Drug-coated balloon angioplasty with rescue stenting versus intended stenting for the treatment of *de novo* coronary artery lesions (REC-CAGEFREE I): an investigator-initiated, multicenter, randomized, non-inferiority trial

Prof. Chao Gao, Ph.D.[1*]; Xingqiang He, M.D.[1*]; Prof. Fan Ouyang, Ph.D.[2*]; Prof. Zhihui Zhang, Ph.D.[3*]; Prof. Guidong Shen, Ph.D.[4]; Prof. Mingxing Wu, Ph.D.[5]; Prof. Ping Yang, Ph.D.[6]; Prof. Likun Ma, Ph.D.[7]; Prof. Feng Yang, Ph.D.[8]; Prof. Zheng Ji, Ph.D.[9]; Prof. Hua Wang, Ph.D.[10]; Prof. Yanqing Wu, Ph.D.[11]; Prof. Zhenfei Fang, Ph.D.[12]; Prof. Hong Jiang, Ph.D.[13]; Prof. Shangyu Wen, Ph.D.[14]; Prof. Yi Liu, Ph.D.[1]; Prof. Fei Li, Ph.D.[1]; Prof. Jingyu Zhou, Ph.D.[1]; Bin Zhu, Ph.D.[1]; Yunpeng Liu, M.D.[1]; Ruining Zhang, BSc[1]; Tingting Zhang, Ph.D.[1]; Ping Wang, Ph.D.[1]; Jianzheng Liu, BSc[1]; Zhiwei Jiang, Ph.D.[15]; Prof. Jielai Xia, Ph.D.[16]; Prof. Robert-Jan van Geuns, Ph.D.[17]; Prof. Davide Capodanno, Ph.D.[18]; Prof. Scot Garg, Ph.D.[19]; Prof. Yoshinobu Onuma, Ph.D.[20]; Prof. Duolao Wang, Ph.D.[21]; Prof. Patrick. W. Serruys, Ph.D.[20]; Prof. Ling Tao, Ph.D.[1]; for the REC-CAGEFREE I Investigators

Affiliations:

1. Department of Cardiology, Xijing Hospital, Xi'an, China.
2. Department of Cardiovascular Medicine, Zhuzhou Hospital Affiliated to Xiangya School of Medicine, Central South University, Zhuzhou, China.
3. Department of Cardiovascular Medicine, Center for Circadian Metabolism and Cardiovascular Disease, Southwest Hospital, and Key Laboratory of Geriatric Cardiovascular and Cerebrovascular Disease, Ministry of Education, Chongqing, China.
4. Department of Cardiology, Ankang Hospital of Traditional Chinese Medicine, Ankang, China.
5. Department of Cardiology, Xiangtan Central Hospital, Xiangtan, China.
6. Department of Cardiology, China-Japan Union Hospital of Jilin University, Changchun, China.
7. Department of Cardiology, The First Affiliated Hospital of USTC, Hefei, China.
8. Department of Cardiology, The First Hospital of Kunming, Kunming, China.
9. Department of Cardiology, Tangshan Workers Hospital, Tangshan, China.
10. Department of Cardiology, West China Hospital Sichuan University, Chengdu, China.
11. Department of Cardiology, The Second Affiliated Hospital of Nanchang University, China.
12. Department of Cardiology, The Second Xiangya Hospital of Central South University, China.

13. Department of Cardiology, Renmin Hospital of Wuhan University, Wuhan, China.
14. Department of Cardiology, Tianjin Fourth Central Hospital, Tianjin, China.
15. Beijing KeyTech Statistical Consulting Co., Beijing, China.
16. Department of Statistics, Air Force Medical University, Xi'an, China.
17. Department of Cardiology, Radboud UMC, Nijmegen, the Netherlands.
18. Department of Cardiology, Azienda Ospedaliero-Universitaria Policlinico 'G. Rodolico—San Marco', University of Catania, Catania, Italy.
19. Department of Cardiology, Royal Blackburn Hospital, Blackburn, UK.
20. Department of Cardiology, University of Galway, Galway, Ireland.
21. Biostatistics Unit, Liverpool School of Tropical Medicine, Liverpool, UK.

*These authors contributed equally. Prof Ling Tao is the chairwoman of the REC-CAGEFREE I study and the primary corresponding author.

Address for correspondence:

Ling Tao, MD, Ph.D., FAHA
Professor of Cardiology
Xijing Hospital, Changle West Road, Xi'an, 710032, China
Email: lingtaofmmu@qq.com

Patrick W. Serruys, M.D. Ph.D., FESC
Established Professor of Interventional Medicine and Innovation
Professor of Cardiology
Emeritus Professor of Medicine
University of Galway, P.O. University Road, Galway, H91 TK33, Ireland
Email: patrick.w.j.c.serruys@gmail.com

Running title: DCB vs DES for *de novo* coronary artery disease

Total Word count: 3601 words; 3 Tables and 4 Figures

Abstract (Words: 332)

Background

The long-term efficacy and safety of the strategy of drug-coated balloon (DCB) angioplasty with rescue stenting to percutaneous coronary intervention (PCI) with intended drug-eluting stent (DES) in *de novo* lesions, regardless of coronary artery diameters, remains uncertain.

Methods

REC-CAGEFREE I was an open-label, randomized, non-inferiority trial conducted at 43 sites in China. After successful lesion pre-dilatation, 2,272 patients with an indication for PCI who had *de novo*, non-complex coronary artery disease (irrespective of target vessel diameter) were randomly assigned (1:1) to paclitaxel-coated balloon angioplasty with the option of rescue stenting due to an unsatisfactory result versus intended deployment of second-generation thin-strut sirolimus-eluting stents. The primary endpoint was the Device-oriented Composite Endpoint (DoCE, including cardiovascular death, target vessel myocardial infarction, and clinically and physiologically indicated target lesion revascularization [TLR]) at 24 months in the intent-to-treat population. The non-inferiority margin was an absolute risk difference of 2·68%.

Results

Between February 5th 2021, and May 1st 2022, 1,133 patients were randomly assigned to the DCB group and 1,139 to the DES group. The mean diameters of the two devices were 3·0±0·4 and 3·1±0·5 mm in the DCB and DES groups, respectively. One hundred six (9·4%) patients received rescue DES after unsatisfactory DCB angioplasty. At 24 months, DoCE occurred in 72 (6·4%) patients in the DCB group and 38 (3·4%) in the DES group, with a difference of 3·04% (95%CI:1·27 to 4·81, p<0·001) in the cumulative event rate, failing to meet the criterion for non-inferiority. The rates of cardiovascular death were 2·3% and 1·2% (difference:1·07%, 95%CI:-0·02 to 2·16, p=0·053), target-vessel myocardial infarction were 1·9% and 1·6% (difference:0·28%, 95%CI:-0·79 to 1·36, p=0·606), and clinically and physiologically indicated TLR were 3·1% vs. 1·2% (difference:1·90%, 95%CI:0·69 to 3·11, p=0·002) in the DCB and DES groups, respectively.

Conclusions

In patients with *de novo*, non-complex coronary artery disease and irrespective of vessel diameter, a

strategy of DCB angioplasty with rescue stenting failed to achieve non-inferiority compared to the intended DES implantation in terms of the device-oriented composite endpoint at two years.

