Emerging antiplatelet and lipid lowering therapies

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Antiplatelet therapy is used widely with proven benefit for the primary prevention of cardiovascular disease as well as for the prevention of further ischemic cardiovascular events in patients with proven coronary artery disease (CAD) and in those with a history of acute coronary syndrome (ACS). The limitations of conventional antiplatelet therapy with aspirin, clopidogrel, or prasugrel, as well as the fact that rates of recurrent ischemic events still remain high with use of these agents, underscore the need to investigate alternative molecules that may be effective in further reducing the occurrence of events without increasing the risk of bleeding. The armamentarium of antiplatelet therapy has been further enriched by ticagrelor, cangrelor, vorapaxar, prasugrel and atopaxar. Ticagrelor was approved in 2011 by the European Medicines Agency swiftly followed by the US Food and Drug Administration. Reversible antiplatelet agents acting as P2Y12 antagonists similar to ticagrelor are cangrelor, and elinogrel. A new class of oral protease-activated receptor-1 (PAR-1) inhibitors, vorapaxar and atopaxar has also been proposed as effective antiplatelets but their clinical benefit is still under debate. The P2Y12 antagonists prasugrel and ticagrelor prevent adverse cardiac outcomes albeit their absolute benefit is very small. The beneficial effect of prasugrel and ticagrelor comes at a cost of an increased risk of bleeding. Furthermore, new adverse effects have also become evident with the new P2Y12 antagonists and these include dyspnea (for all of the reversible P2Y12 antagonists: ticagrelor, cangrelor, and elinogrel) and ventricular pauses for ticagrelor. In addition, the newer P2Y12 antagonists have a peculiar pharmacodynamic profile with a fast onset and offset. Two of these agents, cangrelor and elinogrel, are available as intravenous formulations, which may provide additional benefits in patients who undergo coronary artery bypass graft (CABG) surgery. Trials with the PAR-1 inhibitors have also shown trends toward reductions in cardiac events, but not without the possibility of increased bleeding. Physicians must carefully assess patient-specific factors such as risk of thrombosis, concomitant disease states, age, drug adherence, and aspirin dose, and plan for those patients who will be undergoing CABG when selecting antiplatelet therapy in order to optimally balance bleeding and thrombosis risk.

In addition to adequate anti-platelet therapy the treatment of blood lipids is important for the primary and secondary prevention of cardiovascular disease. Elevated low-density lipoprotein cholesterol is an important risk factor for cardiovascular and cerebrovascular events. HMG-CoA reductase inhibitors, or statins, are very effective in lowering cholesterol levels, and in reducing mortality and cardiovascular events in patients with and without cardiovascular disease. The evidence cumulated with the studies conducted with statin has led to the recent recommendations that all patients with known vascular disease, or who are at high risk for vascular disease, should be considered candidates for statin therapy. Nonstatin therapies (either as monotherapy or in addition to statins) to reduce LDL cholesterol by mechanisms that do not involve inhibition of HMG-CoA reductase are likely to be useful for patients in need of LDL reduction; particularly those who either cannot take statins or respond only partially or not at all to statins alone. These therapies include cholesterol absorption inhibitors, Acyl-CoA cholesterol acyl transferase inhibitors, farnesoid X receptor antagonists, sterol-regulating binding protein cleavage activating protein, and microsomal triglyceride transfer protein. Recent studies with the PCSK9 have shown that these drugs significantly reduce total and LDL cholesterol in patients with familial hypercholesterolaemia and that are effective in further reducing plasma cholesterol levels in patients receiving statins.

Therefore, therapeutic options are becoming available for patients who cannot tolerate full dose statin therapy or for those few patients who are intolerant to statin therapy.

doi:10.1016/j.ijcme.2015.05.010

Innovative therapeutic approaches for the treatment of myocardial ischemia and angina

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Coronary artery disease is the leading cause of death in the industrialised Countries and angina pectoris is a common symptom of this disease. “Angina” is a term used to describe the clinical symptoms that are induced by physical exertion or emotional stress and subside with rest or treatment with sublingual nitrates. Some patients, especially those with type II diabetes mellitus, do not experience chest discomfort but complain of dyspnoea, breathlessness or tiredness. All those symptoms are related to myocardial ischemia and are anginal equivalents.

The treatment of angina and myocardial ischemia involves a number of strategies. The first step in angina management includes aggressive control of risk factors, such as smoking, hypertension, dyslipidemia, diabetes mellitus, obesity, and physical inactivity. While alterations in these risk factors may improve symptoms and reduce cardiac events, the majority of patients with chronic stable angina require specific antianginal medications. Beta-adrenergic blocking drugs are recommended as first-line therapy for patients with angina. However the cardioprotective effects of these drugs have been shown only in patients with left ventricular dysfunction and post an acute myocardial infarction. Other therapies for chronic angina include calcium channel blocking agents and nitrates, but such medical therapy often does not provide adequate symptomatic relief. A number of novel therapies are directed at angina treatment, including new pharmacologic agents, gene therapy, enhanced external counterpulsation (EECP), spinal cord stimulation, and innovations in revascularization therapy.

New pharmacologic agents. Metabolic modulators are a class of drugs with a novel approach to the treatment of myocardial ischemia and angina. During increased metabolic demands as well during myocardial ischemia, glucose oxidation is a more efficient way of generating energy high-energy phosphates (ATP) than free fatty acid oxidation. Unlike most current classes of anti-anginals, metabolic modulators are effective without having haemodynamic effects and therefore without affecting heart rate or blood pressure.

Trimetazidine, has demonstrated anti-ischemic effects in several studies of patients with angina and in patients with heart failure. Trimetazidine increases effort tolerance and delays the appearance of ischemic symptoms and electrocardiographic (ECG) changes. In addition, patient safety and tolerance with trimetazidine has been good. The efficacy of trimetazidine has also been demonstrated in patients with diabetes, who showed improved exercise capacity and duration after 4 weeks of treatment. Left ventricular dysfunction has improved during therapy with trimetazidine.

Ranolazine is another metabolic agent that inhibits free fatty acid oxidation and blocks the myocardium inward late sodium currents thereby limiting the accumulation of intracellular calcium and reducing the cellular energy expenditure. Ranolazine has been shown to improve exercise induced myocardial ischemia alone and in association with other anti-anginal drugs. Furthermore, Ranolazine has anti-arrhythmic properties that have been shown in patients with acute coronary syndromes and in patients with stable coronary artery disease. Currently studies are underway to elucidate a potential use of Ranolazine in patients with atrial fibrillation.