Cardiovascular and Metabolic Science www.ancam.org.mx

Vol. 32 Suppl. 3
July-September 2021

doi: 10.35366/100800

# Statin treatment. The evidence and role in primary and secondary prevention

## *Tratamiento con estatinas. La evidencia y el papel en la prevención primaria y secundaria*

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### ENDO, GOLDSTEIN, AND BROWN. THE PIONEERS

In 1976, the Japanese biochemist Akira Endo discovered the first statin (ML-236B or compactin), extracted from *Penicillium citrinum*.[1] Four and five years later, Yamamoto and Endo[2] and Mabuchi,[3,4] published the first two clinical trials demonstrating a significant reduction in total cholesterol (TC) and LDL-C with a statin in individuals with familial hypercholesterolemia (FH). During the 1970s, Michael Brown, Joseph Goldstein, and Richard Anderson described a low-density lipoprotein receptor (LDL-R) in cultured fibroblasts and established that mutations in the gene that encode it cause severe hypercholesterolemia and early atherosclerosis in individuals with homozygous and heterozygous HF.[5]

In their Nobel Lecture[6] and their account of the discovery of LDL-R, Goldstein, and Brown[7] summarized a series of investigations whose results marked the beginning of the statin's era, namely:

1. LDL transports 66% of circulating cholesterol.
2. Hepatic LDL-Rs, are designed to recognize apoB100 in the circulating LDL, and by endocytosis, introduce 66% of these lipoproteins into the hepatocyte for the intracellular metabolism of the 1,500 molecules of esterified cholesterol contained in each LDL. LDL-R is encoded by a gene located in the short arm of chromosome 19 (19p13.1-13.3).
3. The concentration of nonesterified cholesterol in the membranes of the hepatocyte's endoplasmic reticulum is the biological signal that initiates transcription and translation processes leading to the synthesis of LDL-R. When this concentration decreases, the expression of the transcription factor called sterol regulatory element-binding protein 2 (SREBP2) initiates the synthesis of LDL-R.
4. Statins recreate the cellular environment that determines LDL-R synthesis by competitively inhibiting HMG-CoA-reductase activity, blocking the cellular synthesis of cholesterol.
5. Thus, statins increase the synthesis of LDL-R, favor the hepatic clearance of LDL, and increase the hepatobiliary elimination of the esterified cholesterol without compromising the cellular concentration of cholesterol.

For his discovery, Akira Endo was «baptized» by Goldstein and Brown as «the father of the penicillin for cholesterol». Recognizing that, the millions of lives saved and prolonged using statins is due to the discovery of compactin.[8]

### CTT 2005 AND 2010 META-ANALYSES. EVIDENCE IN 170,000 INDIVIDUALS

The evidence of therapeutic benefit of statins is summarized in the 2005[9] and 2010[10] CTT meta-analyses. These studies evaluated 170,000 individuals, «patient-by-patient», included in 26 statin-era RCTs. For this reason,

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*Received:*
*01/07/2021*
*Accepted:*
*09/07/2021*

**How to cite:** Morales-Villegas EC, Ray KK. Statin treatment. The evidence and role in primary and secondary prevention. Cardiovasc Metab Sci. 2021; 32 (s3): s212-s216. https://dx.doi.org/10.35366/100800

they are considered one of the strongest scientific evidence for the efficacy and safety of HMG-CoA inhibitors.

### CTT 2005 meta-analysis[9]

This first meta-analysis included 90,000 individuals in 14 RCTs and analyzed the benefit of treatment with statins (moderate-intensity statins) versus control or placebo. The now-classic results showed that treatment with statins for five years, with a reduction of 1 mmol/L in LDL-C (≈ 40 mg/dL) is associated with a 20% relative risk reduction for an ASCVD (cardiovascular death, non-fatal myocardial infarction, non-fatal stroke, and/or coronary revascularization). On average, 0.50% relative risk reduction for each mg/dL decrease in LDL-C *(Figure 1)*.

