A randomised trial on platelet function-guided de-escalation of antiplatelet treatment in ACS patients undergoing PCI

Rationale and design of the Testing Responsiveness to Platelet Inhibition on Chronic Antiplatelet Treatment for Acute Coronary Syndromes (TROPICAL-ACS) Trial

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Summary

Outcomes of acute coronary syndrome (ACS) patients undergoing percutaneous coronary intervention (PCI) have been significantly improved with the use of potent P2Y12 receptor inhibitors like prasugrel. While most of the ischaemic risk reduction for prasugrel versus clopidogrel was demonstrated in the early treatment period, the risk of bleeding became particularly prominent during the chronic course of therapy. It may therefore be a valid approach to substitute prasugrel for clopidogrel in the early phase of chronic antplatelet treatment after PCI. In the Testing Responsiveness To Platelet Inhibition On Chronic Antiplatelet Treatment For Acute Coronary Syndromes (TROPICAL-ACS) trial, we aim to compare standard prasugrel therapy with a de-escalating antiplatelet treatment approach guided by platelet function testing (PFT). The study is an investigator-initiated European multicentre, randomised clinical trial in biomarker-positive ACS patients after successful PCI. Two thousand six hundred patients will be randomised prior to hospital discharge in a 1:1 fashion to either receive standard prasugrel therapy (control group) or de-escalating therapy (one-week prasugrel followed by one-week clopidogrel and PFT-guided maintenance therapy from day 14 after hospital discharge, monitoring group). Patients of the monitoring group with high on-clopidogrel platelet reactivity (HPR) based on Multiplate analyzer testing (HPR: ≥ 46U per consensus definition) will be switched back to prasugrel, whereas those without HPR (<46 U) will continue clopidogrel treatment. The overall study treatment duration will be one year in both groups. The primary endpoint of the study is net clinical benefit (combined incidence of cardiovascular death, myocardial infarction, stroke and bleeding ≥ grade 2 according to BARC criteria) one-year after randomisation. TROPICAL-ACS is the first large-scale, randomised controlled trial assessing the clinical value of a PFT-guided de-escalation of antiplatelet treatment in biomarker positive ACS patients undergoing PCI.

Keywords

Acute coronary syndrome, platelets, antiplatelet drugs

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Background

Activation of platelets plays a key role in the evolution and early phase of an acute coronary syndrome (ACS) (1). Hence, potent platelet inhibition is essential during ACS, especially in patients undergoing percutaneous coronary intervention (PCI). The thienopyridine-type P2Y₁₂ receptor inhibitor clopidogrel has been the standard of treatment in the past decade and is still among the recommended treatment options for subsets of ACS patients (2, 3). However, due to clopidogrel’s pharmacological properties including delayed onset of action (4), large response variability (5, 6) and on average modest P2Y₁₂-inhibition with high on-treatment platelet reactivity (HPR) in a substantial proportion of patients (7, 8), the 3rd generation thienopyridine-type P2Y₁₂ inhibitor prasugrel has been developed. This drug is characterised by a faster, reliable and more potent platelet inhibition (9, 10). Prasugrel significantly reduced the risk of thrombotic events in the TRial to Assess Improvement in Therapeutic Outcomes by Optimising Platelet Inhibition in Unstable Coronary Syndromes (TRITON-TIMI) 38 study (11). As a consequence, potent P2Y₁₂ receptor inhibitors, including prasugrel, are now the therapy of choice for most ACS patients undergoing PCI (12). Along and consistent with its boosted antplatelet efficacy, a higher risk for bleeding, including major and life-threatening bleeding, was observed for prasugrel (11). However, harm due to bleeding complications and benefit due to potent anti-ischaemic effects predominates at different time points during prasugrel treatment: Platelet reactivity is highest in the very early phase of ACS and rapidly drops thereafter, reflecting the physiological life span of platelets of approximately 5–7 days. This corresponds to the timing of stent thrombosis in ACS patients undergoing PCI, clustering in the first days after PCI (13). Accordingly, a landmark analysis (14) of the TRITON-TIMI 38 trial revealed that a significant benefit for prasugrel regarding thrombotic risk reduction was particularly seen during the acute and sub-acute treatment period (11, 14). The risk of bleeding with prasugrel was similar compared to clopidogrel in the first three days during the in-hospital treatment period, whereas it was significantly higher during the maintenance treatment phase from day 3 post PCI out to the end of the study (14). A higher bleeding risk in the chronic treatment phase was also found for other potent P2Y₁₂ inhibitors in large-scale clinical trials, such as the cyclo-pentyl-triazolo-pyrimidine derivative ticagrelor (15, 16). Hence, while there is a clear benefit of intensified antplatelet therapy in the early phase of ACS, a misbalance between ischaemic risk reduction and increase of bleeding risk arises during the chronic phase of treatment. Strategies that adjust the level of platelet inhibition using intensified inhibition (e.g. with prasugrel) only in the acute phase and de-escalated inhibition with clopidogrel in the maintenance phase of treatment could therefore potentially improve outcomes of ACS patients. However, any de-escalation of antplatelet therapy in ACS patients from a potent P2Y₁₂ inhibitor to the less potent clopidogrel has to account for HPR on clopidogrel. HPR patients exhibit a higher risk for ischaemic events including stent thrombosis (7, 8, 13). Platelet function testing (PFT) allows to monitor individual platelet reactivity and to adjust antplatelet regimens potentially improving outcomes of HPR patients (17). Nevertheless, prior randomised trials (18–20) failed to show a clinical superiority of a PFT-guided antplatelet therapy. However, these studies have limitations as they 1) Predominantly evaluated low risk patients after elective PCI, 2) Used platelet monitoring to mainly intensify/escalate antplatelet therapy, 3) adjusted doses of clopidogrel with little utilisation of potent antplatelet agents like prasugrel or ticagrelor, and 4) Exclusively relied on one of the available PFT assays (VerifyNow P2Y₁₂). Whether PFT proves useful to de-escalate antplatelet therapy in the maintenance phase in ACS patients undergoing PCI is unknown. In the Testing Responsiveness To Platelet Inhibition On Chronic Antiplatelet Treatment For Acute Coronary Syndromes (TROPICAL-ACS) trial, we will therefore test the safety and efficacy of a PFT-guided de-escalation of antplatelet treatment compared to standard 12-month prasugrel therapy in ACS patients undergoing PCI.

