# Stepwise dual antiplatelet therapy de-escalation in patients after drug coated balloon angioplasty (REC-CAGEFREE II): multicentre, randomised, open label, assessor blind, non-inferiority trial

Chao Gao,[1] Bin Zhu,[1] Fan Ouyang,[2,11] Shangyu Wen,[3] Yanmin Xu,[4] Wenxia Jia,[5] Ping Yang,[6] Yuquan He,[6] Yiming Zhong,[7] Yimeng Zhou,[8] Zhifu Guo,[9] Guidong Shen,[10] Likun Ma,[11] Liang Xu,[12] Yuzeng Xue,[13] Tao Hu,[1] Qiong Wang,[1] Yi Liu,[1] Ruining Zhang,[1] Jianzheng Liu,[1] Zhiwei Jiang,[14] Jielai Xia,[15] Scot Garg,[16] Robert-Jan van Geuns,[17] Davide Capodanno,[18] Yoshinobu Onuma,[19] Duolao Wang,[20] Patrick Serruys,[19] Ling Tao[1]; on behalf of: for the REC-CAGEFREE II Investigators

For numbered affiliations see end of the article

Correspondence to: L Tao
lingtaofmmu@qq.com;
(ORCID 0000-0002-7076-1185)

Additional material is published online only. To view please visit the journal online.

Cite this as: *BMJ* 2025;388:e082945
http://dx.doi.org/10.1136/bmj-2024-082945

Accepted: 13 February 2025

## ABSTRACT

### OBJECTIVES

To investigate whether a less intense antiplatelet regimen could be used for people receiving drug coated balloons.

### DESIGN

Multicentre, randomised, open label, assessor blind, non-inferiority trial (REC-CAGEFREE II).

### SETTING

41 hospitals in China between 27 November 2021 and 21 January 2023.

### PARTICIPANTS

1948 adults (18-80 years) with acute coronary syndrome who received treatment exclusively with paclitaxel-coated balloons according to the international drug coated balloon consensus.

### INTERVENTIONS

Participants were randomly assigned (1:1) to either the stepwise dual antiplatelet therapy (DAPT) de-escalation group (n=975) consisting of aspirin plus ticagrelor for one month, followed by five months of ticagrelor monotherapy, and then six months of aspirin monotherapy, or to the standard DAPT group (n=973) consisting of aspirin plus ticagrelor for 12 months.

### MAIN OUTCOME MEASURES

The primary endpoint was net adverse clinical events (all cause death, stroke, myocardial infarction, revascularisation, and Bleeding Academic Research Consortium (BARC) type 3 or 5 bleeding) at 12 months in the intention-to-treat population. Non-inferiority was established if the upper limit of the one sided 95% confidence interval (CI) for the absolute risk difference was smaller than 3.2%.

### RESULTS

The mean age of participants was 59.2 years, 74.9% were men, 30.5% had diabetes, and 20.6% were at high bleeding risk. 60.9% of treated lesions were in small vessels, and 17.8% were in-stent restenosis. The mean drug coated balloon diameter was 2.72 mm (standard deviation 0.49). At 12 months, the primary endpoint occurred in 87 (8.9%) participants in the stepwise de-escalation group and 84 (8.6%) in the standard group (difference 0.36%; upper boundary of the one sided 95% CI 2.47%; $P_{non\text{-}inferiority}$=0.013). In the stepwise de-escalation versus standard groups, BARC type 3 or 5 bleeding occurred in four versus 16 participants (0.4% *v* 1.6%, difference −1.19% (95% CI −2.07% to −0.31%), P=0.008), and all cause death, stroke, myocardial infarction, and revascularisation occurred in 84 versus 74 participants (8.6% *v* 7.6%, difference 1.05% (95% CI −1.37% to 3.47%), P=0.396). Treated as having hierarchical clinical importance by the win ratio method, more wins were noted with the stepwise de-escalation group (14.4% wins) compared with the standard group (10.1% wins) for the predefined hierarchical composite endpoint of all cause death, stroke, myocardial infarction, BARC type 3 bleeding, revascularisation, and BARC type 2 bleeding (win ratio 1.43 (95% CI 1.12 to 1.83), P=0.004). Results from the per-protocol and the intention-to-treat analysis were similar.

### CONCLUSIONS

Among participants with acute coronary syndrome who could be treated by drug coated balloons exclusively, a stepwise DAPT de-escalation was non-inferior to 12 month DAPT for net adverse clinical events.

### TRIAL REGISTRATION

Clinicaltrials.gov NCT04971356

## WHAT IS ALREADY KNOWN ON THIS TOPIC

In comparison to drug eluting stents, drug coated balloons (DCB) are associated with quicker vessel healing and less thrombotic burden

People treated with DCB theoretically require less intense antiplatelet therapy

However, to date, no randomized trials have investigated appropriate antiplatelet medications for people treated with DCB

## WHAT THIS STUDY ADDS

The REC-CAGEFREE II is a randomised controlled trial investigating a tailored antiplatelet strategy for patients receiving DCB

People with acute coronary syndrome who received DCB, one month aspirin plus ticagrelor followed by five months of ticagrelor, could be a viable option to standard 12 months of dual antiplatelet therapy

## Introduction

Bleeding after percutaneous coronary intervention remains a substantial clinical challenge, especially in people with acute coronary syndrome who are known to have a greater susceptibility to bleeding and ischaemic events.[1 2] The administration of antiplatelet medications is a major contributing factor to bleeding

events following percutaneous coronary intervention, and providing patients with optimal antiplatelet regimens has emerged as a key treatment modifier for maximising the net clinical benefit.[2] The conventional antiplatelet regimen after treating patients with acute coronary syndrome and percutaneous coronary intervention involves dual antiplatelet therapy (DAPT) using aspirin in combination with a potent P2Y12 inhibitor for 12 months.[1] While this approach effectively reduces the risk of ischaemic events, patients are at a considerable risk of bleeding. To address this issue, alternative antiplatelet strategies, such as the de-escalation of DAPT,[2 3] have been investigated for reducing bleeding after drug eluting stent implantation.

Drug coated balloons (DCBs) have emerged as an attractive therapeutic option for percutaneous coronary intervention, and have been evaluated in randomised trials and used in the real world for treating patients with de novo small-vessel disease,[4 5] who are at high bleeding risk,[6] and being treated with in-stent restenosis lesions,[7 8] which respectively account for 40%,[9] 10%,[10 11] and 10%[8] of all patients with percutaneous coronary intervention. Patients who receive exclusive treatment with DCBs may have the theoretical advantage of adopting a low intensity antiplatelet regimen because of the absence of a metallic scaffold and polymer inside the coronary artery, as well as the shorter local retention of the anti-proliferative drug.[12 13] Among the randomised studies investigating DCBs, such as the BASKET-SMALL 2 trial for de novo small-vessel disease,[4] the DEBUT trial for patients with high bleeding risk,[6] and the AGENT IDE trial for in-stent restenosis,[7] nearly half of the participants had acute coronary syndrome. In real-world registries of DCBs,[14-17] acute coronary syndrome also presented in more than half of the overall population who received DCBs. However, despite extensive research on the optimal antiplatelet strategy for patients with acute coronary syndrome treated with drug eluting stents,[18-26] randomised data investigating the optimal DAPT regimen for the patients receiving DCB is lacking.

To fill this gap in knowledge, we conducted a randomised trial involving patients with acute coronary syndrome who received treatment exclusively with a DCB (eg, for small vessel disease, in-stent restenosis, high bleeding risk, etc) according to the international DCB consensus. We aimed to evaluate a stepwise DAPT de-escalation strategy compared with standard 12 months DAPT with respect to clinical outcomes, including both ischaemic and bleeding events.

## Methods

### Trial design and oversight

The REC-CAGEFREE II trial was an investigator initiated, multicentre, randomised, open label, non-inferiority trial conducted in 41 sites across China. The rationale and design of the trial have been described previously.[27] The trial was conducted in accordance with the Declaration of Helsinki and Good Clinical Practice guidelines, and the protocol was approved by the ethics committee of Xijing Hospital (ID: KY20212080-F-1) and responsible ethics committees in all participating centres. Written informed consent was obtained from all patients. The study protocol and statistical analysis plan are provided in the appendix. An independent data and safety monitoring board provided external oversight to ensure the safety of trial participants. Committee members and participating investigators are listed in the appendix and table S1. This trial is registered at ClinicalTrials.gov, NCT04971356.

### Participants

Participants who had a clinical presentation of acute coronary syndrome (ST/non-ST elevation myocardial infarction or unstable angina) and underwent percutaneous coronary intervention with paclitaxel-coated balloons with no stent implantation were eligible for enrolment. The selection of suitable patients and lesions for DCB treatment and subsequent procedural techniques followed the recommendations of the German Consensus Group on DCB interventions and the third report of the International DCB Consensus Group,[28 13] as detailed in the methods section of the appendix. No restrictions were placed on the type of lesion (de novo or in-stent restenosis), treated vessel diameter, or the specific brand of paclitaxel coated balloon that was used (brands and features of DCBs used are summarised in table S2). Key exclusion criteria included people younger than 18 years and older than 80 years, prior haemorrhagic stroke, need for long term oral anticoagulant therapy, cardiogenic shock, or treatment for in-stent thrombosis. A full list of the inclusion and exclusion criteria are listed in table S3. Data for patient sex, race, and ethnic group were collected from medical records.

