Unguided de-escalation from ticagrelor to clopidogrel in stabilised patients with acute myocardial infarction undergoing percutaneous coronary intervention (TALOS-AMI): an investigator-initiated, open-label, multicentre, non-inferiority, randomised trial

Chan Joon Kim, Mahn-Won Park*, Min Chul Kim, Eun-Ho Choo, Byung-Hee Hwang, Kwan Yong Lee, Yun Seok Choi, Hee-Yeol Kim, Ki-Dong Yoo, Doo-Soo Jeon, Eun-Seok Shin, Young-Hoon Jeong, Ki-Bae Seung, Myung Ho Jeong, Hyeon Woo Yim, Youngkeun Ahn, Kiyuk Chang, TALOS-AMI investigators†*

Summary

Background In patients with acute myocardial infarction receiving potent antiplatelet therapy, the bleeding risk remains high during the maintenance phase. We sought data on a uniform unguided de-escalation strategy of dual antiplatelet therapy (DAPT) from ticagrelor to clopidogrel after acute myocardial infarction.

Methods In this open-label, assessor-masked, multicentre, non-inferiority, randomised trial (TALOS-AMI), patients at 32 institutes in South Korea with acute myocardial infarction receiving aspirin and ticagrelor without major ischaemic or bleeding events during the first month after index percutaneous coronary intervention (PCI) were randomly assigned in a 1:1 ratio to a de-escalation (clopidogrel plus aspirin) or active control (ticagrelor plus aspirin) group. Unguided de-escalation without a loading dose of clopidogrel was adopted when switching from ticagrelor to clopidogrel. The primary endpoint was a composite of cardiovascular death, myocardial infarction, stroke, or bleeding type 2, 3, or 5 according to Bleeding Academic Research Consortium (BARC) criteria from 1 to 12 months. A non-inferiority test was done to assess the safety and efficacy of de-escalation DAPT compared with standard treatment. The hazard ratio (HR) for de-escalation versus active control group in a stratified Cox proportional hazards model was assessed for non-inferiority by means of an HR margin of 1·34, which equates to an absolute difference of 3·0% in the intention-to-treat population and, if significant, a superiority test was done subsequently. To ensure statistical robustness, additional analyses were also done in the per-protocol population. This trial is registered at ClinicalTrials.gov, NCT02018055.

Findings From Feb 26, 2014, to Dec 31, 2018, from 2901 patients screened, 2697 patients were randomly assigned: 1349 patients to de-escalation and 1348 to active control groups. At 12 months, the primary endpoints occurred in 59 (4·6%) in the de-escalation group and 104 (8·2%) patients in the active control group ($p_{non\text{-}inferiority}$<0·001; HR 0·55 [95% CI 0·40–0·76], $p_{superiority}$=0·0001). There was no significant difference in composite of cardiovascular death, myocardial infarction, or stroke between de-escalation (2·1%) and the active control group (3·1%; HR 0·69; 95% CI 0·42–1·14, p=0·15). Composite of BARC 2, 3, or 5 bleeding occurred less frequently in the de-escalation group (3·0% *vs* 5·6%, HR 0·52; 95% CI 0·35–0·77, p=0·0012).

Interpretation In stabilised patients with acute myocardial infarction after index PCI, a uniform unguided de-escalation strategy significantly reduced the risk of net clinical events up to 12 months, mainly by reducing the bleeding events.

Funding ChongKunDang Pharm, Medtronic, Abbott, and Boston Scientific.

Lancet 2021; 398: 1305–16

*Contributed equally

†Investigators are listed in the appendix

Department of Internal Medicine, Division of Cardiology, Uijeongbu St Mary's Hospital (C J Kim MD), **Department of Internal Medicine, Division of Cardiology, Daejeon St Mary's Hospital** (M-W Park MD), **Department of Internal Medicine, Division of Cardiology, Seoul St Mary's Hospital** (E-H Choo MD, B-H Hwang MD, K Y Lee MD, K-B Seung MD, K Chang MD), **Department of Internal Medicine, Division of Cardiology, Yeouido St Mary's Hospital** (Y S Choi MD), **Department of Internal Medicine, Division of Cardiology, Bucheon St Mary's Hospital** (H-Y Kim MD), **Department of Internal Medicine, Division of Cardiology, St Vincent's Hospital** (K-D Yoo MD), **Department of Internal Medicine, Division of Cardiology, Incheon St Mary's Hospital** (D-S Jeon MD), **and Department of Preventive Medicine** (H W Yim MD), **College of Medicine, The Catholic University of Korea, Seoul, South Korea; Department of Cardiology, Chonnam National University Hospital** (M C Kim MD, M H Jeong MD, Y Ahn MD); **Department of Internal Medicine, Division of Cardiology, Ulsan University Hospital, Seoul, South Korea** (E-S Shin MD); **Department of Internal Medicine, Division of Cardiology, Gyeongsang National University Changwon Hospital, Changwon, South Korea** (Y-H Jeong, MD)

Introduction

In acute myocardial infarction, adequate platelet inhibition is essential to reduce the risk of recurrent thrombotic events. Thus, the current guidelines preferentially recommend the use of potent $P2Y_{12}$ inhibitors (such as ticagrelor or prasugrel) over clopidogrel in patients with acute myocardial infarction undergoing percutaneous coronary intervention (PCI).[1] However, along with the strong antiplatelet efficacy, a higher risk of bleeding was observed for potent $P2Y_{12}$ inhibitors compared with clopidogrel in pivotal randomised trials.[2,3] Although the ischaemic benefit was consistent throughout the first year after an index event, the benefit of ticagrelor and prasugrel over clopidogrel for reducing thrombotic risk was prominent in the early period (<30 days) after acute coronary syndrome when the risk

Correspondence to:
Prof Kiyuk Chang, Department of Internal Medicine, Division of Cardiology, Seoul St Mary's Hospital, College of Medicine, The Catholic University of Korea Seocho-gu, Seoul 06591, South Korea
kiyuk@catholic.ac.kr

or

Prof Youngkeun Ahn, Department of Cardiology, Chonnam National University Hospital–Chonnam National University Medical School, Dong-gu, Gwangju 61469, South Korea
cecilyk@chonnam.ac.kr

See Online for appendix

Research in context

Evidence before this study

The current guidelines recommend the use of potent $P2Y_{12}$ receptor inhibitors over clopidogrel for up to 1 year in patients with acute myocardial infarction undergoing percutaneous coronary intervention (PCI). Although the ischaemic risk is greater in the early phase, the bleeding risk remains high during the maintenance phase of acute myocardial infarction. These findings have resulted in the development of a stepwise de-escalation of dual antiplatelet therapy (DAPT) by means of a potent $P2Y_{12}$ inhibitor only in the acute phase and the less potent clopidogrel during the chronic phase of treatment. We searched PubMed on May 1, 2021, for articles published in English, with the search terms "dual antiplatelet therapy", "antiplatelet treatment de-escalation", "switching antiplatelet therapy", "acute coronary syndrome", and "percutaneous coronary intervention". Our search identified only a few relevant randomised, clinical trials that investigated this issue. Unlike ticagrelor monotherapy trials such as TWILIGHT and TICO, and a study using reduced dose of prasugrel, the HOST-REDUCE-POLYTECH-ACS trial, multiple options of de-escalation dual antiplatelet therapy exist: unguided, platelet function test-guided, and *CYP2C19* genotype-guided. In the TROPICAL-ACS study, the de-escalation strategy of switching to clopidogrel guided by platelet function test was non-inferior to prasugrel-based DAPT in terms of net clinical benefit. However, the complexity of the testing and protocols are impractical in clinical practice. The POPular Genetics trial adopting *CYP2C19* genotype-guided strategy for selection of an appropriate $P2Y_{12}$ inhibitor showed a lower incidence of bleeding but has similar weakness to that of the TROPICAL-ACS study. Although data on the unguided de-escalation DAPT switching from potent $P2Y_{12}$ inhibitors to clopidogrel are scarce, unguided de-escalation commonly occurs in clinical practice.

Added value of this study

The Ticagrelor versus Clopidogrel in Stabilized Patients with Acute Myocardial Infarction (TALOS-AMI) trial investigated the hypothesis that de-escalation DAPT with clopidogrel might be non-inferior to ticagrelor-based antiplatelet therapy in stabilised patients with acute myocardial infarction. In 2697 patients with acute myocardial infarction who had no major ischaemic or bleeding events and tolerated aspirin plus ticagrelor therapy during the first month after an index PCI, a uniform unguided de-escalation antiplatelet therapy switching from ticagrelor to clopidogrel was superior to the ticagrelor-based continuing DAPT in terms of net clinical benefit (a composite of cardiovascular death, myocardial infarction, stroke, and bleeding type 2, 3, or 5 according to Bleeding Academic Research Consortium (BARC) criteria from 1 to 12 months after the index PCI. The de-escalation strategy was associated with a 45% lower risk of net clinical benefits for the next 11 months than the ticagrelor-based dual antiplatelet strategy. The absolute risk reduction was 3·6%, which was mainly caused by a significant decrease in bleeding risk. Additionally, a composite of BARC 3 or 5 bleeding occurred less frequently in the de-escalation group but was marginally significant. Even a composite of ischaemic events and serious bleeding such as BARC bleeding type 3 or 5 showed a significant difference between the two groups. In this study, the incidence of primary ischaemic events from 1 to 12 months after an index event were similar to those of other de-escalation trials including the TROPICAL-ACS, TWILIGHT-ACS, POPular Genetics, and TWILIGHT trials, which might indicate the safety of a uniform unguided de-escalation antiplatelet strategy in stabilised patients with uncomplicated acute myocardial infarction.