Study principle and study population

The TROPICAL-ACS study (ClinicalTrials.gov Identifier: NCT01959451, EudraCT: 2013–001636–22) is an investigator-initiated, randomised, parallel-group, open-label, assessor-blinded, European multicentre trial of a long-term standard prasugrel treatment (12 month) versus a de-escalation treatment approach (short-term prasugrel followed by clopidogrel therapy) in ACS patients undergoing PCI. The study is to be conducted in 33 investigational centres in Europe (2 study sites in Austria, 4 study sites in Poland, 7 study sites in Hungary and 20 study sites in Germany). Study centres must meet the structural and personnel requirements for performing the planned regular trial-related investigations. All patients with biomarker-positive ACS and a successful PCI fulfilling the inclusion and exclusion criteria of the study will be eligible for possible study inclusion. Definition of biomarker-positive ACS is based on the clinical, enzymatic and electrocardiographic criteria recommended in the ESC guidelines (2, 21). Patients with unstable angina and a negative biomarker status (biomarker-negative ACS, unstable angina) will not be eligible for study inclusion. For TROPICAL-ACS, the Multiplate Analyzer® (Roche Diagnostics, Rotkreuz, Switzerland) (22) will be used for platelet function testing.

The main objective of the study is to investigate net clinical benefit of a PFT-guided de-escalation of the antplatelet treatment intensity compared to standard prasugrel-based antplatelet therapy at one year after successful PCI in ACS patients. Further potential advantages of the strategy under investigation may include a bleeding risk reduction (11, 14–16), improved treatment compliance (23, 24) and reduced overall treatment costs (25).

