

Rosuvastatin Prevents Aortic Stenosis Associated with Renovascular Hypertension in an Animal Model: a New Piece to the Unsolved Puzzle.

EDUARDO FRANCO, JOSÉ L. ZAMORANO

Statins hold beneficial effects independent from their lipid-lowering effect. These so called “pleiotropic effects” (due to their work at several phenotypic levels), that involve multiple fields in medicine, may not be really cause of their work at multiple levels, but the expression of the decrease in cholesterol in cell membranes produced by plasma cholesterol reduction and the decrease in the concentration of isoprenoid metabolites that synthesizes the target enzyme of statins (3-hydroxy-3-methylglutaryl-coenzyme A reductase). (1) Changes in lipid concentration of cell membranes involve modifications in cell signalling, while the reduction of isoprenoids in the cytoplasm involves a low regulation of certain intermediates of biochemical vias of atherosclerosis and intravascular thrombosis (mainly Rho and Ras). (2)

Concerning cardiovascular health, the main pleiotropic effect of statins is the ability to stabilize and stop the progression of atheromas. (3) ASTEROID study (4) demonstrated that one dose of rosuvastatin of 40 mg/day in patients with atheromas in coronary arteries (with luminal stenosis of about 20% and 50%) produced a regression of up to 6.8% of the volume of the atheromas (quantified through intravascular ultrasound). In Table 1 the main pathophysiological mechanisms that explain the atheroprotective properties of statins are mentioned. (1)

This atheroprotective role would be the theoretical basis for a possible beneficial effect of statins on aortic stenosis. Calcified aortic stenosis share risk factors with atherosclerosis (elevation in LDL cholesterol levels and lipoprotein “a”, diabetes, nicotine, hypertension) (5) and nowadays it is believed that the pathophysiological process which produces both pathologies is similar; (6) thus, a cumulus of subendothelial aortic C-LDL would recruit an infiltration of T lymphocyte and macrophages that would induce the transformation of aortic fibroblasts in myofibroblasts with osteoblastic phenotype, able to form bone and calcium nodes. (7) This mechanism could also explain calcification at mitral ring level that in many occasions accompanies calcified aortic stenosis. (8) However, despite the theoretical frame, the available scientific evidence could not demonstrate if statins treatment is able to stop or at least slow the progression of calcified aortic stenosis. Between

2001 and 2004 several retrospective studies showing a reduction in the progression of calcified aortic stenosis (according to echocardiographic parameters) in patients treated with statins with regard to patients with no treatment were published. (9) One of the studies also showed that that effect was independent of the concentration of plasma C-LDL, (10) suggesting a pleiotropic benefit of statins treatment.

Another study, this one prospective but non randomized (RAAVE study), (11) included 121 patients with moderate to severe aortic stenosis; those with elevated C-LDL and indication to receive statins received 20 mg/day of rosuvastatin (61 patients), the rest did not receive treatment. After a follow-up of 6 years, rosuvastatin treatment demonstrated that it decreases the progression, through echocardiographic assessment, of aortic stenosis.

In order to confirm the findings described by the observational studies mentioned, controlled and randomized clinical trials have been performed; the available evidence came from retrospective series or from a limited number of patients and so it was subject to a probability of significant bias. SALTIRE study (12) included 155 patients with asymptomatic aortic stenosis and randomized them to receive 80 mg/day of atorvastatin or placebo; after a follow-up of 2 years no significant differences in the primary objectives (progression of the transvalvular aortic peak velocity measured by Doppler echocardiography and increase in aortic valve calcium score measured by computed tomography) between the two groups were appreciated. SEAS study (13) included 1983 patients with mild to moderate asymptomatic aortic stenosis and assigned them to receive simvastatin + ezetimibe or placebo; the follow-up was of 4 years and no differences with the primary objective between the two groups were found (in this case, a compound clinical objective made up of cardiovascular death, unstable angina, non fatal myocardial infarction, heart failure triggered by aortic stenosis, aortic valve replacement, percutaneous or surgical coronary revascularization and non hemorrhagic ictus). The recent ASTRONOMER study (14) randomized 269 patients with aortic stenosis at least moderate to receive rosuvastatin 20 mg/day or placebo; after a 3.5-year median follow-up no significant differences

Table 1. Atheroprotective properties of statins

Atheroprotective effect	Pathophysiological mechanisms involved
Anti-inflammatory properties	↓ leukocyte adhesion
	↓ macrophage migration
	↓ metalloproteinase
	↓ cytokines (TNF- α , IL-1 β , IL-6)
Protection against endothelial dysfunction	↓ eNos activity → ↑ nitric oxide
	↓ tPA expression
	↓ endothelial expression of adhesion molecules
	↓ endothelial expression of MHC-II molecules
Decrease of platelet activation	↓ nitric oxide
	↓ thromboxane A2
	↓ endothelin-1
Stability increase of the plaque	↓ SMC apoptosis
	↓ NAD oxidase activity in SMC
	↓ migration and proliferation of SMC
	↓ lipidic "core" (a1 ↓ C-LDL)

* Adapted by Badimon L, Vilahur G. (1)

TNF- α : Tumor necrosis factor-alpha. IL: Interleukin. eNOS: Endothelial nitric oxide synthase. tPA: Tissue plasminogen activator. MHC: Major histocompatibility complex. SMC: Smooth muscle cells.

in echocardiographic parameters of aortic stenosis progression were appreciated.