### Randomisation, masking, and follow-up

Immediately after percutaneous coronary intervention, patients were randomly assigned in a 1:1 ratio using a web based centralised system to receive either stepwise DAPT de-escalation or standard 12 months DAPT.[3] Randomisation sequences were computer generated with the dynamic permuted block method, with block sizes of two or four, and stratified by site and the type of lesion being treated (de novo or in-stent restenosis). Patients and the investigators were not masked to treatment allocation; however, members of the independent clinical event committee who adjudicated the endpoints and statisticians who developed the statistical programmes were masked to treatment allocation.

Follow-up visits were scheduled to occur at months 1 (within 14 days), 3, 6, and 12 (within 30 days) after randomisation. Visits 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 and one year visits. A mobile application operating on the WeChat platform was developed to facilitate

adherence to the allocated medications; participants were contacted monthly through this application to assess their health status and medication compliance.

### Randomised treatment

Participants who had been randomly assigned to the stepwise DAPT de-escalation group received aspirin plus ticagrelor for one month after the procedure, followed by ticagrelor monotherapy for five months, and then aspirin monotherapy for six months. Participants who had been randomly assigned to the standard DAPT group received aspirin plus ticagrelor for 12 months (figure S1). For maintenance, aspirin was prescribed at 100 mg daily and ticagrelor was prescribed at 90 mg twice daily. Ticagrelor was replaced with clopidogrel in patients who had dyspnoea or who were unable to continue taking ticagrelor. Loading doses of aspirin (300 mg) and ticagrelor (180 mg) were administered in patients who had no history of any antiplatelet medications at the time of percutaneous coronary intervention.[29] Patients prescribed clopidogrel before percutaneous coronary intervention were switched to ticagrelor as soon as possible after randomisation.[30] To maximise adherence to treatment allocation, participants were given all antiplatelet medication free of charge during their follow-up visits. Other medical treatments were left to the physician's discretion, but guideline directed medical treatment was strongly recommended.[29]

### Outcomes

The primary efficacy endpoint was net adverse clinical events (a non-hierarchical composite of all cause death, stroke, myocardial infarction, revascularisation, and Bleeding Academic Research Consortium (BARC) type 3 or 5 bleeding) assessed at 12 months. If non-inferiority was met for the primary efficacy endpoint, then the prespecified secondary efficacy endpoints were assessed in a fixed sequence in the following order: clinically relevant ischaemic or bleeding event, BARC type 2, 3 or 5 bleeding, BARC type 3 or 5 bleeding, BARC type 2 bleeding (table S4). A clinically relevant ischaemic or bleeding event was predefined as a hierarchical composite of all cause death, stroke, myocardial infarction, BARC type 3 bleeding, revascularisation, and BARC type 2 bleeding events with the individual components treated as having different clinical importance by using the win ratio method.[31] This hierarchy was established based on previous studies.[31 32] The safety endpoints include the patient oriented composite endpoint (a non-hierarchical composite of all cause death, stroke, myocardial infarction, and revascularisation), device oriented composite endpoint (a non-hierarchical composite of cardiovascular death, target vessel myocardial infarction, and clinically and physiologically indicated target lesion revascularisation), target vessel failure (a non-hierarchical composite of cardiovascular death, target vessel myocardial infarction, and clinically and physiologically indicated target vessel revascularisation), their individual components, and definite or probable stent (device) thrombosis.

Outcome events were adjudicated by an independent clinical event committee, according to definitions of the Academic Research Consortium-2,[33] the fourth universal definition of myocardial infarction for spontaneous myocardial infarction,[34] and BARC (detailed definitions in appendix methods).[35] Adverse events were centrally collected, and any document that could lead to unblinding of treatment assignment was redacted before submission to the clinical event committee.

### Statistical analysis

Sample size and power calculations were based on a non-inferiority assumption for the primary outcome. According to data from previous trials,[21 36] we assumed that 8% of patients in the standard DAPT group would reach the primary endpoint at one year. The non-inferiority margin of 3.2%, which corresponded to 40% of the estimated event rate, was chosen based on clinically acceptable thresholds of difference,[37] (summarised in table S5) based on previous non-inferiority trials comparing antiplatelet regimens after stent implantation.[18 19 22] Considering an anticipated 5% patient attrition rate, 1908 patients were required for the study to have 80% power to show non-inferiority with a 5% one sided type I error rate. Although a one sided type I error rate of 2.5% is considered more robust for a non-inferiority assessment, we opted for a one sided type I error rate of 5% because this rate has been used previously for evaluating the de-escalation of DAPT.[18 22-24] Nevertheless, the assessment of non-inferiority based on a one sided 97.5% confidence interval (CI) of the primary endpoint was also reported as a sensitivity analysis.

The primary analysis was based on a covariate-adjusted analysis of treatment difference in the cumulative event rate of the primary endpoint in the intention-to-treat population. The prespecified covariates were age, sex, hypertension, hyperlipidaemia, diabetes, smoking status, history of cardiovascular disease, stroke, clinical presentation, lesion characteristics (de novo or in-stent restenosis), and centre effect (with details in appendix methods). The treatment difference was defined as the stepwise DAPT de-escalation group minus standard DAPT group. The cumulative event rate was estimated at 360 days by the Kaplan-Meier method, with the standard error of difference calculated using Greenwood's method and P value calculated using an approximate z test. Non-inferiority was concluded when the upper limit of a one sided 95% CI in the treatment difference of the primary endpoint was less than 3.2%. Additionally, an unadjusted measurement of the treatment difference (crude analysis) was conducted as a sensitivity analysis.

If non-inferiority was met with the primary endpoint, a predefined hierarchical testing structure for the secondary endpoints was implemented with the fixed sequence outlined in the appendix methods. The

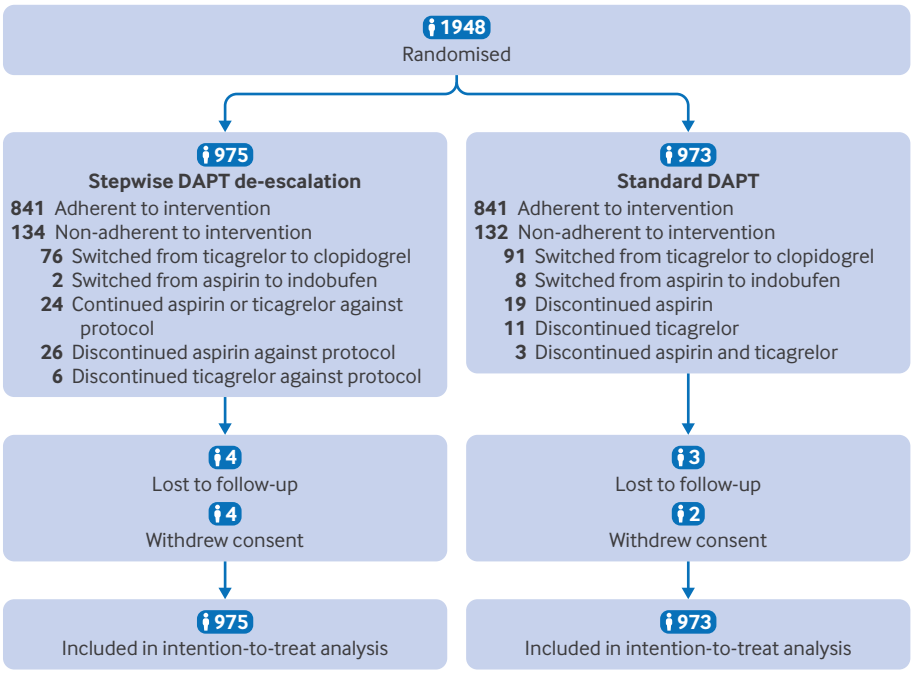


**Fig 1 | Randomisation, treatment, and follow-up of the patients. DAPT=dual antiplatelet therapy. Outcomes of patients who were lost to follow-up or withdrew consent were included to the point of final contact. Their time-to-event measure was censored at the last contact date**

secondary endpoint of clinically relevant ischaemic or bleeding events was analysed using the win ratio method. For other secondary endpoints, the difference in cumulative event rates and their two sided 95% CIs are reported. As post hoc sensitivity analyses of the secondary outcome, we used the cumulative incidence function (Aalen-Johansen estimator) to account for the competing risk of death. The main results are presented in the intention-to-treat population. The analyses of the primary and secondary outcomes were also performed in the per protocol population.

