Supplementary Appendix

This appendix has been provided by the authors to give readers additional information about their work.

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Data Sharing Statement

The REC-CAGEFREE II trial is planning to continue follow-up until 2028. Individual participant data will be available upon request. Any relevant inquiry should be emailed to Dr. Ling Tao (Email: lingtaofmmu@qq.com)

Supplementary Methods

1. The recommendations of DCB angioplasty

The selection of appropriate patients to be treated with drug-coated balloons (DCB) and subsequent procedural maneuvers should adhere to the recommendations of the German Consensus Group on DCB interventions [1] and the Third Report of the International DCB Consensus Group. [2]

It should be noted that NOT all patients with acute coronary syndrome (ACS) could and were advised to undergo a DCB treatment. DCB treatment can be considered if the patients have one or more of the following comorbidities or lesion characteristics: in-stent restenosis, *de novo* lesions in small vessels, and high bleeding risk. [2-4] The use of DCB solely for other emerging indications [2] such as diabetes, bifurcation lesions, *de novo* large vessels, and long/diffuse lesions was not prohibited; however, it should be performed with great caution.

The DCB angioplasty should follow the below step [5]:

1. With or without a conventional balloon angioplasty, a pre-dilation prior to DCB angioplasty shall be performed with a non-compliant balloon, cutting balloon, scoring balloon at 0.8-1.0 balloon/vessel size ratio.

2. After lesion preparation, a 10-minute observational period should be conducted, followed by an angiogram to ensure satisfactory lesion preparation, which consists of the following criteria:

   1) ≤30% residual stenosis (visual);
   2) Thrombolysis In Myocardial Infarction (TIMI) flow grade 3; and
   3) the absence of a flow-limiting dissection.

   The DCB should ONLY be used after successful pre-dilatation.

3. Subsequently, the DCB, on each side longer than the DCB by at least 2-3 mm to avoid geographical mismatch, is inflated at nominal pressure for ~45 seconds. In cases where subjects experience TIMI flow<3, severe dissection (type D, E, and F), or visual residual stenosis>30% (visual) post-DCB, a bailout DES is recommended to be implanted for rescue treatment. However, patients with bailout stents will be disqualified from participating in this trial.

2. Statistical Considerations

2.1. Multiplicity considerations and hierarchical testing

The primary hypothesis is to analyze the non-inferiority of the NACE rates at 12 months between experimental and reference groups. A hierarchical (sequential) testing structure will be used to maintain overall alpha for secondary endpoints at 12 months, and no additional multiplicity adjustment to the hypothesis testing will be needed.

This structure follows the fixed sequence procedure. If the primary endpoint is statistically significant, the remaining secondary endpoints will be tested in the following order: Non-inferiority testing of the primary endpoint -> Superiority testing of the secondary endpoints in the order of the following:

- The occurrence of clinically relevant ischemic or bleeding event, including all-cause death, any stroke, MI, BARC-defined type 3 bleeding, any revascularization, and BARC-defined type 2 bleeding events at 12 months (Analyzed by Win Ratio)
- The occurrence of BARC type 2, 3, or 5 bleeding events with the cumulative event rate calculated at 12 months
- The occurrence of BARC type 3 or 5 bleeding events with the cumulative event rate calculated at 12 months
- The occurrence of BARC 2 bleeding events with the cumulative event rate calculated at 12 months
- The occurrence of BARC 3 bleeding events with the cumulative event rate calculated at 12 months
- The occurrence of BARC 5 bleeding events with the cumulative event rate calculated at 12 months

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. Analyses of other secondary outcomes and additional analyses for the primary outcome are regarded as exploratory in nature; therefore, multiplicity adjustment will not be applied.

2.2. Covariate adjusted analysis

The pre-specified covariables included in the adjusted analyses are age (continuous), sex (binary), lesion characteristics (binary: in-stent restenosis, de novo), hypertension (binary), hyperlipidemia (binary), diabetes (binary), smoking status (categorical), history of cardiovascular disease (binary), stroke (binary), and clinical presentation (categorical: STEMI, NSTEMI, UA).
A propensity score was calculated through a logistic regression model with treatment as the dependent variable (1 for the stepwise DAPT de-escalation group and 0 for the standard DAPT group), all covariates listed above as independent variables, and the center as a random effect. Then, an Inverse Probability Treatment Weighting (IPTW) analysis (weighted KM) was performed to estimate the covariate-adjusted difference with its one-sided 95%CI in cumulative primary outcome rate between the treatment groups in the intention-to-treat population.

2.3. Win ratio analysis

The unmatched win ratio method was employed to analyze the hierarchical composite endpoint of clinically relevant ischemic or bleeding events, which consists of six time-to-event outcomes including all-cause death, stroke, myocardial infarction (MI), BARC type 3 bleeding, revascularization, and BARC type 2 bleeding events. The endpoints will be evaluated by clinical importance in hierarchical order as follows:

- Time to all-cause death

- Time to stroke
- Time to MI
- Time to BARC type 3 bleeding
- Time to revascularization
- Time to BARC type 2 bleeding

Following Pocock et al's methodology [6], in the unmatched win ratio approach, each patient in the stepwise de-escalation group is compared with each patient in the DAPT escalation group; therefore, there were a total of 975 * 973 paired comparisons. The algorithm for calculating the unmatched win ratio analysis can be described as follows:

Step 1: All pairs (975 * 973 patient pairs) will be compared for the time until death, truncated at 360 days. If both participants die, the "winner" will be the one who had a longer time until death. If one participant dies but another does not, the "winner" will be the one who had a longer censored time. Otherwise, the match is tied and then go to Step 2.

Step 2: The tied pairs from the previous step will be compared for the time until a stroke, truncated at 360 days. If both participants have a stroke, the "winner" will be the one who had a longer time until a stroke. If one participant has a stroke but another does not have a stroke, the "winner" will be the one who had a longer censored time. Otherwise, the match is tied and then go to Step 3.

Step 3-6: Repeat Step 2 for other outcomes in the order of MI, BARC type 3 bleeding, revascularization, and BARC type 2 bleeding events.

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. The point estimate, together with 95% CI of the win ratio, is estimated using the *WINS* package (Version 1.3.3) in R statistical software version 4.2.1 (R Project for Statistical Computing). The P-value in the win ratio analysis was from the method based on U-statistics described by Dong et al [7].

3. Definitions of study endpoints

3.1. Definition of Death

Death is defined according to Standardized End Point Definitions for Coronary Intervention Trials -The Academic Research Consortium-2 Consensus Document (ARC-2) [8]

Type of Death	Definition
Cardiovascular mortality	1. Death due to proximate cardiac cause, e.g. myocardial infarction, cardiac tamponade, worsening heart failure, and endocarditis.
	2. Death caused by non-coronary, non-CNS vascular conditions such as pulmonary embolism, ruptured aortic aneurysm, dissecting aneurysm, or other vascular disease.

	3. Death from vascular CNS causes • From hemorrhagic stroke • From ischemic stroke
	4. All procedure-related deaths, including those related to a complication of the procedure or treatment for a complication of the procedure.
	5. Sudden or unwitnessed death defined as non-traumatic, unexpected fatal event occurring within 1h of the onset of symptoms in an apparently healthy subject. If death is not witnessed, the definition applies when the victim was in good health 24h before the event.
	6. Death of unknown cause.
Non-cardiovascular mortality	Death of a primary cause that is clearly related to another condition (e.g. trauma, cancer, suicide).

3.2. Definition of Stroke

This study classifies stroke according to two classification methods.

2.1. According to TIA, ischemic stroke, hemorrhagic stroke, and indeterminate classification [9 10] (primary)

Cerebrovascular Accident (CVA)/Stroke: A stroke is defined as a sudden onset of focal neurological deficits due to vascular lesions of the brain that persist for >24 hours. Any neurological symptom that lasts < 24 hours is classified as a transient ischemic attack (TIA). Stroke results from either of two types of cerebral vascular disturbance: ischemia or hemorrhage.

Ischemic stroke: Infarction caused by focal occlusion or stenosis of single or multiple intracranial or extracranial arteries.

Hemorrhagic stroke: Infarction caused by nontraumatic intraparenchymal, intraventricular, or subarachnoid hemorrhage.

Indeterminate: Insufficient information to determine stroke of ischemic or hemorrhagic origin.

Transient ischemic attack (TIA): TIAs are focal neurologic abnormalities of sudden onset and brief duration (i.e., lasting less than 24 hours) that reflect dysfunction in the distribution of the affected artery. TIAs include transient monocular blindness (e.g., amaurosis fugax defined as a transient episode of monocular blindness, or partial blindness, lasting ten minutes or less) and transient hemispheric attacks.

2.2. Defined according to the Proposed standardized neurological endpoints for cardiovascular clinical trials -An academic research consortium initiative (NeuroARC) [11] (as sensitivity analysis)

Type 1, Overt CNS injury: Acutely Symptomatic Brain or Spinal Cord injury	
Type 1a, Ischemic stroke	1. Sudden onset of neurological signs or symptoms fitting a focal or multifocal vascular territory within the brain, spinal cord, or retina, that: Persist for ≥24h or until death, with pathology or neuroimaging evidence that demonstrates either: a. CNS infarction in the corresponding vascular territory (with or without hemorrhage); or b. Absence of other apparent causes (including hemorrhage), even if no evidence of acute ischemia in the corresponding vascular territory is detected or 2. Symptoms lasting <24h, with pathology or neuroimaging confirmation of CNS infarction in the corresponding vascular territory. Note: When CNS infarction location does not match the transient symptoms, the event would be classified as covert CNS infarction (type 2a) and a TIA (type 3a), but not as an ischemic stroke. Signs and symptoms consistent with stroke typically include an acute onset of 1 of the following: focal weakness and/or numbness; impaired language production or comprehension; homonymous hemianopia or quadrantanopia; diplopia; altitudinal monocular blindness; hemispatial neglect; dysarthria; vertigo; or ataxia.
Subtype 1aH, Ischemic stroke with hemorrhagic conversion	Ischemic stroke includes hemorrhagic conversions. These should be subclassified as Class A or B when ischemic stroke is the primary mechanism and pathology or neuroimaging confirms a hemorrhagic conversion. Class A: Petechial hemorrhage: Petechiae or confluent petechiae within the infarction or its margins, but without a space-occupying effect Class B: Confluent hemorrhage: Confluent hemorrhage or hematoma originating from within the infarcted area with space-occupying effect.
Type 1b, Symptomatic intracerebral hemorrhage	Rapidly developing neurological signs or symptoms (focal or global) caused by an intraparenchymal, intraventricular, spinal cord, or retinal collection of blood, not caused by trauma.
Type 1c, Symptomatic subarachnoid hemorrhage	Rapidly developing neurological signs or symptoms (focal or global) and/or headache caused by bleeding into the subarachnoid space, not caused by trauma.

