The role of prasugrel in the management of acute coronary syndromes: a systematic review

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Abstract. – OBJECTIVE: Dual antiplatelet therapy (DAPT) is the treatment of choice in the medical management of patients with acute coronary syndrome (ACS). The combination of aspirin and a P2Y12 inhibitor in patients who receive a coronary stent reduces the rate of stent thrombosis and the rates of major adverse cardiovascular events. However, patients with acute coronary syndrome remain at risk of recurrent cardiovascular events despite the advance of medical therapy. The limitations of clopidogrel with variable antiplatelet effects and delayed onset of action are well established and lead to the development of newer P2Y12 inhibitors. Prasugrel is a selective adenosine diphosphate (ADP) receptor antagonist indicated for use in patients with ACS. Prasugrel provides greater inhibition of platelet aggregation than clopidogrel and has a rapid onset of action. We have conducted a systematic review to retrieve current evidence regarding the role of prasugrel in the management of ACS. Evidence comparing prasugrel, clopidogrel, and ticagrelor remain scant.

MATERIALS AND METHODS: A complete literature survey was performed using PubMed database search to gather available information regarding management of acute coronary syndromes and prasugrel. An explorative comparison of the safety and efficacy of prasugrel, clopidogrel, and ticagrelor was also conducted.

RESULTS: Prasugrel and ticagrelor are more efficacious than clopidogrel in reducing the occurrence of non-fatal myocardial infarction, stroke, or cardiovascular (CV) death but they have also an increased risk of major bleeding in comparison to clopidogrel.

CONCLUSIONS: Prasugrel and ticagrelor are today the recommended first-line agents in patients with ACS. The estimation of which drug is superior over the other cannot be reliably established from the current trials.

Key Words:
Prasugrel, Clopidogrel, Ticagrelor, Cardiovascular.

Abbreviations
ACS = acute coronary syndrome; ADP = adenosine diphosphate; AUC = area under the curve; CABG = coronary artery bypass graft; CI = confidence interval; CV = cardiovascular; COX = cyclooxygenase; DAPT = dual antiplatelet therapy; DM = diabetes mellitus; ESC = European Society of Cardiology; ESRD = end stage renal disease; FDA = food and drug administration; GFR = glomerular filtration rate; GP = glycoprotein; HCPR = high on-clopidogrel platelet reactivity; LAD = left anterior descending; LM = left main; MI = myocardial infarction; NSAIDs = non steroidal anti-inflammatory drugs; NSTEMI = non ST elevation myocardial infarction; PCI = percutaneous coronary intervention; PPIs = proton pump inhibitors; STEMI = ST elevation myocardial infarction; TAVI = transcatheter aortic valve implantation; TIA = transient ischemic attack; TIMI = thrombolysis in myocardial infarction study group; UA = unstable angina.

Introduction

Prasugrel is a prodrug that requires conversion to active metabolites and irreversibly blocks the P2Y12 platelet receptor with a much faster onset
and a more potent antiplatelet inhibition. Platelets play a vital role in thrombosis so that platelet inhibition can reduce cardiovascular events. Prasugrel is a selective adenosine diphosphate (ADP) receptor antagonist indicated for use in patients with acute coronary syndromes (ACS). Adenosine diphosphate (ADP) receptor antagonists block the ADP-induced pathway of platelet activation by specific inhibition of the P2Y12 receptor. Prasugrel is a third generation thienopyridine.

We have conducted a systematic review to retrieve current evidence regarding the role of prasugrel in the management of ACS.

Background
A study in the large, randomized, double-blind, multicentre, TRITON-TIMI 38 trial in adult patients with ACS, proved that prasugrel has a quicker onset of action and provides greater inhibition of platelet aggregation than clopidogrel. Treatment with prasugrel was more effective than clopidogrel in reducing the incidence of the primary endpoint of non-fatal myocardial infarction, stroke, or cardiovascular (CV) death. Prasugrel also reduced all-cause mortality compared with clopidogrel. The benefit with prasugrel was seen mostly in invasively managed patients. Prasugrel was well tolerated and was associated with an increased risk of major bleeding in comparison to clopidogrel. The potential for major bleeding with prasugrel (including bleeds related to CABG and non-CABG) was higher than with clopidogrel. Despite the higher bleeding rates, the net clinical benefit still favored prasugrel use compared with clopidogrel. However, patients with prior stroke or transient ischemic attack (TIA), patients older than 75 years, and patients weighing <60 kg did not demonstrate a net clinical benefit with prasugrel use compared with clopidogrel. Despite the higher bleeding rates, the net clinical benefit still favored prasugrel use compared with clopidogrel.

