Ticagrelor alone versus ticagrelor plus aspirin from month 1 to month 12 after percutaneous coronary intervention in patients with acute coronary syndromes (ULTIMATE-DAPT): a randomised, placebo-controlled, double-blind clinical trial

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Summary

Background Following percutaneous coronary intervention with stent placement to treat acute coronary syndromes, international clinical guidelines generally recommend dual antiplatelet therapy with aspirin plus a $P2Y_{12}$ receptor inhibitor for 12 months to prevent myocardial infarction and stent thrombosis. However, data on single antiplatelet therapy with a potent $P2Y_{12}$ inhibitor earlier than 12 months after percutaneous coronary intervention for patients with an acute coronary syndrome are scarce. The aim of this trial was to assess whether the use of ticagrelor alone, compared with ticagrelor plus aspirin, could reduce the incidence of clinically relevant bleeding events without an accompanying increase in major adverse cardiovascular or cerebrovascular events (MACCE).

Methods In this randomised, placebo-controlled, double-blind clinical trial, patients aged 18 years or older with an acute coronary syndrome who completed the IVUS-ACS study and who had no major ischaemic or bleeding events after 1-month treatment with dual antiplatelet therapy were randomly assigned to receive oral ticagrelor (90 mg twice daily) plus oral aspirin (100 mg once daily) or oral ticagrelor (90 mg twice daily) plus a matching oral placebo, beginning 1 month and ending at 12 months after percutaneous coronary intervention (11 months in total). Recruitment took place at 58 centres in China, Italy, Pakistan, and the UK. Patients were required to remain event-free for 1 month on dual antiplatelet therapy following percutaneous coronary intervention with contemporary drug-eluting stents. Randomisation was done using a web-based system, stratified by acute coronary syndrome type, diabetes, IVUS-ACS randomisation, and site, using dynamic minimisation. The primary superiority endpoint was clinically relevant bleeding (Bleeding Academic Research Consortium [known as BARC] types 2, 3, or 5). The primary non-inferiority endpoint was MACCE (defined as the composite of cardiac death, myocardial infarction, ischaemic stroke, definite stent thrombosis, or clinically driven target vessel revascularisation), with an expected event rate of 6·2% in the ticagrelor plus aspirin group and an absolute non-inferiority margin of 2·5 percentage points between 1 month and 12 months after percutaneous coronary intervention. The two co-primary endpoints were tested sequentially; the primary superiority endpoint had to be met for hypothesis testing of the MACCE outcome to proceed. All principal analyses were assessed in the intention-to-treat population. This trial is registered with ClinicalTrials.gov, NCT03971500, and is completed.

Findings Between Sept 21, 2019, and Oct 27, 2022, 3400 (97·0%) of the 3505 participants in the IVUS-ACS study were randomly assigned (1700 patients to ticagrelor plus aspirin and 1700 patients to ticagrelor plus placebo). 12-month follow-up was completed by 3399 (>99·9%) patients. Between month 1 and month 12 after percutaneous coronary intervention, clinically relevant bleeding occurred in 35 patients (2·1%) in the ticagrelor plus placebo group and in 78 patients (4·6%) in the ticagrelor plus aspirin group (hazard ratio [HR] 0·45 [95% CI 0·30 to 0·66]; p<0·0001). MACCE occurred in 61 patients (3·6%) in the ticagrelor plus placebo group and in 63 patients (3·7%) in the ticagrelor plus aspirin group (absolute difference –0·1% [95% CI –1·4% to 1·2%]; HR 0·98 [95% CI 0·69 to 1·39]; $p_{non\text{-}inferiority}<0·0001$, $p_{superiority}=0·89$).

Interpretation In patients with an acute coronary syndrome who had percutaneous coronary intervention with contemporary drug-eluting stents and remained event-free for 1 month on dual antiplatelet therapy, treatment with ticagrelor alone between month 1 and month 12 after the intervention resulted in a lower rate of clinically relevant bleeding and a similar rate of MACCE compared with ticagrelor plus aspirin. Along with the results from previous studies, these findings show that most patients in this population can benefit from superior clinical outcomes with aspirin discontinuation and maintenance on ticagrelor monotherapy after 1 month of dual antiplatelet therapy.

Funding The Chinese Society of Cardiology, the National Natural Scientific Foundation of China, and the Jiangsu Provincial & Nanjing Municipal Clinical Trial Project.

Published **Online** April 7, 2024 https://doi.org/10.1016/S0140-6736(24)00473-2

See **Online/Comment** https://doi.org/10.1016/S0140-6736(24)00586-5

For the Mandarin translation of the abstract see **Online** for appendix 1

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See Online for appendix 2

Research in context

Evidence before this study

We searched PubMed on March 11, 2019, using the search terms "intravascular ultrasound", "angiography", "percutaneous coronary intervention", "antiplatelet therapy", and "acute coronary syndrome (ACS)" using MeSH terms and appropriate variations, with no language or date restrictions, before designing our study. Subgroup analyses from several randomised trials suggested that a course of dual antiplatelet therapy lasting 1–3 months using different $P2Y_{12}$ inhibitors might safely reduce bleeding events in patients with an acute coronary syndrome after implantation of drug-eluting stents. We found no previous randomised, placebo-controlled trials in patients with an acute coronary syndrome who remained event-free after 1 month of dual antiplatelet therapy that compared ticagrelor alone with ticagrelor plus aspirin between month 1 and month 12 of follow-up.

Added value of this study

ULTIMATE-DAPT is the first randomised controlled trial to compare dual antiplatelet therapy with a potent platelet $P2Y_{12}$ inhibitor plus aspirin versus a potent $P2Y_{12}$ inhibitor plus placebo in patients with an acute coronary syndrome treated with percutaneous coronary intervention and who remained event-free after only 1 month of dual antiplatelet therapy. The results of this study show that patients with an acute coronary syndrome treated with contemporary drug-eluting stents and who are event-free after a 1-month course of dual antiplatelet therapy can be safely maintained on ticagrelor monotherapy from 1 month after to 12 months after percutaneous coronary intervention, and that this regimen will substantially reduce major and minor bleeding compared with standard ongoing treatment with ticagrelor plus aspirin. In addition, no increase in ischaemic events such as myocardial infarction, stent thrombosis, or cardiac death was observed with the ticagrelor monotherapy regimen in patients with a high-risk acute coronary syndrome, and net adverse clinical events occurred less frequently with ticagrelor monotherapy than with ticagrelor plus aspirin.

Implications of all the available evidence

The data from ULTIMATE-DAPT (along with that of previous studies) provide strong evidence that, in patients with an acute coronary syndrome treated with percutaneous coronary intervention with contemporary drug-eluting stents and who are event-free after 1 month of post-procedural dual antiplatelet therapy, ticagrelor monotherapy can safely reduce major and minor bleeding during follow-up.

Introduction

Despite advances in prevention and treatment, cardiovascular disease remains the leading cause of mortality worldwide, with ischaemic heart disease among the top contributors to burden of disease after the age of 25 years.[1] Patients with an acute coronary syndrome are at increased risk of death and myocardial infarction compared with patients with chronic coronary syndrome. The prognosis of these patients can be improved by early revascularisation.[2,3] Following percutaneous coronary intervention for acute coronary syndromes, international guidelines currently recommend that most patients receive dual antiplatelet therapy with aspirin plus a $P2Y_{12}$ receptor inhibitor for 12 months to reduce the risk of myocardial infarction and stent thrombosis.[2,3] Ticagrelor or prasugrel are preferred to clopidogrel in this setting.[4,5] However, the benefit of these potent $P2Y_{12}$ receptor inhibitors is obtained at the cost of an increased risk of bleeding events, which can be life-threatening.

