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Physiological Level of LDL Cholesterol: The Master Key *A Nobel Dream Comes True*

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Introduction

The primary goal of cardiologist in the 21st century, is the eradication or, at least, the significant reduction of atherosclerotic cardiovascular diseases (ASCVD); for that purpose, our best approach is the estimation of the risk for an ASCVD and our best strategy is to reduce the gap between the pathological values observed in our patients and the physiological values of the so-called cardiovascular risk factors, in order of importance: hypercholesterolemia, hypertension, hyperglycemia and adiposity.

In this brief paper, we will review the concept of physiological level of cholesterol contained in low density lipoproteins (LDL-C), and we will review current strategies to bridge the gap between the so-called ill "normal" or average value and the value called by Reich, Myant, Goldstein and Brown as "biologically active" or physiological value of LDL-C, the former averaging 125 mg/dL and the latter averaging 25 mg/dL. These strategies, especially those that increase the catabolism of low density lipoprotein (LDL) through increased synthesis, expression and function of the LDL receptor, have shown with unquestionable scientific evidence, to bridge the gap between the average level and the physiological level of circulating LDL-C, to reduce the progression of atherosclerosis and to reduce the incidence of events by ASCVD, arguably the best story in cardiology within the last century.

Biologically Active or Physiological Level of LDL Cholesterol

In 1982, Goldstein and Brown questioned [1] *"The LDL cholesterol levels that we now consider normal are really normal or are they actually excessively high levels?"* This questioning was based on several investigations carried out in the 70's. In 1975, Keys [2] based on several epidemiological studies [3-5] reported that LDL-C levels in industrialized societies compared with those in non-industrialized societies were excessively high; he also established that LDL-C levels in non-human mammals are less than 50 mg/dL, similar to those of newborn human mammals, and that in the latter, the LDL-C levels are doubled in adolescence and quadrupled in adulthood (Figure 1). In 1978, the English group of Reich and Myant in collaboration with the American group of Brown and Goldstein [6] demonstrated that, in "*in vitro*" studies with the use of radioactive I-labeled LDL, LDL receptors (LDLR) were saturated with an average plasma LDL level of 25 mg/dL, equivalent to 2.5 mg/dL in lymph (Figure 2), likewise, they demonstrated that with this LDL level, the enzymatic activity of the Hydroxy-Methyl-Glutaryl-Coenzyme-A Reductase (HMGCoAR)-pivotal enzyme of the cellular cholesterol synthesis was completely inhibited. Finally, in 1979, Bilheimer who at that time was a collaborator of Goldstein and Brown and tutor of Grundy and Stone (collaborators of the work referred to and ultimately lead authors of ATP III and IV) [7] and in 1981, Kovanen [8] in pharmacokinetic studies of lipoproteins, confirmed that, in dogs, chimpanzees and humans, LDL production is similar, about 15 mg/kg weight; however, the elimination of such lipoprotein differs significantly between the three mammalian species; Bilheimer and Kovanen reported that the elimination of LDL expressed as the "Fractional Catabolic Rate" (FCR) or the ratio between the "pool" of circulating LDL and the "pool" eliminated was 1.6 in dogs, 0.8 in chimpanzees and 0.4 in humans , this reduction in FCR being the variable that explained the differences in the circulating level of LDL-C, 25 mg/dL in the dog, 50 mg/dL in the chimpanzee, and ≥ 100 mg/dL in the adult human (Figure 3). At that time and until today, the mechanisms explaining the reduction of the FCR in adult humans, determined in turn by the synthesis, expression and function of the LDLR, are not known [1].

Almost three decades ago, three fundamental concepts to understand the current cardiovascular therapeutics have been demonstrated. These concepts are as follows:

- The adult human has a level of LDL-C three times higher than the newborn human and non-human mammals.
- Although cholesterol is an essential lipid for life, all mammalian cells have the ability to synthesize it from acetate and, if required, an LDL level of not more than 25 mg/dL provides the "supplementary" cholesterol for cellular metabolism.
- Supraphysiological levels of LDL-C in the adult human are mainly explained by a reduction in LDL catabolism secondary to down-regulation in the synthesis, expression and/or function of LDLR.