Prasugrel dosage consists of 60 mg loading dose and 10 mg daily maintenance dose. Wiviott et al. in the TRITON-TIMI-38 trial tested prasugrel prementioned dosage against the 300 mg loading dose of clopidogrel. Both were administered in the catheterization laboratory after diagnostic angiography and proved beneficial with respect to a composite ischemic outcome. The TRITON-TIMI 38 trial showed an 18% reduction in the primary endpoint of cardiovascular death, non-fatal MI or non-fatal stroke in the population of patients with unstable angina (UA) and non-ST-elevation myocardial infarction (NSTEMI) treated with prasugrel.

Prasugrel is currently challenged by ticagrelor, a P2Y12 receptor antagonist with different pharmacokinetic/pharmacodynamic properties. The aim of this review is to give a conceptual description of the role of prasugrel in the management of ACS, bleeding risk, current evidence, prasugrel resistance, drug interaction, hepatic impairment, renal impairment, drug withdrawal and safety and efficacy comparison with other antiplatelet agents (clopidogrel and ticagrelor).

Materials and Methods
The MEDLINE/PubMed database was searched for publications with the medical subject heading “prasugrel” and keywords “acute coronary syndromes” or “clopidogrel and ticagrelor” or “clopidogrel and ticagrelor and acute coronary syndromes” or “clopidogrel and ticagrelor and safety and efficacy”. Our selection criteria were the English language, the cardiovascular relevance (publications irrelevant to the management of acute coronary syndromes, were excluded), a time frame of the last five years (2012-2017), and the availability of full-text articles. We enrolled fifty-one articles. A comprehensive flowchart with exclusion criteria is reported in Figure 1.

Results
Current Evidence
Prasugrel dosage consists of 60 mg loading dose and 10 mg daily maintenance dose. Wiviott et al. in the TRITON-TIMI-38 trial tested prasugrel prementioned dosage against the 300 mg loading dose of clopidogrel. Both were administered in the catheterization laboratory after diagnostic angiography and proved beneficial with respect to a composite ischemic outcome. The TRITON-TIMI 38 trial showed an 18% reduction in the primary endpoint of cardiovascular death, non-fatal MI or non-fatal stroke in the population of patients with unstable angina (UA) and non-ST-elevation myocardial infarction (NSTEMI) treated with prasugrel.

Patients with stent thrombosis who do not respond to clopidogrel therapy should benefit from a switch to prasugrel. There are only three
cases in the literature describing hyporesponsiveness in all three antiplatelets. All of them resulted in stent thrombosis²⁰.

Prasugrel should not be administered to patients with prior stroke or TIA. Treatment with prasugrel is not recommended for patients of ≥75 years of age. If, after a careful individual risk-benefit evaluation, treatment is deemed necessary in the ≥75 years age- or low body weight (<60 kg) subgroups then, after a loading dose of 60 mg, a low dose of 5 mg should be used¹,²,⁵,¹⁰,¹²,²¹.

In diabetic patients presenting with ACS, prasugrel confers a particularly greater treatment effect than clopidogrel, without significantly increased bleeding⁵.