Primary and secondary study endpoints

The primary endpoint of the study is a combined ischaemic and bleeding endpoint (net clinical benefit), which is a composite endpoint consisting of death from cardiovascular causes (all deaths will be assumed cardiovascular in nature unless a non-cardio-
vascular cause can be clearly provided, e.g. malignancy, trauma, and infection), myocardial infarction (defined according to the 3rd universal definition of MI (26)), nonfatal stroke and bleeding grade ≥2 defined according to BARC criteria (27) at one-year after randomisation. The ischaemic component of this endpoint is similar to the combined primary efficacy endpoint of the TRITON-TIMI 38 trial (11, 14). The bleeding component of the endpoint reflects the proposed classification of bleeding events according to BARC criteria (27) and captures clinically relevant bleeding events (28) by including bleedings with a grade ≥2 defined according to BARC criteria. The key secondary endpoint was defined as class ≥2 bleeding events at 12 months defined according to BARC criteria (27). Other secondary endpoints include stent thrombosis (combined definite and probable) defined according to Academic Research Consortium (ARC) criteria (29), incidence of death from any cause, urgent ischaemia-driven revascularisation and all individual ischaemic components of the primary endpoint (cardiovascular death, MI, nonfatal stroke) at 12 months. In addition, a cost-effectiveness analysis on the economic impact of monitored and individualised antiplatelet treatment for ACS patients will be conducted, reflecting the costs of (a) platelet function testing, (b) drug treatment (clopidogrel vs. prasugrel) and (c) treatment for possible ischaemic or bleeding events.

### Inclusion and exclusion criteria

The TROPICAL-ACS study is an all-comer clinical trial enrolling biomarker-positive ACS patients between 18 and 80 years undergoing successful PCI. Major exclusion criteria include patients requiring chronic oral anticoagulation and contraindications to one of the study drugs, clopidogrel or prasugrel. Table 1 provides a detailed summary of all inclusion and exclusion criteria of the study.

### Randomisation and study groups

In each participating centre, allocation to one of the two treatment groups (control group vs monitoring group) will be made by means of a computer- and internet-based randomisation procedure. Patients will be randomised prior to their discharge from the primary care hospital where the PCI procedure was performed in a 1:1 fashion into one of the two study groups on the basis of the random list, which is stored electronically in the data base system. The treatment groups will be studied concurrently. Patients will be 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 and the principle of the TROPICAL-ACS study. ACS patients with successful PCI (defined as a post PCI diameter stenosis ≥2 defined according to BARC criteria (27) at one-year after randomisation).

#### Table 1: Study inclusion and exclusion criteria.

The Table lists all inclusion and exclusion criteria of the trial as stated in the latest version of the trial protocol.

<table>
<thead>
<tr>
<th>Inclusion criteria</th>
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<tbody>
<tr>
<td>Patients with troponin positive ACS</td>
</tr>
<tr>
<td>Successful PCI (defined as a post PCI diameter stenosis &lt;20 % and TIMI flow ≥2)</td>
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<tr>
<td>A planned treatment of prasugrel for 12 months after the procedure</td>
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<tr>
<td>Written informed consent</td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>Exclusion criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age &lt;18 years and &gt;80 years</td>
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<tr>
<td>Subjects with known contraindications to clopidogrel treatment, which are hypersensitivity to the drug substance or any component of the product and active pathological bleeding such as peptic ulcer or intracranial haemorrhage</td>
</tr>
<tr>
<td>Subjects with known contraindications to prasugrel treatment, which are hypersensitivity to the drug substance or any component of the product, active pathological bleeding such as peptic ulcer or intracranial haemorrhage and a history of prior transient ischaemic attack (TIA) or stroke</td>
</tr>
<tr>
<td>Subjects with a history of a complicated or prolonged cardiogenic shock in the last two weeks prior to the beginning of this clinical trial. A complicated or prolonged cardiogenic shock is defined by a cardiogenic shock that required mechanical ventilation or the cardiovascular support with positive inotropic drugs (i. v. catecholamines) for ≥7 days.</td>
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<tr>
<td>Subjects requiring concomitant treatment with an anticoagulant agent (vitamin-K antagonists or novel oral anticoagulants such as rivaroxaban, dabigatran or apixaban)</td>
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<tr>
<td>Indication for major surgery (per decision of the treating physician) for the planned duration of the study</td>
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<tr>
<td>Simultaneous participation in another clinical trial that involves the administration of an investigational medicinal drug within 30 days prior to the beginning of this clinical trial</td>
</tr>
<tr>
<td>Known or persistent abuse of medication, drugs or alcohol</td>
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<tr>
<td>Current or planned pregnancy or nursing women, women 90 days after childbirth. Females of childbearing potential, who do not use and are not willing to use medically reliable methods of contraception for the entire study duration (such as oral, injectable, or implantable contraceptives, or intrauterine contraceptive devices) unless they are surgically sterilised / hysterectomised or there are any other criteria considered sufficiently reliable by the investigator in individual cases</td>
</tr>
<tr>
<td>Evidence of significant active neuropsychiatric disease, in the investigator’s opinion</td>
</tr>
</tbody>
</table>
<20% and TIMI flow ≥2) will be randomised to either receive a standard of care 12-month prasugrel treatment at a dose of 10 or 5 mg according to the current ESC guideline recommendations (2) (control group) or to receive a treatment, which consists of one-week prasugrel treatment (either 10 or 5 mg OID) followed by one week of clopidogrel treatment 75 mg OID and a platelet function measurement (on clopidogrel) two weeks after hospital discharge (monitoring group) (30). Based on this two-week post discharge PFT with assessment of on-clopidogrel platelet reactivity in the monitoring group, patients will be switched back to prasugrel, when a status of HPR (defined as ≥46 U by ADPtest per consensus definition on the Multiplate analyzer) is detected, whereas patients with an adequate response to clopidogrel (<46 U) will continue their clopidogrel treatment for the remaining 11.5 months of the study. The 14-day follow-up visits were set with the rationale to find the best available compromise with respect to minimising the duration of HPR status after switching back to clopidogrel and also to be feasible in clinical practice to determine the overall level of P2Y12 receptor directed platelet reactivity in the very early maintenance phase of treatment prior to discharge from hospital or subsequent rehabilitation. Based on prior observations (31–33) it can be expected that the majority (>60%) of patients will continue on clopidogrel treatment, whereas only a minor proportion of patients will have to be switched back to prasugrel due to a status of HPR on clopidogrel. Thus, most of the patients within the monitoring arm of the study will be on long-term clopidogrel treatment.

