Oral antiplatelet therapy in acute coronary syndromes: update 2012

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Abstract

Dual antiplatelet therapy (DAPT), usually consisting of clopidogrel and acetylsalicylic acid (ASA), has come into discussion in recent years due to an increasing number of major adverse cardiac events based on insufficient ADP-mediated platelet inhibition with clopidogrel, mainly explained by drug interactions or genetic variants slowing or hindering the bioactivation of the prodrug clopidogrel into an active metabolite. Accordingly, new antiplatelet agents like prasugrel and ticagrelor were investigated in large prospective randomized clinical trials in patients with different entities of acute coronary syndromes (ACS). Based on their beneficial results in comparison to clopidogrel, these agents have found their way into the recent international guidelines for treatment of patients with acute coronary syndromes. Both antiplatelet agents demonstrated superiority with respect to the primary composite endpoint (cardiovascular death/non-lethal myocardial infarction/stroke). Ticagrelor even exhibited a mortality benefit over the comparator, but both compounds also increased the risk of spontaneous major bleedings to a significant extent. However, the efficacy/safety ratio of prasugrel and ticagrelor compared to clopidogrel is better. This article widens the insight into the recent changes in antiplatelet therapy in ACS by discussing the clinically most important data derived from the TRITON-TIMI 38 trial and the PLATO trial, including also the retrospective and pre-defined subgroup analyses. This article also gives information about the recommended duration of DAPT and the situation when patients who need permanent anticoagulation (e.g. in case of non-valvular atrial fibrillation) deserve also DAPT after coronary stenting ('triple therapy').

Keywords

Acute coronary syndrome, antiplatelet therapy, prasugrel, ticagrelor, triple therapy

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Background

The complexity of pathophysiological basic mechanisms (atherosclerosis, plaque formation, and plaque rupture) in acute coronary syndromes (ACS) leads to a subtotal or total occlusion of an epicardial coronary artery by formation of a platelet rich thrombus leading to necrosis of myocardial tissue. Hyperreactivity of platelets in these situations has been identified as an important prognostic factor,¹ which makes dual antiplatelet therapy (DAPT) obligatory in order to avoid recurrent target vessel occlusion in terms of the 'no reflow phenomenon' in patients immediately after successful percutaneous coronary intervention (PCI) or in terms of early or late stent thrombosis.² DAPT is usually recommended for 12 months and consisted until recently of acetylsalicylic acid (ASA) and clopidogrel. Unfortunately, clopidogrel is associated with a considerable interindividual variability in inhibition of platelet function. Low- or

non-respondership (also called clopidogrel resistance) is mainly caused by a delayed and/or insufficient conversion of the prodrug clopidogrel into its active metabolite^{3–6} and is frequently associated with increased cardiovascular events, e.g. stent thrombosis, recurrent myocardial infarction, or cardiovascular death.^{6,7} The bioactivation of clopidogrel depends on two metabolic steps in the liver, which can be influenced by various genetic^{8–11} or non-genetic¹² mechanisms. Accordingly, optimal inhibition of platelet activity cannot be guaranteed to the individual patient,

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especially if patients are homozygote carriers of the most important CYP2C19*2 loss-of-function polymorphism, while heterozygotes might react to increasing doses of clopidogrel (ELEVATE-TIMI 56 trial).¹³

In contrast, the new P2Y₁₂-receptor blockers prasugrel and ticagrelor do not depend on these loss-of-function genetic variants.^{9,14}

In addition, as a reaction to clopidogrel 'resistance', several trials investigated the impact of increasing loading and maintenance doses of clopidogrel on clinical outcome, but no single study could clearly demonstrate a significant clinical benefit despite improved platelet inhibition in platelet function assays.^{15–18}

Prasugrel

Prasugrel, a new thienopyridine, irreversibly binds to the P2Y₁₂-receptor – thus inhibiting the ADP-mediated platelet aggregation – and shows a more rapid action and a higher potency of inhibiting platelet aggregation compared to clopidogrel. Similar to clopidogrel, prasugrel is a pro-drug and needs to be bioactivated into its active metabolite. In contrast to clopidogrel, however, prasugrel only needs one metabolic step resulting in a faster and more consistent antiplatelet effect.