Montalescot et al²²–²⁴ in the ACCOAST study, the largest and the first pre-treatment study, compared the use of 30 mg prasugrel vs. placebo before PCI in 4033 NSTE-ACS patients. Overall, 69% of patients underwent PCI and 5% CABG. An extra dose of 30 mg prasugrel was administered after diagnostic coronary angiography in the pre-treatment group, and 60 mg prasugrel was administered in the other group. The primary endpoint, a composite of cardiovascular death, myocardial infarction, stroke, urgent revascularization, and bail-out GP IIb/IIIa inhibitor use at seven-day was similar for both groups (HR with pre-treatment, 1.02; 95% CI 0.84-1.25; P 1⁄4 0.81). The rate of the safety endpoint of TIMI major bleeding, through day 7, was very high with pre-treatment (HR 1.90; 95% CI 1.19-3.02; P 1⁄4 0.006). The study was stopped one month before the end of enrollment due to major bleeding episodes, emphasizing the lack of benefit of pre-treatment in NSTE-ACS patients²²–²⁴. Pre-treatment with 30 mg prasugrel (6 hours before coronary angiography) led to a much faster and more potent inhibition of platelet aggregation than a 600 mg clopidogrel loading dose as administered in the ARMYDA-5 study. Within one hour after angioplasty, there was a catch-up phenomenon of the pharmacodynamics profile of pre-treatment and in lab treatment group with 60 mg prasugrel. These very different pharmacodynamics profiles may account for the excess of periprocedural major bleedings reported in the pre-treatment group, namely access site-related
bleeds and pericardium drainage. No such dramatic differences were observed with 600 mg clopidogrel, with which safety profiles of in-lab vs. pre-treatment were similar22-24.

There is a study by Cornel et al25 suggesting that prasugrel in medically managed ACS patients reduced the ischemic outcomes in comparison to clopidogrel among smokers and nonsmokers.

All of the above indicate that there is a clinical benefit from prasugrel use in ACS patients undergoing PCI and a similar safety profile between prasugrel and clopidogrel in ACS patients treated medically. Greenhalgh et al3 also displayed the cost-effectiveness of prasugrel use in comparison to clopidogrel in ACS treated with PCI patients25.

Elderly medically managed ACS patients, however, are associated with substantially increased cardiovascular risk and bleeding. Roe et al26 compared low dose prasugrel with clopidogrel in these patients with no significant results. A multicenter, randomized clinical trial27 comparing a strategy of DAPT therapy with a low dose of prasugrel and a standard dose of clopidogrel in elderly patients with ACS undergoing PCI is ongoing. Qaderan et al28 in the Popular AGE trial will assess whether the treatment strategy with clopidogrel will result in fewer bleeding events without compromising the net clinical benefit in patients >70 years of age with NSTE-ACS when compared with a treatment strategy with ticagrelor or prasugrel.

In acute coronary syndromes, mortality increases when the culprit lesion is in the left anterior descending (LAD) artery. De Servi et al29 investigated the effects of prasugrel versus clopidogrel according to the site of culprit lesion causing ACS treated with PCI. Prasugrel benefit was most favorable when LAD-LM was the culprit artery, resulting in CV mortality reduction in all ACS population and STEMI patients when treated with primary PCI.

High on-clopidogrel platelet reactivity (HCPR) has been associated with adverse outcomes following ACS. The use of prasugrel in patients with HCPR resulted in a consistent and marked reduction in platelet reduction30. Geisler et al31 also concluded that a strategy of prasugrel in these patients with high platelet reactivity provides a more sustained suppression of platelet reactivity. Berlochner et al18 failed to establish prasugrel or ticagrelor as the treatment of choice in patients with high on platelet reactivity. Both seem to be of the same effectiveness. All of the above suggest that prasugrel is an effective solution in patients with clopidogrel resistance.

Motovska et al32 in the Prague 18 study compared the efficacy and safety of prasugrel and ticagrelor in acute myocardial infarction treated with PCI. A total of 1230 patients was randomly assigned to either prasugrel or ticagrelor, which started before PCI. The study was prematurely terminated because it failed to show any significant difference in safety and efficacy between prasugrel and ticagrelor. Westman et al4 and Rollini et al33 came up with the same results.

In a study by Bonello et al19 a loading dose of ticagrelor before PCI proved to be superior to a prasugrel dose at the time of PCI. A study comparing ticagrelor and prasugrel administration at the same time could help discriminating the superiority of the two antiplatelets.

Alexopoulos et al6 examined the antiplatelet action of ticagrelor and prasugrel in ACS patients with high platelet reactivity and showed that ticagrelor was superior to prasugrel twenty-four hours post PCI.