Thus, the ≥ 100 mg/dl gap between the "normal" or average level of LDL-C (125 mg/dL) and the physiological level of LDL-C (about 25 mg/dL) explains a major part of the risk for ASCVD. From a mechanistic point of view, Steinberg and Witztum [9], demonstrated in the 70s-80s that the supraphysiological excess of LDL favors its oxidation and recognition as a proinflammatory molecular pattern that activates innate immunity and triggers the process known as atherogenesis.

The Master Tactic for Achieving a Physiological Level of LDL Cholesterol

Considering that in our body only 7% of cholesterol is in

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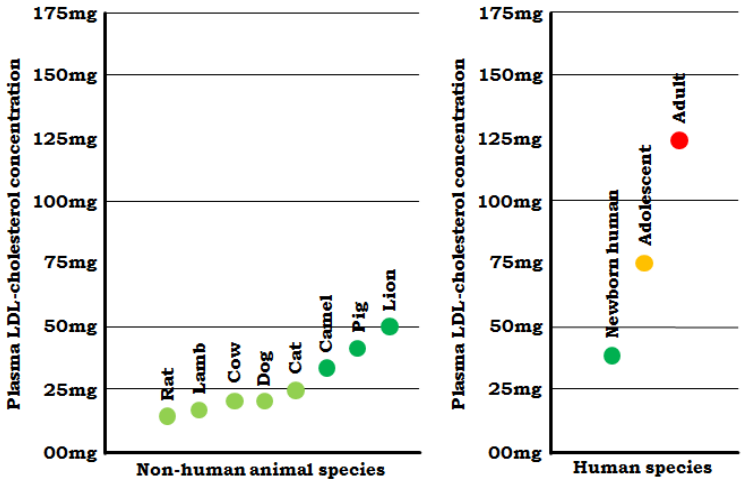

Figure 1: Plasma LDL-cholesterol concentration in mg/dL in non-human mammals and in newborn, adolescent and adult humans [2].

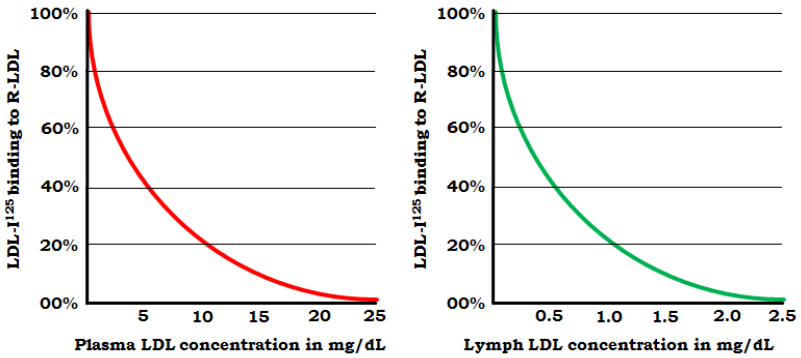

Figure 2: Binding of I^{125}-labeled LDL to RLDL at different LDL plasma and lymph concentrations. At a 25 mg/dL LDL plasma concentration (left) or at a 2.5 mg/dL lymph concentration (right), it is observed that the uptake of I^{125}-labeled LDL is virtually non-existent, which translates the RLDLs saturation [6].

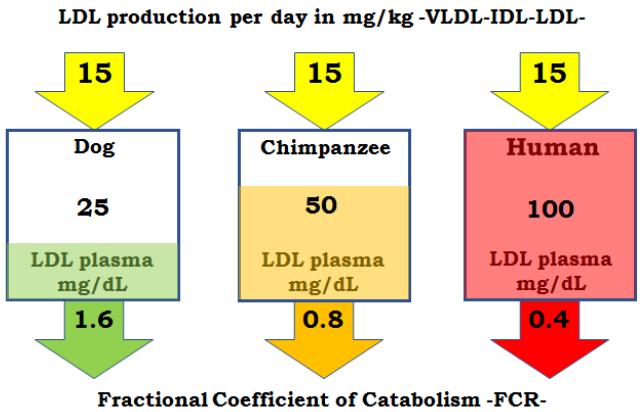

Figure 3: The LDL kinetics in the dog, the chimpanzee and the human are schematized. It is outlined that the synthesis or production of LDL is equal in all three species and that the catabolism or elimination (RLDL- dependent) is inversely proportional to the level of circulating LDL in plasma-the lower the fractional coefficient of catabolism, the higher the circulating level of LDL- [7,8].

