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Statins: The Great Age and beyond Biologically LDL Level, Revisited Forty Years Later

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Abstract

The LDLR and its mutations were described, determinants of the FH phenotype in 1974, at the same time, the first statin (compactin) with hypocholesterolemic effect was discovered in 1976. Statins, by inhibiting HMGCoAR and blocking the cellular synthesis of cholesterol, induce its main therapeutic effect, namely: the activation of the synthesis, expression and function of LDLR and with it, a greater hepatic clearance of LDL and lower blood cholesterol level. Statins also reduce the synthesis of VLDL and have non-lipid or pleiotropic effects. The canonical meta-analysis of CTT with one hundred and seventy thousand individuals treated with statins in twenty-six RCT and their "patient by patient" analyses, allow us to establish the following therapeutic postulate: reduction of 40, 80 and 120 mg/dL of LDL-cholesterol with a statin results in a 20%, 40% and 50% risk reduction of an ASCVD. A significant benefit without a doubt. This therapeutic benefit with statins has been the "master key" for all groups of experts in Lipidology and Cardiology to consider this pharmacological group as the gold standard in the prevention of ASCVD. All Guidelines for hypercholesterolemia treatment and prevention of ASCVD contemplate the following three fundamental concepts: LDL-cholesterol is the main atherogenic risk factor and therapeutic target. Estimating the absolute 10-year cardiovascular risk is our best tactic to guide the therapeutic strategy. Up today, statins are our best therapeutic strategy for controlling hypercholesterolemia and preventing ASCVD. In the PCSK9 inhibition era and before the first CVOT with MAbs-PCSK9 publication, this paper reviews briefly the amazing statin's history since Endo, Goldstein and Brown´s discoveries until their solid and evidence-based position in all guidelines devoted to hypercholesterolemia and ASCVD risk reduction.

Keywords: Statins; LDL Level; ASCVD

Abbreviations: LDLR: Low Density Lipoprotein Receptor; HMGCoAR: Hydroxy-methyl-glutaryl-coenzyme A reductase; LDL: Low Density Lipoprotein; VLDL: Very Low Density Lipoprotein; ASCVD: Atherosclerotic Cardiovascular Diseases; CTT: Cholesterol Treatment Trialists' Collaboration; RCT: Randomized and Controlled Studies; HoFH: Homozygous Familial Hypercholesterolemia; HeFH: Heterozygous Familial Hypercholesterolemia; NFH: Non-Familial hypercholesterolemia; AHA: American Heart Association; ACC: American College of Cardiology; ESC: European Society of Cardiology; EAS: European Atherosclerosis Society; NOM: Official Mexican Standard; ATP-III: Adult Treatment Panel number three; NNT: Number Needed to Treat for Benefit; NNH: Number Needed to Treat for Harm; QALY: Quality-Adjusted Life Year; siRNA: small interfering RNA

Akira Endo, Joseph Goldstein and Michael Brown. The Pioneers

The Japanese biochemist Akira Endo discovered in 1976 the first statin, compactin, extracted from "*Penicillium citrinum*" [1]; between 1976 and 1979, Endo and collaborators confirmed in animals and humans the hypocholesterolemic activity of compactin by inhibition of HMGCoAR [2-5] and finally in 1980 Yamamoto, Sudo and Endo published the first clinical trial with this statin with a significant 27% reduction of total cholesterol levels in 11 individuals with FH [6]. One year later, Mabushi, Haba, Tatami and collaborators communicated the effect of compactin on ubiquinone-10 and lipoproteins levels in 7 individuals with FH, without change in serum ubiquinone level and significant reduction in total cholesterol, IDL-cholesterol and LDL-cholesterol [7], this pivotal trial was editorialized by Brown and Goldstein with the title "Lowering plasma cholesterol by raising LDL receptors" [8].

