アスピリン反応性を追加することによりクロピドグレルの予測値が上昇する

RECLOSE 2-ACS:クロピドグレルとアスピリン両者の血小板反応性を計測した方がクロピドグレル単独の反応性を計測するよりもよい

RECLOSE 2-ACS: Measuring platelet responsiveness to both clopidogrel and aspirin is better than measuring response to clopidogrel alone

虚血性イベント高リスクの急性冠症候群(ACS)患者を見極めるにはクロピドグレルのみへの有効性を計測するよりも血小板全体の反応性を計測した方がより有効であるとの研究結果が2012年ESC学会で発表された。Responsiveness to Clopidogrel and Stent thrombosis 2-ACS (RECLOSE 2-ACS)スタディは、経皮的冠動脈インターベンションを施行された急性冠症候群1,789人を対象とした前向き、観察、紹介施設コホートスタディである。研究者らはアスピリンおよびクロピドグレルに対する血小板反応性を計測した。その結果約20%の患者がアスピリンに対し高血小板反応性を有し、したがって非反応者であった。これらの患者は2年後の経過観察時に虚血性イベントや心臓死などの率が有意に高かった(主要な心臓有害事象[MACE]:HR=1.4[1.0-1.8]; *P* <0.04、心臓死:HR=1.7 [1.2-2.6]; *P* =0.004)。約9%の患者においてクロピドグレルとアスピリン両者に対し血小板反応性が高かった(つまり非反応者)。このフェノタイプは全体的高血小板反応性(GHPR)として知られる。GHPRは心血管虚血性イベントおよび心臓死と有意に関連する(MACE: HR=1.5[1.0-2.2]; *P* =0.02、心臓死: HR=1.9[1.2-3.2]; *P* =0.008)。GHPRを有する患者はこれを有さない患者よりもMACEからの生存率が低く(*P* =0.001)、心臓死率が高かった(*P* <0.0001)。

Full Text

Global platelet reactivity is more effective than responsiveness to clopidogrel in identifying acute coronary syndrome (ACS) patients at high risk of ischemic events, according to research presented at the ESC Congress 2012. The results from the RECLOSE 2-ACS study were presented at the ESC Congress 2012 by Dr. Rossella Marcucci from Italy.

The Responsiveness to Clopidogrel and Stent thrombosis 2 – ACS (RECLOSE 2-ACS) study is a prospective, observational, referral center cohort study of 1,789 patients with acute coronary syndromes undergoing percutaneous coronary intervention (PCI) at the Division of Cardiology, Acreage Hospital, Florence, Italy.

Dual antiplatelet therapy with aspirin and clopidogrel is the cornerstone of therapy in these patients to improve prognosis and reduce adverse cardiovascular events, stent thrombosis and cardiovascular death.

"In recent years, we and other groups have focused our attention on the role of platelet inhibition," said Dr. Marcucci. "We found that a significant percentage of patients on clopidogrel therapy – the so-called nonresponders to clopidogrel – had a high platelet reactivity (HPR) on clopidogrel and a significantly higher risk of developing an adverse ischemic event at a follow-up of 2 years."

A number of genetic and acquired conditions are associated with a high platelet reactivity on clopidogrel. Carriers of a genetic variant (the CYP2C19*2 polymorphism), diabetics, older patients, females and patients with a reduced renal and cardiac function have a higher risk of maintaining a high platelet reactivity on clopidogrel. In addition, the concomitant use of drugs such as proton pump inhibitors (PPIs) is associated with a reduced metabolization of clopidogrel (which is a prodrug and needs to be metabolized to the active drug by the liver) and a high risk of high platelet reactivity.

The aim of the current study was to evaluate whether a high platelet reactivity due to nonresponsiveness to aspirin could also identify ACS patients at high risk of ischemic events. The investigators also evaluated whether the combination of aspirin and clopidogrel nonresponsiveness could identify high risk patients more effectively than one measure alone.

The researchers measured platelet reactivity in response to aspirin and clopidogrel in patients enrolled in the RECLOSE 2-ACS study. They found that approximately 20% of patients had a high platelet reactivity to aspirin and were therefore nonresponders. These patients had a significantly higher prevalence of an ischemic event or cardiac death at the 2 year follow-up (major adverse cardiac events [MACE]: Hazard Ratio [HR]=1.4 [1.0-1.8], p<0.04; Cardiac death: HR=1.7 [1.2-2.6],p=0.004).

The researchers calculated the net reclassification index (NRI), which is a method to define whether the addition of a new parameter increases the predictive value. Dr. Marcucci said: "We found that adding the response to aspirin to the response to clopidogrel enabled us to recognize a higher number of patients at risk of ischemic events and cardiac events."

Approximately 9% of patients had high platelet reactivity (ie were nonresponders) to both clopidogrel and aspirin. This phenotype is known as global high platelet reactivity (GHPR).

GHPR was significantly associated with cardiovascular ischemic events and cardiac death in a Cox regression analysis (MACE: HR=1.5[1.0-2.2], p=0.02; cardiac death: HR= 1.9[1.2-3.2], p=0.008). The analysis was adjusted for age, sex, body mass index, smoking, diabetes, hypertension, hypercholesterolemia, history of myocardial infarction, serum creatinine higher than 1.5 mg/dl, left ventricular ejection fraction <40%, Killip class III or IV at admission, 3-vessel coronary disease, use of drug eluting stents, total stent length, multivessel PCI and use of abciximab.

Patients with GHPR have lower survival rates from MACE (p=0.001) and cardiac death (p<0.0001) than patients without GHPR.

Dr. Marcucci said: "These results show that global high platelet reactivity is the most effective parameter for identifying ACS patients at high risk of ischemic events."

She added: "This shifts the focus of risk stratification from response to clopidogrel to assessing response to both clopidogrel and aspirin. Responsiveness to both antiplatelet drugs should be assessed in all patients with ACS in order to identify and reduce their risk of ischemic events."

Conference News