Funding: Xijing Hospital and Shenqi Medical

Key Words: drug-coated balloon; drug-eluting stents; *de novo* lesions

Trial registration: Registered on clinicaltrial.gov (NCT04561739)

Introduction

The contemporary percutaneous treatment of coronary artery disease (CAD) typically involves initial lesion preparation with balloon angioplasty, followed by the intended deployment of drug-eluting stents (DES) to provide an immediate scaffold and to reduce the long-term risk of restenosis. However, stent implantation continues to face notable challenges, primarily because the metallic scaffold left behind, which may distort and permanently cage the coronary vessel from adaptive remodeling, impeding vessel pulsatility, interfering with cell signaling and mechano-transduction, and promoting chronic inflammation.[1-3]

Drug-coated balloon (DCB) angioplasty represents a novel approach to the treatment of CAD.[4] Following adequate lesion preparation, the expansion of a DCB can rapidly deliver antiproliferative drugs into the arterial wall through a lipophilic matrix, avoiding the need to implant a permanent scaffold, and thereby minimizing the adverse effects associated with maladaptive stent-related biological responses.[1,2,5] The current European Society of Cardiology Guidelines for revascularization give DCBs a Class IA recommendation for the management of in-stent restenosis. [6] The safety and effectiveness of DCB angioplasty with the option of rescue stenting have also been shown to be non-inferior to intended stenting for the treatment of *de novo* small vessel CAD[7] and in patients at high-bleeding risk;[8] however, these results were not yet included in guidelines and were contested due to the small sample size and the lack of standard of care comparator. The feasibility of using DCBs to treat *de novo* coronary arteries irrespective of vessel diameter has also been explored, but only in pilot non-randomized studies and small-scale randomized controlled trials with surrogate endpoints.[1,2,9] Consequently, in contemporary practice, the unrestricted use of DCBs in *de novo* lesions remains controversial.[1]

To fill this gap in knowledge, we designed the REC-CAGEFREE I trial, which enrolled patients with *de novo*, non-complex CAD, irrespective of target vessel diameter, and compared DCB angioplasty with rescue stenting versus intended stenting using the device-oriented composite endpoint assessed at two years.

Methods

Trial design and oversight

The REC-CAGEFREE I trial was an investigator-initiated, multicenter, randomized, open-label, non-inferiority trial conducted in 43 sites across China. The rationale and design of the trial have been described previously.[10] The trial was designed by the first and last authors, conducted in accordance with the Declaration of Helsinki and Good Clinical Practice guidelines, and was approved by the institutional review board at each center. Written informed consent was obtained from all patients. An independent data and safety monitoring board provided external oversight to ensure the safety of trial participants. The committee members and participating investigators can be found in the Appendix.

Participants

Patients requiring percutaneous coronary intervention (PCI) either due to acute or chronic coronary syndrome with *de novo*, non-complex target lesions(s) were eligible for enrolment.[6] There were no restrictions on the treated vessel diameter. Importantly, randomization was only conducted after successfully achieving satisfactory pre-dilatation of the target lesion, as per the consensus group recommendations,[2,5] and defined as no dissection type D, E, or F according to National Heart, Lung, and Blood Institute [NHLBI] classification, no decreased blood flow [TIMI, thrombolysis in myocardial infarction flow≤2], or no residual stenosis >30% by visual assessment. The standby eligibility screening committees assessed all cases to ensure that enrolled participants had fulfilled the requirements for lesion types and pre-dilatation. Patients who had unsuccessful pre-dilatation were not randomized but were included in a separate nested registry. Non-complex PCI [11,12] was defined as meeting all the following criteria: 1) planned treated lesions/vessels <3, planned DES or DCB <3, or planned total DES/DCB length≤60 mm; 2) Bifurcations not requiring treatment in both main and side branch; 3) Non left main lesion; 4) Non venous or arterial graft lesion; 5) Non chronic total occlusion; and 6) Not requiring atherectomy. Key exclusion criteria included age below 18, cardiogenic shock, or in-stent restenosis requiring revascularization. A full list of the inclusion and exclusion criteria are listed in **Table S2**. Patient sex data were collected from medical records.

Randomization, masking, and follow-up

Eligible patients were randomized in a 1:1 ratio using a web-based centralized system to receive

either the strategy of DCB angioplasty with the option of rescue stenting or intended DES deployment. Randomization sequences were computer-generated with dynamic permuted block method with block sizes of two, four, or six and were stratified by site. Patients and investigators who enrolled them were not blinded to the treatment allocation; however, members of the independent clinical event committee (CEC) who adjudicated the endpoints and statisticians who developed statistical programs, were blinded to treatment allocation.

Follow-up visits, which were scheduled at 1 (±14 days), 3, 6, 12, 18, and 24 (±30 days) months after randomization, were preferably conducted on-site; however, if patients were unable or unwilling to visit the outpatient clinic, the scheduled visit could be replaced by a telephone call except for the 30-day, 1- and 2-year visits. After the 2-year visit, follow-up will be conducted annually and kept for up to 10 years. A mobile application operating on the WeChat platform was developed to assess patient's health status, with participants contacted through this application monthly in the first two years of follow-up and then every three months.

Randomized treatment

For patients randomized to the DCB group, the procedural techniques employed were required to follow the recommendations of the German Consensus Group on DCB interventions[5] and the Third Report of the International DCB Consensus Group,[2] as detailed in the Appendix Methods. Following DCB angioplasty, rescue stenting, which used the same stent in the DES group, was mandated in cases of (i) an NHLBI Type D, E, or F dissection, (ii) TIMI flow ≤2, or (iii) a visual residual stenosis >30%. Patients in the DCB group received the Swide DCB (Shenqi Medical, Shanghai, China, Figure S1), which is a balloon spray coated via ultrasound with crystals <2μm containing a mixture of paclitaxel (dose 3μg/mm^2) and iopromide.[13] Previously, the Swide DCB was shown to be non-inferior to the SeQuent Please DCB (B Braun, Germany), which is also a paclitaxel-iopromide coated DCB with 3μg of paclitaxel per mm^2, for the primary endpoint of 9-month in-segment late loss in patients with in-stent restenosis.[14] For patients randomized to the DES group, the procedural techniques employed needed to follow routine local clinical practice and established guidelines.[6] Patients in the DES group received the Firebird 2 DES (MicroPort, Shanghai, China), which is a sirolimus-eluting DES with an L605 cobalt chromium alloy platform, 86 μm thick struts, and a durable polymer which elutes 80% of the sirolimus

within 30 days. The effectiveness and safety of the Firebird2 DES have been confirmed in real-world populations and randomized studies.[15,16]

All study patients received antithrombotic drugs according to international guidelines.[6] All subjects received dual-antiplatelet therapy (DAPT) for at least one month, with the final duration left to the discretion of the implanting physician, following which patients were required to receive aspirin or clopidogrel monotherapy indefinitely. Physicians had discretion over other medical treatments. However, it was strongly advised they implemented guideline-directed medical therapy to address the patient's specific condition.

Trial outcomes

The primary endpoint was the Device-oriented Composite Endpoint (DoCE, a composite of cardiovascular death, target vessel myocardial infarction [MI], and clinically and physiologically indicated target lesion revascularization [TLR]) assessed at 24 months (Table S3). A TLR was considered clinically and physiologically indicated if associated with wire-based/angiography-derived fractional flow reserve ≤0.80 or diameter stenosis ≥70% by quantitative coronary angiography (detailed definitions in Appendix)[17,18]. Secondary endpoints included Patient-oriented Composite Endpoint (PoCE, all-cause death, any stroke, any MI, and any revascularization), target vessel failure (TVF, cardiovascular death, target vessel-MI, and clinically and physiologically indicated target vessel revascularization [TVR]), Bleeding Academic Research Consortium [BARC]-defined type 3 or 5 bleeding, Net Adverse Clinical Events (NACE, including PoCE and BARC 3 or 5 bleeding events), definite or probable device/vessel thrombosis, and the individual components of DoCE, PoCE, and TVF. Outcome events were adjudicated by an independent CEC according to the definitions of the Academic Research Consortium (ARC)-2,[17] the SCAI consensus for peri-procedure MI within 48 hours of the index procedure, [19] the Fourth Universal Definition of MI for spontaneous MI, [20] and BARC (detailed definitions in Appendix)[21]. Adverse events were centrally collected. Any document that could lead to the unblinding of treatment assignment was redacted before submission to the CEC.

