Needs Assessment

Target Audience

This activity is intended for interventional cardiologists, non-invasive cardiologists, internists, emergency care physicians, and other health care professionals who manage and treat patients with acute coronary syndromes (ACS).

Literature Review of Antithrombotic Therapy in ACS

Acute coronary syndromes are projected to result in 1.4 million hospitalizations in 2012 and by 2030, 40.5% of the US population is expected to have some form of cardiovascular disease. Approximately every 25 seconds, an American will experience a coronary event underscoring an urgent call to action in understanding evolving treatment options and therapeutic guidelines. [1]

Antiplatelet and anticoagulant therapies are the fundamental cornerstones of management of patients with ACS. With recent advances and trial evidence over the past 5 years, a number of novel antiplatelet and anticoagulant therapies are available on the market. Selection of the appropriate antithrombotic therapy is based upon but not limited to considerations of patient risk and benefit, type of ACS, plan for invasive versus conservative strategy, treatment in the catheterization laboratory and use of bare metal versus drug eluting stents. In 2011, the American College of Cardiology Foundation (ACCF) and the American Heart Association (AHA) updated their joint guidelines for the management of patients with Unstable Angina/Non ST-segment elevation myocardial infarction.[2] These guidelines incorporate a large degree of flexibility in the choice of antiplatelet therapy and anticoagulant therapy, which can make the implementation of these recommendations complex and challenging.

Despite increases in use of newer and more potent antithrombotic therapies in-hospital and antiplatelet therapies post discharge, the residual risk of death, myocardial infarction, or stroke up to 1 year after ACS remains high.[2] This represents a therapeutic challenge, since the balance between risk (major bleeding) and benefit (reduction in ischemic events) becomes more delicate with time as the ischemic risk trends to diminish. Recently, a number of novel oral anticoagulant therapies have been tested for secondary prevention of ischemic events post-discharge in patients with acute coronary syndrome. Although the early data for these novel oral anticoagulants in post-ACS secondary prevention is mixed, future studies are required to elucidate time dependency of risks during long-term treatment and how prediction of these risks will inform treatment selection.

Practice Gap #1: There is a need to increase awareness among health care providers regarding advances and availability of new antiplatelet and anticoagulant therapies for patients with ACS.

There are several concerns with current antithrombotic therapies such as their non-selective nature, inability to inhibit of clot-bound thrombin, bleeding risks and unpredictable pharmacodynamics. Agents which inhibit platelet function have an established role in the management of patients with ACS but still

do not eliminate the risk of break through thrombosis.[3] In the anticoagulant category, new agents which target specific enzymes in the coagulation pathway and can be given in fixed doses without extensive coagulation monitoring, are an active area of research. Therefore, in order to optimize outcomes in patients with ACS, health care providers must become familiar with recently available antithrombotic agents for the care of patients with ACS. These include medications both for acute treatment in-hospital and those used to transition to outpatient after discharge for secondary prevention.

Antiplatelet Medications

Dual antiplatelet therapy with ASA and clopidogrel (a thienopyridine) has played a significant role in the management of patients with ACS with and without coronary intervention demonstrating both short and long term benefits. [4-6] Newer agents tested against clopidogrel have shown clinical efficacy in large clinical trials and are now available on the market. These include prasugrel and ticagrelor.

Prasugrel

Prasugrel is a thienopyridine that inhibits platelet aggregation by irreversibly binding to the P2Y12 component of the adenosine diphosphate (ADP) receptor on platelets. . Compared to clopidogrel, prasugrel inhibits platelet aggregation more rapidly and more consistently in patients with ACS specifically those undergoing percutaneous coronary intervention (PCI).[7] Among 13,608 patients randomized to receive either clopidogrel or prasugrel, patients in the prasugrel group had significantly reduced rates of ischemic events and stent thrombosis, but had an increase in the risk of major bleeding, including fatal bleeding, compared to clopidogrel. Overall, mortality was similar between the two treatment groups. Studies have shown however that, if used with predefined patient selection guidelines (i.e. patients without a previous history of stroke, <75 years of age and >60kg), the bleeding risk may be attenuated while still providing maximum benefits.[8]

Ticagrelor

Ticagrelor is a non-thienopyridine that inhibits platelet aggregation by reversibly and noncompetitively binding to the P2Y12 component of the ADP receptor on platelets. This oral drug has the benefit of overcoming the slow onset of clopidogrel and offers a more potent ADP receptor blockade. [3] Unlike clopidogrel or prasugrel, ticagrelor has to be take twice daily which may have an impact on patient compliance. In the PLATO trial, a multicenter, double-blind, randomized trial comparing ticagrelor to clopidogrel in patients with ACS with or without ST-segment elevation, patients randomized to ticagrelor had lower composite of death from vascular causes, myocardial infarction, or stroke (9.8% vs. 11.7%, p<0.001). The rate of death from any cause was also reduced with ticagrelor (4.5% vs. 5.9%, p<0.0010, however, ticagrelor was associated with higher rate of major bleeding not related to coronary artery bypass grafting (4.5% vs. 3.8%, p=0.03), including more instances of fatal intracranial bleeding.[9]

Anticoagulant Medications

Intravenous agents

Factor Xa Inhibitors

Factor Xa is a key component of the prothrombinase complex that drives the final common pathway of the coagulation cascade, generating thrombin, which then converts fibrinogen to insoluble fibrin. Thrombin is also a potent activator of platelets via cleavage and consequent stimulation of the protease-activated receptor (PAR) 1 on the platelet surface. Thus, inhibition of thrombin generation, activity, or both, is a logical aim in the treatment of acute coronary syndromes.