Type 1d, Stroke, not otherwise specified	An episode of acute focal neurological signs or symptoms and/or headache presumed to be caused by CNS ischemia or CNS hemorrhage, persisting≥24h or until death, but without sufficient evidence to be classified (i.e., no neuroimaging performed).
Type 1e, Symptomatic hypoxic-ischemic injury	Non focal (global) neurological signs or symptoms due to diffuse brain, spinal cord, or retinal cell death (confirmed by pathology or neuroimaging) in a nonvascular distribution, attributable to hypotension and/or hypoxia
Type 2, covert CNS injury: acutely asymptomatic brain or spinal cord injury detected by neuroimaging	
Type 2a, Covert CNS infarction	Brain, spinal cord, or retinal cell death attributable to focal or multifocal ischemia, on the basis of neuroimaging or pathological evidence of CNS infarction, without a history of acuter neurological symptoms consistent with the lesion location.
Subtype 2aH, Covert CNS infarction with hemorrhagic conversion	Covert CNS infarction includes hemorrhagic conversions. These should be subclassified as Class A or B when CNS infarction is the primary mechanism and neuroimaging or pathology confirms a hemorrhagic conversion. Class A: petechial hemorrhage petechiae or confluent petechiae within the infarction or its margins, but without a space-occupying effect Class B: confluent hemorrhage: confluent hemorrhage originating from within the infarcted area with a space-occupying effect.
Type 2b, Covert CNS hemorrhagic	Neuroimaging or pathological evidence of CNS hemorrhage within the brain parenchyma, subarachnoid space, ventricular system, spinal cord, or retina on neuroimaging that is not caused by trauma, without a history of acute neurological symptoms consistent with the bleeding location
Type 3, Neurological dysfunction (acutely symptomatic) without CNS injury	
Type 3a, TIA	Transient focal neurological signs or symptoms (lasting＜ 24h) presumed to be due to focal brain ,spinal cord, or retinal ischemia, but without evidence of acute infarction by neuroimaging or pathology (or in the absence of imaging)
Type 3b, Delirium without CNS injury	Transient non focal (global) neurological signs or symptoms (variable duration) without evidence of cell death by neuroimaging or pathology.
Composite neurological endpoints	

CNS infarction	Any brain, spinal cord, or retinal infarction on the basis of imaging, pathology, or clinical symptoms persisting for ≥24h (includes types 1a, 1aH, 1d, 1e, 2a, 2aH)
CNS hemorrhagic	Any brain, spinal cord, or retinal infarction on the basis of imaging or pathology, not caused by trauma (includes types 1b, 1c, 2b)

3.3. Definition of Myocardial infarction

3.3.1. Target Vessel Myocardial Infarction
Myocardial Infarction is not clearly attributable to a non-target vessel.
3.3.2. Non-target Vessel Myocardial Infarction
Myocardial Infarction is clearly attributable to a non-target vessel.
3.3.3. Spontaneous Myocardial infarction (according to Fourth universal definition of myocardial infarction 2018) [12]

MI type 1
Detection of a rise and/or fall of cTn values with at least one value above the 99th percentile URL and with at least one of the following: • Symptoms of acute myocardial ischemia; • New ischemic ECG changes; • Development of pathological Q waves; • Imaging evidence of new loss of viable myocardium or new regional wall motion abnormality in a pattern consistent with an ischemic aetiology; • Identification of a coronary thrombus by angiography including intracoronary imaging or by autopsy.
MI type 2
Detection of a rise and/or fall of cTn values with at least one value above the 99th percentile URL, and evidence of an imbalance between myocardial oxygen supply and demand unrelated to acute coronary athero-thrombosis, requiring at least one of the following: • Symptoms of acute myocardial ischemia • New ischemic ECG changes; • Development of pathological Q waves; Imaging evidence of new loss of viable myocardium or new regional wall motion abnormality in a pattern consistent with an ischemic etiology.
MI type 3
Patients who suffer cardiac death, with symptoms suggestive of myocardial ischemia accompanied by presumed new ischemic ECG changes or ventricular fibrillation, but die before blood samples for biomarkers can be obtained, or before increases in cardiac biomarkers can be identified, or MI is detected by autopsy examination.
MI type 4a: MI related to PCI (<48 hours post PCI)
Adjudicated per SCAI definition only, see below.

MI type 4b:
A subcategory of PCI-related MI is stent/scaffold thrombosis, type 4b MI, as documented by angiography or autopsy using the same criteria utilized for type 1 MI. It is important to indicate the time of the occurrence of the stent/scaffold thrombosis in relation to the timing of the PCI procedure.
MI type 4c:
Occasionally MI occurs and—at angiography, in-stent restenosis, or restenosis following balloon angioplasty in the infarct territory—is the only angiographic explanation since no other culprit lesion or thrombus can be identified. This PCI-related MI type is designated as type 4c MI, defined as focal or diffuse restenosis, or a complex lesion associated with a rise and/or fall of cTn values above the 99th percentile URL applying, the same criteria utilized for type 1 MI.
MI type 5: CABG-related MI 48h after the index procedure
Adjudicated per SCAI definition only, see below.

3.3.4. Peri-procedural MI after PCI or CABG (<48 hours post- PCI or CABG) according to the 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 2013) definition [13]

For patients with normal baseline cardiac biomarkers: any of the following criteria:

- CK-MB ≥10×ULN or cTn (I or T) ≥70×ULN

OR: CK-MB ≥ 5×ULN or cTn (I or T) ≥35×ULN may be accepted in combination with any of the following:

- New pathologic Q-waves in ≥2 contiguous leads
- OR: new persistent LBBB

For patients with elevated baseline cardiac biomarkers, any of the following criteria:

- When biomarker levels are stable or falling, there should be new CK-MB elevation by an absolute increment of ≥10×ULN (or ≥70×ULN for cTnI or T) from the previous nadir level
- When biomarker levels have not been shown to be stable or falling, there should be a further rise in CK-MB or troponin beyond the most recently measured value by an absolute increment of ≥10×ULN in CK-MB or ≥70×ULN in cTn plus new ST-segment elevation or depression plus signs consistent with a clinically relevant MI, such as new onset or worsening heart failure or sustained hypotension.

Note: Any peri-procedural MI that occurred due to the PCI that was performed prior to randomization is considered a baseline clinical presentation rather than an event.

3.4. Definition of Revascularization

Revascularization is defined according to Standardized End Point Definitions for Coronary Intervention Trials -The Academic Research Consortium-2 Consensus Document (ARC-2) [8]

Classification	**Definition**

Target lesion	The target lesion is defined as the treated segment including the 5-mm margin proximal and distal to the stent
Target lesion revascularization (TLR)	Target lesion revascularization is defined as a repeat percutaneous intervention of the target lesion or bypass surgery of the target vessel performed for restenosis or other complication of the target lesion.
Target vessel	The target vessel is defined as the entire major intervened coronary vessel, including side branches.
Target vessel revascularization (TVR)	Target vessel revascularization is defined as any repeat percutaneous intervention or surgical bypass of any segment of the target vessel including the target lesion.
Target vessel non–target lesion revascularization	Target vessel nontarget lesion revascularization is defined as any repeat percutaneous intervention or surgical bypass of the target vessel for pre-existing disease, disease progression or other reasons unrelated to the target lesion as defined above.
Non-Target Lesion Revascularization (Non-TLR)	Any revascularization in the target vessel for a lesion other than the target lesion is considered a non-TLR.
Non-Target Vessel Revascularization (Non-TVR)	Revascularization of the vessel identified and treated as the non-target vessel at the time of the index procedure.

Clinically and physiologically indicated revascularization (CPI-TLR/TVR)
A revascularization is considered clinically and physiologically indicated if associated with any of the following (Hierarchically):

1. Positive invasive functional ischemia test (e.g. FFR, iFR). When invasive functional assessment is available, use the following hierarchy:
   a) Core laboratory–reported fractional flow reserve ≤0.80 or instant wave-free ratio ≤0.89.
   b) Site-reported fractional flow reserve ≤0.80 or instant wave-free ratio ≤0.89.
   c) Core laboratory–reported angiography-derived fractional flow reserve ≤0.80.
2. Angiographic diameter stenosis ≥50% (by core laboratory QCA based on the average of multiple views) and positive non-invasive ischemia test (e.g. dobutamine stress test, nuclear test, exercise test, FFR-CT).
3. Angiographic diameter stenosis ≥50% (by core laboratory QCA based on the average of multiple views) and ischemic symptoms (stable angina or acute coronary syndrome).
4. Angiographic diameter stenosis ≥70% (by core laboratory QCA based on the average of multiple views).
5. Angiographic diameter stenosis ≥70% (by core laboratory QCA based on the worst view).

Additional notes:

- In case a revascularization occurs in a vessel and the core laboratory-reported angiography-derived fractional flow reserve > 0.80, and the target lesions have a core

laboratory-reported angiographic diameter stenosis ≥70% by QCA based on multiple views, the revascularization will be considered as non-clinically indicated.

- When the diameter stenosis is <50%, the presence of severe ischemic signs and symptoms (e.g., acute myocardial infarction) would also confirm the diagnosis of a clinically indicated revascularization.

3.5. Definition of Bleeding

3.5.1. Bleeding Academic Research Consortium (BARC) definition [14] for Bleeding is used in the primary analyses. Clinically relevant bleeding is defined as any bleeding event that meets the BARC types 2, 3 or 5.

Type 0:	No evidence of bleeding
Type 1:	Bleeding that is not actionable and does not cause the patient to seek unscheduled performance of studies, hospitalization, or treatment by a health-care professional; may include episodes leading to self-discontinuation of medical therapy by the patient without consulting a health-care professional.
Type 2:	Any overt, actionable sign of haemorrhage (e.g., more bleeding than would be expected for a clinical circumstance, including bleeding found by imaging alone) that does not fit the criteria for type 3, 4, or 5 but does meet at least one of the following criteria: • Requiring medical or percutaneous intervention guided by a health care professional includes (but is not limited to) temporary/permanent cessation of a medication, coiling, compression, local injection • Leading to hospitalization or an increased level of care • Prompting evaluation, defined as an unscheduled visit to a healthcare professional resulting in diagnostic testing (laboratory or imaging)
Type 3:	Type 3a: • Overt bleeding plus haemoglobin drop of 3 to < 5 g/dL (provided haemoglobin drop is related to bleed). • Any transfusion with overt bleeding. Type 3b: • Overt bleeding plus haemoglobin drop ≥5 g/dL (provided haemoglobin drop is related to bleed), • Cardiac tamponade, • Bleeding requiring surgical intervention for control (excluding dental/nasal/skin/haemorrhoid), • Bleeding requiring intravenous vasoactive agents. Type 3c:

	• Intracranial haemorrhage (does not include microbleeds or haemorrhagic transformation, does include intraspinal), Subcategories confirmed by autopsy or imaging or lumbar puncture, • Intraocular bleed compromising vision.
Type 4:	CABG-related bleeding, • Perioperative intracranial bleeding within 48 h, • Reoperation after closure of sternotomy for the purpose of controlling bleeding, • Transfusion of ≥ 5 U whole blood or packed red blood cells within a 48-h period, • Chest tube output more than or equal to 2L within a 24-h period.
Type 5:	Fatal bleeding Type 5a: • Probably fatal bleeding; no autopsy or imaging confirmation but clinically suspicious Type 5b: • Definite fatal bleeding is bleeding that is directly observed (either by clinical specimen – blood, emesis, stool, etc. – or by imaging) or confirmed on autopsy.

