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Temporal modulation (early escalation and late de-escalation) of antiplatelet therapy in patients undergoing complex high-risk PCI: rationale and design of the TAILORED-CHIP trial

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ABSTRACT

Despite the use of conventional dual antiplatelet therapy (DAPT) after percutaneous coronary intervention (PCI), the risk of adverse events remains high among patients with increased thrombotic risk. Until recently, the optimal antiplatelet strategy to balance the ischaemic and bleeding risks in patients who are undergoing complex high-risk PCI has been unclear. The TAILored Versus COnventional AntithRombotic StratEgy IntenDed for Complex HIgh-Risk PCI (TAILORED-CHIP) trial is an investigator-initiated, multicentre, prospective randomised trial to evaluate the efficacy and safety of a time-dependent tailored antiplatelet therapy with an early (<6 months post-PCI) escalation (low-dose ticagrelor at 60 mg twice daily plus aspirin) and a late (>6 months post-PCI) de-escalation (clopidogrel monotherapy) in patients undergoing complex high-risk PCI as compared with standard DAPT (clopidogrel plus aspirin for 12 months). Eligible patients had to have at least one high-risk anatomical or procedural feature or clinical characteristic associated with an increased risk of ischaemic or thrombotic events. The primary endpoint was the net clinical outcome, a composite of death from any cause, myocardial infarction, stroke, stent thrombosis, urgent revascularisation, or clinically relevant bleeding (Bleeding Academic Research Consortium type 2, 3, or 5) at 12 months after randomisation. (ClinicalTrials.gov: NCT03465644)

KEYWORDS: adjunctive pharmacotherapy; bleeding; clinical trials; drug-eluting stent; stent thrombosis

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The current guidelines recommend dual antiplatelet therapy (DAPT) including aspirin and a platelet receptor $P2Y_{12}$ inhibitor as the standard of care for the prevention of atherothrombotic events in patients who have undergone percutaneous coronary intervention (PCI)[1,2]. In these guidelines, according to the clinical presentation and concomitant bleeding risk, different potencies and durations of DAPT are recommended.

In routine clinical practice, there are common clinical circumstances in which physicians are particularly concerned about the risk of thrombotic events, bleeding events, or both; therefore, the recommended potency or duration of DAPT after PCI or acute coronary syndromes (ACS) is still a moving target that is going beyond the traditional approach. In particular, complex high-risk PCI (complex high-risk and indicated PCI [CHIP] procedure) is rapidly increasing in contemporary PCI practice. Even with DAPT, the risk of adverse events remains unacceptably high among patients with increased thrombotic risk due to various anatomical features (e.g., complex and CHIP procedures involving the left main, multivessel PCI, complex bifurcation, diffuse long lesions, chronic total occlusion, and severely calcified lesions) and clinical factors (e.g., diabetes mellitus, chronic renal insufficiency, or depressed ventricular function)[3-6]. However, the optimal antiplatelet strategy for such high-risk patients undergoing complex PCI is still undetermined.

It is well known that the risk of thrombotic or bleeding events after an ACS or PCI may substantially differ over time[7,8]; in general, thrombotic risk is higher in the early phase, but bleeding risk is higher in the late phase **(Figure 1)**. In this context, temporal-dependent antiplatelet modulation (i.e., early escalation and late de-escalation) in high-risk patients who are undergoing a CHIP-PCI procedure could facilitate an ischaemic benefit in the early period and lower the risk of bleeding in the late period while preserving the ischaemic benefit. Therefore, the TAILored Versus COnventional AntithRombotic StratEgy IntenDed for Complex HIgh-Risk PCI (TAILORED-CHIP) trial will assess the potential benefit of temporal modulation (early escalation and late de-escalation) of antiplatelet therapy in patients undergoing complex high-risk PCI.

Methods

TRIAL DESIGN

The TAILORED-CHIP trial (ClinicalTrials.gov: NCT03465644) is an investigator-initiated, multicentre, open-labelled, randomised superiority trial. The primary objective of this trial is to evaluate the efficacy and safety of a tailored antiplatelet therapy with an early (<6 months post-PCI) escalation (low-dose ticagrelor [60 mg twice daily] plus aspirin [100 mg once daily]) and late (>6 months post-PCI) de-escalation (clopidogrel [75 mg once daily] monotherapy) strategy compared with standard DAPT (clopidogrel [75 mg once daily] plus aspirin [100 mg once daily] for 12 months) in patients undergoing complex high-risk PCI **(Figure 2)**. Detailed information on ethics approval is provided in **Supplementary Appendix 1**.

STUDY POPULATION

For enrolment in the TAILORED-CHIP trial, eligible patients had to have at least 1 high-risk anatomical or procedural feature or clinical characteristic associated with an increased risk of ischaemic or thrombotic events[3,5,6,9,10]. Anatomical or procedural criteria for high-risk CHIP-PCI included an unprotected left main PCI, a complex bifurcation PCI requiring a 2-stent technique, a chronic total occlusion, a severely calcified lesion, a diffuse long lesion (lesion length ≥30 mm), a multivessel PCI (≥2 major epicardial vessels being stented), or a complex PCI requiring ≥3 planned stents, ≥3 lesions treated, or a total stent length >60 mm. The clinical criteria for a high thrombotic risk were medically treated diabetes mellitus, chronic renal dysfunction (creatinine clearance <60 ml/min), or severe left ventricular dysfunction (ejection fraction <40%). Detailed lists of the inclusion and exclusion criteria are presented in **Table 1**.

RANDOMISATION, TRIAL REGIMEN AND RATIONALE

Eligible patients were randomly assigned in a 1:1 ratio to receive either a tailored antiplatelet therapy (early 6-month escalation therapy with low-dose ticagrelor plus aspirin and then late 6-month de-escalation therapy with clopidogrel monotherapy) or standard 12-month DAPT (clopidogrel plus aspirin). Randomisation was performed after diagnostic coronary angiography and before the time of the index PCI procedure. Randomisation was conducted with an Interactive Web Response System (IWRS) with the use of randomly permuted block sizes of 4 or 6, with stratification according to the presence or absence of diabetes and the participating centre.

