P2Y12-receptor-inhibiting antiplatelet strategies in acute coronary syndromes

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Keywords
Antiplatelet agents, ticagrelor, prasugrel, cangrelor, acute coronary syndrome

Summary
Antiplatelet therapy in acute coronary syndromes is essential for preventing stent thrombosis and for reducing major adverse cardiovascular events. Treatment strategy has changed over the last years by frequent use of more active agents inhibiting the ADP mediated activation of platelets instead of clopidogrel, such as prasugrel and ticagrelor. Compared to clopidogrel these modern antiplatelet drugs showed a significant reduction of efficacy endpoints as well as an acceptable safety profile in large multicenter randomized trials (TRITON TIMI 38, PLATO). Going in with higher efficacy a generally higher bleeding risk of prasugrel could be reduced by optimizing the maintenance dose in elderly and underweight patients (TRILOGY-ACS). However even prasugrel and ticagrelor have shown a delayed onset of action in special patient populations (e.g. STEMI) suggesting that the optimal ADP inhibitor has not been found yet. Results of the CHAMPION PHOENIX trial indicate that cangrelor, an intravenous agent, might fulfill these high expectations of an ideal platelet inhibitor in the first hours of an ACS in special patient cohorts.

This review summarizes the results of most important clinical studies investigating the novel P2Y12 receptor inhibiting antiplatelet drugs.

Schlüsselwörter
Thrombozytenaggregationshemmer, Ticagrelor, Prasugrel, Cangrelor, akutes Koronarsyndrom

Zusammenfassung

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It consisted of acetylsalicylic acid (ASA) and clopidogrel, a thienopyridine, for nearly a decade. Clopidogrel has been identified to be associated with a huge inter-individual variability in platelet function inhibition leading in up to 40% of patients to a low- or non-responsiveness as a consequence of a delayed or insufficient conversion of the prodrug clopidogrel into its active metabolite (3–6). Low- or non-responsiveness in turn is associated with a
higher risk of cardiovascular events, e. g. stent thrombosis, recurrent myocardial infarction, or cardiovascular death (7).

Two metabolic steps are necessary for bio-activation of clopidogrel, which can be influenced by various genetic (8–11) and non-genetic (12) mechanisms. Especially in homozygote carriers of the CYP2C19*2 loss-of-function polymorphism, optimal inhibition of platelet activity cannot be guaranteed, while heterozygote might react on increasing doses of clopidogrel (13).

As a reaction to clopidogrel “resistance” several trials investigated the impact of increasing loading and maintenance doses of clopidogrel on clinical outcome. However, no single study could clearly demonstrate a significant clinical benefit, even though clopidogrel action in platelet function assays yielded better results (14–17).

The new P2Y12-receptor blockers prasugrel and ticagrelor do not depend on these loss-of-function genetic variants (9, 18), have only one hepatic step of bioactivation (prasugrel) or are active drugs when reabsorbed (ticagrelor). Accordingly, low- or non-response to these new P2Y12-inhibitors is less frequent, which makes these substances of interest in patients who have increased platelet reactivity and turnover, as it is the case in patients with ACS.

**Prasugrel**

Prasugrel is a thienopyridine, which irreversibly binds to the P2Y12-receptor thus inhibiting the ADP-mediated platelet aggregation. Compared to clopidogrel it shows a more rapid action and a higher potency of inhibiting platelet aggregation.

