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REVIEW ARTICLE

Statins and percutaneous coronary intervention: A complementary synergy

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Abstract The inclusion of statins and stents in coronary disease management during the 1980s has marked a dramatic change in the natural history of the disease. Separately, each of these therapies have progressed rapidly and have achieved a prime position in the current armamentarium. The simultaneous use of statins in patients undergoing percutaneous coronary revascularization procedures with stent implantation has shown a significant beneficial synergistic effect by reducing ischemia and necrosis, and improving coronary blood flow in patients with stable coronary disease, as well as in acute coronary syndromes. The use of high dose statins in conjunction with coronary angioplasty with stent implantation has shown great efficacy and safety in patients with severe coronary disease.

PALABRAS CLAVE
Enfermedad Coronaria;
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Stents;
Estatinas

Las estatinas e Intervención Coronaria Percutánea: una sinergia complementaria

Resumen La inclusión de las estatinas y stents en el manejo de la enfermedad coronaria durante la década de 1980 marcó un cambio dramático en la historia natural de la enfermedad. Cada una de estas terapias por separado han mostrado una rápida evolución y ha alcanzado una posición privilegiada en el arsenal terapéutico actual. El uso simultáneo de las estatinas en los pacientes sometidos a procedimientos de revascularización coronaria percutánea con implantación de stent ha demostrado un efecto sinérgico significativo para reducir la isquemia y necrosis, mejorando el flujo sanguíneo coronario en pacientes con enfermedad coronaria estable, así como en los síndromes coronarios agudos. El uso de estatinas dosis altas en relación con la angioplastia coronaria con implantación de stent ha demostrado una gran eficacia y seguridad en pacientes con enfermedad coronaria severa.

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Statins

The relationship between elevated serum cholesterol and coronary artery disease (CAD) was established at the end of the 1950s with the Framingham study.[1] This observation led to a wide development of new pharmacological treatments to reduce CAD mortality by reducing cholesterol. Around 1984, the NIH concluded that reducing elevated LDL-C levels with diet and medications should reduce the risk of CAD.[2]

The first 3-hydroxy-3-methyl-glutaryl-CoA (HMG-CoA) reductase, was discovered in 1970 by Akira Endo through fermentation of *Penicillium citrinum* during antimicrobial agent research.[3,4] In 1978, even though another HMG-CoA reductase inhibitor (lovastatin) was discovered through the fermentation of *Aspergillus terreus*,[5] it was not until 1982 that lovastatin was used in patients with familial hypercholesterolemia, showing a important reduction of LDL-C with a favorable safety profile.[6,7]

Around the 80s decade, large-scale, randomized, double-blind clinical studies showed the beneficial effect of lovastatin, achieving FDA approval in 1987, and becoming the first commercially available statin.[5,8,9] A 40% reduction in average LDL-C levels was obtained with maximum doses of 80 mg of lovastatin.[8–10] Other statins have been developed and are available today: simvastatin in 1988, pravastatin in 1991, fluvastatin in 1991, atorvastatin in 1994, rosuvastatin in 2003, and pitavastatin in 2009. In the mid 1990s the beneficial effect of statins in primary and secondary prevention of CAD was clearly established.[11–13] As an understanding of statins grew, percutaneous coronary intervention techniques and stents were developed in parallel.

Percutaneous coronary interventions

During the 60s decade, Dotter and Judkins proposed the concept of the percutaneous use of devices to maintain the luminal integrity of stenotic blood vessels.[14] When A. Grüentzig introduced percutaneous transluminal coronary angioplasty (PTCA) in 1977, the field of percutaneous coronary intervention was born.[15] In spite of the new technology available for the treatment of CAD, PTCA was limited by the relatively high incidence of acute vessel occlusion and the need for repeated revascularization procedures due to the phenomenon of restenosis. The introduction of bare metal stents (BMS), demonstrated an important advance in interventional cardiology.

In 1987, Sigwart et al. were the first to describe the use of BMS for emergency management of an acute occlusion during a PTCA.[16] The first commercially available BMS was the Palmaz–Schatz (Johnson and Johnson Interventional Systems, Warren, NJ) stent, showing superior results to PTCA alone according to the first two large studies,[17–19] the Belgium Netherlands Stent (BENESTENT) study and the North American Stent Restenosis Study (STRESS). These results led to an era of ''elective coronary stent'' use resulting in an 84% penetration of BMS use in all PCI by 1999.[20] The most recent advance in interventionist cardiology was the introduction of drug-eluting stents (DES), which have significantly been proven to be the best currently available therapy to reduce instent restenosis. The sirolimus-eluting stent (Cipher®, Cordis Johnson & Johnson) was the first DES to provide positive clinical results. The Sirolimus-Eluting Stent in De novo Coronary Lesions (SIRIUS) trial was a large, randomized, double-blind study which showed a low incidence of instent restenosis compared with BMS (3.2 vs. 35.4%, respectively; $p < 0.001$).[21]

Recently, the percutaneous treatment of CAD has had different local options using mechanical techniques with stents and in some cases rotational atherectomy, angioplasty balloons with special characteristics (*cutting balloon*, drug eluting balloons, etc.) which allow focal treatment of the lesion, and in addition drug options are available with systemic action such as the statins. In spite of the fact that these two therapeutic methods act in different ways, there is growing evidence that suggests that they have a significant positive synergistic effect.

Arterial effects after coronary stents implantation

The microembolization of bioactive particles of the atherosclerotic plaque is a frequent phenomenon following PCI,[22–24] producing microinfarcts which favor an inflammatory process characterized by local leukocyte infiltration which negatively affects contractile function.[23–26] However, this contractile dysfunction induced by local inflammatory phenomena seems to spontaneously recover within one week following coronary microembolization.[27]

Stent implantation in coronary circulation inherently causes mechanical trauma in the vessel wall and induces an inflammatory response of varying degrees of severity.[28,29] In addition to distal embolization of micro-particles, endothelial stripping and dysfunction, media dissection, and exposure of the plaque components to inflammatory mediators, platelets and coagulation factors are induced.[30] Within a few minutes after stent implantation a local invasion of inflammatory cells (macrophages and T cells) is generated, and a small wall thrombus is formed[31,32] which is generally self limited by physiological mechanisms and routine antithrombotic medications. The local production of inflammatory mediators stimulates the liver's production of PCR, VSMC and local macrophages from the vessel wall,[33,34] reduces the synthesis of nitric oxide (NO) even more, incites thrombotic processes, increases the expression of adhesion molecules, modulates the chemotaxis of monocytes and modifies the local capture of LDL-C by macrophages.[35–37] Systemically, a proinflammatory response is seen with the higher levels of PCR.[38–40]

Potential vascular protection mechanisms of statins

While the beneficial effects of statins in improving clinical results in patients undergoing PTCA is well established, the mechanisms that seek to explain these findings are less well understood. These mechanisms suggest that there are acute (hours to days), subacute (days to weeks) and chronic (months to years) effects (Fig. 1).

The hypolipemic effect of statins has been widely accepted through all the clinical studies carried out.