3.5.2. TIMI Bleeding Definition[15] (as sensitivity analyses)

Type	**Definitions**
Major bleeding	● Any intracranial bleeding (excluding microhemorrhages <10 mm evident only on gradient-echo MRI)
	● Clinically overt signs of hemorrhage associated with a drop in hemoglobin of ≥5g/dL or a ≥15% absolute decrease in hematocrit
	● Fatal bleeding (bleeding that directly results in death within 7d) ● Life threatening bleeding is a TIMI major bleeding event that meets any of the following criteria o Symptomatic intracranial hemorrhage o Fatal bleeding o Leads to hypotension requiring inotropic agents o Requires surgical intervention for ongoing bleeding o Necessitates transfusion of 4 or more units of whole blood or packed red blood cells over a 48-hour period
Minor bleeding	● Clinically overt (including imaging), resulting in hemoglobin drop of 3 to <5 g/dL or ≥10% decrease in hematocrit
	● No observed blood loss: ≥4 g/dL decrease in the hemoglobin concentration or ≥12% decrease in hematocrit

	● Any overt sign of hemorrhage that meets one of the following criteria and does not meet criteria for a major or minor bleeding event, as defined above o Requiring intervention (medical practitioner-guided medical or surgical treatment to stop or treat bleeding, including temporarily or permanently discontinuing or changing the dose of a medication or study drug) o Leading to or prolonging hospitalization o Prompting evaluation (leading to an unscheduled visit to a healthcare professional and diagnostic testing, either laboratory or imaging)
Minimal bleeding	● Any overt bleeding event that does not meet the criteria above
	● Any clinically overt sign of hemorrhage (including imaging) associated with a <3 g/dL decrease in hemoglobin concentration or <9% decrease in hematocrit.

3.5.3. International Society on Thrombosis and Hemostasis (ISTH) definition for Bleeding [16 17] (as sensitivity analyses)

Type	Definitions
Major bleeding	Having a symptomatic presentation and: ● Fatal bleeding, and/or ● Bleeding in a critical area or organ, such as intracranial, intraspinal, intraocular, retroperitoneal, intraarticular or pericardial, or intramuscular with compartment syndrome, and/or ● Bleeding causing a fall in hemoglobin level of 20 g L-1 (1.24 mmol L-1) or more or leading to transfusion of two or more units of whole blood or red cells.
Clinically relevant non-major bleeding	Any sign or symptom of haemorrhage (e.g., more bleeding than would be expected for a clinical circumstance, including bleeding found by imaging alone) that does not fit the criteria for the ISTH definition of major bleeding but does meet at least one of the following criteria: ● Requiring medical intervention by a healthcare professional ● Leading to hospitalization or increased level of care
Minimal bleeding	Bleeding events that do not require any medical attention and do not meet criteria for major or clinically relevant non-major bleeding

3.5.4. GUSTO Bleeding Definition[18] (as sensitivity analyses)

Type	Definitions
Severe or life-threatening	Intracerebral bleeding or bleeding resulting in substantial hemodynamic compromise requiring treatment
Moderate	Any bleeding not meeting the requirements for severe/life-threatening bleeding that requires transfusion
Minor	Other bleeding not requiring transfusion or causing hemodynamic compromise

3.5.5. High bleeding risk is defined according to the Defining high bleeding risk in patients undergoing percutaneous coronary intervention: a consensus document from the Academic Research Consortium for High Bleeding Risk (HBR-ARC) [19]. Bleeding is considered high risk if it meets one of the major bleeding or two of the minor risk criteria listed below.

Major	Minor
	Age ≥75 y
Anticipated use of long-term oral anticoagulation	
Severe or end-stage CKD (eGFR <30 mL/min)	Moderate CKD (eGFR 30–59 mL/min)
Haemoglobin <11 g/dL	Haemoglobin 11–12.9 g/dL for men and 11–11.9 g/dL for women
Spontaneous bleeding requiring hospitalisation or transfusion in the past 6 months or at any time, if recurrent	Spontaneous bleeding requiring hospitalisation or transfusion within the past 12 months not meeting the major criterion
Moderate or severe baseline thrombocytopenia (platelet count $<100 \times 10^9$/L)	
Chronic bleeding diathesis	
Liver cirrhosis with portal hypertension	
	Long-term use of oral NSAIDs or steroids
Active malignancy (excluding non-melanoma skin cancer) within the past 12 months	
Previous spontaneous ICH (at any time) Previous traumatic ICH within the past 12 months Presence of a bAVM Moderate or severe ischemic stroke within the past 6 months	Any ischemic stroke at any time not meeting the major criterion
Non-deferrable major surgery on DAPT	
Recent major surgery or major trauma within 30 days before PCI	

3.6. Definition of Stent (device) Thrombosis

Stent (device) thrombosis is defined according to Standardized End Point Definitions for Coronary Intervention Trials -The Academic Research Consortium-2 Consensus Document (ARC-2) [8].

A thrombosis within the segment of DCB is considered as stent thrombosis.

Classification	Criteria
Definite stent (device) thrombosis	1. Angiographic confirmation of stent (device) thrombosis
	The presence of a thrombus that originates in the stent (device) or in the segment 5 mm proximal or distal to the stent (device) that was used during the index PCI or in a side branch originating from the treated segment and the presence of at least 1 of the following criteria:
	Acute onset of ischemic symptoms at rest
	New electrocardiographic changes suggestive of acute ischemia
	Typical rise and fall in cardiac biomarkers (refer to definition of spontaneous myocardial infarction)
	2. Pathological confirmation of stent (device) thrombosis
	Evidence of recent thrombus within the stent (device) was used during the index PCI determined at autopsy
	Examination of tissue retrieved following thrombectomy (visual/histology)
Probable (device) thrombosis	Regardless of the time after the index procedure, any myocardial infarction that is related to documented acute ischemia in the territory of the implanted stent (device) without angiographic confirmation of stent (device) thrombosis and in the absence of any other obvious cause.

Supplementary Tables

Table S1. Site List

No.	Site	Number of enrollments
1	Xijing Hospital	403
2	Zhuzhou Central Hospital	149
3	Tianjin Fourth Central Hospital	133
4	The Second Hospital of Tianjin Medical University	110
5	People's Hospital of Qingyang	98
6	China-Japan Union Hospital of Jilin University	93
7	The First Affiliated Hospital of Gannan Medical University	74
8	Yangpu Hospital of Tongji University	73
9	The First Affiliated Hospital of Naval Medical University	72
10	Ankang Central Hospital	70
11	The First Affiliated Hospital of USTC	64
12	The Seventh People's Hospital of Zhengzhou	63
13	Liaocheng People's Hospital	56
14	Fuwai Central China Cardiovascular Hospital	50
15	The First Hospital of Kunming	45
16	Cardio Cerebrovascular Disease Hospital of Ningxia Medical University General Hospital	41
17	The Second Affiliated Hospital of Nanchang University	36
18	Xi'an Central Hospital	34
19	Yanan University Affiliated Hospital	32
20	Xiangtan Central Hospital	28
21	Gansu Provincial Hospital	26
22	The First Affiliated Hospital of Anhui University of Science and Technology	26
23	Beijing Friendship Hospital Capital Medical University	21
24	West China Hospital Sichuan University	20
25	Linyi People's Hospital	16
26	The Southwest Hospital of AMU	15
27	Yueyang Hospital of Integrated Traditional Chinese and Western Medicine, Shanghai University of Traditional Chinese Medicine	15
28	Qilu Hospital of Shandong University	13
29	The Affiliated Hospital of Qingdao University	10
30	Hunan Provincial People's Hospital	9
31	Tangshan Workers Hospital	8
32	Tongji Hospital of Tongji University	7
33	Tianjin First Central Hospital	7
34	First Hospital of Shanxi Medical University	6
35	Tianjin Third Central Hospital	6
36	The Seventh People's Hospital of Shanghai University of Traditional Chinese Medicine	5
37	Shandong Provincial Hospital	4
38	The First Affiliated Hospital of Wenzhou Medical University	4
39	Henan Provincial Chest Hospital	3
40	The Second Affiliated Hospital of Zhengzhou University	2
41	The Second Xiangya Hospital of Central South University	1

Table S2. Features of the DCBs used in the current study

Device	Company	Drug	Additive	Dose (mg/mm^2)	Drug retention	Approval	Number of patients
SeQuent Please	Braun, Germany	Paclitaxel	Iopromide	3	28 days	CE NMPA	327
RESTORE	Cardionovum, Germany	Paclitaxel	Shelloic Acid	3	150 hours	CE NMPA	513
Bingo	Yinyi Biotech, China	Paclitaxel	Iohexol	3	14 days	NMPA	523
Swide	Shenqi Medical, China	Paclitaxel	Iopromide	3	28 days	NMPA	288
Vesselin	Lepu Medical, China	Paclitaxel	Urea	3	28 days	NMPA	242
Others	-	-	-	-		-	55

National Medical Products Administration of China (NMPA)

Table S3. Trial inclusion and exclusion criteria

Inclusion criteria
1. Patients with an indication for PCI due to acute coronary syndrome (including STEMI, NSTEMI, and unstable angina)
2. All intended target lesion(s) are successfully treated by PCI with only drug-coated balloon(s)
3. Patients who are able to complete the follow-up and comply to the prescribed medication
Exclusion criteria
1. Under the age of 18 or older than 80 years old
2. Unable to give informed consent
3. Patient is a woman who is pregnant or nursing
4. Known contraindications to medications such as heparin, antiplatelet drugs, or contrast
5. Currently participating in another trial and not yet at its primary endpoint
6. Planned elective surgery
7. Concurrent medical condition with a life expectancy of less than 1 year
8. Previous intracranial hemorrhage
9. Required long-term oral anticoagulant therapy
10. Cardiogenic shock
11. Previous stent implantation within 6 months
12. In-stent thrombosis
13. Target lesion located in surgical conduit