A pre-treatment strategy, in comparison to a delayed administration of ticagrelor, has not yet been investigated. Wallentin et al in the PLATO study (Wallentin L, Becker RC, Budaj A, Cannon CP, Emanuelsson H, Held C, Horrow J, Husted S, James S, Katus H, Mahaffey KW, Scirica BM, Skene A, Steg PG, Storey RF, Harrington RA; PLATO Investigators, Freij A, Thorén M. Ticagrelor versus clopidogrel in patients with acute coronary syndromes. N Engl J Med 2009; 361: 1045-1057), administered to all patients pre-treatment with clopidogrel or ticagrelor, irrespective of treatment goal (invasive or non-invasive) and patients undergoing PCI received P2Y12 receptor inhibitors at a median of 4 hours before the intervention30. In conclusion, the risk-benefit ratio of pre-treatment using ticagrelor before diagnostic coronaryography is unknown.

There is a number of studies in the literature comparing prasugrel, clopidogrel, and ticagrelor. Sheikh Rezaei et al14 showed that prasugrel and ticagrelor were associated with lower incidence of death and lower number of ACS recurrence35. A study by Mont’Alverne-Filho et al16 investigated the effects of upstream prasugrel or ticagrelor or clopidogrel for patients with STEMI undergoing primary PCI. Prasugrel and ticagrelor had better results and improved reperfusion. Abdel-Qadir et al17 compared the cost-effectiveness of the three drugs resulting in ticagrelor as the most cost-effective. Bednar et al studied the platelet inhibition of these antiplatelets in survivors after cardiac arrest due to MI, that have been subjected to mild
therapeutic hypothermia. Prasugrel and ticagrelor were more efficient in platelet inhibition than clopidogrel.

**Bleeding Risk**

Wiviott et al\(^3\) in the TRITON-TIMI 38 trial concluded that treatment with prasugrel resulted in more bleeding than with the standard dose of clopidogrel. The key safety endpoint of TIMI major bleeding was increased from 1.8% to 2.4% over 15 months. This increase in bleeding was also observed for life-threatening and fatal bleeding.\(^{4,5,9,12}\) Chandrasekhar et al\(^3\) studied prasugrel use in anemic ACS patients treated with PCI. The bleeding rates in these patients were even greater than with clopidogrel.

Motovska et al\(^1\) in the PRAGUE 18 study showed that there was no difference in efficacy or bleeding rates between prasugrel and ticagrelor in patients who underwent primary PCI\(^1\).\(^3\)\(^3\).

Different studies tried to establish predictors of bleeding like pretreatment, age, gender and procedural variables\(^2\) and arterial hypertension, diabetes mellitus, age and severe left ventricular dysfunction\(^3\).

**Prasugrel Resistance**

Prasugrel resistance or more aptly termed variability in response is not clearly defined and depends on the in vitro system used. With these limitations, prasugrel resistance has been reported to occur in very few cases.\(^4\)\(^,5\)\(^,7\) Orban et al\(^4\) reported a case of a patient with STEMI, cardiogenic shock and early stent thrombosis, which was successfully overcome by switching to ticagrelor. The mechanism of prasugrel resistance is still under investigation. Despite small studies that have shown few prasugrel resistant patients due to low inhibition of platelet aggregation the clinical significance of this phenomenon remains uncertain\(^4\)\(^,5\).

**Drug Interaction**

The combination of prasugrel with oral vitamin K antagonists has not been investigated. It is recommended only after risk assessment since it may potentially increase the possibility of bleeding. The combination of prasugrel and non-steroids anti-inflammatory drugs (NSAIDs) also remains under consideration. It can increase the bleeding risk, and these two should be administered simultaneously with caution.\(^7\)\(^,40\). Concomitant use of prasugrel with heparin, fibrinolytic agents, and glycoprotein IIb/IIIa receptor antagonists increases the risk of bleeding. There is no drug interaction with inhibitors or inducers of cytochrome P450 enzymes. Therefore, prasugrel can be used in patients already receiving rifampicin, carbamazepine, ketoconazole, verapamil, diltiazem, ciprofloxacin, and clarithromycin\(^17\)\(^,40\).

