# Prasugrel-based de-escalation of dual antiplatelet therapy after percutaneous coronary intervention in patients with acute coronary syndrome (HOST-REDUCE-POLYTECH-ACS): an open-label, multicentre, non-inferiority randomised trial

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## Summary

**Background** A potent P2Y12 inhibitor-based dual antiplatelet therapy is recommended for up to 1 year in patients with acute coronary syndrome receiving percutaneous coronary intervention (PCI). The greatest benefit of the potent agent is during the early phase, whereas the risk of excess bleeding continues in the chronic maintenance phase. Therefore, de-escalation of antiplatelet therapy might achieve an optimal balance between ischaemia and bleeding. We aimed to investigate the safety and efficacy of a prasugrel-based dose de-escalation therapy.

**Methods** HOST-REDUCE-POLYTECH-ACS is a randomised, open-label, multicentre, non-inferiority trial done at 35 hospitals in South Korea. We enrolled patients with acute coronary syndrome receiving PCI. Patients meeting the core indication for prasugrel were randomly assigned (1:1) to the de-escalation group or conventional group using a web-based randomisation system. The assessors were masked to the treatment allocation. After 1 month of treatment with 10 mg prasugrel plus 100 mg aspirin daily, the de-escalation group received 5 mg prasugrel, while the conventional group continued to receive 10 mg. The primary endpoint was net adverse clinical events (all-cause death, non-fatal myocardial infarction, stent thrombosis, repeat revascularisation, stroke, and bleeding events of grade 2 or higher according to Bleeding Academic Research Consortium [BARC] criteria) at 1 year. The absolute non-inferiority margin for the primary endpoint was 2·5%. The key secondary endpoints were efficacy outcomes (cardiovascular death, myocardial infarction, stent thrombosis, and ischaemic stroke) and safety outcomes (bleeding events of BARC grade ≥2). The primary analysis was in the intention-to-treat population. This trial is registered with ClinicalTrials.gov, NCT02193971.

**Results** From Sept 30, 2014, to Dec 18, 2018, 3429 patients were screened, of whom 1075 patients did not meet the core indication for prasugrel and 16 were excluded due to randomisation error. 2338 patients were randomly assigned to the de-escalation group (n=1170) or the conventional group (n=1168). The primary endpoint occurred in 82 patients (Kaplan-Meier estimate 7·2%) in the de-escalation group and 116 patients (10·1%) in the conventional group (absolute risk difference −2·9%, $p_{non\text{-}inferiority}<0·0001$; hazard ratio 0·70 [95% CI 0·52–0·92], $p_{equivalence}=0·012$). There was no increase in ischaemic risk in the de-escalation group compared with the conventional group (0·76 [0·40–1·45]; p=0·40), and the risk of bleeding events was significantly decreased (0·48 [0·32–0·73]; p=0·0007).

**Interpretation** In east Asian patients with acute coronary syndrome patients receiving PCI, a prasugrel-based dose de-escalation strategy from 1 month after PCI reduced the risk of net clinical outcomes up to 1 year, mainly driven by a reduction in bleeding without an increase in ischaemia.

**Funding** Daiichi Sankyo, Boston Scientific, Terumo, Biotronik, Qualitech Korea, and Dio.



Published **Online** August 31, 2020 https://doi.org/10.1016/S0140-6736(20)31791-8

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See **Online** for appendix

## Introduction

For patients with acute coronary syndrome after percutaneous coronary intervention (PCI), a potent P2Y12 inhibitor-based dual antiplatelet therapy is recommended for up to 1 year due to the superior effects of these agents in reducing thrombotic outcomes compared with clopidogrel.[1,2] However, these effects are achieved at the expense of an increased risk of bleeding.[1–3] Considering the association of bleeding events with mortality, the trade-off between thrombotic risk and bleeding risk is an integral part of decision making during pharmacotherapy.

In the early phase, the thrombotic risk outweighs the bleeding risk, whereas during the chronic phase, the decrease in thrombotic risk is more pronounced than that of bleeding risk.[1,2,4] This is one of the reasons why de-escalation of the antiplatelet regimen is quite common in clinical practice.[5,6] However, due to the scarcity of clear clinical evidence, de-escalation strategies are not yet implemented in the guidelines. De-escalation

## Research in context

### Evidence before this study

A potent P2Y12 inhibitor-based dual antiplatelet therapy is recommended for up to 1 year in patients with acute coronary syndrome receiving percutaneous coronary intervention (PCI). De-escalation of the antiplatelet regimen is commonly performed in clinical practice but is not yet implemented in guidelines due to a scarcity of clear clinical evidence.

We searched PubMed on Aug 1, 2020, for articles published in English with the search terms "dual antiplatelet therapy", "de-escalation", "switching antiplatelet therapy", "percutaneous coronary intervention", and "acute coronary syndrome". Our search identified only a few randomised studies that focused on clinical outcomes. In the TWILIGHT study, de-escalation to ticagrelor monotherapy as compared with aspirin–ticagrelor dual therapy showed a lower incidence of clinical events, especially major bleeding. In the TROPICAL ACS study, de-escalation guided by platelet function testing was non-inferior to standard treatment with prasugrel. However, the multistep protocol of this strategy would be cumbersome and impractical in real-world practice.

### Added value of this study

HOST-REDUCE POLYTECH-ACS is the first randomised trial to investigate a prasugrel-based dose de-escalation strategy in patients with acute coronary syndrome receiving PCI. In 2338 patients, prasugrel dose de-escalation was non-inferior to conventional therapy in preventing net adverse clinical events (a composite of all-cause death, non-fatal myocardial infarction, stent thrombosis, clinically driven revascularisation, stroke, and Bleeding Academic Research Consortium grade ≥2 bleeding). Subsequent equality testing showed that de-escalation significantly reduced the occurrence of the primary endpoint. The main driver of the difference was a reduction in bleeding, without an increase in ischaemic outcomes. Post-hoc analysis also showed that the beneficial effect of prasugrel de-escalation was consistent in various subgroups without any significant interaction. By showing non-inferiority of prasugrel de-escalation during the chronic maintenance phase, our trial provides important justification for dose reduction of prasugrel in east Asian patients with acute coronary syndrome receiving PCI.

### Implications of all the available evidence

In patients with acute coronary syndrome receiving PCI who are indicated to take the full dose of prasugrel, de-escalation of prasugrel dose to 5 mg might be a feasible alternative strategy during chronic maintenance therapy, especially when the risk of bleeding is a concern.

studies have mostly tested switching from prasugrel to clopidogrel[4,7] or stopping aspirin and using a potent antiplatelet agent as monotherapy.[8] Because clopidogrel has innate limitations, such as drug-to-drug interaction and a large response variability,[9] an alternative de-escalation method could be a dose reduction of the potent P2Y12 inhibitor.