circulation-70% contained in LDL-and 93% is found in the membranes and inside the cells, the key question that Goldstein and Brown formulated when starting in 1972 their research on familial hypercholesterolemia (FH) was the following [10]: *how to reduce the level of circulating cholesterol, mainly contained in LDL, without affecting the cellular cholesterol content?* Answering this question took them four years of research and eventually-thirteen years later-made them winners of the Nobel Prize in Physiology and Medicine [11].

Goldstein and Brown published the discovery of the LDLR in 1974 [12] and thereby clarified the mechanism by which our body eliminates 70% of circulating LDL-C without cellular cholesterol content depletion; the other 30% is eliminated by several cellular scavenger receptors within the reticulo-endothelial system (SR-A, CD-36, SR-B1, CD-68, SR-PSOX, LOX-, etc.) [9]. In addition to discovering the LDLR and its biological cycle (see below), Goldstein and Brown confirmed that mutations of one or both alleles of the LDLR encoding gene, located on chromosome 19, were the cause of severe hypercholesterolemia in individuals with the FH phenotype and anticipated that their manipulation could influence the incidence of ASCVD even in individuals with "normal" levels of LDL-C [10,11].

Goldstein and Brown postulated that the increase in LDLR synthesis, expression and/or function could be "the master key" to answer their original question. As will be reviewed later, this postulate found resonance with the discovery by Akira Endo et al. in 1976 of a potent inhibitor of cellular synthesis of cholesterol, compactin [13-17]. In their subsequent investigations, Brown, Goldstein et al. [18] established that cholesterol content in membranes of the endoplasmic reticulum and the Golgi apparatus is the biological constant that modulates the synthesis, expression, and function of LDLR; a decrease in cellular cholesterol concentration leads to disinhibition-by proteolysis of its anchor or SCAP proteins-, of the transcription factor Sterol-Regulatory-Element-Binding-Protein-2 (SREBP-2); this transcription factor initially migrates from the endoplasmic reticulum to the Golgi apparatus and from this organelle to the cell nucleus where it encodes on chromosome 5 for the synthesis of HMGCoAR and on chromosome 19 for the synthesis of LDLR. In this way, the cell optimizes cell synthesis and extracellular uptake of cholesterol contained in LDL and thereby re-establishes its biological cholesterol constant; the excess cholesterol not required for cellular metabolism is esterified by the action of Acyl-CoA-Cholesterol-Acyl-Tranferase-2 (ACAT-2) and stored as drops of esterified cholesterol or eliminated by the hepatobiliary route [11].

The LDLR is a glycoprotein with five domains, as already mentioned, it is transcribed by the transcription factor SREBP-2 and encoded on chromosome 19 [19-21]. In short, the LDLR cycle is as follows: once the LDLR is synthesized, it migrates to the cell membrane and is anchored in membrane vesicles coated by the clathrin protein; domain 1 of the LDLR has the apo-B100 of the circulating LDL as substrate; the LDL once recognized by the LDLR, with an average of 1,500 molecules of esterified cholesterol in its core and bound to its receptor, are endocytosed; inside the cell, membrane vesicles fuse with endolysosomes transferring them their contents - LDL/LDLR-; by allosteric dissociation induced by the acid pH of the lysosome, LDLR is excluded from this organelle and has the ability to migrate to the cell membrane to initiate a new cycle. The protein and lipid component of LDL is hydrolysed in lysosomes; specifically, de-esterified cholesterol is transported from the endolysosome to the cell membranes by an intracellular transport mechanism called hydrophobic transport, thus the transcription factor SREBP-2 is inactivated and the synthesis of LDLR and HMGCoAR ceases (Figure 4).