Contemporaneously with compactin discovery, in 1972 Michael Brown and Joseph Goldstein began their work for understanding the etiology of FH, disease described by Muller in 1938 [9] and Khachadurian in 1964 [10]. In their 1985 Nobel Lecture [11], summarized by themselves in 2009 [12], Brown and Goldstein describe their amazing research journey which allow the characterization of the LDLR structure, its physiologic pathway including the receptor-endocytosis concept and its four type mutations as the cause of severe hypercholesterolemia and accelerated and severe ASCVD in these children and adolescents. In this way, statins, discovered by Endo who was designated by Brown and Goldstein as "the father of the penicillin for cholesterol" [13] are super-selective inhibitors of HMGCoAR; through this mechanism, by inhibiting the synthesis of cholesterol and isoprenoids, the following is determined: increased synthesis and expression of LDLR by activation of the SREBP2 transcription factor with increased LDL-cholesterol clearance, decreased VLDL lipidation and synthesis, and attenuation of isoprenylation of inflammatory signaling molecules [11-12].

From these three fundamental facts, the discovery of compactin by Akira Endo, the publications by Yamamoto and Mabushi on the beneficial effect of compactin on the lipid profile of individuals with FH, and the characterization of LDLR anatomy, physiology and genetics by Goldstein and Brown, it was clear that the inhibition of the cellular synthesis of cholesterol with statins and its consequence, the over expression of LDLR, would evolve to be one of the strategies with greater therapeutic success in Medicine. To date, statins are the pharmacological group with most evidence in the reduction of LDL-cholesterol, atherosclerosis, and cardiovascular diseases associated with it [14,15].

Meta-analysis CTT 2005-2010. Evidence on 170,000 Individuals

The therapeutic success story referred to in the previous section was masterly summarized in the CTT meta-analyzes 2005 [14] and 2010 [15]. These "patient-by-patient" meta-analyzes, analyzed the 170,000 individuals included in the best 26 RCT of the statin era; and are therefore considered one of the strongest scientific evidence to weight the efficacy and safety of HMGCoAR inhibitors.

a) Meta-analysis CTT 2005: This first meta-analysis of 90,000 individuals included in 14 RCT, analyzed the benefit of statin treatment versus control (placebo). The result of this first meta-analysis, already classic, was that a 1 mmol/L reduction in LDL-cholesterol (40 mg/dL didactically) showed a 20% reduction in the relative risk of an ASCVD (cardiovascular death, non-fatal myocardial infarction, non-fatal cerebral infarction and/or coronary revascularization); on average, 0.50% risk reduction per mg/dL of LDL-cholesterol reduction. In current terms, any statin of medium intensity (simvastatin 20 mg or 40 mg, atorvastatin 10 mg or 20 mg or rosuvastatin 5 mg or 10 mg), is able to reduce the average LDL-cholesterol by approximately 30%, approximately 40 mg/dL of LDL-cholesterol and thus reduce the risk of atherosclerosis-related cardiovascular disease by 20% [14].

b) Meta-analysis CTT 2010: In an attempt to confirm the hypothesis "lower equals to a greater benefit with equal safety", this second meta-analysis of 170,000 individuals included in 26 RCT analyzed 39,612 individuals included in 5 studies comparing the benefit of treatment with "potent" statins at "high" doses. (atorvastatin 40 mg and 80 mg or rosuvastatin 10 mg or 20 mg) versus "standard" statins at "lower-medium" doses, plus 129,526 individuals included in 21 studies (cohort 2005 extended with 7 more RCT) that compared the benefit of treatment with statins versus control (placebo). In the first subgroup (more statin versus less statin), with an average LDL-cholesterol level of 98 mg/dL, high-intensity statins versus medium-intensity statins showed an additive reduction of 0.50 mmol/L in LDL-cholesterol (20 mg/dL didactically) and a 15% additive decrease in the risk of an ASCV; on average, 0.75% additive risk reduction per mg/dL of LDL-cholesterol decrease. In the second subgroup (statin vs. control), with a mean LDL-cholesterol level of 143 mg/dL, the result was similar to that reported in the 2005 CTT meta-analysis, on average, 0.50% risk reduction per mg/dL decrease in LDL-cholesterol. In the pooled analysis of both subgroups (more statin versus less statin and statin versus control), the benefit on the different types of events was as follows: a) 24% significant reduction for non-fatal and fatal cardiac infarction; b) 25% significant reduction for surgical or percutaneous coronary revascularization; c) 16% significant reduction for stroke, with a significant reduction of 31% for non-fatal ischemic stroke, non-significant reduction for fatal stroke and non-significant increase of 12% for hemorrhagic stroke; d) 10% significant reduction for total deaths, mainly influenced by reduction for coronary death, without being significant for non-cardiovascular death [15].

