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Mini Review

Dual Antiplatelet Therapy in Acute Coronary Syndrome

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Abstract

Although a large volume of evidence supporting the use of dual antiplatelet therapy in patients with the acute coronary syndrome, there remains major uncertainty regarding the optimal duration of treatment. Clinical trials have varied markedly in the length of treatment. Some systematic reviews and meta-analyses assert that shorter durations of dual antiplatelet therapy are superior because the avoidance of thrombotic events is counterbalanced by the greater risks of significant excess bleeding with definite enhances in all-cause mortality with longer durations. These findings did not demonstrate remarkable heterogeneity according to whether patients had coronary artery disease. Therefore, the potential damages and benefits may differ when applied to the broad patients met in clinical practice who have notably higher complication rates. Clinicians have no definitive information regarding the duration of therapy in patients with the acute coronary disease. The clinical evidence would further clear up future research into strategies for personalized medicine.

Introduction

An unstable coronary plaque is the primary cause of the coronary syndrome. Risk period is during this early phase of plaque instability and healing, with recurrent event rates peaking in the first month. By three months, the plaque has usually stabilized, ensuring event rates return to the background rates seen in patients with stable disease [1–3]. Indeed, beyond three months, recurrent events commonly occur on plaques at other sites within the coronary circulation [3]. From first principles, the first quarter is the most critical time for interventions to decrease recurrent events after an Acute Coronary Syndrome (ACS).

Antiplatelet therapy

Thrombus formation occurs under conditions of high shear stress and is principally driven by platelet aggregation in acute coronary syndrome. Platelet aggregation during intracoronary thrombus represents the dramatic effects that antiplatelet therapies have on clinical outcomes. Aspirin was the first antiplatelet therapy which had antiplatelet effect in patients with acute coronary syndrome: such a large effect size has rarely surpassed in other domains of cardiology [4-7]. The P2Y12 receptor antagonists are a class of drugs that have obtained widespread recognition since they seem to ensure additional thrombotic protection at the expense of modest increases in bleeding.Their use is principally associated with reductions in recurrent myocardial infarction [4,5,8] and decreases in cardiovascular mortality [5,8]. Other antiplatelet therapies are available but have variable net clinical benefit.

Dual antiplatelet therapy

The effect of dual antiplatelet therapy following an acute coronary syndrome was confirmed by the trials [1,9]. Combined aspirin and clopidogrel therapy decreased the 1-year incidence of cardiovascular events by up to 20% compared with aspirin alone. More potent P2Y12 receptor inhibition with either prasugrel or ticagrelor was superior to clopidogrel in the many trials [4,5]. In the CHARISMA trial, (2) the addition of clopidogrel to aspirin in patients with the determined cardiovascular disease or at high risk of disorder did not decrease cardiovascular events and was related to an enhance in bleeding. There was a suggestion of improved outcomes in patients with the determined atherosclerotic disease, particularly those with a history of myocardial infarction. The PEGASUS-TIMI 54 [10] trial compared aspirin to aspirin and ticagrelor in patients with a prior infarction. At a mean of 33 months, ticagrelor (60mg) decreased the incidence of cardiovascular death and myocardial infarction. By these trials, combination antiplatelet therapy would appear to confer only a small ischemic benefit at the cost of a significant bleeding risk. European [11] and North American [12] guidelines, unlike for ACS, there is currently no evidence of a survival benefit or a reduction of thromboembolic complications with DAPT in patients with stable CAD undergoing CABG. However, there is limited evidence suggesting that the use of DAPT in patients with stable CAD mitigates the risk of vein (but not arterial) graft occlusions.

