Refining the Role of Antiplatelet Therapy in Medically Managed Patients With Acute Coronary Syndrome

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Dual-antiplatelet therapy with aspirin plus a $P2Y_{12}$ receptor inhibitor is recommended for use as first-line therapy in patients with acute coronary syndromes (ACS) who undergo high-risk percutaneous coronary intervention. However, revascularization may not be a beneficial option for some subgroups of patients with ACS. This includes a broad spectrum of lower risk patients as well as high-risk patients with numerous previous revascularizations and those who are at high risk for complications, such as those with complex coronary anatomy and comorbidities such as diabetes mellitus, chronic kidney disease, or advanced age and frailty. For such patients, there remains an unmet need for evaluation of alternatives to the currently recommended treatment options. Notably, there is a paucity of prospective data regarding management approaches to medically managed patients with ACS. Thus, this group of medically managed patients with ACS would benefit from inclusion in clinical trials investigating therapeutic options for patients not scheduled to undergo invasive procedures, such as those who are targeted for pharmacologic management only. In conclusion, in this review, the investigators revisit data from clinical studies of dual-antiplatelet therapy in ACS to highlight areas of unmet need in antiplatelet therapy in patients with ACS and to examine the use of newer agents in subgroups, such as medically managed patients with ACS, that would potentially benefit from more potent platelet inhibition after ACS. **(Am J Cardiol 2013;111:439−444)**

Efforts to improve antiplatelet therapy and reduce the incidence of recurrent events in patients with acute coronary syndromes (ACS) have resulted in a field that is very dynamic and fluid with respect to pharmacologic intervention. The availability of newer adenosine diphosphate $P2Y_{12}$ receptor inhibitors that are more potent than clopidogrel, such as prasugrel[1−3] and ticagrelor,[4,5] has increased therapeutic choices for platelet inhibition after ACS. The purposes of this review are to highlight important areas of unmet need in antiplatelet therapy in patients with unstable angina (UA) and non−ST-segment elevation myocardial infarctions (NSTEMIs) using clinical data from studies of dual-antiplatelet therapy (DAPT) in ACS and to examine the use of newer agents in ACS subgroups that would benefit from more potent antiplatelet therapy.

Unmet Need for Dual-Antiplatelet Therapy in Patients With Acute Coronary Syndromes

Although clopidogrel has long been promulgated as a standard of care in ACS treatment guidelines, the newer antiplatelet therapies prasugrel and ticagrelor are now recognized as alternatives to clopidogrel in certain groups of patients with ACS and have been recommended in several recently updated clinical practice guidelines.[6−9] However, the availability of prasugrel and ticagrelor, and support for their use in evidence-based guidelines for UA or NSTEMI and ST-segment elevation myocardial infarction,[7,9] has not translated to their use in place of clopidogrel in many patients with ACS as much as was envisioned.[10,11] As such, there remains an important unmet therapeutic need in patients who may benefit from alternatives to clopidogrel.

Clopidogrel is approved for use in a wide population of patients with ACS, including those who undergo percutaneous coronary intervention (PCI) and those who are to be medically managed.[12] In the Clopidogrel in Unstable Angina to Prevent Recurrent Events (CURE) trial, the relative risk for cardiovascular death, myocardial infarction, or stroke was 0.80 (95% confidence interval [CI] 0.69 to 0.92) for patients receiving 12 months of DAPT with clopidogrel only compared to 0.72 (95% CI 0.57 to 0.90) for those who underwent PCI.[13] However, compared to invasive management strategies, clopidogrel-based DAPT is still underused in the NSTEMI ACS patient population, suggesting a general reluctance to use DAPT.[11]

Prasugrel is approved for use only in patients with ACS who undergo PCI, not in those who undergo medical management, and it is not recommended in patients with histories of stroke or transient ischemic attack, additional factors that may be limiting its use. Ticagrelor is approved for use in patients with ACS and was evaluated in populations of patients with ACS with and without scheduled PCI in the Platelet Inhibition and Patient Outcomes (PLATO) trial.[4] Specifically, the incidence of the composite primary end point (the rate of cardiovascular death, myocardial infarction,

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or stroke) was lower in patients initially intended for noninvasive management who received ticagrelor versus clopidogrel (12.0% vs 14.3%, respectively; hazard ratio 0.85, 95% CI 0.73 to 1.00, p = 0.04).[14] There was no significant difference in the rate of overall Thrombolysis In Myocardial Infarction (TIMI) major bleeding with ticagrelor versus clopidogrel (7.9% vs 7.7%, respectively, p = 0.57). However, ticagrelor was associated with a higher rate of non-coronary artery bypass graft (CABG)-related TIMI major bleeding compared to clopidogrel (2.8% vs 2.2%, respectively, p = 0.03). There was no significant difference in the rate of TIMI CABG-related major or minor bleeding with ticagrelor versus clopidogrel (11.4% vs 10.9%, respectively, p = 0.33).[4] Despite its efficacy in improving cardiovascular outcomes, the twice-daily dosing for ticagrelor may lead to concerns about patient adherence.[7,9] In addition, the increased rate of dyspnea with ticagrelor compared to clopidogrel[4] may have clinical implications in patients with chronic obstructive pulmonary disease and congestive heart failure and may be an additional factor limiting the adoption of ticagrelor in patients with ACS.[15]