Prasugrel is a third-generation potent thienopyridine that irreversibly binds to the platelet P2Y12 receptor and inhibits adenosine diphosphate-induced platelet aggregation. Compared with clopidogrel, prasugrel has a faster onset, is more potent, and has less response variability.[10] Its efficacy was confirmed in planned PCI patients in the TRITON-TIMI 38 trial,[2] whereas in patients treated medically without revascularisation, prasugrel did not significantly improve ischaemic outcomes as compared with clopidogrel.[11] Previous pharmacodynamic data have shown that the extent of platelet inhibition achieved by reduced-dose prasugrel (5 mg) is weaker than that of the conventional dose of prasugrel (10 mg), but is stronger than that of 75 mg clopidogrel.[12–14] Therefore, the use of 5 mg prasugrel during the chronic maintenance phase could be an attractive de-escalation strategy to minimise both thrombotic and bleeding events after PCI. In particular, previous consensus documents have suggested that reduced-dose regimens of potent P2Y12 inhibitors are a theoretically plausible option in east Asian people, who are known to have a higher bleeding risk and a larger response variability to clopidogrel.[15–17] One pharmacodynamic study in Asian patients suggested a potential benefit of half-dose versus standard-dose prasugrel treatment in patients with acute coronary syndrome;[18] the percentage of patients in the therapeutic target range of antiplatelet therapy was more than two-times higher in the 5 mg group compared with the 10 mg group.[18] In the present study, we sought to compare a prasugrel-based de-escalation therapy (5 mg) with the conventional maintenance dose (10 mg) after PCI in patients presenting with acute coronary syndrome.

## Methods

### Study design and participants

The HOST-REDUCE-POLYTECH-ACS trial is an investigator-initiated, randomised, parallel-group, open-label, adjudicator-blinded, multicentre trial done at 35 hospitals in South Korea. The design of the study was described previously.[19] Briefly, the study had a 2×2 factorial design testing two independent hypotheses and thus had two arms, the dual antiplatelet therapy (DAPT) arm and the drug-eluting stent (DES) arm. The DAPT arm compared prasugrel-based dose de-escalation therapy with conventional dose therapy and the DES arm compared durable polymer DES with absorbable polymer DES. The current study reports the analysis and findings from the DAPT arm. Patients aged 19 years or older with a clinical diagnosis of acute coronary syndrome and with at least one culprit coronary

lesion in a native coronary artery with significant stenosis eligible for stent implantation were screened to participate in the trial. Major exclusion criteria were known hypersensitivity or contraindication to heparin, aspirin, clopidogrel, prasugrel, ticagrelor, or contrast media; patients with any major or active pathologic bleeding; women of childbearing potential; presence of non-cardiac comorbid conditions with life expectancy less than 1 year; or conditions that might result in protocol non-compliance. All conscious patients who were able to make an informed decision gave written informed consent for participation in the study before randomisation. Patients who could not provide written informed consent were excluded. The full inclusion and exclusion criteria are provided in the appendix (pp 11–12).

An independent data and safety monitoring board reviewed the safety of the trial and had full access to the trial data. The study complied with the provisions of the Declaration of Helsinki and was approved by the institutional ethics committee of each participating site.

### Randomisation and masking

Immediately after the initial coronary angiogram, but before PCI, eligible patients were centrally randomised (1:1) to either a de-escalation group or a conventional group. Patients who met the exclusion criteria of prasugrel (age ≥75 years, bodyweight <60 kg, or history of transient ischaemic attack or stroke) were excluded from the antiplatelet randomisation process and were registered in the observation group. The randomisation sequence was generated by a web-based application (MRCC IWRS System; software configuration: Apache 2, PHP 5, and mysql 5) developed by the Medical Research Collaborating Center (Seoul, South Korea). No blocking or stratification methods were applied. Participants were not masked to their assigned group. Randomisation was done by an independent research nurse or clinical nurse coordinator, who was not involved with the rest of the trial. All clinical events were adjudicated by an independent event adjudication committee, who were unaware of the treatment allocations.

### Procedures

The recommended protocol was that all patients receive 300 mg aspirin and a loading dose of 60 mg prasugrel before PCI. In patients who were not pretreated with a P2Y12 inhibitor, and those who were pretreated with a P2Y12 inhibitor other than prasugrel, a loading dose of prasugrel was recommended.

Coronary angiogram and PCI were done according to current standard techniques. The choice of stent, predilatation, post-stenting adjunctive balloon inflation, and the use of intravascular imaging or glycoprotein IIb and IIIa inhibitors was at the surgeons' discretion. No restrictions were placed on the number of lesions treated or the number of stents implanted.

After PCI, all patients in both randomised groups were given aspirin 100 mg daily with 10 mg of maintenance prasugrel until the 1-month follow-up. After the first month, patients in the de-escalation group received a de-escalated prasugrel dose of 5 mg, and patients in the conventional group received the conventional 10 mg daily dose (appendix p 27). All patients continued aspirin throughout the follow-up period. DAPT was recommended for at least 1 year after PCI; however, the treatment strategy could be adjusted at the clinician's discretion in patients with any clinical event. Clinical follow-up was scheduled at 1, 6, and 12 months after the index PCI through an office visit or telephone interview. At follow-up, the clinical status and medication adherence were checked along with the occurence of any clincial events or adverse events. The study population is to be followed up for 3 years after the index PCI. There will be no mandatory angiographic follow-up unless clinically necessary.

Data were collected with use of a web-based electronic case report form with Pharmaco-epidemiology and Clinical Trial Application X (PhactaX), which was developed by the Medical Research Collaborating Center of Seoul National University Hospital (Seoul, South Korea). PhactaX is based on Java and Oracle databases, in compliance with international standards and regulations. Central and on-site data were monitored by the central laboratory at Seoul National University Hospital Cardiovascular Clinical Research Center. All participating sites received multiple onsite monitoring visits to verify informed consent in all participants and to check key data in enrolled patients. Using the Korean health system's unique identification numbers, the vital status of all patients enrolled in the study was cross-checked.

### Outcomes

The primary endpoint was net adverse clinical events, defined as a composite of all-cause death, non-fatal myocardial infarction, stent thrombosis, clinically driven revascularisation, stroke, and bleeding events of grade 2 or higher according to Bleeding Academic Research Consortium (BARC) criteria, at 1 year. The key secondary endpoints were the efficacy outcomes (cardiovascular death, myocardial infarction, stent thrombosis, and ischaemic stroke) and safety outcomes (bleeding events of BARC grade ≥2). Other secondary endpoints included the individual components of the primary endpoint, cardiac death, clinically driven target lesion revascularisation, clinically driven target vessel revascularisation and clinically driven non-target vessel revascularisation, and bleeding events of grade 3 or higher according to BARC criteria at 1 year. Clinically driven revascularisation was defined as repeat revascularisation in the presence of a diameter of stenosis of 70% or higher, or 50% or higher with at least one of the following: recurrence of angina symptoms; positive non-invasive test; or positive