Prasugrel has been approved for use in ACS patients due to the exciting results of the TRITON TIMI-38 trial (Trial to assess Improvement of Therapeutic Outcomes by Optimizing Platelet Inhibition with Prasugrel – Thrombolysis in Myocardial Infarction 38) (19), which enrolled more than 13000 patients with ACS (unstable angina, NSTEMI, STEMI). With the exception of STEMI-patients, in whom study medication was given even without knowledge of coronary anatomy a diagnostic angiogram was obligatory prior to randomization. Only if PCI was the treatment of choice patients either received a 60 mg loading dose (LD) of prasugrel followed by a 10 mg maintenance dose (MD) daily or a 300 mg LD of clopidogrel followed by a MD of 75 mg daily for the whole treatment period of up to 15 months. The main results of the study are depicted (Fig. 1): The primary composite efficacy endpoint (cardiovascular mortality, nonfatal myocardial infarction and nonfatal stroke) could be significantly reduced by 19% in patients with prasugrel compared to clopidogrel (9.9% vs. 12.1%; p<0.001). Moreover, the rate of stent thrombosis was more than halved (1.1% vs. 2.4%; p<0.001).

These advantages were already documented after only three days and remained significant throughout the study period. Besides its higher efficacy prasugrel was associated with an increased number of spontaneous non-CABG-related major bleeding events (TIMI bleeding classification: 2.4% vs. 1.8%; p = 0.03) as well as with more frequent fatal bleedings although these were rare in general (0.4% vs. 0.1%; p = 0.002). Moreover, patients with the need for urgent coronary bypass surgery were at a significantly higher perioperative bleeding risk after the intake of at least one dose of prasugrel (13.4% vs. 3.2%, p<0.001). Particularly elderly individuals (>75 years old) as well as patients with a low body weight (<60 kg) were at a higher risk of bleeding complications.

As a consequence, in elderly and underweight patients the net clinical benefit of prasugrel (primary combined endpoint plus major hemorrhage) was similar with that of clopidogrel, while for the whole patient cohort a net clinical benefit of prasugrel over clopidogrel could be demonstrated (12.2% vs. 13.9% HR 0.87; 95%-CI: 0.79–0.95; p=0.004) (19). Patients with a history of any cerebrovascular events (ischaemic or haemorrhagic stroke or transient ischaemic attacks) had an unfavourable outcome when they were on prasugrel.
Tab. 1 Differences of results between prasugrel and ticagrelor with respect to subgroup analyses in TRITON TIMI 38 und PLATO (20, 21, 31, 32)

<table>
<thead>
<tr>
<th>subgroup</th>
<th>primary endpoint at study end (%)</th>
<th>prasugrel vs. clopidogrel</th>
<th>ticagrelor vs. clopidogrel</th>
</tr>
</thead>
<tbody>
<tr>
<td>STEMI</td>
<td>TRITON</td>
<td>10.0 vs. 12.4; p = 0.02</td>
<td>9.4 vs. 10.8; p = 0.07</td>
</tr>
<tr>
<td></td>
<td>primary PCI</td>
<td>10.2 vs. 11.6; p = 0.226</td>
<td>secondary PCI</td>
</tr>
<tr>
<td></td>
<td></td>
<td>9.6 vs. 14.1; p = 0.015</td>
<td></td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td></td>
<td>12.2 vs. 17.0; p &lt; 0.001</td>
<td>14.1 vs. 16.2; p = n.s</td>
</tr>
<tr>
<td>no diabetes</td>
<td></td>
<td>9.2 vs. 10.6; p = 0.02</td>
<td>8.4 vs. 10.2; p &lt; 0.05</td>
</tr>
</tbody>
</table>

due to a higher risk of severe (also intracerebral) bleedings.

Accordingly, prasugrel is contraindicated in patients with a history of stroke or TIA.

Apart from main results several pre-specified subgroup analyses have been performed and published; the subgroup of patients with STEMI referred for primary PCI exhibited a clear benefit for prasugrel by a 32% relative risk reduction of the primary composite endpoint (cardiovascular death, myocardial infarction, or stroke) after 30 days (6.5% vs. 9.5%; p = 0.017), which remained visible after 15 months (10.0% vs. 12.4%; p = 0.022) as compared to standard therapy (20) (▶ Tab. 1). Interestingly, in STEMI patients referred for primary PCI the study groups showed no difference with respect to severe bleeding complications (prasugrel 1.0% vs. 1.3% with clopidogrel, p = 0.34).

