EDITORIAL

Secondary prevention of coronary artery disease – what is new?

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Coronary artery disease (CAD) remains an important cause of morbidity and mortality worldwide. Despite the lifestyle modification and the cardioprotective medicines given, patients with known CAD are at greater risk for new events[1].

It seems that the increased risk is explained partly by mechanisms which involve the endothelial injury caused by the inflammation of the coronary arteries and of the entry of oxidatively modified LDL cholesterol into the artery wall[2].

Large scale studies, such as the Euroaspire surveys[3], conducted across the European continent, have evidenced that despite lifestyle changes and protective medical therapy, the potential risk for cardiovascular events, remains high, since the traditional predisposing conditions related to coronary artery disease such as lipids, diabetes, smoking, obesity and hypertension, are largely not satisfactorily managed.

The need therefore for new studies and new medicines, to further influence favourably the progress of coronary artery disease and to prevent new events, is high.

In this context the results of some well designed clinical studies which tested the influence of new medicines on cardiovascular events, in patients with established coronary artery disease, are discussed.

PEGASUS-TIMI 54, was a randomized double-blind trial, which tested the effects of ticagrelor (90 mg bid and 60 mg bid) among 21,162 clinically stable patients with history of myocardial infarction, who were already receiving aspirin. After 33 months of follow up, ticagrelor was found to reduce significantly the risk of cardiovascular death, myocardial infarction or stroke at a cost of an increase in the risk of major bleeding[4].

The COMPASS study, compared the effects of the new anticoagulant, Rivaroxaban, given alone at a dose of 5 mg bid or 2.5 mg bid in combination with Aspirin 100 mg, or Aspirin 100 mg given alone, on cardiovascular events (CV death, MI, stroke) among 27,395 patients with stable cardiovascular disease. After a mean follow up period of 23 months it was found that the best cardiovascular outcome was among patients assigned to rivaroxaban 2.5 mg bid plus aspirin 100 mg, at the cost of somewhat more major bleeding complications[5].

The FOURIER trial, addressed the LDL and specifically it studied the effects of the human monoclonal antibody Evolocumab, a Proprotein Convertase Subtilisin-Kexin type 9 (PCSK9) inhibitor, in 27,564 patients aged 40-85 years, with chronic cardiovascular disease (MI, stroke, PVD) and LDL cholesterol levels of 70 mg/dL or higher. Evolocumab was given subcutaneously at a dose of 140 mg every 2 weeks or 420 mg once a month. The median baseline LDL cholesterol was 92 mg/dL. After 48 weeks a reduction in LDL levels of 59% was observed and this was maintained over time. The risk of myocardial infarction, stroke and coronary revascularization, was significantly reduced by evolocumab, but the overall and the cardiovascular mortality were not influenced[6].

A second trial, the ODYSSEY, studied the human monoclonal antibody Alirocumab, in 18,924 patients with recent acute coronary syndromes (ACS) and LDL 70 mg/dL or higher, who were already on statins and or ezetimibe. Both the cardiovascular events and the all-cause

mortality were reduced by approximately 15% in the therapeutic arm[7].

More recently, the ORION-10 and ORION-11 trials, in 1561 and 1617 patients, respectively, with cardiovascular disease and elevated LDL, on maximally tolerated statin therapy, were given Inclisiran, a proprotein convertase subtilisin-kexin type 9 inhibitor, 284 mg or placebo, as subcutaneous injections, on day 1, day 90 and every six months thereafter, for 540 days. The levels of LDL were reduced by 52.3% in the ORION-10 and by 49.9% in the ORION-11 trial, with the adverse events being similar in the inclisiran and the placebo groups[8].

In order to address the relationship between the inflammatory risk and the cardiovascular events, another trial, the CANTOS, studied 10,061 patients with history of myocardial infarction, on cardioprotective therapy and with hs-CRP levels equal or greater than 2 mg/dL. The patients were given Canakinumab, an interleukin-1β antibody, which reduces among others the CRP. After a median time of 3.7 years, a dose–dependent reduction in hs-CRP was achieved and this was related with a reduction of cardiovascular events but not of cardiovascular or overall death[9].

In conclusion, secondary prevention may include other than the traditional treatments with β-blockers, ACE inhibitors, aspirin and statins, which have definitely proved their usefulness in reducing events and cardiovascular mortality. The trials discussed in this, evidenced that new drugs, addressing either the atherogenic LDL cholesterol or the inflammatory C- Reactive Protein, can be used in addition to the traditional treatment, to achieve further reduction in the cardiovascular events. This opens a new horizon in the difficult task of the secondary prevention of coronary artery disease.

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