Statistical analysis

Sample size and power calculations were based on a non-inferiority assumption for the primary outcome. According to data from previous trials,[11,22] we assumed that 6·7% of patients in the intended

DES group would reach the primary endpoint at two years. The non-inferiority margin of 2·68% (40% of the difference in the event rate) was chosen based on clinically acceptable relevance according to the margins in previous pivotal trials comparing DCB to DES [7] or one DES to another.[23,24] Considering an anticipated 5% patient attrition rate, with a total of 2,270 patients, the study is estimated to have 80% power to show non-inferiority with a 5% one-sided α error rate.[7,23,24]

The primary analysis was based on an unadjusted estimate of treatment difference (DCB group minus DES group) in the cumulative event rate of the primary endpoint in the intention-to-treat (ITT) population, which was estimated at 720 days by the Kaplan-Meier (KM) method, with the standard error of difference calculated using Greenwood's method. Non-inferiority would be concluded when the upper limit of the one-sided 95%CI in the treatment difference of the primary endpoint was less than 2·68%. In addition, a covariate-adjusted analysis of the primary endpoint, considering the pre-specified covariates and center effect, was conducted as a sensitivity analysis (Appendix Methods). All reported secondary endpoints were pre-specified, but the CIs were not adjusted for multiple comparisons, so these intervals should not be used to infer definitive treatment effects. The secondary endpoints involving hierarchical orders were analyzed using the win ratio method (Appendix Methods).[10] For other secondary endpoints, the differences in cumulative event rates and their two-sided 95%CIs are reported. Prespecified subgroup analyses (age, sex, diabetes, acute coronary syndrome, chronic kidney disease, proximal LAD, small vessel CAD, bifurcation, multivessel treated, and center volume) were done with Cox proportional-hazards regression models, presented as hazard ratios (HRs) with 95%CIs, and incorporated an interaction term. The proportional hazards assumption was assessed using Schoenfeld residuals and visual assessment of log(−log) plots.

The main results are described in the ITT population. The primary outcome and secondary outcomes were also analyzed in the per-protocol (patients received their assigned treatment without major protocol violation, detailed in Table S5) and as-treated populations (patients analyzed by the treatment they actually received). The analysis was done using the R statistical software version 4.2.1 (R Project for Statistical Computing). This trial is registered at Clinicaltrial.gov, NCT04561739.

Role of the funding source

This trial is an investigator-initiated trial sponsored by Xijing Hospital. The study obtained grant

226 support from Xijing Hospital (Xi'an, China; Grant No. XJZT24LY36) and unrestricted grant support
227 from Shenqi Medical (Shanghai, China). Apart from this sponsorship, Shenqi was not involved in the
228 study design, data collection, analysis, interpretation, or writing of the report, and did not participate in
229 the decision to submit the manuscript for publication. The corresponding authors had final responsibility
230 for the decision to submit for publication.

Results

Between February 5th, 2021, and May 1st, 2022, 2,902 eligible patients with *de novo* and non-complex CAD underwent lesion preparation; 2,272 (78.3%) patients had successful lesion pre-dilatation and were included in the randomized cohort, whereas 630 (21·7%) met at least one criterion of unsuccessful pre-dilatation and were included in the separate nested registry. Of those patients who were included in the randomized cohort, 1,133 were assigned to the DCB group and 1,139 to the DES group (Figure 1).

Patient demographic and lesion characteristics at baseline are shown in Tables 1 and 2. The mean age of patients was 61·4 years, 69·3% were men, 27·3% were diabetics, 8·3% had prior stroke, 8·2% had prior MI, 12·3% had prior PCI, and 55·4% of patients had acute coronary syndrome. The SYNTAX score was low, with a mean value of 7·4±4·8. Half of the lesions were in the left anterior descending artery, 48·4% were small vessel CAD, and 31·8% involved bifurcation. In 64·5% of patients, pre-dilatation was performed using cutting or scoring balloons. The mean diameters of the two devices were 2.99±0·44 and 3·06±0·47 mm in the DCB and DES groups, respectively. Medications at discharge and follow-up were presented in Table S4.

For patients allocated to the DCB group, 106 (9·4%) patients received rescue DES after unsatisfactory DCB angioplasty, in which 87 patients were due to dissection type D, E, or F and 19 patients due to visual residue stenosis >30%. These patients were included in the DCB group in the ITT and PP populations (not considered as protocol violations) but were incorporated into the DES group in the as-treated analysis. At 720 days, complete follow-up data were available for 2,258 patients (99·4%); follow-up data for the two patients who withdrew consent and the 12 who were lost to follow-up were censored at their last contact.

In the ITT population, DoCE occurred in 72 (6·4%) patients in the DCB group and 38 (3·4%) in the DES group at 24 months, with the difference of 3·04% (95%CI:1·27 to 4·81, p<0·001) in the cumulative event rate, failing to meet the criterion of 2·68% for non-inferiority (upper boundary of the one-sided 95%CI:4·52%, $p_{noninferiority}$=0·654, Figure 2A, Table 3). The covariate-adjusted analysis of the primary endpoint showed consistent results with the primary analysis (difference 3·10%, 95%CI:1·34 to 4·86, p=0·001). In the per-protocol population, DoCE occurred in 71 (6·4%) patients in the DCB

group and 37 (3·3%) in the DES group at 24 months (difference 3·08%, 95%CI:1·30 to 4·86, p<0·001, Tables S5, S6, and Figure S2); in the as-treated analysis, DoCE occurred in 60 (6·0%) patients in the DCB group and 49 (4·0%) in the DES group (difference 1·96%, 95%CI:0·13 to 3·79, p=0.036, Table S6 and Figure S3). Non-inferiority was not met in the per-protocol or as-treated analyses.

At 24 months, the rates of cardiovascular death were 2·3% and 1·2% (difference:1·07%, 95%CI:-0·02 to 2·16, p=0·053, Figure 2B, Table 3), target-vessel myocardial infarction were 1·9% and 1·6% (difference:0·28%, 95%CI:-0·79 to 1·36, p=0·606, Figure 2C), and clinically and physiologically indicated TLR were 3·1% vs. 1·2% (difference:1·90%, 95%CI:0·69 to 3·11, p=0·002, Figure 2D) in the DCB and DES groups, respectively.

The rates of death, stroke, or MI at 24 months did not differ significantly between the two groups. However, the rates of any revascularization (7·0% vs. 4·6%, difference:2·39%, 95%CI:0·45 to 4·32, p=0·016) and TVR (4·8% vs. 1·8%, difference:3·07%, 95%CI:1·60 to 4·55, p<0·001) were both significantly higher in the DCB versus the DES group; consequently, the rates of PoCE, NACE, and TVF were all significantly higher in the DCB group. There was no acute vessel closure in the DCB group but one in the DES group. Peri-procedural MI occurred in 10 (0·9%) patients in the DCB group and 9 (0·8%) in the DES group (Table 3). Other secondary outcomes are shown in Table S7 and a list of all adverse events is shown in Table S8.

There was no significant treatment by subgroup interactions for the primary endpoint (Figure 4) except for the small vessel CAD subgroup ($p_{interaction}$=0.020, Figure 3). In the non-small vessel CAD subgroup (defined by device diameter≥3.0 mm), DoCE occurred in 45 (7·5%) patients in the DCB group and 16 (2·5%) in the DES group (difference:4·98%, 95%CI:2·54 to 7·42), whereas in the small vessel CAD subgroup, DoCE occurred in 27 (5·1%) patients in the DCB group and 22 (4·4%) in the DES group (difference:0·72%, 95%CI:-1·88 to 3·32). Nevertheless, it should be noted that the secondary outcomes and subgroup analyses were not adjusted for multiple comparisons and, therefore, should be interpreted cautiously and as considered as exploratory.

Commented [DW1]: This statement is not a presentation of statistical result but a comment and should be removed as it is already mentioned in the Discussion.

Discussion

The REC-CAGEFREE I study investigated the use of DCB with the option of rescue stenting versus intended stenting in patients with *de novo*, non-complex CAD regardless of the target vessel diameter. We found that at two years, patients in the DCB group had a significantly higher rate of DoCE than the DES group. The rate of clinically and physiologically indicated TLR was also significantly higher in the DCB group.