Furthermore, prasugrel yielded a significant 28% relative risk reduction of the primary composite endpoint to a statistically greater extent (12.2% vs. 17.0%; p < 0.001) in diabetic patients with ACS compared to non-diabetics (9.2% vs. 10.6%; p = 0.02; RR 1.3%) (▶ Tab. 1) (21). Especially, in diabetics the incidence of myocardial infarction could be reduced by 40% (p < 0.001) during the follow up period. Interestingly, the rate of severe TIMI-bleedings was increased in prasugrel- vs. clopidogrel treated non-diabetics (2.4% vs. 1.6%; p = 0.02) while it was comparable between prasugrel- and clopidogrel-treated diabetics (2.6% vs. 2.5%; p = 0.81).

Another substudy analysed the impact of the two antiplatelet agents in high-risk patients who had already suffered from an initial non-fatal primary endpoint event. Prasugrel was not only associated with a significant lower rate of further events in contrast to clopidogrel (10.8% vs. 15.4%; HR 0.65, 95%-CI 0.46–0.92; p = 0.016) but also showed its superiority by a reduction of the secondary endpoint of cardiovascular death (3.7% vs. 7.1%; HR 0.46, 95%-CI 0.25–0.82; p = 0.008) (22).

A genetic substudy showed that clopidogrel-treated carriers of the CYP2C19*2 loss of function polymorphism were at higher risk of adverse cardiovascular outcome than non-carriers (12.1% vs. 8.0%; p = 0.014), while there was no association with the carrier status of this polymorphism in prasugrel-treated patients (8.5% vs. 9.8%; p = 0.27) (9). A possible explanation is the much wider spectrum of cytochrome P450 enzymes, which are involved in the bio-activation step of prasugrel thus guaranteeing sufficient bio-activation of the prodrug into its active metabolite even in the absence of the CYP2C19 enzyme system (23). Moreover, the ABCB1 genotype (50% of the patients in TRITON TIMI-38 were carriers of this polymorphism) was associated with a worse absorption of clopidogrel resulting in a higher incidence of cardiovascular adverse events (TT homozygote vs. CT/CC individuals 12.9% vs. 7.8%; p = 0.002). In contrast no impact of this polymorphism existed in the prasugrel-treated group (9).

Recently, outcome results of 346 patients in TRITON-TIMI 38 undergoing CABG were published. Despite a higher bleeding rate with significant more blood loss via the chest tube and higher rates of platelet transfusion in prasugrel-treated patients the amount of blood cell transfusions remained statistically independent of the used antiplatelet agent. Furthermore, prasugrel yielded a significant reduction in all cause mortality compared to clopidogrel in patients undergoing bypass surgery (relative risk reduction 84%; 2.3% vs. 8.7%; p = 0.03) (24).

Prasugrel has also been tested in patients with a primarily conservative medical treatment strategy and compared vs. Clopidogrel: More than 9000 ACS patients in the TRILOGY-ACS trial (25) referred for medical therapy only were randomized to either receive prasugrel 10 mg or clopidogrel 75 mg for up to 30 months. The combined primary efficacy endpoint consisted of cardiovascular death, MI and stroke. Moreover, patients older than 75 years and/or with a body weight below 60 kg received a reduced maintenance dose of prasugrel. Unexpectedly, prasugrel failed to show superiority over clopidogrel as the primary combined endpoint was comparable between treatment groups (13.9% vs. 16.0%; p = 0.21). However, a pre-specified analysis of multiple recurrent events disclosed a lower risk with prasugrel, especially in patients younger than 75 years of age, after 12 months. Severe bleeding complications occurred with a similar frequency in prasugrel-treated patients younger than 75 years as compared to patients under clopidogrel.

In a pre-specified subgroup analysis the elderly (>75 years) showed a twofold higher cumulative risk in efficacy and safety endpoints compared to younger patients, but safety data were comparable between clopidogrel and the reduced prasugrel dose regimen (TIMI major bleeding 4.1% vs. 3.4%; HR 1.09; 95%-CI: 0.57–2.08 (26).