In the tailored antiplatelet group, the choice of low-dose (60 mg twice daily) ticagrelor as the early escalation regimen was based on supportive pharmacodynamic data from the Comparison of Low-Dose, Standard-Dose Ticagrelor and Clopidogrel for Inhibition of Platelet Reactivity in Patients With Acute Coronary Syndromes (OPTIMA) trial[11] and clinical data from the Prevention of Cardiovascular Events in Patients With Prior Heart Attack Using Ticagrelor Compared to Placebo on a Background of Aspirin–Thrombolysis in Myocardial Infarction 54 (PEGASUS-TIMI 54) trial[12]. In OPTIMA, low-dose (60 mg twice daily) ticagrelor demonstrated better efficacy of platelet inhibition than clopidogrel, but its efficacy was similar to that of standard-dose ticagrelor in patients with ACS and PCI[11]. In the substudy of PEGASUS-TIMI 54, ticagrelor at 60 mg twice daily achieved high peak and trough platelet inhibitor levels, similar to ticagrelor dosed at 90 mg twice daily[13]. PEGASUS-TIMI 54 demonstrated that low-dose (60 mg twice daily)

Abbreviations

ACS	acute coronary syndrome	**CHIP**	complex high-risk and indicated PCI	**DES**	drug-eluting stent
BARC	Bleeding Academic Research Consortium	**DAPT**	dual antiplatelet therapy		

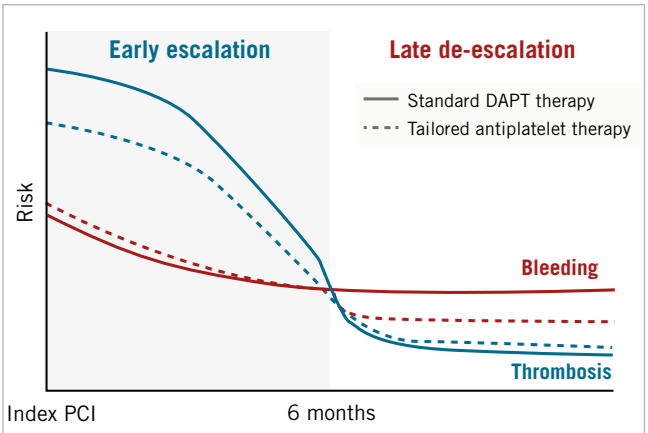

Figure 1. *Risks of ischaemic and bleeding events after complex high-risk PCI. In the early period after a complex high-risk PCI, the benefits of intensive antiplatelet therapy generally outweigh the increased risk of bleeding. However, this benefit dissipates with additional time after such complex PCI procedures, favouring a therapeutic approach that considers the risks of both bleeding and ischaemic events. DAPT: dual antiplatelet therapy; PCI: percutaneous coronary intervention*

ticagrelor showed a similar magnitude of efficacy but a better safety profile (a lower rate of bleeding and dyspnoea) than standard-dose (90 mg twice daily) ticagrelor in patients who had a prior myocardial infarction (MI)[12]; based on this trial, a ticagrelor dose of 60 mg twice daily is now approved for long-term use in patients with a history of MI.

A late DAPT de-escalation approach (switching to clopidogrel monotherapy) may be attractive for reducing late bleeding risk while preserving the ischaemic benefit after PCI with contemporary safer drug-eluting stent (DES) platforms[14,15]. Reducing the duration of aspirin therapy may allow for more prolonged use of potent $P2Y_{12}$ inhibitors while avoiding aspirin-related bleeding risk, particularly with respect to gastrointestinal toxicity[16]. At the time of switching from ticagrelor to clopidogrel at 6 months, because ticagrelor has a relatively fast offset of action and to avoid any significant gap in platelet inhibition, the use of a 600 mg loading dose of clopidogrel should be considered when de-escalating from ticagrelor; at 24 hours from the last dose of ticagrelor, a 600 mg loading dose of clopidogrel should be given to all patients in the tailored-strategy arm[17].

In the conventional DAPT group, enrolled patients were prescribed clopidogrel (75 mg once daily) and aspirin (100 mg once daily) for 12 months after the index PCI. In both groups, adherence was assessed with manual pill counts,