Implications of all the available evidence

In stabilised patients with acute myocardial infarction who had no major ischaemic or bleeding events and tolerated aspirin plus ticagrelor therapy during the first month after an index PCI, a uniform unguided de-escalation antiplatelet strategy switching from ticagrelor to clopidogrel was superior to the ticagrelor-based DAPT strategy at preventing net adverse clinical events, including the thrombotic composite and clinically relevant bleeding.

of ischaemic complications was the highest,[4,5] whereas most bleeding events occurred predominantly during the maintenance period of treatment.[6,7] These findings have resulted in the development of a stepwise de-escalation of dual antiplatelet treatment (DAPT) that makes use of a potent $P2Y_{12}$ inhibitor only in the acute phase of treatment and the less potent clopidogrel during the chronic phase of treatment.[8] Although data regarding guided de-escalation of antiplatelet therapy to optimise treatment outcomes in the acute phase in patients with acute coronary syndrome undergoing PCI are supported by several large-scale clinical trials,[8,9] and a systematic review and meta-analysis,[10] data regarding unguided de-escalating DAPT switching from potent $P2Y_{12}$ inhibitors to clopidogrel after the acute phase in patients with acute myocardial infarction are based on a small study with important limitations and registry data.[11,12] However, de-escalation commonly occurs in clinical practice owing to a perceived high bleeding risk, side-effects, and for economic reasons, without the guidance of the platelet function test (PFT) or genotyping.[12–14] Moreover, the improved performance of current generation drug-eluting stents compared with earlier generation drug-eluting stents sets the stage for investigating various de-escalating antiplatelet strategies.

The Ticagrelor versus Clopidogrel in Stabilized Patients with acute myocardial infarction (TALOS-AMI) trial investigated the hypothesis that de-escalation of DAPT with clopidogrel would be non-inferior to ticagrelor-based DAPT in terms of net clinical benefit in stabilised patients who did not have major ischaemic or bleeding events during the first month after an index acute

myocardial infarction.[15] If the non-inferiority is met, this kind of de-escalating antiplatelet strategy might possibly offer improved safety, better compliance, or reduced economic burden in the stabilised acute myocardial infarction population. Owing to the paucity of clinical evidence for the routine use of PFT and genotyping in stabilised patients with acute myocardial infarction,[16] and considering the situation that unguided de-escalation was not uncommon in clinical practice,[12,13,17] we adopted and tested a uniform unguided de-escalation antiplatelet strategy at the time of randomisation.

Methods

Study design

The TALOS-AMI trial was an investigator-initiated, prospective, open-label, multicentre, non-inferiority, assessor-masked, parallel group, randomised trial. Patients were enrolled at 32 institutes in South Korea. The trial rationale and design have been described previously.[15] In brief, we assumed that adoption of potent $P2Y_{12}$ inhibitor-based DAPT in the first month and then de-escalating DAPT thereafter would balance ischaemic and bleeding risks in patients with acute myocardial infarction. Accordingly, we designed a non-inferiority test to prove the similarity of the safety and efficacy of this de-escalation strategy to that of current guidelines. The College of Medicine of the Catholic University of Korea, Korea designed and sponsored the trial. The steering committee was responsible for doing the trial, integrity of data analysis, and reporting of the results. The protocol was approved by the institutional review board at each participating institute and all participants provided written informed consent. The present trial complied with the principles of the Declaration of Helsinki. An independent data and safety monitoring board provided external oversight to ensure the safety of the study participants. All events were adjudicated by an independent clinical event adjudication committee (CEAC) whose members were unaware of the trial group assignments. Members of the CEAC received medical records of adverse events after removal of any reference to the treatment group. All authors vouch for the adherence of the trial to the protocol and the accuracy and completeness of the data. The committee members, all participating centres, and investigators are listed in the appendix (p 4).

Participants

Patients with biomarker-positive acute myocardial infarction who underwent successful PCI by means of current generation drug-eluting stents and tolerated aspirin and ticagrelor treatment during an index admission were selected as candidates for this study. Only patients who provided informed consent were screened for completing the aspirin and ticagrelor treatment without major adverse ischaemic (myocardial infarction, stroke, or unplanned revascularisation) or bleeding events (defined in the exclusion criteria) during 1 month after acute myocardial infarction. Patients received guideline-directed medical therapy including statin or renin–angiotensin system blockade. The selected patients were randomly assigned to aspirin plus ticagrelor or aspirin plus clopidogrel groups until 12 months. The key exclusion criteria included cardiogenic shock, active bleeding of any major organs, bleeding diathesis or coagulopathy, gastrointestinal or genitourinary bleeding, and haemoptysis within 2 months. In addition, patients who had history of intracranial bleeding, intracranial aneurysm, arteriovenous malformation, or neoplasm were excluded. Detailed inclusion and exclusion criteria are presented in the appendix (p 14).

Randomisation and masking

All participants received a loading dose of ticagrelor (180 mg), and the patients naive to aspirin received a loading dose of aspirin (250–325 mg) before index PCI, and then were administered ticagrelor 90 mg twice a day and aspirin 100 mg daily thereafter for 30 days. At 30±7 days after an index PCI, eligible patients were randomly assigned in a 1:1 ratio to continue ticagrelor (active control group) or switched to clopidogrel 75 mg daily (de-escalation group) by oral route with the continuation of aspirin by an interactive web-based response system (IWRS Medical Excellence, South Korea). The randomisation sequence was created by an independent statistician using SAS 9.3 (SAS Institute, Cary, NC, USA) and stratified by study centre and type of acute myocardial infarction (ST-segment elevation myocardial infarction [STEMI] or non-ST-segment elevation myocardial infarction [NSTEMI]), with a 1:1 allocation by means of hidden random block size.

Procedures

In the de-escalation group, when switching from ticagrelor to clopidogrel, patients took 75 mg clopidogrel without the loading dose at the time of the next scheduled dose after the final dose of ticagrelor (eg, approximately 12 h from the last dose of ticagrelor). The steering committee decided this switching strategy of no loading dose on the basis of the hypothesis that our study population would be stable at the time of random assignment (30 days after index PCI) and de-escalation without the loading dose of clopidogrel commonly occurs in clinical practice.[11–14,17] The safety monitoring process for the switching protocol from ticagrelor to clopidogrel is detailed in the appendix (pp 16–17). After random assignment, patients continued the allocated medication for 11 months. Patients were scheduled to visit at 3, 6, and 12 months after the index PCI (11 months after randomisation). During the follow-up, the patients filled in a questionnaire regarding the occurrence of dyspnoea and any signs of bleeding and were monitored for any clinical events. The investigators followed-up the patients as necessary, either by office visits or by telephone contact. Drug adherence was assessed with manual pill counting.

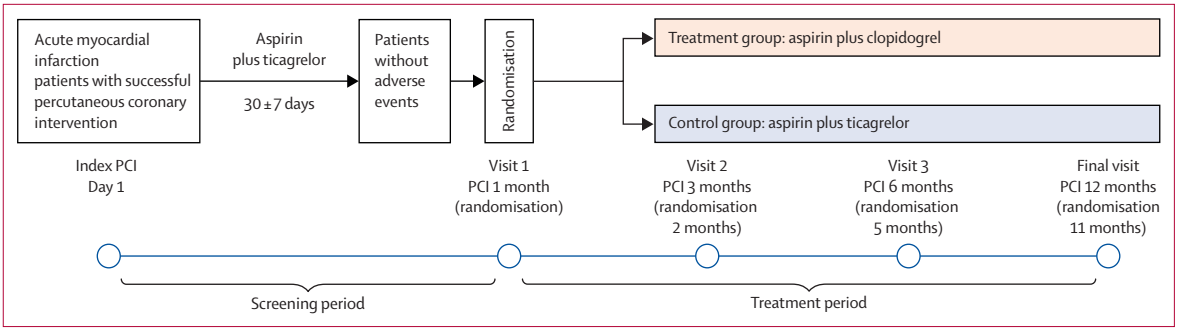

Figure 1: **Study design and groups**
The figure shows patients with acute myocardial infarction with successful percutaneous coronary intervention randomly assigned to acute control group or de-escalation group after 1 month of aspirin and ticagrelor. In the de-escalation group, patients received unguided de-escalation antiplatelet therapy. PCI=percutaneous coronary intervention.