Table S4. Study endpoints

Primary efficacy endpoint
Net adverse clinical events (NACE), defined as a composite clinical endpoint of all-cause death, stroke, MI, revascularization, and BARC-type 3 or 5 bleeding events
Secondary efficacy endpoints (hierarchical)
1. Clinically relevant ischemic or bleeding events, including any death, stroke, MI, BARC-type 3 bleeding events, revascularization, and BARC-type 2 bleeding events, will be treated as having hierarchical clinical importance and analyzed using the win ratio method
2. BARC type 2, 3, or 5 bleeding events
3. BARC type 3 or 5 bleeding events
4. BARC type 2 bleeding events
5. BARC type 3 bleeding events
6. BARC type 5 bleeding events
Primary Safety Endpoint
Patient-oriented composite endpoint (PoCE), defined as a composite clinical endpoint of all-cause death, stroke, MI, revascularization
Safety Endpoints
1. Individual components of the primary safety endpoint
2. Device-oriented Composite Endpoint (DoCE), defined as a composite clinical endpoint of cardiac cause death, target vessel myocardial infraction (TV-MI), and clinically and physiologically indicated target lesion revascularization (CPI-TLR)
3. Individual components of DoCE
4. Target vessel failure (TVF), defined as a composite of cardiovascular death, TV-MI, and clinically and physiologically indicated target vessel revascularization
5. Clinical and physiologically indicated target vessel revascularization
6. Definite/Probable Stent thrombosis rates according to ARC-II classification

Table S5. Noninferiority margins used in previous trials comparing the de-escalation of DAPT to the standard 12-month DAPT in patients with drug-eluting stents

	Trial	**Journal**	**Sample size**	**Randomization** (DAPT duration in Months)	**Primary endpoint** (noninferiority unless specified)	**Absolute margin**	**Relative margin** (% of margin to estimated event rates in the Reference arm)
	ACS						
1	TROPICAL-ACS [20]	Lancet 2017	2610	12 (P2Y12i de-escalation) vs. 12	Cardiac death, MI, stroke, BARC ≥2 bleeding	3.15%	30%
2	SMART DATE [21]	Lancet 2018	2712	6 (+6m aspirin monotherapy) vs. 12	Death, MI, stroke	2.0%	44.4%
3	DAPT STEMI [22]	BMJ 2018	870	6 (+6m aspirin monotherapy) vs. 12	Death, MI, revascularization, stroke, TIMI major bleeding	NA	HR: 1.66
4	POPular Genetics [23]	NEJM 2019	2488	12 (P2Y12i de-escalation) vs. 12	Co-primary endpoints Death, MI, definite ST, stroke, major bleeding (non-inferiority) PLATO major or minor bleeding (Superiority)	2.0%	10.6%
5	REDUCE [24]	Eurointervention 2019	1496	3 (+9m aspirin monotherapy) vs. 12	Death, MI, ST, stroke, TVR, BARC ≥2 bleeding	5.0%	41.7%
6	TICO [25]	JAMA 2020	3056	3 (+9m P2Y12i monotherapy) vs. 12	Primary endpoint: Death, MI, ST, stroke, TVR, TIMI major bleeding (Superiority)	NA	NA
7	HOST-REDUCE-POLYTECH-ACS [26]	Lancet 2020	2338	1 (+11m P2Y12i de-escalation) vs. 12	Death, MI, ST, repeat revascularization, stroke, BARC ≥2 bleeding	2.5%	31.3%
8	TALOS-AMI [27]	Lancet 2021	2697	1 (+11m P2Y12i de-escalation) vs. 12	Cardiac death, MI, stroke, BARC ≥2 bleeding	3.0%	HR: 1.34
9	STOPDAPT-2 ACS [28]	JAMA Cardiol 2022	4136	1-2 (+10-11m P2Y12i monotherapy) vs. 12	Cardiac death, MI, stroke, definite ST, TIMI major or minor bleeding	2.0%	50%

10	T-PASS [29]	Circulation 2024	2850	<1 (+>11m P2Y12i monotherapy) vs. 12	Death, MI, definite or probable ST, stroke, BARC 3 or 5 bleeding	4.2%	30%
11	OPT-BIRISK [30]	JAMA Cardiol 2024	7758	9-12 (+9m P2Y12i monotherapy) vs. 9-12+9	Primary endpoint: BARC 2, 3, or 5 bleeding (Superiority); key secondary endpoint: Death, MI, stroke, clinically driven revascularization (Non-inferiority)	1.6%	20%
12	ULTIMATE-DAPT [31]	Lancet 2024	3400	1 (+11m P2Y12i monotherapy) vs. 12	Sequentially tested: 1. BARC 2, 3, or 5 bleeding (Superiority); 2. Cardiac death, MI, ischemic stroke, definite ST, clinically driven TVR (Non-inferiority)	2.5%	40%
	ACS+CCS						
13	EXCELLENT [32]	Circulation 2012	1443	6 (+6m aspirin monotherapy) vs. 12	Cardiac death, MI, ischemia-driven TVR	4.0%	40%
14	RESET [33]	JACC 2012	2117	3 (+9m aspirin monotherapy) vs. 12	Cardiac death, MI, ST, TVR, major or minor bleeding	4.0%	36.4%
15	OPTIMIZE [34]	JAMA 2013	3119	3 (+9m aspirin monotherapy) vs. 12	Death, MI, stroke, major bleeding	2.7%	30%
16	SECURITY [35]	JACC 2014	1399	6 (+6m aspirin monotherapy) vs. 12	Cardiac death, MI, stroke, definite or probable ST, BARC 3 or 5 bleeding	2.0%	44.4%
17	ISAR-SAFE [36]	Eur Heart J 2015	4000	6 (+6m aspirin monotherapy) vs. 12	Death, MI, ST, stroke, TIMI major bleeding	2.0%	20%
18	IVUS XPL [37]	JACC Cardiovasc Interv 2016	1400	6 (+6m aspirin monotherapy) vs. 12	Cardiac death, TV-MI, stroke, TIMI major bleeding (Superiority)	NA	NA
19	I-LOVE-IT 2 [38]	Circ Cardiovasc Interv 2016	1829	6 (+6m aspirin monotherapy) vs. 12	Cardiac death, TV-MI, or ischemia-driven TLR	3.7%	44.6%

20	OPTIMA-C [39]	Eurointervention 2018	1367	6 (+6m aspirin monotherapy) vs. 12	Cardiac death, TV-MI, ischemia-driven TLR	4.0%	57.1%
21	GLOBAL LEADERS [40]	Lancet 2018	15968	1 (+23m P2Y12i monotherapy) vs. 12 (+12m aspirin monotherapy)	Death, new Q-wave MI (Superiority)	NA	NA
22	SMART-CHOICE [41]	JAMA 2019	2993	3 (+9m P2Y12i monotherapy) vs. 12	Death, MI, stroke	1.8%	45%
23	STOPDAPT-2 [42]	JAMA 2019	3009	1 (+11m P2Y12i monotherapy) vs. 12	Cardiac death, MI, stroke, definite ST, major or minor bleeding	2.3%	50%
24	TWILIGHT [9]	NEJM 2019	7119	3 (+9m P2Y12i monotherapy) vs. 12	Primary endpoint: BARC 2, 3, or 5 bleeding (Superiority); Key secondary endpoint: Death, MI, stroke (Non-inferiority)	1.6%	20%
25	MASTER DAPT [43]	NEJM 2021	4579	1 (+11m aspirin or P2Y12i monotherapy) vs. 3-12	Sequentially tested: 1. Death, MI, stroke, BARC ≥3 bleeding (Non-inferiority); 2. Death, MI, or stroke (Non-inferiority); 3. BARC ≥2 bleeding (Superiority).	3.6%	30%
26	HOST-IDEA [44]	Circulation 2023	2013	3-6 (+6-9m aspirin or P2Y12i monotherapy) vs. 12	Cardiac death, TVMI, clinically driven TLR, ST, BARC 3 or 5 bleeding	3.2%	33.7%

The noninferiority margins used in previous studies comparing the de-escalation of DAPT to the standard 12-month DAPT in patients with drug-eluting stents were summarized based on trials mentioned in the consensus paper of "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" [45]

Table S6. Days from PCI to randomization

Days from PCI to randomization	Overall (N = 1,948)	Stepwise DAPT de-escalation (N = 975)	Standard DAPT (N = 973)
0	434 (22.3%)	218 (22.4%)	216 (22.2%)
1	1,111 (57.0%)	554 (56.8%)	557 (57.2%)
2	253 (13.0%)	118 (12.1%)	135 (13.9%)
3	74 (3.8%)	46 (4.7%)	28 (2.9%)
4	36 (1.8%)	17 (1.7%)	19 (2.0%)
5	12 (0.6%)	7 (0.7%)	5 (0.5%)
6	9 (0.5%)	5 (0.5%)	4 (0.4%)
7	8 (0.4%)	4 (0.4%)	4 (0.4%)
8	5 (0.3%)	3 (0.3%)	2 (0.2%)
9	1 (0.1%)	0 (0.0%)	1 (0.1%)
10	2 (0.1%)	2 (0.2%)	0 (0.0%)
11	3 (0.2%)	1 (0.1%)	2 (0.2%)

Table S7. Type of antiplatelet therapy and other medications at baseline and follow-up

