Antiplatelet and anticoagulation agents in acute coronary syndromes: What is the current status and what does the future hold?

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Mortality and morbidity in acute coronary syndromes (ACSs), caused principally by plaque erosion or rupture leading to thrombus formation and myocardial ischemia, have been reduced by a combination of antithrombotic agents (antiplatelet drugs and anticoagulants) and early revascularization. Aspirin is the foundation antiplatelet agent. New $P2Y_{12}$ receptor inhibitors (prasugrel and ticagrelor) have clear benefits compared with clopidogrel for dual antiplatelet therapy, and cangrelor or vorapaxar, a thrombin receptor inhibitor, may be of value in specific settings. Anticoagulation uses 1 of 4 choices: bivalirudin, unfractionated heparin, enoxaparin, and fondaparinux. Moreover, some patients (such as those who have chronic atrial fibrillation) require triple therapy with aspirin, clopidogrel, plus an anticoagulant, frequently a vitamin K antagonist. New oral anticoagulants have been shown to be at least as effective as vitamin K antagonists in atrial fibrillation and led to fewer bleeding complications. Finally, the combination of aspirin, clopidogrel, and low-dose rivaroxaban has recently been approved by the European Medicines Agency (but not the Food and Drug Administration) for secondary prevention after ACS. Several strategies have been developed to balance the potential benefit of antithrombotic therapy against the risk of bleeding complications, for example, radial access in coronary angiography or restricted use of combination therapy, and others are under investigation, such as discontinuation of aspirin. This overview summarizes the current status of antithrombotic therapy in ACS and describes strategies currently explored to optimize its benefit/risk ratio. (Am Heart J 2014;168:611-21.)

Acute coronary syndromes (ACSs) are usually initiated by atherosclerotic plaque erosion, fissuring, or rupture and subsequent coronary thrombus formation. Over the last few decades, improvements in antiplatelet and anticoagulant treatment have decreased the morbidity and mortality associated with ACS and have resulted in standardization of therapy.[1-4]

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Harmony R Reynolds, MD, served as guest editor for this article.
Submitted February 7, 2014; accepted June 17, 2014.

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0002-8703

http://dx.doi.org/10.1016/j.ahj.2014.06.014

The potential benefit of reducing ischemic complications with antithrombotic therapy has to be balanced against the risk of bleeding complications. Bleeding risk increases with the number of agents coadministered and is of particular concern with chronic administration of dual antiplatelet therapy (DAPT) plus an oral anticoagulant (triple therapy).[5-7] Importantly, major bleeding has been associated with subsequent worse clinical outcomes, including increased mortality, in randomized clinical trials and observational reports.[8] Although acute bleeding, especially intracerebral hemorrhage, can be fatal, premature interruption of therapy due to acute bleeding can result in stent thrombosis, myocardial infarction (MI), systemic embolism, stroke, or death. Therefore, many challenges need to be addressed to optimize the benefit/risk ratio with antithrombotic therapy.

Current status

Oral antiplatelet agents

Antiplatelet therapy should be initiated as soon as possible after the diagnosis of ACS is made.[1-4] A loading dose of aspirin should be given to patients without

contraindications and continued indefinitely at a low daily dose of 75 to 100 mg. DAPT with a combination of aspirin and a $P2Y_{12}$ inhibitor for 12 months is recommended for all patients with a definite diagnosis of ACS, whether they undergo revascularization, unless the risk of bleeding exceeds the potential benefit. Prescribing a proton pump inhibitor in patients with increased risk of bleeding and avoiding nonsteroidal anti-inflammatory drugs are 2 strategies that decrease bleeding risk. The immediate start of DAPT is recommended for all patients with ST-segment elevation MI (STEMI). The necessity of "upstream" DAPT in patients with non–ST-segment elevation MI (NSTEMI) undergoing percutaneous coronary intervention (PCI) with prasugrel has recently been challenged.[9]