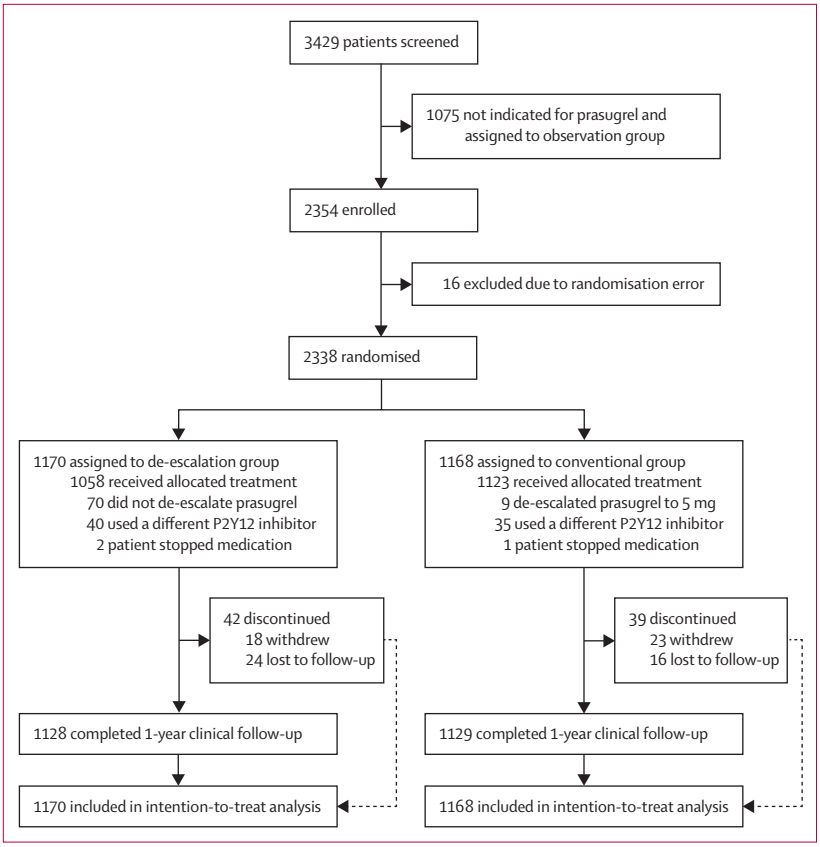


*Figure 1:* **Trial profile**

invasive physiological test. The target lesion included 5 mm margins proximal and distal to the stent and the stent itself. All clinical outcomes followed the definitions from the Academic Research Consortium.[20]

### Statistical analysis

Based on the event rates in previous trials,[2,15] the estimated incidence of the primary endpoint of this study was 7·0% for the de-escalation group and 8·0% for the conventional group. A non-inferiority margin of 2·5% was estimated and, based on a one-sided type 1 error of 2·5%, power of 75%, and a 5% attrition rate, a total of 2348 patients was needed for adequate analysis.

For comparison among groups, the $\chi^2$ test (or Fisher's exact test when any expected count was <5 for a 2×2 table) was applied for categorical variables, and the unpaired Student's *t* test or one-way analysis of variance was applied for continuous variables. To estimate the adjusted effect of randomisation groups on clinical endpoints, a multivariable Cox proportional hazards regression model with 0·05 as the significance level was performed. Cox proportional hazards assumption was tested by the Schoenfeld residual test and graphically inspected by the graph of the scaled Schoenfeld residuals against the transformed time. Event rates were calculated based on Kaplan-Meier censoring estimates, and the log-rank test

| | De-escalation group (n=1170) | Conventional group (n=1168) |
|---|---|---|
| Age, years | | |
| Mean | 58·7 (9·0) | 58·9 (9·1) |
| ≥75 | 2 (0·2%) | 0 |
| Sex | | |
| Female | 120 (10·3%) | 131 (11·2%) |
| Male | 1050 (89·7%) | 1037 (88·8%) |
| Body-mass index, kg/m² | 25·7 (2·8) | 25·8 (2·9) |
| Bodyweight | | |
| Mean | 72·4 (8·7) | 72·0 (9·0) |
| <60 kg | 7 (0·6%) | 6 (0·5%) |
| Hypertension | 733 (62·6%) | 743 (63·6%) |
| Diabetes | 512 (43·8%) | 478 (40·9%) |
| Dyslipidaemia | 890 (76·1%) | 909 (77·8%) |
| Chronic kidney disease | 30 (2·6%) | 34 (2·9%) |
| Peripheral vessel disease | 20 (1·7%) | 9 (0·8%) |
| Smoking status | | |
| Never smoker | 471 (40·3%) | 511 (43·8%) |
| Current smoker | 443 (37·9%) | 395 (33·8%) |
| Ex-smoker | 256 (21·9%) | 262 (22·4%) |
| Previous myocardial infarction | 35 (3·0%) | 55 (4·7%) |
| Previous revascularisation | 113 (9·7%) | 148 (12·7%) |
| Previous stroke | 14 (1·2%) | 17 (1·5%) |
| Family history of coronary artery disease | 78 (6·7%) | 90 (7·7%) |
| Left ventricular ejection fraction, % | 59·3 (9·7) | 59·3 (10·0) |
| Clinical presentation | | |
| ST-elevation myocardial infarction | 173 (14·8%) | 153 (13·1%) |
| Non-ST-elevation myocardial infarction | 308 (26·3%) | 283 (24·2%) |
| Unstable angina | 689 (58·9%) | 732 (62·7%) |
| Laboratory findings | | |
| Haemoglobin, g/dL | 14·5 (1·6) | 14·4 (1·6) |
| Platelets, ×10³ per mL | 232·6 (59·7) | 232·4 (58·3) |
| Blood urea nitrogen, mg/dL | 16·6 (9·5) | 16·3 (7·0) |
| Creatinine, mg/dL | 1·05 (0·95) | 1·02 (0·85) |
| Total cholesterol, mg/dL | 175·5 (46·4) | 174·9 (44·4) |
| LDL, mg/dL | 106·4 (39·3) | 106·1 (38·9) |
| HDL, mg/dL | 43·3 (12·4) | 43·5 (11·1) |
| Triglyceride, mg/dL | 158·3 (119·6) | 156·9 (105·9) |
| Medication at discharge | | |
| Aspirin | 1147/1160 (98·9%) | 1150/1160 (99·1%) |
| β blocker | 653/1156 (56·5%) | 621/1155 (53·8%) |
| ACE inhibitor or ARB | 674/1155 (58·4%) | 640/1154 (55·5%) |
| Calcium channel blocker | 263/1157 (22·7%) | 240/1154 (20·8%) |
| Proton pump inhibitor | 219/1157 (18·9%) | 199/1155 (17·2%) |
| Statin | 1103/1157 (95·3%) | 1089/1155 (94·3%) |

Data are mean (SD), n (%), or n/N (%). ACE=angiotensin converting enzyme. ARB=angiotensin receptor blocker.