Medication	Stepwise DAPT de-escalation (N=975)	Standard DAPT (N=973)
At 0-30 days		
Dual antiplatelet therapy	948/975 (97.2%)	959/973 (98.6%)
Single antiplatelet therapy	3/975 (0.3%)	6/973 (0.6%)
No antiplatelet therapy	4/975 (0.4%)	3/973 (0.3%)
P2Y12 inhibitor	970/975 (99.5%)	966/973 (99.3%)
Ticagrelor	918/975 (94.2%)	914/973 (93.9%)
Clopidogrel	31/975 (3.2%)	37/973 (3.8%)
Aspirin	944/975 (96.8%)	958/973 (98.5%)
Indobufen	3/975 (0.3%)	2/973 (0.2%)
Oral anticoagulant	2/975 (0.2%)	4/973 (0.4%)
Sacubitril valsartan	261/975 (26.8%)	261/973 (26.8%)
Angiotensin-converting enzyme inhibitor	107/975 (11.0%)	106/973 (10.9%)
Angiotensin II receptor blocker	222/975 (22.8%)	235/973 (24.2%)
Beta-blocker	692/975 (71.0%)	688/973 (70.7%)
Calcium-channel blocker	258/975 (26.5%)	252/973 (25.9%)
Spironolactone	73/975 (7.5%)	72/973 (7.4%)
Thiazide or loop diuretics	92/975 (9.4%)	96/973 (9.9%)
Insulin	76/975 (7.8%)	82/973 (8.4%)
Oral hypoglycemic drug	194/975 (19.9%)	183/973 (18.8%)
Statin	920/975 (94.4%)	924/973 (95.0%)
PCSK9i	96/975 (9.8%)	113/973 (11.6%)
Ezetimibe	104/975 (10.7%)	126/973 (12.9%)
Proton pump inhibitor	503/975 (51.6%)	498/973 (51.2%)
SGLT2i	134/975 (13.7%)	160/973 (16.4%)
Nitrate	174/975 (17.8%)	179/973 (18.4%)
At 31-90 days		
Dual antiplatelet therapy	24/970 (2.5%)	951/969 (98.1%)
Single antiplatelet therapy	908/970 (93.6%)	10/969 (1.0%)
No antiplatelet therapy	2/970 (0.2%)	0/969 (0.0%)
P2Y12 inhibitor	963/970 (99.3%)	964/969 (99.5%)
Ticagrelor	880/970 (90.7%)	882/969 (91.0%)
Clopidogrel	69/970 (7.1%)	73/969 (7.5%)
Aspirin	24/970 (2.5%)	949/969 (97.9%)
Indobufen	1/970 (0.1%)	2/969 (0.2%)
Oral anticoagulant	2/970 (0.2%)	3/969 (0.3%)

Sacubitril valsartan	238/970 (24.5%)	246/969 (25.4%)
Angiotensin-converting enzyme inhibitor	92/970 (9.5%)	88/969 (9.1%)
Angiotensin II receptor blocker	213/970 (22.0%)	219/969 (22.6%)
Beta-blocker	649/970 (66.9%)	644/969 (66.5%)
Calcium-channel blocker	252/970 (26.0%)	247/969 (25.5%)
Spironolactone	56/970 (5.8%)	59/969 (6.1%)
Thiazide or loop diuretics	75/970 (7.7%)	84/969 (8.7%)
Insulin	75/970 (7.7%)	82/969 (8.5%)
Oral hypoglycemic drug	193/970 (19.9%)	184/969 (19.0%)
Statin	892/970 (92.0%)	892/969 (92.1%)
PCSK9i	89/970 (9.2%)	99/969 (10.2%)
Ezetimibe	95/970 (9.8%)	112/969 (11.6%)
Proton pump inhibitor	240/970 (24.7%)	271/969 (28.0%)
SGLT2i	128/970 (13.2%)	153/969 (15.8%)
Nitrate	139/970 (14.3%)	146/969 (15.1%)
At 91-180 days		
Dual antiplatelet therapy	30/966 (3.1%)	936/968 (96.7%)
Single antiplatelet therapy	910/966 (94.2%)	16/968 (1.7%)
No antiplatelet therapy	4/966 (0.4%)	3/968 (0.3%)
P2Y12 inhibitor	951/966 (98.4%)	955/968 (98.7%)
Ticagrelor	850/966 (88.0%)	854/968 (88.2%)
Clopidogrel	88/966 (9.1%)	88/968 (9.1%)
Aspirin	32/966 (3.3%)	936/968 (96.7%)
Indobufen	1/966 (0.1%)	3/968 (0.3%)
Oral anticoagulant	3/967 (0.3%)	2/968 (0.2%)
Sacubitril valsartan	226/966 (23.4%)	239/968 (24.7%)
Angiotensin-converting enzyme inhibitor	88/966 (9.1%)	83/968 (8.6%)
Angiotensin II receptor blocker	217/966 (22.5%)	218/968 (22.5%)
Beta-blocker	615/966 (63.7%)	611/968 (63.1%)
Calcium-channel blocker	246/966 (25.5%)	250/968 (25.8%)
Spironolactone	49/966 (5.1%)	46/968 (4.8%)
Thiazide or loop diuretics	66/966 (6.8%)	76/968 (7.9%)
Insulin	73/966 (7.6%)	82/968 (8.5%)
Oral hypoglycemic drug	188/966 (19.5%)	182/968 (18.8%)
Statin	872/966 (90.3%)	876/968 (90.5%)
PCSK9i	76/966 (7.9%)	86/968 (8.9%)
Ezetimibe	91/966 (9.4%)	105/968 (10.8%)
Proton pump inhibitor	193/966 (20.0%)	213/968 (22.0%)
SGLT2i	121/966 (12.5%)	148/968 (15.3%)

Nitrate	126/966 (13.0%)	139/968 (14.4%)
At 181-360 days		
Dual antiplatelet therapy	38/959 (4.0%)	907/967 (93.8%)
Single antiplatelet therapy	885/959 (92.3%)	34/967 (3.5%)
No antiplatelet therapy	8/959 (0.8%)	8/967 (0.8%)
P2Y12 inhibitor	62/959 (6.5%)	934/967 (96.6%)
Ticagrelor	33/959 (3.4%)	822/967 (85.0%)
Clopidogrel	25/959 (2.6%)	102/967 (10.5%)
Aspirin	901/959 (94.0%)	905/967 (93.6%)
Indobufen	3/959 (0.3%)	12/967 (1.2%)
Oral anticoagulant	2/959 (0.2%)	2/967 (0.2%)
Sacubitril valsartan	224/959 (23.4%)	229/967 (23.7%)
Angiotensin-converting enzyme inhibitor	77/959 (8.0%)	79/967 (8.2%)
Angiotensin II receptor blocker	203/959 (21.2%)	202/967 (20.9%)
Beta-blocker	587/959 (61.2%)	582/967 (60.2%)
Calcium-channel blocker	231/959 (24.1%)	243/967 (25.1%)
Spironolactone	40/959 (4.2%)	37/967 (3.8%)
Thiazide or loop diuretics	60/959 (6.3%)	65/967 (6.7%)
Insulin	72/959 (7.5%)	82/967 (8.5%)
Oral hypoglycemic drug	188/959 (19.6%)	177/967 (18.3%)
Statin	842/959 (87.8%)	850/967 (87.9%)
PCSK9i	64/959 (6.7%)	64/967 (6.6%)
Ezetimibe	87/959 (9.1%)	101/967 (10.4%)
Proton pump inhibitor	156/959 (16.3%)	166/967 (17.2%)
SGLT2i	113/959 (11.8%)	140/967 (14.5%)
Nitrate	107/959 (11.2%)	128/967 (13.2%)

* Number (%) in patients in whom medications were assessed.

The use of medication is defined as taking the medication for ≥ 80% of the time period. ACE, angiotensin converting enzyme; ARB, angiotensin II receptor antagonist; SGLT2i, sodium-glucose transport protein 2 inhibitors; PCSK9i, proprotein convertase subtilisin/kexin type 9 inhibitors.

Table S8. Reasons for not adherent to the assigned regimen

Reasons	Patients (%)
Stepwise DAPT de-escalation	**N = 975**
Not adherent to the assigned regimen	134 (13.7%)
Ticagrelor switched to clopidogrel	76 (7.8%)
Dyspnea	68 (7.0%)
Minor bleeding episodes (Physicians' discretion)	6 (0.6%)
Gastrointestinal symptom	1 (0.1%)
Urticaria	1 (0.1%)
Aspirin switched to indobufen	2 (0.2%)
Dyspnea	1 (0.1%)
Minor bleeding episodes (Physicians' discretion)	1 (0.1%)
Continued aspirin violating the protocol	21 (2.2%)
Physicians’ discretion considering patients’ ischemic risks	21 (2.2%)
Continued ticagrelor violating the protocol	3 (0.3%)
Physicians’ discretion considering patients’ ischemic risks	3 (0.3%)
Discontinued aspirin violating the protocol	26 (2.7%)
Gastrointestinal symptom	5 (0.5%)
Easy bruise	4 (0.4%)
Hyperuricemia	2 (0.2%)
Dyspnea	1 (0.1%)
Physicians’ discretion considering patients’ bleeding risks	8 (0.8%)
Minor bleeding episodes	5 (0.5%)
Required anticoagulation	1 (0.1%)
Discontinued ticagrelor violating the protocol	6 (0.6%)
Dyspnea	2 (0.2%)
Urticaria	1 (0.1%)
Physicians’ discretion considering patients’ bleeding risks	1 (0.1%)
Minor bleeding episodes	2 (0.2%)
Standard DAPT	**N = 973**
Not adherent to the assigned regimen	132 (13.6%)
Ticagrelor switched to clopidogrel	91 (9.4%)
Dyspnea	73 (7.5%)
Minor bleeding episodes (Physicians' discretion)	18 (1.8%)
Aspirin switched to indobufen	8 (0.8%)
Gastrointestinal symptom	2 (0.2%)
Minor bleeding episodes (Physicians' discretion)	6 (0.6%)
Discontinued aspirin violating the protocol	19 (2.0%)
Gastrointestinal symptom	2 (0.2%)
Easy bruise	6 (0.6%)
Hyperuricemia	1 (0.1%)

Urticaria	1 (0.1%)
Physicians' discretion considering patients' bleeding risks	4 (0.4%)
Minor bleeding episodes	5 (0.5%)
Discontinued ticagrelor violating the protocol	11 (1.1%)
Dyspnea	3 (0.3%)
Urticaria	1 (0.1%)
Physicians' discretion considering patients' bleeding risks	4 (0.4%)
Minor bleeding episodes	3 (0.3%)
Discontinued both aspirin and ticagrelor violating the protocol	3 (0.3%)
Physicians' discretion considering patients' bleeding risks	1 (0.1%)
Minor bleeding episodes	2 (0.2%)

Non-adherence was defined as not taking the assigned regimen for more than 20% of the study time for any reason.