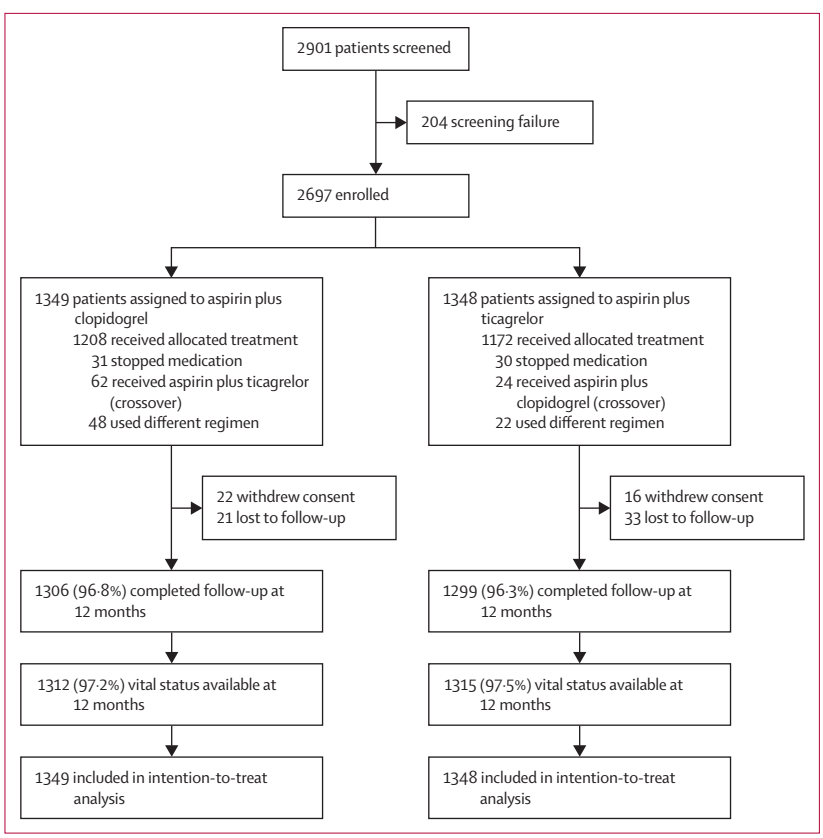

Figure 2: **Trial profile**

Outcomes

The primary endpoint was a net adverse clinical event, which is a composite of cardiovascular death, myocardial infarction, stroke, and bleeding type 2, 3, or 5 according to the Bleeding Academic Research Consortium (BARC) criteria,[18] from 1 to 12 months after an index PCI. The main secondary endpoints included a composite of cardiovascular death, myocardial infarction, and stroke; a composite of BARC bleeding type 2, 3, or 5; and a composite of cardiovascular death, myocardial infarction, stroke, and BARC bleeding type 3 or 5 between 1 and 12 months after the index PCI. Other secondary endpoints were individual components of the primary and main secondary endpoints, all-cause death, ischaemia-driven revascularisation, and stent thrombosis. Detailed definitions of all outcomes are provided in the appendix (p 22).

Statistical analysis

The sample size was selected on the basis of the combined occurrence rate of ischaemic and bleeding events between 1 and 12 months after acute myocardial infarction. On the basis of the results in the Study of Platelet Inhibition and Patient Outcomes (PLATO) trial,[3] we assumed that the expected event rate of the primary endpoint from 1 to 12 months after the index PCI was 9·35% in the active control group and 9·59% in the de-escalation group. Assuming an absolute difference in the event rate of the primary endpoint of 3·0% (which was equivalent to a 32% increase in the estimated event rate of the active control group) between groups, the non-inferiority margin by the hazard ratio (HR) was calculated as 1·34 (ln[1–0·1235]/ln[1–0·0935]). Then, the sample size was calculated with a one-sided α of 0·05 and a power of 80% (PASS 13, NCSS, Kaysville, UT, USA). After considering a rate of loss to follow-up of 10%, we calculated that at least 1295 patients per group and a total of 2590 patients would be needed to show non-inferiority. Additional information on the sample size calculation of the present study is described in the appendix (p 23).

Primary analysis of the primary endpoint was done in the intention-to-treat population with the use of a non-inferiority test by means of a stratified Cox proportional hazards model. The HR for de-escalation versus active control group in a stratified Cox proportional hazards model was assessed for non-inferiority by means of an HR margin of 1·34. If the upper limit of the one-sided 95% CI of the HR was less than the prespecified non-inferiority margin, the de-escalation group therapy was considered non-inferior to the active control group therapy. If the requirement for non-inferiority was met, its superiority was subsequently tested. Cumulative

	De-escalation group (n=1349)	Active control group (n=1348)
Age, years	60·1 (11·3)	59·9 (11·4)
≥75	157 (11·6%)	164 (12·2%)
Female sex	217 (16·1%)	237 (17·6%)
Male sex	1132 (83·9%)	1111 (82·4%)
Body-mass index*, kg/m²	24·6 (3·1)	24·5 (3·1)
Cardiovascular risk factors		
Hypertension	655 (48·6%)	663 (49·2%)
Diabetes	362 (26·8%)	369 (27·4%)
Diabetes treated with insulin	28 (2·1%)	28 (2·1%)
Dyslipidaemia	563 (41·7%)	556 (41·2%)
Current smoker	670 (49·7%)	674 (50·0%)
Impaired renal function†	160 (12·1%)	145 (10·9%)
Past medical history		
Previous percutaneous coronary intervention	61 (4·5%)	60 (4·5%)
Previous coronary artery bypass graft	3 (0·2%)	1 (0·1%)
Previous cerebrovascular accident	53 (3·9%)	50 (3·7%)
Clinical presentation		
STEMI	734 (54·4%)	721 (53·5%)
NSTEMI	615 (45·6%)	627 (46·5%)
Left ventricular ejection fraction <40%	103/1325 (7·8%)	93/1304 (7·1%)

Data are n (%) or mean SD. NSTEMI=non-ST-segment elevation myocardial infarction. STEMI=ST-segment elevation myocardial infarction. *The body-mass index is the weight in kilograms divided by the square of the height in metres. †Impaired renal function was defined as an estimated glomerular filtration rate of less than 60 mL/min per 1·73 m² of body-surface area at presentation.

Table 1: **Baseline characteristics**

	De-escalation group (n=1349)	Active control group (n=1348)
Access site		
Radial	666 (49·4%)	686 (51·0%)
Femoral	667 (49·4%)	644 (47·8%)
Glycoprotein IIb–IIIa inhibitor	322 (23·9%)	322 (23·9%)
Infarct related artery (culprit)		
Left main coronary artery	21 (1·6%)	24 (1·8%)
Left anterior descending artery	685 (50·8%)	634 (47·1%)
Left circumflex artery	202 (15·0%)	264 (19·6%)
Right coronary artery	440 (32·6%)	424 (31·5%)
Number of treated vessels	1·3 (0·6)	1·3 (0·6)
Multivessel treatment		
2 vessels	300 (22·2%)	322 (23·9%)
3 vessels	71 (5·3%)	61 (4·5%)
Number of stents for infarct-related artery	1·2 (0·4)	1·2 (0·4)
Total stent length of infarct-related artery, mm	29·8 (13·2)	29·6 (13·8)
Stent diameter of infarct-related artery, mm	3·2 (0·4)	3·2 (0·5)
Optical coherence tomography	47 (3·5%)	35 (2·7%)
Intravascular ultrasonography	333 (24·9%)	307 (23·1%)

*Data are n (%) or mean (SD).

Table 2: **Procedural characteristics of the intention-to-treat population**

event rates for the primary and secondary endpoints were estimated by the Kaplan-Meier method and compared by log-rank tests. HR and 95% CI were calculated with stratified Cox hazard regression analysis for primary and secondary endpoints. The stratification factor was the presence of STEMI. The proportional hazards assumption was confirmed by the Schoenfeld residuals and supremum tests. We did not detect any substantial violations. To ensure statistical robustness, additional analyses were also done in the per-protocol and as-treated populations. A sensitivity analysis was done including a complete case, a best case, and a worst case for the patients who were lost to follow-up or withdrawn from the trial. Continuous variables are presented as the mean (SD) and were compared by means of Student's *t* test. Categorical variables are presented as frequencies (percentage) and were compared by means of the χ^2 test or Fisher's exact test. Prespecified subgroup analyses included clinical presentation of acute myocardial infarction, sex, age, diabetes, left ventricular ejection fraction of less than 40%, estimated glomerular filtration rate, stent length, and multivessel treatment. A test for interaction was used to establish whether the relative effects of study treatments vary significantly between subgroups. No imputation was used to infer missing values. Those with missing primary and secondary endpoint data were censored at the time of withdrawal of consent or loss to follow-up. The analysis was done with SAS (version 9.4). This trial is registered at ClinicalTrials.gov, NCT02018055.