*Table 1:* **Baseline characteristics**

 Published online August 31, 2020 https://doi.org/10.1016/S0140-6736(20)31791-8

| | De-escalation group (n=1170) | Conventional group (n=1168) |
|---|---|---|
| Diseased vessels | | |
| One | 585/1164 (50·3%) | 573/1161 (49·4%) |
| Two | 354/1164 (30·4%) | 337/1161 (29·0%) |
| Three | 225/1164 (19·3%) | 251/1161 (21·6%) |
| Multivessel disease | 579/1164 (49·7%) | 588/1161 (50·6%) |
| Anticoagulant agent for PCI | | |
| Unfractionated heparin | 230/1170 (19·7%) | 247/1168 (21·1%) |
| Enoxaparin | 93/1170 (7·9%) | 86/1168 (7·4%) |
| Glycoprotein IIb and IIIa inhibitor | | |
| Abciximab | 14/1170 (1·2%) | 11/1168 (0·9%) |
| Tirofiban | 0 | 1/1168 (0·1%) |
| Culprit lesion | | |
| Left main coronary artery | 36/1155 (3·1%) | 38/1146 (3·3%) |
| Left anterior descending artery | 570/1155 (49·4%) | 587/1146 (51·2%) |
| Left circumflex artery | 207/1155 (17·9%) | 215/1146 (18·8%) |
| Right coronary artery | 342/1155 (29·6%) | 306/1146 (26·7%) |
| Treated lesions | | |
| Left main coronary artery | 44/1590 (2·8%) | 47/1583 (3·0%) |
| Left anterior descending artery | 727/1590 (45·7%) | 737/1583 (46·6%) |
| Left circumflex artery | 344/1590 (21·6%) | 359/1583 (22·7%) |
| Right coronary artery | 475/1590 (29·9%) | 440/1583 (27·8%) |
| Lesion complexity | | |
| Multilesion intervention | 327/1158 (28·2%) | 337/1153 (29·2%) |
| Heavy calcification | 141/1149 (12·3%) | 153/1149 (13·3%) |
| Bifurcation lesion | 236/1148 (20·6%) | 226/1146 (19·7%) |
| Thrombotic lesion | 166/1149 (14·4%) | 140/1149 (12·2%) |
| ACC/AHA type B2/C lesion | 660/1147 (57·5%) | 634/1148 (55·2%) |
| In-stent restenosis lesion | 29/1149 (2·5%) | 30/1149 (2·6%) |
| Intravascular ultrasound use | 382/1153 (33·1%) | 393/1150 (34·2%) |
| Stent type | | |
| Durable polymer DES | 589/1170 (50·3%) | 588/1168 (50·3%) |
| Absorbable polymer DES | 581/1170 (49·7%) | 580/1168(49·7%) |
| Treated lesions per person | 1·4 (0·7) | 1·4 (0·7) |
| Stents per person | 1·6 (1·0) | 1·6 (1·0) |
| Total stent length, mm | 41·4 (29·4) | 41·2 (31·7) |
| Procedural success | 1146/1156 (99·1%) | 1146/1152 (99·5%) |

Data are mean (SD) or n/N (%). PCI=percutaneous coronary intervention. ACC/AHA=American College of Cardiology/American Heart Association. DES=drug-eluting stent.

***Table 2:*** **Lesion and procedural characteristics**

| | De-escalation group (n=1170) | Conventional group (n=1168) | Hazard ratio (95% CI) | p value |
|---|---|---|---|---|
| Net adverse clinical events* | 82 (7·2%) | 116 (10·1%) | 0·70 (0·52–0·92) | 0·012 |
| Efficacy events† | 16 (1·4%) | 21 (1·8%) | 0·76 (0·40–1·45) | 0·40 |
| Safety events | | | | |
| BARC grade ≥2 | 33 (2·9%) | 67 (5·9%) | 0·48 (0·32–0·73) | <0·0007 |
| BARC grade ≥3 | 9 (0·8%) | 8 (0·7%) | 1·12 (0·43–2·90) | 0·82 |
| BARC bleeding grade | | | | |
| 2 | 24 (2·1%) | 59 (5·1%) | .. | .. |
| 3A | 3 (0·3%) | 4 (0·3%) | .. | .. |
| 3B | 3 (0·3%) | 2 (0·2%) | .. | .. |
| 3C | 3 (0·3%) | 2 (0·2%) | .. | .. |
| BARC bleeding site | | | | |
| Subcutaneous bleeding | 8 (0·7%) | 36 (3·1%) | .. | .. |
| Gastrointestinal system | 9 (0·8%) | 15 (1·3%) | .. | .. |
| Intracranial bleeding | 4 (0·3%) | 1 (0·1%) | .. | .. |
| Epistaxis | 4 (0·3%) | 6 (0·5%) | .. | .. |
| Genitourinary system | 1 (0·1%) | 1 (0·1%) | .. | .. |
| Intraocular haemorrhage | 1 (0·1%) | 3 (0·3%) | .. | .. |
| Pulmonary haemorrhage | 0 | 1 (0·1%) | .. | .. |
| Haemopericardium | 0 | 1 (0·1%) | .. | .. |
| Unknown origin | 2 (0·2%) | 1 (0·1%) | .. | .. |
| Bleeding events leading to discontinuation or non-adherence | 11 (0·9%) | 35 (3·0%) | .. | .. |
| Target lesion failure‡ | 20 (1·8%) | 20 (1·7%) | 1·00 (0·54–1·85) | 0·99 |
| Deaths | | | | |
| All-cause death | 10 (0·9%) | 14 (1·2%) | 0·71 (0·32–1·60) | 0·41 |
| Cardiac death | 3 (0·3%) | 10 (0·9%) | 0·30 (0·08–1·09) | 0·066 |
| Non-fatal myocardial infarction | 7 (0·6%) | 8 (0·7%) | 0·87 (0·32–2·40) | 0·79 |
| Stent thrombosis | 1 (0·1%) | 3 (0·3%) | 0·33 (0·03–3·19) | 0·34 |
| Repeat revascularisation | 35 (3·1%) | 37 (3·3%) | 0·94 (0·59–1·50) | 0·81 |
| Target vessel revascularisation | 21 (1·8%) | 16 (1·4%) | 1·32 (0·68–2·51) | 0·41 |
| Target lesion revascularisation | 15 (1·3%) | 11 (1·0%) | 1·36 (0·62–2·96) | 0·44 |
| Non-target vessel revascularisation | 19 (1·7%) | 25 (2·2%) | 0·76 (0·42–1·37) | 0·36 |
| Stroke | 10 (0·9%) | 8 (0·7%) | 1·24 (0·49–3·15) | 0·65 |
| Ischaemic stroke | 6 (0·5%) | 4 (0·4%) | 1·49 (0·42–5·29) | 0·53 |
| Haemorrhagic stroke | 4 (0·4%) | 4 (0·4%) | 0·99 (0·25–3·97) | 0·99 |

Data are n (Kaplan-Meier estimate, %). BARC=Bleeding Academic Research Consortium. *Composite of all-cause death, non-fatal myocardial infarction, stent thrombosis, repeat revascularisation, stroke, and BARC grade ≥2 bleeding. †Cardiac death, myocardial infarction, stent thrombosis, and ischaemic stroke. ‡Includes cardiac death, target lesion revascularisation, and target vessel myocardial infarction.

