MAEDICA – a Journal of Clinical Medicine
2022; 17(3): 555-556
https://doi.org/10.26574/maedica.2022.17.3.555

MÆDICA - a Journal of Clinical Medicine
EDITORIAL POINT OF VIEW

# Weapons

Mircea CINTEZA, MD, PhD[a, b]

[a]Department of Cardiology, Emergency University Hospital, Bucharest, Romania
[b]"Carol Davila" University of Medicine and Pharmacy, Bucharest, Romania

The name of "weapons" is too often encountered lately, unfortunately.

However, in the good sense, this name could be displayed to describe how we can defend ourselves from a danger, not only how to attack. Or to attack for defence.

Such an example is to describe the weapons we use or could use to fight against atherosclerosis.

Atherosclerosis (ATS) is the principal cause of mortality and morbidity in the developed and medium developed countries. In the underdeveloped ones, only infections surpass it.

Atherosclerosis usually develops under the effect of risk factors, with the infiltration of arteries by lipids being the main mechanism. The plaques developed as such may become unstable and recruiting thrombi. Finally, atherothrombosis is the main way to kill.

In an excellent State-of-the-art review, *European Heart Journal* has recently published a synthesis of Tokgozoglu and Libby regarding the history and future of the weapons used to fight unstable atherosclerosis (1).

Let us begin with something which preceded the actual era of fighting against ATS. But let us notice that the knowledge linking lipids with atherosclerosis and the fight against this brought at least 11 Nobel Prizes (2).

Cholesterol was discovered in the XVIII$^{th}$ century. François Poulletier de la Salle was the first who isolated cholesterol in gallstones, in 1769. For almost 200 years, research on cholesterol gave various results, but the linkage to atherosclerosis was not nominated.

In the 1950s of the XX$^{th}$ century, "The Cholesterol War" began (2). It had a peak in the 1970s and ended in the 1990s. Michael Oliver, Paul Wood and Sir John McMichael, all from Great Britain, were among the main names of scientists involved in it. At the end of this period, the linkage between lipids, especially cholesterol, and cardiovascular diseases was universally accepted (2). In the 1970s, the LDL receptor was also discovered, for which the Nobel Prize was awarded to Michael Brown and Joseph Goldstein (2, 3).

The weapons against the enemy were however weak during that period of time. First, nicotinic acid, then clofibrate and then cholestyr-

*Address for correspondence:*
*Mircea Cinteza, MD, PhD*
*Department of Cardiology, Emergency University Hospital, 169 Independentei Avenue, District 5, Bucharest, Romania*
*Email: mirceacinteza@gmail.com*

*Article received on the 29$^{th}$ of September 2022 and accepted for publication on the 30$^{th}$ of September 2022*

amine were used, each with some clinical benefits. Nicotinic acid and cholestyramine could not be used on a large scale because of side effects, while clofibrate was discontinued in 2002 because it could lower cardiovascular deaths but also increase non-cardiovascular mortality (for instance, gallstones with surgical complications and some types of cancer)(2, 4).

However, in that period, the era of statins had already begun. The first statin – triparanol – was used from 1959, but it was removed in 1963 because of a lawsuit regarding its side effects. From the 1970s to 2003, different statins, starting with compactin, then lovastatin, simvastatin, pravastatin, atorvastatin, pitavastatin and rosuvastatin were introduced in clinical practice. In many studies, they clearly showed that cardiovascular mortality and even total mortality were clearly reduced in cardiovascular disease (2, 3). Statins clearly entered as a main successful weapon in the fight against atherosclerosis.

The next period enabled clinicians not only to use some auxiliary – although very useful – drugs such as ezetimibe and bempedoic acid, but also to find the way to secure against side effects by using the therapy with associate fibrates.

After the first years of the second decade of the XX$^{th}$ century, a new very strong weapon against atherosclerosis was developed: the PCSK9 inhibitors. Their power to lower LDL-cholesterol is higher than that of statins and their side effects are few. They clearly reduce cardiovascular mortality.

New drugs and novel ways to attack atherogenesis are under clinical investigation (1). Volanesorsen and Inclisiran are just two examples.

Other weapons such as antisense therapy and vaccination against different lipid metabolism targets are examined in phase 1 or 2 trials (1).

From daily use, new therapies could be administered at longer time intervals such as one month apart or longer.

And new enemies are identified, such as lipoprotein a or APO CIII.

Finally, experiments are imagined to edit genes. This would give solutions once for the whole life.

But there is still a very long way to go. ❑

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