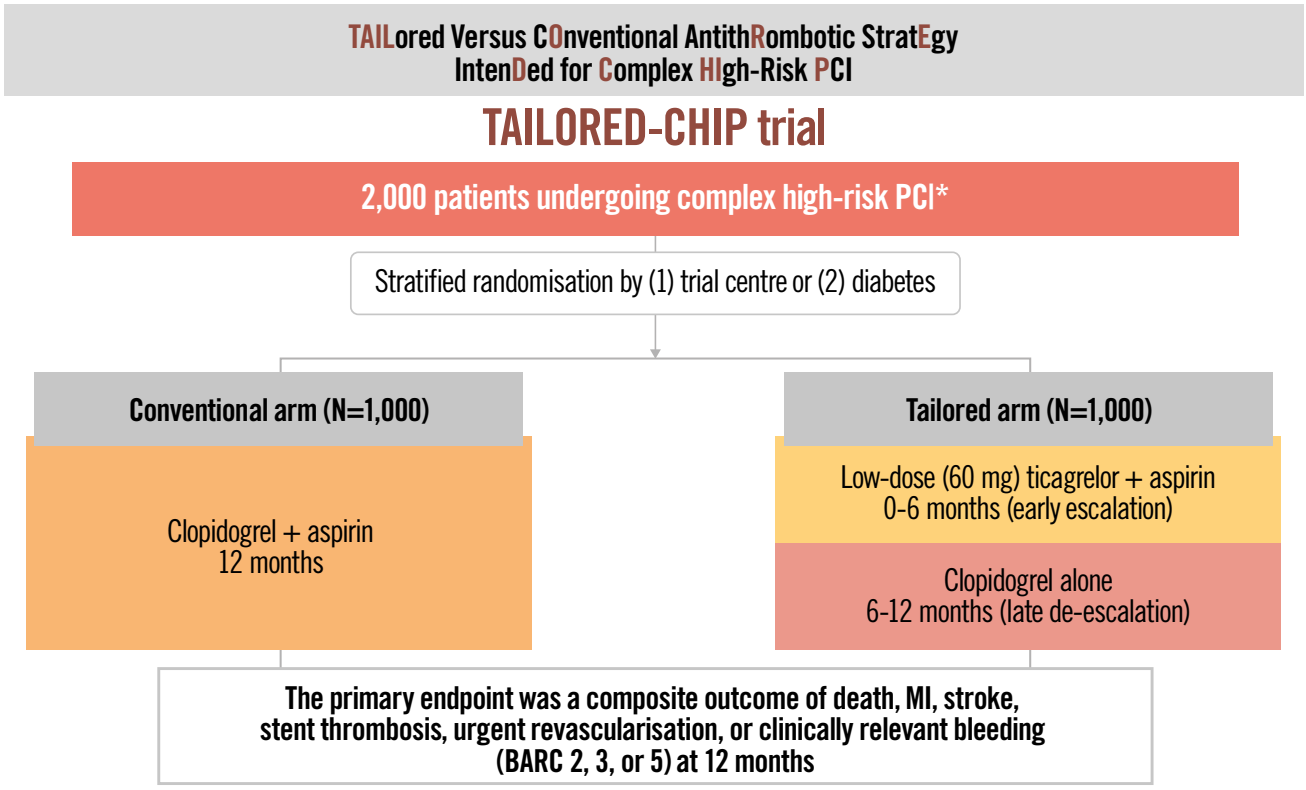

Figure 2. *Study flow diagram of the TAILORED-CHIP trial. *Complex high-risk PCI: left main PCI, chronic total occlusion, bifurcation with 2 stents implanted, severe calcification, diffuse long lesion (lesion length ≥30 mm), multivessel PCI (≥2 vessels stented), ≥3 stents implanted, ≥3 lesions treated, total stent length >60 mm, diabetes, CKD (creatinine clearance <60 mL/min) or severe LV dysfunction (EF <40%). BARC: Bleeding Academic Research Consortium; CKD: chronic kidney disease; EF: ejection fraction; LV: left ventricular; MI: myocardial infarction; PCI: percutaneous coronary intervention*

Table 1. Inclusion and exclusion criteria.

Inclusion criteria: the subject had to meet all of the following criteria to be eligible for treatment in the study:	
1.	The subject was >19 years of age
2.	The subject was scheduled for PCI with a contemporary DES
3.	Patients must have at least one of any features of complex high-risk anatomical, procedural, or clinical-related factors
	3-1 Lesion- or procedure-related factors: left main PCI, chronic total occlusion, bifurcation lesion requiring 2-stent technique, severe calcification, diffuse long lesion (lesion length ≥30 mm), multivessel PCI (≥2 vessels requiring stent implantation), complex PCI requiring implantation of ≥3 stents, ≥3 lesions to be treated, or predicted total stent length for revascularisation >60 mm
	3-2 Clinical factors: medically treated diabetes, chronic kidney disease (defined as a creatinine clearance <60 mL/min), or severe LV dysfunction (LVEF <40%)
4.	The patient or guardian agreed to the study protocol and the schedule of clinical follow-up and provided informed, written consent, as approved by the appropriate institutional review board/ethics committee of the respective clinical site
Exclusion criteria: subjects were excluded from the study if any of the following criteria were met:	
1.	Enzyme-positive acute myocardial infarction (NSTEMI or STEMI)
2.	Contraindications to aspirin or $P2Y_{12}$ inhibitors (ticagrelor or clopidogrel)
3	Use of glycoprotein IIb/IIIa inhibitors at the time of randomisation
4.	Cardiogenic shock
5.	Treatment with only BMS or balloon angioplasty during the index procedure
6.	Requirement for chronic oral anticoagulation (warfarin or NOACs)
7.	Active bleeding or extremely high risk for major bleeding (e.g., active peptic ulcer disease, gastrointestinal pathology with a high risk for bleeding, malignancies with a high risk for bleeding)
8.	History of intracranial haemorrhage or an intracranial aneurysm
9.	Planned surgery within 180 days
10.	Severe liver disease (ascites and/or coagulopathy) or dialysis-dependent renal failure at screening
11.	Platelet count <80,000 cells/mm^3 or haemoglobin level <10 g/dL
12.	At risk of bradycardia (subjects with sinus node dysfunction or atrioventricular block >2^{nd} degree but without a permanent pacemaker)
13.	Use of a strong cytochrome P450 3A inhibitor or inducer within 2 weeks of the date of enrolment: ketoconazole, clarithromycin, nefazodone, ritonavir, atazanavir, rifampin/rifampicin, rifabutin, dexamethasone, phenytoin, carbamazepine, phenobarbital
14.	Pregnant and/or lactating women
15.	Concurrent medical condition with a life expectancy of less than 1 year
16.	Active participation in another investigational study of a drug or device that has not completed the primary endpoint or follow-up period
17.	Inability to provide written informed consent or to participate in long-term follow-up

BMS: bare metal stent; DES: drug-eluting stent; LV: left ventricular; LVEF: left ventricular ejection fraction; NOAC: non-vitamin K antagonist oral anticoagulant; NSTEMI: non-ST-segment elevation myocardial infarction; PCI: percutaneous coronary intervention; STEMI: ST-segment elevation myocardial infarction

and non-adherence was classified according to the underlying reason[18]. After 12 months of protocol-mandated therapy, patients were switched to a standard-of-care antiplatelet regimen at the discretion of their treating physician.

PCI PROCEDURE AND POST-PCI SUBSEQUENT CARE

The PCI procedure was performed using standard techniques. Detailed information on PCI procedures and post-PCI subsequent care are described in **Supplementary Appendix 2**.

TRIAL ENDPOINTS AND FOLLOW-UP

The primary endpoint of this trial is a net clinical outcome, which is a composite of death from any cause, MI, stroke, stent thrombosis, urgent revascularisation, or clinically relevant bleeding (Bleeding Academic Research Consortium [BARC] type 2, 3, or 5) at 12 months after randomisation. The key secondary endpoints include individual components of the primary composite endpoint, a composite of ischaemic clinical endpoints (all-cause death, MI, stroke, stent thrombosis, or unplanned revascularisation), a composite of hard clinical endpoints (all-cause death, MI, or stroke), and safety outcomes (major bleeding, clinically relevant non-major bleeding, fatal bleeding, or any major or minor bleeding). Detailed lists and definitions of all the primary and secondary clinical endpoints are summarised in **Table 2** and **Supplementary Table 1**. All trial endpoints are adjudicated by a clinical events committee (CEC) whose members are unaware of the trial-group assignments (detailed information is described in **Supplementary Appendix 3**).

