# Prasugrel versus clopidogrel: Practical guidance for use according to the evidence

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ABSTRACT

Presently, there are two inhibitors of ADP-induced platelet activation and aggregation available in the Czech Republic – "golden standard" clopidogrel and more potent but also more agressive prasugrel. There are pros and cons of both drugs with regards to their pharmacodynamic, pharmacokinetic and clinical profile. Having reviewed existing evidence for clinical use of both agents, we summarize that prasugrel is superior to clopidogrel in patients presenting with acute coronary syndrome with ST elevations (STEMI), with ACS without ST elevations/unstable angina (non-STEMI/UA) with early interventional strategy, in patients with diabetes mellitus and those presenting with stent thrombosis. On the contrary, clopidogrel remains a drug of choice in non-STEMI patients without early interventional approach and in those medically treated, in ACS patients under 60 kg of weight and/or aged 75 yrs and older because of an increased risk of bleeding, in patients with prior stroke/transitory ischemic attack, with the need of triple therapy with an anticoagulant and patients with stable coronary artery disease after stent implantation.

## Introduction

Prasugrel is a novel thienopyridine antiplatelet drug that – after metabolic conversion to an active metabolite R-138727 – binds to and irreversibly blocks platelet P2Y12 receptors and inhibits platelet activation and aggregation [1]. This adenosine diphosphate (ADP) induced thrombocyte activity, when compared to widely used and well-established clopidogrel, is much less susceptible to genetic variations of CYP enzymes and drug interactions [2,3]. Active metabolites of clopidogrel and prasugrel in equimolar plasma concentrations have a very similar antiplatelet effect but the conversion of prasugrel is more rapid, consistent, and efficient. The peak plasma concentration of the active prasugrel metabolite is achieved higher (12-fold) and sooner (within 60 min, clopidogrel 4–6 hours) which translates into 2,5-fold increase of inhibition of platelet activity (IPA 79 ± 9% vs 33 ± 23%) [4]. In several recent studies with stable ischemic heart disease patients, 10–40% of subjects were recognized as non-responders to clopidogrel and subsequently had significantly higher occurrence of ischemic adverse events during follow-up [5,6].

Several cross-over and dose-ranging studies compared head-to-head various loading and maintenance doses of clopidogrel (LD 300–900 mg and MD 75–150 mg, respectively) with prasugrel (LD 40–60 mg and MD 7.5–15 mg). These studies (ACAPULCO, PRINCIPLE-TIMI 44, JUMBO-TIMI 26) were not powered to assess clinical outcomes but provided sufficient and promising data regarding safety (occurrence of bleeding) and "pharmacodynamic" efficacy of prasugrel (level of anti-aggregation achieved) and served as a rationale for a big, randomized, double blind trial. The only phase-III trial completed and designed to evaluate short- and long-term outcomes in patients with ischemic heart disease taking prasugrel was TRITON-TIMI 38 trial (Phase III Trial to Assess Therapeutic Outcomes by Optimizing Platelet Inhibition with Prasugrel). This study proved that patients with STE acute coronary syndrome (ACS), non-STEMI or unstable angina (UA) scheduled to percutaneous coronary intervention (PCI) profited more from prasugrel than clopidogrel therapy during 14.5-month follow up – achieved net clinical benefit of 13% (reduction of adverse ischemic events versus increased bleeding complications) [7]. Nevertheless, this study also demonstrated that prasugrel was not suitable for all ACS patients, did not focus on ACS patients with medical treatment only, excluded those with the need for oral anticoagulation, etc. We will discuss these groups of patients in our article.

With regards to the results of the studies, particularly TRITON-TIMI 38, the use of prasugrel was approved by the European Commission in February 2009, by the US Food and Drug Administration (FDA) in July 2009 [8] and launched on market in the Czech Republic in October 2011.

Presently, there are 2 irreversible P2Y12 thrombocyte receptor blockers available – deeply ingrained and widely used "golden standard" clopidogrel and more aggressive and potent prasugrel. Our choice should be guided by evidence-based medicine but needs to be modified and adjusted to individual patient needs balancing predictable benefits against potential risks. The cost and availability of both drugs is also an issue and needs to be taken into account. Results of the study by Mahoney et al. [9] that demonstrated cost-effectiveness of prasugrel treatment is not much applicable in our health insurance system.