In the TRILOGY ACS Platelet Function sub-study prasugrel was associated with lower remaining platelet reactivity units (PRU, as measured by the VerifyNow assay) in contrast to clopidogrel over time. In other words, about 10–15% of patients under prasugrel vs. 50% of patients under clopidogrel were low- or non-responders to therapy over time. Despite this finding, no association was found between platelet reactivity and the occurrence of ischemic
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Ticagrelor

Ticagrelor is another new P2Y12-inhibiting antiplatelet agent. In contrast to clopidogrel and prasugrel it is not a thienopyridine and has another mechanism of action by antagonizing ADP-induced receptor signalling in order to inhibit platelet function. Changing the confirmation of the P2Y12 ADP binding site, ticagrelor causes a reversible and concentration dependent inhibition of the receptor. As mentioned, it is an active compound and therefore does not need any bio-activation process by hepatic pathways.

Another difference to other ADP receptor inhibiting agents is the obligatory administration of 90 mg twice daily (loading dose 180 mg) in order to achieve a constant platelet inhibition.

The most important trial investigating ticagrelor’s efficacy and safety in ACS patients was the multicenter, double blind, randomized phase-3 PLATO trial (A Comparison of AZD6140 and Clopidogrel in Patients With ACS) (Fig. 1b) (28), which enrolled more than 18,000 patients with ACS (non-ST segment elevation and ST-segment elevation) regardless which treatment approach (interventional, primarily conservative or conservative only) was chosen. Patients were randomly assigned to either receive ticagrelor in the dose mentioned above or clopidogrel starting with a loading dose of 300–600 mg followed by 75 mg daily for the full study duration. Pre-treatment with clopidogrel before randomization was allowed. The primary endpoint was a composite of cardiovascular death, myocardial infarction and stroke, which was significantly reduced in ticagrelor-treated patients as compared to the clopidogrel group (9.8% vs. 11.7%; HR 0.84; 95%-CI 0.77 to 0.92; p<0.001). Moreover, also the secondary endpoints cardiovascular death (4.0% vs. 5.1%, p=0.001), all-cause death (4.5% vs. 5.9%, p<0.001), and myocardial infarction (5.8% vs. 6.9%, p=0.05) were reported significantly less frequent by use of ticagrelor. Study-specific classification of severe bleedings including also peri-operative CABG-related bleedings was not significantly different between the two treatment arms (ticagrelor: 11.6% vs. clopidogrel 11.2%; p=0.43). However, spontaneous severe bleedings were reported significantly more frequently in ticagrelor-treated patients independent of the chosen bleeding classification: PLATO classification 4.5% vs. 3.8%, p=0.03; TIMI classification 2.8% vs. 2.2% (p=0.025).

Interestingly, dyspnoea (in most instances only temporarily seen) was an important and increased adverse effect in ticagrelor-treated patients compared with the clopidogrel-treated group (13.8% vs. 7.8%; p<0.001), but led only rarely to discontinuation of the study drug (in 0.9% of patients) (28). Moreover, dyspnoea was not associated with changes in cardiac or pulmonary function in previous dose-finding and safety studies (29). As even mortality rates were substantially lower in patients with dyspnoea treated with ticagrelor compared to clopidogrel-treated patients with dyspnoea, it seems to be an acceptable side effect. Furthermore, the overall benefit of ticagrelor as seen in the main trial can be seen in patients with shortness of breath as well. Apart from dyspnoea bradycardia (4.4% vs. 4.0%; p=0.21) and asymptomatic ventricular pauses of >3 seconds (5.8% vs. 3.6%; p=0.01) were more frequently reported in the first week of treatment with ticagrelor. In addition, a slight increase in creatinine and uric acid levels was observed, which normalized after treatment discontinuation at the end of the trial. All these adverse events, however, did not cause specific medical interventions and might have their explanation in a ticagrelor-induced blockage of adenosine re-uptake into red blood cells (30).

