Guided de-escalation of antiplatelet treatment in patients with acute coronary syndrome undergoing percutaneous coronary intervention (TROPICAL-ACS): a randomised, open-label, multicentre trial

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Summary

Background **Current guidelines recommend potent platelet inhibition with prasugrel or ticagrelor for 12 months after an acute coronary syndrome managed with percutaneous coronary intervention (PCI). However, the greatest anti-ischaemic benefit of potent antiplatelet drugs over the less potent clopidogrel occurs early, while most excess bleeding events arise during chronic treatment. Hence, a stage-adapted treatment with potent platelet inhibition in the acute phase and de-escalation to clopidogrel in the maintenance phase could be an alternative approach. We aimed to investigate the safety and efficacy of early de-escalation of antiplatelet treatment from prasugrel to clopidogrel guided by platelet function testing (PFT).**

Methods **In this investigator-initiated, randomised, open-label, assessor-blinded, multicentre trial (TROPICAL-ACS) done at 33 sites in Europe, patients were enrolled if they had biomarker-positive acute coronary syndrome with successful PCI and a planned duration of dual antiplatelet treatment of 12 months. Enrolled patients were randomly assigned (1:1) using an internet-based randomisation procedure with a computer-generated block randomisation with stratification across study sites to either standard treatment with prasugrel for 12 months (control group) or a step-down regimen (1 week prasugrel followed by 1 week clopidogrel and PFT-guided maintenance therapy with clopidogrel or prasugrel from day 14 after hospital discharge; guided de-escalation group). The assessors were masked to the treatment allocation. The primary endpoint was net clinical benefit (cardiovascular death, myocardial infarction, stroke or bleeding grade 2 or higher according to Bleeding Academic Research Consortium [BARC]) criteria) 1 year after randomisation (non-inferiority hypothesis; margin of 30%). Analysis was intention to treat. This study is registered with ClinicalTrials.gov, number NCT01959451, and EudraCT, 2013-001636-22.**

Findings **Between Dec 2, 2013, and May 20, 2016, 2610 patients were assigned to study groups; 1304 to the guided de-escalation group and 1306 to the control group. The primary endpoint occurred in 95 patients (7%) in the guided de-escalation group and in 118 patients (9%) in the control group ($p_{non\text{-}inferiority}$=0·0004; hazard ratio [HR] 0·81 [95% CI 0·62–1·06], $p_{superiority}$=0·12). Despite early de-escalation, there was no increase in the combined risk of cardiovascular death, myocardial infarction, or stroke in the de-escalation group (32 patients [3%]) versus in the control group (42 patients [3%]; $p_{non\text{-}inferiority}$=0·0115). There were 64 BARC 2 or higher bleeding events (5%) in the de-escalation group versus 79 events (6%) in the control group (HR 0·82 [95% CI 0·59–1·13]; p=0·23).**

Interpretation **Guided de-escalation of antiplatelet treatment was non-inferior to standard treatment with prasugrel at 1 year after PCI in terms of net clinical benefit. Our trial shows that early de-escalation of antiplatelet treatment can be considered as an alternative approach in patients with acute coronary syndrome managed with PCI.**

Funding **Klinikum der Universität München, Roche Diagnostics, Eli Lilly, and Daiichi Sankyo.**

Lancet 2017; 390: 1747–57

Published **Online** August 27, 2017 http://dx.doi.org/10.1016/S0140-6736(17)32155-4

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Introduction

Activation of blood platelets plays a key part both in the initiation and during the early phase of an acute coronary syndrome. Consequently, clinical outcomes of patients with acute coronary syndrome undergoing percutaneous coronary intervention (PCI) have been significantly improved and ischaemic risk has been reduced with the use of potent $P2Y_{12}$ receptor inhibitors like prasugrel or ticagrelor, albeit at the expense of an increased bleeding risk.[1–4] Current acute coronary syndrome guidelines recommend potent $P2Y_{12}$ receptor inhibitors for 1 year in patients with acute coronary syndrome managed by PCI.[5] However, the greatest benefits of these potent drugs are seen early, when the risk of ischaemic complications is highest, while most haemorrhagic events with potent platelet inhibitors arise during chronic treatment.[3,4] This rationale has fuelled interest in strategies of step-wise de-escalation[6] using potent $P2Y_{12}$ inhibitors only in the early phase of treatment,

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See Online for appendix

Research in context

Evidence before this study

International guidelines recommend potent platelet inhibition with prasugrel or ticagrelor in the first year after an acute coronary syndrome. Despite these recommendations, a regimen implying early de-escalation from potent antiplatelet agents to the less potent and off-patent clopidogrel is appealing both from a conceptual and economic perspective. We searched MEDLINE on July 1, 2017, for articles in English with the search terms "antiplatelet treatment de-escalation", "switching antiplatelet therapy", and "acute coronary syndrome guidelines", and found only a few studies with a focus on clinical outcomes (TRANSLATE-ACS, SCOPE registry, TOPIC trial). Data from the TRANSLATE-ACS registry showed that de-escalation is common clinical practice with up to 28% of patients with acute coronary syndrome switching from potent platelet inhibition down to clopidogrel within the first year post discharge on their own or their physician's initiative. The reasons for de-escalation most predominantly include adverse events and issues with reimbursement or availability of potent platelet inhibitors. However, to date, evidence supporting safety and efficacy and thereby justifying de-escalation is lacking and even conflicting. While data from a single registry (SCOPE) pointed towards potential hazards of de-escalating treatment after acute coronary syndrome, a smaller single-centre randomised trial (TOPIC) favoured uniform de-escalation of treatment in event-free patients with acute coronary syndrome at 1 month after percutaneous coronary intervention, mainly driven by a reduction of Bleeding Academic Research Consortium (BARC) grade 2 or higher bleeding in patients receiving de-escalated antiplatelet treatment.

Added value of this study

To the best of our knowledge, TROPICAL-ACS is the first randomised trial to investigate a strategy of early and guided de-escalation of $P2Y_{12}$ inhibition in patients with acute coronary syndrome. The trial population represents a high-risk cohort of biomarker-positive patients with acute coronary syndrome including more than 1400 patients with ST-elevation myocardial infarction. De-escalation guided by platelet function testing (PFT) ensured sufficient platelet inhibition in all patients with acute coronary syndrome in the experimental arm, with about 60% of patients continuing on clopidogrel treatment and 40% of patients requiring escalation back to prasugrel. By showing non-inferiority of PFT-guided de-escalation compared with a standard of potent platelet inhibition for 12 months, our trial provides important evidence justifying tailored de-escalation as an alternative strategy in patients with acute coronary syndrome after coronary stenting. Study results are applicable to all scenarios of de-escalation, regardless of whether the need to de-escalate arises from clinical or economic issues. PFT results can help to justify de-escalation in clopidogrel responders, while they might also help to overcome budgetary issues for patients that would require escalation back to prasugrel.