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.

Results

From Feb 26, 2014, to Dec 31, 2018, a total of 2901 patients with acute myocardial infarction who provided informed consent were screened after successful PCI. Of these, 204 patients were excluded before random assignment, and 2697 patients were randomly assigned to receive either clopidogrel plus aspirin (de-escalation group) or ticagrelor plus aspirin (active control group) at 1 month after index PCI (figure 1). Of the 1349 patients assigned to the de-escalation group, 1208 received the allocated treatment during the study period: 31 stopped antiplatelet medication, 62 received ticagrelor plus aspirin, and 48 used other antiplatelet regimens. Of the 1348 patients

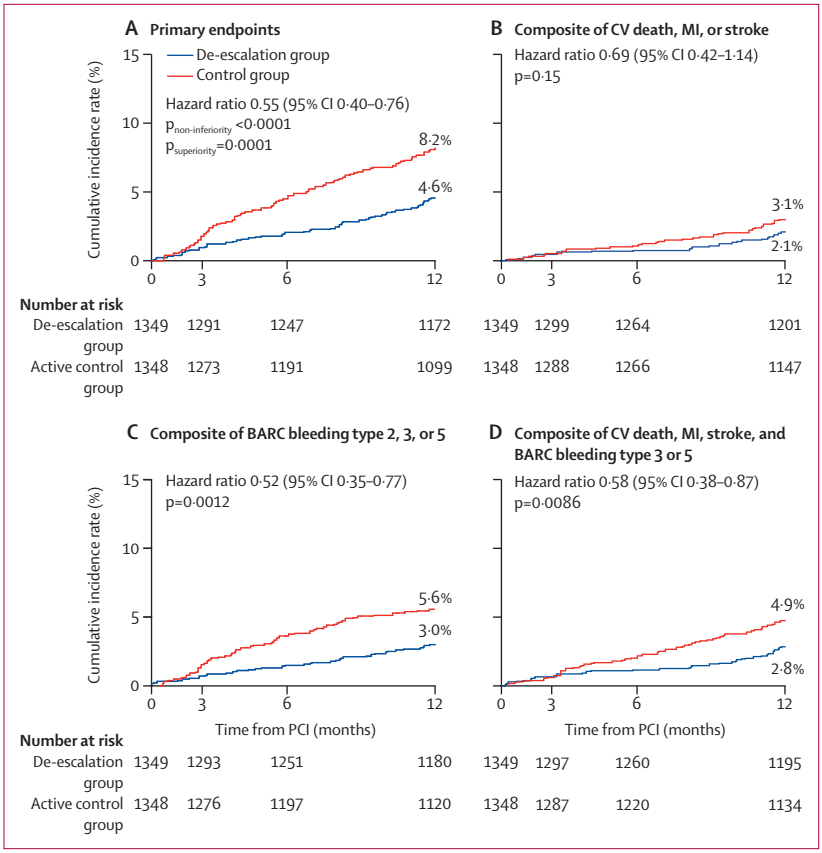

Figure 3: **Kaplan-Meier estimates**
Estimates for the primary endpoints—a composite of CV death, MI, stroke, and BARC bleeding type 2, 3, or 5 from 1 to 12 months after PCI (A), the key secondary endpoints: composite of CV death, MI, or stroke (B), composite of BARC bleeding type 2, 3, or 5 (C), and composite of CV death, MI, stroke, and BARC bleeding type 3, or 5 (D). The hazard ratio shown is for the de-escalation versus active control group. CV=cardiovascular. MI=myocardial infarction. BARC=Bleeding Academic Research Consortium. PCI=percutaneous coronary intervention.

assigned to the active control group, 1172 received the allocated treatment during the study period: 30 stopped antiplatelet medications, 24 patients received clopidogrel plus aspirin, and 22 used different antiplatelet regimens (figure 2). The first patient was randomly assigned on Feb 26, 2014, and the last on Dec 31, 2018. Ascertainment of the primary endpoint was complete in 2605 (96·5%) of 2697 patients who underwent random assignment, and data on vital status were obtained for 2627 (97·4%) patients (figure 2).

Demographic, clinical, and procedural data were similar between the two groups; among the enrolled patients, the mean age was 60 years (SD 11·4), 454 (16·8%) were female, 731 (27·1%) had diabetes, 1318 (48·9%) had hypertension, and 1455 (53·9%) presented with STEMI (table 1). Lesion and procedural characteristics were also similar between the two groups; PCI was done by radial access in 1352 (50·1%), left anterior descending artery was an infarct-related artery in 1319 (48·9%), and multivessel treatment was done in 754 (28·0%) enrolled patients. Detailed procedural characteristics are shown in table 2. Adherence to the study medication after random assignment was similar in both groups (97·3% *vs* 98·4% at 12 months after index PCI; appendix p 32). Within 2 weeks after switching (randomisation) from ticagrelor to clopidogrel without a loading dose, there were no deaths or stent thrombosis, except one case of non-target lesion myocardial infarction (not stent thrombosis) reported 5 days after switching to clopidogrel. In the active control group, there were no ischaemic events during the 2 weeks after randomisation.

At 12 months, the primary endpoint (composite of cardiovascular death, myocardial infarction, stroke, and BARC bleeding type 2, 3, or 5) occurred in 59 (4·6%) in the de-escalation group and 104 (8·2%) patients in the active control group ($p_{non\text{-}inferiority}$<0·001; HR 0·55 [95% CI 0·40–0·76], $p_{superiority}$=0·0001). The requirements for both non-inferiority and superiority were met in the intention-to-treat population as well as in the per-protocol and as-treated populations (appendix p 33). The Kaplan-Meier curves for the primary outcome are presented in figure 3A.

There was no significant difference in the composite of cardiovascular death, myocardial infarction, and stroke between the de-escalation and active control groups (27 [2·1%] *vs* 38 [3·1%]; HR 0·69, 95% CI 0·42–1·14, p=0·15; table 3, figure 3B). By contrast, a composite of BARC bleeding type 2, 3, or 5 occurred significantly less frequently in the de-escalation group than in the active control group (38 [3·0%] *vs* 71 [5·6%]; HR 0·52, 95% CI 0·35–0·77, p=0·0012; table 3, figure 3C). Furthermore, a composite of BARC bleeding type 3 or 5 occurred less frequently in the de-escalation group than in the active control group, which was marginally significant (15 [1·2%] *vs* 28 [2·3%]; HR 0·53, 95% CI 0·28–0·99; p=0·048). Even a composite of cardiovascular death, myocardial infarction, stroke, and BARC bleeding 3 or 5 occurred significantly less frequently in the de-escalation group compared with the active control group (36 [2·8%] *vs* 61 [4·9%]; HR 0·58, 95% CI 0·38–0·87; p=0·0086; table 3, figure 3D). In the individual outcomes, there was no significant difference in cardiovascular death, death from any cause, myocardial infarction, stroke, ischaemia-driven revascularisation, or stent thrombosis between the two groups (appendix p 34). Landmark analysis was done at 6 months from an index PCI (5 months from randomisation) and 6 months to 12 months in terms of composite of BARC 2, 3, or 5 bleeding. Bleeding events occurred less frequently within the first 6 months in the de-escalation group (HR 0·37, 95% CI 0·27–0·69, p=0·0004) but the difference was mitigated after 6 months (appendix p 48)

The HRs for the primary endpoint were consistent across the prespecified subgroups (figure 4). Sensitivity analyses done for the patients who were lost to follow-up and withdrew consent exhibited consistent results regardless of the imputation methods, confirming the robustness of the primary analysis (appendix p 29).

Discussion

The TALOS-AMI trial is the first large-scale randomised, controlled trial investigating the efficacy and safety of a uniform, unguided de-escalation from ticagrelor to clopidogrel in stabilised patients with acute myocardial infarction without major ischaemic or bleeding events during the first month after an index PCI. Key findings from the current study are that the adoption of an unguided de-escalation DAPT strategy of switching from ticagrelor to clopidogrel 1 month after a myocardial infarction was non-inferior and even superior to the ticagrelor-based continuing standard DAPT. The uniform, unguided de-escalation DAPT strategy was associated with 45% lower risk of net clinical benefits for the next 11 months than the ticagrelor-based DAPT strategy. The absolute risk reduction was 3·6%, which was mainly attributed to a significant decrease in bleeding risk.

