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EDITORIAL

Alternatives to clopidogrel for acute coronary syndromes: Prasugrel or ticagrelor?

Giuseppe Biondi-Zoccai, Marzia Lotrionte, Fiorenzo Gaita

Giuseppe Biondi-Zoccai, Marzia Lotrionte, Fiorenzo Gaita, Division of Cardiology, University of Turin, San Giovanni Battista "Molinette" Hospital, 10126 Turin, Italy; Unit for Heart Failure and Cardiac Rehabilitation, Catholic University, 00136 Rome, Italy
Author contributions: Biondi-Zoccai G conceived and drafted the manuscript; Lotrionte M and Gaita F provided critical comments to the manuscript and final approval.
Correspondence to: Dr. Giuseppe Biondi-Zoccai, Division of Cardiology, University of Turin, San Giovanni Battista "Molinette" Hospital, Corso Bramante 88-90, 10126 Turin, Italy. gbiondizoccai@gmail.com
Telephone: +39-11-6334195 Fax: +39-11-6967053
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Abstract

Clopidogrel is a mainstay in the treatment of patients with acute coronary syndromes or those receiving endovascular prostheses. However, its efficacy has been challenged in the recent past by studies suggesting variable individual responsiveness and by new, more potent competitors, such as prasugrel and ticagrelor. But what is the actual body of evidence in support of clopidogrel? Is there any dark side of the moon? What is the role of prasugrel, which has already been approved in Europe and in the United States? And what will be the future role of ticagrelor, when approved for routine clinical practice? We hereby concisely summarize the scope of this clinical choice, providing arguments in favor and against each of the three antiplatelet agents: clopidogrel, prasugrel, and ticagrelor.

Key words: Acute coronary syndrome; Clopidogrel; Prasugrel; Ticagrelor

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THE WELL-KNONW PAST: CLOPIDOGREL

The crucial role of clopidogrel in association with aspirin in patients with acute coronary syndromes (ACS) is testified by the fact that this drug is among the best selling drugs worldwide, together with statins, proton-pump inhibitors, and angiotensin-Ⅱ receptor antagonists.

Clopidogrel is a thienopyridine which selectively and irreversibly inhibits the platelet adenosine 5'-diphosphate (ADP) P2Y12 receptor, providing synergistic inhibitory effects on platelet aggregation. Several studies strongly support the favorable risk-benefit balance of clopidogrel in ACS patients managed conservatively as well as invasively, and the most important of these is the Clopidogrel in Unstable angina to prevent Recurrent Events (CURE) trial, which randomly assigned 12 562 patients with ACS to receive clopidogrel (300 mg loading followed by 75 mg once daily) or placebo in addition to aspirin for 3 to 12 mo[1]. As the devil is often in the details, it is timely to review the main findings of this study. After an average follow-up of 9 mo, the composite event of death from cardiovascular causes, myocardial infarction or stroke occurred in 9.3% *vs* 11.4%, respectively ($P < 0.001$), a difference largely driven by significantly fewer myocardial infarctions in those treated with clopidogrel (5.2% *vs* 6.7%, $P < 0.001$). Conversely, the number of deaths from