Implications of all the available evidence

Based on all the available evidence, uniform and potent platelet inhibition in patients with acute coronary syndrome probably remains standard of care, because TROPICAL-ACS did not show superiority of de-escalation. Notwithstanding, alternative treatment concepts are desired for a significant proportion of patients in clinical practice. Our trial now supports the safety and efficacy of an early and guided de-escalation of platelet inhibition in patients with acute coronary syndrome as an alternative strategy that can be followed whenever necessary for medical or socioeconomic reasons. The regimen of guided treatment seems also practical beyond the framework of a randomised controlled trial, because patients in many countries worldwide typically have planned outpatient visits within the first weeks after an acute coronary syndrome.

and using the less potent clopidogrel during the chronic treatment course. However, to date, the evidence supporting safety and efficacy and thereby justifying de-escalation is limited and the few available data from smaller studies are conflicting.[7,8] Despite the absence of unequivocal evidence, de-escalation of antiplatelet therapy after acute coronary syndrome is quite common in clinical practice[8–11] and about 15–28% of patients with acute coronary syndrome[9] are switched from potent to less potent treatment after discharge. This occurs for several reasons, including adverse bleeding events or non-bleeding events, a perceived high bleeding risk, and economic issues favouring off-patent clopidogrel.[1,9,11]

Nevertheless, any de-escalation of antiplatelet therapy from a potent $P2Y_{12}$ inhibitor to the less potent clopidogrel should account for large response variability of the latter[12] and the consequential issue of high on-treatment platelet reactivity (HPR), which exists in a substantial proportion of patients with acute coronary syndrome.[13–15] Patients with HPR exhibit an increased risk for recurrent ischaemic events, including myocardial infarction and stent thrombosis.[13–15] Hence, platelet function testing (PFT) could serve to make de-escalation safer by identifying patients with HPR on clopidogrel, who might be exposed to an increased risk of thrombotic events due to insufficient $P2Y_{12}$ inhibition and who should therefore continue potent $P2Y_{12}$ inhibitors like prasugrel. Thus, we aimed to investigate the safety and efficacy of a PFT-guided early de-escalation of antiplatelet treatment compared with standard prasugrel therapy in patients with acute coronary syndrome undergoing PCI.

Methods

Study design and patients

The Testing Responsiveness To Platelet Inhibition On Chronic Antiplatelet Treatment For Acute Coronary Syndromes (TROPICAL-ACS) trial was an investigator-initiated, randomised, parallel-group, open-label,

assessor-blinded, multicentre trial that was done at 33 European sites (two in Austria, 20 in Germany, seven in Hungary, and four in Poland) and had an academic sponsor (Klinikum der Universität München). Patients were eligible if they had biomarker-positive acute coronary syndrome with a successful PCI (defined as a post-PCI diameter stenosis <20% and thrombolysis in myocardial infarction [TIMI] flow ≥2), and planned treatment of prasugrel for 12 months after the procedure. The appendix (p 2) lists all inclusion and exclusion criteria; the study protocol with further details has been published previously.[16]

Patients provided written informed consent. An independent data safety monitoring board (DSMB) oversaw the trial and had full access to unblinded data. Study monitoring for all patients was done by an external service provider (Münchner Studienzentrum, MSZ, Munich, Germany). The institutional ethics committee of each participating site, as well as the competent national agencies approved the trial. The study was conducted in accordance with the principles of the Declaration of Helsinki.

Randomisation and masking

Using an internet-based randomisation procedure with a computer-generated block randomisation with stratification across study sites, patients with acute coronary syndrome were randomly assigned before planned discharge in a 1:1 fashion to the two study groups of either PFT-guided de-escalation or control group. Patients were considered enrolled in the study and eligible for the final intention-to-treat analysis at the time of randomisation. Figure 1 summarises the study flow of the TROPICAL-ACS study. Patients in the control group received a standard care of 12 month prasugrel treatment at a dose of 10 mg or 5 mg according to the label and the current guideline recommendations.[5,17] Patients in the de-escalation group received a post-discharge treatment, consisting of 1 week prasugrel treatment (10 mg or 5 mg per day) followed by 1 week of clopidogrel treatment (75 mg per day) and a platelet function measurement (on clopidogrel) 2 weeks after hospital discharge (PFT-guided de-escalation group). Based on PFT results in the guided de-escalation group, patients were either switched back to prasugrel, when a status of HPR with insufficient platelet inhibition was detected, whereas patients with sufficient platelet inhibition (no HPR) continued with clopidogrel.

Study group-related treatment was planned to start on the day after discharge and study drugs for the first 14 days post discharge were packed and provided by the pharmacy department of the Klinikum der Universität München (Munich, Germany). We deemed this necessary to guarantee an exact intake of tablets during a time frame covering the switch of treatment in the guided de-escalation group. For both groups, three extra tablets (provisional medication) were included in the box for week 2 to ensure flexibility regarding the timing of the first follow-up visit out to day 17. Treatment after day 14 post discharge until 12 months was planned according to the assigned randomisation and HPR status in the guided de-escalation group and was prescribed by the patient's primary care physician in both study groups. Further details on randomisation procedures and study drugs were published previously.[16]

Procedures

2 weeks after discharge from the primary care hospital, where the index PCI was done, all patients had an outpatient visit. In addition, patients were contacted by phone call at 30 days, 6 months, and 12 months after randomisation. These calls were made to explore study endpoints and adverse events and to assess adherence to the assigned antiplatelet therapy using a study-specific designed standardised questionnaire. In case of a suspected clinical event all source data were collected to allow for precise event adjudication by the event adjudication committee.

For the on-site follow-up visit, participants from both study groups underwent planned and prescheduled blood sampling for PFT under steady-state conditions. The Multiplate analyser (Roche Diagnostics, Rotkreuz, Switzerland) was used for testing. Details of this method and its predictive value have been published previously.[13,14,16] A status of HPR was defined based on the results of previous studies and the consensus documents of the Working Group on HPR as an adenosine diphosphate test aggregation value of 46 units or higher on the Multiplate analyser.[13,14] In the control group, testing was done only for observational purposes and results did not affect drug selection or dosing. In the guided de-escalation group, testing results determined the further course of treatment: patients with HPR were immediately switched back to prasugrel, while those without HPR continued on clopidogrel (figure 1).

