

Anti-Inflammatory Therapy to Treat Atherothrombosis

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Atherosclerosis kills when the plaque ruptures and thrombus develops. Plaque develops mainly by including more low density cholesterol (LDL-C).

So, for decades, LDL-C was considered the

main bad mechanism which develops to bring major cardiovascular events and death in atherosclerosis. In consequence, therapies to attack it developed. Indeed, these showed to reduce atherosclerotic cardiovascular morbidity and mortality.

However, during the last decade it became more and more clear that another mechanism, possible as important as cholesterol appeared. It is constituted by low level but constant inflammation. The most commonly used parameter to monitor these inflammatory process is the high-sensitivity C-reactive protein (hs-CRP).

Patients with higher cardiovascular risk factors and mortality, such as individuals with hypertension, obesity or diabetes, had always higher hs-CRP than cohorts without those risk factors. It was therefore logical that treating this kind of inflammation could lower the atherosclerotic risk.

Various ways to attack hs-CRP have been used, including substances like ezetimibe and colchicine, or antibodies. In large clinical trials, adding those therapies on top of anti LDL-C treatments began to bring results.

An interesting synthesis on this topic was done by Ridker in 2023 (1). From the clinical studies cited by him at that moment, there were different antibodies directed against interleukins or components acting on PCSK9. The greatest rumor of the moment was produced by the CANTOS clinical trial, which used alirocumab directed against interleukin 1- beta (2). However, the relative risk reduction obtained was low (minus 15%).

At the time when Ridker's analysis was published, in the year 2023 (1), better results were obtained with low dose colchicine on long term (minus 30%).

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A meta-analysis on colchicine from 2021 seemed to confirm this efficacy (3). However, recent data from 2025 (4) did not confirm the efficacy of colchicine on long term in secondary prevention therapy.

An important analysis of the different ways in which inflammation could be attacked therapeutically in atherosclerosis has been published by Crea F in the *European Heart Journal* (5).

One way of attack was the inflammation–interleukin-1 β –interleukin-6 pathway (5), but patients' main clinical outcomes did not improve.

The new generation of anti-inflammatory agents against atherosclerosis, called CC-motif chemokine ligand 2/monocyte-chemo attractant protein-1 (CCL2/MCP-1), seems to be the actual way to combat inflammation in atherosclerosis (6).

It has been demonstrated that, in the presence of hs-CRP, bone marrow is activated (8) and different components, which are produced in larger amounts in these conditions (such as neutrophils and monocytes), accompany inflammation in atherosclerosis and may contribute to its more aggressive progression (9).

To conclude, it is now clear that the contribution of atherosclerosis to cardiovascular morbidity and even mortality is due to the LDL-C component, but – probably – always accompanied by inflammation components. There could be different mechanisms for this increased inflammation and different therapeutic modalities to lower it. Today, drugs like colchicine and different antibodies are tried to improve outcome.

What is the main mechanism and which are the ways to develop the best therapies remain to be demonstrated. $\square$

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