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Editorial Open Access

Ticagrelor: What's New?

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Abreviations: ACS: acute coronary syndrome; ALI: acute limb ischemia; APC: adenosine plasma concentration ATLANTIC: Administration of Ticagrelor in the cath Lab or in the Ambulance for New ST elevation myocardial Infarction to open the Coronary artery; EPC: endothelial progenitor cell; MACE: major adverse cardiovascular events; MALE: major adverse limb events; MI: myocardial infarction; PAD: peripheral artery disease; PCI: percutaneous coronary intervention; PEGASUS-TIMI 54: Prevention of Cardiovascular Events in Patients With Prior Heart Attack Using Ticagrelor Compared to Placebo on a Background of Aspirin–Thrombolysis in Myocardial Infarction 54; PLATO: PLATelet inhibition and patient Outcomes; PRU: platelet reactivity unit RHI: reactive hyperaemia index; STEMI: ST-segment elevation myocardial infarction; TIMI: Thrombolysis in Myocardial Infarction

Editorial

Ticagrelor in diabetic patients

Diabetic patients with a history of myocardial infarction (MI) are a high-risk group of patients. In part due to heightened platelet reactivity, both longer term and more potent antiplatelet therapy appear to have particular benefits as part of the secondary prevention strategy [1].

The subgroups of patients with diabetes N=6806 and without diabetes (N=14,355) from PEGASUS-TIMI 54, in which 21,162 patients with a history of MI 1-3 years prior and with additional risk factors were randomized to ticagrelor (90 mg or 60 mg twice daily) or placebo with a median follow up of 33 months. The primary efficacy endpoint was major adverse cardiovascular events (MACE: cardiovascular death, MI, stroke) and the primary safety endpoint was TIMI major bleeding.

The relative risk reduction in MACE for the pooled ticagrelor doses versus placebo was consistent in diabetic patients and in non-diabetic patients (-26% in both cases). As diabetic patients were at higher risk of MACE, the absolute risk reduction tended to be greater in diabetic patients versus non-diabetic patients (1.5% *vs.* 1.1%). TIMI major bleeding was significantly increased in diabetic patients treated with ticagrelor (2.56% *vs.* 0.98%, p=0.0004), similar to what was seen in the non-diabetic patients (2.39% *vs.* 1.09% in placebo, p<0.0001). There was no significant difference between ticagrelor and placebo in the diabetic subgroup in the rate of fatal or intracranial bleeding though there were few events (0.62% *vs.* 0.63%, p=0.78).

Despite the fact that the diabetic subgroup was not specifically powered for the primary endpoint or for individual secondary endpoints, in diabetic patients with prior MI, adding ticagrelor to aspirin significantly reduces the risk of recurrent ischemic events, including cardiovascular and coronary heart disease death.

Ticagrelor in patients with PAD and prior MI

In stable outpatients with a history of myocardial infarction (MI), concomitant peripheral arterial disease (PAD) is associated with significantly heightened risk of systemic ischemic events, limb ischemic events, bleeding and all-cause mortality [2].

This subgroup from PEGASUS-TIMI 54 (N=1143) was investigated to determine the effects of ticagrelor on major adverse cardiovascular events (MACE: cardiovascular death, MI, stroke) and major adverse limb events (MALE defined as acute limb ischemia or peripheral revascularization for ischemia).

In the placebo group, the PAD was associated with a significantly higher rate of MACE at three years compared to patients without PAD (19.3% *vs.* 8.4%, p<0.001). She was also associated with a higher rate of acute limb ischemia (1.0% *vs.* 0.1%) and peripheral revascularization procedures (9.15% *vs.* 0.46%). The relative risk reduction of MACE was similar with and without PAD (-25% and -14%, respectively). But the absolute risk reduction was much greater in the presence of PAD, since the initial absolute risk of MACE was higher. The MACE rate decreased from 19.3% in placebo group to 15.2% in ticagrelor group with PAD, while it decreased from 8.4% to 7.4% without PAD. The increased risk of bleeding with ticagrelor at three years was lower in the presence of PAD (+0.12%) than without (+1.46%). Ticagrelor also significantly reduced the risk of MALE by 35%.

In conclusion, in stable patients with prior MI, concomitant PAD is associated with heightened ischemic risk. In these patients ticagrelor appeared to reduce MACE with a large absolute risk reduction. Ticagrelor also significantly reduced major adverse limb outcomes.