Since the first approval of bare-metal stents (BMS),[25,26] there was concern that intended BMS implantation without first trying to obtain satisfactory results with plain old balloon angioplasty (POBA) alone would increase the occurrence of in-stent restenosis. Consequently, studies were conducted to compare POBA with rescue BMS versus intended BMS deployment.[27,28] The OPUS-1 trial[28] in the setting of native coronary arteries with a reference diameter of at least 3·0 mm showed that clinical outcomes with intended BMS were better than that of POBA with rescue BMS, which was mainly driven by the lower risk of TVR. Notably, the study also highlighted the difficulty in attaining a satisfactory result solely with POBA, with 37% of patients in the POBA group crossing over to BMS implantation.[28] In the current study, because it has been suggested that pre-dilatation using cutting or scoring balloons can increase the chance of achieving a satisfactory result and reducing the risk of needing rescue stenting,[9] we recommended their use in the study protocol. Consequently, for pre-dilatation (before randomization), a high proportion of lesions (65%) were treated by cutting or scoring balloons. Nevertheless, there were still 21·7% of our patients failed to reach the criteria of successful pre-dilatation and were not randomized, while 9·4% of those who were randomized needed rescue stenting after DCB angioplasty.

In the era of local dispensing of anti-restenotic drugs directly into the coronary artery, the introduction of DES has revolutionized the field and established itself as the preferred treatment for patients undergoing PCI.[6] DCBs were also introduced with the aim of avoiding the adverse effects associated with the maladaptive biological response induced by the implantation of a permanent prosthesis, which transiently elutes cytostatic or cytotoxic drugs.[2,4,6] Two decades after the early trials comparing provisional POBA versus intended BMS, now new studies have been conducted to test the next iteration of the same strategy, with POBA being replaced with a DCB and BMS with DES. The

safety and efficacy of using DCBs in *de novo* lesions in coronary arteries irrespective of vessel diameter have been inferred; however, these conclusions are based on data of limited power, being derived from small-scale angiographic investigations or non-randomized studies.[1,2,9,29] In the current study, with a large population, we found that the strategy of DCB with rescue stenting was inferior to the intended DES in terms of the DoCE at 2 years. Notably, the KM curves of DoCE and revascularization between DCB and DES began to diverge at approximately 100 days favoring DES. This finding is similar to the studies comparing POBA to BMS,[25,27,28] in which the KM curves for revascularization also started to diverge, this time in favor of BMS, at 80-100 days.[26,28]

Notwithstanding this, in patients with *de novo* small vessel CAD, randomized studies have demonstrated good efficacy and safety with use of DCB.[1,2,7] The BASKET-SMALL 2 trial,[7] which is the largest randomized study investigating DCB to date (758 participants), demonstrated that in patients with *de novo* small vessel CAD, DCB with rescue DES was non-inferior to intended DES in terms of major adverse cardiovascular events over a period of 3 years. In the current study, despite the overall inferior results of the DCB strategy, we found that there was a notable heterogeneity in the treatment effect regarding vessel diameters. While DES was the more favorable option in the non-small vessel CAD cohort, in the small vessel CAD group, which had more than 1,000 patients, our results were in line with previous studies showing that DCB and DES had similar rates of DoCE through two-year follow-up. However, given the hypothesis-generating nature of the subgroup analyses, further dedicated study is still needed to provide a confirmatory conclusion.

The incidence of TVR in the DES group was lower compared with previous studies. In the all-comers GLOBAL LEADERS trial, the definition of non-complex CAD was similar to the current study and 68% of patients had non-complex PCI.[11] At 2 years, the rate of TVR among these patients was 2·7%. In the PRECISE-DAPT pooled dataset (from 8 randomized controlled trials), 79% of patients underwent non-complex PCI and the rate of TVR at 2 years was approximately 3·4%.[12] In the current study, while the rates of target-vessel MI were numerically similar between the two groups, the rates of TVR were 1·8% in the DES group and 4·8% in the DCB group. Although target vessel or lesion revascularization has been frequently used as the component of the composite primary endpoint in trials involving coronary interventions[7,8,23,24] and endorsed by the ARC-2 consensus,[17] the unblinded design of the

current study could have introduced biases by the lower thresholds for suspecting device failure and ordering stress testing and/or repeat invasive angiography in the DCB arm, resulting in more frequent revascularization.[30] Nevertheless, we endeavored to minimize biases by using a blinded CEC, and adjudicating clinical and physiologically indicated TLR as an outcome. In addition, the study will also continue to follow patients for at least 10 years to explore if there is a late catch-up effect with revascularization in the DES group, and to ascertain if the higher risk of revascularization in the DCB group translates into increased mortality or MIs.

Limitations

This study has several limitations. First, this study was an open-label trial. Blinding of the assignment group might not be feasible because of the absence of a metallic scaffold in the DCB group; however, the primary endpoint was based on clinical endpoints, which are less subject to observational and measurement bias and were adjudicated by an independent and blinded CEC. Second, the secondary outcomes and subgroup analyses were not adjusted for multiple comparisons and should be interpreted as exploratory only.[31] Third, patients were treated with paclitaxel-coated balloons only, since sirolimus-coated balloons (SCB) were not commercially available in China during the study period. Therefore, the results should not be extrapolated to SCB, with their clinical efficacy in non-small vessel CAD patients currently being tested in large-scale randomized studies (NCT04859985, NCT04893291). Fourth, it should also be noted that the DCB utilized in the current study (Swide DCB), which is a balloon coated with the mixture of paclitaxel and iopromide (paclitaxel of 3μg/mm^2), is not approved worldwide. Although the DCB has been demonstrated to be non-inferior to other paclitaxel-iopromide-coated balloons such as SeQuent Please DCB (paclitaxel of 3μg/mm^2), caution is advised when considering these paclitaxel-iopromide-coated balloons having a class effect. Fifth, only 30% of the study population is female. Although this proportion is similar to other RCTs on PCI, it should be noted that female patients are still underrepresented.[32] Finally, this study was only conducted in China with an East Asian population. Extrapolating these results to other ethnic groups warrants further investigation.

Commented [DW2]: This should not be accounted as a limitation as we did not draw any conclusion from the subgroup analysis.

Conclusions

In patients with *de novo*, non-complex CAD and regardless of vessel diameter, the strategy of the paclitaxel-coated balloon angioplasty with the option of rescue stenting failed to achieve non-inferiority

compared to the intended DES implantation with respect to the occurrence of device-oriented composite endpoint at 2 years.

Contributors

TL and CG conceived and designed the trial; TL acquired the financial support; TL, CG, and XH wrote the original and final version of the manuscript; FO, ZZ, GS, MW, PY, LM, FY, ZJ, HW, YW, ZF, HJ, SW, YL, FL, JZ, BZ, YL, RZ, TZ, and PS enrolled the participants or collected the data; JL, ZJ, JX, and DW performed the statistical analyses and wrote the statistical analysis plan; SG, RJvG, YO, DC, DW, and PWS contributed to the interpretation of the results and revised the manuscript. RJvG, DC, YO, and PWS participated in conceiving the study protocol, RJvG, YO, and PWS edited the study protocol. All authors provided critical feedback, helped shape the manuscript, and accepted responsibility for submitting it for publication.

Conflict of interest statement

PS reported receiving consulting fees from Sahajanand Medical Technologies, Novartis, Merillife, Xeltis, and Philips/Volcano outside the submitted work. DC reported receiving honoraria from Terumo, Sanofi Aventis, and Medtronic and participated in the advisory board of Abbott Vascular outside the submitted work. ZJ is the founder of Beijing KeyTech Statistical Consulting Co and has stock of the company. RJvG reported receiving unrestricted research grant and honoraria from AstraZeneca. No other disclosures were reported. No co-authors received fees to write this article.

Data Sharing

The REC-CAGEFREE I trial is planning to continue follow-up until 2032. Until then, no individual participant data will be available. Any relevant inquiries should be sent to the corresponding author.

Protocol and statistical analysis plan

The Protocol and statistical analysis plan of the REC-CAGEFREE I trial were submitted in the supplementary files.