***Table 3:*** **Primary and specified secondary outcomes**

or the Breslow test was used to compare groups. All probability values were two-sided and p values of less than 0·05 were considered statistically significant, except for the non-inferiority testing of the primary endpoint. For missing values, no imputation methods were used to infer missing values of baseline variables. The number needed to treat was calculated by the reciprocal of the absolute risk difference based on 1-year Kaplan-Meier estimates. For the study endpoints, patients lost to follow-up were censored in the estimation of Kaplan-Meier event rates. Endpoints were analysed first on an intention-to-treat basis, then on a per-protocol basis. The non-inferiority margin for the primary endpoint was 2·5%. A prespecified landmark analysis was done 4 weeks after index PCI (corresponding to the planned date of prasugrel dose reduction in the de-escalation group), with hazard ratios (HRs) and 95% CIs calculated separately for events up to and beyond the landmarks. A post-hoc subgroup analysis was done to detect any interaction of the clinical effect of each strategy in various

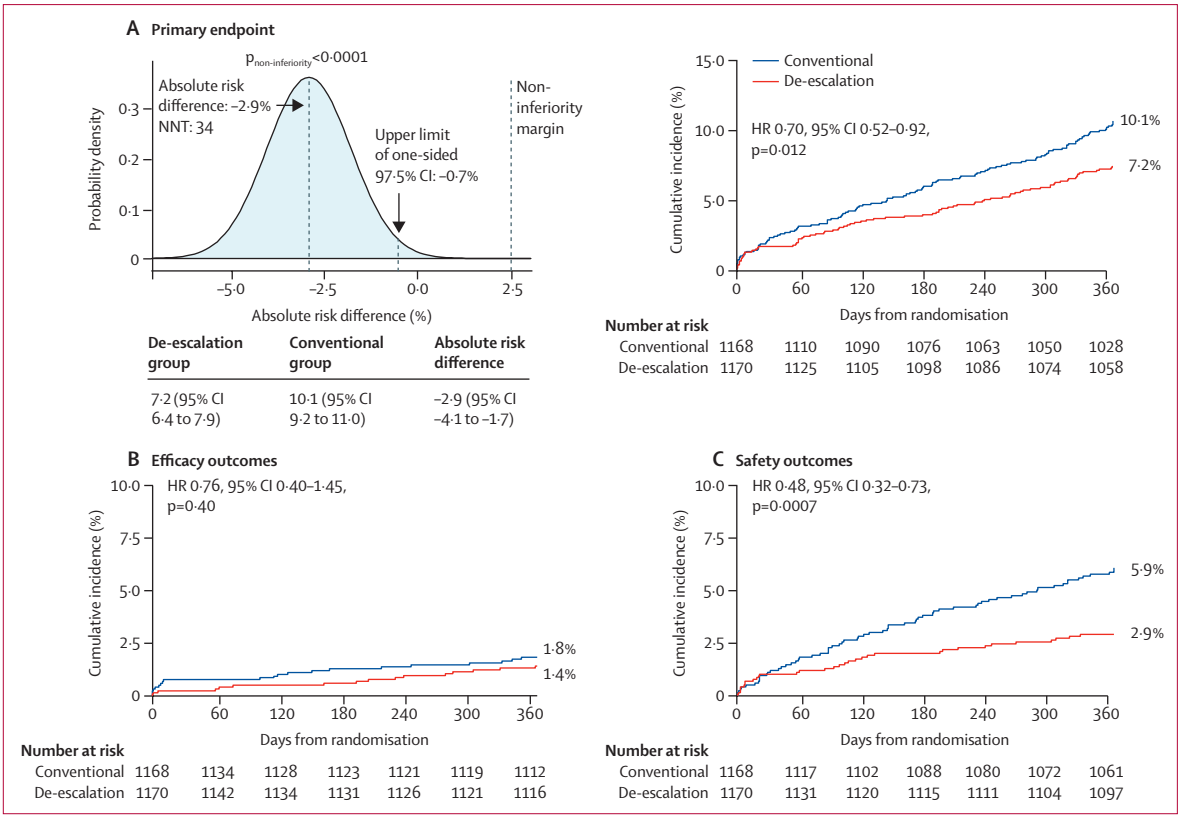


***Figure 2:*** **Primary endpoint and key secondary endpoints in the intention-to-treat population at 1-year follow-up**
(A) Density plot for absolute risk difference between the treatment groups in the incidence of the primary endpoint (left panel) and Kaplan-Meier curve of the primary endpoint (right panel). (B) Efficacy outcomes (cardiac death, myocardial infarction, stent thrombosis, and ischaemic stroke). (C) Safety outcomes (Bleeding Academic Research Consortium grade ≥2 bleeding events). HR=hazard ratio. NNT=number needed to treat.

subgroups. An additional set of analysis was done in the observation group, which included patients for whom prasugrel was not indicated. Statistical tests were done using SPSS version 22 and R programming language version 3.4.4.

This study is registered with ClinicalTrials.gov, NCT02193971.

### Role of the funding source

The funders of this study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. H-SK, JK, DH, and KWP had full access to all the data in the study and had final responsibility for the decision to submit for publication.

## Results

From Sept 30, 2014, to Dec 18, 2018, 3429 eligible patients with acute coronary syndrome from 35 hospitals in South Korea were screened. Among this population, 1075 patients did not meet the core indication for prasugrel and were assigned to the observation group. 2338 patients were randomly assigned to the de-escalation group (n=1170) or the conventional group (n=1168) and 16 patients were excluded due to randomisation error (figure 1). The mean age of patients was 58·8 years and 326 (13·9%) of 2338 presented with ST-segment elevation myocardial infarction. Table 1 summarises the baseline demographic and clinical characteristics, and table 2 describes the angiographic and procedural characteristics at index PCI, showing a balanced distribution between the two randomised groups. Approximately half of the enrolled patients had multivessel coronary artery disease, and 664 (28·7%) of 2311 received multivessel intervention. The culprit lesion was located in the left anterior descending artery in 1157 (50·3%) of 2301 patients; 462 (20·1%) were bifurcation lesions; and 1294 (56·4%) were type B2/C lesions according to American College of Cardiology/American Heart Association classification. The stent type (durable polymer *vs* absorbable polymer DES) was evenly distributed in both groups, as per the randomisation protocol, and the mean number implanted was 1·61 stents per patient (SD 1·0; mean length 41·3 mm [30·6]). The characteristics of the observation group are shown in the appendix (pp 16–19).

At 1 year, clinical follow-up was complete in 1128 (96·4%) of 1170 patients in the de-escalation group and 1129 (96·7%) of 1168 patients in the conventional group. The specific causes of early termination are shown in figure 1. At 1 year, the primary endpoint occurred in 82 patients (7·2%) in the de-escalation group and

116 patients (10·1%) in the conventional group (absolute risk difference –2·9%, one-sided 97·5% CI –0·7%; $p_{non\text{-}inferiority}$<0·0001, number needed to treat=34; table 3, figure 2A). The Kaplan-Meier event curves showed a significant reduction in the risk for the primary endpoint (HR 0·70 [95% CI 0·52–0·92]; $p_{equivalence}$=0·012). Regarding the key secondary endpoints, efficacy events occurred in 16 patients (1·4%) in the de-escalation group and in 21 patients (1·8%) in the conventional group (0·76 [0·40–1·45]; p=0·40; figure 2B). BARC grade 2 or higher bleeding events occurred in 33 patients (2·9%) in the de-escalation group compared with 67 patients (5·9%) in the conventional group (0·48 [0·32–0·73]; p=0·0007; figure 2C). The specific BARC bleeding grade, anatomic site, and incidence of discontinuation or non-adherence is shown in table 3 and in the appendix (p 28). The incidence of other secondary endpoints was similar between the two groups (table 3). The per-protocol analyses yielded similar results to the intention-to-treat analyses for the primary study endpoint ($p_{non\text{-}inferiority}$<0·0001; HR 0·72 [95% CI 0·54–0·96]; $p_{equivalence}$=0·027) and for the key secondary endpoints (appendix pp 29–30).