Unguided de-escalation of DAPT from potent $P2Y_{12}$ inhibitors to clopidogrel after the acute phase in patients with acute myocardial infarction commonly occurs in clinical practice despite the absence of large-scale randomised trial data.[12–14,17] The potential reasons for the de-escalation from potent $P2Y_{12}$ inhibitors to clopidogrel are concerns regarding bleeding during potent $P2Y_{12}$ inhibitor treatment, medication costs,[14] and side-effects, such as dyspnoea in the case of ticagrelor.[13] Various approaches to finding an optimal strategy for balancing ischaemic and bleeding risks in patients with acute coronary syndrome have been tested, including early-stage potent $P2Y_{12}$ inhibitor monotherapy,[19,20] dose reduction of a potent $P2Y_{12}$ inhibitor,[21] and guided[8,9] or unguided[11] switching from potent $P2Y_{12}$ inhibitors to clopidogrel. Although a direct comparison among these approaches might be difficult owing to substantial differences in the study design, population, and definitions of bleeding and ischaemic events, the unique characteristics of our study design and population need to be addressed. First, we adopted a uniform, unguided de-escalation antiplatelet treatment strategy without the guidance of PFT or *CYP2C19* genotyping and showed its superiority to continuing the standard DAPT. Second, our study population was based on acute myocardial infarction and included a larger proportion of patients with STEMI who are usually younger and have fewer comorbidities and fewer multivessel diseases than patients with non-ST elevation-acute coronary syndrome,[22] similar to the population of the TROPICAL-ACS trial in which patients with STEMI showed a greater benefit from DAPT de-escalation than patients with NSTEMI.[8] Third, the randomisation was done beyond the acute phase of acute myocardial infarction in uncomplicated patients without major ischaemic or bleeding events who tolerated aspirin plus ticagrelor treatment for 1 month after an index PCI. This kind of randomisation is well reflected in the ischaemic event incidence rate of our study population. The overall incidences of the primary endpoint events of the active control group in our trial were slightly lower than the estimated rates inferred from the PLATO trial (8·2% *vs* 9·35% in the active control group).[3] This was primarily driven by fewer ischaemic events than expected (observed *vs* estimated rate, 3·1% *vs* 5·28% in the active control group). The observed incidence of bleeding events was close to the estimated event rate (5·6% *vs* 4·07% in the active control group). There are several plausible explanations for a lower-than-expected incidence of the primary endpoint events.

	De-escalation group (n=1349)	Active control group (n=1348)	Hazard ratio (95% CI)	p value†
Primary endpoints				
Composite of cardiovascular death, mycocardial infarction, stroke, and BARC bleeding type 2, 3, or 5	59 (4·6%)	104 (8·2%)	0·55 (0·40–0·76)	$p_{non\text{-}inferiority}$<0·001 $p_{superiority}$=0·0001
Secondary endpoints				
Main secondary endpoints				
Composite of cardiovascular death, myocardial infarction, or stroke	27 (2·1%)	38 (3·1%)	0·69 (0·42–1·14)	0·15
Composite of BARC bleeding type 2, 3, or 5	38 (3·0%)	71 (5·6%)	0·52 (0·35–0·77)	0·0012
Composite of BARC bleeding type 3 or 5	15 (1·2%)	28 (2·3%)	0·53 (0·28–0·99)	0·046
BARC bleeding type 2	27 (2·1%)	50 (3·9%)	0·53 (0·33–0·85)	0·0080
BARC bleeding type 3	15 (1·2%)	28 (2·3%)	0·53 (0·28–0·99)	0·046
BARC bleeding type 5	1 (<1%)	0	2·95 (0·03–271·44)	0·64
Composite of cardiovascular death, myocardial infarction, stroke, and BARC bleeding type 3 or 5	36 (2·8%)	61 (4·9%)	0·58 (0·38–0·87)	0·0086
Other secondary endpoints				
All-cause death	11 (0·9%)	10 (0·8%)	1·07 (0·45–2·52)	0·88
Cardiovascular death	6 (0·5%)	6 (0·5%)	0·98 (0·32–3·03)	0·97
Myocardial infarction				
Any myocardial infarction	12 (1·0%)	20 (1·6%)	0·59 (0·29–1·21)	0·15
Spontaneous	9 (0·7%)	14 (1·1%)	0·64 (0·28–1·47)	0·29
Periprocedural	3 (0·2%)	6 (0·5%)	0·52 (0·13–2·06)	0·35
Target vessel myocardial infarction	7 (0·6%)	8 (0·7%)	0·86 (0·31–2·36)	0·76
Stroke	9 (0·7%)	13 (1·0%)	0·69 (0·29–1·61)	0·39
Ischaemia-driven revascularisation (percutaneous coronary intervention or coronary artery bypass graft)				
Target lesion revascularisation	14 (1·1%)	9 (0·7%)	1·48 (0·64–3·42)	0·36
Target vessel revascularisation	17 (1·4%)	17 (1·4%)	0·97 (0·50–1·90)	0·93
Any revascularisation	32 (2·6%)	39 (3·2%)	0·80 (0·50–1·27)	0·34
Stent thrombosis	3 (0·2%)	3 (0·2%)	0·97 (0·20–4·80)	0·97

Data are n (Kaplan-Meier estimates, %). BARC=Bleeding Academic Research Consortium. *The intention-to-treat population included all patients in the trial who were randomly assigned. Percentages indicate patients who had an event at 335 days after randomisation (365 days after the index percutaneous coronary intervention). †The primary endpoint was analysed by non-inferiority test. After the primary endpoints passed non-inferiority test, a superiority test was done. Absolute difference was −3·6 percentage points. The primary endpoints met both the non-inferiority and superiority test. p value was calculated using the Com-Nougue approach Z statistic with SE estimated by Greenwood's formula.

Table 3: **Primary and secondary outcomes (intention-to-treat population)***

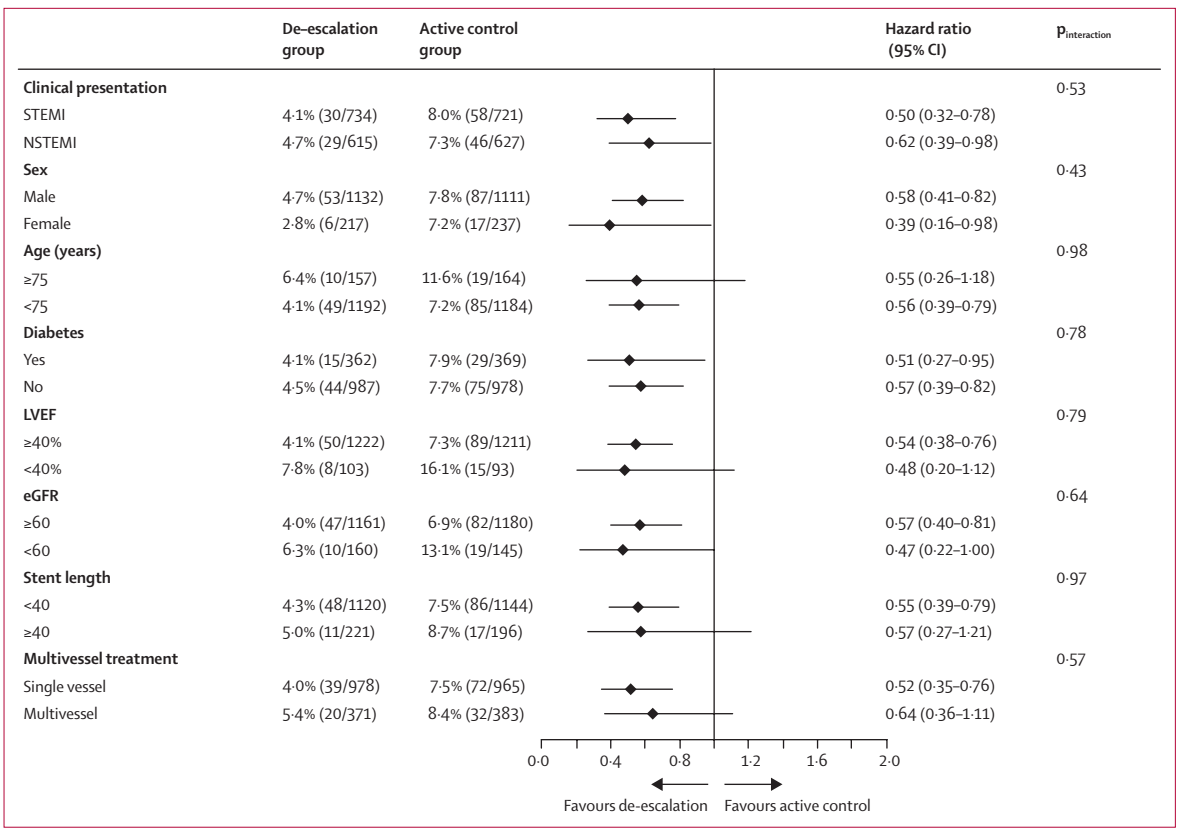

Figure 4: **Subgroup analysis**
Subgroup analysis of the primary endpoint in prespecified subgroups of the present study population. STEMI=ST-segment elevation myocardial infarction. NSTEMI=non-ST-segment elevation myocardial infarction. LVEF=left ventricular ejection fraction. eGFR=estimated glomerular filtration rate.