Thus, LDLR with a 20 hour-half-life and a membrane-endolysosome-membrane time of 10 minutes is capable of transporting into the cell an average of 180,000 molecules of esterified cholesterol, undoubtedly, a mechanism of high efficiency transport. Accordingly, the LDLR discovery opened up the option to raise the following hypothesis: "*could increase LDLR synthesis, expression and/or function, increase the catabolism of LDL and thus hepatobiliary elimination of cholesterol without compromising the cell content thereof?*" [10,11].

Strategies to Increase the Synthesis, Expression and/or Function of LDLR

Cholestyramine

The first pharmacological strategy that retrospectively demonstrated that the increase in the synthesis, expression and function of LDLR determined a reduction in the circulating

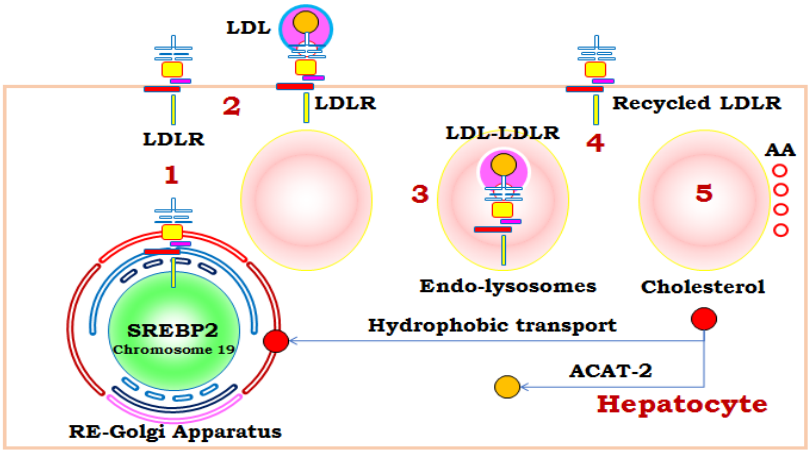

Figure 4: [1] The LDLR cycle is presented: at a low cholesterol concentration in the RE-AG system, the SREBP-2 transcription factor encodes on chromosome 19 for the synthesis of LDLR. [2] LDLR migrates to the cell membrane and recognizes an apo-B100 to LDL. [3] The LDLR-LDL binomial is endocytosed. [4] By acidification of the endo-lysosome the LDLR is recycled. [5] The protein content and esterified cholesterol of LDL are hydrolyzed. [6] Cholesterol is transported hydrophobically to the membranes of the RE-AG system or is re-esterified by the ACAT-2 effect.

level of LDL-C was cholestyramine. Cholestyramine-a bile-sequestering resin used since the 60s in individuals with FH-, by sequestering cholesterol-rich bile acids in the intestine and by reducing the enterohepatic pool of cholesterol, "forces" the liver to synthesize and capture more cholesterol for the synthesis of bile acids, this is accompanied by a discrete reduction in the level of circulating LDL-C; ultimately, Kovanen, Goldstein and Brown [1,8] demonstrated that, in dogs, the increase in circulating cholesterol uptake induced by cholestyramine was due to an increase in the number of LDLR in the hepatocyte.

Compactin

The pharmacological strategy that consolidated the hypothesis of Goldstein and Brown occurred with the discovery of the compactin by Akira Endo in 1976 [13-17]. Akira Endo, after studying several hundred strains of fungi, discovered compactin in a purified extract of *Penicillium Citrinum*. In his investigations, Endo showed that compactin blocked the synthesis of cholesterol by binding to HMGCoAR with a 10,000 higher affinity than its natural substrate and thus inhibited its function [13-14]. This biological effect was associated with an average reduction of 25-30% in the circulating level of total cholesterol in experimental animals and in humans with FH [15-17]. One year later, Mabushi [22], by quantifying lipoproteins, showed that compactin led to an average reduction of 25% in the circulating level of LDL-C with no change in high-density lipoprotein cholesterol (HDL-C). The latter work was editorialized by Goldstein and Brown [23], under the title "*Lowering Plasma Cholesterol by Raising LDL Receptors*", referring to compactin as the "penicillin for hypercholesterolemia" and to Akira Endo as the discoverer of "penicillin for cholesterol" [24], predicting that if this type of compounds demonstrated long-term safety, they would be an unprecedented alternative to fight ASCVD (Figure 5).