Detailed information regarding the multiplicity considerations, covariate adjusted analysis, and win ratio analysis is provided in the appendix methods. The analysis was done using R statistical software version 4.2.1 (R Project for statistical computing).

### Patient and public involvement

No funding was allocated for involvement of patients or the public in the design, conduct, reporting, or dissemination plans of our research. Nevertheless, we spoke to the patients about the concept of the study during study designing and collected their opinions, and asked a member of the public to read our manuscript after submission.

## Results

Between 27 November 2021 and 21 January 2023, 1948 eligible participants were enrolled and randomly assigned to either the stepwise DAPT de-escalation group (n=975) or the standard DAPT group (n=973, fig 1). The median time from the index percutaneous coronary intervention to randomisation was one day for both groups (table S6). Patient characteristics at baseline are shown in table 1. Overall, the mean age of patients was 59.2 years; 74.9% of the patients were men, 30.5% had diabetes, 8.8% had history of a stroke, 13.2% had history of a myocardial infarction, 32.2% had history of a percutaneous coronary intervention, and 20.6% were defined as at high bleeding risk (according to the Academic Research Consortium for High Bleeding Risk.[10] The mean PARIS bleeding score was 3.5 and the thrombotic risk score was 3.4.[38] The mean DCB diameter was 2.72 mm (standard deviation 0.49). In terms of the target lesion, 17.8% were in-stent restenosis, 42.7% were bifurcation lesions, and 60.9% were in small vessel disease. The combinatorial characteristics of patients for DCB treatment are shown by the UpSet diagram in figure S2.

After randomisation, 76 (7.8%) participants in the stepwise de-escalation group and 91 (9.4%) in the standard group had ticagrelor replaced by clopidogrel (tables S7 and S8). Adherence to the allocated regimens during the 12 month study period was noted in 833 (85.4%) participants in the stepwise de-escalation group and 836 (85.9%) in the standard group (figure S3); if patients receiving clopidogrel are also included, these numbers increase to 912 (93.5%) and 926 (95.2%), respectively. In the stepwise de-escalation group, 901 (94.0%) participants were taking aspirin monotherapy six months after randomisation (table S7).

At 360 days, complete follow-up data were available for 1935 (99.3%) participants; we censored the follow-up data at their last contact for six patients who withdrew consent and seven who were lost to follow-

**Table 1 | Patient, lesion, and procedural characteristics. Data are numerator (%), unless otherwise specified**

| Baseline characteristics | Stepwise DAPT de-escalation (n=975) | Standard DAPT (n=973) |
|---|---|---|
| Age, years; mean (SD) | 59.4 (10.7) | 59.0 (11.0) |
| Sex: | | |
| Female | 248/975 (25.4) | 240/973 (24.7) |
| Male | 727/975 (74.6) | 733/973 (75.3) |
| Body mass index; mean (SD) | 25.0 (3.3) | 25.2 (3.4) |
| Smoking: | | |
| Former | 99/954 (10.4) | 97/953 (10.2) |
| Current | 308/954 (32.3) | 361/953 (37.9) |
| Comorbid conditions: | | |
| Arterial hypertension | 583/975 (59.8) | 594/973 (61.0) |
| Diabetes mellitus | 288/975 (29.5) | 307/973 (31.6) |
| Insulin treated | 71/268 (26.5) | 80/294 (27.2) |
| Hyperlipidaemia | 761/957 (79.5) | 784/953 (82.3) |
| Left ventricular ejection fraction <40% or previous episode of heart failure | 47/975 (4.8) | 36/973 (3.7) |
| Left ventricular ejection fraction, %*; mean (SD) | 59.5 (8.4) | 59.5 (7.9) |
| Myocardial infarction | 135/972 (13.9) | 121/970 (12.5) |
| PCI | 319/975 (32.7) | 308/973 (31.7) |
| CABG | 5/975 (0.5) | 5/973 (0.5) |
| Stroke | 93/973 (9.6) | 78/971 (8.0) |
| COPD | 43/937 (4.6) | 30/929 (3.2) |
| Chronic kidney disease† | 58/973 (6.0) | 59/971 (6.1) |
| Peripheral vascular disease | 31/974 (3.2) | 24/971 (2.5) |
| High bleeding risk‡ | 197/936 (21.0) | 190/939 (20.2) |
| Clinical presentation: | | |
| ST-elevation myocardial infarction | 159/975 (16.3) | 167/973 (17.2) |
| Non-ST-elevation myocardial infarction | 268/975 (27.5) | 264/973 (27.1) |
| Unstable angina | 548/975 (56.2) | 542/973 (55.7) |
| Risk scores: | | |
| PRECISE-DAPT score§; mean (SD): | 10.5 (7.9) | 10.3 (7.8) |
| 0-25 | 878/923 (95.1) | 877/926 (94.7) |
| ≥25 | 45/923 (4.9) | 49/926 (5.3) |
| PARIS bleeding risk score¶; mean (SD): | 3.5 (2.0) | 3.5 (2.0) |
| Low (0-3) | 500/942 (53.1) | 506/944 (53.6) |
| Intermediate (4-7) | 421/942 (44.7) | 409/944 (43.3) |
| High (≥8) | 21/942 (2.2) | 29/944 (3.1) |
| PARIS thrombotic risk score¶; mean (SD): | 3.3 (1.6) | 3.5 (1.7) |
| Low (0-2) | 305/942 (32.4) | 296/944 (31.4) |
| Intermediate (3-4) | 438/942 (46.5) | 390/944 (41.3) |
| High (≥5) | 199/942 (21.1) | 258/944 (27.3) |
| PCI configurations and lesion characteristics: | | |
| Radial access approach | 927/975 (95.1) | 912/973 (93.7) |
| IVUS/OCT | 128/975 (13.1) | 124/973 (12.7) |
| Multivessel disease | 368/975 (37.7) | 352/973 (36.2) |
| Multivessel treated | 125/975 (12.8) | 102/973 (10.5) |
| Complex PCI** | 196/975 (20.1) | 188/973 (19.3) |
| Complete revascularisation | 812/954 (85.1) | 791/940 (84.1) |
| Number of DCB used per patient; mean (SD) | 1.3 (0.7) | 1.3 (0.7) |
| Total DCB length, mm; mean (SD) | 32.8 (20.1) | 32.7 (20.0) |
| Mean diameter of DCB, mm; mean (SD) | 2.71 (0.50) | 2.72 (0.48) |
| Predilation | 1167/1171 (99.7) | 1149/1149 (100.0) |
| Predilation balloon types: | | |
| Semi-compliant balloon | 826/1171 (70.5) | 825/1149 (71.8) |
| Non-compliant balloon | 425/1171 (36.3) | 439/1149 (38.2) |
| Cutting or scoring balloon | 771/1171 (65.8) | 775/1149 (67.4) |
| Lesion location: | | |
| Left main | 4/1171 (0.3) | 4/1149 (0.3) |
| Left anterior descending artery | 555/1171 (47.4) | 527/1149 (45.9) |
| Left circumflex artery | 347/1171 (29.6) | 349/1149 (30.4) |
| Right coronary artery | 265/1171 (22.6) | 269/1149 (23.4) |
| Target lesion characteristics††: | | |
| In-stent restenosis | 208/1171 (17.8) | 206/1149 (17.9) |
| Small vessel (<3.0 mm in DCB diameter) | 717/1171 (61.2) | 697/1149 (60.7) |
| Bifurcation | 495/1143 (43.3) | 470/1115 (42.1) |
| Long lesion (≥28 mm) | 429/1171 (36.6) | 449/1149 (39.1) |

(Continued)

**Table 1 | Continued**

| Baseline characteristics | Stepwise DAPT de-escalation (n=975) | Standard DAPT (n=973) |
|---|---|---|

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.
CABG=coronary artery bypass graft; COPD=Chronic obstructive pulmonary disease; DAPT=dual antiplatelet therapy; DCB=drug coated balloon; eGFR=estimated glomerular filtration rate; IVUS=intravascular ultrasound; OCT=optical coherence tomography; PCI=percutaneous coronary intervention; SD=standard deviation.
*Left ventricular ejection fraction was available for 881 patients in the standard DAPT group and 874 in the stepwise DAPT de-escalation group.
†Defined as kidney damage (pathological abnormalities or markers of damage, including abnormalities in blood or urine tests or imaging studies) or an eGFR (by Modification of Diet in Renal Disease formula) of less than 60 mL per minute per 1.73 $m^2$ of body surface area for at least three months. eGFR was available for 944 patients in the standard DAPT group and for 942 in the stepwise DAPT de-escalation group.
‡Defined by the Academic Research Consortium for High Bleeding Risk.
§PRECISE-DAPT score was available for 926 patients in the standard DAPT group and 923 in the stepwise DAPT de-escalation group.
¶PARIS bleeding/thrombotic risk scores were available for 944 patients in the standard DAPT group and 942 in the stepwise DAPT de-escalation group.
**Defined as having at least one: multivessel PCI, ≥3 DCB used, ≥3 lesions treated, bifurcation PCI with ≥2 DCB, and total DCB length >60 mm.
††Small vessel disease for DCB was defined as using the criterion of the BASKET-SMALL 2 and REC-CAGEFREE I trial; Bifurcation was classified when at least 50% lumen narrowing occurs within 3 mm of the bifurcation point, according to the SYNTAX score definition.