Randomisation, not at the time of an index PCI, but after 1 month, might partly explain the lower incidence of ischaemic events. Since we enrolled stabilised patients with acute myocardial infarction who had no major ischaemic or bleeding complications during 1 month after an index PCI, the early ischaemic events within 30 days after the index PCI were not included in the analysis. However, the incidence of ischaemic outcomes 1–12 months after an index event in the active control group of this trial was similar to those of other de-escalation trials. The event rates of a composite of cardiovascular death, myocardial infarction, or stroke from 1 to 12 months in the standard treatment group which used potent $P2Y_{12}$ inhibitors were 3·1% in the TALOS-AMI trial, 2·1% in the TROPICAL-ACS[8] trial (rates were estimated from Kaplan-Meier survival curves of the published article under the corresponding author's permission), and 1·1% in the HOST-REDUCE-POLYTECH-ACS trial[21] (directly adopted from the original article). In the TWILIGHT-ACS population, the incidence of a composite of cardiovascular death, myocardial infarction, or stroke from randomisation 3–12 months after an index event was 3·3% (provided by the authors). Notably, any type of de-escalation strategies in these trials did not increase ischaemic events. The coronary stent performance (current generation drug-eluting stents were predominantly used in our study), procedural skills, and equipment have evolved over the study period compared with the time when the PLATO study was done. In the PLATO study,[3] only 60% of the population underwent PCI, 40% of patients with PCI received bare-metal stent, and older generation drug-eluting stents were implanted. The frequent use of intravascular imaging at the time of the procedure which is associated with high quality of stent deployment is another plausible explanation. Given these specific characteristics, our results should be carefully applied to real-world patients with acute myocardial infarction, and thus the uncomplicated, stabilised, and ticagrelor-tolerated population of patients with acute myocardial infarction would be good candidates for unguided de-escalation therapy with aspirin plus clopidogrel.

With regard to de-escalation of DAPT in patients with acute coronary syndrome, the current guidelines only offer the option to de-escalate in patients who are deemed unsuitable for potent platelet inhibition.[1] In clinical practice, de-escalation from potent $P2Y_{12}$ inhibitors to clopidogrel might be done without guidance based on clinical judgement[11–14] or with guidance based on PFT[8] or *CYP2C19* genotyping[9] in patients with acute coronary

syndrome. Although the unguided de-escalation strategy has already been used by many physicians when treating patients with acute coronary syndrome with PCI, dedicated large-scale trials on a uniform unguided DAPT de-escalation that reflect the real-world clinical situation are lacking, and the available data are contradictory.[11,12] Although PFT or genotyping-guided de-escalation antiplatelet therapy showed non-inferiority to the standard DAPT with a potent $P2Y_{12}$ inhibitor,[8,9] these trials failed to provide strong evidence supporting the routine use of PFT or *CYP2C19* genotyping in patients with acute coronary syndrome. Therefore, the expert consensus recommends that PFT or genotype-guided de-escalation be considered only in specific clinical scenarios such as in cases of bleeding events, a high bleeding risk, and socioeconomic indications in patients with acute coronary syndrome.[23] A systematic review and meta-analysis paper comparing the safety and efficacy of guided versus standard antiplatelet therapy showed that PFT-guided or genotyping-guided treatment approach (either escalation or de-escalation) was associated with a reduction of ischaemic events and minor bleeding in patients undergoing PCI.[10] However, among 14 studies in this meta-analysis, only three clinical trials were on de-escalation from a potent $P2Y_{12}$ inhibitor to clopidogrel. Although the overall results of guided antiplatelet therapy were promising, its adoption into clinical practice has several hurdles, including lack of widespread availability of PFT or genotyping, result-variability of PFT over time and across different devices, and an impractical approach for patient routines.[24] Although the clinical usefulness of potent $P2Y_{12}$ inhibitor monotherapy following short DAPT in patients with acute coronary syndrome is emerging,[19] few data exist on the comparison between potent $P2Y_{12}$ inhibitor monotherapy and de-escalating DAPT after the acute phase in patients with pure acute myocardial infarction. Current guidelines still recommend continuing DAPT for at least 12 months in patients with acute myocardial infarction.[16] In this regard, this TALOS-AMI trial provides strong clinical evidence for the usefulness of a uniform, unguided DAPT de-escalation strategy after the acute phase of acute myocardial infarction, which is more practical and feasible than a guided de-escalation strategy or potent $P2Y_{12}$ inhibitor monotherapy in clinical practice.

To our knowledge, this is the first large-scale trial revealing the safety of switching from ticagrelor to clopidogrel without a clopidogrel loading dose in patients with acute myocardial infarction beyond the acute phase. The current clinical practice guidelines offer no clear recommendations on when and how to administer a loading dose when de-escalating ticagrelor to clopidogrel. One expert consensus has given a recommendation based on pharmacodynamics studies.[25] According to this, when de-escalating ticagrelor to clopidogrel, a 600 mg loading dose at 24 h after the last dose of ticagrelor is recommended. However, data from registries showed that switching from potent $P2Y_{12}$ inhibitors to clopidogrel without a loading dose both in the hospital[13] and after hospital discharge was not uncommon,[12,14,17] despite a potential ischaemic risk due to possible increased platelet activity when switching. In this study, we did not observe any clustering of thrombotic events during the early period of switching as mentioned in the results when ticagrelor was switched to clopidogrel without a loading dose in the de-escalation group. It is well known that the prevalence of *CYP2C19* loss-of-function alleles, which is associated with high on-treatment platelet reactivity, is significantly greater in east Asians than in the white population.[26] Given this specific genetic profile, it is noteworthy that the occurrence of ischaemic events was very rare when switching from ticagrelor to clopidogrel without a loading dose after the acute phase in acute myocardial infarction. This can be partially explained by the stable condition of patients at the time of random assignment due to time-dependent risk diminution after a successful PCI.[11]

This study was done only in South Korea and thus included only east Asian patients, which makes the generalisability of our results unclear. Caution is needed when extrapolating these results to regions outside South Korea. However, despite the higher prevalence of the *CYP2C19* loss-of-function alleles in east Asians,[26] this study showed the clinical safety of switching from ticagrelor to clopidogrel in this population, suggesting the potential of applying this de-escalation strategy to patients with acute myocardial infarction of other ethnicities. In addition, reviewing studies undergoing unguided de-escalation of switching from potent $P2Y_{12}$ inhibitors to clopidogrel in western Europeans might provide a possibility that this kind of strategy can be carefully applied to other ethnic populations as well. In the TOPIC trial, which was a small randomised trial done in France, and which showed similar results to those of our study, unguided de-escalation to aspirin plus clopidogrel was associated with a reduction in bleeding complications without an increase in ischaemic events in patients who have been event-free for the first month after an acute coronary syndrome on a combination of aspirin plus a potent $P2Y_{12}$ inhibitor, although with important limitations.[11] The TRANSLATE-ACS study also showed that in-hospital or post-discharge (a median of 50 days) switching from potent $P2Y_{12}$ inhibitors to clopidogrel occurred in about 10% of patients with acute myocardial infarction, and was not associated with increased ischaemic or bleeding events.[13,17] When de-escalating a $P2Y_{12}$ inhibitor in the early period of just after an index event (<30 days), PFT-guided or genotyping-guided de-escalation strategy might be needed to reduce the potential risk of ischaemic events because the risk of thrombotic events during the acute period of acute myocardial infarction is very high. In this perspective, the TROPICAL-ACS[8] and POPular-Genetics[9] trials showed the usefulness of a guided de-escalation strategy during the acute period of acute coronary syndrome.

Alternatively, after the acute period of acute myocardial infarction (>30 days), ischaemic risks decrease but bleeding risks increase over time. Hence, in the maintenance phase, the role of PFT or genotyping guidance might be insufficient for de-escalating $P2Y_{12}$ inhibitors. In this regard, this study differs from other de-escalation studies by randomly assigning stabilised patients with acute myocardial infarction at 30 days after an index PCI. Therefore, taken together, we cautiously speculate that adopting an unguided de-escalation strategy of $P2Y_{12}$ inhibitor in stabilised and uncomplicated patients with acute myocardial infarction after acute phase might be a safe and feasible treatment strategy regardless of ethnicities. However, large-scale randomised trials enrolling other ethnicities are needed to confirm our findings in a non-east Asian population.

