have yearly number of stenting ULMb > 50. Before the study, each qualified center should provide 3 stenting cases of ULMb for PS and DK crush, respectively. If stenting techniques did not comply with protocol by steering committee, training on additional 3 cases was performed.

10.3. Management during the study

The study will be monitored according to the GCP rules by independent professionals. During the study period, monitor will have regular contact to the participating departments to ensure that the trial is conducted in compliance with the protocol, GCP and applicable regulatory requirements. The monitor will ensure that the used products are all right and will review source documents for verification of consistency with the data recorded in the CRF's. The monitors will also provide information and support to the investigators(s).

Investigators and other responsible personnel must be available during the monitoring visits, audits and inspections and should devote sufficient time to these processes.

The investigator should provide a CV or equivalent documentation of suitability to be responsible for the trial. All investigators and other responsible personnel should be listed together with their function in the trial on the signature list.

The investigator(s)/Institution(s) will permit study-related monitoring, audits, IEC review and regulatory inspection(s), providing direct access to source/hospital records. The investigator verifies that each patient has consented in writing to direct access to the original source data/hospital records by the use of written information and signed informed consent.

During the monitoring, the data recorded in the e-CRFs by the investigator will be controlled for consistency with the source data/hospital records by the study monitor (source data verification). Any discrepancies of data will be documented and explained in the monitoring reports.

The progress of the study will be checked on a weekly basis by the steering committee. They will receive and evaluate data on inclusion rate and the primary endpoint event rate.

The steering committee will receive data by e-mail and answer by e-mail with copy to all members. The study will be monitored by the coordinating investigators based on input from independent professionals.

10.4. Treatment of patients with ISR

The options of treatment for patients with ISR were left at physician's discretion. However, re-PCI with drug-eluting balloon, different DES and kissing balloon inflation was recommended for focal ISR. Otherwise, CABG was recommended for patients with multiple or diffuse ISR [18,19].

10.5. Summary

The DKCRUSH V trial is investigating whether DK crush stenting versus PS reduces TLF in patients with true ULMb.

Disclosure

There is nothing to disclose.

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