up. In the intention-to-treat population, the primary endpoint of net adverse clinical events occurred in 87 (8.9%) participants in the stepwise DAPT de-escalation group as compared with 84 (8.6%) in the standard DAPT group. The 0.36% difference in the cumulative event rate and the upper boundary of the one sided 95% CI 2.47% met the prespecified criteria of 3.2% for non-inferiority ($P_{non\text{-}inferiority}$=0.013, fig 2 and table 2). Non-inferiority was also met for the primary endpoint when using a one sided α of 2.5% (upper boundary of the one sided 97.5% CI 2.87%; $P_{non\text{-}inferiority}$=0.013, table S9). Non-inferiority of the primary endpoint was also met if the criteria of Thrombolysis in Myocardial Infarction, International Society on Thrombosis and Haemostasis, or Global Utilization Of Streptokinase and TPA for Occluded Arteries were used to define

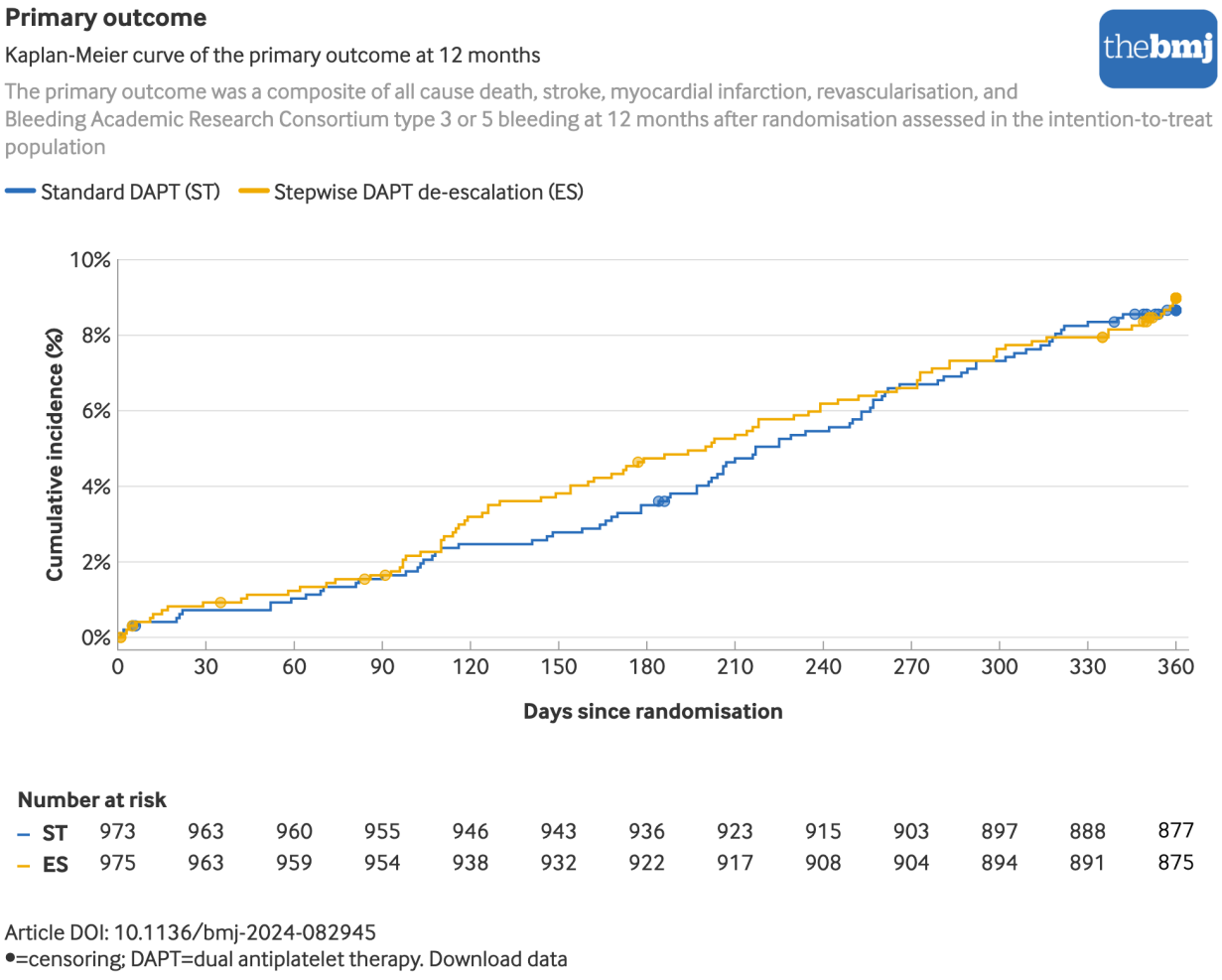


**Fig 2 | Kaplan-Meier curve of the primary outcome at 12 months. The primary outcome was a composite of all cause death, stroke, myocardial infarction, revascularisation, and Bleeding Academic Research Consortium type 3 or 5 bleeding at 12 months after randomisation assessed in the intention-to-treat population. DAPT=dual antiplatelet therapy. An interactive version of this graphic is available at https://public.flourish.studio/visualisation/22156733/**

**Table 2 | Primary and secondary outcomes**

| Outcomes | Stepwise DAPT de-escalation (%) (n=975) | Standard DAPT (%) (n=973) | Difference % (two sided 95% CI) | P value |
|---|---|---|---|---|
| **Primary endpoint** | | | | |
| Net adverse clinical events (composite of all cause death, stroke, myocardial infarction, revascularisation, and BARC type 3 or 5 bleeding) | 87 (8.9) | 84 (8.6) | 0.36 (−1.75 to 2.47)* | 0.01† |
| **Secondary endpoints, tested in prespecified fixed sequence‡** | | | | |
| Clinically relevant ischaemic or bleeding event (hierarchical composite of all cause death, stroke, myocardial infarction, BARC type 3 bleeding, revascularisation, and BARC type 2 bleeding)§ | 136 903 (14.4) | 95 450 (10.1) | 1.43 (1.12 to 1.83) | 0.004 |
| BARC type 3 or 5 bleeding | 4 (0.4) | 16 (1.6) | −1.19 (−2.07 to −0.31) | 0.008 |
| BARC type 2, 3, or 5 bleeding | 23 (2.3) | 90 (9.3) | −7.00 (−9.07 to −4.93) | <0.001 |
| BARC type 2 bleeding | 19 (1.9) | 75 (7.8) | −5.90 (−7.81 to −4.00) | <0.001 |
| **Safety endpoints** | | | | |
| Device oriented composite endpoint (cardiovascular death, target vessel myocardial infarction, and clinically and physiologically indicated target lesion revascularisation) | 51 (5.2) | 45 (4.6) | 0.56 (−1.36 to 2.49) | 0.57 |
| Cardiovascular death | 13 (1.3) | 6 (0.6) | 0.69 (−0.17 to 1.55) | 0.12 |
| Target vessel myocardial infarction | 7 (0.7) | 8 (0.9) | −0.16 (−0.96 to 0.65) | 0.70 |
| Clinically and physiologically indicated target lesion revascularisation | 37 (3.8) | 35 (3.6) | 0.26 (−1.42 to 1.95) | 0.76 |
| Patient oriented composite endpoint (all cause death, stroke, myocardial infarction, revascularisation) | 84 (8.6) | 74 (7.6) | 1.05 (−1.37 to 3.47) | 0.40 |
| Death | 13 (1.3) | 7 (0.7) | 0.60 (−0.28 to 1.48) | 0.18 |
| Stroke | 7 (0.7) | 8 (0.8) | −0.09 (−0.84 to 0.67) | 0.82 |
| Ischaemic | 6 (0.6) | 4 (0.4) | 0.22 (−0.39 to 0.84) | 0.47 |
| Haemorrhagic | 1 (0.1) | 5 (0.5) | −0.41 (−0.89 to 0.08) | 0.10 |
| Myocardial infarction | 9 (0.9) | 10 (1.1) | −0.15 (−1.04 to 0.75) | 0.74 |
| Revascularisation | 65 (6.8) | 61 (6.3) | 0.52 (−1.69 to 2.73) | 0.65 |
| Target vessel failure (composite of cardiovascular death, target vessel myocardial infarction, and clinically and physiologically indicated target vessel revascularisation) | 56 (5.7) | 47 (4.8) | 0.87 (−1.12 to 2.86) | 0.39 |
| Clinically and physiologically indicated target vessel revascularisation | 42 (4.3) | 38 (3.9) | 0.48 (−1.29 to 2.25) | 0.60 |
| Stent thrombosis | 2 (0.2) | 2 (0.2) | −0.02 (−0.42 to 0.38) | 0.92 |