The benefit was homogenous for the different subgroups; regardless of the baseline risk (high, medium, low), gender (men or women), age (<75 years or ≥75 years), baseline LDL- cholesterol (>100, 70-100 or <70 mg/dL) and HDL cholesterol (mg/dL by tertiles). In no subgroup, an excess risk for any type of cancer was observed, the incidence of rhabdomyolysis was 4/10,000 individuals treated in the more statin versus less statin studies, all with simvastatin 80 mg and 1/10,000 individuals treated in the statin versus control studies [15].

The authors concluded, according to their analysis, that a reduction in LDL-cholesterol of 1 mmol/L (40 mg/dL) reduces 20%, 2 mmol/L (80 mg/dL) reduces 40% and 3 mmol/L (120 mg/dL) reduces 50% the risk of an ASCVD, without a significant increase in the risk of cancer, intracranial hemorrhage and/or rhabdomyolysis.

It is relevant to note that clinical application of this evidence has evolved over the past 15 years [16]. From its application based on a cost of brand-statins/benefit concept, on which the ATP-III established "therapeutic targets" according to the cardiovascular risk: <160, <130 and <100 mg/dL of LDL-cholesterol for individuals with low, moderate and high risk, respectively - introducing the optional "therapeutic target" of <70 mg/dL for very high-risk individuals -, to its contemporary application based on a net benefit concept (benefit+save/harm+cost of generic-statins), on which the new Guidelines (analyzed below) suggest the strategy of reducing intensity of LDL-cholesterol according to the cardiovascular risk: high intensity for individuals with ASCVD and/or severe hypercholesterolemia (LDL-cholesterol ≥190 mg/dL) and medium intensity for individuals with DM without ASCVD or individuals without any of these conditions but with a high cardiovascular risk (≥7.5% at 10 years calculated with the AHA/ACC 2013 equation).This evolution in therapeutic strategies is explained by the accumulation of favorable evidence on the therapeutic benefit and the low incidence of adverse events of the statins and especially with the very favorable ratio between saving/therapeutic cost; this last variable has been reduced from 2 USD to $ 0.100 USD per day of treatment with a medium intensity statin. This condition, already anticipated by Mark Hlatki [17], has reduced the therapeutic threshold for prescribing medium intensity statins for primary prevention, being a strategy with a NNT/NNH ratio of 40/100 and a cost per QALY of about 35,000 USD (optimal value <50,000 USD/QALY) [18].

Guidelines for Hypercholesterolemia Control

Regardless of the Guideline reviewed, in the control of hypercholesterolemia aimed at reducing the likelihood of atherosclerotic cardiovascular disease, the following concepts are universal:

1. Hypercholesterolemia, understood as an inappropriate or proatherogenic level of LDL-cholesterol, and not as the average population level (131.5 mg/dL in Mexico), is the most important causal risk factor for an ASCVD. Among the many basic, genetic, experimental, epidemiological and clinical evidences, the best of them to support this concept is the early incidence of atherosclerosis, atherosclerotic cardiovascular disease and cardiovascular death in children and adolescents with HoFH, in the absence of any other risk factors [11]. Without treatment, these children reach their "annual cholesterol burden" for the development of atherosclerotic cardiovascular disease at an average age of 12.5 years (deaths due to myocardial infarction have been reported at 18 months of age). Unlike them, and observing a biological gradient, the adult individuals with HeFH and NFH reach this "annual cholesterol burden" at average ages of 35 and 55 years respectively [19].
2. The absolute risk estimation over a 10-year period under the concept of net benefit is our best tactic to establish a therapeutic strategy aimed at controlling blood cholesterol level and reducing the likelihood of an ASCVD [20-23].
3. As previously demonstrated, to date, statins are our best therapeutic strategy for the reduction with net benefit (benefit+saving >harm+cost) of LDL-cholesterol, atherosclerosis progression, and incidence of ASCVD [14,15,20-23].