Pre-specified subgroup analyses confirm the beneficial effects of ticagrelor over clopidogrel. In 7544 patients with STEMI referred for primary PCI the effects of ticagrelor were consistent with those seen in the overall PLATO trial (31): Ticagrelor reduced the primary combined efficacy endpoint by 13% (9.4% vs. 10.8%; p=0.07) as well as the rate of a recurrent myocardial infarction by 19% compared to clopidogrel (4.7% vs. 5.8%; p=0.07). However, results did not yield the border of significance. In STEMI patients major bleeding complications were not significantly affected by ticagrelor when compared with clopidogrel.

In diabetic patients (n=4662), Ticagrelor, consistently to the main results, reduced the primary composite endpoint (HR: 0.88, 95%-CI: 0.76–1.03) as well as all-cause mortality (HR: 0.82, 95%-CI: 0.66–1.01) and stent thrombosis (HR: 0.65, 95% CI: 0.36–1.17) even though the difference reached no statistical significance (p<0.05). With respect to major bleeding again no difference could be observed between ticagrelor and clopidogrel treated diabetics (HR: 0.95, 95%-CI: 0.81–1.12) (32).

Patients with the need for coronary artery bypass grafting (CABG) showed a better outcome by an impressive reduction of the primary combined endpoint when they had been treated with tigagrelor within seven days before surgery. Total mortality (4.7% vs. 9.7%; p<0.01) and both cardiovascular (4.1% vs. 7.9%; p<0.01) as well as non cardiovascular death (0.7% vs. 2.0%; p=0.07) were all significantly reduced in ticagrelor-treated patients, while the bleeding risk remained similar between study drugs (33).

Moreover, ticagrelor showed superiority over clopidogrel especially in patients with chronic kidney disease (CKD; creatinine clearance <60 ml/min) as the primary combined end point was reduced by 21% (17.3% vs. 22.0%, hazard ratio 0.77; 95%-CI 0.65 to 0.90), which was more pronounced than in patients with normal renal function (RRR 11%; 7.9% vs. 8.9%; HR, 0.90; 95%-CI, 0.79 to 1.02; p=0.13) (34). However, the reduction of the secondary single endpoint cardiovascular mortality reached no statistical significance in ticagrelor- vs. clopidogrel-treated patients.
with CKD (RR 29%; 10.0% vs. 14.0%; HR, 0.72; 95%-CI 0.58 to 0.89; p = 0.14). Major bleedings (15.1% vs. 14.3%; HR 1.07; 95%-CI 0.88 to 1.30), fatal bleedings (0.34% vs. 0.77%; HR 0.48; 95%-CI, 0.15 to 1.54), and non-CABG-related major bleedings (8.5% vs. 7.3%; HR 1.28; 95%-CI 0.97 to 1.68), showed no statistically significant difference between randomized groups.

High age did not influence the results of PLATO: No significant difference neither in efficacy nor in safety endpoints could be observed in a subgroup analysis comparing ticagrelor’s effects in patients beyond and over the age of 75 years, respectively (35).

Ticagrelor did not only show superiority over clopidogrel in invasively treated (surgery/PCI) patients, but also significantly reduced outcome events in patients with a primarily conservative treatment strategy: in 3143 conservatively managed patients ticagrelor significantly reduced the primary combined endpoint by 15% as compared to clopidogrel (12.0% vs. 14.3%; p = 0.04). In particular, overall mortality rate was significantly lower in ticagrelor-treated patients. Moreover, despite a generally higher bleeding risk in this patient cohort due the higher age and more co-morbidities (diabetes mellitus, renal failure, heart failure), bleeding complications were comparable between ticagrelor and clopidogrel when the PLATO definition of major bleeding (primary safety endpoint: 11.9% vs. 10.3%; p = 0.08) or the TIMI bleeding classification (7.9% vs. 7.2%; p = 0.3) was used (36).