Primary and secondary outcomes were evaluated in the intention-to-treat population at 12 months after randomisation. The listed percentages were estimated with the use of the Kaplan-Meier method, so values may not be calculated mathematically.
BARC=Bleeding Academic Research Consortium; CI=confidence interval; DAPT=dual antiplatelet therapy.
*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 2.47 percentage points; the upper boundary of the one sided 97.5% confidence interval was 2.87 percentage points.
†P value of non-inferiority test.
‡Secondary endpoints are shown in the pre-specified order for hierarchical testing. When the non-inferiority was met for the primary endpoint, the fixed sequence testing structure was used to maintain overall α. If the test fails to reject the null hypothesis at a 5% significance level, the hierarchical sequential testing will stop; otherwise, carry on to the next test, and family-wise type I error will not be inflated.
§The first secondary endpoint was assessed with the use of win ratio approach. The total number of wins (proportion) in each group, unmatched win ratio (95% CI), and P value are displayed.

bleeding (table S9). The definition of the per protocol population is shown in table S10. In this population, net adverse clinical events occurred in 70 (8.4%) in the stepwise de-escalation group and 77 (9.2%) in the standard group (difference −0.80%; upper boundary of the one sided 95% CI 1.49%; $P_{non\text{-}inferiority}$=0.002, table S11 and figure S4). The sensitivity analysis of the primary endpoint using unadjusted Kaplan-Meier estimates showed consistent results with the primary analysis (table S12).

In the prespecified hierarchical testing of secondary endpoints, the first secondary endpoint in the hierarchy (clinically relevant ischaemic or bleeding event) was analysed by the win ratio approach to account for the different clinical importance within this composite endpoint. This endpoint showed that the stepwise de-escalation group was associated with significantly more wins when compared with the standard group (14.4% wins *v* 10.1% wins, win ratio 1.43 (95% CI 1.12 to 1.83); P=0.004, fig 3). Following the first secondary endpoint, the cumulative incidence of other secondary endpoints, BARC type 3 or 5 bleeding, BARC type 2, 3 or 5 bleeding, and BARC type 2 bleeding (table 2, figure S5), were all significantly lower in the stepwise de-escalation group compared with the standard group. The results of the sensitivity analyses accounting for the competing risk of death for the secondary endpoints are provided in table S13. All cause death, stroke, myocardial infarction, and revascularisation (patient oriented composite endpoint) occurred in 84 (8.6%) patients in the stepwise de-escalation group and 74 (7.6%) patients in the standard group (difference 1.05% (95 CI −1.37% to 3.47%), table 2 and figure S6). Cardiovascular death, target vessel myocardial infarction, and clinically and physiologically indicated target lesion revascularisation (device-oriented composite endpoint) occurred in 51 (5.2%) patients in the stepwise de-escalation group and 45 (4.6%) in the standard group (difference 0.56% (95 CI −1.36% to 2.49%)). The cumulative incidences of all individual components of the patient oriented composite endpoint, device oriented composite endpoint, and stent (device) thrombosis are also shown in table 2.

The data do not show any significant treatment (stepwise de-escalation or standard DAPT) interactions by subgroups (eg, de novo or in-stent restenosis, small vessel disease, between DCB brands, or subgroups with higher ischaemic risks, including diabetes, lesion in the proximal vessel, treatment of multivessel disease, complex percutaneous coronary intervention, and

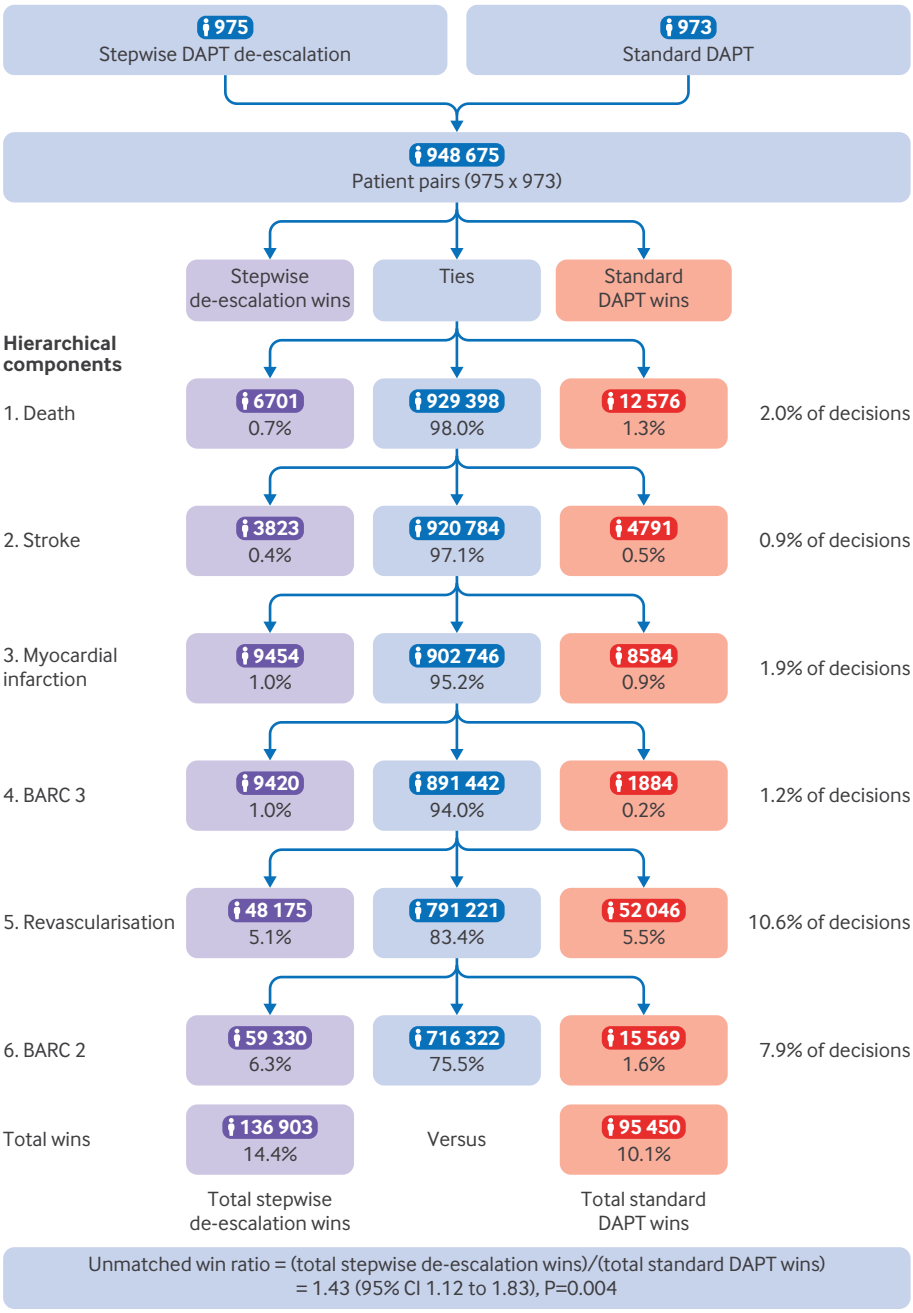


**Fig 3 | Win ratio diagram for the first secondary endpoint. Shown is the result of the unmatched win ratio analysis 31 of the first secondary endpoint, clinically relevant ischaemic or bleeding event, assessed in the pre-specified hierarchical order of all cause death, stroke, myocardial infarction, Bleeding Academic Research Consortium (BARC) type 3 bleeding, revascularisation, and BARC type 2 bleeding (appendix). For each component of the hierarchical analysis, numbers (proportions) of pairs that are determined to be wins in the stepwise de-escalation group, ties, or wins in the standard dual antiplatelet therapy (DAPT) group. The unmatched win ratio was calculated as the total number of wins in the stepwise de-escalation group divided by the total number of wins in the standard DAPT group. Percentages in several categories may not sum to the stated values because of rounding**

high PARIS thrombotic score) for the primary endpoint (figure S7), except for the high bleeding risk subgroup.

## Discussion

### Principal findings

This study provides evidence investigating a dedicated antiplatelet regimen for people treated by DCB. We found that stepwise DAPT de-escalation with one month aspirin plus ticagrelor, followed by five months of ticagrelor monotherapy and then aspirin monotherapy, was non-inferior for net adverse clinical events compared with the standard 12 months of DAPT with aspirin plus ticagrelor. Furthermore, if all clinically relevant ischaemic or bleeding events were considered and treated as having hierarchical clinical importance, an overall benefit would have been seen

with stepwise DAPT de-escalation compared with standard 12 month DAPT.