The effects of early cessation of antiplatelet therapy with aspirin after percutaneous coronary intervention in acute and chronic coronary syndromes have been studied in various settings.[4–15] A 2023 meta-analysis[16] of 32 randomised trials testing numerous pharmacological strategies reported that $P2Y_{12}$ inhibitor monotherapy after percutaneous coronary intervention and a 6-month or less treatment period with dual antiplatelet therapy was associated with the lowest risk of major bleeding and all-cause death in patients with an acute coronary syndrome. However, $P2Y_{12}$ inhibitor monotherapy after percutaneous coronary intervention and only 1 month of dual antiplatelet therapy in acute coronary syndromes has not been widely studied, and most of the included trials were open label.[16] Therefore, we performed a placebo-controlled randomised trial in patients with an acute coronary syndrome who remained event-free after percutaneous coronary intervention and 1 month of dual antiplatelet therapy. The aim of the study was to assess whether the use of ticagrelor alone, compared with ticagrelor plus aspirin, could reduce the incidence of clinically relevant bleeding events without an accompanying increase in major adverse cardiovascular or cerebrovascular events (MACCE).

Methods

Study design and participants

This randomised, placebo-controlled, double-blind clinical trial was part of the IVUS-ACS and ULTIMATE-DAPT integrated study programme (comparison of 1-month *vs* 12-month dual antiplatelet therapy after implantation of drug-eluting stents guided by either intravascular ultrasound or angiography in patients with an acute coronary syndrome), an investigator-initiated international study. The programme incorporated two integrated randomised trials that were conducted at 58 centres (ie, teaching hospitals; appendix 2 pp 5–6) in China (n=52), Pakistan (n=4), the UK (n=1), and

Italy (n=1). The study complied with the Declaration of Helsinki, and the protocol was approved by the institutional review board or ethics committee at each centre. All patients provided written informed consent. A data safety and monitoring board oversaw the trial (appendix 2 pp 2–4).

The protocol integrated two trials in a two-stage factorial design to assess the utility of intravascular ultrasound guidance of percutaneous coronary intervention (IVUS-ACS trial) and ticagrelor monotherapy after 1 month of dual antiplatelet therapy following percutaneous coronary intervention in patients with an acute coronary syndrome (ULTIMATE-DAPT). The present report describes the outcomes of the ULTIMATE-DAPT trial. The principal results from the IVUS-ACS trial are discussed in a separate publication.[17] This trial is registered with ClinicalTrials.gov, NCT03971500, and is completed.

Patients were eligible for inclusion in the trial if they were aged 18 years or older; had an acute coronary syndrome (ie, unstable angina [angiography showing a severely narrowed or ruptured plaque or thrombotic lesion without cardiac biomarker elevation], non-ST-segment elevation myocardial infarction [NSTEMI], or ST-segment elevation myocardial infarction [STEMI]) caused by a culprit lesion in an untreated coronary artery segment, up to 30 days before randomisation;[18] and had an indication for percutaneous coronary intervention with a second-generation drug-eluting stent (appendix 2 p 8). Exclusion criteria were stroke within 3 months or any permanent neurological deficit; any previous intracranial bleed or intracranial disease (eg, aneurysm or fistula); previous coronary artery bypass graft surgery; any planned surgery within 12 months; any reason for which antiplatelet therapy might need to be discontinued within 12 months; severe chronic kidney disease (defined as an estimated glomerular filtration rate <20 mL/min per 1·73 m²); need for chronic oral anticoagulation (ie, warfarin or coumadin or direct oral anticoagulants); a platelet count of less than 100 000 mm³; contraindication to aspirin or ticagrelor; liver cirrhosis; people intending to become pregnant; a life expectancy of less than 1 year; and any condition likely to interfere with study processes, including medication compliance or follow-up visits (eg, dementia, alcohol abuse, severe frailty, or required to travel a long distance for follow-up visits).

Eligible patients were initially randomly assigned to receive percutaneous coronary intervention, guided by either intravascular ultrasound or angiography (first randomisation [IVUS-ACS trial]), of all lesions that each site operator believed were responsible for the acute coronary syndrome, as well as of other angiographically severe lesions that warranted treatment per standard clinical practice. After the procedure, all patients were treated with oral ticagrelor (90 mg twice daily) plus oral enteric-coated aspirin (100 mg daily) with the first doses initiated before percutaneous coronary intervention (timing was dependent upon whether the patient had angina, NSTEMI, or STEMI).

All patients or their family members provided written informed consent before random assignment; for patients with unstable angina or NSTEMI, there was sufficient time to introduce the percutaneous coronary intervention procedure and this study to patients; for patients with STEMI, research staff briefly explained the details to patients and their families immediately after wiring and thrombolysis in myocardial infarction (TIMI) flow restoration. Sex data were collected according to physical examination.

Randomisation and masking

After 1 month, surviving patients who remained free from major bleeding events (Bleeding Academic Research Consortium [BARC] types 3 or 5),[19] adverse ischaemic events (myocardial infarction, ischaemic stroke, definite stent thrombosis, or clinically driven target vessel revascularisation), and who had not discontinued dual antiplatelet therapy for more than 48 h continued treatment with open-label ticagrelor and were randomly assigned for a second time, in a 1:1 ratio, to receive dual antiplatelet therapy (90 mg ticagrelor twice daily plus 100 mg enteric-coated aspirin once daily) or monotherapy (ie, 90 mg ticagrelor twice daily plus a matching enteric-coated oral placebo) for an additional 11 months (second randomisation for the ULTIMATE-DAPT trial). 30 days was selected as the timepoint for the second randomisation because this corresponds to when a clinician would decide whether the patient is sufficiently stable (ie, free from ischaemic and bleeding events) to undergo aspirin discontinuation.[6,11] Moreover, if randomisation for this decision was made before 30 days while the patient was in hospital, inclusion of late event data (>30 days) from patients who would not have been eligible at 30 days might confound the results, and inclusion of early event data (<30 days) that would be expected to be the same in both randomised groups still on dual antiplatelet therapy could bias the results toward the null.

Research staff were responsible for enrolling and randomly assigning participants. Randomisation was done using a web-based system, stratified by acute coronary syndrome type (unstable angina *vs* NSTEMI *vs* STEMI), diabetes (yes *vs* no), the first-stage randomisation (percutaneous coronary intervention with intravascular ultrasound or angiography guidance), and site, using dynamic minimisation.[20] The nurses and research staff did not have any involvement in the rest of the trial. The allocation probability for each eligible patient was generated using the Pocock and Simon method.[21] Drugs in both groups were labelled with pre-generated, randomly shuffled numbers. When the algorithm generated allocation results for a participant, the tool would map the allocation result to one of the drug

numbers of the same group without exposing the allocation to the investigators. All patients and their families, researchers, and treating physicians and staff remained masked to random assignment during the 1-year follow-up.

Procedures

Post-discharge visits after the initial percutaneous coronary intervention were scheduled at 1, 4, 6, and 12 months (with the second random assignment for eligible patients done at the 1-month visit after physician interview and physical examination demonstrated that they met eligibility criteria). A window of 23–37 days after percutaneous coronary intervention was allowed for the 1-month visit and second randomisation. Angiographical follow-up was done only for clinical indications. If dyspnoea developed on ticagrelor, the dosage was reduced from 90 mg twice daily to 60 mg twice daily; if dyspnoea persisted, ticagrelor was replaced with oral clopidogrel (75 mg daily, based on physician judgement). Ticagrelor plus open-label aspirin was prescribed for any patient who had a revascularisation procedure during the follow-up period. Management of antiplatelet therapy in patients who had a bleeding or ischaemic event was left to the physician's discretion. Unmasking was allowed by the data safety monitoring board if knowledge of the antiplatelet agent allocation was necessary for management of a major adverse event (appendix 2 p 23) and did not lead to data censoring. Baseline angiograms of the target lesion or lesions responsible for the acute coronary syndrome, as identified by the operator, were analysed at an independent core laboratory. A masked independent clinical events committee (appendix 2 p 2) adjudicated all outcomes to prespecified endpoint definitions upon review of hospital documents and reports.