Statins

The Goldstein and Brown prophecy was fulfilled and after seven years of research and debate [25,26], lovastatin, originally termed mevinolin by Alberts and monacolin-K by Endo [27] was the first statin approved by the Food and Drug Administration (FDA) in 1987 [24], starting with the EXCEL study [28] the era of "Randomized and Controlled Trials" (RCT) with statins.

The age of statins includes more than two dozen RCTs of statins versus placebo and of moderate versus high intensity statins and 169,138 individuals analyzed one by one by the collaborative group called "Cholesterol Treatment Trialists" (CTT). The 2005 and 2010 CTT reports [29,30], (Tables 1 and 2) have allowed the establishment of the following paradigms on the use of statins in individuals at risk of ASCVD or with ASCVD:

Paradigm 1: In individuals at primary or secondary prevention of ASCVD, over a 5-year treatment period, the 39 mg/dL mean reduction of LDL-C with a moderate intensity statin versus placebo is associated with a 23% mean reduction in the relative risk of a coronary cardiovascular event and with a 21% mean reduction in the relative risk of any non-coronary cardiovascular event. Specifically, a 12% reduction in total mortality, determined by a 19% reduction in coronary cardiovascular mortality, a 23% reduction in coronary events, a 24% reduction in coronary revascularization, a 17% reduction in stroke, and a 21% reduction in vascular events. In other words, in primary prevention, for each 39 mg/dL reduction of LDL-C, 18 major coronary events, 12 coronary revascularizations and 5 strokes are avoided, and in secondary prevention, for each 39mg/dL reduction of LDL-C, 39 major coronary events, 27 coronary revascularizations and 8 strokes per 1,000 individuals treated for 5 years are avoided (Figure 6).

Paradigm 2: In individuals at primary or secondary prevention of ASCVD, over a 5-year treatment period, the use of a high-intensity statin versus a moderate-intensity statin adds to the latter a 20 mg/dL mean reduction of LDL-C and a 15% mean reduction in the relative risk of an ASCVD (Figure 7)."

Paradigm 3: The benefit from the use of statins is significant from the first year of treatment (10% relative risk reduction) and is amplified from the second year of treatment (25% relative risk reduction) per 39 mg/dL reduction in LDL-C.

Paradigm 4: The relative risk reduction with the use of statins is homogeneous regardless of the baseline level of LDL-C per 39 mg/dL reduction in LDL-C.

Paradigm 5: The relative risk reduction with the use of statins is homogeneous regardless of gender, age, ethnicity and level of cardiovascular risk per 39 mg/dL reduction in LDL-C.

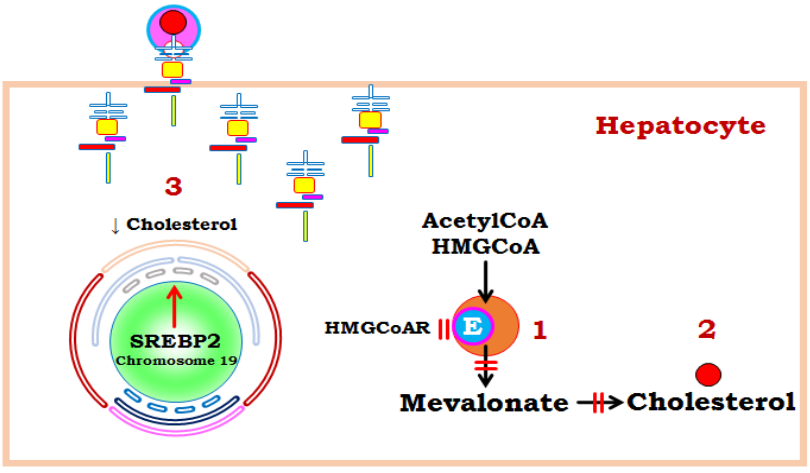

Figure 5: [1] The effect of statins is presented: The high affinity of statins for HMGCoAR. [2] Inhibits the transformation of HMGCoA into mevalonate and of mevalonate into cholesterol and isoprenoids. [3] The reduction of cholesterol inside the cell exerts a "pharmacological delusion" and the cell initiates its mechanism for the synthesis of LDLR, thus increasing catabolism or elimination of circulating LDL [13-17].

