

Cardioprotective Effect of Rosuvastatin under Conditions of Normocholesterolemia and Hypercholesterolemia

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Cardiovascular disease (CVD), including ischemic heart disease, is the most important cause of mortality worldwide in men and women. Mortality rates have decreased during the last years in developed countries; nevertheless, this reduction has not occurred in developing countries, such as Argentina, where the situation is even worse taking into account poor eating habits. The incidence of CVD differs among the different communities, and is greater in men between 55 and 65 years old. In Argentina, CVD is the cause of more than 30% of deaths and physical disabilities related to the after effects of ischemic heart disease. (1)

Myocardial infarction occurs when coronary blood flow decreases as a consequence of an obstruction in the coronary arteries, resulting in impairment in heart muscle. In 95% of the cases, this obstruction is produced by the disruption of an atherosclerotic plaque. (2) Prevention should begin before the occlusion of the artery. Atherosclerosis starts in childhood when cholesterol deposits in the arteries increase and, according to the genetic pattern, blood pressure and glycemia may also rise; habits such as smoking, diet and exercise affect the outcomes. Then, controlling these risk factors is the key to prevent CVD from establishing or progressing. (3) Several studies, as the Framingham Heart Study, have demonstrated that high cholesterol levels have a linear association with the risk of myocardial infarction or stroke. (4) In the last 10 years, new evidence has showed that the reduction and normalization in cholesterol levels produce a significant reduction of these events. The last survey performed by the Ministry of Health informed that 27% of the Argentinean population presents high cholesterol levels. (5) Few people are aware of serum cholesterol levels and of blood pressure values. It is currently known that its reduction and normalization may not only decrease the possibility of a myocardial infarction, but may also produce atherosclerosis regression. It is important to remark that myocardial infarction is a medical emergency and its outcomes depend mostly on a rapid diagnosis and onset of treatment.

HMG-CoA reductase inhibitors (statins) have been used for the treatment of hypercholesterolemia for more than 20 years. (6) Therapy with statins has proved to produce a significant reduction in the risk of ischemic heart disease in people with this condition or without it, within a wide range of serum cho-

lesterol levels. These inhibitors are the principal tool for primary and secondary prevention of CVD. (8) One of the most important effects of statins is the reduction of low-density lipoprotein-cholesterol (LDL-C). Even more, these inhibitors also affect other lipid variables related with the risk of CVD, such as high-density lipoprotein-cholesterol (HDL-C) and triglycerides. It is believed that the clinical use of statins is related to the effects it exerts on cholesterol levels. Nevertheless, several studies have demonstrated that statins have beneficial cardiovascular effects that might be independent of cholesterol reduction. (8-10) During the last years rosuvastatin, a new statin, has come out into the market. Like other statins, rosuvastatin also induces beneficial effects on multiple target organs – pleiotropic effects - which might be independent of its hypolipidemic action. (11) These effects improve endothelial function, cardiovascular function and neural function. (12) A few experimental papers have suggested that statins exert a protective role on myocardial ischemia-reperfusion injury. Bulhak et al demonstrated that rosuvastatin reduces the infarct size induced by ischemia/reperfusion via a mechanism unrelated to cholesterol lowering which involves nitric oxide. (13) In addition, these authors have proved that the inhibition of the synthesis of isoprostanooids might also be involved in the cardioprotective effect of statins. These findings were confirmed by Weinberg et al, who observed that the treatment with rosuvastatin reduced the infarct size 60 minutes after ischemia-reperfusion injury but not after total coronary occlusion. (14) On the other hand, Zacà et al demonstrated that chronic therapy with high doses of rosuvastatin prevented progressive left ventricular dysfunction and remodeling in dogs with heart failure. The improvement in ventricular function might be attributed to the normalization in the expression of tumoral necrosis factor, at least in part. (15)

A large bibliography shows that pretreatment with rosuvastatin reduces the infarct size after ischemia-reperfusion injury and improves ventricular function. Nevertheless, there is few experimental evidence of this effect when rosuvastatin is administered during reperfusion. In consequence, the study by Lorenzo Carrión et al (16) is original, as their results confirm the cardioprotective effects of rosuvastatin and dem-

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onstrate that the drug reduces the infarct size when it is administered in normocholesterolemic and hypercholesterolemic animals during reperfusion. Interestingly, the authors assessed the presence of hypercholesterolemia, as 30-40% of patients with ischemic heart disease present certain degree of increased levels in serum cholesterol. Even more, they demonstrated a significant improvement in contractile status and a less increase in myocardial stiffness only in the hearts of hypercholesterolemic animals. These findings suggest that this effect might be related to a greater reduction in the infarct size compared to normocholesterolemic animals. The study by Lorenzo Carrión et al assessed not only the primary efficacy of rosuvastatin (as a statin it lowers cholesterol levels) but also its probable secondary efficacy (a reduction in cardiovascular morbidity and mortality). Finally, the findings of this paper are of clinical interest as the intervention is performed during the period of reperfusion, once the ischemic event has begun, and this cardioprotection might be extrapolated to the clinical practice, especially in patients submitted to reperfusion therapies. These interesting results open a way in the explanation of the pathophysiological mechanisms involved in the regulation of cardiovascular function. The scientific community should focus its efforts on healthy populations, especially children and adolescents, remarking the benefits of healthy habits in order to prevent cardiovascular disease in the future.

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