Due to gastrointestinal discomfort caused by all antiplatelets, there is an increased use of proton pump inhibitors (PPIs) simultaneously to antiplatelets. Small et al\(^5\) concluded that concurrent use of prasugrel and lansoprazole did not lower the inhibition of platelet aggregation by prasugrel, while lansoprazole decreased the level of inhibition of platelet aggregation when used concurrently with clopidogrel. O’Donoghue et al\(^5\) showed that PPIs could be used in patients taking either clopidogrel or prasugrel. Nicolau et al\(^5\) investigated the concomitant use of prasugrel and PPI, which resulted in lower occurrence of MI. There is limited and conflicting evidence about the concomitant use of prasugrel and PPIs, which needs further assessment.

**Hepatic Impairment**

Patients with mild to moderate impaired hepatic function (Child-Pugh Class A and B) need no dose adjustment. Prasugrel pharmacokinetics and its inhibition of platelet aggregation were the same in subjects with mild to moderate hepatic impairment compared to healthy individuals. Pharmacodynamics and pharmacokinetics of prasugrel in patients with severe hepatic impairment have not yet been studied. Prasugrel should be avoided in patients with severe hepatic impairment\(^21\).

**Renal Impairment**

Patients with renal impairment, including patients with end-stage renal disease (ESRD) need no dosage adjustment. Prasugrel pharmacokinetics and its inhibition of platelet aggregation are the same in patients with moderate renal impairment (GFR 30<50 ml/min/1.73 m\(^2\)) and healthy individuals. Prasugrel-mediated inhibition of platelet aggregation was also similar in patients who required hemodialysis in comparison to healthy individuals, although C\(_{\text{max}}\) and AUC of the active metabolite decreased 51% and 42% in ESRD patients\(^16\). Prasugrel and clopidogrel appear safer compared to ticagrelor in patients with renal impairment. Ticagrelor increases creatinine and uric acids levels and is associated with serious adverse effects and worst outcomes\(^48\).
Table I. Summary of the landmark trials that compare the safety and efficacy of prasugrel, clopidogrel, and ticagrelor in the management of acute coronary syndromes.

<table>
<thead>
<tr>
<th>Trial</th>
<th>Population</th>
<th>Methods</th>
<th>Results</th>
<th>Prasugrel (n=6813), %</th>
<th>Clopidogrel (n=6795), %</th>
</tr>
</thead>
<tbody>
<tr>
<td>TRITON-TIMI 38</td>
<td>13608 Patients with ACS and planned PCI&lt;sup&gt;7,9&lt;/sup&gt;</td>
<td>Randomized double-blind prasugrel 60 mg LD/10 mg MD vs clopidogrel 300 mg LD/75 mg MD</td>
<td>CV death/MI/stroke</td>
<td>9.9</td>
<td>12.1</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>Death from any cause</td>
<td>3.0</td>
<td>3.2</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>Stent thrombosis</td>
<td>1.1</td>
<td>2.4</td>
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<td></td>
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<td></td>
<td>Major or minor bleeding</td>
<td>5.0</td>
<td>3.8</td>
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<td></td>
<td></td>
<td></td>
<td>Fatal bleed</td>
<td>0.4</td>
<td>0.1</td>
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<td></td>
<td></td>
<td></td>
<td>Life-threatening bleed</td>
<td>1.4</td>
<td>0.9</td>
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<td></td>
<td></td>
<td></td>
<td>CABG-related TIMI major bleed</td>
<td>13.4</td>
<td>3.2</td>
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<td></td>
<td></td>
<td></td>
<td>non-CABG TIMI major bleed</td>
<td>2.4</td>
<td>1.8</td>
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<tr>
<td>TRILOGY-ACS</td>
<td>9326 Patients with ACS and treatment strategy of medical management without revascularization within ten days of the index event&lt;sup&gt;10,12&lt;/sup&gt;</td>
<td>Randomized double-blind prasugrel 30 mg LD/5 or 10 mg MD vs clopidogrel 300 mg LD/75 mg MD</td>
<td>Primary efficacy endpoint (CV death, MI, or stroke)</td>
<td>13.9</td>
<td>16.0</td>
</tr>
<tr>
<td>ACCOAST</td>
<td>4100 Patients, pretreatment of NSTE-ACS with prasugrel at the time of diagnosis vs. after angioplasty&lt;sup&gt;22,24&lt;/sup&gt;</td>
<td>Randomized double-blind prasugrel in the early-or standard-strategy group with placebo pretreatment given in the standard group</td>
<td>Primary endpoint (CV death, MI, stroke, urgent revascularization, or GP IIb/IIIa bailout), 7d</td>
<td>10       </td>
<td>9.8       </td>
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<td></td>
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<td>Primary endpoint, 30d</td>
<td>10.8</td>
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<td>All CABG or non-CABG TIMI major bleeding, 7d</td>
<td>2.6</td>
<td>1.4</td>
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<td></td>
<td></td>
<td></td>
<td>All CABG or non-CABG TIMI major bleeding, 30d</td>
<td>2.8</td>
<td>1.5</td>
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<td></td>
<td></td>
<td></td>
<td>Life-threatening bleeding</td>
<td>1.1</td>
<td>0.2</td>
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</table>