The current study has several limitations. First, this trial was open-label and not placebo-controlled, which could have resulted in bias. However, all clinical events were assessed by an independent event adjudication committee, who were masked to the treatment allocations. Periodic monitoring was done in more than 90% of the enrolled cases and regular investigator meetings were held to ensure site investigators' adherence to the study protocol. The vital status of patients who were lost to follow-up was checked on the basis of national databases. The presence of masking in clinical trials might affect the compliance rate and percentages of patients lost to follow-up. However, this TALOS-AMI trial showed similarly high compliance rate and low percentages of patients lost to follow-up between de-escalation and active control groups. Accordingly, it is assumed that the open-label design of this trial would not have a significant effect on the outcome. Second, the non-inferiority margin of HR 1.34 seemed to be wide and a one-sided α of 0·025 would be preferable in the non-inferiority trial. We chose the non-inferiority margin in accordance with clinical judgement, the feasibility of study recruitment, and the non-inferiority margin of available antithrombotic trials at the time of study design. The steering committee decided that the non-inferiority margin in our study should be less than a 40% increase compared with the expected event rate of the control group on the basis of the non-inferiority margin of two available contemporary trials of antiplatelet treatment.[27,28] After considering clinically acceptable relevance and the feasibility of study recruitment, we finally selected the non-inferiority margin for HR of 1·34, which was equivalent to an absolute difference of 3·0% and a 32% increase in the expected event rate. In the previous major trials on antithrombotic therapy, the non-inferior margin was equivalent to a 20–60% increase in the expected event rate.[27–30] In addition, published TROPICAL-ACS (30%)[8] and SMART-CHOICE (45%)[31] trials also adopted a relatively wide non-inferiority margin. Hence, we think that the non-inferiority margin of the current trial is not exceptionally wide but is within a similar range compared with that of the previous major trials. Furthermore, if we input the actual observed values of the present study, our results still meet non-inferiority criteria ($p<0·001$) when we use a non-inferiority margin for HR of 1·11 (equivalent to an absolute difference of 1·0%) and a one-sided α of 0·05; post-hoc power is 96% when we use a non-inferiority margin for HR of 1·34 (equivalent to an absolute difference of 3·0%) and a one-sided α of 0·025. Of note, the results of our sensitivity analysis show that the worst-case analysis does not meet superiority, which suggests that the interpretation of our study needs caution, especially in patients at high cardiovascular risk. According to the Consolidated Standards of Reporting Trials statement of non-inferiority and equivalence in trials,[32] a one-sided α of 0·05 is acceptable in non-inferiority clinical trials. Moreover, of the 110 CV non-inferiority trials published in *JAMA*, *The Lancet*, or the *New England Journal of Medicine* from 1990 to 2016, the one-sided α was 0·05 in 66 trials.[33] Third, including less severe BARC type 2 bleeding in a net clinical outcome might bias results in favour of the de-escalation group. Indeed, BARC type 2 bleeding might not have the same weight as death, myocardial infarction, or stroke. However, because BARC type 2 bleeding implies an actionable sign of haemorrhage requiring intervention or hospitalisation,[18] this event can be associated with medication change and poor treatment compliance. Hence, although BARC 2 bleeding events might not be life threatening, they might have important effects on treatment adherence and this might translate into poor clinical outcomes and high health-care costs.[34] In addition, when compared with BARC 3 and higher bleeding, the predictive power of BARC 2 for 1-year mortality after PCI was quite similar in the previous studies.[35] Moreover, several trials of de-escalating DAPT have also included BARC type 2 bleeding as a component of net clinical outcomes.[8,11,21] Fourth, we did not do PFT or genotyping during the study conduct. Genotyping for clopidogrel metabolism as a prespecified subgroup analysis is scheduled for the investigation of the clinical effect of *CYP2C19* loss-of-function alleles in stabilised patients with acute myocardial infarction. Fifth, we solely used ticagrelor for potent $P2Y_{12}$ inhibition. Of note, the ISAR-REACT 5 study has shown a superiority of prasugrel over ticagrelor for patients with acute coronary syndrome with planned invasive management.[36] For this reason, the European Society of Cardiology updated its Non-ST-segment Elevation-acute coronary syndrome 2020 guidelines by adding a COR IIa LOE B recommendation to prefer prasugrel over ticagrelor for acute coronary syndrome treated with PCI.[37] However, this study lacked a prasugrel-treated group, and thus to what extent our findings can be extrapolated to prasugrel remains unclear. Sixth, in the subgroup analysis, whereas patients with single vessel treatment favoured a de-escalation strategy, those with multivessel treatment did

not show this trend, although interaction was not observed. However, patients with multivessel treatment amounted to only 371 (27·5%) in the de-escalation and 383 (28·4%) in the active control groups. Thus, the results of this TALOS-AMI trial have a limitation in applying a de-escalation strategy to patients with acute myocardial infarction with multivessel disease or complex lesions. In this regard, the de-escalation of ticagrelor monotherapy in patients with acute coronary syndrome with multivessel PCI might be another promising option to balance ischaemic and bleeding risks in this population.[38] Lastly, the reported DAPT adherence rates seemed rather high. Of the several methods to assess medication adherence, we chose the pill count method because it was easy to do and known to correlate with electronic medication monitors. However, it does not accurately capture the exact timing of medication and can be manipulated by patients.[39] In addition, some patients did a telephone interview instead of an outpatient clinic visit. Therefore, medication adherence should be cautiously interpreted. However, those who well tolerated DAPT during the first month after acute myocardial infarction were enrolled in this study, which might contribute to high adherence rate in this study.

In conclusion, a uniform, unguided de-escalation DAPT strategy switching from ticagrelor to clopidogrel in stabilised patients with acute myocardial infarction who had no major ischaemic or bleeding events during the first month after an index PCI was superior to the ticagrelor-based continuing DAPT strategy in terms of net clinical benefit, with a significant decrease in bleeding risk and no increase in ischaemic risk. However, findings from this study should be confined to uncomplicated, stabilised patients with acute myocardial infarction undergoing PCI. In patients with acute myocardial infarction with complex lesions, major adverse events in the acute phase, ticagrelor intolerance, or only medical treatment, this kind of de-escalation strategy cannot be extrapolated.

Contributors

KC, CJK, M-WP, YA, and MCK conceived and designed the study. KC, CJK, M-WP, HWY, E-HC, KYL, and B-HH accessed and verified the data. HWY did statistical analyses. KC, CJK, M-WP, YA, and MCK participated in the steering committee, and contributed to implementation of the study. KC, CJK, and M-WP wrote the first draft and submitted the final version for publication. All authors participated in enrolment of patients, did clinical follow-up, have reviewed the article, and agreed with the content and conclusions. KC and YA were responsible for the decision to submit the manuscript. KC, CJK, M-WP, MCK, and YA had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Declaration of interests

KC has received researched grants from Chongkundang Pharm, Medtronic, Abbott, and Boston Scientific. CJK has received research grants and speaker's fees from Chongkundang Pharm.

Data sharing

The TALOS-AMI trial plans to continue follow-up for an additional 2 years, which will end in December, 2021. Until then, no participant data will be available. Relevant enquiries should be emailed to the corresponding author (kiyuk@catholic.ac.kr).

Acknowledgments

This study was supported by ChongKunDang Pharm, Medtronic, Abbott, and Boston Scientific.

References

1 Collet JP, Thiele H, Barbato E, et al. 2020 ESC Guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation. *Eur Heart J* 2021; **42:** 1289–367.

2 Wiviott SD, Braunwald E, McCabe CH, et al. Prasugrel versus clopidogrel in patients with acute coronary syndromes. *N Engl J Med* 2007; **357:** 2001–15.

3 Wallentin L, Becker RC, Budaj A, et al. Ticagrelor versus clopidogrel in patients with acute coronary syndromes. *N Engl J Med* 2009; **361:** 1045–57.

4 Morrow DA, Wiviott SD, White HD, et al. Effect of the novel thienopyridine prasugrel compared with clopidogrel on spontaneous and procedural myocardial infarction in the Trial to Assess Improvement in Therapeutic Outcomes by Optimizing Platelet Inhibition with Prasugrel-Thrombolysis in Myocardial Infarction 38: an application of the classification system from the universal definition of myocardial infarction. *Circulation* 2009; **119:** 2758–64.

5 Velders MA, Abtan J, Angiolillo DJ, et al. Safety and efficacy of ticagrelor and clopidogrel in primary percutaneous coronary intervention. *Heart* 2016; **102:** 617–25.

6 Becker RC, Bassand JP, Budaj A, et al. Bleeding complications with the P2Y12 receptor antagonists clopidogrel and ticagrelor in the PLATelet inhibition and patient Outcomes (PLATO) trial. *Eur Heart J* 2011; **32:** 2933–44.

7 Antman EM, Wiviott SD, Murphy SA, et al. Early and late benefits of prasugrel in patients with acute coronary syndromes undergoing percutaneous coronary intervention: a TRITON-TIMI 38 (TRial to Assess Improvement in Therapeutic Outcomes by Optimizing Platelet InhibitioN with Prasugrel-Thrombolysis In Myocardial Infarction) analysis. *J Am Coll Cardiol* 2008; **51:** 2028–33.