Table S9. Sensitivity analyses of the primary endpoint

Sensitivity analyses

- To assess the non-inferiority at one-sided alpha of 2.5% (ITT cohort)

Primary Endpoint	Stepwise DAPT de-escalation (N=975)	Standard DAPT (N=973)	Difference	One Sided 97.5% Upper Confidence Limit	Non-inferiority margin	p value for non-inferiority
NACE	87 (8.9%)	84 (8.6%)	0.36%	2.87%	3.2%	0.01

- To assess the influence of different definitions for the bleeding events (ITT cohort)

Primary Endpoint	Stepwise DAPT de-escalation (N=975)	Standard DAPT (N=973)	Difference	One Sided 95% Upper Confidence Limit	Non-inferiority margin	p value for non-inferiority
NACE (bleeding defined by TIMI major or minor bleeding events)	8.8%	8.5%	0.37%	2.47%	3.2%	0.01
NACE (bleeding defined by ISTH major bleeding events)	9.4%	9.8%	-0.31	1.89%	3.2%	0.004
NACE (bleeding defined by GUSTO moderate or severe bleeding events)	8.7%	7.9%	0.77%	2.83%	3.2%	0.03

Table S10. Definition of per-protocol population

Reasons	Patients (%)
Stepwise DAPT de-escalation group	**N = 975**
No protocol violation	825 (84.6%)
Not fulfilling the inclusion and exclusion criteria	8 (0.8%)
Required anticoagulation	5 (0.5%)
Prior intracranial hemorrhage	1 (0.1%)
Had DCB in combination with DES	1 (0.1%)
Had DES 6 months ago	1 (0.1%)
Not adherent to the assigned regimen	134 (13.7%)
Lost to follow-up or withdrew consent	8 (0.8%)
Standard DAPT group	**N = 973**
No protocol violation	826 (84.9%)
Not fulfilling the inclusion and exclusion criteria	10 (1.0%)
Required anticoagulation	9 (0.9%)
Age > 80 years	1 (0.1%)
Not adherent to the assigned regimen	132 (13.6%)
Lost to follow-up or withdrew consent	5 (0.5%)

Table S11. Clinical outcomes at 1 year in the per-protocol population

	Stepwise DAPT de-escalation (N=825)	Standard DAPT (N=826)	Difference % (2-sided 95%CI)	*P* value
Primary Endpoint				
Net adverse clinical events**,** NACE	70 (8.4%)	77 (9.2%)	-0.80 (-3.10 to 1.49)[a]	0.002[b]
Secondary endpoints, tested in pre-specified fixed sequence [c]				
Clinically relevant ischemic or bleeding event [d]	85,339 (9.0%)	60,415 (6.4%)	1.41 (1.06 to 1.88)	0.02
BARC type 3 or 5 bleeding	4 (0.5%)	14 (1.7%)	-1.19 (-2.18 to -0.20)	0.02
BARC type 2, 3, or 5 bleeding	13 (1.5%)	51 (6.1%)	-4.62 (-6.45 to -2.78)	<0.001
BARC type 2 bleeding	9 (1.1%)	37 (4.5%)	-3.43 (-5.01 to -1.86)	<0.001
Safety endpoints				
Device-oriented Composite Endpoint**,** DoCE	40 (4.8%)	42 (5.1%)	-0.33 (-2.42 to 1.76)	0.76
Cardiovascular death	10 (1.2%)	6 (0.7%)	0.44 (-0.48 to 1.36)	0.35
Target vessel myocardial Infarction	7 (0.8%)	7 (0.9%)	-0.06 (-0.96 to 0.85)	0.90
Clinically and physiologically indicated target lesion revascularization	29 (3.5%)	33 (3.9%)	-0.46 (-2.30 to 1.37)	0.62
Patient-oriented Composite Endpoint**,** PoCE	67 (8.1%)	69 (8.3%)	-0.21 (-2.85 to 2.43)	0.88
Death	10 (1.2%)	7 (0.8%)	0.33 (-0.61 to 1.28)	0.49
Stroke	7 (0.8%)	8 (0.9%)	-0.11 (-0.99 to 0.78)	0.81
Ischemic	6 (0.7%)	4 (0.5%)	0.26 (-0.46 to 0.98)	0.48
Hemorrhagic	1 (0.1%)	5 (0.6%)	-0.48 (-1.05 to 0.09)	0.10
Myocardial Infarction	9 (1.1%)	9 (1.1%)	-0.05 (-1.06 to 0.97)	0.93
Revascularization	51 (6.2%)	57 (6.9%)	-0.63 (-3.03 to 1.77)	0.61
Target vessel failure, TVF	44 (5.2%)	44 (5.3%)	-0.07 (-2.24 to 2.09)	0.95
Clinically and physiologically indicated target vessel revascularization	33 (4.0%)	36 (4.3%)	-0.32 (-2.25 to 1.61)	0.75
Stent thrombosis	2 (0.2%)	2 (0.2%)	-0.02 (-0.49 to 0.44)	0.92

[a] For the between-group difference in the primary outcome, the upper boundary of the one-sided 95% confidence interval was 1.49 percentage points

[b] P value of non-inferiority test.

[c] 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 alpha. 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.

[d] 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.

Table S12. Sensitivity analyses: clinical outcomes at 1 year in the intention-to-treat population by unadjusted Kaplan-Meier estimates

	Stepwise DAPT de-escalation (N=975)	Standard DAPT (N=973)	Difference % (2-sided 95%CI)	*P* value
Primary Endpoint				
Net adverse clinical events**,** NACE	87 (9.0%)	84 (8.7%)	0.31 (-1.81 to 2.43) [a]	0.01 [b]
Secondary endpoints, tested in pre-specified fixed sequence [c]				
Clinically relevant ischemic or bleeding event [d]	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 (1.7%)	-1.24 (-2.14 to -0.33)	0.007
BARC type 2, 3, or 5 bleeding	23 (2.4%)	90 (9.3%)	-6.92 (-8.98 to -4.85)	<0.001
BARC type 2 bleeding	19 (2.0%)	75 (7.8%)	-5.79 (-7.76 to -3.89)	<0.001
Safety endpoints				
Device-oriented Composite Endpoint**,** DoCE	51 (5.3%)	45 (4.6%)	0.62 (-1.31 to 2.55)	0.53
Cardiovascular death	13 (1.3%)	6 (0.6%)	0.72 (-0.16 to 1.60)	0.11
Target vessel myocardial Infarction	7 (0.7%)	8 (0.8%)	-0.10 (-0.88 to 0.69)	0.80
Clinically and physiologically indicated target lesion revascularization	37 (3.9%)	35 (3.6%)	0.23 (-1.46 to 1.93)	0.79
Patient-oriented Composite Endpoint**,** PoCE	84 (8.7%)	74 (7.6%)	1.03 (-1.40 to 3.47)	0.41
Death	13 (1.3%)	7 (0.7%)	0.62 (-0.28 to 1.52)	0.18
Stroke	7 (0.7%)	8 (0.8%)	0.10 (-0.88 to 0.69)	0.81
Ischemic	6 (0.6%)	4 (0.4%)	0.21 (-0.43 to 0.85)	0.52
Hemorrhagic	1 (0.1%)	5 (0.5%)	-0.41 (-0.91 to 0.08)	0.10
Myocardial Infarction	9 (0.9%)	10 (1.0%)	-0.10 (-0.98 to 0.78)	0.83
Revascularization	65 (6.8%)	61 (6.3%)	0.46 (-1.74 to 2.67)	0.68
Target vessel failure, TVF	56 (5.8%)	47 (4.9%)	0.93 (-1.07 to 2.93)	0.36
Clinically and physiologically indicated target vessel revascularization	42 (4.4%)	38 (3.9%)	0.45 (-1.34 to 2.23)	0.62
Stent thrombosis	2 (0.2%)	2 (0.2%)	0.00 (-0.41 to 0.41)	0.99

[a] For the between-group difference in the primary outcome, the upper boundary of the one-sided 95% confidence interval was 2.43 percentage points

[b] P value of non-inferiority test.

[c] 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 alpha. 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.

[d] 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.

Table S13. Sensitivity analyses: clinical outcomes at 1 year in the intention-to-treat population by Aalen-Johansen estimator

	Stepwise DAPT de-escalation (N=975)	Standard DAPT (N=973)	Difference % (2-sided 95%CI)	*P* value
BARC type 3 or 5 bleeding	4 (0.4%)	16 (1.7%)	-1.24% (-2.14 to -0.34)	0.007
BARC type 2, 3, or 5 bleeding	23 (2.4%)	90 (9.3%)	-6.92% (-8.99 to -4.86)	<0.001
BARC type 2 bleeding	19 (2.0%)	75 (7.7%)	-5.79% (-7.68 to -3.89)	<0.001
Device-oriented Composite Endpoint, DoCE	51 (5.3%)	45 (4.6%)	0.62% (-1.31 to 2.55)	0.53
Cardiovascular death	13 (1.3%)	6 (0.6%)	0.72% (-0.16 to 1.60)	0.11
Target vessel myocardial Infarction	7 (0.7%)	8 (0.8%)	-0.10% (-0.88 to 0.68)	0.79
Clinically and physiologically indicated target lesion revascularization	37 (3.8%)	35 (3.6%)	0.21% (-1.48 to 1.90)	0.81
Stroke	7 (0.7%)	8 (0.8%)	-0.10% (-0.89 to 0.68)	0.80
Myocardial Infarction	9 (0.9%)	10 (1.0%)	-0.10% (-0.98 to 0.77)	0.82
Revascularization	65 (6.7%)	61 (6.3%)	0.42% (-1.78 to 2.62)	0.71
Target vessel failure, TVF	56 (5.8%)	47 (4.9%)	0.93% (-1.07 to 2.93)	0.36
Clinically and physiologically indicated target vessel revascularization	42 (4.3%)	38 (3.9%)	0.42% (-1.36 to 2.19)	0.65
Stent thrombosis	2 (0.2%)	2 (0.2%)	-0.00% (-0.40 to 0.40)	0.99

