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## Editorial

# Dual antiplatelet therapy and newer agents: More efficacy but lets keep the brain safe!!



Following an ACS (acute coronary syndrome) or an ischemic stroke, it becomes imperative to recognize and treat the underlying etiology for appropriate secondary prevention of vascular events. Antiplatelet agents remain the mainstay of therapy among such patients, including patients undergoing PCI or carotid stenting and the ones managed medically for prevention of future atherothrombotic events. As per consensus guidelines, early revascularization and intensive antiplatelet therapy have been proposed as key strategies to minimize complications secondary to myocardial ischemia and future recurrent events.<sup>1</sup>

For advent of a more effective treatment, apart from the standard therapies with aspirin and clopidogrel, newer P2Y<sub>12</sub> receptor antagonist antiplatelet agents have been discovered and studied in major cardiology RCT's for efficacy and safety.<sup>2</sup> These include oral agents prasugrel,<sup>3–6</sup> ticagrelor,<sup>7,8</sup> and vorapaxar, as well as intravenous agents cangrelor and elinogrel.<sup>9</sup> However, the efficacy of these agents has to be balanced against bleeding complications, with intracranial bleeding being a very serious event. Moreover, they may increase the risk of traumatic hemorrhage, which may be difficult to control and disastrous, especially in the elderly.

In the current issue of this journal, Suryanarayana and colleagues describe a case of nontraumatic subdural hematoma (SDH) in a patient on treatment with dual antiplatelet therapy with aspirin and ticagrelor following a PCI for unstable angina. The patient presented with a recent onset headache with no other focal neurological deficits, and neuroimaging with a brain CT revealed a small right-sided SDH. Luckily, for the patient, the bleed did not expand and was managed conservatively. However, the patient was shifted from ticagrelor to clopidogrel based on concerns of a recent stenting procedure. The authors discuss the concerns of ICH with special reference to the newer antiplatelet therapy.

Risk of intracranial bleed with antiplatelet agents has been studied in various stroke and ACS trials as an important safety endpoint (Table 1). With increasingly intensive antiplatelet therapy, the risk of bleeding complications is likely to rise. In the randomized blinded trial of clopidogrel versus aspirin in patients at risk of ischemic events, among a total of 19,185 patients, the risk of intracranial hemorrhage with clopidogrel

and aspirin was 0.33% and 0.47%, respectively.<sup>10</sup> In the MATCH trial<sup>11</sup> comparing dual antiplatelet arm to a single antiplatelet agent among 7599 patients with a recent ischemic stroke and high risk of vascular events, there was no difference in efficacy outcomes, but the risk of life-threatening bleeds was higher in the clopidogrel and aspirin group [2.6%] vs. [1.3%]; absolute risk increase was 1.3% [95% CI 0.6–1.9] in the clopidogrel group alone.<sup>11</sup> Primary intracranial hemorrhage occurred in 1% of the patients in the clopidogrel and aspirin group as compared to less than 1% in the clopidogrel group [% difference 0.40 (0.04–0.76)]. Monotherapy thus remained a preferred treatment for secondary stroke prevention. In a systematic review of RCT's with mono versus dual antiplatelets among stroke patients, the authors concluded a improved stroke recurrence with the use of dual antiplatelets at the expense of a nonsignificant trend for major bleeding complications, although the overall events were small in number with wide confidence intervals (CIs).<sup>12</sup> The recent CHANCE trial,<sup>13</sup> conducted among patients with “minor stroke” and TIA, compared efficacy of aspirin and clopidogrel given for first 21 days versus aspirin alone in reducing recurrence of stroke at 90 days. There was a significant reduction in stroke occurrence with no major increase in any bleeding or intracerebral hemorrhage. An updated meta-analysis, including the CHANCE trial, suggested that early dual antiplatelet agents for a limited period reduce risk of stroke recurrence (risk ratio, 0.69; 95% CI 0.60–0.80;  $p < 0.001$ ) with a nonsignificantly increased risk of major bleeding (risk ratio, 1.35; 95% CI 0.70–2.59,  $p = 0.37$ ).<sup>14</sup> However, two recent meta-analyses for long-term stroke prevention suggest single agent as the preferred long-term stroke prevention strategy in view of safety concerns for bleeding events.<sup>15,16</sup> Monotherapy thus remains a standard treatment for long-term secondary stroke prevention.<sup>17</sup>

Among patients with acute coronary syndrome, however, the standard practice is to treat with dual antiplatelet agents for a year or even longer, especially following a stenting procedure. In the CURE (Clopidogrel in Unstable Angina to Prevent Recurrent Events) trial<sup>18</sup> assessing addition of clopidogrel with aspirin for unstable angina, although major bleeding in the dual antiplatelet group was higher (3.7% vs. 2.7%; relative risk, 1.38;  $p = 0.001$ ), the episodes of