Outcomes

The trial had two primary endpoints (appendix 2 p 8). The primary superiority endpoint was the occurrence of clinically relevant bleeding (BARC types 2, 3, or 5).[19] The primary non-inferiority endpoint was the occurrence of MACCE (ie, the composite of cardiac death, myocardial infarction, ischaemic stroke, definite stent thrombosis, and clinically driven target vessel revascularisation). The key secondary endpoints were the time to first occurrence of composite net adverse clinical events (defined as any MACCE or any BARC bleeding [types 1, 2, 3, or 5]) and percentage of crossover from ticagrelor to clopidogrel in each group. BARC type 1 bleeding was included in the net clinical adverse event endpoint to fully reflect the totality of bleeding events that patients might have. Additional endpoints (appendix 2 pp 8–14) were BARC types 3 or 5 bleeding; major or minor bleeding according to the TIMI risk assessment score;[22] moderate, severe, or life-threatening bleeding according to definitions from Global Utilization of Streptokinase and Tissue Plasminogen Activator for Occluded Arteries (GUSTO);[23] major bleeding according to definitions from International Society of Thrombosis and Haemostasis (ISTH);[24] individual components of the primary endpoints; and the composite of cardiac death, non-fatal myocardial infarction, or ischaemic stroke. Other secondary endpoints were target vessel failure without procedural myocardial infarction, non-fatal myocardial infarction, and probable stent thrombosis (protocol version 2.0, appendix 2 p 97).

Statistical analysis

Historical data from previous clinical trials used to estimate control arm event rates are shown in appendix 2 (p 15). Assuming a 3·0% rate of clinically relevant bleeding between month 1 and month 12 of ticagrelor plus aspirin, 3400 patients provided 80% power to detect a 50% reduction in clinically relevant bleeding with ticagrelor plus placebo with a two-sided α of 0·05. Assuming a 6·2% rate of MACCE between month 1 and month 12 of ticagrelor plus aspirin, inclusion of 3068 patients provided 80% power to show non-inferiority of ticagrelor plus placebo with an absolute margin of 2·5 percentage points with a one-sided α of 0·025. Acknowledging the inherent uncertainty in selecting a non-inferiority margin[25] and the likelihood that the majority of MACCE between month 1 and month 12 would consist of repeat revascularisations, the steering committee selected a margin of 2·5% to represent a reasonable estimate for therapeutic interchangeability in the estimated difference in MACCE between groups, given the expected magnitude for the reduction in major and minor bleeding in this period with ticagrelor alone. The two primary endpoints were tested sequentially; the clinically relevant bleeding (superiority) endpoint had to pass for hypothesis testing of the MACCE (non-inferiority) endpoint to proceed. The protocol prespecified that, if non-inferiority of MACCE was demonstrated, the hypothesis of superiority on MACCE of monotherapy over dual antiplatelet therapy would also be tested at a one-sided significance level of 0·025. Protocol amendments were minor, did not affect study processes, and were approved by the Institutional Research Board on March 28, 2021 (protocol version 2.0, appendix 2 pp 121–24).

Continuous data were reported as mean (SD) and compared using *t* test if normally distributed, or as median (IQR) and compared using Mann–Whitney *U* test if not normally distributed. Binary data were compared using the χ^2 test or Fisher's exact test. Event rates were estimated using the Kaplan–Meier method and compared using the log-rank test. Treatment effects were estimated using Cox proportional hazards regression, with results presented as hazard ratios (HRs) and 95% CIs. Absolute differences and 95% CIs for the primary and secondary endpoints were calculated with standard errors estimated by Greenwood's method.[26] MACCE were analysed using

the subdistribution method of Fine and Gray to account for the competing risk of non-cardiac death. The treatment effects for both primary analyses were adjusted in the multivariable models for acute coronary syndrome type, the first randomisation, diabetes, and geographical region (ie, Italy, Pakistan, the UK, east China, north China, south China, or west China).

The principal analyses were assessed in the intention-to-treat population, including all randomly assigned patients, regardless of medication adherence. Sensitivity analyses were done in the per-protocol population, excluding patients who did not take their assigned treatment for at least 7 days (unless medication interruption or discontinuation was required due to adverse events), or who did not comply with the medication schedule (defined as a medication possession ratio of >80% of dispensed tablets based on manual pill count at the 4-month and 12-month office visits). Adjustment for multiplicity was not done for the secondary endpoints, and these results should not be used to infer definitive treatment effects.

Patients were censored if they withdrew, were lost to follow-up, or died. The latest available follow-up data were used for each patient. Missing data were not replaced; all outcomes are reported as a complete-case analysis. All superiority tests were two-sided and $p<0·05$ was considered significant for superiority testing. All analyses were done using SAS (version 9.4). This study is registered with ClinicalTrials.gov, NCT03971500, and is completed.

Role of the funding source

The funders of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report.