Study drug preparation

Study drugs for the first 14 days of post-discharge treatment will be manufactured in the pharmacy department of the Klinikum der Universität München. The approved drugs Efient® and Plavix® will be packed and labelled study-specific. Implementing a dedicated study drug package ensures correct intake of study-arm associated drugs with high compliance. Study drugs are prepared in two boxes (one box per week labelled with “week 1” and “week 2”) that contain the treatment for patients and that are labelled with the name of the drug and the period of intake. Patients receive their specific study-related medication for a period of two weeks (time period from discharge to follow-up visit with platelet function testing). For the control group of the study, both weekly boxes include prasugrel tablets (10 mg or 5 mg dose, according to the decision of the investigator taking into account the patients’ age and body weight). For the monitoring arm the box labeled with “week 1” and covering the first week post-discharge contains prasugrel tablets (10 mg or 5 mg dose), whereas the box labelled with “week 2” contains clopidogrel (75 mg) tablets being taken by the patients during the 2nd week post randomisation and up to the follow-up visit. Per protocol, the first intake of study drug (=treatment for the first 14 days after discharge) starts at the first day after discharge from the primary care hospital. For both groups, three extra tablets (provisional medication) are included in the box for week two to ensure flexibility regarding the timing of the two-week follow-up visit out to day 17. During the out-patient follow-up visit at 14 days after discharge, patients are asked to bring the study drug boxes to check-up drug compliance. Treatment after day 14 post-discharge is done according to the assigned randomisation and prescribed by the primary care physician of the patient. During the follow-up calls the patients are explicitly asked about the type and amount of daily antiplatelet treatment for compliance evaluation.

Study related platelet function testing

One dedicated time point of blood sampling for PFT is planned per study protocol (Figure 1). Two weeks after hospital discharge, study patients from both study groups will have a planned visit

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**Figure 1: Study flow chart and treatment groups.** The figure illustrates the control group and the monitoring group of the study. 1:1 randomisation is done after PCI and directly before discharge of patients. The response to antiplatelet treatment is measured for all study participants in both arms of the study. Based on the derived on clopidogrel treatment aggregation values at day 14 of the study in the monitoring group, the further course of treatment is defined, which is clopidogrel in no-HPR patients and a switch back to prasugrel in HPR patients.
where blood for testing is drawn under steady-state conditions by direct venipuncture. Sampling will be done after the morning intake of the study medication (75 mg clopidogrel or 5/10 mg prasugrel) for testing the response to antiplatelet treatment with the Multiplate analyzer. All procedures will be done according to standard protocols as recommended by the manufacturer of the device. Aggregation measured with the device is quantified as aggregation units (U). The method and in particular the predictive value of measurements for the outcome of PCI-treated patients have been tested in numerous prior clinical studies (7, 8, 34). HPR is defined based on the results of prior studies and the consensus documents of the Working Group on HPR by an ADP test aggregation value of ≥ 46 U on the Multiplate analyzer (7, 8, 34). In the control group of the study (prasugrel treated patients), the testing is performed only for observational purposes and testing results will not impact antiplatelet drug selection or dosing. In the monitoring group, this measurement will determine the further course of treatment (prasugrel in patients with HPR, clopidogrel in patients without HPR). All study patients receive aspirin treatment (recommended dose: 100 mg/day) and in addition to the ADP-test, arachidonic acid-induced platelet aggregation will also be tested with the ASPI-test in both groups, but only for observational purposes without any influence on the antiplatelet therapy.