Furthermore, in contrast to clopidogrel, the action of ticagrelor was not influenced by the presence or absence of the CYP2C19 or the ABCB1 loss-of-function polymorphisms as observed in a genetic subgroup analysis (18): Ticagrelor was associated with a significant 23% reduction of the primary combined endpoint compared to clopidogrel (8.6% vs. 11.2%; p = 0.038) in patients with any loss of function alleles of the CYP2C19 genotype at 30 days after study inclusion. However, at the end of the study this early statistical benefit was no longer significant thus indicating that the presence of loss-of-function metabolisms is more important in the acute and sub-acute phases of disease as compared to the chronic phase, as residual platelet reactivity usually is higher early after the index event.

### What the guidelines say

Due to these remarkable results both prasugrel and ticagrelor have already found their way into the current European guidelines for NSTE-ACS and STEMI (37, 38). In patients with STEMI referred for primary PCI both agents received an IB recommendation and therefore should be preferred over clopidogrel (37) (▶Tab. 2). In NSTE-ACS the new antiplatelet agents (IB) have also superseded clopidogrel (IC) with respect to first line recommendation: while ticagrelor is recommended for all patients with ACS regardless of the initial treatment strategy (invasive or conservative), prasugrel, as tested in the TRITON-TIMI-38 trial, is only recommended for patients whose coronary anatomy is already known (after diagnostic angiography) and who need coronary intervention. Clopidogrel stays the agent of choice in ACS patients with clear contraindications against the newer agents or if these agents are not available, but might also be considered in the elderly and/or patients with a higher bleeding risk. Furthermore, clopidogrel still plays an essential role in patients with stable coronary artery disease and planned PCI (IA) (2, 38). In case of a non-emergent major surgery (including CABG) prasugrel should be discontinued not earlier than 7 days and clopidogrel and ticagrelor not later than 5 days before surgery in order to keep peri-procedural bleeding complications low (IIaC) (38).

### Open questions

Potential differences between prasugrel and ticagrelor are rather hypothetical as a direct head to head comparison of the anti-platelet is missing. Therefore, both new agents should primarily be used as indicated in the guidelines.

### Bleeding risk

Due to an increased risk of bleeding with the conventional dose of prasugrel and based on pharmacokinetic data, a lower maintenance dose (i.e. 5 mg instead of 10 mg) has been recommended by the EMA for elderly and low-body weight patients. Whether the proposed reduction of the MD of prasugrel to 5 mg daily in the elderly and/or underweight patients is efficacious and safe was recently tested in the TRILOGY ACS study as mentioned above. Interestingly, results for a prolonged prasugrel therapy (up to 30 months) showed neither a better outcome nor a higher bleeding risk for patients with a primarily conservative treatment approach when compared to clopidogrel (25).

### Kidney function

While ticagrelor seems to be especially beneficial in patients with chronic kidney disease (CKD), prasugrel achieved the same amount of platelet inhibition in CKD patients as in patients with normal renal function despite a 51% lower exposure to prasugrel’s active metabolite in end stage kidney disease (39).
Pre-treatment before the catheter laboratory

With respect to pretreatment of patients with ACS with P2Y12 inhibitors a recent meta-analysis could not show any major benefit for clopidogrel with respect to hard clinical endpoints (40). Although results from prospective randomized trials for the new P2Y12-inhibitors are missing at moment, many networks, especially in Europe, already initiate prasugrel (to a lesser extent ticagrelor) pre-hospitaly in STEMI patients in the organization phase for acute PCI (usually in the ambulance during transportation). Up to now two studies have been investigating the impact of a pre-hospital initiation of modern P2Y12-inhibitors:

- The ACCOAST trial (41) was performed in order to assess the effect of an early pretreatment with prasugrel (30 mg pre-hospitally, 30 mg in the catheter laboratory) on clinical outcome compared to standard loading (60 mg) at the time of PCI in patients with NSTE-ACS. While the rate of the primary efficacy endpoint (cardiovascular death, myocardial infarction, stroke, urgent revascularization or GPIIb/IIIa bailout use) was statistically the same in the two treatment groups at seven (10.0% vs. 9.8%; p = 0.812) and 30 days (10.8% vs. 10.8%; p = 0.976), pretreated patients were at a significantly higher risk of TIMI major bleeding complications, which could already be seen in the first seven days (2.6% vs. 1.4%; p = 0.006). Due to these results the study was prematurely stopped.