References

1. Yerasi C, Case BC, Forrestal BJ, et al. Drug-Coated Balloon for De Novo Coronary Artery Disease: JACC State-of-the-Art Review. *Journal of the American College of Cardiology* 2020; **75**(9): 1061-73.
2. Jeger RV, Eccleshall S, Wan Ahmad WA, et al. Drug-Coated Balloons for Coronary Artery Disease: Third Report of the International DCB Consensus Group. *JACC Cardiovascular interventions* 2020; **13**(12): 1391-402.
3. Serruys PW, Garcia-Garcia HM, Onuma Y. From metallic cages to transient bioresorbable scaffolds: change in paradigm of coronary revascularization in the upcoming decade? *Eur Heart J* 2012; **33**(1): 16-25b.
4. Scheller B, Speck U, Abramjuk C, Bernhardt U, Bohm M, Nickenig G. Paclitaxel balloon coating, a novel method for prevention and therapy of restenosis. *Circulation* 2004; **110**(7): 810-4.
5. Kleber FX, Rittger H, Bonaventura K, et al. Drug-coated balloons for treatment of coronary artery disease: updated recommendations from a consensus group. *Clinical research in cardiology : official journal of the German Cardiac Society* 2013; **102**(11): 785-97.
6. Neumann FJ, Sousa-Uva M, Ahlsson A, et al. 2018 ESC/EACTS Guidelines on myocardial revascularization. *Eur Heart J* 2019; **40**(2): 87-165.
7. Jeger RV, Farah A, Ohlow MA, et al. Long-term efficacy and safety of drug-coated balloons versus drug-eluting stents for small coronary artery disease (BASKET-SMALL 2): 3-year follow-up of a randomised, non-inferiority trial. *Lancet* 2020; **396**(10261): 1504-10.
8. Rissanen TT, Uskela S, Eranen J, et al. Drug-coated balloon for treatment of de-novo coronary artery lesions in patients with high bleeding risk (DEBUT): a single-blind, randomised, non-inferiority trial. *Lancet* 2019; **394**(10194): 230-9.
9. Muramatsu T, Kozuma K, Tanabe K, et al. Clinical expert consensus document on drug-coated balloon for coronary artery disease from the Japanese Association of Cardiovascular Intervention and Therapeutics. *Cardiovasc Interv Ther* 2023; **38**(2): 166-76.
10. Gao C, He X, Liu Y, et al. Drug-coated balloon angioplasty with provisional stenting versus primary stenting for the treatment of de novo coronary artery lesions: REC-CAGEFREE I trial rationale and design. *BMC Cardiovasc Disord* 2024; **24**(1): 319.
11. Serruys PW, Takahashi K, Chichareon P, et al. Impact of long-term ticagrelor monotherapy following 1-month dual antiplatelet therapy in patients who underwent complex percutaneous coronary intervention: insights from the Global Leaders trial. *Eur Heart J* 2019; **40**(31): 2595-604.
12. Costa F, Van Klaveren D, Feres F, et al. Dual Antiplatelet Therapy Duration Based on Ischemic and Bleeding Risks After Coronary Stenting. *Journal of the American College of Cardiology* 2019; **73**(7): 741-54.
13. Zhu Z, Han H, Zhu J, et al. Safety and efficacy of a novel iopromide-based paclitaxel-eluting balloon following bare metal stent implantation in rabbit aorta abdominalis. *Biomed Mater Eng* 2015; **26**(1-2): 79-88.
14. Zhu J, Liu L, Zhu Z, et al. A randomized comparison of a novel iopromide-based paclitaxel-coated balloon Shenqi versus SeQuent Please for the treatment of in-stent restenosis. *Coron Artery Dis* 2021; **32**(6): 526-33.
15. Han Y, Xu B, Jing Q, et al. A randomized comparison of novel biodegradable polymer- and durable

polymer-coated cobalt-chromium sirolimus-eluting stents. *JACC Cardiovascular interventions* 2014; **7**(12): 1352-60.
16. Ge JB, Zhang F, Qian JY, Ge L, Liu XB, Zhou J. Six-month clinical outcomes of Firebird 2TM sirolimus-eluting stent implantation in real-world patients with coronary artery diseases. *Chin Med J (Engl)* 2011; **124**(6): 831-5.
17. Garcia-Garcia HM, McFadden EP, Farb A, et al. Standardized End Point Definitions for Coronary Intervention Trials: The Academic Research Consortium-2 Consensus Document. *Eur Heart J* 2018; **39**(23): 2192-207.
18. Wang R, Kawashima H, Hara H, et al. Comparison of Clinically Adjudicated Versus Flow-Based Adjudication of Revascularization Events in Randomized Controlled Trials. *Circ Cardiovasc Qual Outcomes* 2021; **14**(11): e008055.
19. Moussa ID, Klein LW, Shah B, et al. Consideration of a new definition of clinically relevant myocardial infarction after coronary revascularization: an expert consensus document from the Society for Cardiovascular Angiography and Interventions (SCAI). *J Am Coll Cardiol* 2013; **62**(17): 1563-70.
20. Thygesen K, Alpert JS, Jaffe AS, et al. Fourth universal definition of myocardial infarction (2018). *Eur Heart J* 2019; **40**(3): 237-69.
21. Mehran R, Rao SV, Bhatt DL, et al. Standardized bleeding definitions for cardiovascular clinical trials: a consensus report from the Bleeding Academic Research Consortium. *Circulation* 2011; **123**(23): 2736-47.
22. Gao C, Kogame N, Sharif F, et al. Prospective Multicenter Randomized All-Comers Trial to Assess the Safety and Effectiveness of the Ultra-Thin Strut Sirolimus-Eluting Coronary Stent Supraflex: Two-Year Outcomes of the TALENT Trial. *Circ Cardiovasc Interv* 2021; **14**(3): e010312.
23. Zaman A, de Winter RJ, Kogame N, et al. Safety and efficacy of a sirolimus-eluting coronary stent with ultra-thin strut for treatment of atherosclerotic lesions (TALENT): a prospective multicentre randomised controlled trial. *Lancet* 2019; **393**(10175): 987-97.
24. Lansky A, Wijns W, Xu B, et al. Targeted therapy with a localised abluminal groove, low-dose sirolimus-eluting, biodegradable polymer coronary stent (TARGET All Comers): a multicentre, open-label, randomised non-inferiority trial. *Lancet* 2018; **392**(10153): 1117-26.
25. Fischman DL, Leon MB, Baim DS, et al. A randomized comparison of coronary-stent placement and balloon angioplasty in the treatment of coronary artery disease. Stent Restenosis Study Investigators. *The New England journal of medicine* 1994; **331**(8): 496-501.
26. Serruys PW, de Jaegere P, Kiemeneij F, et al. A comparison of balloon-expandable-stent implantation with balloon angioplasty in patients with coronary artery disease. Benestent Study Group. *The New England journal of medicine* 1994; **331**(8): 489-95.
27. Al Suwaidi J, Berger PB, Holmes DR, Jr. Coronary artery stents. *Jama* 2000; **284**(14): 1828-36.
28. Weaver WD, Reisman MA, Griffin JJ, et al. Optimum percutaneous transluminal coronary angioplasty compared with routine stent strategy trial (OPUS-1): a randomised trial. *Lancet* 2000; **355**(9222): 2199-203.
29. Niehe SR, Vos NS, Van Der Schaaf RJ, et al. 5-Year Clinical Outcomes of Paclitaxel-Coated Balloon Angioplasty vs DES in Acute MI: The REVELATION Trial. *JACC Cardiovascular interventions* 2024.
30. Lamelas P, Belardi J, Whitlock R, Stone GW. Limitations of Repeat Revascularization as an

476 Outcome Measure: JACC Review Topic of the Week. *Journal of the American College of Cardiology*
477 2019; **74**(25): 3164-73.
478 31. Pocock SJ, Rossello X, Owen R, Collier TJ, Stone GW, Rockhold FW. Primary and Secondary
479 Outcome Reporting in Randomized Trials: JACC State-of-the-Art Review. *Journal of the American*
480 *College of Cardiology* 2021; **78**(8): 827-39.
481 32. Mas-Llado C, Gonzalez-Del-Hoyo M, Siquier-Padilla J, et al. Representativeness in randomised
482 clinical trials supporting acute coronary syndrome guidelines. *Eur Heart J Qual Care Clin Outcomes*
483 2023; **9**(8): 796-805.
484

Panel research in context

Evidence before this study

Second-generation drug-eluting stents (DES) are the standard treatment for coronary artery disease (CAD). However, stent implantation continues to face notable challenges as the metallic scaffold left behind in the vessel may distort and constrain the coronary vessel, impede vessel pulsatility and adaptive remodeling, and promote chronic inflammation. Drug-coated balloons (DCB) are an established treatment option for in-stent restenosis, with studies also confirming their efficacy and safety in the treatment of native small vessel CAD. The use of DCBs with rescue stenting for the treatment of *de novo* coronary arteries, irrespective of vessel diameter, has also been explored and was tentatively supported by non-randomized data and small-scale randomized controlled trials (RCT) with surrogate endpoints.