Thus, the strategy of reducing the circulating level of LDL-cholesterol through exaltation of the LDLR function is a universally accepted concept for reducing the probability of a first or subsequent ASCVD. The way to practice this strategy towards its objective-target differs conceptually between the different Guidelines. The most solid and current American, European and Mexican recommendations (Indications Class I or II)

for prescribing statins and non-statin biologics/drugs in primary and secondary prevention are described below.

Guideline AHA/ACC 2013-ATP-IV-. Primary and Secondary Prevention

Recommendation 1: In individuals with ASCVD (secondary prevention) [20], the recommendation is: high-intensity statin (atorvastatin 40 mg or 80 mg or rosuvastatin 20 mg or 40 mg) for ≤75 years of age (level A recommendation). Moderate-intensity statin (atorvastatin 10 mg or 20 mg, rosuvastatin 5 mg or 10 mg or simvastatin 20 mg or 40 mg) for >75 years of age or ≤75 years of age intolerant to high-intensity statin (level E recommendation).

Recommendation 2: In individuals with LDL-cholesterol ≥190 mg/dL (primary prevention), the recommendation is: high-intensity statin for >21 years of age (level B recommendation). Moderate-intensity statin for >21 years intolerant to high-intensity statin (level E recommendation).

Recommendation 3: In individuals with Diabetes Mellitus, in the absence of severe hypercholesterolemia and/or ASCVD (primary prevention), the recommendation is: moderate-intensity statin in all individuals with Diabetes Mellitus between 40 and 75 years of age and LDL-cholesterol level between 70 mg/dL and 189 mg/dL (level A recommendation).

Recommendation 4: In individuals with an absolute 10-year risk of an ASCVD ≥7.5% - calculated with the PCE AHA-ACC 2013, in the absence of severe hypercholesterolemia, Diabetes Mellitus and/or ASCVD (primary prevention), the recommendation is: moderate-intensity statin in every individual between 40 and 75 years of age and LDL-cholesterol level between 70 mg/dL and 189 mg/dL (level A recommendation).

Expert Consensus ACC/NLA 2016-. Primary and Secondary Prevention

This Consensus publication follows the philosophy of the United States Institute of Medicine (IOM) "to update and publish the recommendations when new evidence with high scientific value is available" [21]. Thus, following the publication of the results for the IMPROVE-IT studies with ezetimibe [24], OSLER I-II with evolocumab [25] and ODYSSEY Long-Term with alirocumab [26], the American College of Cardiology experts supported by the National Lipid Association (NLA) published a document known as "Lipid Pathway", whose main characteristics are the following:

1. It is based on the ACC/AHA Guideline 2013. It maintains the recommendations in the 4 net benefit groups described by the ATP-IV (20), privileges statins as the pharmacological group with the highest evidence in reducing the risk of an ASCVD and endorses the reduction in LDL- cholesterol as the best indicator of the therapeutic efficacy of HMGCoAR inhibitors.
2. Introduces the concept of "therapeutic threshold". The therapeutic threshold is the level of LDL or non-HDL cholesterol (especially in diabetic population) from which the addition of a non-statin drug/biological is justified in an individual optimally treated with statins.
3. It presents the scenarios with six algorithms (based on the evidence published until December 2015) in which, after certain patient and drug/biological centered considerations, the addition of ezetimibe, resins, evolocumab or alirocumab, mipomersen or lomitapide is justified.

The authors of "Lipid Pathway" make it clear that the document is not a new Guideline; it is a document that serves as a necessary guide at a time when, after approval of PCSK9 MAbs for clinical use, physicians and health care providers require academic endorsement. The Lipid Pathway is a bridge to the new Guideline that will emerge once currently ongoing studies are terminated.