In the clinical trials mentioned, the included patients did not have the indication to receive statins due to their lipid levels, so statins effect depended on their supposed pleiotropic effects. Scientific evidence indicates that statins treatment is not justified in patients with aortic stenosis and with no other indication to receive them, as in this case they do not alter the progression of the disease; however, (according to the observational studies results'), in those patients with aortic stenosis and dislipidemia, statins treatment slows the progression of aortic stenosis through a mechanism that does not depend on the reduction of plasma lipid levels.

In this issue of the Journal, Giunta et al. publish the results of a randomized pre-clinical study in a model of aortic stenosis in animals, where aortic stenosis is caused by nefrovascular hypertension. (15) In this context, rosuvastatin treatment reduced, after a follow-up of 6 months, the progression of aortic valve thickening and the reduction of the valve area; besides, those animals treated with rosuvastatin showed smaller numbers of blood pressure. Those so called "pleiotropic" effects of statins had an important role in the lower progression of aortic stenosis and in the numbers of blood pressure in the treated animals, since the results were independent of total cholesterol levels. Perhaps the pathophysiological context of nefrovascular hypertension while administering statins, with an important activation of the axis rennin-angiotensin-aldosterone, endothelial dysfunction and a proinflammatory state, may be the responsible for the improvement of endothelial function and the

inflammatory parameters determined by these drugs would be able to slow the progression of a problem (aortic stenosis) which the only cause seems to be this special context. The patients of the clinical trials published have additional risk factors, among them we can mention advanced middle age, which can justify, the absence of favourable results given that statins do not have effects on them.

So far, scientific evidence does not recommend the use of statins as a treatment of aortic stenosis. However, as it is shown in the preclinical study by Giunta et al., those patients whose known mechanism for the appearance of aortic stenosis is the presence of hypertension, mainly if they are young, perhaps they can benefit from the pleiotropic effects of statins treatment. Before proving if this theory is true, it would be necessary to perform prospective and randomized studies.

BIBLIOGRAPHY

1. Badimon L, Vilahur G. Beneficio clínico de las estatinas: ¿hemos cubierto todo el espectro? Rev Esp Cardiol Supl 2011;11(Supl B):3-13.
2. Blum A, Shamburek R. The pleiotropic effects of statins on endothelial function, vascular inflammation, immunomodulation and thrombogenesis. Atherosclerosis 2009; 203:325-30.
3. Undas A, Brozek J, Musial J. Anti-inflammatory and antithrombotic effects of statins in the management of coronary artery disease. Clin Lab 2002;48:287-96.
4. Nissen SE, Nicholls SJ, Sipahi I, Libby P, Raichlen JS, Ballantyne CM, et al. Effect of very high-intensity statin therapy on regression of coronary atherosclerosis: the ASTEROID trial. JAMA 2006; 295:1556-65.
5. Peltier M, Trojette F, Sarano ME, Grigioni F, Slama MA, Tribouilloy CM. Relation between cardiovascular risk factors and nonrheumatic severe calcific aortic stenosis among patients with a three-cuspid aortic valve. Am J Cardiol 2003;91(1):97-9.

6. Moura LM, Zamorano J, Pérez-Oteiza C, Rocha-Gonçalves F, Rajamannan NM. The role of statins in aortic stenosis. Myth or reality? *Rev Port Cardiol* 2007;26(1):51-62.
7. Rajamannan NM, Subramanian M, Rickard D, Stock SR, Donovan J, Springett M, et al. Human aortic valve calcification is associated with a osteoblast phenotype. *Circulation* 2003;107(17):2181-4.
8. Pachón M, Zamorano JL. Mitral annular calcifications and aortic valve stenosis. *Eur Heart J* 2008;29:1478-80.
9. Rajamannan NM, Otto CM. Targeted therapy to prevent progression of calcific aortic stenosis. *Circulation* 2004;110:1180-2.
10. Aronow WS, Ahn C, Kronzon I, Goldman ME. Association of coronary risk factors and use of statins with progression of mild valvular aortic stenosis in older persons. *Am J Cardiol* 2001;88:693-5.
11. Moura LM, Ramos SF, Zamorano JL, Barros IM, Azevedo LF, Rocha-Gonçalves F, et al. Rosuvastatin affecting aortic valve endothelium to slow the progression of aortic stenosis. *J Am Coll Cardiol* 2007;49:554-61.
12. Cowell SJ, Newby DE, Prescott RJ, Bloomfield P, Reid J, Northridge DB, et al. Scottish Aortic Stenosis and Lipid Lowering Trial, Impact on Regression (SALTIRE) Investigators. A randomized trial of intensive lipid-lowering therapy in calcific aortic stenosis. *N Engl J Med* 2005;352:2389-97.
13. Rossebø AB, Pedersen TR, Boman K, Brudi P, Chambers JB, Egstrup K, et al. SEAS Investigators. Intensive lipid lowering with simvastatin and ezetimibe in aortic stenosis. *N Engl J Med* 2008;359:1343-56.
14. Chan KL, Teo K, Dumesnil JG, Ni A, Tam J; ASTRONOMER Investigators. Effect of lipid lowering with rosuvastatin on progression of aortic stenosis. Results of the Aortic Stenosis Progression Observation: Measuring Effects of Rosuvastatin (ASTRONOMER) Trial. *Circulation* 2010;121(2):306-14.
15. Giunta G, Guevara E, Marziali L, Gómez Rosso L, Meroños T, Favaloro R y col. La rosuvastatina atenúa la progresión de la estenosis aórtica generada por hipertensión arterial, independientemente de sus efectos hipolipemiantes. *Rev Argent Cardiol* 2011;79:14-20.