Effect of pre-hospital ticagrelor during the first 24 hours after primay PCI in patients with ST- segment elevation myocardial infarction

In the randomized, double-blind,placebo-controlled ATLANTIC (Administration of Ticagrelor in the cath Lab or in the Ambulance for New ST elevation myocardial Infarction to open the Coronary artery) study, in-ambulance administration of the P2Y12 antagonist ticagrelor shortly before percutaneous coronary intervention (PCI) did not improve pre-PCI reperfusion of the culprit artery compared with in-catheterisation laboratory administration, as measured by the presence of Thrombolysis In Myocardial Infarction (TIMI) flow grade 3 on the angiogram and ≥ 70% ST-segment elevation resolution on the electrocardiogram. The median times from randomization to angiography and between the two ticagrelor loading doses (i.e., pre-hospital *vs.* in-hospital) were only 48 and 31 min, respectively. These short intervals may explain the absence of a detectable benefit of in-ambulance ticagrelor on coronary reperfusion evaluated before the PCI procedure [3].

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Pre-hospital administration of ticagrelor, was, however, associated with a reduction in the risk of stent thrombosis at 30-day follow up. The hypothesis that the effect of earlier administration of ticagrelor did not become manifest until after the procedure because of the short delay in transfer to the catheterisation laboratory was investigated by examinating more closely all the data available during the first 24 hrs after the primary PCI, including platelet function analysis, coronary reperfusion,ischemic endpoints and safety outcomes (ATLANTIC H24 analysis).

A total of 1862 consenting patients were randomized to receive either pre or in-hospital ticagrelor. Of these, 1629 patients underwent primary PCI, received study treatment, and had evaluable data for the first 24 hrs after PCI. In the platelet function substudy, platelet reactivity unit (PRU) levels showing the biological effect of ticagrelor did not become apparent until 1 hr after PCI. The largest but non-significant difference in mean PRU level between the 2 strategies (pre-hospital *vs.* in-hospital) was observed 1 to 6 hrs after PCI.

There were no significant differences between the pre - and in - hospital ticagrelor groups in terms of either post- PCI TIMI flow grade 3 or ≥ 70% ST-segment elevation resolution at 1 hr. However, both endpoints showed numerical differences in favor of the pre-hospital group. ST-segment elevation resolution ≥ 70% measured 1 hr after PCI occured in 57.5% of patients in the pre-hospital group and in 52.5% of patients in the in-hospital group (P=0.055). The degree of ST-segment elevation resolution after PCI was significantly different between the 2 groups (median of 75.0% in the pre-hospital group *vs.* 71.4% in the in-hospital group, P= 0.049).

So, the largest difference in platelet aggregation between the 2 strategies occurred immediatly after PCI and the largest difference in ST-segment elevation resolution was observed 1 hr after PCI. During the procedure

At 24 hr, the composite myocardial ischemic endpoint of death, MI, urgent revascularization, definite stent thrombosis, or bail-out glycoprotein IIb/IIIa inhibitor use was significantly lower proprotionally by 27% with pre versus in-hospital administration of ticagrelor (10.4% *vs.* 1.7%, P=0,039). This reflects coronary complications of PCI while bail-out use of glycoprotein IIb/IIIa inhibitors was an endpoint reflecting thrombotic complications or concerns.

The 2 individual endpoints of definite stent thrombosis and new MI were significantly lower in the pre-hospital group (0.0 *vs.* 1.0 P=0,008 and 0.0 *vs.* 0,7 P=0,031 respectively). The double endpoint of new MI or stent thrombosis was also significatly lower with pre-hospital ticagrelor administration (0.0 *vs.* 1.6 P ≤ 0,001).

All but 1 of the MI events were unrelated to a simultaneous stent thrombosis suggesting that the pre-hospital group was better protected against coronary occlusion that might also occur in a non-culprit artery when patients have multivessel disease. However, all-cause deaths during the 24 hrs after PCI, although infrequent, occurred more often in the pre-hospital ticagrelor group (1.1 *vs.* 0.2, P=0.048).

Analysis of the specific causes of death suggests also that these deaths were not related to either ischemic or bleeding events but to the severity of the initial MI more frequently leading to mechanical complications and shock. The patients who died were generally much older than those who survived, were more often women, patients with diabetes, patients presenting with heart failure, a higher TIMI risk score, and mechanical complications or shock that developed rapidly after PCI. There was also less use of drug- eluting stents and radial access.