*Table continued*
Table I. Continued. Summary of the landmark trials that compare the safety and efficacy of prasugrel, clopidogrel, and ticagrelor in the management of acute coronary syndromes.

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<tr>
<td></td>
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<td></td>
<td>CV death/MI/stroke</td>
<td>4.0</td>
<td>5.1</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>Death from any cause</td>
<td>4.5</td>
<td>5.9</td>
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<tr>
<td>PLATO</td>
<td>18624 Patients within 24 hours of onset of ACS (NSTE-ACS moderate to high risk and STEMI if primary PCI)</td>
<td>Randomized double-blind ticagrelor 180 mg LD/90 mg BID vs. clopidogrel 300 mg LD/75 mg MD</td>
<td>Red cell transfusion</td>
<td>8.9</td>
<td>8.9</td>
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<td></td>
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<td></td>
<td>TIMI Major bleeding</td>
<td>7.9</td>
<td>7.7</td>
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<td></td>
<td></td>
<td></td>
<td>Fatal bleed</td>
<td>5.8</td>
<td>5.8</td>
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<td></td>
<td></td>
<td></td>
<td>Life-threatening bleed</td>
<td>11.6</td>
<td>11.2</td>
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<td></td>
<td>Major bleeding</td>
<td>2.8</td>
<td>2.2</td>
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<td></td>
<td></td>
<td></td>
<td>non-CABG TIMI major bleed</td>
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<tr>
<td>PRAGUE-18</td>
<td>1230 Patients with STEMI and primary PCI</td>
<td>Randomized double-blind prasugrel 60 mg LD/10 mg MD vs ticagrelor 180 mg LD/90 mg BID</td>
<td>Primary efficacy endpoint (Death, re-infarction, stroke, urgent target vessel revascularization, serious bleeding requiring transfusion, or prolonged hospitalization at seven days)</td>
<td>Prasugrel, % 4.0</td>
<td>Ticagrelor, % 4.1</td>
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<td></td>
<td></td>
<td></td>
<td>Secondary endpoint (CV death, non-fatal MI, or stroke within 30 days)</td>
<td>2.7</td>
<td>2.5</td>
</tr>
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</table>
Withdrawal of Prasugrel

In patients on P2Y12 inhibitors who need to undergo non-emergency major surgery (including CABG), it is recommended to postpone surgery for at least five days after the last dose of ticagrelor or clopidogrel. For prasugrel, the cessation begins seven days before, if clinically feasible and unless the patient is at high risk of ischemic events should be considered1,4,15,17,49.

Discussion

Prasugrel is a novel thienopyridine and has faster and more complete antiplatelet action in vivo compared with other thienopyridines. Due to its better absorption and a more efficient metabolism, prasugrel has lesser interpatient variability in its antiplatelet effects when compared with clopidogrel1-6.