The prespecified landmark analyses showed that the risk of the primary endpoint was similar between groups during the initial 4 weeks after the index procedure (HR 0·80 [95% CI 0·44–1·43]; p=0·45; figure 3A). However, after the first 4 weeks, the curves diverged, with a significantly lower risk of the primary endpoint occurring in the de-escalation group (0·66 [0·48–0·91]; p=0·012). In the landmark analyses of key secondary endpoints, the risk of ischaemic outcomes was similar between groups both before and after 4 weeks (figure 3B), whereas the risk of BARC grade 2 or higher bleeding events was significantly lower in the de-escalation group than the conventional group after 4 weeks (0·38 [0·23–0·63]; p=0·0002; figure 3C). In post-hoc subgroup analyses, the clinical effect of de-escalation was consistent regardless of subgroup, with no significant interaction (figure 4).

Patients that did not meet the core indication criteria for prasugrel use were enrolled in a non-randomised observation group. Patients in the observation group had more clinical risk factors and higher angiographic complexity compared with the randomised prasugrel groups (appendix pp 20–23). Clopidogrel was used in 767 (72·1%), and ticagrelor in 242 (22·7%) patients. Kaplan-Meier cumulative estimates of the primary endpoint were significantly higher in the observation group than the prasugrel groups (HR 1·69 [95% CI 1·37–2·09]; $p_{equivalence}$<0·0001; appendix pp 24–25). Among key secondary endpoints, efficacy outcomes occurred more frequently in the observation group, whereas the incidence of safety outcomes was similar between the two groups (appendix pp 31–33). Because the observation group had significantly worse baseline characteristics compared with the prasugrel groups, we did a multivariate Cox proportional hazards regression analysis. After adjustment, the independent predictors of clinical events were older age, lower body-mass index, and chronic kidney disease. Antiplatelet regimen was not a significant predictor of clinical events in this model (appendix p 26).

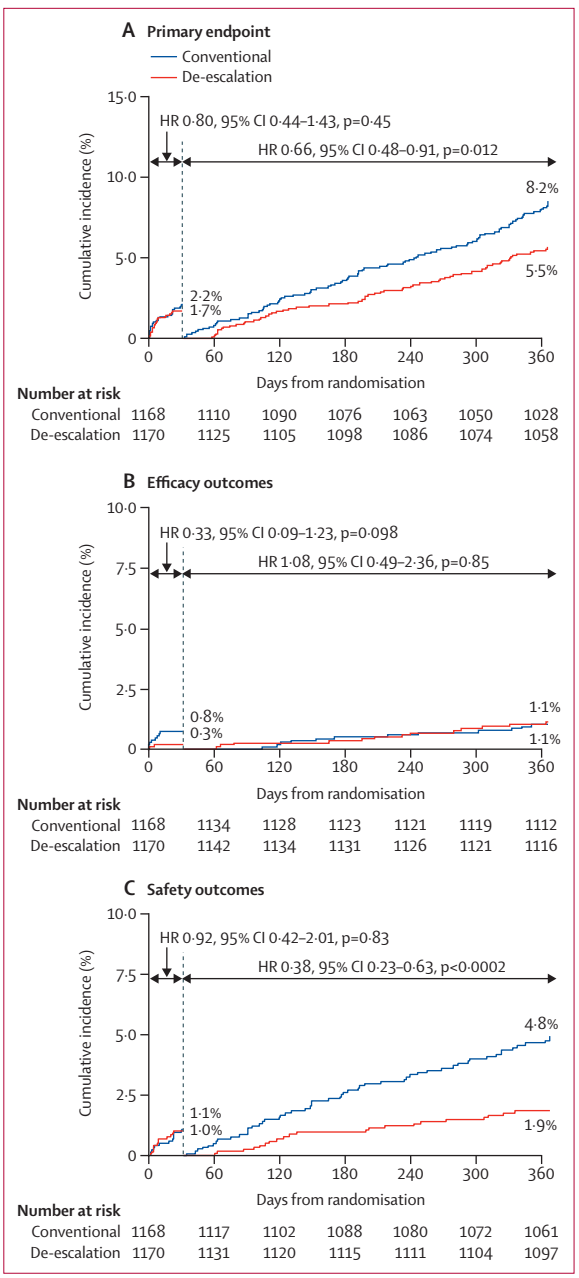


***Figure 3:*** **Prespecified landmark analyses at 4 weeks after index procedure**
(A) Primary endpoint. (B) Efficacy outcomes (cardiac death, myocardial infarction, stent thrombosis, and ischaemic stroke). (C) Safety outcomes (Bleeding Academic Research Consortium grade ≥2 bleeding events). The dashed line represents the 4-week timepoint for landmark analysis. HR=hazard ratio.

## Discussion

The concept of de-escalation is based on the hypothesis that there is a temporal change of ischaemic and bleeding