- The ATLANTIC trial (42) is still ongoing and investigates the early (pre-hospital) vs. in-hospital use of ticagrelor in patients with STEMI referred for primary PCI. Final data analysis is expected in late 2014.

Is there any need for faster acting (intravenous) P2Y12-inhibitors?

Pharmacodynamic trials that have demonstrated a faster action of prasugrel and ticagrelor within two hours of ingestion as compared to clopidogrel mainly enrolled healthy volunteers or patients with stable coronary artery disease (43–46). Accordingly, the question arises if these outcome data could also be translated to patients with ACS, in who haemodynamic alterations might influence re-absorption of oral P2Y12-inhibitors, as might be the case haemodynamically compromised STEMI patients.

In the RAPID (Rapid Activity of Platelet Inhibitor drugs) Primary PCI Study (47) was recently performed enrolling and randomly assigning 50 patients with STEMI undergoing a PCI procedure within 12 hours of onset of symptoms to either receive a loading with prasugrel (60 mg) or ticagrelor (180 mg). Assessing platelet function by using VerifyNow detected a high residual platelet reactivity (platelet reactivity units ≥ 240) in 44% and 60% of patients two hours after administration of prasugrel and ticagrelor.

Another study measured platelet reactivity by use of the VerifyNow assay in STEMI patients receiving standard dose prasugrel and ticagrelor at different time points within 24 hours and up to 5 days after receiving the loading dose. Only at day five ticagrelor achieved lower platelet reactivity rates compared to prasugrel (25.6 PRU vs. 50.3 PRU; p = 0.01) while no difference was found within the first 24 hours of therapy. Interestingly, ticagrelor as well as prasugrel showed a high on treatment platelet reactivity (cutoff level in this study was 208 PRU) in 46% and 34% of patients thus indicating low-responsiveness to these agents (48). A significantly lower inhibition of platelet aggregation in STEMI patients receiving prasugrel compared to patients receiving tirofiban in the early phase of therapy (49) further supports the hypothesis of delayed re-absorption of oral P2Y12-inhibitors in STEMI patients as compared to intravenous agents. Whether this has impact on clinical outcome or is only of hypothetical value is not clear at moment. Nevertheless, fast acting IV agents like glycoprotein IIb/IIIa-blockers might still have a role in this clinical setting. But also the new intravenous P2Y12-inhibitor canegrelor might be of interest with this respect.

Cangrelor is an intravenously applicable direct platelet ADP-P2Y12 inhibitor with a rapid onset of action and rapidly reversible effects due to a half life of three to five minutes and was recently investigated in the CHAMPION PHOENIX trial (50): more than 11,000 patients with stable coronary disease or ACS (UA/NSTEMI and STEMI) undergoing urgent or elective PCI were randomly assigned to either receive canegrelor (bolus of 30 µg followed by an infusion of 4 µg/kg/min for at least two hours or clopidogrel (300 mg or 600 mg at the discretion of the interventionist) before PCI. Double blindness was guaranteed by administration of another clopidogrel loading dose (in case of canegrelor) or placebo (in case of clopidogrel) after discontinuation of the infusion (verum or matching placebo). The combined primary efficacy endpoint (all cause-death, MI, ischaemia-driven revascularization and stent thrombosis) within 48 hours could be significantly reduced by canegrelor compared to clopidogrel (4.7% vs. 5.9%; p = 0.005). Especially the secondary endpoint stent thrombosis within 48 hours was nearly halved by the intravenous platelet inhibitor (0.8% vs. 1.4%; p = 0.01). Significance of results remained visible with respect to both primary endpoint (6.0% vs. 7.0%; p = 0.03) and stent thrombosis (1.3% vs. 1.9%; p = 0.01) even after 30 days, independently which oral antiplatelet agent was combined with aspirin after 48 hours of ob-