In the TRITON TIMI-38 trial (Trial to assess Improvement of Therapeutic Outcomes by Optimizing Platelet Inhibition with Prasugrel – Thrombolysis in Myocardial Infarction 38)¹⁹ more than 13,000 patients with ACS [unstable angina, non-ST-segment elevation myocardial infarction (NSTEMI), ST-segment elevation myocardial infarction (STEMI)] were investigated. With the exception of STEMI patients, in whom study medication was given without knowledge of coronary anatomy and pre-treatment with clopidogrel was accepted, a diagnostic angiogram was obligatory prior to randomization. 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. Figure 1 shows a summary of the main results of the study. The primary composite efficacy endpoint (cardiovascular mortality, nonfatal myocardial infarction, and nonfatal stroke) was significantly reduced by 18% in patients with prasugrel compared to clopidogrel (9.9% vs. 12.1%, $p < 0.001$). Moreover the rate of definite stent thrombosis was more than halved (0.88 % vs. 2.03 %; $p < 0.001$). These advantages were already documented after 3 days and remained significant throughout the study period. As expected, the higher efficacy of prasugrel was associated with increased spontaneous non-coronary artery bypass grafting (CABG)-related major bleeding hazards (TIMI bleeding classification:

Figure 1. Main results of prasugrel in TRITON TIMI 38.¹⁹

2.4% vs. 1.8%, $p = 0.03$) as well as with more frequent fatal bleedings (0.4% vs. 0.1%, $p = 0.002$), respectively. Moreover, patients undergoing urgent coronary bypass surgery were at a significantly higher peri-operative bleeding risk after the intake of at least one dose of prasugrel (13.4% vs. 3.2%, $p < 0.001$). Especially elderly individuals (>75 years old) as well as patients with a low bodyweight (<60 kg) tended to bleed more frequently, while in elderly and underweight patients the net clinical benefit of prasugrel (primary combined endpoint plus major haemorrhage) was comparable with that of clopidogrel, patients with a history of any cerebrovascular events (ischaemic or haemorrhagic stroke or transient ischaemic attacks) were at a higher risk for bleeding and had an unfavourable outcome. Accordingly, prasugrel is contraindicated in patients with a history of such cerebrovascular events. Furthermore, a significant net clinical benefit with prasugrel was demonstrated for the whole patient cohort (12.2% vs. 13.9% with clopidogrel, hazard ratio, HR, 0.87, 95% CI 0.79–0.95, $p = 0.004$).¹⁹

Several pre-specified subgroup analyses have been performed and published. In the subgroup of patients with STEMI referred for primary PCI, prasugrel was associated with a 32% relative risk reduction (RRR) of the primary combined endpoint (cardiovascular death, myocardial infarction, or stroke) after 30 days (6.5% vs. 9.5%, $p = 0.017$), which still was 19% after 15 months (10.0% vs. 12.4%, $p = 0.022$) as compared to standard therapy.²⁰ Interestingly, in STEMI patients referred for primary PCI, severe bleeding complications were not different between study drugs (prasugrel 1.0% vs. 1.3% with clopidogrel, $p = 0.34$).

In diabetic patients with ACS, prasugrel yielded a significant 28% RRR 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%, $p = 0.02$, RRR 13%).²¹ Moreover, in

diabetics the incidence of myocardial infarction during the follow-up period could be reduced by 40% ($p < 0.001$). While the rate of severe TIMI bleedings was increased in prasugrel- vs. clopidogrel-treated non-diabetics (2.4% vs. 1.6%, $p = 0.02$), it was comparable between prasugrel- and clopidogrel-treated diabetics (2.6% vs. 2.5%, $p = 0.81$).