After randomisation, trial follow-up assessments are routinely conducted at baseline, 1 month, 3 months, 6 months, and 12 months, with additional evaluations for routine clinical care scheduled as required.

SAMPLE SIZE CALCULATION

We hypothesised that a tailored antiplatelet strategy would be superior to a conventional DAPT strategy with respect to the primary endpoint of net clinical benefit. On the basis of the reported rates of ischaemic and bleeding events in complex high-risk PCI and DAPT-related trials (EXCEL,

Table 2. Primary and secondary endpoints.

Primary endpoints*
Net clinical outcomes – composite of all-cause death, myocardial infarction, stroke, stent thrombosis, urgent revascularisation, or clinically relevant bleeding (BARC 2, 3, or 5) at 12 months after randomisation
Secondary outcomes*
Individual components of the primary composite endpoint
Efficacy outcomes
Death (any, cardiovascular, or non-cardiovascular causes)
Myocardial infarction (any, periprocedural, or spontaneous)
Stroke (any, ischaemic, or haemorrhagic)
Stent thrombosis
Repeat revascularisation (any, target vessel, or non-target vessel)
Composite of ischaemic clinical endpoints (all-cause death, myocardial infarction, stroke, stent thrombosis, or urgent revascularisation)
Composite of hard clinical endpoints (all-cause death, myocardial infarction, or stroke)
Safety outcomes†
BARC major bleeding (type 3 or 5 bleeding)
TIMI major or minor bleeding
GUSTO moderate or severe bleeding
ISTH major bleeding
Any major or minor bleeding

*Detailed definitions of the primary and secondary clinical endpoints are available in **Supplementary Table 1**. †Although bleeding events were assessed primarily using BARC criteria, bleeding events were also adjudicated according to different criteria including TIMI, GUSTO, or ISTH. BARC: Bleeding Academic Research Consortium; GUSTO: Global Utilization of Streptokinase and Tissue Plasminogen Activator for Occluded Coronary Arteries; ISTH: International Society of Thrombosis and Haemostasis; TIMI: Thrombolysis in Myocardial Infarction

DAPT, and a pooled meta-analysis of randomised controlled trials [RCTs])[6,9,19], we assumed a 1-year event rate of the primary composite endpoint of 14% in the conventional DAPT group. We estimated that enrolment of 2,000 patients would provide the study with 80% power to detect a relative reduction of 30% in the primary composite endpoint in the tailored antiplatelet group compared with those in the conventional DAPT group, assuming an attrition rate of 5% (e.g., follow-up loss or non-compliance) at an alpha significance level of 0.05.

STATISTICAL ANALYSIS PLAN

Details regarding the statistical methods are provided in **Supplementary Appendix 4**. All endpoint analyses will be performed according to the intention-to-treat principle of all randomised patients at the time of the first event. Cumulative event curves will be generated using the Kaplan-Meier method and compared with the log-rank test. Statistical comparisons (a test of superiority) of the two randomised groups will be based on a time-to-first-event analysis using the Cox proportional hazards model. Relative risks will be expressed as hazard ratios with associated 95% confidence intervals and will be derived from the Cox model. Absolute differences and 95% confidence intervals for primary and key secondary endpoints at 1 year will be calculated with Kaplan-Meier estimates and Greenwood standard errors[20]. To evaluate the consistency of results among clinically relevant subgroups, prespecified subgroup analyses will be performed. Several prespecified sensitivity analyses of the primary outcome will be conducted, including other methods to analyse recurrent events[21].

Landmark analyses will be performed according to prespecified landmark points at 6 months post-PCI, at which time the tailored antiplatelet strategy will be changed in the experimental arm (from low-dose ticagrelor plus aspirin to clopidogrel alone); the relative risks will be calculated separately for events up to the landmark point from randomisation and for events occurring after the landmark point up to 12 months. We will also estimate the difference in the restricted mean event-free time analyses over 12 months. The restricted mean event-free survival time is the mean time that a patient is free from an outcome event, adjusted for loss to follow-up, and reflects the area under the survival curve[22].

TRIAL ORGANISATION

Details regarding the organisation of the trial are provided in **Supplementary Appendix 5**. An independent data safety monitoring board is responsible for monitoring safety during the trial and thus will periodically review the safety data according to a dedicated charter and make recommendations based on safety analyses, protocol deviation, and clinical follow-up reports.

Recruitment status

Between February 2019 and January 2024, 2,018 patients from 24 participating sites in South Korea were enrolled and randomised in the TAILORED-CHIP trial. Follow-up of the last enrolled patient will be completed in January 2025, and the primary results of the TAILORED-CHIP trial are expected to be available by mid or late 2025.

Discussion

To our knowledge, TAILORED-CHIP is the first large-scale RCT to investigate the potential role of temporal antiplatelet modulation with early escalation and late de-escalation in high-risk patients undergoing CHIP procedures. The TAILORED-CHIP trial mainly targets temporal (i.e., time-dependent) modulation of escalation and de-escalation strategies after complex high-risk PCI. We assumed that efficacy and safety outcomes might be optimised according to the strategy used, with an early (<6 months post-PCI) escalation approach being more effective in reducing ischaemic events without a relevant increase in bleeding than standard DAPT therapy and a late (>6 months post-PCI) de-escalation approach being more effective in reducing bleeding risk without any trade-off in efficacy.

Although there is a paucity of data supporting potent $P2Y_{12}$ agents such as ticagrelor and prasugrel in a broad population inclusive of both patients with ACS and chronic coronary syndromes, their use is increasing across the diverse clinical spectrum of patients undergoing PCI[23]. Given increasing clinician familiarity with these $P2Y_{12}$ agents, administrative data indicate that ticagrelor and prasugrel are prescribed off-label in 1 in 3 patients with non-ACS indications[24]. Until recently, relatively few studies have been conducted on the escalation antiplatelet strategy using ticagrelor in contemporary PCI settings. In the Effect of Ticagrelor on Health Outcomes in Diabetes Mellitus Patients Intervention Study (THEMIS), ticagrelor added to aspirin reduced cardiovascular death, MI, and stroke, although with increased major bleeding in diabetic patients with stable coronary artery disease and a history of previous PCI; overall, ticagrelor provided a favourable net clinical benefit[25]. In the Ticagrelor With Aspirin or Alone in High-Risk Patients After Coronary Intervention (TWILIGHT) trial[18], 35.2% of enrolled patients underwent PCI for non-ACS (silent ischaemia or stable angina). In the Assessment of Loading With the $P2Y_{12}$ Inhibitor Ticagrelor or Clopidogrel to Halt Ischemic Events in Patients Undergoing Elective Coronary Stenting (ALPHEUS) trial, ticagrelor was not superior to clopidogrel in reducing periprocedural myocardial necrosis within 48 hours after elective PCI and did not cause an increase in major bleeding[26,27].