Duration of dual antiplatelet therapy

Clinical trials: Current European [13] and North American [12] guidelines advise continuing dual antiplatelet therapy for one year following an acute coronary syndrome. These recommendations are made by early studies [4,5,14,15] showing increased risk of thrombotic complications, including stent thrombosis, beyond six months. But, the largest absolute reductions in cardiovascular events with dual antiplatelet therapy are seen in the first quart er, and since these studies, advances in drug-eluting stent technology have led to a substantially reduced incidence of stent thrombosis [16]. Briefer times of dual antiplatelet therapy (3 months to 6 months) were non-inferior to 12 [17–22] months or 24 [23] months of treatment about either a composite of cardiovascular events or cardiovascular events plus major bleeding in some new trials. Therefore, all of the trials involved patients with an acute coronary syndrome and no heterogeneity in treatment effect between stable and unstable disease observed. There remains a residual risk of atherothrombotic complications [24], and some studies have examined whether extended dual antiplatelet therapy (>12months) following percutaneous coronary intervention may be beneficial.Prolonged treatment with dual antiplatelet therapy (18–30 months vs. 12 months) neither decreased the incidence of cardiovascular events nor enhanced the risk of major bleeding in trials [25,26]. Among those patients presenting with an acute coronary syndrome, primary and secondary ischemic end points did not differ from the global population. In the DAPT trial, [27] extended dual antiplatelet therapy (30 months vs. 12 months) decreased the risk of major adverse cardiovascular events, myocardial infarction, and stent thrombosis but at the cost of enhanced moderate or severe bleeding and a minimal rise in mortality (2.0% vs. 1.0%; p=0.05). Therapy effect did not differ between patients with or without a history of myocardial infarction for any of the coprimary end points including bleeding.

Meta-analyses trials using dual antiplatelet treatment in patients receiving intracoronary stents have contrasted short (3–6 months), 12-month and prolonged (>12months) durations of treatment [28,29]. Longer periods decreased the incidence of myocardial infarction and stent thrombosis but at the cost of enhanced major bleeding and with a tendency to increase overall mortality because of an increase in noncardiovascular death. But, the majority of patients involved in analyses had stable coronary artery disease and few patients with acute coronary syndrome treated with ≤6months of dual antiplatelet therapy. In a recent meta-analysis that contained only patients with a history of the acute syndrome, prolonged dual antiplatelet therapy decreased the risk of cardiovascular death without an enhance in noncardiovascular death or all-cause mortality [30].

Duration suspence: There are variations in dual antiplatelet therapy practices that are confusing for patients, primary care physicians and cardiologists. Indeed, while European (13) and North American(12) guidelines advise dual antiplatelet therapy for 12 months after an acute coronary syndrome. Duration of treatment is seen as a top priority for future research by many guideline committees as well as having significant financial effects.But, major pharmaceutical companies have to date not funded trials comparing shorter . Newer generation P2Y12 inhibitors ensure more effective antithrombotic protection than clopidogrel but at the cost of enhanced bleeding. Given these agents and the remarkable temporal reduce in thrombotic risk that is obvious over the first few months, an early 'switch' from ticagrelor or prasugrel to clopidogrel after one month to 6 months has been advocated. While evidence from the RCT reduced bleeding events [31]. TROPICAL-ACS (NCT 01959451) is an ongoing clinical trial investigating whether a switch to clopidogrel treatment after one week of prasugrel is non-inferior to 12 months of standard treatment with prasugrel. Results from this and other similar randomized studies (SWAP-4, NCT 02287909) should ensure insights into defining the best strategy for switching between P2Y12 antagonists.

Conclusions

It has been 15 years since the CURE trial showed the profit of dual antiplatelet therapy following an acute syndrome and yet the optimal time remains uncertain. About thrombotic complications, recent clinical trials and meta-analyses suggest that with newer generation drug-eluting stents, three months to 6 months of dual antiplatelet therapy is non-inferior to 12 months of treatment. Prolonged treatment (>12months) decrease the risk of stent thrombosis, myocardial infarction, and possibly cardiovascular death but at the cost of enhanced major bleeding and with no net mortality benefit. However, these potential hazards and benefits of intervention may differ when applied to the broad general population of patients encountered in everyday practice who have higher bleeding and atherothrombotic event rates. While ongoing randomized clinical trials may address some of the residual uncertainties in select subgroups, we believe there is a pressing stand undertake a full inclusive trial of shorter durations of therapy in broad populations of patients with the acute coronary syndrome. Such a test will need to be able to explore specific subgroups, such as those who are medically managed, undergoing percutaneous coronary intervention or have coronary artery bypass graft surgery, as well as permit better identification of atherothrombotic and bleeding risks from real world data to inform a more personalized approach to decisions regarding treatment duration.

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