Outcomes

The primary endpoint was a combined ischaemic and bleeding endpoint (net clinical benefit), which was the composite of death from cardiovascular causes (all deaths were assumed cardiovascular in nature unless a non-cardiovascular cause could be clearly provided), myocardial infarction (defined according to the 3rd universal definition of myocardial infarction[18]), stroke, and bleeding grade 2 or higher defined according to Bleeding Academic Research Consortium (BARC) criteria[19] at 12 months after randomisation. The key secondary endpoint was defined as BARC class 2 or higher bleeding events at 12 months. Further secondary endpoints included the ischaemic components (combined and singular) of the primary endpoint (cardiovascular death, myocardial infarction, and stroke), stent thrombosis defined according to Academic Research Consortium (ARC) criteria,[20] the incidence of death from any cause, and urgent ischaemia-driven revascularisation at 12 months. With respect to

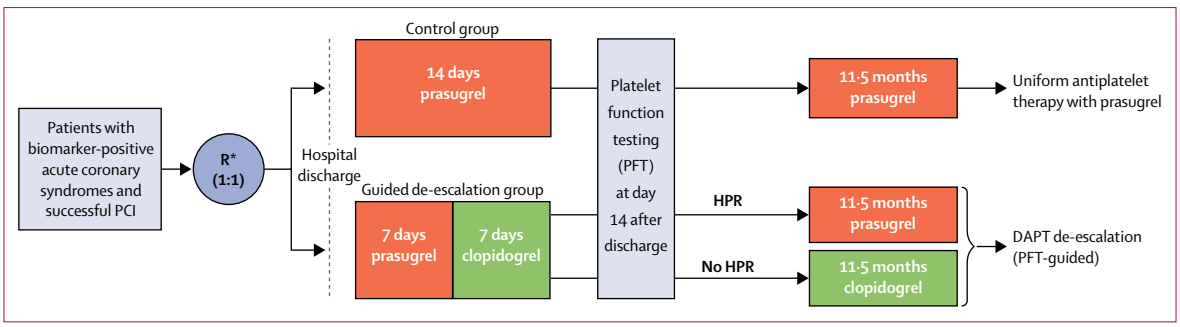

Figure 1: **Study design and groups**
The figure shows the control group and the experimental group with guided de-escalation of antiplatelet treatment. Patients were randomly assigned (1:1) after PCI and directly before planned discharge from hospital. On-treatment platelet reactivity was measured in both study groups. In the control group, on-prasugrel testing results had no effect on further treatment, which was prasugrel for all patients. Based on the testing results in the guided de-escalation group (on clopidogrel treatment), the further treatment was determined at day 14 post discharge. Protocol-mandated treatment required clopidogrel in no-HPR patients and a switch back to prasugrel in HPR patients. PCI=percutaneous coronary intervention. HPR=high on-treatment platelet reactivity. R*=randomisation. DAPT=dual antiplatelet therapy.

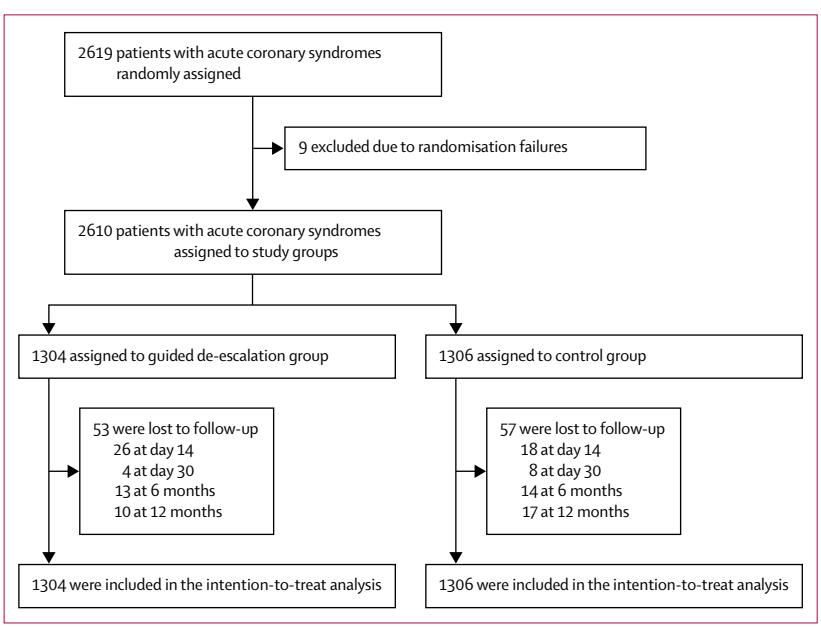

Figure 2: **Trial profile**

bleeding events, all reported bleedings were assessed and reported according to BARC classification (BARC types 1–5). An independent event adjudication committee masked to treatment assignment adjudicated all suspected clinical events.

Statistical analysis

The study was designed to show non-inferiority for the guided de-escalation group versus the control group regarding the primary composite endpoint. Considering the results of a landmark analysis from the TRITON-TIMI 38 trial,[3] based on the incidence of early versus late major bleeding events[3] and based on the incidence of BARC 2 or higher bleeding complications in a PCI cohort,[21] the incidence of the primary endpoint of this study was assumed to be 10·5% in the control group. A non-inferiority margin of 30% was estimated, which is in accordance with non-inferiority margins used in contemporary trials of antithrombotic treatment in cardiovascular diseases.[22,23] Sample size calculations (nQuery Advisory, Statistical Solutions, Farmer's Cross, Cork, Ireland) were done based on a one-sided type 1 error of 5% and a power of 80%. For the primary endpoint assumptions, 1172 patients in each group were needed. Assuming an incidence of BARC 2 or higher bleeding in the control group of 4·9% and an expected reduction of BARC 2 or higher bleeding by 45% in the de-escalation group, 1179 patients per group would be required to show superiority (based on two-sided type 1 error of 5% and a power of 80% for the key secondary endpoint (BARC 2 or higher bleeding). To compensate for losses to follow-up and to be powered for the primary and secondary endpoint assessment the enrolment of a total of 2600 patients (1300 patients per group) was planned. All analyses were done on an intention-to-treat basis. In addition, per-protocol analyses were done. Differences in endpoints were analysed in Cox-regression models for survival analysis. In all cases of the use of the Cox proportional hazards model, the proportional hazards assumption was met. Kaplan-Meier plots were generated to visualise the risk of outcome events in both groups. Binary and other categorical variables were compared using Fisher's exact test and χ^2 test, respectively, for continuous data two-sided unpaired Wilcoxon test or Student's *t* test were used as appropriate. Data were analysed with R version 3.3.0.