Current evidence indicates that prasugrel is a useful option for the prevention of thrombotic CV events in ACS patients managed invasively. Wiviott et al18 in the TRITON-TIMI 38 trial showed that prasugrel therapy lowered the rate of cardiovascular events in moderate- to high-risk patients with ACS who were planned for PCI. This better antiplatelet effect in comparison to clopidogrel, comes, however, at the cost of an increase in major bleeding, especially among three high-risk groups: patients ≥75 years old, patients weighing ≤60 kg, and patients with a history of stroke or transient ischemic attack (TIA)7-11,50.

Prasugrel benefits the most patients with diabetes mellitus (DM). Prasugrel improves net outcomes among patients with DM rather than in those without DM5.

All available evidence in the literature suggests that PPIs can be safely used in patients taking prasugrel24.

Bleeding, including fatal and life-threatening bleeding, is the most common adverse reaction of prasugrel use8,10,11,39,40,51.

Prasugrel is currently questioned by ticagrelor, a P2Y12 receptor antagonist with different pharmacokinetic/pharmacodynamic properties. The superiority of one drug over the other cannot be reliably estimated from the current trials. Prasugrel and ticagrelor are currently the recommended first-line agents in patients with NSTE-ACS and STEMI, due to large-scale randomized trials that demonstrated a net clinical benefit of these agents over clopidogrel, as stated in the ESC guidelines. Ticagrelor and prasugrel for the time being seem, to have the same efficacy and the same overall bleeding rates34-36,52. Further comparison of efficacy and tolerability data are required to definitively position prasugrel with respect to other antiplatelet agents, including ticagrelor. Randomized and observational studies will help to provide valuable information about the safety and efficacy of the two drugs and their respective places with ACS patients3,27,28,53.

Dual antiplatelet therapy remains the cornerstone in the management of acute coronary syndromes10,34. The 12-month treatment after ACS or PCI needs to be reassessed. Prolongation of the treatment could eventually lower cardiovascular events. Further investigation needs to assess the safety of low dose (5-10 mg of prasugrel) in selected ACS patients (elderly), if it can lower the bleeding risk26-28,54.

It also remains to be investigated when prasugrel should be reinitiated after coronary artery bypass graft (CABG). The crucial period between surgery and continuation of the antiplatelet drug needs to be clarified1,14,17.

Further investigation needs to evaluate the combination of prasugrel and vitamin K antagonist. Many patients with atrial fibrillation and valvular disease (mechanical valves) have no choice but to take vitamin K antagonist7,40. These patients may lose the benefit from not being able to take prasugrel along with their appropriate medication.

Extensive research needs to be conducted in the setting of transcatheter aortic valve implantation (TAVI) to help define the optimal antiplatelet regimen. Current practice consists of dual antiplatelet therapy (DAPT) with aspirin (indefinitely) and clopidogrel one to six months. There are no studies yet questioning the safety and clinical benefit from prasugrel use in TAVI cases55.

For all these purposes, large prospective studies should be designed to evaluate the role of prasugrel in reducing the burden of cardiovascular disease. A large on-going, prospective, observational study (the Rijnmond Collective Cardiology Research registry) that follows-up 4000 ACS patients treated with PCI and prasugrel as first choice antiplatelet agent maybe will shed light in the conflicting aforementioned evidence1.

Conclusions

The purpose of direct oral anticoagulants in combination with dual antiplatelet therapy in secondary prevention of ACS is promising, but the in-
terpretation of the totality of evidence for the class of oral anticoagulants is inconclusive and requires further study. Prasugrel is superior to clopidogrel in reducing cardiovascular events but with the cost of an increased bleeding risk. A definite clinical benefit has been established for prasugrel use in ACS patients, scheduled for PCI. Ticagrelor and prasugrel, for the time being, seem to have the same efficacy and the same overall bleeding rates. Patients with a history of active pathological bleeding or stroke/TIA, should not receive prasugrel. Patients with diabetes mellitus and ACS seem to have the most benefit from prasugrel use.

We do believe that the role of prasugrel in cardiovascular diseases deserves further experimental investigation and large-scale prospective randomized clinical trials.

**Conflict of interest**
The authors declare no conflicts of interest.

**References**


The role of prasugrel in the management of acute coronary syndromes: a systematic review


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