Conference Paper

Antithrombotic Therapy in Patients with Acute Coronary Syndromes: Biological Markers and Personalized Medicine

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Antithrombin and antiplatelet therapies have been in the focus of pharmacological developments over recent years with an increasing number of anticoagulants and antiplatelets becoming available. While these drugs share common pharmacological characteristics (i.e., antiplatelet drugs binding to the P2Y₁₂ receptor), they also differ substantially regarding metabolism, type of receptor binding, clinical end points that have been reduced as compared to the current gold standard, and, consequently, the spectrum of indication. These differences pose the need and, above that, great chances for therapy personalization. Understanding the challenges and opportunities that arise from the use of biological markers in guiding antiplatelet therapy is mandatory to provide best medical practice for patients with acute coronary syndromes.

1. Introduction

The management of patients with acute coronary syndromes requires a number of decisions including risk stratification, treatment strategy, and selection of appropriate drugs that have to be made within a short period of time. Emergency services and hospitals, therefore, have to standardize a number of key processes in order to provide best medical care. This is also the case for the appropriate use of novel antiplatelet drug like prasugrel and ticagrelor. Biological markers like laboratory values (i.e., glucose, creatinine) and classical biomarkers like troponins are helpful in identifying the appropriate clinical indications for an individual drug and are also capable of identifying those patients who benefit the most from a specific drug (“gradient of benefit”). Over the last decades, the prognosis of patients with acute coronary syndromes (ACS) has improved dramatically by optimization of pre- and in-hospital processes, risk stratification, treatment strategies, and medication. Balancing chances and risks of personalized medicine as well as standardization of key processes currently poses one of the greatest challenges in the treatment of patients with acute coronary syndromes.

2. Clopidogrel: The Rise and Fall of a Gold Standard

Thienopyridines have significantly improved clinical results after implantation of coronary stents. Initially, antiplatelet therapy with aspirin in combination with the Ticlopidine has been shown to be superior to either aspirin alone or aspirin and anticoagulation with warfarin [1]. Ticlopidine treatment, however, has been shown to be limited by its potential severe gastrointestinal and hematological adverse effects with neutropenia constituting a life-threatening complication. The ADP receptor antagonist clopidogrel, in contrast, did not only exhibit much less side effects. In the large CURE study Clopidogrel in combination with aspirin was also tested against aspirin alone in patients with non ST-elevation acute coronary syndromes, irrespective of the initial treatment strategy (medically or invasively) [2]. As a result, clopidogrel in addition to aspirin, for more than one decade, represented the gold standard for patients with stable coronary artery disease and acute coronary syndromes undergoing coronary stent implantation as well as those patients with acute coronary syndromes that were treated conservatively.

FIGURE 1: Clopidogrel: a gold standard perishes. Goldfinger, Ian Flemming, 1964.

FIGURE 2: Gradient of benefit: “diabetes.” Wiviott et al. circulation 2008 [7]. Kaplan-Meier curves for prasugrel versus clopidogrel stratified by diabetes status. (a) Primary efficacy end point (cardiovascular death/nonfatal MI/nonfatal stroke) stratified by diabetic status. (b) MI (fatal or nonfatal).

FIGURE 3: Gradient of benefit: renal function. James et al. *circulation* 2010 [8].

In 2007 and 2009, however, two novel P2Y₁₂ receptor antagonists, prasugrel and ticagrelor, were tested against Clopidogrel in patients with acute coronary syndromes. Both studies, the TRITON TIMI 38 trial using Prasugrel [3] and the PLATO trial testing Ticagrelor [4], proved superiority against clopidogrel. As a result, clopidogrel cannot be regarded the gold standard in patients with acute coronary syndromes anymore (Figure 1) as also reflected in the current guidelines of the European Society of Cardiology [5, 6].

3. Gradient of Benefit in Antiplatelet Therapy: Guidance by Biological Markers

Although both studies, TRITON TIMI 38 and PLATO, did show superiority of prasugrel and ticagrelor as compared to clopidogrel, respectively, certain patient populations with high-risk characteristics (i.e., diabetes, renal impairment) benefit more than others. These clinical conditions can easily be identified by biological serum markers like glucose, HbA_{1c} or creatinine.

Diabetics are at an increased risk for developing coronary artery disease and acute coronary syndromes. In both settings, diabetic patients always demonstrate a worse outcome as compared to nondiabetics. Of particular interest in this context is the increased platelet reactivity in diabetics potentially requiring a more aggressive antiplatelet regimen. Indeed, a sub-analysis of the TRITON TIMI 38 trial has shown a greater reduction of the primary end point (cardiovascular death, myocardial infarction, stroke) as well as myocardial infarction with prasugrel as compared to clopidogrel in diabetic patients with acute coronary syndrome [7]. Furthermore, the numerically greatest gradient of benefit with a relative risk reduction (RRR) of 37% for the primary end point showed diabetics on insulin treatment as compared to a RRR of 26% in diabetics not being on insulin treatment. Nondiabetics, in contrast, showed a 10.6% risk for cardiovascular death, myocardial infarction, or nonfatal stroke under clopidogrel therapy as compared to 9.2% (RRR 14%) when treated with prasugrel in addition to aspirin (Figure 2).

Impaired renal function—even when mild in nature—is associated with worse clinical outcomes (i.e., death, myocardial infarction) in patients with acute coronary syndromes. Furthermore, the bleeding risk is potentially increased, thus altering the risk-benefit ratio of antiplatelet therapies. In the landmark PLATO trial, ticagrelor as compared to clopidogrel, reduced the risk for cardiovascular death, myocardial infarction and stroke by 16%. Even more important, ticagrelor also resulted in a reduction of all-cause mortality by relative 22%. In the subgroup of patients with chronic kidney disease, ticagrelor compared with clopidogrel significantly reduced ischemic end points and mortality without a significant increase in bleeding events. Interestingly, there was a non-significant trend towards a higher gradient of benefit with decreasing renal function for both, the primary end point and all-cause mortality [8] (Figure 3).

4. Indication for New Antiplatelet Drugs

Classic biomarkers like troponins do also play a role in the context of personalized use of antiplatelet drug. Prasugrel for example, as compared to Ticagrelor and even clopidogrel, is not approved in patients with acute coronary syndromes who are managed medically even when they underwent diagnostic coronary angiography.

It is well documented that patients with high-risk characteristics like a GRACE score above 140 or high troponin levels benefit more from early invasive management than those without a high-risk profile [9]. Troponins, therefore, are pivotal in the risk stratification process of patients with ACS and can help to identify those patients who should be primarily managed medically. In addition, only 50–75% of patients who undergo early coronary angiography receive a coronary intervention. In these cases, which account for more than 50% of all patients with non-ST elevation ACS, ticagrelor and clopidogrel for example are both approved, but prasugrel is not.

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