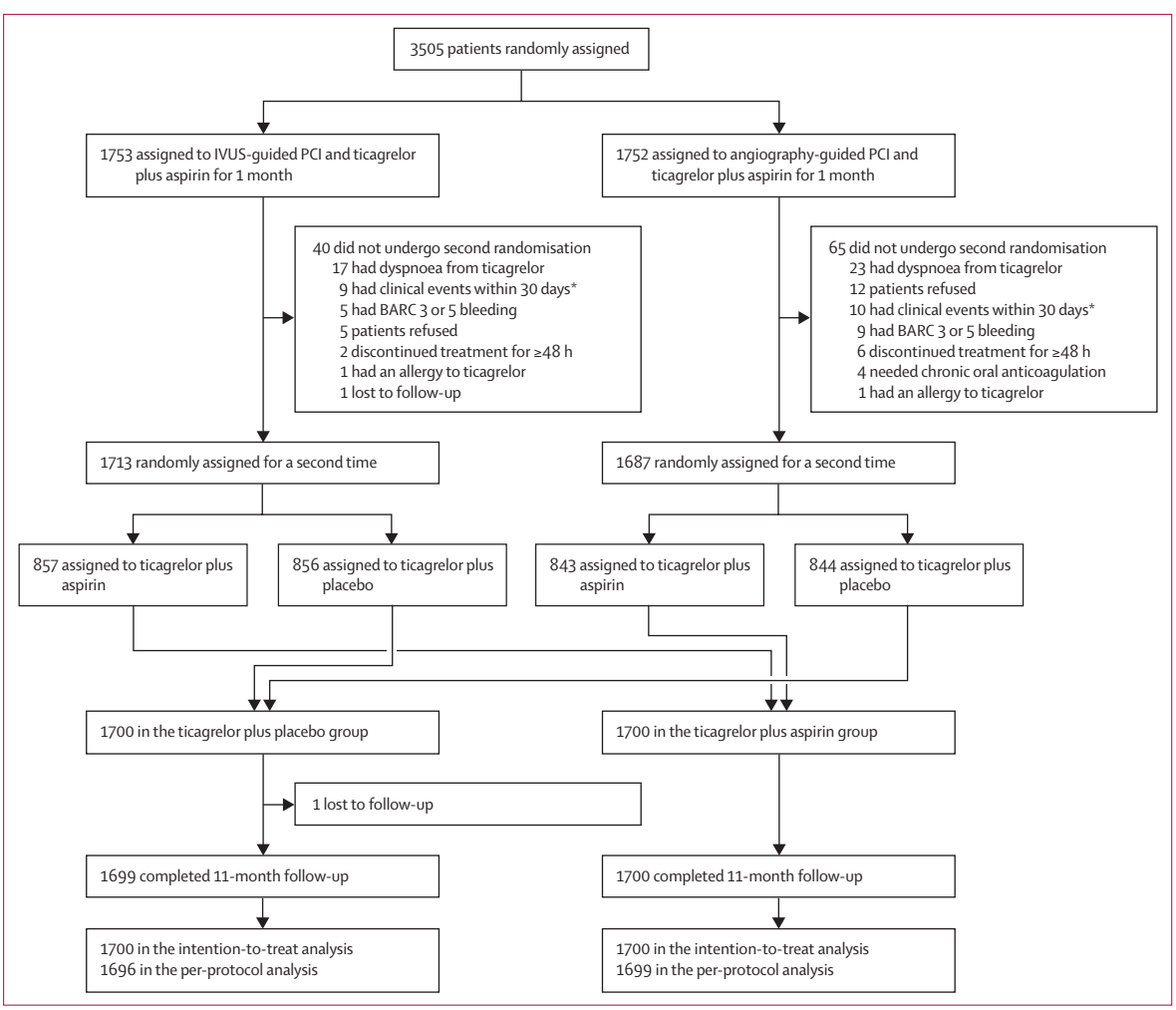

Figure 1: **Trial profile**
The intention-to-treat population included all randomly assigned patients, regardless of therapy received. The per-protocol population consists of all patients as randomised, excluding those who did not take their assigned treatment for at least 7 days (unless medication interruption or discontinuation was required for adverse events), or who did not comply with the medication schedule. BARC=Bleeding Academic Research Consortium. IVUS=intravascular ultrasound. PCI=percutaneous coronary intervention. *Clinically driven target vessel revascularisation, definite stent thrombosis, stroke, ST-segment elevation myocardial infarction, BARC 3 or 5 major bleeding, or death.

	Ticagrelor plus placebo (n=1700)	Ticagrelor plus aspirin (n=1700)
Age, years		
Median (IQR)	62 (54–70)	63 (54–69)
Sex		
Male	1264 (74·4%)	1257 (73·9%)
Female	436 (25·7%)	443 (26·1%)
Race		
Chinese	1476 (86·8%)	1519 (89·4%)
Other	224 (13·2%)	181 (10·7%)
Country of enrolment		
China	1476 (86·8%)	1519 (89·4%)
Pakistan	202 (11·9%)	159 (9·4%)
UK	12 (0·7%)	11 (0·7%)
Italy	10 (0·6%)	11 (0·7%)
Initial presentation		
Unstable angina	668 (39·3%)	708 (41·7%)
With ischaemic changes on electrocardiogram	650/668 (97·3%)	685/708 (96·8%)
Acute myocardial infarction	1032 (60·7%)	992 (58·4%)
Non-STEMI	545 (32·1%)	531 (31·2%)
STEMI	487 (28·7%)	461 (27·1%)
Killip class		
1	475/1032 (46·0%)	442/992 (44·6%)
2	457/1032 (44·3%)	468/992 (47·2%)
3	100/1032 (9·7%)	82/992 (8·3%)
Medical history		
Hypertension	1058 (62·2%)	1063 (62·5%)
Diabetes	540 (31·8%)	535 (31·5%)
Insulin-treated diabetes	136 (8·0%)	144 (8·5%)
Dyslipidaemia	1178 (69·3%)	1157 (68·1%)
Current smoking*	486 (28·6%)	482 (28·4%)
Chronic renal insufficiency†	119 (7·0%)	129 (7·6%)
Previous percutaneous coronary intervention	171 (10·1%)	174 (10·2%)
Previous coronary artery bypass graft surgery	2 (0·1%)	4 (0·2%)
Previous myocardial infarction	143 (8·4%)	156 (9·2%)
Previous stroke	154 (9·1%)	147 (8·7%)
Peripheral arterial disease	76 (4·5%)	79 (4·7%)
Heart failure	109 (6·4%)	101 (5·9%)
Left ventricular ejection fraction (%)‡		
Median (IQR)	62% (55–65)	63% (56–65)
Medication use at 1 month (the time of the second randomisation)		
Aspirin	1700 (100%)	1700 (100%)
Ticagrelor	1700 (100%)	1700 (100%)
β blocker	838 (49·3%)	802 (47·2%)
Angiotensin converting enzyme inhibitor or angiotensin receptor blocker	774 (45·5%)	788 (46·4%)
Calcium antagonist	430 (25·3%)	463 (27·2%)
Statin	1417 (83·4%)	1404 (82·6%)

Data are n (%) unless otherwise specified. STEMI=ST-segment elevation myocardial infarction. *Defined as ≥100 lifetime cigarettes and still smoking at the time of enrolment; other tobacco products were not included. †Defined as an estimated glomerular filtration rate of <60 mL/min per 1·73 m². ‡Includes baseline transthoracic echocardiographic measurements from 1496 patients in the ticagrelor plus placebo group and 1504 patients in the ticagrelor plus aspirin group.

Table 1: **Baseline characteristics and medication use**

Results

Between Sept 21, 2019, and Oct 27, 2022, 3710 patients with an acute coronary syndrome were screened and 3505 (94·5%) were randomly assigned to intravascular ultrasound-guided or angiography-guided percutaneous coronary intervention and subsequently discharged on dual antiplatelet therapy (figure 1). 3400 (97·0%) of the 3505 patients underwent the second random assignment at 1 month (median 31 days [IQR 30–34] for both groups) to receive either ticagrelor plus placebo (n=1700) or ticagrelor plus aspirin (n=1700); these 3400 patients comprise the study population of ULTIMATE-DAPT (appendix 2 p 16).

Baseline clinical characteristics were well matched between groups (table 1), as were index procedural data and angiographical outcomes (appendix 2 pp 17–19). The median patient age was 63 years (IQR 54–70), 2521 (74·1%) patients were men and 879 (25·6%) were women, 1075 (31·6%) had diabetes, and 2024 (59·5%) presented with an acute myocardial infarction. 835 (24·6%) of 3400 culprit vessels before the index procedure had a TIMI flow score of less than 3. The median dual antiplatelet therapy duration was 28 days (IQR 25–33) in the ticagrelor plus placebo group and 365 days (365–365) in the ticagrelor and aspirin group. During follow-up, 12 (0·7%) patients required a reduction in ticagrelor dosage from 90 mg to 60 mg twice daily in the ticagrelor plus placebo group, as did 16 (0·9%) patients in the ticagrelor plus aspirin group. Conversion from ticagrelor to clopidogrel was required in 22 (1·3%) patients in the ticagrelor plus placebo group and 19 (1·1%) patients in the ticagrelor plus aspirin group. Unmasking during follow-up was required for 11 (0·7%) patients in the ticagrelor plus placebo group and 28 (1·7%) in the ticagrelor plus aspirin group due to BARC 3 or 5 bleeding events, and for three (0·2%) patients in the ticagrelor plus placebo group and five (0·3%) in the ticagrelor plus aspirin group due to definite stent thrombosis. Pill counts at 4 months and 12 months and patient reporting of medication use at other time intervals showed acceptable antiplatelet agent adherence during follow-up in both groups (appendix 2 p 22). 12-month clinical follow-up was completed by 3399 (>99·9%) of 3400 participants. Angiographical follow-up was done for clinical indications in 256 (15·1%) patients assigned to ticagrelor plus placebo at a median of 347 days (IQR 329–368) after percutaneous coronary intervention, and in 278 (16·4%) patients assigned to ticagrelor plus aspirin at a median of 347 days (IQR 331–370) after percutaneous coronary intervention.