Role of the funding source

The funders of this study had no role in study design, collection of data and data analysis, or writing of the manuscript. DS and SM had full access to the data and take full responsibility for the decision to submit for publication.

This study is registered with ClinicalTrials.gov, number NCT01959451, and EudraCT, 2013-001636-22.

	Control group (n=1306)	Guided de-escalation group (n=1304)
Age (years)	58·5 (10·2)	59·0 (10·1)
Men	283 (22%)	275 (21%)
Body-mass index (kg/m^2)	28·4 (5·0)	28·1 (4·5)
White	1295 (99%)	1295 (99%)
Previous percutaneous coronary intervention	186 (14%)	173 (13%)
Previous coronary artery bypass surgery	46 (4%)	39 (3%)
Previous myocardial infarction	153 (12%)	140 (11%)
History of peripheral artery occlusive disease	39 (3%)	46 (4%)
History of coronary artery disease	204 (16%)	175 (13%)
Renal insufficiency	34 (3%)	33 (3%)
Diabetes mellitus	287 (22%)	240 (18%)
Current smoker	591 (45%)	591 (45%)
Arterial hypertension	806 (62%)	793 (61%)
Hyperlipidaemia	529 (41%)	546 (42%)
Family history of coronary artery disease	466 (36%)	419 (32%)
Haemoglobin (g/dL)	14·2 (1·6)	14·3 (1·6)
Creatinine (mg/dL)	0·9 (0·2)	0·9 (0·3)
Medication at admission		
Aspirin	343 (26%)	303 (23%)
ADP receptor antagonist	76 (6%)	71 (5%)
Beta blocker	368 (28%)	378 (29%)
ACE inhibitor	341 (26%)	357 (27%)
Angiotensin$_1$ receptor antagonist	161 (12%)	173 (13%)
Calcium antagonist	166 (13%)	178 (14%)
Proton-pump inhibitor	175 (13%)	174 (13%)
Statin treatment	298 (23%)	286 (22%)

Data are n (%) or mean (SD). ADP=adenosine diphosphate. ACE=angiotensin-converting-enzyme.

Table 1: **Baseline characteristics of the intention-to-treat population**

	Control group (n=1306)	Guided de-escalation group (n=1304)
Cause of PCI		
STEMI	722 (55%)	731 (56%)
NSTEMI	584 (45%)	573 (44%)
Access site		
Brachial	3 (<1%)	0
Femoral	541 (41%)	523 (40%)
Radial	762 (58%)	781 (60%)
Number of diseased coronary vessels		
1	682 (52%)	659 (51%)
2	345 (26%)	359 (28%)
3	279 (21%)	286 (22%)
Anticoagulant agent used for PCI		
Bivalirudin	55 (4%)	54 (4%)
Low molecular weight heparin	70 (5%)	72 (6%)
Unfractionated heparin	1181 (90%)	1178 (90%)
Use of glycoprotein IIb/IIIa antagonist	247 (19%)	244 (19%)
TIMI flow grade before PCI		
0	512 (39%)	511 (39%)
1	171 (13%)	173 (13%)
2	302 (23%)	321 (25%)
3	321 (25%)	299 (23%)
Coronary vessels treated		
Left main	12 (1%)	29 (2%)
Left anterior descending	556 (43%)	562 (43%)
Left circumflex	253 (19%)	266 (20%)
Right coronary artery	450 (35%)	433 (33%)
Coronary bypass graft	35 (3%)	14 (1%)
AHA/ACC classification of lesions		
A	155 (12%)	161 (12%)
B1	425 (33%)	434 (33%)
B2	340 (26%)	327 (25%)
C	386 (30%)	382 (29%)
Ostial lesion	98 (8%)	97 (7%)
Bifurcation lesion	195 (15%)	204 (16%)
Stent type		
DES	1002 (77%)	1003 (77%)
BMS	208 (16%)	224 (17%)
BVS	83 (6%)	68 (5%)
None (PTCA only)	13 (1%)	9 (1%)
TIMI flow grade after PCI		
2	38 (3%)	38 (3%)
3	1268 (97%)	1266 (97%)

Data are n (%). STEMI=ST-segment elevation myocardial infarction. NSTEMI=non-ST-segment elevation myocardial infarction. PCI=percutaneous coronary intervention. TIMI=thrombolysis in myocardial infarction. AHA=American Heart Association. ACC=American College of Cardiology. DES=drug-eluting stent. BMS=bare metal stent. BVS=bioresorbable vascular scaffold. PTCA=percutaneous transluminal coronary angioplasty.

Table 2: **Angiographic and procedural characteristics**

Results

Between Dec 2, 2013, and May 20, 2016, 2610 eligible patients with acute coronary syndrome were randomly assigned at 33 European PCI sites (figure 2). These patients constitute the intention-to-treat population, in which 1306 patients were randomly assigned to the control group and 1304 patients to the guided de-escalation group. Mean age of patients was 59 years (SD 10) and 558 (21%) were women. 1453 (56%) patients presented with ST-elevation myocardial infarction (STEMI). Table 1 summarises the baseline characteristics of the study cohort and table 2 provides an overview of procedural characteristics of the index PCI.

For the pre-scheduled follow-up visit at 2 weeks after hospital discharge the follow-up rate was 98% in the guided de-escalation group and 99% in the control group. In the guided de-escalation group, a status of HPR was noted in 511 patients (39% of the intention-to-treat population). In line with the protocol, 506 (99%) of the