**Table 1 – Intracranial bleeding rates in major ACS trials.**

Trial	Number of patients	Group 1	Group 2	Intracranial bleeding group 1	Intracranial bleeding group 2	Hazard ratio, 95% CI, p value
CURE	12,652	Clopidogrel	Placebo	No difference in two group.		
CLARITY-TIMI	3491	Clopidogrel	Placebo	8 (0.5)	12 (0.7)	0.38
COMMIT	45,852	Clopidogrel	Placebo	Fatal cerebral 39 (0.17%) Nonfatal cerebral 16 (0.07%)	Fatal cerebral 41 (0.18%) Nonfatal cerebral 15 (0.07%)	Not significant
CURRENT-OASIS 7	25,086	Double-dose Clopidogrel Higher dose aspirin	Standard dose clopidogrel Low dose aspirin	4 (0.03) 6 (0.05)	6 (0.05) 4 (0.03)	0.67 (0.19–2.37), p = 0.53 1.51 (0.42–5.33), p = 0.53
TRITON-TIMI 38	13,608	Prasugrel	Clopidogrel	19 (0.3%)	17 (0.3%)	1.12 (0.58–2.15), p = 0.74
TRILOGY-ACS	9326	Prasugrel	Clopidogrel	14 (0.3)	19 (0.4)	0.76 (0.38–1.51), p = 0.42
PLATO	18,624	Ticagrelor	Clopidogrel	26(0.3)	14(0.8)	1.87 (0.98–3.58), p = 0.06
CHAMPION PCI	8877	Cangrelor	Clopidogrel	1 (<0.1)	0 (0.0)	
CHAMIPON PLATFORM	5301	Cangrelor	Placebo	2 (0.1)	1 (<0.1)	1.99 (0.18–21.98), p = 0.57
DAPT	9961	Clopidogrel	Placebo	16 (0.34%)	13 (0.28%)	0.06% (–0.17%, 0.28%) p = 0.60

CURE: Clopidogrel in Unstable Angina to Prevent Recurrent Events trial. *N Engl J Med* 2001; 345: 494–502.

CLARITY-TIMI: Clopidogrel as Adjunctive Reperfusion Therapy (CLARITY) – Thrombolysis in Myocardial Infarction (TIMI). *N Engl J Med* 2005; 352: 1179–89.

COMMIT (CLOpidogrel and Metoprolol in Myocardial Infarction Trial) collaborative group. *Lancet* 2005; 366: 1607–21.

CURRENT-OASIS 7. Clopidogrel and Aspirin Optimal Dose Usage to Reduce Recurrent Events–Seventh Organization to Assess Strategies in Ischemic Syndromes. *N Engl J Med* 2010; 363: 930–42.

TRITON-TIMI 38: Trial to Assess Improvement in Therapeutic Outcomes by Optimizing Platelet Inhibition with Prasugrel – Thrombolysis in Myocardial Infarction. *N Engl J Med* 2007; 357: 2001–15.

TRILOGY-ACS: The Targeted Platelet Inhibition to Clarify the Optimal Strategy to Medically Manage Acute Coronary Syndromes.

PLATO: Study of Platelet Inhibition and Patient Outcomes (PLATO). *N Engl J Med* 2009; 361: 1045–57.

CHAMPION PCI: Cangrelor versus Standard Therapy to Achieve Optimal Management of Platelet Inhibition. *N Engl J Med* 2009; 361: 2318–29.

CHAMPION PLATFORM: Cangrelor versus Standard Therapy to Achieve Optimal Management of Platelet Inhibition after PCI. *N Engl J Med* 2009; 361: 2330–41.

DAPT: Dual antiplatelet study. *N Engl J Med* 2014; 371: 2155–66.

life-threatening bleeding were similar (2.1% vs. 1.8%,  $p = 0.13$ ). The rates of hemorrhagic stroke were similar (0.1%). In the CLARITY-TIMI trial, patients between 18 and 75 years with ST-segment elevation myocardial infarction (STEMI) were treated with clopidogrel or placebo plus aspirin with no significant differences in major or intracranial bleeding rates between the two groups.<sup>19</sup>

Ticagrelor, a relatively newer agent, is a reversible allosteric antagonist of ADP receptor of subtype P2Y<sub>12</sub>. In the pivotal PLATO (platelet inhibition and patient outcome) trial,<sup>7</sup> ticagrelor significantly reduced the rate of primary composite endpoint, compared with clopidogrel (9% vs. 10.7%,  $p = 0.0025$ ). This benefit was observed both in the first 30 days and the remaining period of analysis.<sup>20</sup> Also, rates of first or recurrent primary outcome events were in favor of ticagrelor.<sup>21</sup> In a substudy of elderly patients in the PLATO trial, the authors did not observe significant differences in benefits among patients above or below 75 years of age and neither was there any difference in PLATO-defined major bleeding rates among patients below 75 years (hazard ratio, 1.02; 95% CI 0.82–1.27) versus those above 75 years (hazard ratio 1.04; 95% CI 0.94–1.5).<sup>22</sup> Ticagrelor also reduced the relative risk of stent thrombosis among the patients who received a stent during the study by 38%.<sup>23</sup> In a retrospective analysis of the PLATO study, no significant differences were found between the Asian

versus the non-Asian populations with respect to efficacy or bleeding rates.<sup>24</sup>