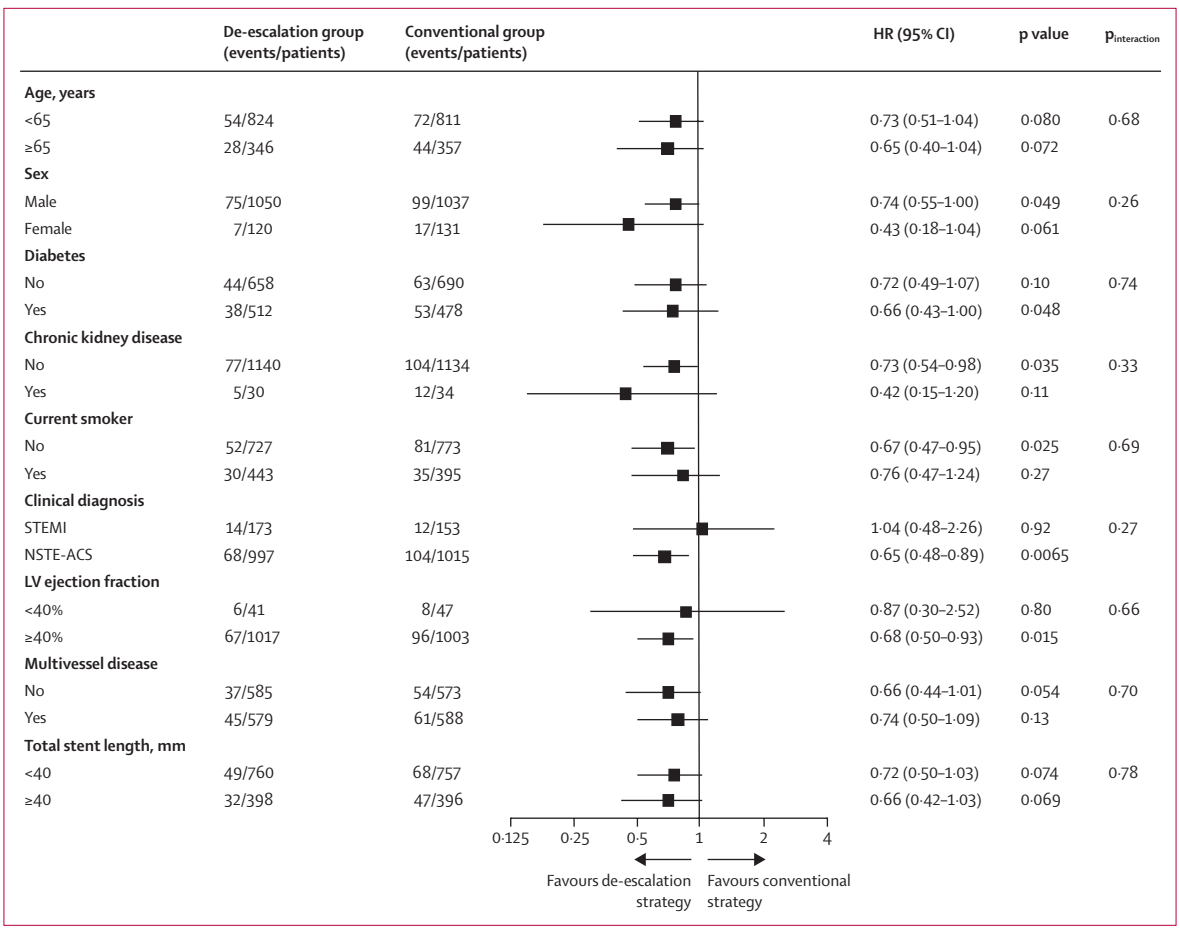


***Figure 4:*** **Subgroup analyses**
Subgroup analyses of the primary endpoint in relevant subgroups. $p_{interaction}$ represents the likelihood of interaction between the subgroup variable and the treatment strategy. HR=hazard ratio. STEMI=ST-elevation myocardial infarction. NSTE-ACS=non-ST-elevation acute coronary syndrome. LV=left ventricular.

risks after PCI. Immediately after PCI, especially in patients with acute coronary syndrome, the risk of thrombosis is greatest because the patient has a thrombotic milieu and the culprit coronary artery needs to recover from balloon-induced injury and dissection with exposure of the subendothelial tissue to blood.[21] Moreover, a foreign material (the DES) is directly exposed to the vascular intraluminal space. As a result, platelets are highly activated, which requires a potent antiplatelet regimen. As the patient stabilises, the thrombotic milieu is normalised and the implanted stents start to be covered by endothelial cells.[22] However, the bleeding risk is maintained, especially when using potent P2Y12 inhibitors,[23] and as such, bleeding risk is a key factor to consider during the chronic phase. In this context, the de-escalation strategy of antiplatelet treatment is an appealing concept, and it is frequently used in real-world practice.[5,24]

The de-escalation of DAPT can be achieved through either antiplatelet monotherapy or decreasing the potency of DAPT.[25,26] In the TWILIGHT study,[8] ticagrelor monotherapy, as compared with aspirin–ticagrelor dual therapy, showed a lower incidence of clinical events, especially with regards to bleeding. A decrease in the potency of DAPT could be achieved by either dose reduction or drug switching, the latter of which was studied in the TOPIC and TROPICAL-ACS trials.[4,7] In the TOPIC study, downgrading DAPT from a potent P2Y12 inhibitor to clopidogrel at 1 month after PCI for acute coronary syndrome was associated with a significant reduction in bleeding complications, whereas the risk of recurrent ischaemic events was similar.[4] However, it was a small study (645 patients) with low protocol adherence (75%). The TROPICAL-ACS study reported that guided de-escalation of antiplatelet treatment from prasugrel to clopidogrel was non-inferior to standard treatment with prasugrel, with no increase in the combined risk of cardiovascular death, myocardial infarction, or stroke.[7] The limitation of the TROPICAL-ACS study was that all patients had to be de-escalated to clopidogrel from prasugrel for a week, and, after a platelet function test, the poor responders to

clopidogrel were re-escalated to prasugrel. This multistep protocol would be cumbersome and impractical in real-world practice. To our knowledge, this was the first large-scale randomised study to evaluate reducing the dose of the potent P2Y12 inhibitor during the chronic phase.

In our study, de-escalation of prasugrel after 1 month of conventional dose therapy was non-inferior to continuing the conventional dose with regard to net adverse clinical events. The actual event rate we observed was similar to what we had expected in the de-escalation group (7·2%), whereas it was much higher than expected in the conventional group (10·1%). On equality testing, the occurrence of the primary endpoint was significantly lower in the de-escalation group (HR 0·70 [95% CI 0·52–0·92]; p=0·012). This decrease was mainly driven by a significantly reduced risk of bleeding without an increase in ischaemic events. The results were consistent in various subgroups, suggesting that the de-escalation strategy could be feasible across a broad spectrum of acute coronary syndrome. To our knowledge, this is the first randomised trial to show the clinical benefit of reduced-dose versus standard-dose prasugrel during the maintenance phase in east Asian patients with acute coronary syndrome that received PCI. Although the trial was originally designed as a non-inferiority study, the results of the primary endpoint not only met the criteria for non-inferiority but also suggested superiority. However, in the trial design, there were no prespecified conditions to test for superiority. This limitation must be taken into account in interpreting the results of our study.

Regarding the key secondary endpoints, the absolute event rate of ischaemic outcomes, defined as cardiac death, myocardial infarction, stent thrombosis, and ischaemic stroke (1·6%) was much lower than that of bleeding complications (4·3%). This finding has been observed in previous trials,[3,7,8,15] suggesting that bleeding risk is a key contributor to clinical events, especially during the chronic phase after contemporary DES with excellent performance, and should be the main target to improve clinical outcomes after PCI. In particular, the evolution of PCI has predominantly focused on reducing ischaemic complications, leading to a paradoxical increase in bleeding.[27] More recently, studies are focusing on the importance of reducing bleeding events to improve clinical outcomes.

The benefit of the de-escalation strategy in this study was not at the cost of an increase in ischaemic events. In fact, the ischaemic event rate was numerically lower in the de-escalation group. This finding implies that ischaemic and bleeding events are not counter-balanced, but they are instead interconnected events. Of note, in the TWILIGHT trial,[8] the ticagrelor monotherapy group showed a slightly higher rate of stent thrombosis but the risk of BARC 3 or 5 bleeding was decreased by half compared with the ticagrelor plus aspirin group. In our study, however, the main contributor to event reduction was BARC 2 bleeding events, and no significant reduction was observed in BARC 3 or 5 bleeding events. Although BARC 2 bleeding events might not be life-threatening, we showed that the rate of discontinuation or non-adherence to the allocated prasugrel dose due to bleeding was significantly lower in the de-escalation group. We believe that minor bleeding events substantially affect treatment compliance and could be a major contributor not only to medical expenses but also to clinical outcomes.[28] Whether prasugrel monotherapy during the chronic maintenance phase could have a similar benefit could be tested in future trials.