	Control group (n=1306)	Guided de-escalation group (n=1304)	Hazard ratio (95% CI)	p value
Net clinical benefit				
Primary endpoint (cardiovascular death, myocardial infarction, stroke, bleeding BARC ≥2)	118 (9%)	95 (7%)	0·81 (0·62–1·06)	$p_{non\text{-}inf}$ =0·0004; p_{sup} =0·12
Combined ischaemic events (cardiovascular death, myocardial infarction, stroke) and all bleeds (BARC bleeding 1–5)	175 (13%)	143 (11%)	0·81 (0·65–1·01)	0·06
Ischaemic events				
Combined ischaemic events (cardiovascular death, myocardial infarction, stroke)	42 (3%)	32 (3%)	0·77 (0·48–1·21)	$p_{non\text{-}inf}$ =0·0115
Cardiovascular death	9 (1%)	7 (1%)	0·78 (0·29–2·10)	0·63
Myocardial infarction	28 (2%)	24 (2%)	0·86 (0·50–1·49)	0·59
Stroke	7 (1%)	3 (<1%)	0·43 (0·11–1·67)	0·22
Stent thrombosis (definite)	3 (<1%)	2 (<1%)	0·67 (0·11–4·03)	0·66
All-cause mortality	12 (1%)	11 (1%)	0·92 (0·41–2·10)	0·85
Urgent revascularisation	29 (2%)	40 (3%)	1·45 (0·89–2·34)	0·13
Bleeding events				
Key secondary endpoint (BARC bleeding ≥2)	79 (6%)	64 (5%)	0·82 (0·59–1·13)	0·23
BARC type 1 or 2	119 (9%)	98 (8%)	0·82 (0·63–1·07)	0·15
BARC type 3 or 5	20 (2%)	17 (1%)	0·85 (0·45–1·63)	0·63
Any BARC bleeding	137 (11%)	114 (9%)	0·83 (0·65–1·06)	0·14
Bleeding events				
BARC type 1	64 (5%)	52 (4%)	0·81 (0·56–1·17)	0·26
BARC type 2	61 (5%)	47 (4%)	0·77 (0·53–1·13)	0·19
BARC type 3	19 (2%)	17 (1%)	0·90 (0·47–1·73)	0·75
BARC type 4	1 (<1%)	2 (<1%)	2·02 (0·18–22·20)	0·57
BARC type 5	1 (<1%)	0	..	0·89

Data are n (%). p values presented are for superiority comparisons unless otherwise stated. BARC=Bleeding Academic Research Consortium. $p_{non\text{-}inf}$=p value for non-inferiority. p_{sup}=p value for superiority.

Table 3: **Clinical outcomes at 12 months' follow-up**

511 patients were switched back from clopidogrel to prasugrel, while only five patients with HPR continued clopidogrel based on an individual decision of the treating physician at the follow-up visit. In the control group, a status of HPR was found in 188 patients (14% of the intention-to-treat population). Adherence to the assigned $P2Y_{12}$ inhibitor therapy was repeatedly assessed throughout the study in all patients. During the study period of 12 months, adherence to the protocol-mandated treatment was high with a rate of 94·2% in the control group and 94·4% in the guided de-escalation group. Use of low-dose (5 mg per day) instead of standard dose prasugrel (10 mg per day) for study drug treatment was low (4·0% in guided de-escalation group *vs* 4·2% in control group) and did not differ between the study groups (p=0·88). During the 1-year study period, 43 patients (2%) withdrew consent and 110 (4%) were lost to follow-up (figure 2).

At 1 year, the combined primary endpoint occurred in 95 patients (7%) in the guided de-escalation group and in 118 patients (9%) in the control group ($p_{non\text{-}inferiority}$=0·0004; HR 0·81 [95% CI 0·62–1·06], $p_{superiority}$=0·12; table 3; figure 3A). The ischaemic components of the primary endpoint (cardiovascular death, myocardial infarction, and stroke) occurred in 32 patients (3%) in the guided de-escalation group and in 42 patients (3%) in the control group (HR 0·77 [95% CI 0·48–1·21]; p=0·25; figure 3C), indicating that early de-escalation did not result in an increased risk of cardiovascular death, myocardial infarction, or stroke ($p_{non\text{-}inferiority}$=0·0115). Table 3 summarises relevant outcome data for all individual components of the combined ischaemic endpoint. No significant differences were observed for any of the ischaemic components of the primary endpoint (p≥0·22) as well as for the rate of urgent revascularisation (p=0·13). All-cause mortality at 1 year was 1% (12 events) in the control group versus 1% (11 events) in the guided de-escalation group (p=0·85). The cumulative incidence of definite stent thrombosis was low with two events (<1%) in the guided de-escalation group versus three events (<1%) in the control group (HR 0·67 [95% CI 0·11–4·03]; p=0·66).

The incidence of the key secondary endpoint of BARC 2 or higher bleedings was 5% (64 events) in the guided de-escalation group versus 6% (79 events) in the control group (HR 0·82 [95% CI 0·59–1·13]; p=0·23; figure 3B). The cumulative incidence of all bleeding events (BARC class 1 to 5) was 9% (114 events) in the guided de-escalation group versus 11% (137 events) in the control group (HR 0·83 [95% CI 0·65–1·06]; p=0·14; figure 3D). Table 3 summarises all bleeding events according to BARC types (1 to 5) across groups. Per-protocol analyses yielded similar results to the intention-to-treat analyses for the primary study endpoint (HR 0·84 [95% CI 0·64–1·19]; $p_{non\text{-}inferiority}$=0·0013 for guided de-escalation *vs* control group) and for the key secondary endpoint of BARC 2 or higher bleedings (HR 0·81 [95% CI 0·58–1·17]; p=0·24 for guided de-escalation *vs* control group) of the study.

Relevant clinical variables like clinical presentation (STEMI *vs* non-ST elevation myocardial infarction [NSTEMI]), age, sex, and status for diabetes were subject to post-hoc subgroup analyses for the primary endpoint. For study group comparisons, patients with STEMI (HR 0·54 [95% CI 0·35–0·83]; p=0·004; $p_{interaction}$=0·0116) and younger (age ≤70 years) patients (0·70 [0·51–0·96]; p=0·0270; $p_{interaction}$ for categorical model =0·11, $p_{interaction}$ for continuous model =0·0229) showed significant differences favouring guided de-escalation. Figure 4 shows the results of relevant subgroups and their outcomes with respect to the study group. Further analyses of all control group patients versus patients treated with clopidogrel from the guided de-escalation group and on patients treated with prasugrel versus those