Time-dependent antiplatelet regimens (i.e., early escalation, late de-escalation) may be reasonable in this complex, high-risk patient population to achieve a balance between timely and sufficient platelet inhibition and an acceptable bleeding risk. Until recently, several therapeutic strategies to decouple thrombotic and haemorrhagic risks have been tested[15,28]. In particular, $P2Y_{12}$ inhibitor monotherapy was found to preserve ischaemic protection while limiting bleeding risk compared with DAPT after complex PCI[14]. Our rationale for late de-escalation of clopidogrel monotherapy is supported by recent relevant RCTs[29,30]. The TicAgrelor Versus CLOpidogrel in Stabilized Patients With Acute Myocardial Infarction (TALOS-AMI) trial supports the uniform unguided de-escalation antiplatelet strategy of switching from ticagrelor to clopidogrel, which was superior to the ticagrelor-based DAPT strategy in stabilised patients with acute MI[29]. In addition, the Harmonizing Optimal Strategy for Treatment of Coronary Artery Stenosis-EXtended Antiplatelet Monotherapy (HOST-EXAM) trial supported the idea that clopidogrel monotherapy was superior to aspirin monotherapy in preventing future adverse clinical events, including both the thrombotic composite endpoint and any bleeding in patients who underwent PCI, and successfully maintained the intended duration of DAPT[30].

Limitations

This trial may have some limitations. First, the open-label design has a potential for bias in outcome reporting and ascertainment. However, all endpoints have a standardised definition and were specifically adjudicated by an independent CEC. Second, the trial sample size was calculated by estimating the occurrence of a net adverse clinical benefit; thus, the efficacy and safety of antiplatelet therapy is a bivariate outcome, and summarising it in a unidimensional variable could be misleading. Third, the trial is underpowered to provide reliable information on hard ischaemic endpoints, such as death, MI, or stent thrombosis. Fourth, the study population is exclusively East Asian patients. Finally, we did not routinely perform platelet function testing or genotyping during the study. Thus, whether a similar strategy would have resulted in a different outcome in a population of patients with poor responses to clopidogrel with high platelet reactivity is unknown.

Conclusions

The TAILORED-CHIP trial has the unique feature of testing early escalation using a potent $P2Y_{12}$ inhibitor of low-dose ticagrelor and late de-escalation with less potent $P2Y_{12}$ monotherapy of clopidogrel after complex high-risk PCI. The impending results of this trial will provide novel and clinically meaningful insights on the potential role of temporal modulation of antiplatelet therapy in high-risk patients who are undergoing CHIP procedures.

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Conflict of interest statement

D.-Y. Kang reports speaker fees from Abbott, Daiichi Sankyo, Viatris, Boryung, and Daewoong Pharmaceutical. S.-J. Park reports research grants and speaker fees from Abbott, Medtronic, Daiichi Sankyo, Chong Kun Dang Pharmaceutical, Daewoong Pharmaceutical, and Edwards Lifesciences. D.-W. Park reports research grants and speaker fees from Chong Kun Dang Pharmaceutical, Abbott, Medtronic, Daiichi Sankyo, Edwards Lifesciences, and Daewoong Pharmaceutical. The other authors have no conflicts of interest to declare.

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Supplementary data

Supplementary Appendix 1. Ethics and dissemination.
Supplementary Appendix 2. PCI procedure and post-PCI subsequent care.
Supplementary Appendix 3. Trial event assessment.
Supplementary Appendix 4. Detailed information on statistical analysis.
Supplementary Appendix 5. Trial organisation.
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The supplementary data are published online at: https://eurointervention.pcronline.com/doi/10.4244/EIJ-D-24-00437

Supplementary data

Supplementary Appendix 1. Ethics and dissemination.

The trial is being conducted in accordance with the Declaration of Helsinki, International Conference on Harmonization, Good Clinical Practice guidelines, and applicable regulatory requirements. This trial has also been approved by National Institute of Food and Drug Safety Evaluation of Republic of Korea (approval number: 31679). The final study protocol and patient informed consent have been reviewed and approved by the appropriate ethics committees, institutional reviewer boards of all participating sites, and corresponding national health authorities. The objective and potential benefits as well as the risks will be fully explained to the participants and their guardians. All enrolled patients have provided written informed consent to confirm voluntary participation. The study results will be disseminated to the participants and the public, including at scientific meetings and publishing our research in peer-reviewed journals.

Supplementary Appendix 2. PCI procedure and post-PCI subsequent care.

During the PCI procedure, unfractionated heparin was administered as appropriate to maintain an activated clotting time greater than 250 to 300 s. If the patients had not been taking $P2Y_{12}$ inhibitors for at least 5 days before randomisation, they were prescribed a loading dose of randomised P2Y12 inhibitors (the tailored arm received a loading dose of ticagrelor 120 mg, and the conventional arm received a 300–600-mg loading dose of clopidogrel at the discretion of the physician before PCI). The choice of specific types of contemporary DESs was left to the operator or institution's preference. Intravascular imaging (e.g., intravascular ultrasonography or optical coherence tomography)-guided or physiology (e.g.., fractional flow reserve or instantaneous flow ratio)-guided PCI was performed at the treating interventional cardiologist's discretion. During follow-up post-PCI, guideline-directed medical therapy and management of risk factors for intensive secondary prevention according to contemporary clinical guidelines were highly recommended. The importance of cardiovascular risk-factor modification was emphasised throughout the study to the patients and their primary physicians.

Supplementary Appendix 3. Trial event assessment.