Supplementary Figures

Figure S1. Antiplatelet regimen schema

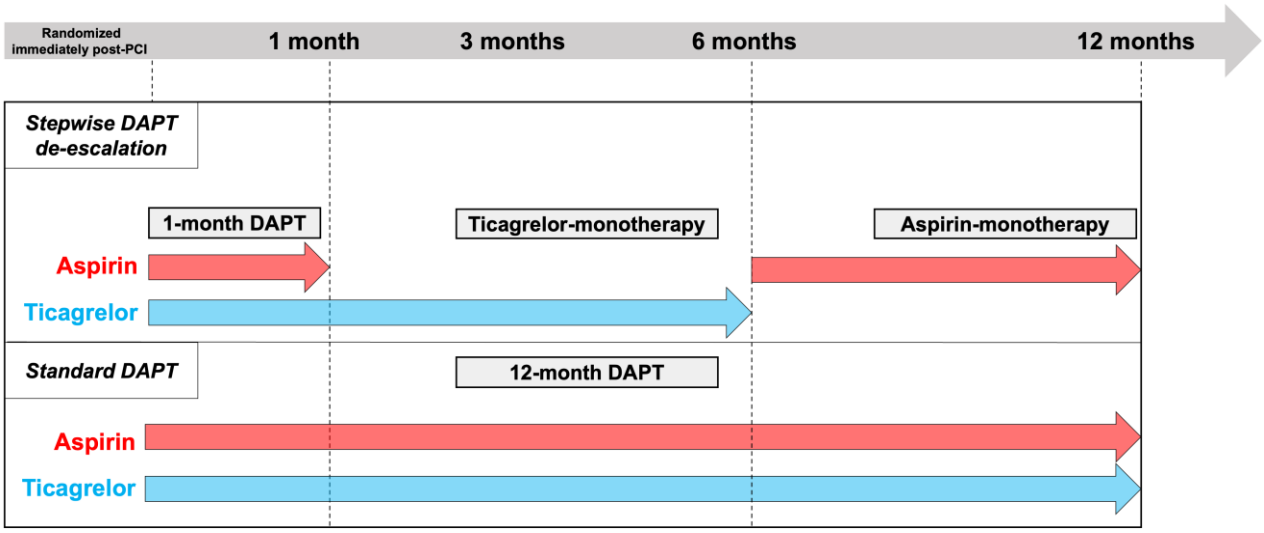
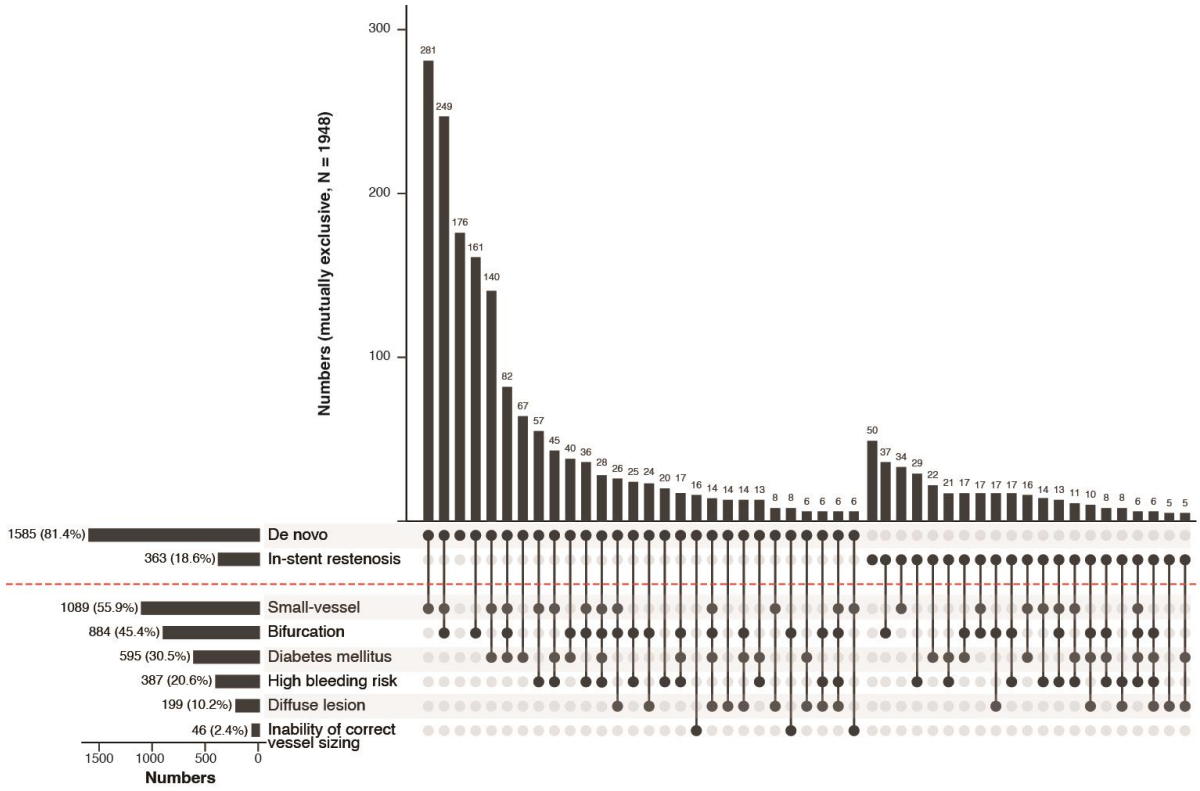


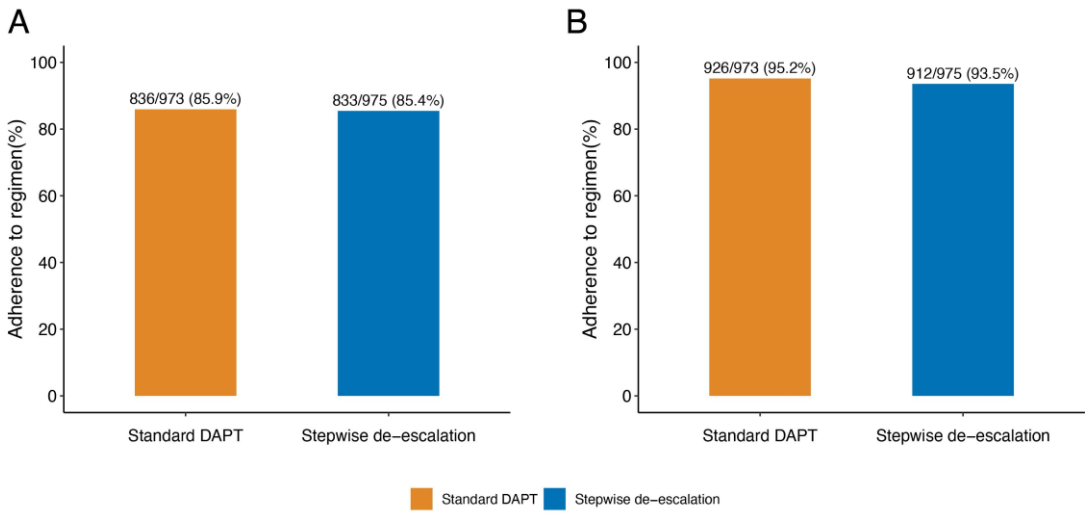
Figure S2. Combinatorial characteristics of patients for having the DCB treatment



The combinatorial characteristics of having the DCB treatment are shown at a patient level by the UpSet diagram. To streamline the figure and prevent excessive length in the upper right panel, categories with less than 5 exclusive counts were merged.

Small vessel disease for DCB is defined as using the criterion of the BASKET-SMALL 2 and REC-CAGEFREE I trial, which is <3 mm in DCB diameter [46 47]. The diffuse lesion is defined as the total length of the used device ≥ 60 mm [48]. High Bleeding Risk is defined by the Academic Research Consortium for High Bleeding Risk (HBR-ARC) [19]. Complex PCI is defined as having at least one of the following features: multivessel PCI, ≥3 DCB used, ≥3 lesions treated, bifurcation PCI with ≥2 DCB, and total DCB length >60 mm. Bifurcation is classified when at least 50% lumen narrowing occurs within 3 mm of the bifurcation point, according to the SYNTAX score definition.

Figure S3. Rates of adherence to the study medications



Adherence ≥80% of the time (day 0 to t days since randomization).

A. Adherence is defined by 80% of the study time following the regimen of aspirin plus ticagrelor for one month, followed by ticagrelor monotherapy for five months, and then aspirin monotherapy for six months in the stepwise DAPT de-escalation group and 12 months aspirin plus ticagrelor in the Standard DAPT group.

B. Adherence is defined by 80% of the study time following the regimen of aspirin plus P2Y12 inhibitors for one month, followed by P2Y12 inhibitors monotherapy for five months, and then aspirin monotherapy for six months in the stepwise DAPT de-escalation group and 12 months aspirin plus P2Y12 inhibitors in the standard DAPT group

Figure S4. KM curves of the primary efficacy endpoint in the per-protocol population