**Study follow-up**

The follow-up of patients throughout the TROPICAL-ACS study is illustrated in Figure 2. In brief, after two weeks post discharge (day 14) from the primary care hospital, where the index PCI was done, all patients will have an outpatient visit including platelet function testing. A range of three additional days for this follow-up visit is allowed (see above), in cases when the patient cannot present at the hospital for a follow-up visit on the exact day 14 post discharge. Further on, patients will be contacted by phone 30 days, six months and one year after the randomisation to collect endpoint events, adverse events and evaluate drug compliance.

**Statistical considerations**

The study is designed to show non-inferiority for the PFT-guided monitoring arm versus the control arm with standard prasugrel treatment. Considering the results of a landmark analysis from the TRITON-TIMI 38 trial (14), based on the incidence of early vs late major bleeding events (14) and based on the incidence of BARC ≥2 bleeding complications in a PCI cohort (28), the incidence of the primary endpoint of this study was assumed to be 10.5% in the control arm. A non-inferiority margin of +3.2% (+30%) was estimated. Sample size calculations (NQuery Advisory, Statistical Solutions Ltd., 7B Airport East Business Park, Farmer’s Cross, Cork, Ireland) were performed based on one-sided α-level of 0.05 and a power of 80%. For the primary endpoint assumptions, 1172 patients in each group are needed. Assuming an incidence of BARC ≥2 bleeding in the control group of 4.9% and an expected reduction of BARC ≥2 bleeding by 45% in the monitoring group, 1179 patients per group are required to demonstrate superiority (based on two-sided α-level of 0.05 and a power of 80%) for the first secondary endpoint (BARC ≥2 bleeding). In order to compensate for losses to follow-up and in order to be powered for the primary and secondary endpoint assessment the enrollment of a total of 2600 patients (1300 patients per group) will be required. Primary analyses will be performed on an intention-to-treat basis.

**Ethical and regulatory aspects**

The sponsor (Ludwig-Maximilians-University, Munich, Germany) has the overall responsibility for the conduct of the study, including assurance that the study is conducted in accordance with the provisions of the Declaration of Helsinki as amended in Seoul (2008), with the International Conference on Harmonisation “Good Clinical Practices” and the relevant national regulations. Project management is conducted by the CSCLMU (Clinical Study Centre, Ludwig-Maximilians-University) and the monitoring of the trial will be done by an independent service provider (Münchner Studienzentrum, Munich, Germany). According to national law every participating subject will be informed of the nature, importance, treatment methods, risks and consequences of the trial by the local investigator. The steering committee is responsible for overseeing the good execution and administrative progress of the protocol. The Data Safety Monitoring Board (DSMB) will be responsible for making risk-benefit assessment and making recommendations regarding endpoint analysis and any potential problems. It is also responsible for reviewing the interim and final results of the clinical study regarding the analysis. The independent Event Adjudication Committee (EAC) will adjudicate the clinical events within the trial. All members of the committee will be blinded to the primary results of the trial and will be blinded to the randomised treatment for any adjudicated patient.

**Status quo**

The first patient in TROPICAL-ACS was enrolled in December 2013. As per May 2016, recruitment is completed for the trial with a total of 2619 patients enrolled (1309 in the control group vs 1310 patients in the monitoring group) at the 33 participating study sites. Currently, the one-year period of follow-up is ongoing at all participating sites. Completion of follow-up is expected in June 2017 with subsequent dataset lock. Reporting of trial results is currently planned for the third quarter of 2017.