The European Society of Cardiology (ESC) guidelines support using the novel, more potent, and consistent $P2Y_{12}$ inhibitors ticagrelor and prasugrel over clopidogrel. Ticagrelor is recommended for NSTEMI patients, even if they have been pretreated with clopidogrel, and also in STEMI patients referred for primary PCI.[1,4] Prasugrel is recommended for clopidogrel-naive patients undergoing primary PCI or in high-risk non–ST-segment elevation ACS (NSTE-ACS) patients going on to PCI, particularly if they have diabetes mellitus, but is contraindicated in patients with previous stroke or transient ischemic attacks, and used with caution in patients with age >75 years or low body weight.[1] In the ESC guidelines, clopidogrel is recommended mainly for those who cannot receive ticagrelor or prasugrel because of contraindications, unavailability, or cost.[1] The American College of Cardiology/American Heart Association (ACC/AHA) guidelines provide a similar level of recommendation for all oral $P2Y_{12}$ inhibitors.[3] The mild discrepancies between the ACC/AHA and ESC guideline recommendations on antiplatelet therapy, despite using the same evidence base, have recently been reviewed.[10]

Interindividual variability in responsiveness to clopidogrel is a problem that is largely addressed by the use of ticagrelor or prasugrel. Platelet function testing and CYP2C19 genotype testing might be considered in selected patients on clopidogrel if the results may alter management.[11] However, routine testing coupled with modification of antiplatelet therapy has not yet been shown to improve clinical outcomes, although studies may not be definitive.[12-14] Before surgery, if feasible, ticagrelor and clopidogrel should be stopped for 5 days, and prasugrel for 7 days, and restarted as soon as possible after surgery. If this is not possible because of clinical urgency, platelet function testing might be useful to decide the timing of surgery.[10,15] In patients at high risk for bleeding, platelet function testing might be considered to determine the optimal $P2Y_{12}$ inhibitor strategy.[11]

Intravenous glycoprotein IIb/IIIa inhibitors

In patients with a low bleeding risk, glycoprotein IIb/IIIa inhibitors (GPIs) (eptifibatide or tirofiban) can be added to DAPT for high-risk PCI (elevated troponin, visible thrombus, and high-risk anatomy) or for high-risk patients (abciximab).[1] The prehospital use of GPIs results in improved inhibition of platelet aggregation and better ST-resolution or clinical outcomes compared to traditional DAPT (On-TIME 2 trial).[16,17] Glycoprotein IIb/IIIa inhibitors may also be used in patients undergoing emergent cardiac catheterization who have not been preloaded with oral antiplatelet therapy.[1] Routine use of GPIs in combination with oral $P2Y_{12}$ inhibitors, before angiography or in those managed noninvasively, is not recommended.[18] Dose reduction is often required in patients with chronic kidney disease receiving eptifibatide or tirofiban, but not abciximab.[1] In general, GPI use has decreased since clopidogrel, prasugrel, ticagrelor, and bivalirudin have become available.

Anticoagulation

Anticoagulation is recommended for all patients; it can be discontinued immediately after successful PCI, but it should be continued to hospital discharge (or up to 5 days, whichever occurs first) in patients not revascularized. In the rare patient requiring prolonged bed rest after PCI, prophylactic dosing is recommended to prevent deep vein thrombosis. There are 4 choices for anticoagulation in the acute setting for NSTE-ACS. In comparison with subcutaneous enoxaparin, subcutaneous fondaparinux is associated with less major bleeding and lower long-term mortality both in NSTE-ACS and STEMI.[19,20] The ESC guidelines, therefore, state that fondaparinux is the anticoagulant with the most favorable efficacy-safety profile in ACS. However, because of a risk of catheter thrombus during PCI, full-dose intravenous unfractionated heparin (UFH) or bivalirudin is required in combination with antiplatelet therapy.[21,22] Importantly, fondaparinux is, conversely, not recommended for STEMI patients undergoing primary PCI. Subcutaneous enoxaparin has efficacy advantages over UFH, but crossover between these heparins should be avoided. Intravenous bivalirudin (3-hour infusion) or UFH is preferred to support urgent or early PCI in patients, with bivalirudin having the lowest risk of bleeding and a possible related survival advantage in patients undergoing primary PCI (HORIZONS study).[23,24] Furthermore, prehospital administration of bivalirudin was associated with a lower rate of net clinical outcome.[25] It has been discussed that a prolongation of bivalirudin infusion after successful PCI of 4 hours might improve clinical outcome by avoiding early stent thrombosis, although this has never been prospectively investigated. Dose adjustment or even avoidance may be required in patients with chronic kidney disease receiving fondaparinux, enoxaparin, or bivalirudin, but not UFH. Long-term anticoagulation in addition to DAPT is required in 5% to 10% of patients for other diagnoses (atrial fibrillation, mechanical valves, and