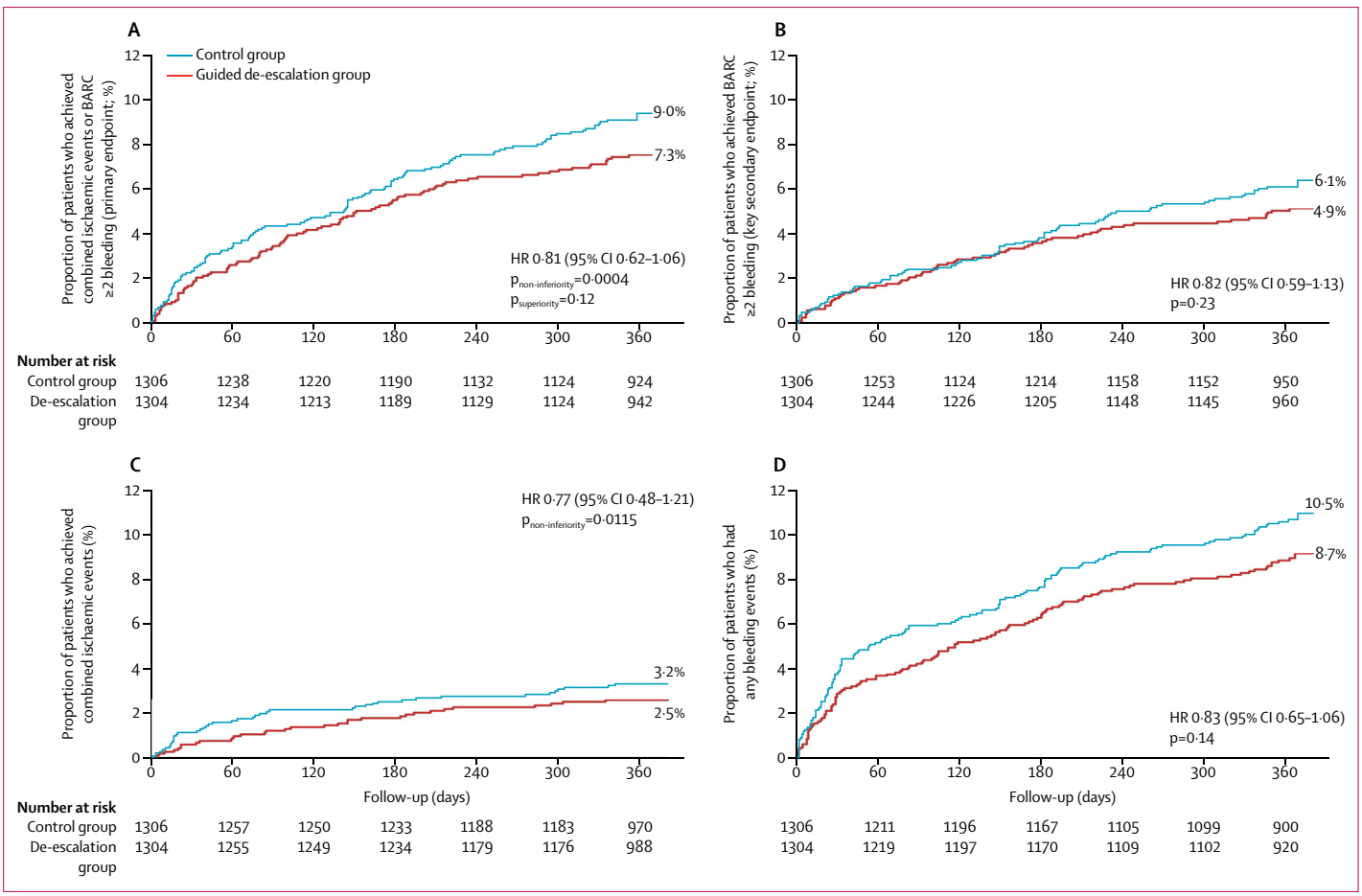

Figure 3: **Kaplan-Meier curves for the primary endpoint (net clinical benefit; A), the key secondary endpoint (BARC 2 or higher bleeding; B), the combined ischaemic endpoint (C), and all bleeding events (BARC class 1–5; D) at 12 months' follow-up**
BARC=Bleeding Academic Research Consortium. HR=hazard ratio.

treated with clopidogrel (as-treated analysis) are shown in the appendix (pp 3–4).

Discussion

De-escalation of antiplatelet treatment after an acute coronary syndrome is conceptually appealing and frequently practised in real-world scenarios.[6,8–11,24–26] Nevertheless, there is little evidence until now to justify switching regimens. TROPICAL-ACS is currently the only trial investigating a concept of guided de-escalation of $P2Y_{12}$ inhibition in an all-comers cohort of patients with acute coronary syndrome. Key findings from this study are that a stage-adapted antiplatelet treatment strategy with initial potent platelet inhibition using prasugrel, followed by guided dual antiplatelet treatment (DAPT) de-escalation to clopidogrel proved to be feasible and non-inferior to conventional 12-month prasugrel therapy. In particular, the rate and distribution of ischaemic events were not increased with guided DAPT de-escalation. Hence, this study identifies guided DAPT de-escalation as an alternative strategy in patients with acute coronary syndrome that are deemed unsuitable for maintained potent platelet inhibition for whatever medical or socioeconomic reasons.[9]

Several further observations are worth mentioning. First, by contrast with previous studies investigating concepts of uniform de-escalation,[7,8] we used individualised PFT-guided de-escalation in this study. Landmark data[3,4] from PLATO and TRITON-TIMI 38 trials showed that even though protection from recurrent ischaemia with potent agents was most prominent during the acute phase, it persisted throughout chronic treatment out to 12 months after an acute coronary syndrome. Hence, PFT guidance of de-escalation was applied to guarantee sufficient platelet inhibition in all patients with acute coronary syndrome during their chronic course of treatment. Second, adherence to per-protocol DAPT was higher than in many other recent trials of acute coronary syndrome[1,7,10] and ischaemic risk was low in both study groups. These observations could be related to the fact that drug treatment was monitored in all patients enrolled into our trial, which potentially had beneficial effects on

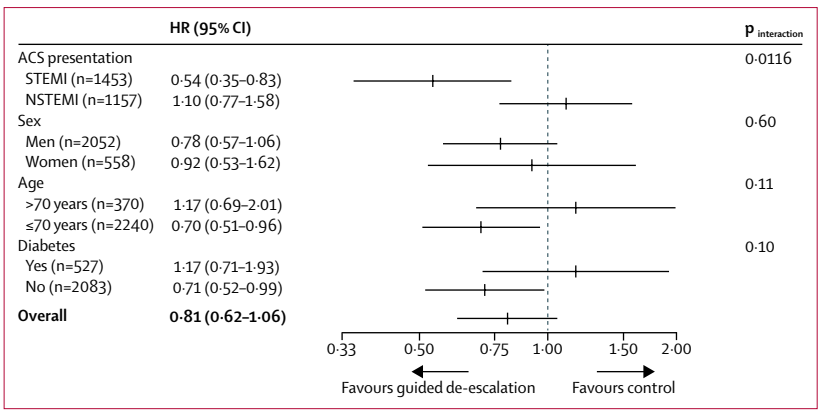

Figure 4: **Subgroup analyses**
Subgroup analyses of the primary composite endpoint (net clinical benefit) in relevant subgroups of the study cohort (clinical presentation: STEMI/NSTEMI, sex, age, and diabetes). $p_{interaction}$ represents the likelihood of interaction between the variable and the treatment strategy (platelet function testing-guided de-escalation *vs* uniform prasugrel treatment). ACS=acute coronary syndrome. HR=hazard ratio. STEMI=ST-segment elevation myocardial infarction. NSTEMI=non-ST-segment elevation myocardial infarction.