The investigators in each participating centre have completed a dedicated electronic case report form (e-CRF) for all clinical events and provided sufficient source documentation for central review. All clinical events are adjudicated by an independent Clinical Event Committee (CEC), the members of which are unaware of the treatment group assignments. Detailed information on definitions of each clinical event is described in Supplementary Table 1. All serious events, primary endpoints, and secondary endpoints are monitored on-site. Source documents have been submitted for any clinical ischemic or bleeding event to allow the independent CEC to evaluate the study endpoints. Cross-validation of survival status will be performed with the use of the Korean National Health Insurance database.

The CEC has been charged with developing specific criteria used to categorise clinical events and clinical endpoints in the study. At the onset of the study, the CEC has established explicit rules outlining the minimum amount of data needed and the algorithm to classify a clinical event.

Supplementary Appendix 4. Detailed information on statistical analysis.

All endpoint analyses will be performed according to the intention-to-treat principle of all randomised patients as the time to the first event. Sensitivity analyses will be performed in the as-treated population (patients analyzed by the treatment they actually received) and in the per-protocol population (patients analyzed according to their assigned treatment group only if they actually received their assigned treatment). Differences between treatment groups will be assessed using Student's t-test for continuous variables and the $\chi 2$ test or Fisher's exact test for categorical variables, as appropriate. Cumulative event curves will be generated using the Kaplan–Meier method and compared with the log-rank test. Data from patients who have not experienced a primary end-point event between randomisation and 12 months will be censored at the time of death, the time of last known contact, or 365 days, whichever occurs first. Statistical comparisons (a test of superiority) of the two randomised groups will be based on a time-to-first-event analysis using the Cox proportional hazards model. Relative risks will be expressed as hazard ratios with associated 95% confidence intervals and will be derived from the Cox model. Absolute differences and 95% confidence intervals for primary and key secondary endpoints at 1 year will be calculated with Kaplan–Meier estimates and

Greenwood standard errors. To evaluate the consistency of results among clinically relevant subgroups, prespecified subgroup analyses will be performed (e.g., age, sex, body-mass index level, indication for PCI, and per each-category of anatomical or clinical risk factors). The confidence intervals have not been adjusted for multiple comparisons among several subgroups; thus, inferences drawn from these intervals may not be reproducible. Several prespecified sensitivity analyses of the primary outcome will be conducted, including other methods to analyze recurrent events.

Landmark analyses will be performed according to pre-specified landmark points at 6 months post-PCI, in which the tailored antithrombotic strategy will be changed in the experimental arm (from low-dose ticagrelor plus aspirin to clopidogrel alone); the relative risks will be calculated separately for events up to the landmark point from randomisation and for events occurring after the landmark point up to 12 months. For each type of event, patients will be censored at the time of the first event: for instance, a patient who experiences an event contributing to the primary composite endpoint during the first 6 months will be censored at the time of the event and excluded from the analysis of the subsequent 6 months after the landmark point. Landmark analyses will be accompanied by a test for interaction between the treatment effect and time (before versus after the landmark point). If the proportional-hazards assumption underlying the Cox model is not met for the primary outcome ($P<0.001$ for time-by-treatment interaction) and several secondary outcomes, the statistical analysis plan specifies that the presentation of the results emphasise nonparametric cumulative event-rate estimates. Differences in these estimates for the tailored group compared with the conventional DAPT group at 6 months and at 12 months will be tabulated and presented with 95% confidence intervals. We will also estimate the difference in the restricted mean event-free time analyses over 12 months. The restricted mean event-free survival time is the mean time free from an outcome event adjusted for loss to follow-up and reflects the area under the survival curve; this quantity is derived from the nonparametric cumulative event-rate curves and is interpreted as the average number of event-free days per patient over the period between randomisation and 12 months.

Trial data will be held by the trial coordination centre at Asan Medical Center. Analyses will be performed by independent statistical analysts who are unaware of the randomised drug. All P-values are 2-sided, and values <0.05 will be considered statistically significant. All the analyses will be conducted using SAS software (SAS Institute) or R

software (R Foundation for Statistical Computing).

Supplementary Appendix 5. Trial organisation.

The executive committee has approved the final trial design, protocol, and clinical sites. This committee are also being responsible for reviewing the final results, determining the presentation and publication methods, and selecting secondary projects and publications. An independent data safety monitoring board (DSMB) is responsible for monitoring safety during the trial and thus periodically review the safety data according to a dedicated charter and make recommendations based on safety analyses, protocol deviation, and clinical follow-up reports. The DSMB members did not have a primary affiliation with the study sponsor or the principal investigator of the trial.

Under the guidance of the authors, the Cardiovascular Clinical Research Center (Asan Institute for Education & Research, Asan Medical Center, and CVRF) has assisted in the selection of the participating centres, supervision or monitoring of the centres, collection and storage of trial data, data analysis, interpretation of the trial results, and preparation of the manuscript. The trial was designed and led by executive steering committee members.

Supplementary Table 1. Definition of clinical endpoints.

Endpoint	Definition
Death	All-cause mortality was used rather than cardiac mortality to eliminate the need for possibly difficult adjudication of causes of death, especially given the relatively low mortality expected. In addition, the cause of death will be adjudicated as being due to cardiovascular causes, non-cardiovascular causes, or undetermined causes. • Cardiovascular death includes sudden cardiac death, death due to acute MI, heart failure or cardiogenic shock, stroke, other cardiovascular causes, or bleeding. • Non-cardiovascular death is defined as any death with known cause not of cardiac or vascular causes. • Undetermined cause of death refers to a death not attributable to one of the above categories of cardiovascular death or to a noncardiovascular cause. For this trial all deaths of undetermined cause will be included in the cardiovascular category.
MI	The protocol definition of myocardial infarction (MI) is based on the criteria of the Society for Cardiovascular Angiography and Interventions (SCAI). 1) Within 48 hours after index procedure (i.e., periprocedural MI); - creatine kinase-myocardial band (CK-MB) above 10x99th percentile upper reference limit (URL) determined on a single measurement, or CK-MB above 5x99th percentile URL determined on a single measurement PLUS at least one of the following: • New pathologic Q wave in at least 2 contiguous leads or new persistent non-rate related left bundle branch block (LBBB), • Angiographically documented coronary artery occlusion or new severe stenosis with thrombosis and/or diminished epicardial flow,