The timing of these deaths also suggests they were unrelated to pre- or in- hospital ticagrelor administration because several deaths occurred very early before ticagrelor was biologically effective. The hypothesis of an immediate mortality effect of ticagrelor observed only in the pre-hospital group and with a difference of only 31 min between the 2 treatment groups is not very plausible. It should be noted, however, that this study was underpowered to compare the patient groups in terms of mortality.

There were no statistically significant differences between the 2 treatment groups in term of major or minor bleeding complications.

Overall, the present exploratory analysis is consistent with the main findings of the ATLANTIC study and demonstrates further that the first hours after PCI are a vulnerable period, with potential benefits of pre-hospital use of ticagrelor in STEMI patients undergoing primary PCI.

These results suggest also that there is room left for intravenous antiplatelet agents during this early period when the full effect of oral P2Y12 antagonists is not yet obtained.

In conclusion, the effects of pre-hospital ticagrelor became apparent after PCI, with numerical differences in platelet reactivity and immediate post-PCI reperfusion, associated with reductions in ischemic endpoints including stent thrombosis over the first 24 hr, while there was a small excess of mortality.

Pleiotropic effects of ticagrelor

The clinical benefit of ticagrelor compared with clopidogrel in patients with an ACS suggested an off-target property [4]. A number of observations led to the hypothesis that ticagrelor has pleiotropic properties, and suggested some novel non-platelet–directed mechanisms of action [5,6].

Ticagrelor was associated with a significant increase in adenosine plasma concentration APC by inhibition of adenosine reuptake by red blood cells [7]. This effect of ticagrelor on APC may be responsible for the so-called "pleiotropic" properties, particularly at sites of ischaemia and tissue injury, where adenosine is formed. Ticagrelor exerts an additional mode of action on endothelial regeneration [8] leading to improvement in endothelial function through an increase in APC [9].

Because low EPC concentration and endothelial dysfunction have been associated with a higher rate of adverse events during follow-up, the adenosine-mediated effects of ticagrelor may explain the PLATO mortality data [10].

References

1. Bhatt DL, Bonaca MP, Bansilal S, Angiolillo DJ, Cohen M, et al. (2016) Reduction in Ischemic Events with Ticagrelor in Diabetic Patients: From the PEGASUS-TIMI 54. J Am Coll Cardiol 67: 2732-2740.

2. Bonaca MP, Bhatt DL, Storey RF, Steg PG, Cohen M, et al. (2016) Efficacy and Safety of Ticagrelor as LongTerm Secondary Prevention in Patients with Peripheral Artery Disease and Prior Myocardial Infarction, J Am Coll Cardiol 67: 2719-2728.

3. Montalescot G, van't Hof AW, Bolognese L, Cantor WJ, Cequier A, et al. ATLANTIC investigators (2016). J Am Coll Cardiol Intv 9: 646-656.

4. De Servi S, Savonitto S (2011) How to explain the reduced cardiovascular mortality in the ticagrelor arm of the PLATO trial?. Int J Cardiol 149: 265-267.

5. Cattaneo M, Schulz R, Nylander S (2014) Adenosine-mediated effects of ticagrelor: evidence and potential clinical relevance. J Am Coll Cardiol 63: 2503-2509.

6. Nanhwan MK, Ling S, Kodakandla M, Nylander S, Ye Y, et al. (2014) Chronic treatment with ticagrelor limits myocardial infarct size: an adenosine and cyclooxygenase-2-dependent effect. Arterioscler Thromb Vasc Biol 34: 2078-2085.

7. Bonello L, Laine M, Kipson N, Mancini J, Helal O, et al. (2014) Ticagrelor increases adenosine plasma concentration in patients with an acute coronary syndrome. J Am Coll Cardiol 63: 872-877.

8. Bonello L, Frere C, Cointe S, Laine M, Mancini J, et al. (2015) Ticagrelor increases endothelial progenitor cell level compared to clopidogrel in acute coronary syndromes: A prospective randomized study. Int J Cardiol 187: 502-507.

9. Fromonot J, Dignat-Georges F, Rossi P, Mottola G, Kipson N, et al. (2016) Ticagrelor improves peripheral arterial function in acute coronary syndrome patients: relationship with adenosine plasma level. J Am Coll Cardiol 67: 1967-1968.

10. Wallentin L, Becker RC, Budaj A, Cannon CP, Emanuelsson H, et al. (2009) Ticagrelor versus clopidogrel in patients with acute coronary syndromes. N Engl J Med 361: 1045-1057.