In recent years, the HOPE-3 trial[11] confirmed the result of the CTT 2005 meta-analysis in individuals with intermediate cardiovascular risk treated with a moderate-intensity statin.

Currently, any moderate-intensity statin (simvastatin 20 mg or 40 mg, atorvastatin 10 mg or 20 mg, or rosuvastatin 5 mg or 10 mg) can reduce the circulating level of LDL-C by 30%. That means an LDL-C reduction of approximately 40 mg/dL in an individual with LDL-C of 120 mg/dL; therefore, it decreases the relative risk of an ASCVD by 20%.

### CTT 2010 meta-analysis[10]

Under the hypothesis «lower equals more benefit with equal safety», this second meta-analysis included 170,000 individuals in 26 RCTs analyzed 39,612 individuals in five trials that compared the benefit of treatment with statins (high-intensity statins, like atorvastatin 40 and 80 mg or rosuvastatin 20 and 40 mg) versus moderate-intensity statins. Likewise, the analysis of the benefit of treatment with moderate-intensity statins versus control or placebo was extended to 129,526 individuals included in 21 RCTs (2005 cohort expanded with 7 more RCTs).

In the first subgroup (high-intensity statin vs moderate-intensity statin), with an average LDL-C level of 98 mg/dL, the high-intensity statins showed an additive reduction of 0.50 mmol/L of LDL-C (20 mg/dL) and an additive decrease of 15% in the relative risk of an ASCVD. In the second subgroup (moderate-intensity statin vs. control or placebo), with an average LDL-C level of 143 mg/dL, the result confirmed previous reports on average, 0.50% relative risk reduction of ASCVD for every mg/dL decreased in LDL-C *(Figure 2)*.

In the joint analysis of both subgroups, the benefit of statin treatment for five years with a reduction of 1 mmol/L in LDL-C (40 mg/dL) in the different types of ASCVD was as follows:

1. 24% significant reduction in the relative risk for non-fatal and fatal myocardial infarction.
2. 25% significant reduction in the relative risk for surgical or percutaneous coronary revascularization.
3. 16% significant reduction in the relative risk for stroke, with a significant reduction of 31% in the relative risk for non-fatal ischemic stroke, non-significant reduction for fatal stroke and a non-significant increase of 12% in risk relative for hemorrhagic stroke.
4. 10% significant reduction in the relative risk for all-cause mortality, mainly influenced by the reduction in risk for coronary death. Reduction in risk for non-cardiovascular death was non-significant.

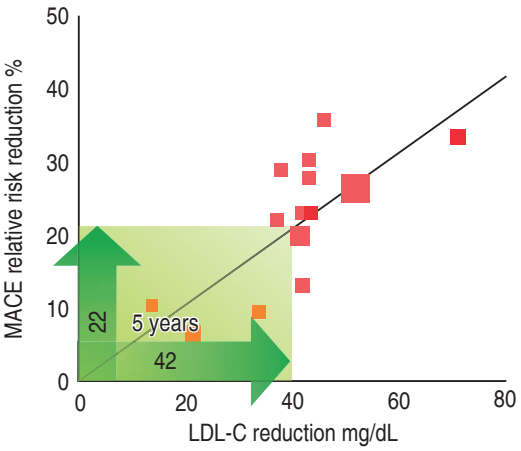


**Figure 1:** Moderate intensity statin vs placebo or control. Starting from a baseline LDL-C of 147 mg/dL without treatment, 42 mg/dL lower LDL-C with an intermediate-intensity statin equals 22% lower risk of a major adverse cardiovascular event (MACE) over five years of treatment. 40/20 rule.
Modified from: Cholesterol Treatments Trialist's (CTT) Collaboration.[10]