	• Imaging evidence of new loss of viable myocardium or new regional wall motion abnormality *In the absence of CK-MB, cardiac troponin (I or T) rises to >70x URL, >35x URL plus ECG, angiographic, or imaging evidence of ischemia. <u>2) More than 48 hours after index procedure (i.e., spontaneous MI);</u> Detection of rise and/or fall of cardiac biomarkers (CK-MB or troponin) with at least one value above the 99th percentile URL together with evidence of myocardial ischemia with at least with at least one of the following: • Symptoms of ischemia • ECG changes indicative of new ischemia (new ST-T changes or new LBBB) • Angiographic, or imaging evidence of ischemia * For comparison of our trial findings with other important trials, MI events will be also evaluated by use of the 4th universal definition of MI. MI events will be classified based on the Universal MI classification system as follows: • Type 1: Spontaneous MI • Type 2: Secondary MI • Type 3: Sudden Death MI • Type 4a: MI related to PCI • Type 4b: MI related to stent thrombosis • Type 4c: MI related to stent restenosis • Type 5: MI related to CABG • Silent MI <u>Spontaneous MI (Types 1, 2, 4b, 4c)</u> Preferentially uses a cardiac troponin (cTn) threshold value reported as MI Decision Limit or the Upper Limit of Normal (ULN). Marker

	elevation is defined as troponin > ULN/MI decision limit. If troponin is not done or not available, then CK-MB > ULN will qualify. Diagnosis of spontaneous MI will be satisfied by a clinical setting consistent with acute myocardial ischemia and any one or more of the following criteria: • Symptoms of myocardial ischemia (usually lasting > 20 minutes in duration); • New ischemic ECG changes (New ischemic ST and/or T wave changes and/or new LBBB); • 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; • Identification of a coronary thrombus by angiography or autopsy (not for type 2 or 3 MIs). - Post-mortem demonstration of acute atherothrombosis in the artery supplying the infarcted myocardium meets criteria for type 1 MI. - Evidence of an imbalance between myocardial oxygen supply and demand unrelated to acute atherothrombosis meets criteria for type 2 MI. - Type 4b MI stent thrombosis and type 4c MI restenosis that both meet type 1 MI criteria; angiographic evidence of intracoronary thrombus, stent thrombosis (4b) or high-grade in-stent restenosis (≥50%) (4c) <u>Sudden death MI (Type 3)</u> - Cardiac death in patients with symptoms suggestive of myocardial ischemia and presumed new ischemic ECG changes before cTn values become available or abnormal meets criteria for type 3 MI. - MI events in which a presentation consistent with infarction is

	present but the patient dies before the biomarkers are drawn or within the first few hours of the event before the biomarkers become positive. Sudden unexpected cardiac death, including cardiac arrest, often with symptoms suggestive of myocardial ischemia, accompanied by presumably new ST-segment elevation, or new LBBB, or evidence of fresh thrombus in a coronary artery by angiography and/or at autopsy, but death occurring before blood samples could be obtained, or at a time before the appearance of cardiac biomarkers in the blood. <u>Procedure-related MI (types 4 and 5 MI)</u> Percutaneous coronary intervention (PCI) related MI is termed type 4a MI. Coronary artery bypass grafting (CABG) related MI is termed type 5 MI. Coronary procedure-related MI ≤48 hours after the index procedure is arbitrarily defined by an elevation of cTn values > 5 times for type 4a MI and > 10 times for type 5 MI of the 99th percentile URL in patients with normal baseline values. Patients with elevated pre-procedural cTn values, in whom the pre-procedural cTn level are stable (≤20% variation) or falling, must meet the criteria for a > 5 or > 10-fold increase and manifest a change from the baseline value of > 20%. In addition, with at least one of the following: • New ischemic ECG changes (this criterion is related to type 4a MI only); • Development of new pathological Q waves; • Imaging evidence of loss of viable myocardium that is presumed to be new and, in a pattern, consistent with an ischemic etiology; • Angiographic findings consistent with a procedural flow-limiting complication such as coronary dissection, occlusion of a major epicardial artery or graft, side-branch occlusion-thrombus, disruption of collateral flow or distal embolization. - Isolated development of new pathological Q waves meet the

	type 4a MI or type 5 MI criteria with either revascularization procedure if cTn values are elevated and rising but less than the pre-specified thresholds for PCI and CABG. - Post-mortem demonstration of a procedure-related thrombus meets the type 4a MI criteria or type 4b MI criteria if associated with a stent.
Stroke	Stroke is defined as the rapid onset of a new neurologic deficit attributed to an obstruction in cerebral blood flow and/or cerebral hemorrhage with no apparent non-vascular cause (eg. trauma, tumor, or infection). Available neuroimaging studies will be considered to support the clinical impression and to determine if there is a demonstrable lesion compatible with an acute stroke. *Diagnostic criteria* • Acute episode of a focal or global neurological deficit with at least one of the following: change in the level of consciousness, hemiplegia, hemiparesis, numbness, or sensory loss affecting one side of the body, dysphasia or aphasia, hemianopia, amaurosis fugax, or other neurological signs or symptoms consistent with stroke • Stroke: duration of a focal or global neurological deficit >24 h; or <24 h if available neuroimaging documents a new hemorrhage or infarct; or the neurological deficit results in death. • Confirmation of the diagnosis by at least one of the following: • Neurologist or neurosurgical specialist • Neuroimaging procedure (CT scan or brain MRI), but stroke may be diagnosed on clinical grounds alone *Stroke classification* • Transient ischemic attack: a transient ischemic attack is defined as an acute episode of focal cerebral, spinal, or retinal dysfunction caused by an ischemia of central nervous system

	tissue which resolves within 24 hrs and without neuroimaging evidence of acute infarction. • Ischemic: an acute episode of focal cerebral, spinal, or retinal dysfunction caused by infarction of the central nervous system tissue, • Hemorrhagic: an acute episode of focal or global cerebral or spinal dysfunction caused by intraparenchymal, intraventricular, or subarachnoid hemorrhage, • A stroke may be classified as undetermined if there is insufficient information to allow categorization as ischemic or hemorrhagic <u>*Stroke severity*</u> • Disabling stroke: a Modified Rankin Scale (mRS) score of 2 or more at 90 days and an increase in at least one mRS category from an individual's pre-stroke baseline, • Non-diabling stroke: a mRS score of <2 at 90 days or one that does not result in an increase in at least one mRS category from an individual's pre-stroke baseline.
Stent thrombosis	Stent thrombosis is defined according to according to the definite or probable criteria of the Academic Research Consortium. • Definite stent thrombosis: defined as occurring when clinical presentation is consistent with acute coronary syndrome and angiography or autopsy examination confirm stent occlusion or thrombus. • Probable stent thrombosis: defined as death occurring within 30 days that cannot be attributed to another cause or when myocardial infarction occurs at any time point and is attributable to the target vessel in the absence of angiography confirming another culprit lesion. • • Possible stent thrombosis: defined as occurring when the patient dies after >30 days and death is not explained by another cause.