Guideline ESC/EAS, August 2016. Primary and Secondary Prevention

Recommendations 1: In individuals with ASCVD (secondary prevention) or subclinical Atherosclerosis, Diabetes Mellitus with target organ damage (proteinuria) and/or some other ASCVD risk factors [22] (smoking, hypertension or dyslipidemia), severe chronic kidney disease (eGFR <30 ml/min/1.73m2) or an estimated SCORE risk ≥10% (high risk primary prevention), the LDL-cholesterol target is <70 mg/dL or a ≥50% reduction (if baseline LDL-cholesterol is between 70 and 135 mg/dL). Indication I-B.

Recommendation 2: In high-risk individuals: total cholesterol >310 mg/dl, blood pressure ≥180/110 mmHg, diabetes mellitus without very high risk criteria (above), moderate chronic kidney disease (eGFR 30 to 59 ml/min/1.73m2) or an estimated SCORE risk ≥5% to <10% (primary prevention), the LDL-cholesterol target to be considered is <100 mg/dL or a ≥50% reduction (if baseline LDL-cholesterol is between 100 and 200 mg/dL). Indication I-B.

Recommendation 3: In individuals at low or moderate risk, with a risk estimated by SCORE <1% or ≥1% to <5% respectively (primary prevention), the target LDL-cholesterol to be considered is <115 mg/dL. Indication IIa-C.

NOM-033-SSA2-2012 and its Update 2016

The NOM-2012 [23] for the treatment of Dyslipidemias, adopted the ATP-III concept (2002-2005) with a LDL-cholesterol and a non-HDL-cholesterol target according to the cardiovascular risk. Thus, the 2012 standard, still current, suggests an LDL-cholesterol target of <160, <130 and <100 (optional <70) mg/dL for individuals with low, moderate and high cardiovascular risk, respectively (calculated using the Framingham Table). The 2016 version of the NOM (currently under revision) [27] neglect the ATP-III therapeutic criteria and proposes treatment based on the therapeutic intensity of statins (low, moderate and high) according to the level of cardiovascular risk, calculated using the Globorisk algorithm 2015 or the PCE AHA/ACC 2013. The therapeutic strategy is very similar to that suggested by the AHA/AHA Guideline 2013 and it is contemplated, if necessary, the use of non-statin medication, according to clinical judgment.

What Guideline I should apply

For now, the author suggests adopting the Guideline with which the Physician feels more familiar and comfortable, all are useful and in general terms are based on the same evidence interpreted under different optics. Being at an optimal time for this, once the drug-biologically optimal level of LDL-cholesterol and its cost-effectiveness are known, it is very likely that the Guidelines can be unified into a universal concept of net benefit.

Conclusion and The Near Future. Author´s perspective

In July 1977, Goldstein, Brown, Myant and Reichl submitted for publication their seminal paper "Biologically active low density lipoprotein in human peripheral lymph" [28] this paper published in 1978 stated forty years ago, that the biologically active level of LDL-cholesterol in human beings is around 25 mg/dL in plasma, equivalent to 2.5 mg/dL in the interstitial space.

This classical and pivotal concept, forty years later, is being supported study by study in the PCSK9 inhibition era. Recent meta-analysis and systematic reviews [29-34] have showed that with MAbs-PCSK9 on top of statins each 39 mg/dL of LDL-cholesterol level reduction or 50% of LDL-cholesterol level reduction is associated with a 24% or 29% respectively risk reduction, without attenuation even at levels <50mg/dl of LDL-cholesterol levels. Following the same direction, very recently Nicholls et

al. [35], in the GLAGOV trial showed that on top of statins evolocumab 420 mg/4 weeks was associated with a linear reduction in the percentage atheroma volume from LDL-cholesterol levels of 110 mg/dL to 20 mg/dL -the lower the LDL-cholesterol level, the higher the atheroregression.

All this evidence has been reviewed recently by the author [36] and support the idea that Endo, Goldstein and Brown´s dream is coming true. During 2017 with the results of the FOURIER [37] and ODYSSEY-Outcomes [38] cardiovascular outcomes trials with evolocumab and alirocumab, we could embrace this dream: on-top of high intensity statins, a sustained 60% lowering in the LDL-cholesterol level should be associated with an extra time-dependent 25-30% reduction in the atherosclerotic cardiovascular disease risk (myocardial infarction, ischemic stroke and cardiac death secondary to atherothrombotic events).

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