In another substudy in high-risk patients who had suffered from an initial nonfatal primary endpoint event, prasugrel demonstrated its superiority over clopidogrel, by preventing not only further events to a significantly higher extent than clopidogrel (10.8% vs. 15.4%, HR 0.65, 95% CI 0.46–0.92, $p = 0.016$), but also the secondary endpoint of cardiovascular death (3.7% vs. 7.1%, HR 0.46, 95% CI 0.25–0.82, $p = 0.008$).²²

In a genetic substudy, it was also shown that clopidogrel-treated carriers of the CYP2C19*2 loss-of-function polymorphism, which is believed to hinder fast and efficacious bioactivation of clopidogrel, were at higher risk of adverse cardiovascular outcome than non-carriers (12.1% vs. 8.0%, $p = 0.014$), while there was no influence of the carrier status of this polymorphism in prasugrel-treated patients (8.5% vs. 9.8%, $p = 0.27$).⁹ This might be explained by the wider spectrum of cytochrome P450 enzymes involved in the single bioactivation step of prasugrel, which guarantees sufficient bioactivation of the prodrug prasugrel into its active metabolite even in the absence of the CYP2C19 enzyme system.²³ With respect to the ABCB1 (translation 3345 C→T) genotype (50% of all patients in TRITON TIMI-38 were carriers of this polymorphism), which has an impact on the absorption of clopidogrel, a higher incidence of cardiovascular adverse events was observed in the patient group treated with clopidogrel (TT homozygote vs. CT/CC individuals: 12.9% vs. 7.8%, $p = 0.002$), while no influence by this polymorphism existed in the prasugrel-treated group.⁹

Ticagrelor

In contrast to clopidogrel and prasugrel, ticagrelor is not a thienopyridine nor a prodrug but a directly active compound. Ticagrelor binds reversibly to the P2Y₁₂ receptor and non-competitively inhibits neither ADP-induced receptor signalling nor ADP-binding itself. Due to its reversibility of action and its short half-life (7–8.5 hours, which is the same half-life for the active metabolite (7.4 hours) of prasugrel), a LD of 180 mg and administration of a MD of 90 mg twice daily is obligatory in order to achieve constant platelet inhibition over time. The reversibility of its action makes ticagrelor hypothetically attractive for situations when dual antiplatelet therapy needs interruption for surgery or when bleeding complications occur.

In the multicentre, double-blind, randomized phase-3 PLATO trial (A Comparison of AZD6140 and Clopidogrel in Patients With ACS) (Figure 2),²⁴ more than 18,000 patients with ACS (non-ST segment elevation and ST-segment elevation) were included regardless which

Figure 2. Main results of prasugrel in PLATO.²⁴

treatment approach (interventional, primarily conservative, or conservative only) was chosen. Patients were randomly assigned to either receive ticagrelor in the doses 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 of ACS patients with off-study clopidogrel before randomization was allowed in this trial. The primary endpoint was a composite of cardiovascular death, myocardial infarction, and stroke, which was reported significantly less often in ticagrelor-treated patients compared to the clopidogrel group (9.8% vs. 11.7%, HR 0.84, 95% CI 0.77–0.92, $p < 0.001$). Moreover, also the secondary single 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 also significantly reduced by ticagrelor. By use of the study-specific classification of severe bleedings including also peri-operative CABG-related bleedings, no statistically significant differences were demonstrated between the two treatment arms (ticagrelor 11.6% vs. clopidogrel 11.2%, $p = 0.43$). However, spontaneous severe bleedings were significantly higher in ticagrelor-treated patients independent of the chosen bleeding classification (PLATO classification: 4.5% vs. 3.8%, $p = 0.03$; TIMI classification: 2.2% vs. 2.8%, $p = 0.025$, respectively).

Dyspnoea was seen more frequently in ticagrelor-treated patients compared with the clopidogrel-treated group (13.8% vs. 7.8%, $p < 0.001$). It was mostly mild to moderate, occurred transient in the first month of treatment and only rarely led to the discontinuation of the study drug (in 0.9% of patients).²⁴ Moreover, dyspnoea has been proven to be unrelated to changes in cardiac or pulmonary function in previous dose-finding and safety studies.²⁵ Interestingly, mortality rates were substantially lower in ticagrelor-treated patients with dyspnoea compared to clopidogrel-treated

patients with dyspnoea, indicating that it is a benign side-effect and that the benefit of ticagrelor as seen in the overall trial translates to patients with shortness of breath as well.²⁶ Furthermore, in ticagrelor-treated patients 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. In addition, a small increase in creatinine and uric acid levels was observed, which subsided after treatment discontinuation at the end of the trial. These adverse events, however, did not cause specific medical interventions. A ticagrelor-induced blockage of adenosine re-uptake into red blood cells has been suggested as the underlying basic mechanism for dyspnoea, bradycardia, and elevated creatinine or uric acid levels.²⁶