8 Sibbing D, Aradi D, Jacobshagen C, et al. Guided de-escalation of antiplatelet treatment in patients with acute coronary syndrome undergoing percutaneous coronary intervention (TROPICAL-ACS): a randomised, open-label, multicentre trial. *Lancet* 2017; **390:** 1747–57.

9 Claassens DMF, Vos GJA, Bergmeijer TO, et al. A Genotype-guided strategy for oral $P2Y_{12}$ inhibitors in primary PCI. *N Engl J Med* 2019; **381:** 1621–31.

10 Galli M, Benenati S, Capodanno D, et al. Guided versus standard antiplatelet therapy in patients undergoing percutaneous coronary intervention: a systematic review and meta-analysis. *Lancet* 2021; **397:** 1470–83.

11 Cuisset T, Deharo P, Quilici J, et al. Benefit of switching dual antiplatelet therapy after acute coronary syndrome: the TOPIC (timing of platelet inhibition after acute coronary syndrome) randomized study. *Eur Heart J* 2017; **38:** 3070–78.

12 De Luca L, D'Ascenzo F, Musumeci G, et al. Incidence and outcome of switching of oral platelet P2Y12 receptor inhibitors in patients with acute coronary syndromes undergoing percutaneous coronary intervention: the SCOPE registry. *EuroIntervention* 2017; **13:** 459–66.

13 Bagai A, Peterson ED, Honeycutt E, et al. In-hospital switching between adenosine diphosphate receptor inhibitors in patients with acute myocardial infarction treated with percutaneous coronary intervention: insights into contemporary practice from the TRANSLATE-ACS study. *Eur Heart J Acute Cardiovasc Care* 2015; **4:** 499–508.

14 Motovska Z, Hlinomaz O, Kala P, et al. 1-year outcomes of patients undergoing primary angioplasty for myocardial infarction treated with prasugrel versus ticagrelor. *J Am Coll Cardiol* 2018; **71:** 371–81.

15 Park MW, Kim CJ, Kim MC, et al. A prospective, multicentre, randomised, open-label trial to compare the efficacy and safety of clopidogrel versus ticagrelor in stabilised patients with acute myocardial infarction after percutaneous coronary intervention: rationale and design of the TALOS-AMI trial. *EuroIntervention* 2021; **16:** 1170–76.

16 Levine GN, Bates ER, Bittl JA, et al. 2016 ACC/AHA Guideline Focused Update on Duration of Dual Antiplatelet Therapy in Patients with Coronary Artery Disease: a Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines: an Update of the 2011 ACCF/AHA/SCAI Guideline for Percutaneous Coronary Intervention, 2011 ACCF/AHA Guideline for Coronary Artery Bypass Graft Surgery, 2012 ACC/AHA/ACP/AATS/PCNA/SCAI/STS Guideline for the Diagnosis and Management of Patients with Stable Ischemic Heart Disease, 2013 ACCF/AHA Guideline for the Management of ST-Elevation Myocardial Infarction, 2014 AHA/ACC Guideline for the Management of Patients with Non-ST-Elevation Acute Coronary Syndromes, and 2014 ACC/AHA Guideline on Perioperative Cardiovascular Evaluation and Management of Patients Undergoing Noncardiac Surgery. *Circulation* 2016; **134:** e123–55.

17 Zettler ME, Peterson ED, McCoy LA, et al. Switching of adenosine diphosphate receptor inhibitor after hospital discharge among myocardial infarction patients: insights from the Treatment with Adenosine Diphosphate Receptor Inhibitors: Longitudinal Assessment of Treatment Patterns and Events after Acute Coronary Syndrome (TRANSLATE-ACS) observational study. *Am Heart J* 2017; **183:** 62–68.

18 Mehran R, Rao SV, Bhatt DL, et al. Standardized bleeding definitions for cardiovascular clinical trials: a consensus report from the Bleeding Academic Research Consortium. *Circulation* 2011; **123:** 2736–47.

19 Mehran R, Baber U, Sharma SK, et al. Ticagrelor with or without aspirin in high-risk patients after PCI. *N Engl J Med* 2019; **381:** 2032–42.

20 Vranckx P, Valgimigli M, Jüni P, et al. Ticagrelor plus aspirin for 1 month, followed by ticagrelor monotherapy for 23 months vs aspirin plus clopidogrel or ticagrelor for 12 months, followed by aspirin monotherapy for 12 months after implantation of a drug-eluting stent: a multicentre, open-label, randomised superiority trial. *Lancet* 2018; **392:** 940–49.

21 Kim HS, Kang J, Hwang D, et al. 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. *Lancet* 2020; **396:** 1079–89.

22 Ndrepepa G, Mehilli J, Schulz S, et al. Patterns of presentation and outcomes of patients with acute coronary syndromes. *Cardiology* 2009; **113:** 198–206.

23 Sibbing D, Aradi D, Alexopoulos D, et al. Updated expert consensus statement on platelet function and genetic testing for guiding $P2Y_{12}$ receptor inhibitor treatment in percutaneous coronary intervention. *JACC Cardiovasc Interv* 2019; **12:** 1521–37.

24 Sibbing D, Kastrati A. Guided $P2Y_{12}$ inhibitor therapy after percutaneous coronary intervention. *Lancet* 2021; **397:** 1423–25.

25 Angiolillo DJ, Rollini F, Storey RF, et al. International expert consensus on switching platelet $P2Y_{12}$ receptor-inhibiting therapies. *Circulation* 2017; **136:** 1955–75.

26 Kim HS, Chang K, Koh YS, et al. CYP2C19 poor metabolizer is associated with clinical outcome of clopidogrel therapy in acute myocardial infarction but not stable angina. *Circ Cardiovasc Genet* 2013; **6:** 514–21.

27 Gwon HC, Hahn JY, Park KW, et al. Six-month versus 12-month dual antiplatelet therapy after implantation of drug-eluting stents: the Efficacy of Xience/Promus Versus Cypher to Reduce Late Loss After Stenting (EXCELLENT) randomized, multicenter study. *Circulation* 2012; **125:** 505–13.

28 Kim BK, Hong MK, Shin DH, et al. A new strategy for discontinuation of dual antiplatelet therapy: the RESET Trial (REal Safety and Efficacy of 3-month dual antiplatelet Therapy following Endeavor zotarolimus-eluting stent implantation). *J Am Coll Cardiol* 2012; **60:** 1340–48.

29 Feres F, Costa RA, Abizaid A, et al. Three vs twelve months of dual antiplatelet therapy after zotarolimus-eluting stents: the OPTIMIZE randomized trial. *JAMA* 2013; **310:** 2510–22.

30 Colombo A, Chieffo A, Frasheri A, et al. Second-generation drug-eluting stent implantation followed by 6- versus 12-month dual antiplatelet therapy: the SECURITY randomized clinical trial. *J Am Coll Cardiol* 2014; **64:** 2086–97.

31 Hahn JY, Song YB, Oh JH, et al. Effect of P2Y12 inhibitor monotherapy vs dual antiplatelet therapy on cardiovascular events in patients undergoing percutaneous coronary intervention: the SMART-CHOICE randomized clinical trial. *JAMA* 2019; **321:** 2428–37.

32 Piaggio G, Elbourne DR, Altman DG, Pocock SJ, Evans SJ. Reporting of noninferiority and equivalence randomized trials: an extension of the CONSORT statement. *JAMA* 2006; **295:** 1152–60.

33 Bikdeli B, Welsh JW, Akram Y, et al. Noninferiority designed cardiovascular trials in highest-impact journals. *Circulation* 2019; **140:** 379–89.

34 Czarny MJ, Nathan AS, Yeh RW, Mauri L. Adherence to dual antiplatelet therapy after coronary stenting: a systematic review. *Clin Cardiol* 2014; **37:** 505–13.

35 Ndrepepa G, Schuster T, Hadamitzky M, et al. Validation of the Bleeding Academic Research Consortium definition of bleeding in patients with coronary artery disease undergoing percutaneous coronary intervention. *Circulation* 2012; **125:** 1424–31.

36 Valina C, Neumann FJ, Menichelli M, et al. Ticagrelor or prasugrel in patients with non-ST-segment elevation acute coronary syndromes. *J Am Coll Cardiol* 2020; **76:** 2436–46.

37 Collet JP, Thiele H, Barbato E, et al. 2020 ESC Guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation. *Eur Heart J* 2021; **42:** 1289–367.

38 Takahashi K, Serruys PW, Chichareon P, et al. Efficacy and safety of ticagrelor monotherapy in patients undergoing multivessel PCI. *J Am Coll Cardiol* 2019; **74:** 2015–27.

39 Ho PM, Bryson CL, Rumsfeld JS. Medication adherence: its importance in cardiovascular outcomes. *Circulation* 2009; **119:** 3028–35.