### Comparison with other studies

Drug eluting stent is generally appropriate for all patients who require percutaneous coronary intervention, however, DCBs are often used for certain indications, as suggested in the consensus documents.[13 28] Therefore, the rates of people with high bleeding risk or small vessel disease and the number of in-stent restenosis or bifurcation lesions are higher in this cohort compared with other studies (eg, TICO,[21] T-PASS,[24] STOPDAPT-2 ACS,[26] and ULTIMATE-DAPT[25]) that investigated DAPT de-escalation in people with acute coronary syndrome treated with drug eluting stent. However, in our study, the mean device diameter was smaller and the rate of multivessel treatment was lower. Notably, the proportion of patients with ST-elevation myocardial infarction (STEMI) in our study (17%) is lower than in these other studies,[21 24-26] which had rates between 27% and 40%. However, the proportion is similar to previous DCB studies: the proportion of STEMIs in the acute coronary syndrome population was 10% in the BASKET SMALL 2 study;[4] 16% in the EASTBOURNE[15] registry, and 19% in the SCAAR[17] registry, whereas patients with STEMI were excluded in the AGENT IDE study.[7] The low proportion of patients with STEMI in studies involving DCBs could be explained by the fact that DCBs are generally not used in the setting of obvious angiographic thrombus, which may inhibit drug delivery to the vessel wall.[39]

Notwithstanding this, the thrombotic risk for patients in the present study was similar to previous studies involving DAPT de-escalation after a drug eluting stent. In the STOPDAPT-2 ACS,[26] TICO,[21] T-PASS,[24] and ULTIMATE-DAPT[25] studies, the average number of stents used per patient was 1.4, mean device lengths ranged between 32 mm and 38 mm, and the rate of all cause death ranged between 0.7% and 1.2%. Similarly, in the present study, the average number of DCBs used per patient was 1.3, the mean device length was 33 mm, and the rate of all cause death was 1.0%. While risk scores were not reported in the TICO, T-PASS, or ULTIMATE-DAPT studies, in the STOPDAPT-2 ACS study, 16% of patients had a high (≥5) PARIS thrombotic score compared with 22% in the present study.

### Rationale, interpretation, and strengths

In the intention-to-treat population of this study, the stepwise DAPT de-escalation group had a 1% higher rate of patient oriented composite endpoint and a 1% lower rate of BARC 3 or 5 bleeding compared with the standard 12 month DAPT therapy group, hinting that a trade-off between ischaemic and bleeding risk may exist. However, participants who were not adherent to the study protocol were also included in the intention-to-treat population. Conversely, in the per protocol analyses (more than half of the non-adherence was due to switching from ticagrelor to clopidogrel and thus not included in the per protocol population), we found no difference in patient oriented composite endpoint between the strictly ticagrelor based stepwise DAPT de-escalation group (8.1%) and the 12 month DAPT group (8.3%) (appendix). Importantly, the incidence of BARC 3 or 5 bleeding remained significantly lower in the stepwise de-escalation group. This disparity between intention-to-treat and per protocol populations was primarily caused by the inclusion or exclusion of patients on clopidogrel based monotherapy. As such, we considered that the 1% higher risk of patient oriented composite endpoint in the intention-to-treat population might be due to the lower potency of clopidogrel based monotherapy compared with protocol-defined ticagrelor based monotherapy.[26] This finding also underscores the importance of adhering to ticagrelor to uphold the efficacy of a P2Y12 inhibitor monotherapy based stepwise DAPT de-escalation approach, especially in patients with higher thrombotic risks.[40]

To better represent the population that is treated with DCB in real-world practice and provide generalisability of the stepwise DAPT de-escalation strategy, we did not pose restrictions on the type of lesion (de novo or in-stent restenosis), treated vessel diameter, or the specific brand of paclitaxel coated balloon that was used. Additionally, the selection of suitable patients or lesions for DCB treatment and subsequent procedural techniques were required to follow the recommendations of the German Consensus Group on DCB interventions[28] and the Third Report of the International DCB Consensus Group.[13] Despite the effort, however, compared with real world observational data involving DCB, the current study population was still associated with a relatively lower risk. Of note, when considering the data in daily practice, people who were deemed not suitable for a standard 12-month DAPT due to excessive bleeding risk, such as previous intracranial haemorrhage or required long term oral anticoagulant therapy, were not included.

Compared with de novo lesions, patients with in-stent restenosis were generally associated with a higher ischaemic risk.[13 29] Consequently, our study used stratified randomisation according to whether lesions were de novo or in-stent restenosis. Reassuringly, the effect of the assigned treatment on the incidences of the primary endpoints was consistent across de novo or in-stent restenosis lesion. This effect was also consistent in other prespecified subgroups with higher ischaemic risks, including diabetes, lesion in the proximal vessel, treatment of multivessel disease, complex percutaneous coronary intervention, and high PARIS thrombotic score.

A numerical imbalance in baseline smoking status was noted between the two study groups, however, subgroup analyses showed no significant heterogeneity in treatment effects when comparing people who smoke versus those who do not. Furthermore, the findings remained consistent across both covariate adjusted analyses (smoking status was deemed clinically

important and included as a prespecified covariate) and the crude analyses. Therefore, we believe that the numerically greater proportion of smokers in the standard DAPT group was due to chance and had no impact on the robustness of our results.

Cardiovascular trials often use composite endpoints to reduce sample size required and to capture the overall impact of therapeutic interventions. However, this approach can be problematic if the individual components are of widely differing importance to patients, the number of events in the components of greater importance is small, and the size of the effect differs markedly across components.[41] If we had used conventional statistical methods such as the Kaplan-Meier estimator, the drawbacks of composite endpoints would be evident when assessing the overall benefit of the treatment by the endpoint of clinically relevant ischaemic or bleeding event (first secondary endpoint). This endpoint included all cause death, stroke, myocardial infarction, BARC type 3 bleeding, revascularisation, and BARC type 2 bleeding. It is important to note that the clinical importance of all cause death and BARC type 2 bleeding is not equal. Consequently, we used the win ratio method, a non-parametric approach to analyse the composite endpoints with varying severity, accounting for the relative priorities of components.[42] However, the method for non-inferiority design of the win ratio approach is still under development, therefore, the primary endpoint was still analysed by the conventional methods.[42]

This study was an open label trial and not double blinded because of budget constraints; therefore, while interpretating the results, biases inherent to this open label design must be recognised, such as unconscious research bias (overestimating the magnitude of the results) and performance bias (participants might have positive expectations or compensation behaviour). Additionally, the knowledge of dyspnoea as a potential side effect could influence patients' decisions to switch from ticagrelor to clopidogrel.[43] To mitigate these biases, several measures were implemented. The primary endpoint was determined based on clinical outcomes, which are less susceptible to measurement biases. Furthermore, the research team endeavoured to reduce bias by consistently emphasising the importance of protocol adherence through telephone communications, conducting regular site monitoring, and adjudicating clinical endpoints using a blinded clinical event committee.[43] Nonetheless, the complete elimination of bias is not possible.

### Limitations

This study has several limitations. Firstly, the sample size calculation for non-inferiority was based on a one sided $\alpha$ of 5%; nevertheless, the sensitivity analysis using a one sided $\alpha$ of 2.5% still showed non-inferiority. Secondly, only patients with paclitaxel coated balloons were included because sirolimus coated balloons were not commercially available in China during the study period. Caution is therefore needed if these results are extrapolated to patients treated with sirolimus coated balloons; additionally, it should be noted that even the paclitaxel coated balloons may not have a uniform class effect in the treatment of coronary disease due to different kinetics of the drug or excipient. Thirdly, the current study only investigated the impact of a less intensive antiplatelet regimen for acute coronary syndrome patients who received DCB based on indications endorsed by international consensus and the results should not be inferred as supporting the unrestricted use of DCB in all acute coronary syndrome patients.[13 28] Furthermore, only 44% of the participants were diagnosed with STEMI or non-ST-elevation myocardial infarction, necessitating caution when generalising the results to these patients. Fourthly, only a quarter of the study population was female. Although this proportion is similar to other randomised trials involving percutaneous coronary intervention, female patients were still under-represented.[44] Finally, this study was only conducted in China with an East Asian population and therefore extrapolating these results to other ethnic groups warrants further investigation.

### Conclusions

Among patients with acute coronary syndrome who could be treated by paclitaxel coated balloons without stents, stepwise DAPT de-escalation therapy was non-inferior to the standard 12 month DAPT with respect to the occurrence of all cause death, stroke, myocardial infarction, revascularisation, and BARC type 3 or 5 bleeding.