Between month 1 and month 12 after percutaneous coronary intervention, the primary superiority endpoint of clinically relevant bleeding occurred in 35 patients (2·1%) treated with ticagrelor plus placebo and in 78 patients (4·6%) treated with ticagrelor plus aspirin (HR 0·45 [95% CI 0·30–0·66]; p<0·0001) in the

intention-to-treat population (table 2; figure 2); similar results were observed in the per-protocol population (appendix 2 p 20). Major bleeding (BARC types 3 or 5) also occurred less frequently with ticagrelor plus placebo compared with ticagrelor plus aspirin, as did other prespecified measures of bleeding (table 2; appendix 2 p 21). The treatment effects for clinically relevant bleeding were consistent across prespecified subgroups (figure 3). Numbers needed-to-treat were 48 to prevent one clinically relevant bleeding event and 100 to prevent one BARC type 3 or 5 bleeding event.

Between month 1 and month 12 after percutaneous coronary intervention, the primary non-inferiority endpoint of MACCE occurred in 61 participants (3·6%) treated with ticagrelor plus placebo and 63 (3·7%) treated with ticagrelor plus aspirin (absolute difference –0·1% [95% CI –1·4% to 1·2%]; HR 0·98 [95% CI 0·69 to 1·39]; $p_{non\text{-}inferiority}<0·0001$, $p_{superiority}=0·89$) in the intention-to-treat population (table 2, figure 2); similar results were observed in the per-protocol population (appendix 2 p 20). The rates of the individual components of the primary non-inferiority endpoint were also similar between the two groups, as were other composite ischaemic outcomes (table 2). The treatment effects for MACCE in the prespecified subgroups are shown in figure 4.

Between month 1 and month 12 after percutaneous coronary intervention, the key secondary endpoint of net clinical adverse events occurred less frequently in the ticagrelor plus placebo group than in the ticagrelor plus aspirin group (table 2; appendix 2 p 23).

	Ticagrelor plus placebo (n=1700)	Ticagrelor plus aspirin (n=1700)	Hazard ratio (95% CI)	p value
Primary endpoints				
Clinically relevant bleeding (BARC types 2, 3, or 5)	35 (2·1%)	78 (4·6%)	0·45 (0·30 to 0·66)	<0·0001
Major adverse cardiovascular or cerebrovascular events*	61 (3·6%)	63 (3·7%)	0·98 (0·69 to 1·39)	0·89†
Key secondary endpoint				
Net adverse clinical events	97 (5·7%)	140 (8·2%)	0·68 (0·53 to 0·88)	0·0066
Secondary bleeding endpoints				
Major bleeding (BARC types 3 or 5)	11 (0·7%)	28 (1·7%)	0·39 (0·19 to 0·79)	0·0087
TIMI major or minor bleeding	11 (0·7%)	27 (1·6%)	0·41 (0·20 to 0·82)	0·012
GUSTO moderate, severe, or life-threatening bleeding	8 (0·5%)	19 (1·1%)	0·42 (0·18 to 0·96)	0·041
ISTH major bleeding	8 (0·5%)	21 (1·2%)	0·38 (0·17 to 0·86)	0·020
Patients with any of the four secondary bleeding endpoints	11 (0·7%)	28 (1·7%)	0·39 (0·19 to 0·79)	0·0087
Patients with all four secondary bleeding endpoints	8 (0·5%)	19 (1·1%)	0·42 (0·18 to 0·96)	0·041
Secondary ischaemic events and mortality				
All-cause death	12 (0·7%)	13 (0·8%)	0·93 (0·42 to 2·03)	0·84
Cardiac death	8 (0·5%)	7 (0·4%)	1·15 (0·42 to 3·18)	0·46
Any stroke	20 (1·2%)	24 (1·4%)	0·83 (0·46 to 1·50)	0·54
Ischaemic	11 (0·7%)	15 (0·9%)	0·74 (0·34 to 1·61)	0·58
Haemorrhagic	4 (0·2%)	3 (0·2%)	1·33 (0·29 to 3·71)	0·71
Uncertain	5 (0·3%)	6 (0·4%)	0·97 (0·49 to 1·92)	0·94
Myocardial infarction	17 (1·0%)	11 (0·7%)	1·45 (0·67 to 3·23)	0·27
Procedural myocardial infarction	1 (0·1%)	1 (0·1%)	0·00 (–0·28 to 0·28)	0·88
Non-procedural myocardial infarction	16 (0·9%)	11 (0·7%)	1·42 (0·66 to 3·03)	0·29
Stent thrombosis	5 (0·3%)	5 (0·3%)	0·97 (0·28 to 3·40)	0·96
Definite	3 (0·2%)	5 (0·3%)	0·59 (0·14 to 2·51)	0·47
Probable	2 (0·1%)	0	..	..
Clinically driven revascularisation‡	40 (2·4%)	41 (2·4%)	0·99 (0·64 to 1·53)	0·95
Target vessel revascularisation	33 (2·0%)	36 (2·1%)	0·93 (0·58 to 1·49)	0·75
Target lesion revascularisation	27 (1·6%)	28 (1·7%)	0·97 (0·57 to 1·65)	0·92
Cardiac death, non-fatal myocardial infarction, or ischaemic stroke	31 (1·8%)	32 (1·9%)	0·98 (0·63 to 1·67)	0·91

Data are n (%) unless otherwise specified. Rates are number of events occurring between month 1 and month 12 after percutaneous coronary intervention (the second randomisation period), with Kaplan–Meier estimated percentages. BARC=Bleeding Academic Research Consortium. GUSTO=Global Utilization of Streptokinase and Tissue Plasminogen Activator for Occluded Arteries. ISTH=International Society on Thrombosis and Haemostasis. TIMI=Thrombolysis in Myocardial Infarction flow grading system. *The composite of cardiac death, myocardial infarction, ischaemic stroke, definite stent thrombosis, and clinically driven target vessel revascularisation. †p<0·0001 for non-inferiority for major adverse cardiovascular or cerebrovascular events. ‡For patients who had revascularisation, oral ticagrelor (90 mg twice daily) plus oral open-labelled aspirin (100 mg once daily) were prescribed after procedure.

Table 2: **Primary and secondary endpoints**

Discussion

The ULTIMATE-DAPT placebo-controlled, double-blind trial showed that, in patients with an acute coronary syndrome treated with percutaneous coronary intervention followed by 1 month of aspirin plus ticagrelor, follow-up treatment with ticagrelor monotherapy for an additional 11 months reduced clinically relevant bleeding without an accompanying increase in MACCE, compared with follow-up treatment with ticagrelor and aspirin for an additional 11 months.