Added value of this study

The REC-CAGEFREE I is the first RCT with a large population and powered clinical endpoint to investigate the strategy of paclitaxel-coated balloon angioplasty with rescue stenting versus intended stenting in patients with *de novo*, non-complex CAD regardless of target vessel diameter. After successful lesion pre-dilatation, 2,272 patients were randomized to one of the two strategy groups. The findings show that at two years, the primary composite endpoint of cardiovascular death, target vessel myocardial infarction, and clinically and physiologically indicated target lesion revascularization occurred in 6·4% of patients in the DCB group and 3·4% in the DES group, with a difference of 3·04% in cumulative event rate, failing to meet the criterion for non-inferiority.

Implications of all the available evidence

The attempted strategy of “leave nothing behind” by using paclitaxel-coated balloons in *de novo* non-complex CAD in all vessel diameters failed to attest non-inferiority compared to an intended DES strategy. DES implantation continues to be the standard of care for these patients, especially those with non-small vessel CAD.

Figure Legends

Figure 1 Patients randomization, treatment, and follow-up of the patients

Figure 2 Kaplan-Meier curves of DoCE and its individual components at 2 years

Figure 3 Kaplan-Meier curves of DoCE by small or non-small vessel CAD at 2 years

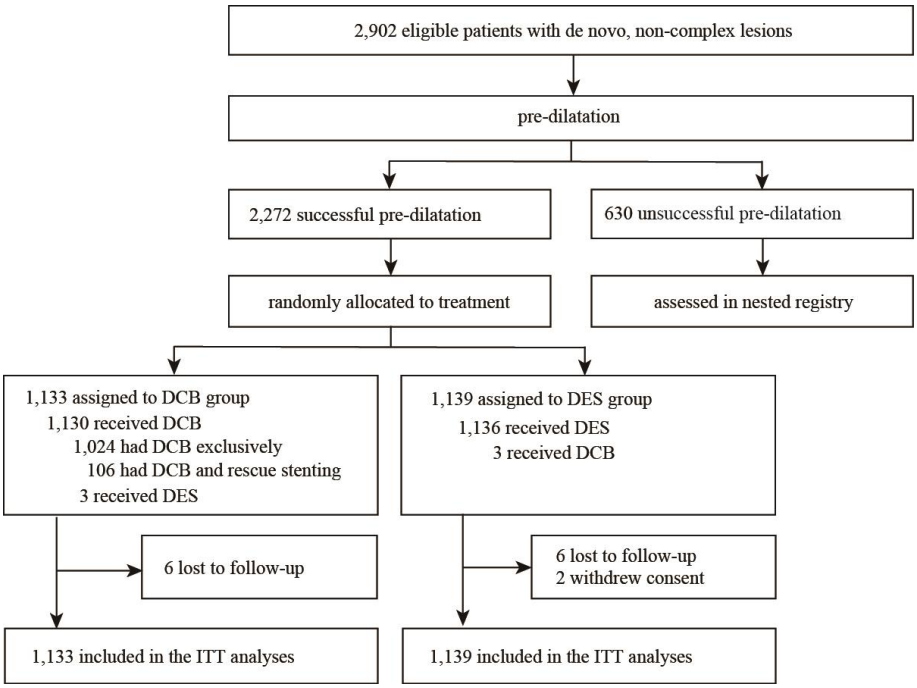
Figure 4 Subgroup analyses and forest plot for DoCE

Table 1 Baseline demographic characteristics in the ITT population

Table 2 Baseline angiographic characteristics in the ITT population

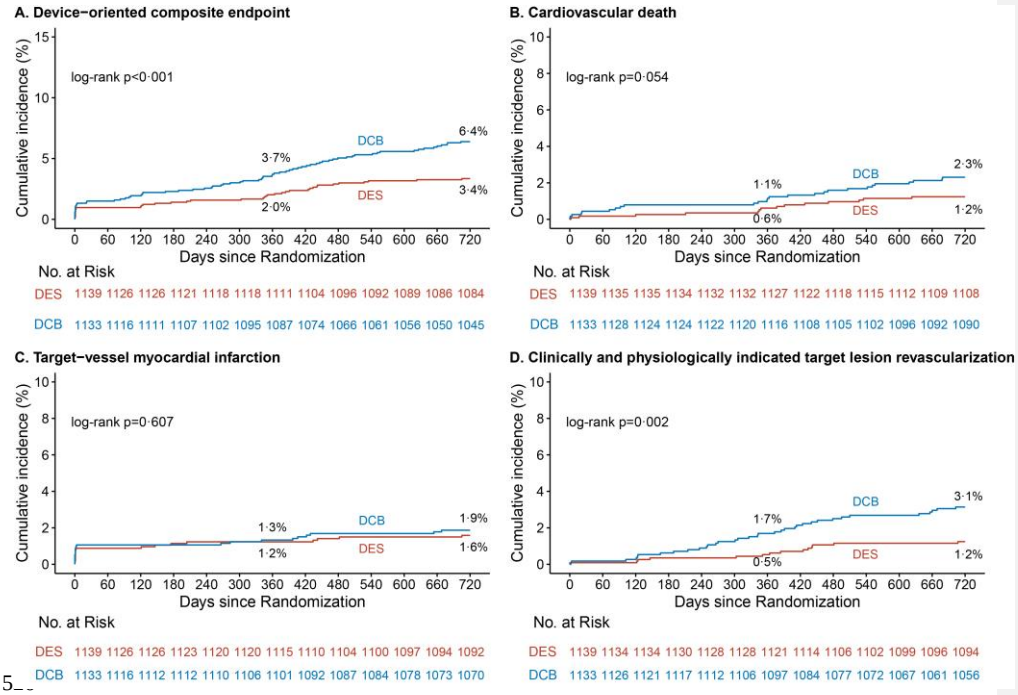
Table 3 Primary and secondary outcomes in the ITT population

Figure 1 Patients randomization, treatment, and follow-up



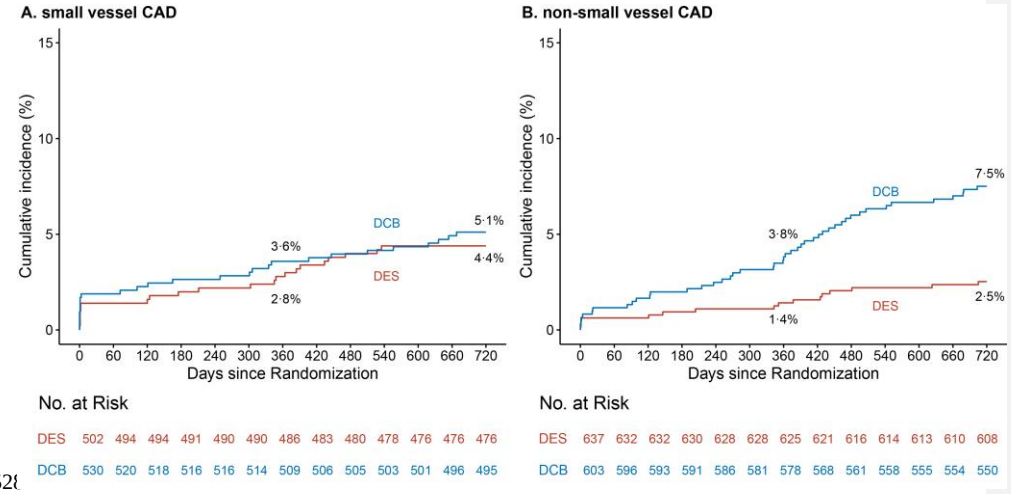
DCB, drug-coated balloon; DES, drug-eluting stent; ITT, intention-to-treat. Outcomes of patients who were lost to follow-up or withdrew consent were included to the point of final contact. Their time-to-event measure was censored at the last contact date.