Pre-specified subgroup analyses also confirmed the beneficial effect of ticagrelor over the comparator clopidogrel. In the 7544 patients with STEMI referred for primary PCI, the effects of ticagrelor were consistent with those seen in the overall PLATO trial:²⁷ ticagrelor reduced the primary combined efficacy endpoint by 13% (9.4% vs. 10.8%, $p=0.07$) and the rate of a recurrent myocardial infarction was 19% lower compared to clopidogrel (4.7% vs. 5.8%, $p=0.07$), in both instances, however, not to a significant extent. In STEMI patients, major bleeding complications were not significantly affected by ticagrelor when compared with clopidogrel.

Beneficial effects for ticagrelor vs. its comparator were also observed in patients with diabetes ($n=4662$) with respect to a reduction of the primary composite endpoint (HR 0.88, 95% CI 0.76–1.03), all-cause mortality (HR 0.82, 95% CI 0.66–1.01), as well as stent thrombosis (HR 0.65, 95% CI 0.36–1.17). Similar to the subgroup of STEMI patients, no increase in major bleeding was observed when ticagrelor was compared with clopidogrel (HR 0.95, 95% CI 0.81–1.12) in diabetics.²⁸

Most importantly, ticagrelor showed an impressive reduction of the primary combined endpoint in patients undergoing CABG within 7 days after the last study drug intake. Total mortality (4.7% vs. 9.7%, $p<0.01$), cardiovascular death (4.1% vs. 7.9%, $p<0.01$), and non-cardiovascular death (0.7% vs. 2.0%, $p=0.07$), were all significantly reduced in ticagrelor-treated patients, while the bleeding risk was similar between study drugs.²⁹

Moreover, ticagrelor was especially effective in patients with chronic kidney disease (CKD; creatinine clearance <60 ml/min) as it achieved a significant RRR of the primary combined end point by 21% over clopidogrel (17.3% vs. 22.0%, HR 0.77, 95% CI 0.65–0.90), which was more pronounced than in patients with normal renal function (RRR 11%, 7.9% vs. 8.9%, HR 0.90, 95% CI 0.79–1.02, $p=0.13$).³⁰ In contrast to the total cohort of ACS patients, the reduction of the secondary single endpoint cardiovascular mortality reached no statistical significance in ticagrelor- vs. clopidogrel-treated patients with CKD (RRR 29%, 10.0% vs. 14.0%, HR 0.72, 95% CI 0.58–0.89, $p=0.14$).

Major bleedings (15.1% vs. 14.3%, HR 1.07, 95% CI 0.88–1.30), fatal bleedings (0.34% vs. 0.77%, HR 0.48, 95% CI, 0.15–1.54), and non-CABG-related major bleedings (8.5% vs. 7.3%, HR 1.28, 95% CI 0.97–1.68) were not statistically different between treatment arms.

In the genetic subgroup analysis of the PLATO trial, ticagrelor achieved consistently better results than clopidogrel, irrespective of the presence or absence of the CYP2C19 or the ABCB1 loss-of-function polymorphisms.¹⁴ In carriers of any loss-of-function allele of the CYP2C19 genotype, ticagrelor led to a significant 23% reduction of the primary combined endpoint compared to clopidogrel (8.6% vs. 11.2%, $p=0.038$) at 30 days after study inclusion. This early statistical benefit was no more significant at the end of the follow-up period, thus indicating that the presence of loss-of-function metabolisms might be of more importance in the acute and subacute phases of disease, when residual platelet reactivity usually is higher.