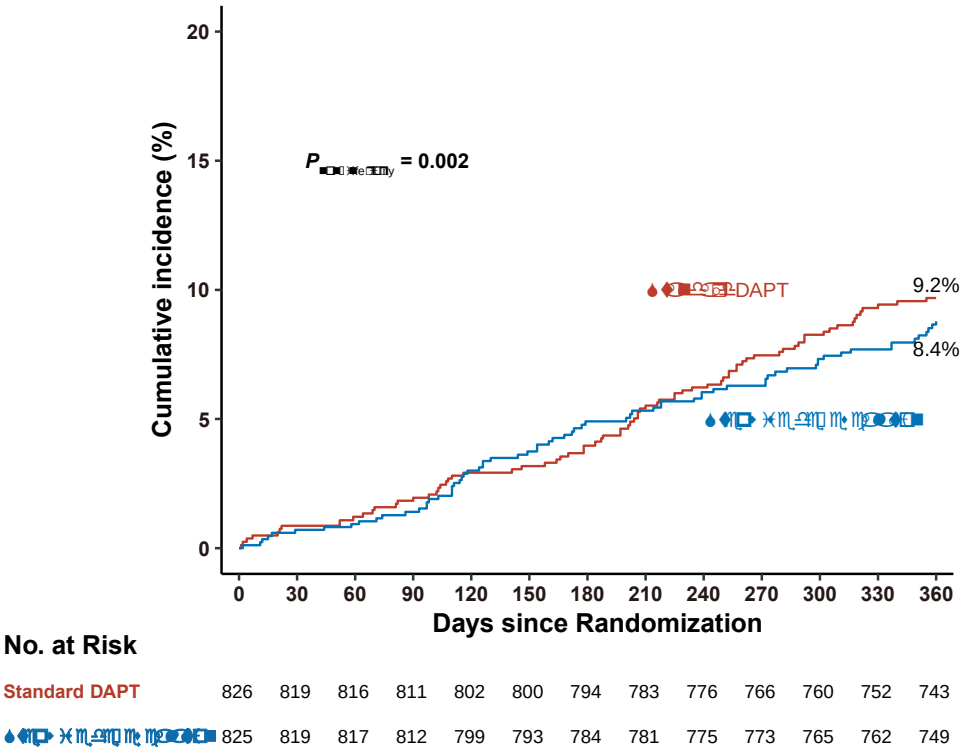


Figure S5. KM curves of the BARC 3 or 5 bleeding

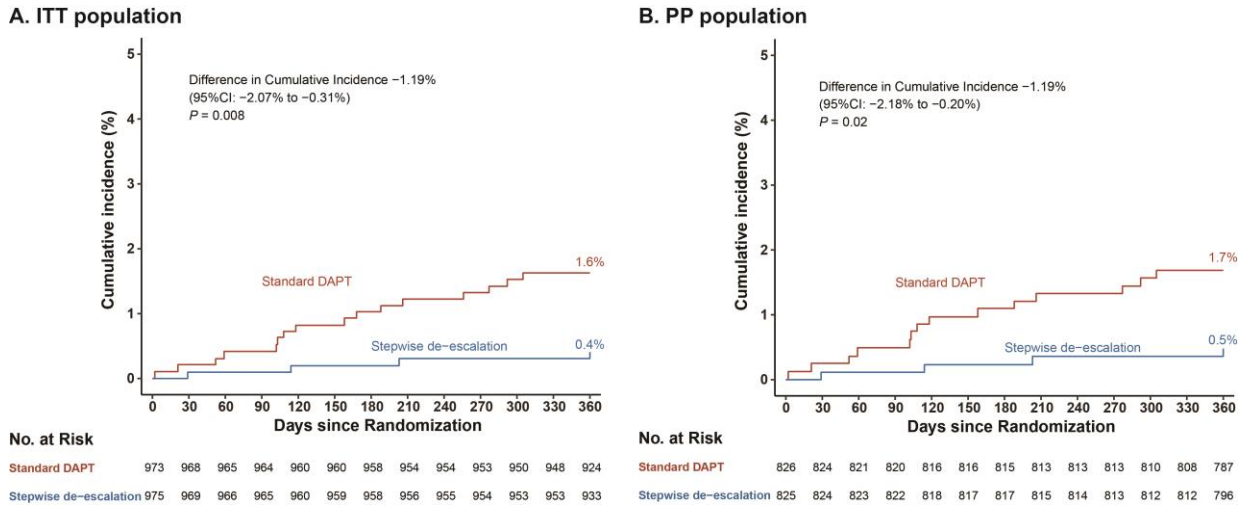
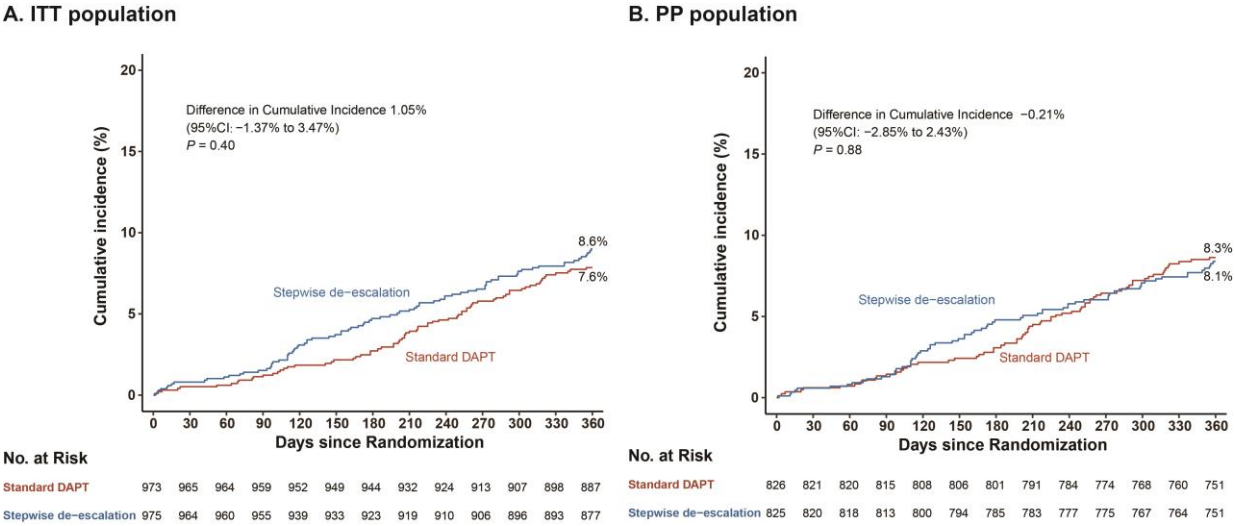


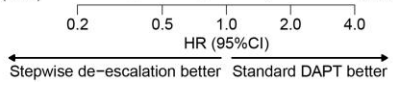
Figure S6. KM curves of the patient-oriented composite endpoint



(PoCE, a composite of all-cause death, stroke, MI, and revascularization)

Figure S7. Subgroup analyses for the primary endpoint in the ITT cohort

Subgroups	N	Stepwise de−escalation	Standard DAPT	HR (95%CI)	*P* value	*P* interaction
Overall	1948	87/975 (9.0)	84/973 (8.7)	1.04 (0.77 to 1.40)	0.80	
Age						0.94
< 75	1829	79/916 (8.7)	76/913 (8.4)	1.04 (0.76 to 1.42)	0.81	
≥ 75	119	8/59 (14.0)	8/60 (13.3)	1.08 (0.41 to 2.89)	0.87	
Sex						0.38
Male	1460	64/727 (8.9)	67/733 (9.2)	0.97 (0.69 to 1.36)	0.84	
Female	488	23/248 (9.4)	17/240 (7.1)	1.33 (0.71 to 2.50)	0.37	
Diabetes						0.33
Yes	595	35/288 (12.2)	42/307 (13.8)	0.89 (0.57 to 1.40)	0.63	
No	1353	52/687 (7.6)	42/666 (6.3)	1.21 (0.81 to 1.82)	0.36	
Renal insufficiency						0.79
Yes	117	9/58 (15.5)	10/59 (16.9)	0.94 (0.38 to 2.30)	0.88	
No	1827	78/915 (8.6)	74/912 (8.2)	1.06 (0.77 to 1.45)	0.74	
Smoker						0.40
Yes	669	24/308 (7.8)	31/361 (8.7)	0.91 (0.53 to 1.55)	0.73	
No	1238	61/646 (9.5)	47/592 (8.0)	1.20 (0.82 to 1.76)	0.34	
Clinical presentation						0.66
STEMI	326	16/159 (10.2)	13/167 (7.8)	1.33 (0.64 to 2.76)	0.45	
NSTEMI	532	26/268 (9.8)	23/264 (8.8)	1.12 (0.64 to 1.97)	0.68	
Unstable Angina	1090	45/548 (8.2)	48/542 (8.9)	0.93 (0.62 to 1.39)	0.71	
High bleeding risk						0.04
Yes	387	20/197 (10.3)	31/190 (16.3)	0.61 (0.35 to 1.08)	0.09	
No	1488	63/739 (8.6)	52/749 (7.0)	1.24 (0.86 to 1.79)	0.25	
PARIS Thrombotic risk score						0.25
Low (0 to 2)	601	23/305 (7.6)	13/296 (4.4)	1.74 (0.88 to 3.44)	0.11	
Intermediate (3 to 4)	828	35/438 (8.1)	35/390 (9.0)	0.89 (0.56 to 1.42)	0.63	
High (≥ 5)	457	25/199 (12.6)	34/258 (13.3)	0.97 (0.58 to 1.62)	0.89	
PARIS bleeding risk score						0.66
Low (0 to 3)	1006	36/500 (7.2)	30/506 (5.9)	1.22 (0.75 to 1.99)	0.41	
Intermediate (4 to 7)	830	43/421 (10.3)	46/409 (11.3)	0.91 (0.60 to 1.38)	0.65	
High (≥ 8)	50	4/21 (19.0)	6/29 (20.7)	0.99 (0.28 to 3.51)	0.99	
Multivessel disease						0.54
Yes	720	44/368 (12.1)	45/352 (12.9)	0.94 (0.62 to 1.43)	0.77	
No	1228	43/607 (7.1)	39/621 (6.3)	1.13 (0.74 to 1.75)	0.57	
Complex PCI						0.34
Yes	384	29/196 (15.0)	22/188 (11.7)	1.30 (0.75 to 2.27)	0.35	
No	1564	58/779 (7.5)	62/785 (7.9)	0.94 (0.66 to 1.35)	0.75	
Complete revascularization						0.55
Yes	1603	64/812 (7.9)	54/791 (6.9)	1.16 (0.81 to 1.67)	0.41	
No	291	23/142 (16.4)	26/149 (17.4)	0.95 (0.54 to 1.67)	0.86	
Proximal located						0.41
Yes	699	36/344 (10.5)	31/355 (8.7)	1.22 (0.75 to 1.97)	0.42	
No	1249	51/631 (8.2)	53/618 (8.6)	0.94 (0.64 to 1.38)	0.76	
Small vessel						0.21
Yes	1089	37/542 (6.9)	44/547 (8.1)	0.85 (0.55 to 1.31)	0.46	
No	859	50/433 (11.6)	40/426 (9.4)	1.24 (0.82 to 1.89)	0.30	
Bifurcation						0.22
Yes	884	51/447 (11.5)	41/437 (9.4)	1.24 (0.82 to 1.87)	0.31	
No	1064	36/528 (6.9)	43/536 (8.1)	0.85 (0.55 to 1.32)	0.47	
Type of lesion						0.59
De novo	1585	63/792 (8.0)	58/793 (7.4)	1.09 (0.77 to 1.56)	0.62	
In-stent restenosis	363	24/183 (13.3)	26/180 (14.4)	0.91 (0.52 to 1.59)	0.74	
Diffused lesion						0.14
Yes	199	20/102 (19.8)	12/97 (12.4)	1.68 (0.82 to 3.43)	0.16	
No	1749	67/873 (7.7)	72/876 (8.3)	0.93 (0.67 to 1.30)	0.69	
IVUS/OCT						0.50
Yes	252	11/128 (8.6)	13/124 (10.5)	0.80 (0.36 to 1.79)	0.59	
No	1696	76/847 (9.0)	71/849 (8.4)	1.08 (0.78 to 1.50)	0.63	
DCB brands						0.85
SeQuent Please (B. Braun)	327	10/170 (6.0)	9/157 (5.7)	1.04 (0.42 to 2.55)	0.94	
Restore (Cardionovum)	513	34/259 (13.2)	28/254 (11.1)	1.20 (0.73 to 1.97)	0.48	
Bingo (Yinyi Biotech)	523	17/266 (6.4)	19/257 (7.4)	0.87 (0.45 to 1.68)	0.68	
Swide (Shenqi Medical)	288	11/135 (8.2)	11/153 (7.2)	1.15 (0.50 to 2.65)	0.74	
Vesselin (Lepu Medical)	242	13/120 (10.9)	17/122 (14.1)	0.76 (0.37 to 1.56)	0.45	



Proximal located is defined as lesion(s) located in LMT, proximal LAD, RCA, or LCX. Small vessel disease for DCB is defined as using the criterion of the BASKET-SMALL 2 trial, which is <3 mm in DCB diameter [47]. The diffuse lesion is defined as the total length of the used device ≥ 60 mm [48]. HBR is defined by the Academic Research Consortium for High Bleeding Risk (ARC-HBR) [19]. Complex PCI is defined as having at least one of the following features: multivessel PCI, ≥3 DCB used, ≥3 lesions treated, bifurcation PCI with ≥2 DCB, and total DCB length >60 mm. Bifurcation is classified when at least 50% lumen narrowing occurs within 3 mm of the bifurcation point, according to the SYNTAX score definition.

Markers represent hazard ratios and lines 95% confidence intervals 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 proportional hazards assumption was assessed using Schoenfeld residuals, and all assumptions were met in the overall population and in all subgroups, except in the high PARIS bleeding score group, which had only 50 patients. The widths of two-sided 95% CIs were not adjusted for multiple comparisons and should not, therefore, be used for inference about treatment effects.

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