Table 1 Alternatives to clopidogrel for patients with acute coronary syndromes

Drug	Main features	Pros	Cons
Cilostazol	Phosphodiesterase inhibitor with antiplatelet and antirestenotic effects, also indicated for the medical treatment of claudication	Different mechanism of action translates into increased antithrombotic efficacy when used in combination with aspirin and a thienopyridine	Tolerability limited by gastro-intestinal side effects in up to 20% of patients
Oral anticoagulants	Several agents directly or indirectly inhibiting the coagulation process, including warfarin and dabigatran	Different mechanism of action translates into increased antithrombotic efficacy when used in combination with aspirin	Specificity for the coagulation process translates into lower efficacy on thrombotic processes largely dependent on platelets (such as stent thrombosis). Narrow therapeutic window and need for frequent monitoring (warfarin) translates in higher incidence of bleeding complications
Prasugrel	Third-generation thienopyridine irreversibly inhibiting the P2Y12 receptor, with quicker, more consistent and more potent action than clopidogrel	Potency and consistency of effect enable homogeneous and nearly complete platelet aggregation inhibition in most patients, with ensuing benefits on myocardial infarction and stent thrombosis	Greater potency may translate into bleeding risk overcoming ischemic benefits in those at moderate or high bleeding risk, such as the elderly and those with previous stroke or transient ischemic attack
Ticagrelor	Non-thienopyridine agent reversibly inhibiting the P2Y12 receptor, with quicker, more consistent, and more potent action, but shorter half-life than clopidogrel	Direct action translates into quicker onset of action and lack of interaction with drugs metabolized by cytochrome P450, such as proton pump inhibitors	Shorter half-life may translate into greater risk of thrombotic recurrences in case of non-compliance
Ticlopidine	First-generation thienopyridine irreversibly inhibiting the P2Y12 receptor, with longer half-life than clopidogrel	Limited cross-unresponsiveness translates into potential role in those lacking complete response to clopidogrel. Off-patent status translates into low cost	Lower tolerability with frequent gastro-intestinal adverse effects. Rarely but significantly associated with life-threatening agranulocytosis and thrombotic thrombocytopenic purpura

cardiovascular causes or stroke, when analyzed individually, was not significantly different in the clopidogrel *vs* placebo group (5.1% *vs* 5.5%, $P = 0.3$ and 1.2% *vs* 1.4%, $P = 0.4$, respectively), a key negative finding for the interpretation of more recent trials. In addition, there were significantly more protocol-defined major bleedings in the clopidogrel group (3.7% *vs* 2.7%, $P = 0.001$), despite similar rates of major bleeding defined according to the Thrombolysis in Myocardial Infarction (TIMI) trial (1.1% *vs* 1.2%, $P = 0.7$) or major bleeding related to coronary artery bypass grafting (CABG, 1.3% *vs* 1.1%, $P = 0.3$).

Clopidogrel is also beneficial in patients with acute ST-elevation myocardial infarction (STEMI) managed with thrombolysis, as reported by the Clopidogrel as Adjunctive Reperfusion Therapy-TIMI 28 study and the Clopidogrel and Metoprolol in Myocardial Infarction Trial (COMMIT)[2,3]. Finally, interventional cardiologists and all endovascular specialists exploit daily the antiplatelet efficacy of clopidogrel in preparation and after deployment of metallic endovascular prostheses, such during percutaneous coronary intervention[4], transcatheter aortic valve replacement[5], percutaneous closure of patent foramen ovale[6], and so forth. Conversely, ACS stemming from coronary vasospasm or local allergic reactions (Kounis syndrome) are unlikely to benefit from antithrombotic therapy, including clopidogrel, unless thrombus is superimposed[7,8].

Despite such prominent role in the management of subjects with atherothrombosis, including patients with only mildly significant coronary atherosclerosis[1], and those treated with implantable cardiovascular devices, clopidogrel has recently been challenged by more potent and, in selected cases, equally safe, antithrombotic agents (Table 1). Besides oral anticoagulants, such as warfarin and the more recent dabigatran[9], and niche agents, such as cilostazol and ticlopidine[10,11], the most promising alternatives to clopidogrel in those with background aspirin therapy are prasugrel and ticagrelor.

THE PRESENT: PRASUGREL

Prasugrel is a thienopyridine ADP receptor inhibitor, which irreversibly binds to the P2Y12 receptor. In comparison to clopidogrel, prasugrel acts more quickly, more consistently, more potently, and has been shown to best in pharmacokinetics studies clopidogrel, even when the latter is administered in high loading doses such as 600 or 900 mg. The pivotal trial appraising the role of prasugrel in patients with ACS, including STEMI, is the Trial to Assess Improvement in Therapeutic Outcomes by Optimizing Platelet Inhibition with Prasugrel-TRITON-TIMI 38[12]. In this randomized study, including 13 608 patients treated with a 60 mg loading dose and a 10 mg daily maintenance dose of prasugrel or a 300 mg loading dose and a 75 mg daily maintenance dose of clopidogrel for 6 to 15 mo, prasugrel proved more effective than clopidogrel in reducing the risk of death from cardiovascular causes, myocardial infarction, or stroke (9.9% *vs* 12.1%, $P < 0.001$), an effect mainly driven by reduction in myocardial infarctions (7.3% *vs* 9.5%, $P < 0.001$),