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Fig. 2 Main results of canegrelor in CHAMPION PHOENIX (50)

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>Cangrelor</th>
<th>Clopidogrel</th>
<th>Significance</th>
</tr>
</thead>
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<tr>
<td>Primary EP</td>
<td>5.9%</td>
<td>4.7%</td>
<td>p = 0.01</td>
</tr>
<tr>
<td>Stent thrombosis</td>
<td>1.4%</td>
<td>0.8%</td>
<td>p = 0.01</td>
</tr>
<tr>
<td>GUSTO severe bleeding</td>
<td>0.11%</td>
<td>0.16%</td>
<td>p = 0.01</td>
</tr>
</tbody>
</table>

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ligatory clopidogrel administration. However, despite higher efficacy in prevention of hard cardiovascular endpoints no difference in severe bleeding complications (GUSTO criteria) (0.16% vs. 0.11%; p=0.44) was detected, indicating a clear net clinical benefit for cangrelor (4.8% vs. 6.0%; p=0.008) when combining the safety endpoint with the primary efficacy outcome (50). Main results of the study are illustrated (Fig. 2).

Based on these results cangrelor seems to be especially attractive in situations where oral administration and gastrointestinal reabsorption cannot be secured e. g. in patients with vegetative symptoms (vomiting) or patients with cardiogenic shock. Furthermore patients with the need for urgent bypass surgery might benefit from a bridging therapy with cangrelor (51).

However, the results of the CHAMPION PHOENIX are limited by the fact that patients randomized to cangrelor had a more sufficient ADP inhibiting platelet aggregation effect in contrast to patients on clopidogrel due to pharmacodynamic differences. Therefore, a head to head comparison with ticagrelor or prasugrel would be interesting, as these drugs have a faster onset of action compared to clopidogrel.

Due to pharmacologic aspects, cangrelor might be of special interest in patients with ACS aligned for sub-acute bypass surgery as suggested by the recently published BRIDGE trial (51): In this trial 210 patients with ACS or after coronary stenting and indication for early CABG surgery were enrolled. After having withdrawn the oral thienopyridine days before surgery, patients were randomized to either receive cangrelor or placebo for at least 48 hours. This therapy was stopped between 1 to 5 hours before surgery. Platelet reactivity, as measured daily, was significantly lower in cangrelor-treated patients compared to placebo (p<0.001). Furthermore, there was no difference with respect to severe bleedings prior or during CABG between treatment arms, while minor bleedings were more frequent in the verum (cangrelor) group, respectively.

**Conclusion**

The use of the new oral antiplatelet agents prasugrel and ticagrelor has stepwise increased in patients with ACS in the last years. Excellent data derived from clinical trials indicate a better clinical outcome compared to the old “golden” standard clopidogrel.

- While prasugrel has a more limited indication in ACS (except in STEMI) due to the clinical proof in patients undergoing PCI,
- ticagrelor has a wider indication and
- both agents should be preferred over clopidogrel if there is no contraindication or side effect.

In situations where an oral administration and gastrointestinal resorption cannot be guaranteed or in patients with the need for urgent bypass surgery initial therapy with cangrelor might become attractive, however, this substance has not been approved for clinical use yet.

Unfortunately, the clinical use of the new P2Y12-inhibitors is – against international guidelines – still behind expectations, especially in many countries where these agents are available far below 50%. This situation should be improved by increasing educational activities in order to offer guideline-recommended strategies more efficiently to the treating physicians.

**Conflict of interest**

The authors declare that they have no conflict of interest.

**References**


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