In the following text, we will summarize current indications of both drugs in ACS patients with special atten-

tion to elderly patients, patients with diabetes mellitus, stroke/transitory ischemic attack, stent thrombosis and the need for anticoagulation. It is important to say that prasugrel has not been investigated in any clinical trial concerning stable coronary artery disease that would be powered to evaluate clinical outcomes. In patients with stable angina with/without coronary intervention only clopidogrel should be used.

## Groups of patients

The results of the trials with clopidogrel and prasugrel have already been implemented in the Czech and European Society of Cardiology guidelines [10–12]. To sum up in short, in *the setting of STEMI*, prasugrel (always with acetyl-salicylic acid) is indicated as soon as possible (LD 60 mg + MD 10 mg daily) with recommendation I, level of evidence B. In such an emergency situation, fast onset of anti-aggregative effect is of advantage and prasugrel in these patients reduces the relative risk of thrombotic cardiovascular events at 30 days (32% reduction), with the effect persisting to 15 months (21% reduction) and without causing more bleeding complications when compared to clopidogrel intake [13]. Both drugs are recommended (class I) but prasugrel seems to be superior in the setting of STEMI.

In *patients presenting with non-STEMI/unstable angina*, the choice of particular drug should be based on our decision whether we manage the patient conservatively (for any reason) or intend to perform a percutaneous angioplasty (PCI). There is no clinical data so far to support prasugrel in conservatively treated patients. The amount of such patients is uncertain. In observational studies, as many as 29% of non-STEMI patients are not catheterized for the index event during the initial hospitalization [14]. For these patients clopidogrel remains the drug of choice. Results of another prasugrel vs clopidogrel phase III trial – TRILOGY ACS (The Targeted Platelet Inhibition to Clarify the Optimal Strategy to Medically Manage Acute Coronary Syndromes) that was recently completed and that enrolled medically treated non-STEMI/UA patients and followed them up for 18 months are desperately awaited [15]. Patients scheduled for PCI and still clopidogrel naive should undergo the procedure within 24 hours and receive prasugrel LD as soon as the decision for coronary intervention has been made. This approach in the TRITON study resulted in absolute 2.1% reduction (9.2% to 7.1%) of non-fatal MI occurence at 15 months at the price of absolute 0.6% increase of major bleeding complications (1.6% to 2.2%). Alternatively, clopidogrel with IA indication is also recommended, especially when a longer delay from manifestation of symptoms to the interventional procedure is expected or the patient is deemed to have a higher risk of bleeding complications (anemia, female gender, obesity, renal insufficiency, etc.)

Potential risks and benefits need to be considered especially in *patients with low body weight ≤ 60 kg and elderly patients aged ≥ 75 yrs* because of changed pharmacokinetic of prasugrel in these patients. While the presence of moderate liver and kidney disease or end-stage renal failure does not effect active metabolite concentrations, patients ≥ 75 years have 19% higher exposure to prasugrel's active metabolite compared to patients < 75 years and 25% higher exposure compared to patients < 60 years. Furthermore, patients weighing < 60 kg have 30% higher exposure than patients ≥ 60 kg and 42% higher exposure than patients ≥ 85 kg [16,17]. When translated to clinical outcomes, both subgroups have neutral net clinical benefit from prasugrel therapy (reduced ischemic events but increased bleeding events). As the safety is the major concern, prasugrel is generally not recommended in elderly patients and low body weight patients and clopidogrel should be used instead. Anyway, in patients at high risk for recurrent ischemic events such as patients with diabetes mellitus or prior myocardial infarction prasugrel may still be considered but the maintenance dose of prasugrel should be lowered to 5 mg daily [18].