What the guidelines say

Due to these remarkable results, prasugrel and ticagrelor have already found their way into the current European guidelines for non-ST-elevation acute coronary syndromes and myocardial revascularization.^{2,31} In patients with STEMI referred for primary PCI, both agents received an IB recommendation (vs. only IC for clopidogrel)² (Table 1). Both agents should also be preferred over clopidogrel in NSTEMI-ACS patients (IB): 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 and who are undergoing a coronary intervention. Clopidogrel should only be used in ACS patients in case of 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 increased bleeding risk. Clopidogrel still remains the agent of choice in patients with stable coronary artery disease and planned PCI (IA).^{2,31} In case of a non-emergent major surgery (including CABG), prasugrel should be discontinued not later than 7 days and clopidogrel and ticagrelor not later than 5 days before surgery in order to keep periprocedural bleeding complications low (IIaC).³¹

Still open questions

Because a direct head-to-head comparison is missing, potential differences between prasugrel and ticagrelor are hypothetical and both new agents should be used as indicated by the guidelines.

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 EU (EMA) for elderly and

Table 1. Recommendations for the use of antiplatelet therapy based on the current guidelines (myocardial revascularization; acute coronary syndromes without ST-segment elevation) of the European Society of Cardiology^{2,31}

Drug	ST-segment elevation myocardial infarction		Non-ST-segment elevation myocardial infarction	
	Class of recommendation	Level of evidence	Class of recommendation	Level of evidence
ASA	I	B	I	A
Clopidogrel	I	C	I	C
Prasugrel	I	B	I	B
Ticagrelor	I	B	I	B

low-bodyweight 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 is currently tested in the TRILOGY ACS study.³² While ticagrelor seemed to be beneficial especially in patients with 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.³³ Based on the recent guidelines, the use of prasugrel in NSTEMI-ACS patients should be restricted to patients whose coronary anatomy is known³¹. On the other hand, the current guidelines recommend to add a P2Y₁₂-inhibitor in suspected ACS 'as soon as possible'³¹ and state that it is not satisfying to withhold optimal medical therapy until intervention. Therefore, many networks, especially in Europe, already initiate prasugrel (to a lesser extent ticagrelor) pre-hospitally in STEMI patients in the organization phase for acute PCI, in the ambulance during transportation. Two currently ongoing studies are believed to answer the important question of pre-hospital initiation of ADP receptor-blocker therapy. In the ACCOAST study, 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 LD) at the time of PCI in patients with NSTEMI-ACS.³⁴ The ATLANTIC trial investigates the early (pre-hospital) vs. in-hospital use of ticagrelor in patients with STEMI referred for primary PCI.

Both new antiplatelet agents vary with respect to their reached benefit observed in subgroups (Figure 3). Ticagrelor lost its statistically significant superiority over clopidogrel in patients with STEMI with respect to the primary composite endpoint (9.4% vs. 10.8%, $p=0.07$, RRR 13%),²⁷ whereas these patients showed a pronounced benefit when treated with prasugrel (10.0% vs. 12.4%, $p=0.022$, RRR 19%).²⁰ An explanation for such a difference is impossible as only a head-to-head comparison of both agents in STEMI patients could bring light into this situation. In this respect it is unlikely that pre-treatment with clopidogrel could explain this difference alone, as in PLATO the results between clopidogrel-pretreated and clopidogrel-naïve patients were not statistically different.²⁷

In diabetics, prasugrel exhibited a marked benefit over clopidogrel (RRR 28%), while the benefit smaller in non-diabetics (RRR 13%).²¹ In contrast, no difference between

Figure 3. Differences of results between prasugrel and ticagrelor with respect to subgroup analyses in TRITON TIMI 38 and PLATO.^{20,21,27,28}

diabetics (RRR of the primary combined endpoint was 13%) and non-diabetics (RRR was 18%) was reported for ticagrelor and in both groups the difference to clopidogrel was not statistically significant.²⁸