Repeat revascularization	A coronary revascularization procedure may be either a CABG or a PCI. Planned staged PCI procedures do not qualify. The coronary segments revascularized will be sub-classified as: • Target-lesion: A lesion revascularized in the index procedure (or during a planned or provisional staged procedure). The length of the target lesion is inclusive of the treated section and the 5 mm proximal and distal to the treated section. • Target-vessel: The target vessel is defined as the entire major coronary vessel proximal and distal to the target lesion including upstream and downstream branches and the target lesion itself. • All revascularization events will be adjudicated as either ischemia-driven or non-ischemia-driven. Revascularization will be considered ischemia-driven if the diameter stenosis of the revascularized coronary segment is ≥50% by QCA and any of the following criteria for ischemia are met: a) History of angina pectoris, presumably related to the target vessel, b) Objective signs of ischemia at rest (electrocardiographic changes) or during exercise test (or equivalent), presumably related to the target vessel c) Abnormal results of any invasive functional diagnostic test (e.g., CFR or FFR).
Bleeding	**Bleeding events are primarily assessed according to the Bleeding Academic Research Consortium (BARC) criteria.** • Type 0: no bleeding • Type 1: bleeding that is not actionable and does not cause the patient to seek an unscheduled performance of studies, hospitalization, or treatment by a health care professional. • Type 2: any overt, actionable sign of hemorrhage (e.g., more bleeding than would be expected for a clinical circumstance, including bleeding found by imaging alone) that does not fit the

	criteria for type 3, type 4, or type 5 but does meet at least one of the following criteria: (1) requiring nonsurgical, medical intervention by a health care professional; (2) leading to hospitalization or increased level of care; or (3) prompting evaluation. • Type 3a: overt bleeding plus Hb drop of 3 to 5 g/dL* (provided the Hb drop is related to bleed); any transfusion with overt bleeding. • Type 3b: overt bleeding plus Hb drop of 5 g/dL (provided the Hb drop is related to bleed); cardiac tamponade; bleeding requiring surgical intervention for control (excluding dental, nasal, skin, and hemorrhoid); bleeding requiring intravenous vasoactive agents. • Type 3c: intracranial hemorrhage (does not include microbleeds or hemorrhagic transformation, does include intraspinal); subcategories confirmed by autopsy or imaging, or lumbar puncture; intraocular bleed compromising vision. • Type 4: CABG-related bleeding; perioperative intracranial bleeding within 48 hours; reoperation after closure of sternotomy for the purpose of controlling bleeding; transfusion of 5 U of whole blood or packed red blood cells within a 48-hour period; chest tube output 2 L within a 24-hour period. • Type 5a: probable fatal bleeding; no autopsy or imaging confirmation but clinically suspicious. • Type 5b: definite fatal bleeding; overt bleeding or autopsy, or imaging confirmation. *BARC type 3–5 indicates severe bleeding. *Life-threatening or disabling bleeding is defined as any one of the following criteria: • Fatal bleeding (BARC type 5), • Bleeding in a critical organ, such as intracranial, intraspinal, intraocular, or pericardial necessitating pericardiocentesis, or

	intramuscular with compartment syndrome (BARC type 3b and 3c), • Bleeding causing hypovolemic shock or severe hypotension requiring vasopressors or surgery (BARC type 3b), • Overt source of bleeding with drop in hemoglobin >5 g/dL or whole blood or packed red blood cells (RBCs) transfusion >4 units* (BARC type 3b) *Major bleeding (BARC type 3a) • Overt bleeding either associated with a drop in the hemoglobin level of at least 3.0 g/dl or requiring transfusion of two or three units of whole blood/RBC, or causing hospitalization or permanent injury, or requiring surgery AND Does not meet criteria of life-threatening or disabling bleeding *Minor bleeding (BARC type 2 or 3a, depending on the severity) • Any bleeding worthy of clinical mention (e.g. access site hematoma) that does not qualify as life-threatening, disabling, or major **<u>TIMI bleeding definitions:</u>** • Major: 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 5 g/dL, Fatal bleeding (bleeding that directly results in death within 7 d) • Minor: Clinically overt (including imaging), resulting in hemoglobin drop of 3 to 5 g/dL, requiring medical attention, 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, 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), leading to or prolonging hospitalization, prompting evaluation (leading to an unscheduled visit to a healthcare professional and diagnostic testing, either laboratory or imaging). **ISTH bleeding definitions:** • Major: 1. Fatal bleeding. and/or 2. Symptomatic bleeding in a critical area or organ, such as intracranial, intraspinal, intraocular, retroperitoneal, intraarticular or pericardial, or intramuscular with compartment syndrome. and/or 3. Bleeding causing a fall in hemoglobin level of 2 g/dL (1.24 mmol/L) or more, or leading to transfusion of two or more units of whole blood or red cells. • Minor: All non-major bleeds will be considered minor bleeds. Minor bleeds will be further divided into those that are clinically relevant and those that are not. • Clinically relevant minor: A clinically relevant minor bleed is an acute or subacute clinically overt bleed that does not meet the criteria for a major bleed but prompts a clinical response, in that it leads to at least one of the following: - A hospital admission for bleeding, or - A physician guided medical or surgical treatment for bleeding, or - A change in antithrombotic therapy (including interruption or discontinuation of study drug). **GUSTO bleeding definitions:** • Severe or life-threatening

	- Intracerebral hemorrhage - Resulting in substantial hemodynamic compromise requiring treatment • Moderate - Requiring blood transfusion but not resulting in hemodynamic. Compromise • Mild - Bleeding that does not meet above criteria

Members of clinical-events committee adjudicated all primary and secondary end-point events in a blinded fashion on the basis of standard, prospectively determined definitions.