## AUTHOR AFFILIATIONS

[1]Department of Cardiology, Xijing Hospital, Xi'an, China
[2]Department of Cardiology, Zhuzhou Central Hospital, Zhuzhou, China
[3]Department of Cardiology, Tianjin Fourth Central Hospital, Tianjin, China
[4]Department of Cardiology, Second Hospital of Tianjin Medical University, Tianjin, China
[5]Department of Cardiology, People's Hospital of Qingyang, Qingyang, China
[6]Department of Cardiology, China-Japan Union Hospital of Jilin University, Changchun, China
[7]Department of Cardiology, First Affiliated Hospital of Gannan Medical University, Ganzhou, China
[8]Department of Cardiology, Yangpu Hospital of Tongji University, Shanghai, China
[9]Department of Cardiology, First Affiliated Hospital of Naval Medical University, Shanghai, China
[10]Department of Cardiology, Ankang Central Hospital, Ankang, China
[11]Department of Cardiology, First Affiliated Hospital of USTC, Hefei, China
[12]Department of Cardiology, Seventh People's Hospital of Zhengzhou, Zhengzhou, China
[13]Department of Cardiology, Liaocheng People's Hospital, Liaocheng, China
[14]Beijing KeyTech Statistical Consulting Co, Beijing, China
[15]Department of Statistics, Air Force Medical University, Xi'an, China
[16]Department of Cardiology, Royal Blackburn Hospital, Blackburn, UK
[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, University of Galway, Galway, Ireland
[20]Biostatistics Unit, Liverpool School of Tropical Medicine, Liverpool, UK

**Contributors:** CG, BZ, FO, and SW contributed equally to this study. LT and CG conceived and designed the trial; LT acquired the financial support; LT, CG, and BZ wrote the original and final version of the manuscript; LT, CG, BZ, FO, SW, YX, WJ, PY, YH, YZhong, YZhou, ZG, GS, LM, LX, YX, TH, QW, YL, and RZ enrolled the participants and collected the data; JL, ZJ, JX, and DW performed the statistical analyses; SG, R-JvG, YO, DC, PS, and DW contributed to the interpretation of the results or edited the manuscript. R-JvG, DC, YO, and PWS participated in conceiving the study protocol. R-JvG, YO, and PWS edited the study protocol. All authors had access to all the included data and vouch for the completeness and accuracy of the reported data and the fidelity of the trial to the protocol. All authors provided critical feedback, revised the manuscript, approved the final manuscript, and accepted responsibility for submitting it for publication. The corresponding author attests that all listed authors meet authorship criteria and that no others meeting the criteria have been omitted. LT and CG are the guarantors.

**Funding:** This trial is an investigator initiated trial sponsored by Xijing Hospital. The study received unrestricted grant support from Yinyi Biotech (Dalian, China). Yinyi Biotech manufactures paclitaxel coated balloons but has no antiplatelet medication products. Apart from this funding, Yinyi Biotech was not involved in the study design, data collection, analysis, interpretation, or writing of the report, and did not participate in the decision to submit the manuscript for publication. The corresponding authors had final responsibility for the decision to submit for publication. Funded by the sponsor, an independent research organisation (Medisets, Hefei, China) participated in site management and safety reporting.

**Competing interests:** All authors have completed the ICMJE uniform disclosure form at https://www.icmje.org/disclosure-of-interest/ and declare: this trial was sponsored by Xijing Hospital; PS received consulting fees from Sahajanand Medical Technologies, Novartis, Merillife, Xeltis, and Philips/Volcano outside of the submitted work. DC received honoraria from Terumo, Sanofi Aventis, and Medtronic and participated in the advisory board of Abbott Vascular outside of the submitted work. ZJ is the founder of Beijing KeyTech Statistical Consulting Co and has stock of the company. R-JvG reported receiving unrestricted research grant and honoraria from AstraZeneca. All other authors declare no competing interests.

**Ethical approval:** The trial was conducted in accordance with the Declaration of Helsinki and Good Clinical Practice guidelines, and the protocol was approved by the ethics committee of Xijing Hospital (ID: KY20212080-F-1) and responsible ethics committees in all participating centers. This trial is registered at ClinicalTrials.gov, NCT04971356.

**Data sharing:** The REC-CAGEFREE II trial is planning to continue follow-up until 2028. Patient level data collected for this study will not be made publicly available but will be available for data sharing on request for collaboration on specific projects. Any relevant inquiries should be sent to the corresponding author Ling Tao (lingtaofmmu@qq.com) or to the first author Chao Gao (woshigaochao@gmail.com).

**Transparency:** The lead authors LT and CG, affirm that the manuscript is an honest, accurate, and transparent account of the study being reported, that no important aspects of the study have been omitted, and that any discrepancies from the study as planned (and if relevant, registered) have been explained.

**Dissemination to participants and related patient and public communities:** The REC-CAGEFREE II results were presented on 15 May 2024, in EuroPCR 2024 in Paris. Once this study is published, we will disseminate the results to the public through social media and write blogs to explain the results. For patients and members of the public, the study group will facilitate dissemination to patient groups and provide a lay summary of the trial findings.

**Provenance and peer review:** Not commissioned; externally peer reviewed.



1 Byrne RA, Rossello X, Coughlan JJ, et al, ESC Scientific Document Group. 2023 ESC Guidelines for the management of acute coronary syndromes. *Eur Heart J* 2023;44:3720-826. doi:10.1093/eurheartj/ehad191.
2 Gorog DA, Ferreiro JL, Ahrens I, et al. De-escalation or abbreviation of dual antiplatelet therapy in acute coronary syndromes and percutaneous coronary intervention: a Consensus Statement from an international expert panel on coronary thrombosis. *Nat Rev Cardiol* 2023;20:830-44. doi:10.1038/s41569-023-00901-2.
3 Capodanno D, Mehran R, Krucoff MW, et al. Defining strategies of modulation of antiplatelet therapy in patients with coronary artery disease: a consensus document from the academic research consortium. *Circulation* 2023;147:1933-44. doi:10.1161/CIRCULATIONAHA.123.064473.
4 Jeger RV, Farah A, Ohlow MA, et al, BASKET-SMALL 2 Investigators. 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;396:1504-10. doi:10.1016/S0140-6736(20)32173-5.
5 Gao C, He X, Ouyang F, et al, REC-CAGEFREE I Investigators. Drug-coated balloon angioplasty with rescue stenting versus intended stenting for the treatment of patients with de novo coronary artery lesions (REC-CAGEFREE I): an open-label, randomised, non-inferiority trial. *Lancet* 2024;404:1040-50. doi:10.1016/S0140-6736(24)01594-0.
6 Rissanen TT, Uskela S, Eränen J, et al, DEBUT trial investigators. 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;394:230-9. doi:10.1016/S0140-6736(19)31126-2.
7 Yeh RW, Shlofmitz R, Moses J, et al, AGENT IDE Investigators. Paclitaxel-coated balloon vs uncoated balloon for coronary in-stent restenosis: the AGENT IDE randomized clinical trial. *JAMA* 2024;331:1015-24. doi:10.1001/jama.2024.1361.
8 Korjian S, McCarthy KJ, Larnard EA, et al. Drug-coated balloons in the management of coronary artery disease. *Circ Cardiovasc Interv* 2024;17:e013302. doi:10.1161/CIRCINTERVENTIONS.123.013302.
9 Sanz-Sánchez J, Chiarito M, Gill GS, et al. Small vessel coronary artery disease: rationale for standardized definition and critical appraisal of the literature. *J Soc Cardiovasc Angiogr Interv* 2022;1:100403. doi:10.1016/j.jscai.2022.100403.
10 Urban P, Mehran R, Colleran R, et al. Defining high bleeding risk in patients undergoing percutaneous coronary intervention: a consensus document from the Academic Research Consortium for High Bleeding Risk. *Eur Heart J* 2019;40:2632-53. doi:10.1093/eurheartj/ehz372.
11 Gragnano F, Heg D, Franzone A, et al. PRECISE-DAPT score for bleeding risk prediction in patients on dual or single antiplatelet regimens: insights from the GLOBAL LEADERS and GLASSY. *Eur Heart J Cardiovasc Pharmacother* 2022;8:28-38. doi:10.1093/ehjcvp/pvaa106.
12 Cortese B, Serruys PW. Single-antiplatelet treatment after coronary angioplasty with drug-coated balloon. *J Am Heart Assoc* 2023;12:e028413. doi:10.1161/JAHA.122.028413.
13 Jeger RV, Eccleshall S, Wan Ahmad WA, et al, International DCB Consensus Group. Drug-coated balloons for coronary artery disease: third report of the international DCB consensus group. *JACC Cardiovasc Interv* 2020;13:1391-402. doi:10.1016/j.jcin.2020.02.043.
14 Silverio A, Buccheri S, Venetsanos D, et al. Percutaneous treatment and outcomes of small coronary vessels: a SCAAR report. *JACC Cardiovasc Interv* 2020;13:793-804. doi:10.1016/j.jcin.2019.10.062.
15 Cortese B, Testa L, Heang TM, et al, EASTBOURNE Investigators. Sirolimus-coated balloon in an all-comer population of coronary artery disease patients: the EASTBOURNE prospective registry. *JACC Cardiovasc Interv* 2023;16:1794-803. doi:10.1016/j.jcin.2023.05.005.
16 Lee SY, Cho YK, Kim SW, et al, Stent Failure Research Group (SFR) Drug coated balloon (DCB) registry investigators. Clinical results of drug-coated balloon treatment in a large-scale multicenter Korean registry study. *Korean Circ J* 2022;52:444-54. doi:10.4070/kcj.2021.0261.
17 Venetsanos D, Omerovic E, Sarno G, et al. Long term outcome after treatment of de novo coronary artery lesions using three different drug coated balloons. *Int J Cardiol* 2021;325:30-6. doi:10.1016/j.ijcard.2020.09.054.
18 Hahn JY, Song YB, Oh JH, et al, SMART-CHOICE Investigators. Effect of P2Y12 inhibitor monotherapy vs dual antiplatelet therapy on cardiovascular events in patients undergoing percutaneous coronary intervention: the SMART-CHOICE randomized clinical trial. *JAMA* 2019;321:2428-37. doi:10.1001/jama.2019.8146.