Study	Number	Follow-up	Station and Dose in mg	Baseline LDL-C mg/dl	ΔLDL-C mg/dl
SSSS-Lancet 1994	4444	5.2	S20-40-5.4% vs Placebo-8.2%	188.85	-8.49
WOSCOPS-NEJM 1995	6,595	4.8	P40-1.5% vs Placebo-2.1%	191.9S	-41.40
CARE-NEJM 1996	4,l59	4.8	P40-4.8% vs Placebo-6.3%	138.54	-36.86
Post-CABG-NEJM 1997	l,35l	4.2	L40-80-3% vs L2.5-5-3.8%	IS5.S7	-41.40
AFCAPS-JAMA 1998	6,605	5.3	L20-40-0.8% vs Placebo-1.2%	150.54	-36.37
LIPID-NEJM 1998	9,104	5.6	P40-4.1% vs Placebo-5.2%	ISO.IS	-39.86
GISSI-P-ITAL H J 2000	4,271	1.9	P20-5.4% vs non-Statin 6.1%.	151.70	-13.54
LIPS-JAMA 2002	1,677	3.1	F80-6.9% vs Placebo-9%	132.3S	-35.60
HPS-LANCET 2002	20,536	5.0	S40-3.1% vs Placebo 4.3%	130.80	-49.92
PROSPER-LAICET 2002	S,804	3.2	P40-4.9% Placebo-5.6%	146.67	-40.24
ALLHAT-LLT-JAMA 2002	10,335	4.8	P40-3.3% vs non-Statin 3.5%.	145.51	-20.89
ASCOT-LLA-LANCET 2003	10,305	3.2	A10-1.3% vs Placebo-1.9%	133.12	-41.40
ALERT-LANCET 2003	2,102	5.1	F40-2.7% vs Placebo-2.7%	160.21	-32.50
CARDS-LANCET2004	2,838	3.9	A10-1.5% vs Placebo-2.4%	117.26	44.11
	90,056	4.7 (2·6)	3.47%/year vs 4.45%/year	147.81	-42.5-RRR 22%

Table 1: The studies with date of publication, number of individuals included and analyzed, average follow-up time, incidence of cardiovascular events/year in the statin group vs the control group, baseline LDL-C, delta of LDL-C on treatment and RRR of cardiovascular events from the 14 studies included in the CTT 2005 are listed from left to right [29].

Study	Number	Follow-up	Station and Dose in mg	Baseline LDL-C mg/dl	ΔLDL-C mg/dl
ALLIANCE-JACC 2004	2442	4.7	A10-80-5.4% vs non-statin-6.4%	147.06	-44.89
4D-NEJM 2005	1235	4.0	A20-9% vs Placebo-3.3%	113.39	-38.31
ASPEN-DIAB CARE 2006	2410	4.0	A10-2.7% vs Placebo-3.3%	113.39	-38.31
MEGA-LANCET 2006	8214	5.0	P10-20-0.5% VS NON-STATION-0.7%	156.73	-25.92
JUPITER-2008	17802	2.0	R20-0.5% VS Placebo-1%	104.49	-42.18
GISSI-HF-LANCET 2008	4574	4.2	R10-2.2% vs Placebo-2.2%	118.42	-35.60
AURORA-NEJM 2009	2773	4.6	R10-8.1% vs Placebo-8.3%	99.84	-38.31
	39470 129526	4.8	2.8%/year vs 3.6%/year	143.19	-41.4 -RR22%
Study	**Number**	**Follow-up**	**Station+vs Statin-**	**Baseline LDL-C mg/dl**	**ΔLDL-C mg/dl**
PROVE-IT-NEJM 2004	4162	2.1	A80-11.3% vs P40-13.1%	101.58	-21.15
A to Z-NEJM 2004	4497	2.0	S40-80-7.2% vs S20-8.1%	81.07	-11.61
TNT-NEJM	10001	5.0	A80-4% vs a10-5.4%	97.52	-14.87
IDEAL-JAMA 2005	8888	4.8	A40-80-5.2% vs S20-40-5.3%	102.36	-21.28
SEARCH-LANCET 2010	12064	7.0	S80-3.6% vs S20-3.8%	96.75	-15.09
	39612	5.1	4.5%/year vs 5.3%/year	97.91	-19.73 -RR15%