patient compliance. Third, high drug adherence and follow-up rates within this study proved the feasibility of guided de-escalation as early as 1 week after patient's discharge. DAPT de-escalation seems clinically most relevant when applied early, considering that adverse events, including side-effects and bleeds, occur over time during maintenance therapy. Nevertheless, it seems reasonable to extrapolate from this study that de-escalation would also be feasible and safe at later stages during chronic antiplatelet treatment. Further on, the rate of ischaemic events was lower in this study than in previous trials, including TRITON-TIMI 38 and PLATO.[1,2] It must be emphasised that randomisation in our trial was done before discharge and hence several days after PCI. Thus, early and peri-procedural events that dominated the overall event rates of previous studies[1,2] were not included in our trial. This together with the increased safety of contemporary PCI with a high rate of radial access and use of latest generation drug-eluting stents (eg, everolimus-eluting or zotarolimus-eluting stents) are likely explanations for the lower risk of ischaemic events in our trial.

Previous trials addressing concepts of de-escalation of antiplatelet treatment are limited and have yielded somewhat conflicting findings. Observational data from the SCOPE[8] registry enrolling 1363 patients with acute coronary syndrome showed that de-escalation from potent antiplatelet inhibitors to clopidogrel was independently associated with adverse events during chronic DAPT. By contrast, the recent TOPIC trial[7] reported that a switch over from ticagrelor or prasugrel to clopidogrel 1 month after PCI for acute coronary syndrome reduced bleeding complications. However, TOPIC differs essentially from this study in various aspects: first, primary endpoint selection (composite of cardiovascular death, unplanned hospital admission leading to urgent coronary revascularisation, stroke, and bleeding episodes as defined by the BARC type ≥2) allowing for a smaller sample size to show superiority (645 patients in TOPIC *vs* 2610 patients in TROPICAL-ACS); second, the monocentric study design in TOPIC; third, a moderate adherence (75%) to treatment in the control group of TOPIC; fourth, TOPIC did not specifically report important ischaemic endpoints like myocardial infarction or stent thrombosis, limiting the conclusions that can be made regarding safety aspects of de-escalation; and most importantly, fifth, TOPIC used uniform de-escalation switching all patients in the de-escalation arm from an established potent $P2Y_{12}$ inhibitor to the less potent clopidogrel. By contrast, our study accounts for the substantial response variability of clopidogrel[12,14,15] and considers the persistent anti-ischaemic potential of sufficient platelet inhibition seen during the chronic treatment phase.[1,2] This is achieved by implementation of drug-response testing precluding de-escalation in patients with HPR, carrying a higher risk of thrombotic events in a background of insufficient $P2Y_{12}$ inhibitor therapy.[14,15] Findings from this study show that PFT-tailored de-escalation is safe, because none of the ischaemic endpoints—alone or in combination—tended to be higher in the guided de-escalation group than in the control group. We also did not observe any clustering of thrombotic events during the early phase of treatment after discharge, where antiplatelet drugs were switched per protocol in the guided de-escalation group.

Besides recurrent ischaemia, bleeding complications are among the most frequent adverse events after PCI, both during the acute and even more so during the maintenance phase of treatment.[3,4] We observed numerically more events across all BARC classes in the control group than in the guided de-escalation group. However, these differences did not reach a level of statistical significance and were most pronounced for minimal and minor bleeds, while we observed no relevant reduction in BARC 3–5 bleeding in the guided de-escalation group. However, even minor bleeds might have important effects on treatment compliance and health-care costs.[27–29] The relative risk reductions observed for bleeding risk in this study are similar to the differences observed in prasugrel versus clopidogrel study groups in the TRITON-TIMI trial.[2] Nevertheless, the overall reduction in bleeding risk by de-escalation was smaller than expected, which might at least in part be due to the fact that about 40% of patients in the guided de-escalation group showed HPR on clopidogrel and continued prasugrel maintenance treatment.

Even though this study uses PFT to back up de-escalation in a cohort of patients in which potent platelet inhibition is established and recommended, it should not be considered primarily a PFT study. Nevertheless, our trial needs to be discussed against the background of previous studies using PFT to tailor DAPT. ADAPT-DES[15] and large meta-analyses[14] have confirmed the predictive value of PFT for ischaemic and bleeding events after PCI. However, subsequent randomised

trials implementing PFT for guidance of antiplatelet therapy failed to show a positive effect of testing on patient outcomes. Yet, the concepts of tailored treatment tested in previous trials substantially differ from the approach of guided de-escalation investigated in this study. Earlier trials aimed to test PFT-guided escalation rather than de-escalation of DAPT focusing predominantly[30,31] or exclusively[32] on low-risk elective PCI patients. The recent ANTARCTIC trial[33] is the only previous trial using PFT to tailor DAPT in a dedicated acute coronary syndrome cohort. However, there are substantial differences in study design between ANTARCTIC and this study: ANTARCTIC randomly assigned patients with acute coronary syndrome who were aged 75 years or older to receive oral prasugrel 5 mg daily with or without dose or drug adjustment for escalation or de-escalation depending on platelet function monitoring. In essence, ANTARCTIC compared the effect of prasugrel 5 mg to a regimen in which low-dose prasugrel was replaced by clopidogrel 75 mg in less than half of patients. This is a limitation of ANTARCTIC, because superiority of low dose prasugrel (5 mg) compared with clopidogrel 75 mg with respect to clinical outcomes has never been confirmed. Hence, TROPICAL-ACS is the only trial designed to test PFT-guided de-escalation of standard dose prasugrel to clopidogrel in all-comers patients with acute coronary syndrome. Generally, standardised platelet function assays are practical and have already been implemented into clinical routine.[34] From an economic point of view, costs for PFT are marginal, while cost savings when using off-patent clopidogrel instead of potent platelet inhibitors can be substantial.[29]

Our study population was characterised by a high proportion (>50%) of high-risk STEMI patients. STEMI patients derived a net clinical benefit from guided DAPT de-escalation. This is not contradictory to observations made in TRITON-TIMI,[35] where STEMI patients showed the greatest benefit of potent inhibition very early after PCI, a time frame where also in TROPICAL-ACS both groups received uniform prasugrel treatment. One underlying reason for the positive interaction observed for STEMI patients might be related to the fact that this cohort is characterised by less comorbidities and a lower frequency of multivessel disease when compared with NSTEMI patients.[36] In fact, the idea of tailored de-escalation in STEMI patients was brought up years ago,[37] based on the results of the STEMI subgroup in TRITON-TIMI.[35] Our study tackles this hypothesis and suggests that STEMI patients could be good candidates for DAPT de-escalation, whenever this is deemed necessary. In addition, younger patients (≤70 years), constituting 86% of the entire study population, also showed favourable outcomes with guided de-escalation. Nevertheless, subgroup analyses should be understood as descriptive and hypothesis generating. Definite answers on what subgroups derive a significant clinical benefit from guided de-escalation would require even larger clinical trials powered to show superiority.