**Conclusions and outlook**

Based on the results of the two large-scale clinical trials TRITON-TIMI 38 and PLATO (11, 35), two potent antiplatelet agents (prasugrel and ticagrelor) are now approved and established for the treatment of ACS patients. When compared to clopidogrel, both...
agents at their standard dose reduced ischaemic risk, but showed a higher risk for major and minor bleeds, while a reduced dosing regimen for prasugrel – in an albeit smaller study in Japanese ACS patients (36) – showed a similar efficacy and safety profile. Of note, prior studies have highlighted that the prognostic importance of MI and bleeding is similar (37). Therefore, future strategies will have to focus on minimising bleeding complications without losing efficacy. With this in mind, a risk-adapted and individualised P2Y₁₂ inhibitor selection with treatment intensity de-escalation in the chronic anti-platelet treatment phase (beyond day 7–14) after the index event is of potential interest. Cardiologists are steadily gaining clinical experience with the potent antiplatelet drugs and major clinical trials in ACS patients addressing their net clinical benefit are ongoing. Table 2 summarises key characteristics of important ongoing clinical trials (38–42) on antiplatelet treatment strategies in ACS patients undergoing PCI. Among those trials, the ANTARCTIC trial (42) and TROPICAL-ACS follow a PFT-guided approach to optimise and individualise antiplatelet treatment for ACS patients. However, there are substantial differences between ANTARCTIC and TROPICAL-ACS with respect to the study cohort and design. While ANTARCTIC focuses on elderly patients with a biomarker positive or negative ACS, TROPICAL-ACS studies an all-comer cohort of biomarker positive ACS patients (STEMI and NSTEMI). With respect to the strategic approach, ANTARCTIC aims to treat patients into a therapeutic window of platelet inhibition with a default strategy of low-dose prasugrel (5 mg). TROPICAL-ACS follows a different approach with high potent platelet inhibition (=prasugrel) for all patients during the acute and sub-acute phase of treatment and clopidogrel based on platelet function as the default therapy during the chronic treatment course. In TROPICAL-ACS, platelet function testing is implemented as an important safety tool to prevent clopidogrel-treated patients from returning to high platelet reactivity that may expose them for a higher risk of thrombotic events.

In summary, TROPICAL-ACS will provide clinically important results on the net clinical benefit of a strategy of a monitored treatment de-escalation of dual antiplatelet treatment in ACS patients. The novelty of such an approach is also substantiated by the circumstance that medical treatment is not adjusted according to patient’s characteristics, the clinical condition (e.g. ACS vs non-ACS) and age or co-morbidities, but basically to the stage of disease (acute vs chronic treatment) and the temporal distance from the index event (ACS) and procedure (PCI). Complementary to
Table 2: Major ongoing clinical trials on antiplatelet treatment strategies in ACS patients undergoing PCI.