525 **Figure 2 Kaplan-Meier curves of DoCE and its individual components at 2 years**



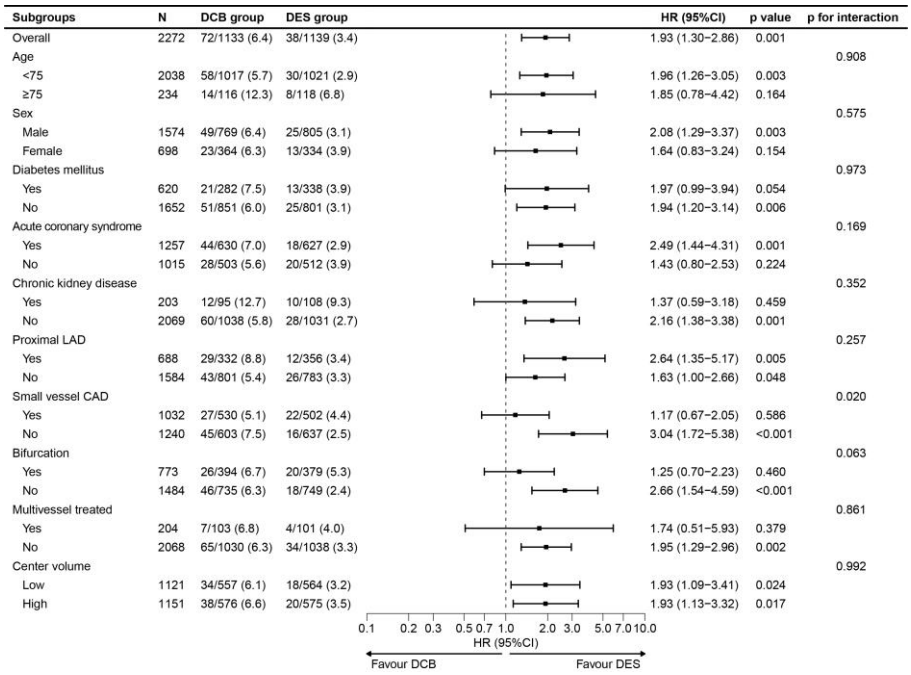
5_

527 **Figure 3 Kaplan-Meier curves for DoCE by small or non-small vessel CAD at 2 years**



528
529

Figure 4 Subgroup analyses and forest plot for DoCE



Subgroups	N	DCB group	DES group	HR (95%CI)	p value	p for interaction
Overall	2272	72/1133 (6.4)	38/1139 (3.4)	1.93 (1.30−2.86)	0.001	
Age						0.908
<75	2038	58/1017 (5.7)	30/1021 (2.9)	1.96 (1.26−3.05)	0.003	
≥75	234	14/116 (12.3)	8/118 (6.8)	1.85 (0.78−4.42)	0.164	
Sex						0.575
Male	1574	49/769 (6.4)	25/805 (3.1)	2.08 (1.29−3.37)	0.003	
Female	698	23/364 (6.3)	13/334 (3.9)	1.64 (0.83−3.24)	0.154	
Diabetes mellitus						0.973
Yes	620	21/282 (7.5)	13/338 (3.9)	1.97 (0.99−3.94)	0.054	
No	1652	51/851 (6.0)	25/801 (3.1)	1.94 (1.20−3.14)	0.006	
Acute coronary syndrome						0.169
Yes	1257	44/630 (7.0)	18/627 (2.9)	2.49 (1.44−4.31)	0.001	
No	1015	28/503 (5.6)	20/512 (3.9)	1.43 (0.80−2.53)	0.224	
Chronic kidney disease						0.352
Yes	203	12/95 (12.7)	10/108 (9.3)	1.37 (0.59−3.18)	0.459	
No	2069	60/1038 (5.8)	28/1031 (2.7)	2.16 (1.38−3.38)	0.001	
Proximal LAD						0.257
Yes	688	29/332 (8.8)	12/356 (3.4)	2.64 (1.35−5.17)	0.005	
No	1584	43/801 (5.4)	26/783 (3.3)	1.63 (1.00−2.66)	0.048	
Small vessel CAD						0.020
Yes	1032	27/530 (5.1)	22/502 (4.4)	1.17 (0.67−2.05)	0.586	
No	1240	45/603 (7.5)	16/637 (2.5)	3.04 (1.72−5.38)	<0.001	
Bifurcation						0.063
Yes	773	26/394 (6.7)	20/379 (5.3)	1.25 (0.70−2.23)	0.460	
No	1484	46/735 (6.3)	18/749 (2.4)	2.66 (1.54−4.59)	<0.001	
Multivessel treated						0.861
Yes	204	7/103 (6.8)	4/101 (4.0)	1.74 (0.51−5.93)	0.379	
No	2068	65/1030 (6.3)	34/1038 (3.3)	1.95 (1.29−2.96)	0.002	
Center volume						0.992
Low	1121	34/557 (6.1)	18/564 (3.2)	1.93 (1.09−3.41)	0.024	
High	1151	38/576 (6.6)	20/575 (3.5)	1.93 (1.13−3.32)	0.017	

Markers represent hazard ratios and lines 95% confidence intervals (CI) for treatment effects within each subgroup using Cox models. Interaction testing on the log hazard scale was performed using the subgroup X treatment group as an additional term in the Cox model. Cumulative incidence was estimated using the Kaplan-Meier method and displayed in the bracket as a percentage. The widths of two-sided 95% CIs were not adjusted for multiple comparisons and should not, therefore, be used for inference about treatment effects.

Table 1 Baseline demographic characteristics in the intention-to-treat population

	DCB (N=1,133)	DES (N=1,139)
Age, years	61·5 (10·3)	61·2 (10·5)
Male sex	769/1,133 (67·9%)	805/1,139 (70·7%)
Body-mass index, kg/m²	24·7 (3·4)	24·9 (3·5)
Smoking		
Former	123/1,133 (10·9%)	125/1,139 (11·0%)
Current	360/1,133 (31·8%)	404/1,139 (35·5%)
Comorbid conditions		
Arterial hypertension	662/1,133 (58·4%)	704/1,139 (61·8%)
Diabetes mellitus	282/1,133 (24·9%)	338/1,139 (29·7%)
Insulin-treated	67/282 (23·8%)	73/338 (21·6%)
Hyperlipidemia	903/1,133 (79·7%)	908/1,139 (79·7%)
Left ventricular ejection fraction ≤40% or previous episode of heart failure	59/1,133 (5·2%)	55/1,139 (4·8%)
Left ventricular ejection fraction, %	59·5 (8·5)	59·7 (8·2)
Previous stroke	94/1,133 (8·3%)	95/1,139 (8·3%)
Previous myocardial infarction	81/1,133 (7·1%)	105/1,139 (9·2%)
Previous PCI	137/1,133 (12·1%)	142/1,139 (12·5%)
COPD	62/1,130 (5·5%)	60/1,134 (5·3%)
Chronic kidney disease	95/1,133 (8·4%)	108/1,139 (9·5%)
Peripheral vascular disease	41/1,133 (3·6%)	59/1,139 (5·2%)
Clinical presentation		
ST-elevation myocardial infarction	181/1,133 (16·0%)	185/1,139 (16·2%)
Non-ST-elevation myocardial infarction	214/1,133 (18·9%)	201/1,139 (17·6%)
Unstable angina	235/1,133 (20·7%)	241/1,139 (21·2%)
Chronic coronary syndrome	503/1,133 (44·4%)	512/1,139 (45·0%)

Data are from the intent-to-treat population and are shown as n/N (%) or mean (SD). Percentages may not total 100 because of rounding. DCB, drug-coated balloon; DES, drug-eluting stent; PCI, percutaneous coronary intervention; COPD, chronic obstructive pulmonary disease. Data on the left ventricular ejection fraction were available for 1,092 patients in the DCB group and for 1,102 in the DES group. Chronic kidney disease was defined as kidney damage (pathologic abnormalities or markers of damage, including abnormalities in blood or urine tests or imaging studies) or an estimated glomerular filtration rate (by the MDRD formula) of less than 60 ml per minute per 1·73 m^2 of body-surface area for at least 3 months. eGFR was available for 1,069 patients in the DCB group and for 1,083 in the DES group.