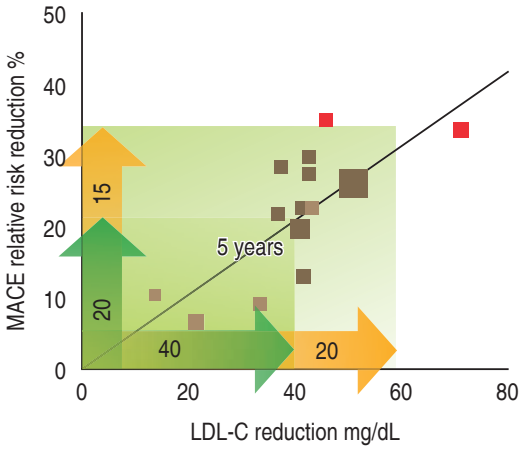


**Figure 2:** High intensity statin vs moderate intensity statin. Starting from a baseline LDL-C of 98 mg/dL on treatment with a medium-intensity statin, 20 mg/dL lower LDL-C with a high-intensity statin equals an extra 15% lower risk of a major adverse cardiovascular event (MACE) over five years of treatment.
Modified from: Yusuf S et al.[11]

The benefit was homogeneous for the different subgroups, regardless of baseline risk (high, moderate, low), gender (men or women), age (< 75 years or ≥ 75 years), baseline LDL-C (> 100, 70-100 or < 70 mg/dL) and high-density lipoprotein cholesterol (mg/dL percentiles). No subgroup showed an excess risk for any type of cancer. Rhabdomyolysis incidence was 4/10,000 individuals treated with high-intensity statins versus moderate-intensity statins, all of them treated with simvastatin 80 mg, and 1/10,000 individuals treated with moderate-intensity statins versus control or placebo.

The authors concluded that statin treatment for five years, that reduction of 1 mmol/L (40 mg/dL), 2 mmol/L (80 mg/dL) and 3 mmol/L (120 mg/dL) in LDL-C reduced the relative risk of an ASCVD by 20%, 40%, or 50% respectively without a significant increase in the risk of cancer, intracranial hemorrhage and/or rhabdomyolysis.

## GUIDELINES FOR HYPERCHOLESTEROLEMIA AND ATHEROSCLEROTIC CARDIOVASCULAR RISK REDUCTION

The guidelines[12,13] for the treatment of hypercholesterolemia and the prevention of ASCVD are based on the following three fundamental concepts:

1. Hypercholesterolemia, understood as an inappropriate or pro-atherogenic level of LDL-C, and not as the average population level (131.5 mg/dL in Mexico), is the most important causal risk factor for an ASCVD.
2. Estimating the absolute risk over ten years is the best strategy with therapeutic benefit for reducing blood LDL-C level and the risk of an ASCVD.
3. To date, statins are the best strategy for reducing LDL-C levels and the risk of an ASCVD.

The way to achieve this goal differs conceptually among the different guidelines. The current American and European recommendations for prescribing statins in secondary and primary prevention are presented separately below.

### AHA/ACC 2018 guidelines (recommendations for starting statins)

The recommendations in this guideline[12] are based exclusively on RCT results. It has a strong orientation towards cost-effectiveness, especially for high-cost strategies (ex. monoclonal antibodies vs. PCSK9). It presents the use of therapeutic thresholds (LDL-C value above which a high-cost strategy is justified by cost-effectiveness) and the efficacy of the treatment is based on the percentage of reduction in LDL-C expected with the different strategies (ex. reduction between 30 and 50% with a moderate-intensity statin and ≥ 50% with a high-intensity statin).

The main recommendations for statins are as follows:

1. In individuals ≤ 75 years with ASCVD, the recommendation is to start a high-intensity statin (atorvastatin 40 or 80 mg or rosuvastatin 20 or 40 mg). Recommendation class I, level A.
   In individuals > 75 years or ≤ 75 years intolerant to a high-intensity statin, the recommendation is to start a moderate-intensity statin (atorvastatin 10 or 20 mg,

rosuvastatin 5 or 10 mg, or simvastatin 20 or 40 mg). Recommendation class I, level A.