Otamixaban

Otamixaban is a novel intravenous, direct, selective factor Xa inhibitor. In the phase II SEPIA-ACS 1 TIMI 42 trial of 3241 patients with non-ST-elevation ACS, primary efficacy endpoint trended lower with increasing doses of otamixaban with similar rate of bleeding complications compared with unfractionated heparin plus eptifibatide.[10]

Oral agents

Direct thrombin inhibitors (DTIs)

These medications specifically bind to thrombin without the need for a cofactor to inhibit the conversion of fibrinogen to fibrin. In contrast to heparin, DTIs inhibit clot-bound thrombin as well as free thrombin increasing their anticoagulant activity.

Dabigatran etexilate

Dabigatran is administered orally and reaches peak plasma levels in 2 to 3 hours. In a phase II trial of patients who had experienced an ACS event within the last 7 days, increasing doses of dabigatran were tested against placebo. Patients were treated for 6 months with over 99% of patients also receiving dual antiplatelet therapy with aspirin and clopidogrel. [11] In this study, bleeding events were more common with higher dabigatran doses, but rates of ischemic events were similar for all doses and no different than placebo.

Factor Xa inhibitors

Rivaroxaban

Rivaroxaban is a reversible oral medication which is rapidly absorbed reaching maximum concentration after 2 to 4 hours.

Results of the large phase III, double-blind, placebo-controlled trial evaluating rivaroxaban for secondary prevention in patients with recent ACS was recently published. [12] Patients were not required to have additional risk factors for recurrent ischemic events and those with previous intracranial hemorrhage or previous ischemic stroke despite dual antiplatelet therapy were excluded. A significant reduction in composite of cardiovascular death and myocardial infarction as well as a reduction in the risk of stent

thrombosis was found with both 2.5mg and 5.0mg twice daily doses of rivaroxaban. The lower dose of rivaroxaban (2.5 mg twice daily) showed a significant reduction in cardiovascular death and death from any cause but no reduction in myocardial infarction. The higher dose (5mg twice daily) showed a reduction in MI but no significant difference in mortality and was associated with an increase in major bleeding and intracranial hemorrhage without a significant increase in fatal bleeding.

Apixaban

Apixaban is an oral, twice daily direct factor Xa inhibitor which reaches peak plasma concentration 3 to 4 hours after administration. It is not recommended for patients with renal impairment.

The phase III double-blind, placebo-controlled trial of patients with and without ST-segment elevation randomized to apixaban vs. placebo followed for a median of 241 days, was stopped prematurely as it did not show improved efficacy at reducing risk of recurrent ischemia and was associated with increased bleeding. [13]

Practice Gap #2: There is a need to increase awareness among clinicians and other health care providers regarding current therapeutic guidelines for the care and management of patients with ACS.

Over the last one year, there have been several updates to the major professional society guidelines. It is our aim to update the healthcare providers on highlights of these guideline statements. These include:

- The 2011 American College of Cardiology Foundation and the American Heart Association Guidelines for the Management of Patients with Unstable Angina/Non-ST Elevation Myocardial Infarction [2]
- The 2011 Guidelines for Percutaneous Coronary Intervention: A Report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines and the Society for Cardiovascular Angiography and Interventions [14]
- Management of acute myocardial infarction in patients presenting without persistent ST-segment elevation: ESC Clinical Practice Guidelines 2011 [15]

Practice Gap #3: There is a need to increase awareness among health care providers regarding potential bleeding risks associated with antithrombotic therapy and the impact of bleeding on clinical outcomes.

Prevention of recurrent ischemic events following an ACS is critical and antithrombotic therapy with coronary revascularization reduces this risk. Greater use of these medications however increases the possibility of bleeding events and can have a negative impact on patient outcomes. Recognizing patients who are at high risk of hemorrhage can guide the decision to choose specific antithrombotic regimes to maximize benefit while decreasing morbidity and health care costs.

Major bleeding is associated with a 60% increased risk of in-hospital death, and a fivefold increase in one year mortality and reinfarction. [16] An analysis of 34,000 patients demonstrated that patients with major bleeding have 30-day mortality rates five times higher than those with no bleeding, but the risk of death over the succeeding six months was lower.[17]

Definitions of bleeding can vary widely; however, an analysis of 2 different bleeding classifications in patients with ACS concluded that bleeding assessed with clinical criteria is more important than that assessed by laboratory criteria in terms of patient outcomes (e.g., bleeding which results in hemodynamic compromise which threatens the patient's life or if the bleeding event leads to an intervention).[18]

Variation in administration practices may also lead to confusion and dosing errors among ACS patients resulting in higher rates of bleeding complications and poor patient outcomes.[19] A 2005 study involving more than 30,000 ACS patients and 350 hospitals, found that 15% of major bleeding was due to excessive dosing. [20]

Learning/Behavioral Objectives

At the conclusion of this activity, the learner should be able to:

- Describe the risks and benefits of various antiplatelet and anticoagulant options available for treatment of patients with acute coronary syndrome.
- Discuss the emerging evidence for novel anticoagulant therapies in the initial treatment and secondary prevention of patients with acute coronary syndrome.
- Implement new antithrombotic therapies for acute coronary syndrome into clinical practice in accordance with current therapeutic guidelines .

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