*Patients with diabetes mellitus* and the manifestation of ACS markedly benefit from prasugrel with all the pathophysiological and clinical data supporting this fact [19]. Although insulin reduces platelet aggregation by inhibiting P2Y12 receptor in healthy subjects this effect is absent in patients with diabetes and insulin resistance [20]. Also glycosylation of platelet membrane proteins, higher oxidative stress, impaired endothelial function – all these conditions lead to increased procoagulant state in diabetics and greater response to platelet agonists and, as a consequence, better clinical response to more potent platelet antagonist prasugrel. Atherothrombotic ischemic events were highly significantly reduced in prasugrel group when compared to clopidogrel group in the TRITON trial [21] – myocardial infarction by 40%, stent thrombosis by 48% – and net clinical benefit of 26% was achieved. Prasugrel is definitely superior to clopidogrel in the treatment of diabetes patients with ACS and planned interventional therapy.

In contrary to patients with diabetes mellitus, *patients with prior stroke/transitory ischemic attack* presenting with ACS may suffer harm from prasugrel therapy and this drug should not be indicated. The reason for that is that not only do these patients have a higher incidence of subsequent ischemic events (particularly stroke) but also have a higher rate of bleeding. To summarize, the net clinical benefit of 54% significantly favours clopidogrel use only in these patients [7].

The most feared complication after coronary stenting is *stent thrombosis* (ST). No matter when it happens, this quite rare emergency event (1–2% of all stents) is responsible for up to 91% rate of death within 7 days of manifestation [22]. The strongest predictor of ST is the discontinuation of dual antiplatelet therapy, other predictors include stent undersizing, dissection, bifurcation lesions, diffuse coronary disease or poor left ventricular function [23]. Prasugrel has been proved to markedly reduce the risk of early and late stent thrombosis (early ST – 1–30 days of implantation by 55%, late ST – 30–450 days of implantation by 32%) regardless the ACS type, bare-metal or drug-eluting stent, length of stent, presence of diabetes or renal

dysfunction when compared to clopidogrel [24]. Patients presenting with stent thrombosis should be given prasugrel or, in our opinion, switched to prasugrel if currently on clopidogrel medication. Although not supported by any studies assessing clinical outcomes, this switching strategy further increased platelet inhibition when compared to loading doses (300–600 mg) or maintenance doses (75–150mg) of clopidogrel in several recent trials [25,26], was well tolerated by the subjects and should be justified.

The last group of subjects that we will comment in this review includes the majority of patients with ACS and atrial fibrillation, artificial valves, reduced left ventricular function or present intracardial thrombus – those with *the need for oral anticoagulation* (both absolute or relative indications). In the European guidelines or Experts Consensus Document [27], triple therapy is only recommended with warfarin, aspirin and clopidogrel with the duration depending on the stent type (drug-eluting stents should be avoided) but randomized data is missing. Neither combinations with prasugrel as the possible replacement for clopidogrel, nor dabigatran (oral direct thrombin inhibitor) or rivaroxaban (oral anti-Xa agent) instead of warfarin have been ever investigated. A decision to prescribe prasugrel in a patient who is receiving oral anticoagulant therapy must be based on the clinical judgment of the prescriber that benefit will outweigh the increased risk of bleeding and such decision should be consulted with the patient.

Even more complex decision-making process will be needed after the currently last antiaggregant drug, ticagrelor has been commercially available. It is a novel thienopyridine that inhibits the P2Y12 thrombocyte receptor reversibly and directly and has been approved for use in unstable angina/non-STEMI/STEMI indications in the European Union but is not yet distributed in the Czech Republic.

## Summary

Both clopidogrel and prasugrel are inhibitors of ADP-induced platelet activation and aggregation. Clopidogrel as "a golden standard" for years in ACS patients has several pharmacokinetic and pharmacodynamic limitations that favour prasugrel in certain subgroups of patients.

On the contrary, prasugrel should be avoided in patients with high risk of bleeding where the positive clinical benefit is then devalued. Caution is also needed in indications where prasugrel has not been investigated. Higher cost of prasugrel is also an issue.

In general, prasugrel is superior to clopidogrel in STEMI patients, non-STEMI/UA patients with early interventional strategy, in patients with diabetes mellitus and those presenting with stent thrombosis.

Clopidogrel remains a drug of choice in non-STEMI patients without early interventional approach and in those medically treated, in ACS patients under 60 kg of weight and/or aged 75 yrs and older because of an increased risk of bleeding, in patients with prior stroke/TIA, with the need of a triple therapy with an anticoagulant and patients with stable coronary artery disease after stent implantation.

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