actually often qualifying for stent thrombosis (1.1% *vs* 2.4%, $P < 0.001$). Indeed, the authors reported similar rates of death from any cause (3.0% *vs* 3.2%, $P = 0.6$), death from cardiovascular causes (2.1% *vs* 2.4%, $P = 0.3$), and stroke (1.0% *vs* 1.0%, $P = 0.9$) in the prasugrel *vs* clopidogrel groups. This remarkable antithrombotic effects were however offset by an increased bleeding risk, clustering particularly in the elderly and those with previous stroke or transient ischemic attack, as major bleeding occurred in 2.5% of those treated with prasugrel *vs* 1.7% of those treated with clopidogrel ($P = 0.001$), with the excess risk mainly due to CABG-related major bleeding (0.4% *vs* 0.1%, $P = 0.001$).

THE FUTURE: TICAGRELOR

Ticagrelor is instead a reversible inhibitor of platelet P2Y12-subtype ADP receptor, and thus does not belong to the thienopyridine family. Given its reversible binding to the target receptor and shorter half-life, ticagrelor holds the promise of a larger therapeutic window, especially for patients who might end up undergoing CABG early after drug administration. Indeed, the pivotal Platelet Inhibition and Patient Outcomes (PLATO) study randomized 18 624 patients with ACS to 180 mg loading dose, 90 mg twice daily thereafter of ticagrelor *vs* 300-600 mg loading dose, 75 mg daily thereafter of clopidogrel for 12 mo[13]. The risk of death from vascular causes, myocardial infarction, or stroke was significantly reduced by ticagrelor (9.8% *vs* 11.7%, $P < 0.001$), an effect stemming from consistent reductions in the risk of death from all causes (4.5% *vs* 5.9%, $P < 0.001$), death from vascular causes (4.0% *vs* 5.1%, $P = 0.001$), and myocardial infarction (5.8% *vs* 6.9%, $P = 0.005$), including stent thrombosis (1.3% *vs* 1.9%, $P = 0.009$). Stroke occurred with similar frequency in the ticagrelor and clopidogrel groups (1.5% *vs* 1.3%, $P = 0.2$), similarly to CABG-related major bleeding (4.8% *vs* 5.2%, $P = 0.3$) and all TIMI major bleeding (7.1% *vs* 6.9%, $P = 0.7$). However, non-CABG related bleeding still occurred more frequently in the ticagrelor group (2.8% *vs* 2.2%, $P = 0.030$).

RECONCILING THE EVIDENCE

Awaiting head-to-head randomized trials of ticagrelor *vs* prasugrel, it is difficult to identify which of these two agents offers the best risk-benefit balance to overcome the limitations of clopidogrel. A superficial review of the PLATO and TRITON-TIMI 38 trials would suggest that ticagrelor is the winner in most patients, including those at moderately increased bleeding risk, given the significant mortality benefit and the similar risk of CABG-related major bleeding. However, formal interaction tests would probably provide more precise adjusted indirect comparison estimates, enabling decision makers to select the most appropriate agent for each individual clinical case, in order to maximize safety but also efficacy[14,15]. Indeed, the dramatic reduction in the risk of stent thrombosis, especially drug-eluting stent thrombosis, achieved by prasugrel (0.8% *vs* 2.3%, $P < 0.001$), would suggest that this agent should probably be considered the first-line one in those at higher risk of thrombotic events[16], such as diabetics and/or those with diffuse coronary stenting[17].

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