Compared with patients with chronic coronary syndrome, patients with an acute coronary syndrome have increased 1-year rates of cardiac death and myocardial infarction arising from both treated culprit lesions and untreated non-culprit lesions.[27] More than two decades ago, the CURE trial showed that inhibition of the platelet $P2Y_{12}$ receptor with clopidogrel for 1 year improved cardiovascular outcomes in patients with an acute coronary syndrome treated with aspirin after percutaneous coronary intervention.[28] The more potent agents ticagrelor and prasugrel subsequently replaced clopidogrel as the standard of care in this setting,[29] on the basis of randomised trials showing further reductions in myocardial infarction, stent thrombosis and, in the case of ticagrelor, mortality, albeit with increased non-surgery-related bleeding.[4,5] The current hypothesis is that, following percutaneous coronary intervention with contemporary drug-eluting stents in acute (and chronic) coronary syndromes, most of the ischaemic protection from dual antiplatelet therapy derives from the $P2Y_{12}$ inhibitor, with aspirin responsible for many of the haemorrhagic complications.[5–11]

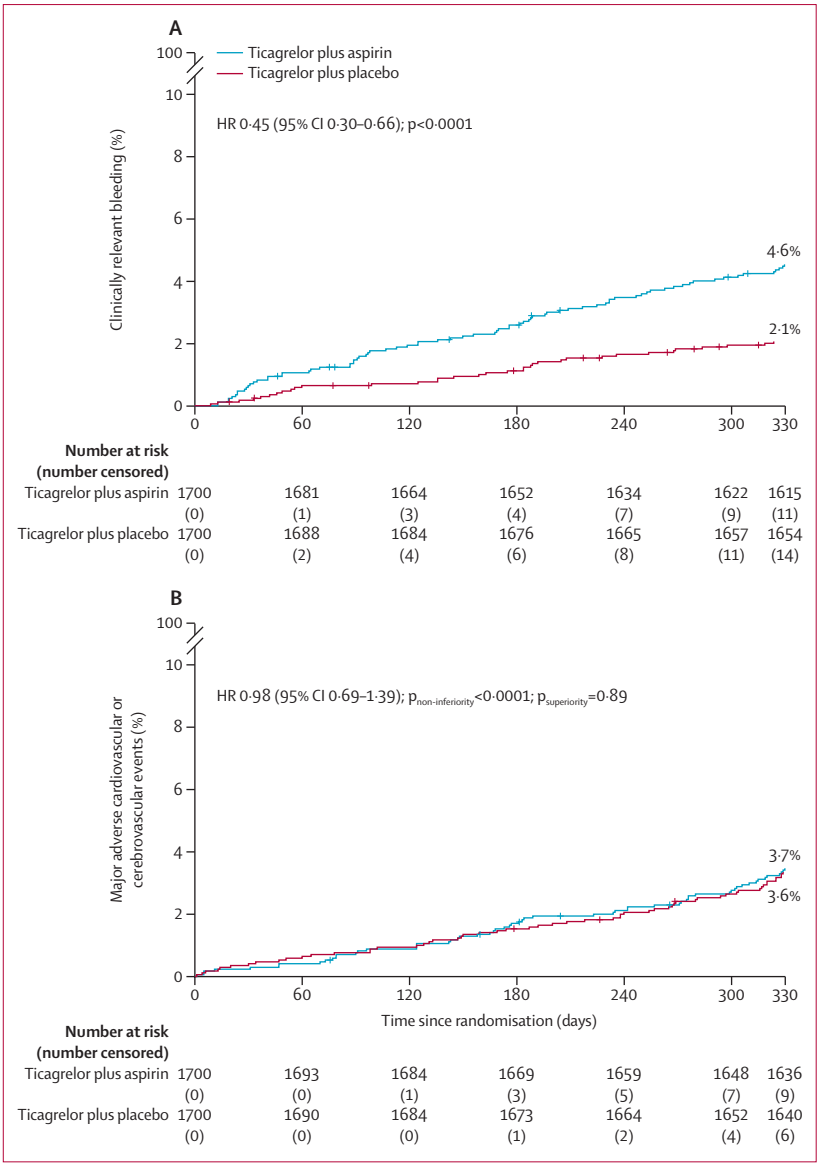

Figure 2: **Primary efficacy and safety outcomes during follow-up between 1 month and 12 months after percutaneous coronary intervention**

(A) The primary efficacy endpoint of clinically relevant bleeding, defined as BARC types 2, 3, or 5 bleeding, was assessed in the intention-to-treat population between 1 month and 12 months after percutaneous coronary intervention in patients who were event-free after 1 month of ticagrelor and aspirin. (B) The primary safety endpoint of major adverse cardiovascular or cerebrovascular events, which comprised cardiac death, myocardial infarction, ischaemic stroke, definite stent thrombosis, and clinically driven target vessel revascularisation, was assessed in the intention-to-treat population between 1 month and 12 months after percutaneous coronary intervention in patients who were event-free after 1 month of ticagrelor and aspirin. Patients treated with ticagrelor monotherapy from month 1 had similar rates of adverse ischaemic events as patients who were maintained on ticagrelor plus aspirin. BARC=Bleeding Academic Research Consortium. HR=hazard ratio.

Six previous trials have investigated $P2Y_{12}$ inhibitor monotherapy after percutaneous coronary intervention and an obligate duration of dual antiplatelet therapy in acute coronary syndromes.[7–11] However, most of these studies were open label and not placebo controlled; tested $P2Y_{12}$ inhibitor monotherapy after 1–3 months of dual antiplatelet therapy; did not always test ticagrelor or prasugrel monotherapy; used variable definitions to define bleeding; had the acute coronary syndrome cohort as a subgroup of a broader population; and included the pre-randomisation period of dual antiplatelet therapy in both arms in the primary outcome. The consequent lack of robust data from previous trials might have hindered widespread adoption of monotherapy with a potent $P2Y_{12}$ inhibitor after percutaneous coronary intervention and only 1 month of dual antiplatelet therapy in high-risk patients with an acute coronary syndrome.

Compared with ticagrelor plus aspirin, continued treatment with ticagrelor plus placebo for an additional 11 months resulted in a significant reduction in clinically relevant bleeding events. Major bleeding (BARC types 3 or 5) was also reduced with ticagrelor monotherapy, as was bleeding according to the TIMI, GUSTO, and ISTH scales. These results are consistent with previous studies reporting that discontinuing aspirin while maintaining $P2Y_{12}$ receptor inhibition after percutaneous coronary intervention and 1–6 months of dual antiplatelet therapy reduces the risk of subsequent major and minor bleeding events in patients with an acute coronary syndrome.[7–11,16] However, the present study extends these findings by showing that, in a double-blind, placebo-controlled trial, treatment of such patients with ticagrelor monotherapy after 1 month and up to 12 months is safe, with no apparent increased risk of thrombotic or ischaemic events. Results were similar in the intention-to-treat and per-protocol populations. Bleeding events were consistently less frequent with ticagrelor monotherapy in all examined subgroups, and MACCE was not increased in any subgroup, although an interaction was identified according to age. However, the examined subgroups were not adjusted for multiple comparisons, and these findings should be viewed accordingly.

The ULTIMATE-DAPT results extend the findings from the unblinded TICO trial, in which ticagrelor alone, compared with ticagrelor plus aspirin, reduced TIMI major or minor bleeding events without an increase in MACCE between 3 months and 12 months after percutaneous coronary intervention in patients with an acute coronary syndrome.[10] The results of the present trial are also consistent with those from the recent T-PASS trial, in which 2850 patients with an acute coronary syndrome in South Korea were randomly assigned to ticagrelor alone or ticagrelor plus aspirin at a median of 16 days after percutaneous coronary intervention.[11] However, like TICO, T-PASS was open label and not placebo controlled; random assignment occurred at the time of discharge, confounding the results by including similar rates of early events in both groups before dichotomisation of the treatment regimens; and was powered for non-inferiority testing for a primary endpoint of net clinical adverse events, rather than separately for safety and efficacy.