The difference in approved patient populations among the available $P2Y_{12}$ receptor inhibitors (clopidogrel, prasugrel, and ticagrelor) is a consequence of the design, execution, and publication of the pivotal clinical trials for each drug; the CURE trial, like the PLATO trial, enrolled "all comers" with ACS without ST-segment elevation,[4,16] while the Trial to Assess Improvement in Therapeutic Outcomes by Optimizing Platelet Inhibition With Prasugrel (TRITON)−TIMI 38 enrolled only those patients with ACS who were expected to undergo an early invasive management approach and prompt PCI during the index hospital admission.[3] The recently published Targeted Platelet Inhibition to Clarify the Optimal Strategy to Medically Manage Acute Coronary Syndromes (TRILOGY ACS) trial was designed to address these gaps in clinical data for prasugrel and compared therapy with clopidogrel versus prasugrel in medically managed patients who did not undergo revascularization.[17,18]

TRILOGY ACS is a randomized, double-blind, multicenter trial in 9,326 patients aged ≥18 years with UA or NSTEMI who underwent medical management with prasugrel (30-mg loading dose and 10-mg maintenance dose; 5 mg if patients weighed <60 kg or were aged ≥75 years) plus aspirin or clopidogrel (300-mg loading dose and 75-mg maintenance dose) plus aspirin for up to 30 months.[17,18] The results of this study were neutral; there was no reduction in the rate of major cardiovascular events in the prasugrel group. There was no significant difference in the primary end point of cardiovascular death, myocardial infarction, or stroke in patients aged <75 years at the mean follow-up of 17 months (prasugrel 13.9% vs clopidogrel 16.9%, hazard ratio 0.91, 95% CI 0.79 to 1.05, p = 0.21), with similar results observed for the overall population. A time-dependent divergence of treatment effects was observed after 12 months. The frequency of the primary end point was similar in the 2 study groups through 12 months; a weak trend toward a reduced risk in the prasugrel group was observed after 12 months (p = 0.07 for interaction). A significant treatment effect of prasugrel on multiple recurrent ischemic events was observed in this study for patients aged <75 years (hazard ratio 0.85, 95% CI 0.72 to 1.00, p = 0.04). There was no significant difference in the risk for major bleeding between the 2 groups.

Reducing the Recurrence of Cardiovascular Events After Acute Coronary Syndromes in Challenging Patient Subsets

There are several groups of patients with ACS who do not receive optimal DAPT regimens that minimize adverse outcomes and reduce recurrence regardless of the current guideline recommendations. These include patients with ACS who present to the hospital with repeated bouts of ACS (despite being treated with PCI and DAPT), the so-called frequent flyers, in whom repeat revascularization may no longer be an appropriate or desirable treatment option; patients with diabetes or chronic kidney disease; patients of very advanced age or frailty; those with complicated coronary anatomy; and those patients who undergo more conservative management (i.e., those without planned invasive strategies).

Approximately 20% of "successfully treated" patients with ACS are rehospitalized within 12 months.[19] Angina is a frequent problem after PCI, with a substantial proportion of patients being readmitted to the hospital because of recurrence. A report from the National Heart, Lung, and Blood Institute Dynamic Registry suggests that approximately 25% of patients who underwent PCI reported angina symptoms at 1-year follow-up.[20] Patients who undergo PCI also have a substantial rate of repeat revascularization; data from the Arterial Revascularization Therapy Study (ARTS) and the Stent or Surgery (SoS) trial suggest that 15% to 20% of patients can undergo repeat revascularization <3 years after the initial procedure.[21,22] In addition, data from the Providing Regional Observations to Study Predictors of Events in the Coronary Tree (PROSPECT) trial show that in patients with ACS who undergo revascularization (despite DAPT with aspirin and clopidogrel), the rate of major adverse cardiovascular events (death, myocardial infarction, or revascularization) remained substantial (20.4% at 3 years), with 12.9% of the events caused by the intervened culprit lesion and 11.6% by the nonculprit lesions.[23]

Data from the CURE trial in patients with ACS without ST-segment elevation who underwent revascularization with dual aspirin and clopidogrel therapy showed that the rates of the composite primary outcome (cardiovascular death, myocardial infarction, or stroke) were lower in those receiving clopidogrel compared to placebo and were similarly reduced in those who underwent PCI (9.6% with clopidogrel, 13.2% with placebo) and CABG (14.5% with clopidogrel, 16.2% with placebo).[13] Data from the Clopidogrel as Adjunctive Reperfusion Therapy (CLARITY) trial in patients with ST-segment elevation myocardial infarctions showed that the addition of clopidogrel to aspirin improved the patency rate of the infarct-related artery and reduced ischemic complications compared to aspirin alone.[24]

Recurrent events in patients treated with PCI may also be due to poor response to aspirin or clopidogrel therapy,[9,25] as individual patients can have variable responsiveness to clopidogrel.[26] The cause of the poor response could be multifactorial and could affect a considerable proportion of patients depending on the definition used.[26] Meta-analyses