A possible explanation for the observed benefit of prasugrel dose de-escalation could be that our study was performed in a dedicated east Asian population. Various studies have reported that east Asian people might be more prone to bleeding and less prone to thrombosis.[15,29,30] Despite a higher prevalence of *CYP2C19* loss-of-function alleles, which are known to increase platelet reactivity, east Asian people do not show an elevated risk for thrombotic complications.[31] By contrast, east Asian people are more susceptible to bleeding risk, a phenomenon referred to as the east Asian paradox.[32] Regarding potent P2Y12 inhibitors, various observational studies and randomised trials have failed to show a clinical benefit in east Asian populations, unlike similar studies done in predominantly white patients,[1,2] mainly due to higher bleeding event rates.[3,30]

Some key exclusion criteria limited the inclusion of all patients with acute coronary syndrome receiving PCI. Post-hoc analysis from the TRITON-TIMI 38 trial[2] showed that full-dose prasugrel (10 mg) as compared with clopidogrel resulted in worse net clinical outcomes in the subgroup of patients whose bodyweight was less than 60 kg, who were aged 75 years or older, or who had a previous history of stroke or transient ischaemic attack.Thus, in most countries, the full prasugrel dose is not indicated and mostly not used in patients with the three aforementioned conditions. To maintain prasugrel at the full 10 mg dose in the first month after PCI, such patients were excluded from prasugrel randomisation in the current study. Also, women in Korea are mostly slim and on average have low bodyweight. As a result, the percentage of male patients was higher (89·3%) and the mean age of the patients enrolled in the current study (59 years) was younger than in recent antiplatelet trials, such as TWILIGHT (mean age 65 years, 76% male patients),[8] ISAR-REACT5 (65 years, 76%),[33] and SMART-DATE (62 years, 75%).[34] Therefore, we need to be cautious to not over-generalise our results to older patients (≥75 years) and all women.

In the post-hoc subgroup analysis the effect of the de-escalation group was mostly consistent in various groups without any significant interaction. However, in the ST-elevation myocardial infarction subgroup, although the interaction p value was insignificant, the effect of

de-escalation was neutral, in contrast to the non-ST-elevation acute coronary syndrome subgroup in which de-escalation seemed to be beneficial. This finding could raise the question of the benefit of the de-escalation strategy in highly thrombogenic situations. Other antiplatelet trials have also shown that the more potent strategy might be associated with better results in patients with ST-elevation myocardial infarction; the HR for ischaemic outcomes in the ST-elevation myocardial infarction subgroup was left-shifted (towards potent agent being better) in the TRITON-TIMI 38 study[2] (for prasugrel *vs* clopidogrel) and in the TICAKOREA study[3] (for ticagrelor *vs* clopidogrel). Our data suggest that in situations with a higher thrombotic risk, the benefit of de-escalation might not be robust and thus clinical judgement considering other factors for thrombosis and bleeding could be necessary.

Due to the general recommendations of prasugrel, our study included a third group (the observation group), in which the participants had at least one of three criteria (age ≥75 years, bodyweight <60 kg, or history of stroke or transient ischaemic attack) that prohibited the use of the standard dose of prasugrel. We found that approximately one-third of patients with acute coronary syndrome receiving PCI had at least one of these criteria and in general, they had higher clinical and lesion-related complexity. As expected, the primary endpoint occurred more frequently in the observation group. Independent predictors of the primary endpoint were innate clinical factors, including old age, low body-mass index and chronic kidney disease, whereas the antiplatelet agent was not one of the independent predictors of outcome. Nevertheless, it remains to be seen whether potent P2Y12 inhibitors used in the right dose or regimen could help to reduce clinical events in this subgroup.

Our study had a high clinical follow-up rate (1·8% of the total population withdrew consent and 1·7% were lost to follow-up) and a high protocol adherence rate (6·7% of the total population did not receive allocated therapy), suggesting good compliance and feasibility of the dose reduction de-escalation protocol, which will be important if it is to be used in clinical practice.

The current study has some limitations. First, the current analysis is one arm of the HOST-REDUCE-POLYTECH-ACS, which is a trial with a 2×2 design. Although the two arms were independent, this type of design carries the risk of power limitation due to multiple testing. Second, regarding the non-inferiority design of the study, a margin of 2·5% could be considered broad and the statistical power of 75% in the study design could be considered low. However, more events occurred than originally anticipated in the conventional group, and the event rate in the de-escalation group was similar to what we had anticipated. Therefore, the one-sided upper margin of the 97·5% CI was well within the non-inferiority margin and did not reach the line of equivalence. Additionally, an equality test showed that the de-escalation group significantly reduced the risk of the primary endpoint. Furthermore, if we input the actual observed values of the present study, our results show a power of 99·7 % (using a non-inferiority design, a non-inferiority margin of 2·5%, and one-sided α of 2·5%). In various subgroups and in the per-protocol analysis, we found consistent results. Third, our study was an open-label trial in which the investigator and patient were not masked. However, the adjudicators were blinded to the treatment allocation, and the clinical endpoints were assessed by an independent clinical event adjudication committee. Fourth, the study was performed in a dedicated east Asian population. Whether the results of the current study can be extrapolated to other ethnicities is unknown and they would need to be reproduced in other populations. However, in a pharmacodynamics study, the levels of platelet inhibition were similar for both 10 mg and 5 mg between east Asian and white people, suggesting the feasibility of de-escalation in white people.[35] Fifth, the de-escalation group received a uniform dose reduction, which was not based on pharmacodynamic testing. However, to date, the guidelines do not recommend routine platelet function testing. Sixth, repeat revascularisation was included in the primary endpoint, which could have diluted significant differences in hard endpoints such as death, myocardial infarction, stent thrombosis, and stroke. However, there were no differences in the two groups in terms of both revascularisation, each individual hard endpoint, and the composite hard endpoint.

In conclusion, in patients with acute coronary syndrome receiving PCI, a prasugrel-based dose de-escalation strategy from 1 month after PCI significantly reduced the risk of net clinical outcomes up to 1 year, which were mainly driven by a reduction in minor bleeding without an increase in ischaemia. Our results suggest that a de-escalation strategy using a potent P2Y12 inhibitor could be the optimal strategy in east Asian patients with acute coronary syndrome after PCI.

#### Contributors

H-SK, J-KH, H-MY, H-JK, B-KK, and KWP conceived and designed the study. All authors participated in the enrolment of patients and performed clinical follow-up. JK, DH, and KWP acquired the data and participated in data analysis and data interpretation. H-SK, JK, and KWP wrote the first draft, reviewed and revised the manuscript. All authors approved the final version of the manuscript.

#### Declaration of interests

H-SK has received research grants or speaker's fees from Daiichi Sankyo, Boston Scientific, Terumo, Biotronik, Dio, Medtronic, Abbott Vascular, Edwards Life Science, Amgen, and Behringer Ingelheim, outside of the submitted work. KWP reports speaker's fees from Daiichi Sankyo, AstraZeneca, Sanofi, Bristol-Myers Squibb, Bayer, and Pfizer, outside of the submitted work. All other authors declare no competing interests.

#### Data sharing

The HOST-REDUCE-POLYTECH-ACS trial is planned to continue follow-up for 3 years, which will end in March, 2022. Until then, no individual participant data will be available. Relevant enquiries should be emailed to the corresponding author or H-SK (hyosoo@snu.ac.kr).

**Acknowledgments**
This study was supported by Daiichi Sankyo, Boston Scientific, Terumo, Biotronik, Qualitech Korea, and Dio.

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