We found a relative risk reduction for the key secondary endpoint of net clinical adverse events with ticagrelor monotherapy (HR 0·68 [95% CI 0·53–0·88]), indicating

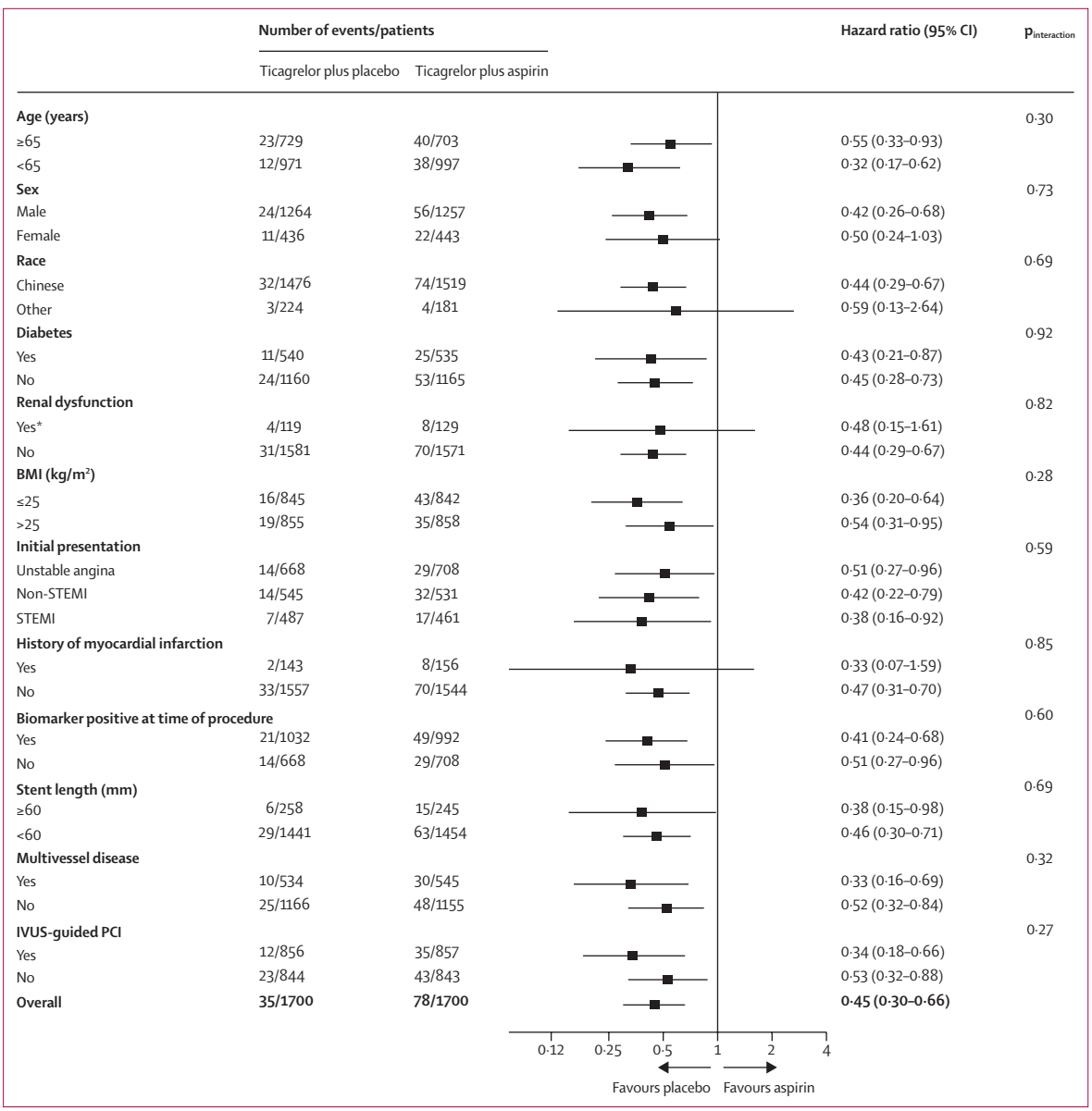

Figure 3: **Clinically relevant bleeding events in prespecified subgroups**
IVUS=intravascular ultrasound. PCI=percutaneous coronary intervention. STEMI=ST-segment elevation myocardial infarction. *Defined as an estimated glomerular filtration rate <60 mL/min per 1·73 m².

improved net clinical outcomes with this regimen. Along with previous studies, the evidence from this trial supports the use of ticagrelor monotherapy in event-free patients to safely reduce major and minor bleeding events during follow-up. This regimen should be particularly considered for patients at high risk of haemorrhagic complications (eg, patients with frailty, those older than 65 years, those with anaemia or previous bleeding history, and those with chronic kidney disease).[30]

Several elements of the trial design contributed to the safety of the ticagrelor monotherapy regimen in our study. Thrombotic events occur most frequently during the first month after percutaneous coronary intervention.[29] Patients who had an ischaemic or bleeding event or were non-adherent with aspirin or ticagrelor for 48 h or more within the first month after percutaneous coronary intervention were excluded at 30 days. The population was therefore identified as compliant at 1 month and likely to tolerate treatment with ticagrelor alone, and few patients required ticagrelor down-titration or conversion to clopidogrel during the 1-year of follow-up. The use of contemporary drug-eluting stents also increased the safety of the ticagrelor monotherapy regimen after 30 days.[31,32] As seen in the subgroup results from the first randomisation in the IVUS-ACS trial,[17] ischaemic event rates can be further reduced