<table>
<thead>
<tr>
<th>Trial</th>
<th>Study cohort</th>
<th>No. of patients</th>
<th>Treatment</th>
<th>Strategy</th>
<th>Primary endpoint</th>
</tr>
</thead>
<tbody>
<tr>
<td>GLOBAL LEADERS</td>
<td>PCI patients (ACS and stable CAD)</td>
<td>&gt; 16,000</td>
<td>ASA for 1 month plus ticagrelor 90 mg bid for 24 months vs standard DAPT with either ticagrelor (ACS) or clopidogrel (stable CAD) for 12 months plus ASA for 24 months</td>
<td>Short term DAPT followed by long-term ticagrelor treatment</td>
<td>Composite of death or non-fatal, new Q-wave MI at 24 months</td>
</tr>
<tr>
<td>ISAR REACT 5</td>
<td>ACS patients with a planned invasive treatment strategy</td>
<td>4,000</td>
<td>Ticagrelor 180 mg loading dose and 90 mg bid maintenance dose vs prasugrel 60 mg loading dose and 10 mg daily maintenance dose</td>
<td>Comparison of two potent P2Y12 inhibitors with claimed superiority for ticagrelor</td>
<td>Composite of death, MI, or stroke at 12 months</td>
</tr>
<tr>
<td>POPULAR Genetics</td>
<td>STEMI patients undergoing primary PCI</td>
<td>2,700</td>
<td>CYP2C19 genotype guided treatment vs routine ticagrelor/prasugrel treatment. In the genotyping group, wild-type patients receive clopidogrel (75 mg daily) and patients with ≥ 1 LoF allele receive ticagrelor/prasugrel (90 mg bid/10 mg daily)</td>
<td>Genotype-guided de-escalation of P2Y12 inhibitor treatment</td>
<td>Composite of death, MI, definite ST, stroke, or PLATO major bleeding at 12 months</td>
</tr>
<tr>
<td>ANTARCTIC</td>
<td>Elderly (≥75 years) ACS patients with planned invasive management</td>
<td>852</td>
<td>Prasugrel 5 mg vs individualised treatment (5/10 mg prasugrel, 75 mg clopidogrel)</td>
<td>Low-dose prasugrel (5 mg) as default treatment with VerifyNow based treatment escalation (prasugrel 10 mg) or de-escalation (75 mg clopidogrel)</td>
<td>Cardiovascular death, myocardial infarction, stroke, definite stent thrombosis, urgent revascularisation, and bleeding complications</td>
</tr>
<tr>
<td>GEMINI-ACS-1</td>
<td>Patients within 10 days of an ACS event</td>
<td>3,000</td>
<td>Rivaroxaban 2.5 mg bid plus P2Y12, inhibitor (clopidogrel/ticagrelor) vs aspirin 100 mg plus P2Y12, inhibitor (clopidogrel/ticagrelor)</td>
<td>Substitution of aspirin by DOC</td>
<td>TIMI clinically significant bleeding (major, minor, or requiring medical attention)</td>
</tr>
<tr>
<td>TWILIGHT</td>
<td>High-risk patients undergoing PCI</td>
<td>8,200</td>
<td>3-month course of DAPT with ticagrelor plus aspirin followed by ticagrelor alone up to 1 year vs ticagrelor plus aspirin for 12 months</td>
<td>De-escalation of DAPT down to ticagrelor alone after 3 months</td>
<td>Clinically relevant bleeding (BARC ≥ 2)</td>
</tr>
<tr>
<td>TROPICAL-ACS</td>
<td>Biomarker-positive ACS patients undergoing PCI</td>
<td>2,600</td>
<td>Platelet function testing guided approach with a short-term (1 week) prasugrel treatment (10 mg daily) and a switchover to clopidogrel treatment (75 mg daily) in adequate responders to clopidogrel vs standard prasugrel therapy (10 mg daily)</td>
<td>De-escalation of antplatelet treatment utilising PFT as safety tool</td>
<td>Composite of CV death, MI, stroke, or bleeding ≥ grade 2 according to BARC criteria at 12 months</td>
</tr>
</tbody>
</table>

ACS = acute coronary syndrome, ASA = arachidonic acid, bid = twice daily, BARC = bleeding academic research consortium, CAD = coronary artery disease, CV = cardiovascular, DAPT = dual antiplatelet therapy, LoF = loss of function, MI = myocardial infarction, PCI = percutaneous coronary intervention, PLATO = platelet inhibition and patient outcomes, ST = stent thrombosis, STEMI = ST-segment elevation myocardial infarction, TIMI = Thrombolysis in Myocardial Infarction.

the results of other important and ongoing phase III/IV studies, the results of TROPICAL-ACS are therefore expected to give a significant contribution to an optimised and individualised antiplatelet therapy for ACS patients undergoing PCI.

Conflicts of interest
Dr. Sibbing: Speaker fees and honoraria for consulting from Eli Lilly, MSD, Pfizer, Daiichi Sankyo, Bayer Vital, Astra Zeneca and Roche Diagnostics, and research grants from Roche Diagnostics; Dr. Aradi: Lecture fees from AstraZeneca, Daiichi Sankyo, Eli Lilly and Sanofi Aventis; Dr. Huczek: Speakers/consulting fees from AstraZeneca, Bayer, Eli Lilly, Aspen and Medtronic; Dr. Trenk: Consulting and lecture fees from AstraZeneca, Bayer, Bristol-Myers Squibb, Pfizer, Boehringer Ingelheim, Daiichi Sankyo, Eli Lilly, MSD, Otsuka, and Sanofi; Dr. Gori: Speaker fees from Daiichi Sankyo; Dr. Kiss: Speaker fees from MSD, Bayer, Pfizer and Boehringer Ingelheim; Dr. Jacobs: Speaker fees from Eli Lilly, Daiichi Sankyo and Astra Zeneca; Dr. Geisler: lecture/advisory board honoraria and travel fees by Astra Zeneca, Bayer Healthcare, Boehringer Ingelheim, Pfizer, Bristol-Myers Squibb (BMS), Daiich Sankyo, Eli Lilly, Medicines Company, MSD; restricted grants by Bayer Healthcare, BMS, Daiichi Sankyo, Siemens Healthcare and Spartan Bioscience Inc.

References


