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Current strategies in antiplatelet therapy — Does identification of risk and adjustment of therapy contribute to more effective, personalized medicine in cardiovascular disease?

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ABSTRACT

There is a wide consensus that intensified antiplatelet therapy contributes to the reduction of major atherothrombotic complications in cardiovascular (CV) disease. In the setting of PCI (percutaneous coronary intervention) and acute coronary syndromes, dual antiplatelet therapy at optimal dosing and timing has significantly lowered the risk of thrombotic complications. There is a growing body of evidence that there is variability in response to antiplatelet treatments and this represents a potentially important clinical problem. Understanding the mechanisms underlying this phenomenon is important in improving patient care, but due to the diversity of factors involved, a clear predictive model for responsiveness to antiplatelet therapy is still missing. Attempts have been made to characterize the efficacy of antiplatelet therapy using platelet function testing but based on current information, its routine use is not recommended particularly as costs and cost effectiveness have not been established and agreement between laboratory methods is lacking. Hence, it is necessary to identify risk factors for decreased efficacy of standard antiplatelet drug treatment. It may be useful to adjust antiplatelet therapy based on individual risk assessment, especially as new platelet inhibitors are being introduced or are in development including prasugrel as well as the non-thienopyridines, ticagrelor, elinogrel, the ATP analog cangrelor, and thrombin receptor antagonists. This article focuses on antiplatelet therapy in patients at high risk for cardiovascular events and discusses the options for individual risk assessment and strategies to personalize therapy in the light of the large number of recent developments.

Contents

Abbreviations: ACC, American College of Cardiology; ACS, Acute Coronary Syndrome; ADP, Adenosine Diphosphate; AHA, American Heart Association; ASA, Acetylic Salicylic Acid; ATP, Adenosine Triphosphate; AUC, Area Under the Curve; BMS, Bare Metal Stent; CAD, Coronary Artery Disease; COX1, Cyclooxygenase-1; CV, Cardiovascular; CYP, Cytochrome P450; DES, Drug Eluting Stent; ESC, European Society of Cardiology; GWAS, Genome Wide Association Studies; GPIIb/IIIa, Glycoprotein IIb/IIIa; LTA, Light Transmittance Aggregometry; MEA, Multiple Electrode Aggregometry; NSAIDS, Nonsteroidal Antiinflammatory Drugs; NSTE-ACS, Non ST elevation ACS; NSTEMI, Non ST elevation Myocardial Infarction; NICE, National Institute of Health and Clinical Excellence; PCI, Percutaneous Coronary Intervention; PAR, Protease activated receptor; PFA-100, Platelet Function Analyser-100; PRU, Platelet Reactivity Units; RPA, Residual Platelet Aggregation; STEMI, ST Elevation Myocardial Infarction.

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1. Introduction

There is a progressive shift towards questioning the "one-size-fits-all" concept of antiplatelet therapy for secondary prophylaxis in cardiovascular (CV) disease. This is due to the following major issues:

1. Increasing information exists that there are some patient subgroups in whom the efficacy of dual antiplatelet therapy does not meet expectations.
2. Monitoring of antiplatelet drug responsiveness has gained attention and a link between the observed variability of responsiveness to antiplatelet agents and adverse cardiovascular outcome has been established. Prompted by this guidelines allow for the consideration of the use of platelet function testing in patients at high risk for stent thrombosis. Although previous studies generally support that drug efficacy might be influenced by a broad interindividual response variability affected by several mechanisms, monitoring of platelet function has certain limits to its integration into routine therapeutic decision making. In particular, there is no consensus regarding the most appropriate cut-off value for any one single method to predict major CV risk and there is only a moderate correlation between different assays.
3. The use of percutaneous coronary interventions has increased throughout the last several years. Additionally, the overall risk of interventionally treated cardiovascular patients has significantly changed and with this the risk for stent thrombosis and major ischemic events after PCI. Thus, more intensified antiplatelet and antithrombotic regimens are needed, but with them comes the potential costs of increased bleeding rates. A careful weighing of benefits and risk is therefore warranted to improve the individual net outcome.