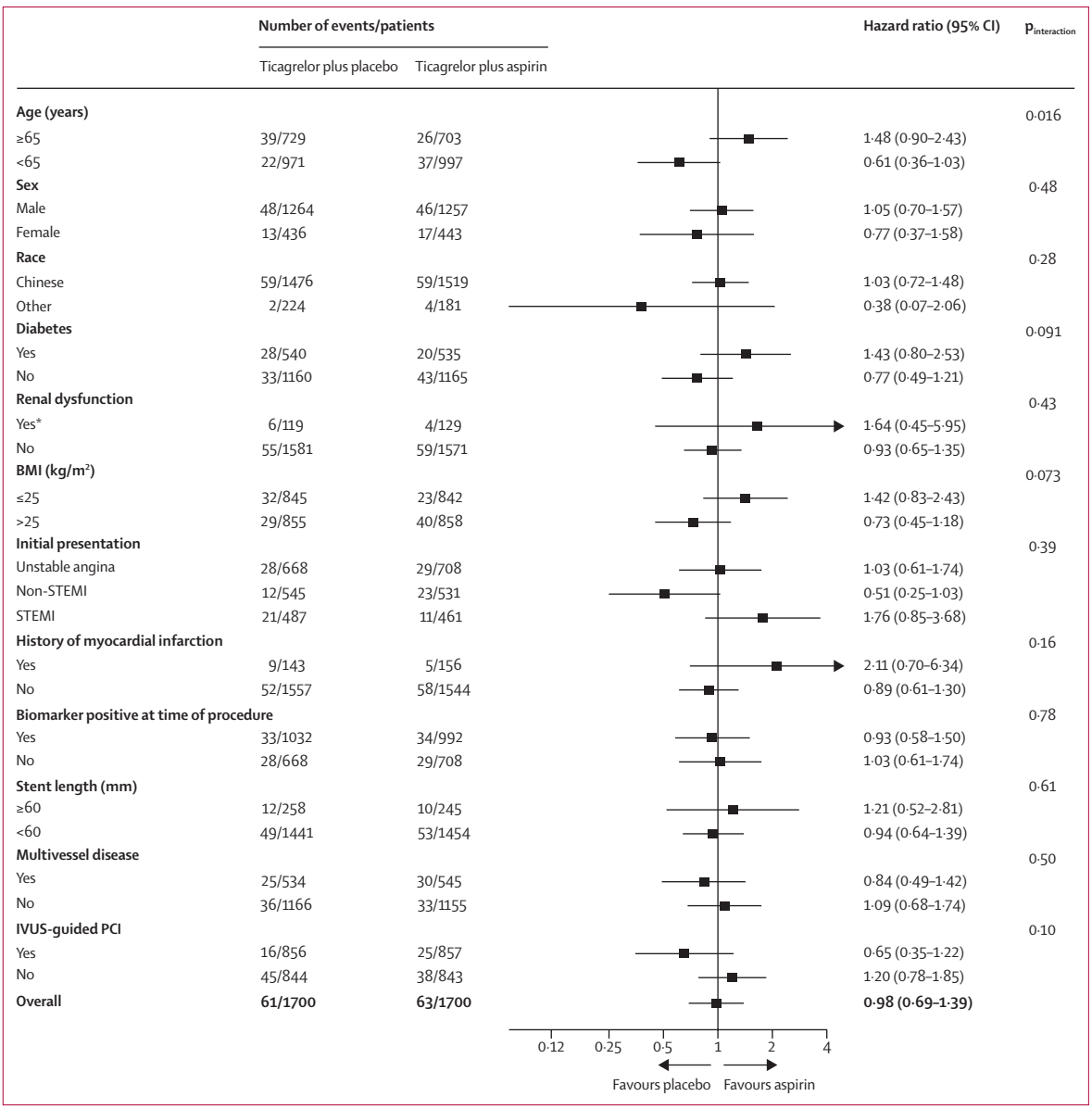

Figure 4: **Composite major adverse cardiovascular or cerebrovascular events in prespecified subgroups**
IVUS=intravascular ultrasound. PCI=percutaneous coronary intervention. STEMI=ST-segment elevation myocardial infarction. *Defined as an estimated glomerular filtration rate <60 mL/min per 1·73 m².

by the use of intravascular imaging guidance, as compared with angiography guidance, during the index percutaneous coronary intervention procedure in patients with an acute coronary syndrome. Detailed outcomes from all four groups of the trial will be reported subsequently.

Our study has some limitations. First, the primary efficacy endpoint included minor bleeding (BARC type 2). However, we also observed lower rates of major bleeding (BARC types 3 or 5; ie, severe or fatal bleeding); TIMI major or minor bleeding; GUSTO moderate, severe, or life-threatening bleeding; and ISTH bleeding with ticagrelor monotherapy, all of which have been associated with subsequent mortality.[19,22–24] Second, we tested non-inferiority for MACCE with an absolute margin of 2·5%. Given the lower than anticipated observed ischaemic event rate in the ticagrelor plus aspirin group (3·7% observed *vs* 6·2% anticipated), this relative margin for non-inferiority testing is wide. However, considering the large sample size and nearly identical event rates in both groups, the rate of MACCE with ticagrelor alone is unlikely to be much higher than with ticagrelor plus aspirin. Third, approximately 40% of patients had biomarker-negative unstable angina. However, high-sensitivity troponin assays were not widely available in China and Pakistan during the enrolment

period of this trial, and it is likely that many of these patients had NSTEMI. Fourth, this study did not assess the safety of ticagrelor monotherapy initiated less than 1 month after percutaneous coronary intervention. In the T-PASS trial, very early cessation of aspirin (median 16 days, IQR 12–25) followed by ticagrelor monotherapy for 1 year after percutaneous coronary intervention decreased bleeding events without an increase in adverse ischaemic outcomes in patients with an acute coronary syndrome.[11] Further placebo-controlled randomised trials testing very early aspirin cessation (ie, less than 1 month after percutaneous coronary intervention) are necessary before any recommendations for a course of dual antiplatelet therapy of less than 1 month can be made for this population. Fifth, although we saw no interaction between the geography of the enrolling centres and randomisation on the clinical outcomes, 2995 (88·1%) of the 3400 enrolled patients were from China, which can reduce the generalisability of the results. Sixth, although the results were consistent in patients presenting with unstable angina (1376 [40·5%] of 3400 patients) and myocardial infarction (2024 [59·5%] of 3400 patients), additional trials exclusively enrolling patients with myocardial infarction would be warranted to provide confirmatory data of non-inferiority for safety (especially in STEMI). Seventh, these findings might not apply to patients with previous coronary artery bypass graft surgery or with other conditions constituting exclusion criteria for this trial. Eighth, BARC type 1 bleeding was also included in the net clinical adverse events endpoint. However, very few such minor bleeds were reported (appendix 2 p 21), and we believe this inclusion did not have any major influence on the results. Ninth, the present results are specific to a ticagrelor monotherapy regimen and do not apply to treatment with prasugrel or clopidogrel alone. Finally, this study does not inform the optimal pharmacotherapy regimen after 12 months.

In summary, to our knowledge, ULTIMATE-DAPT is the first large-scale randomised, placebo-controlled, double-blinded trial comparing the efficacy and safety of treatment with ticagrelor alone versus ticagrelor plus aspirin between month 1 and month 12 in patients with an acute coronary syndrome who remained event-free on dual antiplatelet therapy for 1 month after percutaneous coronary intervention with contemporary drug-eluting stents. The present results show that, in these patients, treatment with a ticagrelor monotherapy regimen between month 1 and month 12 after the intervention decreases the risk of clinically relevant bleeding events while providing similar protection from MACCE as compared with ticagrelor plus aspirin. Further analyses are warranted to identify which patient subgroups, according to varying bleeding and ischaemic risk, can benefit the most from ticagrelor monotherapy.

Contributors

GWS and S-LC designed the study and analysed the data. ZG, XG, AR, J-JZ, BSM, FG, YS, YWa, HZ, FL, HSK, NM, HC, MW, and LC enrolled patients. GWS and S-LC drafted the manuscript with input from ZG, XG, and AR. JK provided crucial input into the conduct of the trial and the draft of the manuscript. J-JZ, BSM, FG, YS, YWa, HZ, FL, HSK, NM, HC, MW, and LC contributed to manuscript revisions. YWe and FC were the primary biostatisticians. GWS and SLC accessed and verified the data in the study. All authors had unrestricted access to the data, vouch for the accuracy of the data and the fidelity of the trial to the protocol, and had final responsibility for the decision to submit for publication.

Declaration of interests

GWS reports speaker honoraria from Medtronic, Pulnovo, Infraredx, Abiomed, Abbott, Amgen, and Boehringer Ingelheim; has served as a consultant to Daiichi Sankyo, Ablative Solutions, CorFlow, Apollo Therapeutics, Cardiomech, Gore, Robocath, Miracor, Vectorious, Abiomed, Valfix, TherOx, HeartFlow, Neovasc, Ancora, Elucid Bio, Occlutech, Impulse Dynamics, Adona Medical, Millennia Biopharma, and Oxitope; has equity or options from Ancora, Cagent, Applied Therapeutics, Biostar family of funds, SpectraWave, Orchestra Biomed, Aria, Cardiac Success, Valfix, and Xenter; reports research support from Abbott, Abiomed, Bioventrix, Cardiovascular Systems, Phillips, Biosense-Webster, Shockwave, Vascular Dynamics, Pulnovo, and V-wave paid directly to institution; and his daughter is an employee at IQVIA. S-LC reports speaker honoraria from Microport, Pulnovo, Boston International Scientific, Medtronic, Sanofi, and BioMed; grants from the National Scientific Foundation of China; and is a Fellow at the Collaborative Innovation Center for Cardiovascular Disease Translational Medicine, Nanjing Medical University, Nanjing, China. All other authors report no competing interests.

Data sharing

Patient-level data collected for this study will not be made publicly available. However, the investigators will consider collaboration and data sharing for specific projects; requests should be addressed to Shao-Liang Chen.

Acknowledgments

This study was funded by the Chinese Society of Cardiology (grant number CSCF 2019-A0003), the National Natural Scientific Foundation of China (grant numbers 91639303, 81770441, and 82121001), and Jiangsu Provincial & Nanjing Municipal Clinical Trial Project (grant number BE 2019615). Stents were supplied by Medtronic and Microport Medical, and antiplatelet agents were supplied by Yung Shin Pharmaceutical Industrial and Shenzhen Salubris Pharmaceuticals. The study was led by Shao-Liang Chen at the Nanjing Medical University and Nanjing First Hospital, Nanjing, China.

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