Triple therapy

Antithrombotic combination therapy after PCI requiring dual antiplatelet therapy in patients with an indication for anticoagulation, especially in patients with atrial fibrillation, has not or only marginally been included in recent guidelines yet, as no prospective randomized studies are available. The situation has recently become more complex since new anticoagulants for atrial fibrillation (dabigatran is already approved, rivaroxaban and apixaban soon to follow) and more efficacious new antiplatelet agents for ACS (prasugrel, ticagrelor) become used more frequently. Recently two position/consensus papers from Europe³⁵ and North America³⁶ were published in order to support physicians in their decision how and how long to treat such patients. Therapeutic decisions of patients with non-valvular atrial fibrillation following stent placement have to be based upon assessment of bleeding and thrombotic risk of the individual patient. The CHADS₂- and recently the CHA₂DS₂-VASC scores have been proposed in order to stratify for thrombotic risk,^{37–39} while stratification of the

Table 2. Recommendations for antithrombotic combination therapy in patients with non-valvular atrial fibrillation and the need for percutaneous coronary intervention³⁵

Bleeding risk	Indication	Stent type	Recommendation
Low to intermediate	Elective	BMS	<ul style="list-style-type: none"> • one month: triple therapy • followed by: monotherapy
	Elective	DES	<ul style="list-style-type: none"> • 3 (-olimus stent) to 6 (paclitaxel) months triple therapy • then up to 12th month dual therapy • followed by: monotherapy
	ACS	BMS/DES	<ul style="list-style-type: none"> • 6 months triple therapy • Then up to 12th month dual therapy • followed by: monotherapy
High	Elective	BMS	<ul style="list-style-type: none"> • 2-4 weeks triple therapy • followed by: monotherapy
	ACS	BMS	<ul style="list-style-type: none"> • 4 weeks triple therapy • Then up to 12th month dual therapy • followed by: monotherapy

Triple therapy: oral antithrombotic (INR 2.0 to 2.5), ASA (≤ 100 mg per day), clopidogrel (75 mg per day). Dual therapy: oral anticoagulation (INR 2.0 to 2.5), clopidogrel (75 mg per day) or ASA (≤ 100 mg per day). Monotherapy: oral anticoagulation (INR 2.0 to 3.0).

bleeding risk is currently based on the HAS-BLED-Score.⁴⁰ In patients prone to 'triple' therapy also, other important aspects have to be taken into consideration when potential hazards from thrombotic or bleeding complications have to be weighted: radial arterial vascular access vs. femoral access, pure balloon angioplasty vs. PCI plus stenting, and the preference of bare metal stents over drug eluting stents (DES), which might need a longer antithrombotic combination therapy. Both position papers are similar in recommending that DES should be avoided unless clearly indicated due to specific anatomic situations (long lesions, small vessels), comorbidities (e.g. diabetics), and in patients with a high bleeding risk. Furthermore, last-generation DES should be preferred over older-generation stents as they afford a shorter duration of dual antiplatelet therapy. European and North American recommendations, however, differ: Europeans tend to prefer shorter duration of triple therapy in order to support safety while North Americans ask for longer duration of combination antithrombotic therapy in certain subgroups in order to increase efficacy.⁴¹

Because no trials have been performed by use of the new anticoagulants or antiplatelet agents at moment, triple therapy should consist of clopidogrel 75 mg/day plus ASA 100 mg/day plus a vitamin K antagonist (international normalized ratio control between 2.0 and 2.5).^{35,36} Table 2 gives a summary about current European recommendations of triple therapy depending on different bleeding risks and on the acuteness of the clinical situation.

Conclusion

The new oral antiplatelet agents prasugrel and ticagrelor have been rapidly adopted for the treatment of acute coronary syndromes in the past 2 years. The excellent data

derived from clinical trials promise a marked better clinical outcome compared to the old golden standard clopidogrel. Nevertheless, the choice for one of the new compounds should be based on the patient's individual bleeding risk. Since differences in the extent and significance of relative risk reductions are seen in certain subgroup analyses when prasugrel or ticagrelor are compared with clopidogrel but guideline recommendations are comparable on a high level (IB), only the future will tell us which agent will finally be preferred by the treating cardiologist. Still open questions including the combination of antithrombotic agents and the duration of therapy will also be answered in the near future based on clinical practice in real-world situations.

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