2. Antiplatelet treatment in different risk groups

2.1. Dual antiplatelet therapy for primary and secondary prevention in patients without recent PCI

There was no benefit of dual antiplatelet therapy with clopidogrel and aspirin over aspirin alone in the primary prevention cohort of the CHARISMA trial, and subgroup analysis revealed a higher mortality and bleeding risk with the addition of clopidogrel to aspirin therapy in asymptomatic patients (Bhatt et al., 2006; Wang et al., 2007). The CHARISMA primary prevention cohort also comprised a high percentage of diabetics. Thus, for the moment there is no evidence for a benefit of dual antiplatelet therapy in diabetics for primary prevention. However, there was a significant effect on risk reduction for recurrent cardiovascular events in the subgroup of patients with established cardiovascular disease enrolled in the CHARISMA study (Bhatt et al., 2007). These results suggest that appropriate patients with established cardiovascular disease might benefit from a more aggressive antiplatelet regimen for chronic treatment. This may be the addition of clopidogrel to aspirin as demonstrated in the symptomatic cohort of patients from CHARISMA or even clopidogrel alone instead of aspirin as shown in the CAPRIE trial (reference) (CAPRIE Steering Committee, 1996), or the use of new antiplatelet agents either instead of or in combination with aspirin for long-term protection.

2.2. Antiplatelet therapy in PCI

Long-term dual antiplatelet therapy as well as sufficient pre-treatment with clopidogrel has been shown to reduce subsequent cardiovascular events after PCI (Mehta et al., 2001; Steinhubl et al., 2002).

Current guidelines advocate a dual antiplatelet therapy with aspirin and clopidogrel for up to 12 months depending on type of stent and acuity of disease and favour continuation beyond this time period according to individual risk assessment (King et al., 2008). More rapid acting and reversible novel antiplatelet substances might show particular advantage in the setting of acute coronary syndromes (ACS).

There has been no discussion in the use of GPIIb–IIIa inhibitors which are a mainstream class of anti-platelet therapy used in ACS and PCI patients.

The rationale for general peri-procedural administration of glycoprotein (GP) IIb/IIIa inhibitors in the era of high dose thienopyridines has been called into question by the results of some trials. In the ISAR-REACT 2 trial the benefit of peri-interventional GP inhibition with abciximab was restricted to higher risk non-ST-elevation ACS patients presenting with significant elevation of cardiac markers (Kastrati et al., 2006). Additionally, GPI treatment showed a benefit mainly in patients with ACS undergoing PCI (Roffi et al., 2002) rather than in conservatively treated patients (Simoons et al., 2001). Thus the current practice guidelines provide support for the use of GPIIb/IIIa inhibitors in addition to aspirin and heparin rather than aspirin and heparin alone in high risk ACS patients undergoing PCI. The bleeding risk of this combination is particularly noteworthy and the net clinical benefit of heparin and GPI treatment has been shown to be lower compared to single treatment with the direct thrombin inhibitor bivalirudin in high risk non-ST elevation ACS and STEMI patients undergoing primary PCI (Stone et al., 2006, 2008). Optimal timing of GPI administration is a further issue to be resolved. Recent studies have evaluated the benefits of pre-hospital and pre-angiography administration of GPIIb/IIIa-inhibitors. The ON-TIME 2 (Ongoing Tirofiban in Myocardial Infarction Evaluation) study evaluated the effects of early provisional treatment with tirofiban given to STEMI patients in the ambulance. As results, high-bolus dose tirofiban was associated with increased ST-segment resolution and better clinical outcome after PCI (Van't Hof et al., 2008) According to the results of the FINESSE, EARLY-ACS and ACUITY-timing trials there is currently no evidence of a benefit of upstream GPIIb/IIIa antagonism in NSTE-ACS patients who receive guideline adherent treatment, before the coronary anatomy is known and a decision upon PCI is made (Ellis et al., 2004; Ellis, 2007; Stone et al., 2007; Giugliano et al., 2009).

3. Identification of optimal timing of clopidogrel cessation dependent on individual risk

Duration of treatment with dual antiplatelet therapy (aspirin and a thienopyridine) is frequently determined by the perceived individual risk for stent thrombosis. The critical role of maintaining adequate durations of dual antiplatelet therapy is highlighted by the large number of studies identifying premature discontinuation of antiplatelet therapy as a major driver for stent thrombosis. Compared with bare-metal stents (BMS), drug-eluting stents (DES) result in markedly reduced neointima formation and late lumen loss but also in delayed endothelialisation and increased inflammation which might prolong the window of susceptibility to stent thrombosis (Joner et al., 2006). Thus, the FDA along with the American Heart Association/American College of Cardiology (AHA/ACC) recently updated PCI guidelines and empirically recommended the use of clopidogrel for at least 12 months in patients without increased bleeding risk, on a Class I, Level of Evidence B indication. Clopidogrel use beyond 1 year was conferred a Class IIb, Level of Evidence C indication. There does appear to be an important relationship between the duration of dual