Detailed bleeding rates have been analyzed in a post hoc analysis of the PLATO trial.<sup>25</sup> The rates of PLATO major bleeding (11.6 vs. 11.2%;  $p = 0.43$ ), TIMI major bleeding (7.9 vs. 7.7%,  $p = 0.56$ ), GUSTO severe bleeding (2.9 vs. 3.1%,  $p = 0.22$ ), and procedure-related bleeding were similar among the two groups. The occurrence of non-CABG major bleeding (4.5 vs. 3.8%,  $p = 0.02$ ) and nonprocedure-related major bleeding (3.1 vs. 2.3%,  $p = 0.05$ ) was more common in ticagrelor-treated patients, mainly after 30 days on treatment. The rates of intracranial bleeding were small, 26 (0.34%) in the ticagrelor arm and 15 (0.19%) among clopidogrel-treated patients ( $p = 0.08$ ). 22 (0.26%) of the ticagrelor-treated patients and 13 (0.15%) of the clopidogrel-treated patients were reported to have a hemorrhagic stroke ( $p = 0.13$ ). The fatal intracranial events were however higher in ticagrelor arm, 11 (0.21%) versus 2 (0.03%) in the clopidogrel arm ( $p = 0.02$ ). Apart from the previous history of ICH, no specific risk factor for intracranial bleeding could be identified. Interestingly, the authors observed that the non-CABG or nonprocedure-related major bleeding was more often after the initial 30 days. After modeling for control of all baseline factors in the study, non-CABG-related major bleeding did not differ among two groups but higher non-CABG-related major or minor bleeding rates

were found to be associated with ticagrelor therapy, both in the initial 30 days (5.11 vs. 4.02%; HR 1.28; 95% CI 1.10–1.501;  $p = 0.002$ ) and after (3.98 vs. 2.97%; HR 1.35; 95% CI 1.09–1.67;  $p = 0.006$ ).

Based on observations from studies, some authors have suggested that ticagrelor should be avoided among patients with ACS with a past history of ICH, hepatic impairment, high bleeding risk, and concomitant use of anticoagulants.<sup>26</sup> Risk factors observed for bleeding during antiplatelet therapy are advanced age (>75 years), female sex, use of NSAIDs, anticoagulants, or glycoprotein IIb/IIIa inhibitors, history of bleeding, stroke, or transient ischemic attack.<sup>27</sup> Clopidogrel may be a preferred agent in place of newer oral antiplatelet agents in patients with higher bleeding risk, need for concomitant anticoagulation, stable PCI-treated patients, and clear contraindications to either ticagrelor or prasugrel.<sup>28</sup>

In a recent meta-analysis, including 12 RCT's, the authors concluded that the new oral P2Y12 inhibitors reduce ischemic events, "without any obvious increase in major bleeding in patients with CAD", the effect being more favorable among STEMI patients.<sup>2</sup> However, important concerns have been raised about the variability in definitions for bleeding among ACS trials of antiplatelet agents, which seems to create a marked variation of bleeding rates across trials.<sup>29</sup> Authors suggest that three factors, which most consistently determine the bleeding risk, are definition, timing of bleeding assessment, and rates of CABG surgery. Other factors influencing bleeding rates include age, pharmacological and interventional cointerventions, renal dysfunction, and type of ACS presentation. A standardized reporting standard for bleeding has been previously proposed.<sup>30</sup>

The optimum duration of therapy with dual antiplatelet agents in ACS still remains unclear. Following coronary stenting, evidence to treat longer than prescribed period may be associated with higher risk of bleeding, as shown in the recent results of ARCTIC-interruption trial<sup>31</sup> with no benefit in ischemic or stent-related complications.<sup>32</sup> A recent meta-analysis on long-term dual antiplatelet therapy (>1 year) following a drug-eluting stent suggests loss of net benefit due to increased bleeding-related noncardiovascular mortality.<sup>33</sup> A recent meta-analysis on the long-term use of dual antiplatelets in different cardiovascular disorders however does not suggest any long-term mortality differences between the aspirin alone or shorter and longer durations of dual antiplatelet therapy.<sup>34</sup> These variations among published meta-analyses are likely due to differences in study inclusions and methodology.<sup>35</sup>

This case highlights the known bleeding risks of dual antiplatelet therapy, especially in the elderly who may have comorbidities. As for secondary long-term stroke prevention, single antiplatelet therapy is the standard of care apart from situations like vascular stenting and intensive management of intracranial vascular stenosis based on the results of SAMMPRIS trial.<sup>17,36</sup> In cardiology practice, however, dual antiplatelet therapy is an accepted standard of care for ACS patients and even the threat of triple therapy is accepted in situations like associated atrial fibrillation or mechanical valves, where evidence does point towards worrisome bleeding rates.<sup>37,38</sup> Although there is some suggestion from the data that the newer antiplatelet agents may have benefit at the expense of

increase in bleeding, reporting standards needs standardization and no unbiased inferences can be drawn about safety of one versus the other.

Till future guides us about individualized pharmacotherapy and risks with a specific drug, caution, safety, and detailed individual patient risk assessment profile before selecting an agent remain the key to safe outcomes.

## Conflicts of interest

The authors have none to declare.

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