19 Watanabe H, Domei T, Morimoto T, et al, STOPDAPT-2 Investigators. Effect of 1-month dual antiplatelet therapy followed by clopidogrel vs 12-month dual antiplatelet therapy on cardiovascular and bleeding events in patients receiving PCI: the STOPDAPT-2 randomized clinical trial. *JAMA* 2019;321:2414-27. doi:10.1001/jama.2019.8145.
20 Vranckx P, Valgimigli M, Jüni P, et al, GLOBAL LEADERS Investigators. Ticagrelor plus aspirin for 1 month, followed by ticagrelor monotherapy for 23 months vs aspirin plus clopidogrel or ticagrelor for 12 months, followed by aspirin monotherapy for 12 months after implantation of a drug-eluting stent: a multicentre, open-label, randomised superiority trial. *Lancet* 2018;392:940-9. doi:10.1016/S0140-6736(18)31858-0.
21 Kim BK, Hong SJ, Cho YH, et al, TICO Investigators. Effect of ticagrelor monotherapy vs ticagrelor with aspirin on major bleeding and cardiovascular events in patients with acute coronary syndrome: the TICO randomized clinical trial. *JAMA* 2020;323:2407-16. doi:10.1001/jama.2020.7580.
22 Hahn JY, Song YB, Oh JH, et al, SMART-DATE investigators. 6-month versus 12-month or longer dual antiplatelet therapy after percutaneous coronary intervention in patients with acute coronary syndrome (SMART-DATE): a randomised, open-label, non-inferiority trial. *Lancet* 2018;391:1274-84. doi:10.1016/S0140-6736(18)30493-8.
23 Han JK, Hwang D, Yang S, et al. Comparison of 3- to 6-month versus 12-month dual antiplatelet therapy after coronary intervention using the contemporary drug-eluting stents with ultrathin struts: the HOST-IDEA randomized clinical trial. *Circulation* 2023;147:1358-68. doi:10.1161/CIRCULATIONAHA.123.064264.
24 Hong SJ, Lee SJ, Suh Y, et al, T-PASS (Ticagrelor Monotherapy in Patients Treated With New-Generation Drug-Eluting Stents for Acute Coronary Syndrome) Investigators. Stopping aspirin within 1 month after stenting for ticagrelor monotherapy in acute coronary syndrome: the T-PASS randomized noninferiority trial. *Circulation* 2024;149:562-73. doi:10.1161/CIRCULATIONAHA.123.066943.
25 Ge Z, Kan J, Gao X, et al, ULTIMATE-DAPT investigators. Ticagrelor alone versus ticagrelor plus aspirin from month 1 to month 12 after percutaneous coronary intervention in patients with acute coronary syndromes (ULTIMATE-DAPT): a randomised, placebo-controlled, double-blind clinical trial. *Lancet* 2024;403:1866-78. doi:10.1016/S0140-6736(24)00473-2.
26 Watanabe H, Morimoto T, Natsuaki M, et al, STOPDAPT-2 ACS Investigators. Comparison of clopidogrel monotherapy after 1 to 2 months of dual antiplatelet therapy with 12 months of dual antiplatelet therapy in patients with acute coronary syndrome: the STOPDAPT-2 ACS randomized clinical trial. *JAMA Cardiol* 2022;7:407-17. doi:10.1001/jamacardio.2021.5244.
27 Gao C, Zhu B, Liu J, et al, REC-CAGEFREE II Study Group. Randomized evaluation of 5-month Ticagrelor monotherapy after 1-month dual-antiplatelet therapy in patients with acute coronary syndrome treated with drug-coated balloons: REC-CAGEFREE II trial rationale and design. *BMC Cardiovasc Disord* 2024;24:62. doi:10.1186/s12872-024-03709-1.
28 Kleber FX, Rittger H, Bonaventura K, et al. Drug-coated balloons for treatment of coronary artery disease: updated recommendations from a consensus group. *Clin Res Cardiol* 2013;102:785-97. doi:10.1007/s00392-013-0609-7.
29 Neumann FJ, Sousa-Uva M, Ahlsson A, et al, ESC Scientific Document Group. 2018 ESC/EACTS Guidelines on myocardial revascularization. *Eur Heart J* 2019;40:87-165. doi:10.1093/eurheartj/ehy394.
30 Valgimigli M, Bueno H, Byrne RA, et al, ESC Scientific Document GroupESC Committee for Practice Guidelines (CPG)ESC National Cardiac Societies. 2017 ESC focused update on dual antiplatelet therapy in coronary artery disease developed in collaboration with EACTS: The Task Force for dual antiplatelet therapy in coronary artery disease of the European Society of Cardiology (ESC) and of the European Association for Cardio-Thoracic Surgery (EACTS). *Eur Heart J* 2018;39:213-60. doi:10.1093/eurheartj/ehx419.
31 Redfors B, Gregson J, Crowley A, et al. The win ratio approach for composite endpoints: practical guidance based on previous experience. *Eur Heart J* 2020;41:4391-9. doi:10.1093/eurheartj/ehaa665.
32 Milojevic M, Head SJ, Andrinopoulou ER, et alHierarchical testing of composite endpoints: applying the win ratio to percutaneous coronary intervention versus coronary artery bypass grafting in the SYNTAX trial. *EuroIntervention* 2017;13:106-14. doi:10.4244/EIJ-D-16-00745
33 Garcia-Garcia HM, McFadden EP, Farb A, et al, Academic Research Consortium. Standardized end point definitions for coronary intervention trials: the academic research consortium-2 consensus document. *Eur Heart J* 2018;39:2192-207. doi:10.1093/eurheartj/ehy223.
34 Thygesen K, Alpert JS, Jaffe AS, et al, ESC Scientific Document Group. Fourth universal definition of myocardial infarction (2018). *Eur Heart J* 2019;40:237-69. doi:10.1093/eurheartj/ehy462.
35 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;123:2736-47. doi:10.1161/CIRCULATIONAHA.110.009449.
36 Tomaniak M, Chichareon P, Onuma Y, et al, GLOBAL LEADERS Trial Investigators. Benefit and risks of aspirin in addition to ticagrelor in acute coronary syndromes: a post hoc analysis of the randomized GLOBAL LEADERS trial. *JAMA Cardiol* 2019;4:1092-101. doi:10.1001/jamacardio.2019.3355.
37 Greco A, Spagnolo M, Laudani C, et al. Assessment of noninferiority margins in cardiovascular medicine trials. *JACC Adv* 2024;3:101021. doi:10.1016/j.jacadv.2024.101021.
38 Baber U, Mehran R, Giustino G, et al. Coronary thrombosis and major bleeding after PCI with drug-eluting stents: risk scores from Paris. *J Am Coll Cardiol* 2016;67:2224-34. doi:10.1016/j.jacc.2016.02.064.
39 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 Cardiovasc Interv* 2024;17:1185-6. doi:10.1016/j.jcin.2024.01.288.
40 Kwon O, Park DW. Antithrombotic therapy after acute coronary syndromes or percutaneous coronary interventions in East Asian populations. *JACC Asia* 2022;2:1-18. doi:10.1016/j.jacasi.2021.12.005.
41 Ferreira-González I, Busse JW, Heels-Ansdell D, et al. Problems with use of composite end points in cardiovascular trials: systematic review of randomised controlled trials. *BMJ* 2007;334:786. doi:10.1136/bmj.39136.682083.AE.
42 Pocock SJ, Gregson J, Collier TJ, Ferreira JP, Stone GW. The win ratio in cardiology trials: lessons learnt, new developments, and wise future use. *Eur Heart J* 2024;45:4684-99. doi:10.1093/eurheartj/ehae647.
43 Higgins KM, Levin G, Busch R. Considerations for open-label randomized clinical trials: design, conduct, and analysis. *Clin Trials* 2024;21:681-8. doi:10.1177/17407745241244788.
44 Mas-Llado C, Gonzalez-Del-Hoyo M, Siquier-Padilla J, et al. Representativeness in randomised clinical trials supporting acute coronary syndrome guidelines. *Eur Heart J Qual Care Clin Outcomes* 2023;9:796-805. doi:10.1093/ehjqcco/qcad007.


**Web appendix:** Extra material supplied by authors