We acknowledge limitations related to our clinical trial. The non-inferiority margin of 30% chosen for our study can be considered as a potential limitation. However, in post-hoc analyses non-inferiority for the primary endpoint was even maintained with a smaller non-inferiority margin of 10% ($p_{\text{non-inferiority}}=0\cdot0117$). This, together with the fact that both ischaemic as well as bleeding event rates if any were numerically lower, but not higher with guided de-escalation compared with standard treatment, justifies implementation of guided de-escalation as an alternative treatment strategy into clinical practice. Our protocol mandated for choosing prasugrel. Thus, to what extent our findings can be extrapolated to ticagrelor remains unclear. Nevertheless, prasugrel and ticagrelor have very similar $P2Y_{12}$ inhibitory effects[38] and a randomised study comparing the two drugs in patients with acute coronary syndrome showed similar efficacy and safety outcomes.[10] This suggests that our findings could indeed apply to patients with acute coronary syndrome treated with ticagrelor. TROPICAL-ACS was planned as an all-comers trial and did not preferentially enrol patients susceptible to bleeding complications, even though they represent potential and excellent candidates for PFT guided de-escalation and are more likely to de-escalate DAPT post-discharge based on large observational registries.[9] However, patients susceptible to bleeding complications were also excluded from the PLATO and TRITON-TIMI 38 trials.[1,2] Hence, whether these patients derive a net clinical benefit from potent platelet inhibitors in the first place is unclear. As a consequence, enrolment of patients susceptible to bleeding into a trial using prasugrel in one study arm is probably limited by preferential upfront use of clopidogrel in these patients and the reduced adherence to potent platelet inhibition. Finally, further limitations of our trial are the open-label design, the exclusion of patients with a history of stroke, and the proportion of patients lost to follow-up, which was 4% in both study groups.

In conclusion, a guided de-escalation of antiplatelet treatment was non-inferior to standard treatment with prasugrel in terms of net clinical benefit. A concept of guided de-escalation was characterised by a high rate of adherence to treatment and proved feasible in clinical practice. Together, our trial provides important evidence for patients with acute coronary syndrome after successful PCI in whom early de-escalation is considered as an alternative strategy.

Contributors

DS, SM, JM, and DA designed the study and analysed and interpreted the data. DS, SM, F-JN, JM, KH, LK, and DA participated to the steering committee, contributed to implementation of the study, enrolment, and follow-up of patients, and revised the manuscript. CJ, LG, DT, TG, MO, MH, BM, RGK, AK, CAD, LH, SBF, RP, MK, RHGS, JR, and ZH contributed to the implementation of the study, enrolment and follow-up of patients, and review of the manuscript. MH did all statistical analyses.

DS, DA, and SM wrote the first draft and submitted the final version for publication. All authors have seen the version of the article and agree with the content and conclusions.

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Declaration of interests

DS reports grants from Roche Diagnostics and Daiichi Sankyo during the conduct of the study; and personal fees from Bayer AG, Daiichi Sankyo, Eli Lilly, Roche Diagnostics, MSD, Pfizer, and AstraZeneca outside of the submitted work. DA reports personal fees from Roche Diagnostics, DSI/Lilly, AstraZeneca, Pfizer, Bayer AG, and MSD Pharma outside of the submitted work. DT reports personal fees from AstraZeneca, Bayer, Boehringer Ingelheim, Bristol-Myers Squibb, Daiichi Sankyo, Eli Lilly, and Sanofi; and personal fees from Otsuka outside of the submitted work. TG reports personal fees from AstraZeneca, grants and personal fees from Bayer Healthcare, personal fees from Boehringer Ingelheim, grants and personal fees from Bristol-Myers Squibb, personal fees from Pfizer, grants and personal fees from Daiichi Sankyo, grants and personal fees from Eli Lilly, grants and personal fees from The Medicines Company, personal fees from MSD, grants from Siemens Healthcare, and grants from Spartan Bioscience outside of the submitted work. BM reports personal fees from MSD Pharma, Bayer AG, Boehringer Ingelheim, Pfizer, and AstraZeneca outside of the submitted work. RGK reports personal fees from Pfizer, Boehringer Ingelheim, Bayer, MSD, and AstraZeneca outside of the submitted work. AK reports personal fees from Bayer AG and Pfizer outside of the submitted work. SBF reports personal fees from Daiichi Sankyō outside of the submitted work. F-JN reports grants and non-financial support from Daiichi Sankyo during the conduct of the study; grants from Boston Scientific, grants and non-financial support from Edwards, grants from Medtronic, grants from Biotronic, grants from AstraZeneca, non-financial support from Boehringer, non-financial support from Pfizer, grants from St Jude, and grants from Abbottt Vascular, outside of the submitted work. JM reports grants and personal fees from Abbott Vascular and Edwards LifeScience, and personal fees from Terumo, BMS, Lilly/Daiichi Sankyo, and Biotronik outside of the submitted work. ZH reports personal fees from AstraZeneca, Bayer, Aspen, Polpharma, and Abbott, and personal fees from Medtronic outside of the submitted work. All other authors declare no competing interests.

Acknowledgments

TROPICAL-ACS is an independent, investigator-initiated trial, with an academic sponsor (Klinikum der Universität München, Munich, Germany). The trial was financially supported by a research grant from Roche Diagnostics (Rotkreuz, Switzerland). Prasugrel purchase, drug delivery, and related logistics were kindly supported by Eli Lilly and Company and Daiichi Sankyo Company. The valuable project management work of Monika Baylacher (LMU München, Munich, Germany) throughout the entire trial is kindly acknowledged. We also acknowledge the valuable work on data management by Katja Wendrich (TU Dresden, KKS, Dresden, Germany) and the work on study drug preparation by Andreas Thalmeier (LMU München, Munich, Germany).

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