2. In individuals > 21 years with severe hypercholesterolemia with LDL-C ≥ 190 mg/dL without ASCVD, the recommendation is to start a high-intensity statin. Recommendation class I, level B-R.
   In individuals > 21 years who are intolerant to a high-intensity statin, the recommendation is to start a moderate-intensity statin. Recommendation class IIa, level B-R.
3. In individuals with diabetes mellitus (DM) between 40 and 75 years and LDL-C between 70 and 189 mg/dL, without ASCVD, the recommendation is to start a moderate-intensity statin regardless of the absolute risk level of ASCVD. Recommendation class I, level A.
   With the same age and LDL-C parameters, if the absolute risk of ASCVD at ten years estimated by pooled cohort equations (PCE) is ≥ 20%, the recommendation is to start a high-intensity statin. Recommendation IIa, level B-NR.
4. In individuals between 40 and 75 years and LDL-C between 70 and 189 mg/dL, without ASCVD or DM, with an absolute risk of ASCVD at ten years estimated by the PCE between 7.5 and 19% (intermediate risk), the recommendation is to start a moderate-intensity statin. Recommendation class I, level A.
   With the same age and LDL-C parameters, if the absolute risk of ASCVD at ten years estimated by the PCE is ≥ 20%, the recommendation is to start a high-intensity statin. Recommendation class I, level A.

## ESC/EAS 2019 guidelines

Beyond RCT results, the recommendations in this guideline[13] are based on all the evidence that supports the «LDL-centric» principle. It does not consider cost-effectiveness analysis for any strategy. Treatment efficacy is based on target LDL-C values (ex. < 116, < 100, < 70, and < 55 mg/dL for low, moderate, high, and very high-risk individuals, respectively).

The main recommendations for statins are as follows:

1. In very-high-risk individuals with a history of myocardial infarction, unstable angina, stable angina, stroke, cerebral hemorrhage, transient ischemia, peripheral arterial disease, and/or arterial revascularization, start a high-intensity statin, or the maximum tolerated dose with a goal of < 55 mg/dl of LDL-C. Recommendation class I, level A.
2. In individuals at very-high-risk with subclinical atherosclerosis by CT angiography or arterial ultrasound with ≥ 50% stenosis, type 1 or type 2 DM with microangiopathy and/or ≥ 3 risk factors, type 1 DM with ≥ 20 years of evolution, chronic kidney disease (CKD) stages IV-V, FH with ASCVD or ≥ 1 risk factors, or risk estimated by SCORE ≥ 10%, start a high-intensity statin or the maximum tolerated dose with a goal of < 55 mg/dL of LDL-C. Recommendation class I, level C.
3. In individuals at high-risk with TC ≥ 310 mg/dL, LDL-C ≥ 190 mg/dL, blood pressure ≥ 180/≥ 110 mmHg, type 1 or type 2 DM with ≥ 10 years of evolution, without microangiopathy and < 3 risk factors, CKD stage III, FH without ASCVD, and without other risk factors or risk estimated by SCORE ≥ 5% and < 10%, start a high-intensity statin or the maximum tolerated dose with the goal of < 70 mg/dL of LDL-C. Recommendation class I, level A.
4. In individuals at moderate-risk with type 2 DM with < 50 years of age and < 10 years of evolution, without microangiopathy and without risk factors, type 1 DM with < 35 years of age or risk estimated by SCORE ≥ 1 and < 5%, start a high-intensity statin, or the maximum tolerated dose with a goal of < 100 mg/dL of LDL-C. Recommendation class IIa, level A.
5. In low-risk individuals with a risk estimated by SCORE < 1%, start a high-intensity statin, or the maximum tolerated dose with a goal of < 116 mg/dL of LDL-C. Recommendation class IIb, level A.

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