546 **Table 2 Baseline angiographic characteristics in the intention-to-treat population**

	DCB (N=1,133)	DES (N=1,139)
Patient, total no.	1,133	1,139
Number of lesions treated per patient	1·1 (0·3)	1·1 (0·3)
Number of DCB or DES per patient	1·4 (0·7)	1·3 (0·5)
Length of DCB or DES per patient, mm	32·6 (18·1)	30·0 (14·0)
IVUS/OCT	108/1,133 (9·5%)	127/1,139 (11·2%)
Contrast material used, ml	137·2 (55·0)	143·9 (56·0)
Procedure time, min	39·4 (23·3)	41·1 (23·5)
SYNTAX score	7·3 (4·7)	7·4 (4·9)
Residue SYNTAX score	1·4 (3·0)	1·4 (2·8)
Lesion, total no.	1,266	1,263
Lesion location		
Left main	0/1,266 (0·0%)	0/1,263 (0·0%)
Left anterior descending artery	656/1,266 (51·8%)	626/1,263 (49·6%)
Proximal left anterior descending artery	332/1,266 (26·2%)	356/1,263 (28·2%)
Left circumflex artery	292/1,266 (23·1%)	316/1,263 (25·0%)
Right coronary artery	318/1,266 (25·1%)	321/1,263 (25·4%)
Pre-dilatation	1,266/1,266 (100·0%)	1,262/1,263 (99·9%)
Maximum pre-dilatation balloon diameter, mm	2.82 (0.46)	2.77 (0.48)
Pre-dilatation balloon types		
Semi-compliant balloon	1,000/1,266 (79·0%)	974/1,263 (77·1%)
Non-compliant balloon	523/1,266 (41·3%)	453/1,263 (35·9%)
Cutting or scoring balloon	861/1,266 (68·0%)	770/1,263 (61·0%)
Small vessel (<3·0 mm)	638/1,266 (50·4%)	587/1,263 (46·5%)
Bifurcation involved	410/1,261 (32·5%)	388/1,248 (31·1%)
Thrombus aspiration	37/1,266 (2·9%)	37/1,263 (2·9%)
Number of DCB or DES per lesion	1·2 (0·5)	1·2 (0·4)
Diameter of DCB or DES per device, mm	2.99 (0.44)	3.06 (0.47)
Length of DCB or DES per device, mm	24·0 (5·5)	23·5 (6·4)
Inflation duration of DCB or DES, s	56·6 (13·9)	9·7 (6·8)
Maximum dilatation pressure of DCB or DES, atm	8·9 (2·2)	10·3 (2·6)

547 Data are from the intent-to-treat population and are shown as n/N (%) or mean (SD). Percentages may not total
548 100 because of rounding. DCB, drug-coated balloon; DES, drug-eluting stent; IVUS, intravascular ultrasound;

549 OCT, optical coherence tomography; SYNTAX, The SYNergy between percutaneous coronary intervention with
550 TAXus and cardiac surgery.

551 **Table 3 Primary and secondary outcomes in the intention-to-treat population**

	DCB (N=1,133)	DES (N=1,139)	Difference, % (95%CI)	p value
Primary outcome				
Device-oriented Composite Endpoint *	72/1133 (6·4)	38/1139 (3·4)	3·04 (1·27, 4·81)	<0·001
Primary outcome components				
Cardiovascular death	26/1133 (2·3)	14/1139 (1·2)	1·07 (-0·02, 2·16)	0·053
Target-vessel myocardial infarction	21/1133 (1·9)	18/1139 (1·6)	0·28 (-0·79, 1·36)	0·606
Clinically and physiologically indicated target lesion revascularization	35/1133 (3·1)	14/1139 (1·2)	1·90 (0·69, 3·11)	0·002
Secondary outcomes				
Patient-oriented Composite Endpoint	134/1133 (11·9)	90/1139 (7·9)	3·93 (1·48, 6·39)	0·002
Net Adverse Clinical Events	138/1133 (12·2)	105/1139 (9·2)	2·97 (0·42, 5·51)	0·022
Target-vessel failure	74/1133 (6·6)	41/1139 (3·6)	2·95 (1·14, 4·76)	0·001
Any death	37/1133 (3·3)	23/1139 (2·0)	1·25 (-0·07, 2·57)	0·064
Cardiovascular death	26/1133 (2·3)	14/1139 (1·2)	1·07 (-0·02, 2·16)	0·053
Any stroke	15/1133 (1·3)	10/1139 (0·9)	0·46 (-0·41, 1·32)	0·303
Any myocardial infarction †	23/1133 (2·1)	23/1139 (2·0)	0·02 (-1·14, 1·19)	0·968
Q wave	3/1133 (0·3)	5/1139 (0·4)	-0·18 (-0·66, 0·31)	0·482
Non-Q wave	20/1133 (1·8)	18/1139 (1·6)	0·20 (-0·87, 1·26)	0·715
Target-vessel myocardial infarction	21/1133 (1·9)	18/1139 (1·6)	0·28 (-0·79, 1·36)	0·606
Periprocedural myocardial infarction	10/1133 (0·9)	9/1139 (0·8)	0·09 (-0·66, 0·84)	0·808
Any revascularization	78/1133 (7·0)	52/1139 (4·6)	2·39 (0·45, 4·32)	0·016
Target lesion revascularization	49/1133 (4·4)	15/1139 (1·3)	3·07 (1·69, 4·45)	<0·001
Clinically and physiologically indicated	35/1133 (3·1)	14/1139 (1·2)	1·90 (0·69, 3·11)	0·002
Target vessel revascularization	54/1133 (4·8)	20/1139 (1·8)	3·07 (1·60, 4·55)	<0·001
Clinically and physiologically indicated	37/1133 (3·3)	18/1139 (1·6)	1·73 (0·44, 3·01)	0·008
Non-target vessel revascularization	31/1133 (2·8)	37/1139 (3·3)	-0·50 (-1·92, 0·92)	0·492
Definite or probable device/vessel thrombosis	4/1133 (0·4)	3/1139 (0·3)	0·09 (-0·37, 0·55)	0·689
BARC type 3 or 5 bleeding	16/1133 (1·4)	27/1139 (2·4)	-0·96 (-2·09, 0·17)	0·096
Hierarchical composite clinical endpoint of cardiovascular death, TV-MI, and clinically and physiologically indicated TLR ‡	41,614 (3·2)	80,089 (6·2)	0.52 (0·36, 0·76)	<0·001

552 Primary and secondary outcomes were evaluated in the intention-to-treat population at 24 months after
553 randomization. The percentages in brackets were estimated from the Kaplan-Meier method and the test statistics
554 for their differences were calculated using the Z-test with the standard errors calculated from the Greenwood's
555 method. TV-MI, target-vessel myocardial infarction; TLR, target lesion revascularization.

*For the between-group difference in the cumulative event rate of the primary outcome, the upper boundary of the one-sided 95% confidence interval was 4·52 percentage points, and the p value for non-inferiority was 0·654.

†Determined based on the Society for Cardiovascular Angiography and Interventions 2013 definition within 48h post-procedure or the fourth universal definition after 48h post-procedure.

‡Assessed with the use of a win ratio approach. The total number of wins (proportion) in each group, unmatched win ratio (95%CI), and p value are displayed.