Cardiovascular Pharmacology: Open Access

Aronow, Cardiol Pharmacol 2013, 2:4
DOI: 10.4172/2329-6607.1000e116

Editorial Open Access

Use of Ticagrelor in the Treatment of Acute Coronary Syndromes

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Ticagrelor is a non-thienopyridine antiplatelet drug which is an oral, reversible, direct-acting inhibitor of the ADP receptor P2Y12 [1]. Plasma levels of ticagrelor peak rapidly 1.5 to 3.0 hours after administration with antiplatelet effects occurring within 2 hours after administration. Ticagrelor has a half life of 7 to 8.5 hours with the metabolite lasting up to 12 hours [2]. This combined with its reversible binding to the ADP receptor P2Y12 requires twice daily dosing [2]. The rapid reversibility is beneficial if a surgical procedure has to be performed but is a disadvantage in poorly compliant patients. A loading dose of ticagrelor 180 mg achieves faster and greater platelet inhibition than a 600 mg loading dose of clopidogrel and is faster in offset after drug discontinuation than is clopidogrel [3].

In the Study of Platelet Inhibition and Patient Outcomes (PLATO), 18,624 patients hospitalized with an acute coronary syndrome with or without ST-segment elevation were randomized in a double-blind trial to aspirin (98%) plus either ticagrelor (180 mg loading dose followed by 90 mg twice daily) or clopidogrel (300 mg to 600 mg loading dose followed by 75 mg daily) [4]. At 12- month follow-up, the primary endpoint of cardiovascular death, nonfatal myocardial infarction, or nonfatal stroke was significantly reduced from 11.7% in patients treated with clopidogrel to 9.8% in patients treated with ticagrelor, a relative risk reduction of 16% and an absolute risk decrease of 1.9%. The number of patients needed to treat to prevent 1 event=53 [4]. The incidence of all-cause mortality was significantly reduced from 5.9% in patients treated with clopidogrel to 4.5% in patients treated with ticagrelor, a relative risk reduction of 24% and an absolute risk decrease of 1.4%. The number of patients needed to treat to prevent 1 death=71 [4]. No significant difference in major bleeding was found between both groups. However, the incidence of major bleeding not related to coronary artery bypass graft surgery was significantly higher on ticagrelor (4.5%) than on clopidogrel (3.8%). Fatal intracranial bleeding occurred significantly more in patients treated with ticagrelor (0.1%) than in patients treated with clopidogrel (0.01%) [4]. Dyspnea requiring discontinuation of study treatment occurred significantly more in patients treated with ticagrelor (0.9%) than in patients treated with clopidogrel (0.1%) [4].

However, there was an insignificant 27% increase in the primary outcome in patients treated with ticagrelor versus clopidogrel in the United States and Canadian patients [5]. Ticagrelor was approved by the United States Food and Drug Administration for treatment of patients with acute coronary syndromes with the maintenance dose of aspirin to be 75 to 100 mg daily.

In the PLATO study, an invasive strategy was planned for 13,408 of the 18,624 patients (72%) hospitalized for acute coronary syndromes [6]. At 360-day follow-up of these patients, the primary endpoint of cardiovascular death, nonfatal myocardial infarction, or nonfatal stroke was significantly reduced from 10.7% in patients treated with clopidogrel to 9.0% in patients treated with ticagrelor, a relative risk reduction of 16% and an absolute risk decrease of 1.7%. The number of patients needed to treat to prevent 1 event=59 with no significant difference in major bleeding or severe bleeding between both groups [6].

In the PLATO study, in the subgroup of 1,261 patients who underwent coronary artery bypass graft surgery and were receiving study drug treatment less than 7 days before surgery, the primary endpoint at 12 months was significantly reduced from 13.1% in patients treated with clopidogrel to 10.6% in patients treated with ticagrelor, a relative risk reduction of 16% and an absolute risk decrease of 2.5% [7]. The number of patients needed to treat to prevent 1 event=40 with no significant difference in coronary artery bypass graft surgery-related major bleeding between the 2 groups [7]. All-cause mortality was significantly reduced from 9.7% in patients treated with clopidogrel to 4.7% in patients treated with ticagrelor, a relative risk reduction of 51% and an absolute risk decrease of 5.0%. The number of patients needed to treat to prevent 1 death=20 [7].

In the PLATO trial, chronic kidney disease was present in 3,237 patients [8]. In patients with chronic kidney disease, the primary outcome was significantly reduced from 22.0% in patients treated with clopidogrel to 17.3% in patients treated with ticagrelor, a relative risk reduction of 23% and an absolute risk decrease of 4.7%. The number of patients needed to treat to prevent 1 event=21 [8]. All-cause mortality in patients with chronic kidney disease was significantly reduced from 14.0% in patients treated with clopidogrel to 10.0% in patients treated with ticagrelor, a relative risk reduction of 28% and an absolute risk decrease of 4.0%. The number of patients needed to treat to prevent 1 death=25 [8]. Major bleeding, fatal bleeding, and non-coronary bypass-related major bleeding were not significantly different between both groups [8]. In patients with normal renal function, the primary outcome was insignificantly reduced 10% from 8.9% to 7.9% by ticagrelor [8].

Ticagrelor therapy overcomes nonresponsiveness to inhibition of platelet aggregation by clopidogrel [9]. The antiplatelet effect of ticagrelor is similar in clopidogrel responders and nonresponders [9]. In the Plato trial, 4,662 patients had diabetes mellitus [10]. In patients with diabetes mellitus, compared with clopiodogrel, ticagrelor insignificantly reduced the primary outcome 12%, all-cause mortality 18%, and stent thrombosis 35% [10]. However, in patients with a hemoglobin A1c above 6.0% (the median value), compared with clopidogrel, ticagrelor significantly reduced the primary endpoint 20%, all-cause mortality 22%, and stent thrombosis 38% [10]. The clinical benefit of ticagrelor compared with clopidogrel was not significantly different between patients aged 75 years and older versus those younger than 75 years [11].

Contraindications to ticagrelor include a history of intracranial

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Received August 29, 2013; **Accepted** August August 29, 2013; **Published** September 04, 2013

Citation: Aronow WS (2013) Use of Ticagrelor in the Treatment of Acute Coronary Syndromes. Cardiol Pharmacol 2: e116. doi:10.4172/2329-6607.1000e116

hemorrhage, active pathological bleeding, severe hepatic impairment, and hypersensitiviy to ticagrelor or any component of the product. Ticagrelor should not be used in patients planned to undergo urgent coronary artery bypass graft surgery. When possible, ticagrelor should be stopped at least 5 days prior to any surgery.

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