Table 2: The studies with date of publication, number of individuals included and analyzed, average follow-up time, incidence of cardiovascular events/year in the statin group vs the control group (upper panel) or in the moderate intensity statin vs high intensity statin groups (lower panel), baseline LDL-C, delta of LDL-C on treatment, and RRR of cardiovascular events from the 12 studies added by CTT 2010 to CTT 2005 are listed from left to right [29].

Consistent with the relative risk reduction of ASCVD demonstrated by statins, this pharmacological group has also been shown to induce in a statin dose-intensity dependent manner the stabilization and even the regression of coronary atherosclerosis studied through coronary intravascular ultrasound [31,32] (Figure 8).

Thus, it is undeniable that statins, with a scientifically demonstrated mechanism of action-inhibition of HMGCoAR-, through the increase in the catabolism of LDL by exaltation of the synthesis, expression and function of LDLR, determine a significant population and individual reduction in the circulating LDL-C level, in the atherosclerotic plaque burden and in the incidence of cardiovascular events associated with atherosclerosis.

Ezetimibe

This molecule has as a mechanism of action the reduction of intestinal absorption of cholesterol by inhibition of the transporter known as Niemman Pick-C1-Like1 protein (NPC1L1). Although the inhibition of intestinal absorption of cholesterol appears to be the central mechanism of action of ezetimibe, the essence of such mechanism of action lies in its result "similar to that of a bile-sequestering resin". In other words, inhibition of intestinal absorption of cholesterol induces an increase in the synthesis, expression and function of LDLR in the hepatocyte with a reduction of 15% to 20% in the circulating level of LDL-C [33].

The IMPROVE-IT study "*The Improved Reduction of Outcomes: Vytorin Efficacy International Trial*" [33] published in 2015 showed that in individuals at secondary prevention after an acute coronary syndrome (SICA), over a treatment period of 7 years, the 16 mg/dL mean reduction of LDL-C with simvastatin 40 mg+ezetimibe 10mg versus simvastatin 40 mg+placebo is associated with a 6% mean reduction in the relative risk of a cardiovascular event (Figure 9). This benefit, whose interpretation has been controversial, although at first

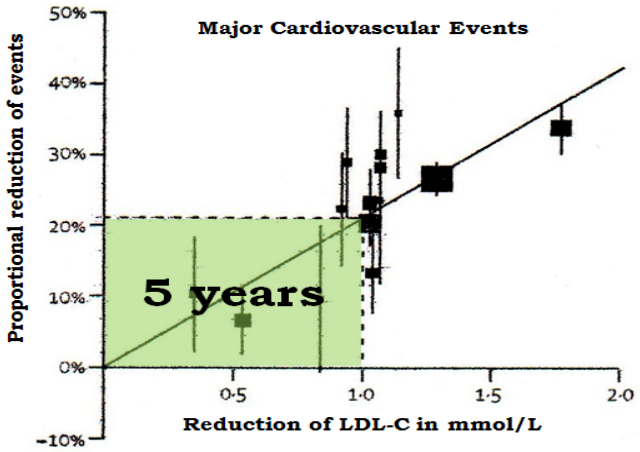

Figure 6: In a linear relationship, reduction of 39 mg/dL (1 mmol/L) LDL-cholesterol with a moderate intensity statin vs placebo or control leads to a relative risk reduction of 22% for a cardiovascular event during a 5-year treatment (cardiovascular death, non-fatal myocardial infarction, stroke or coronary revascularization) [29].

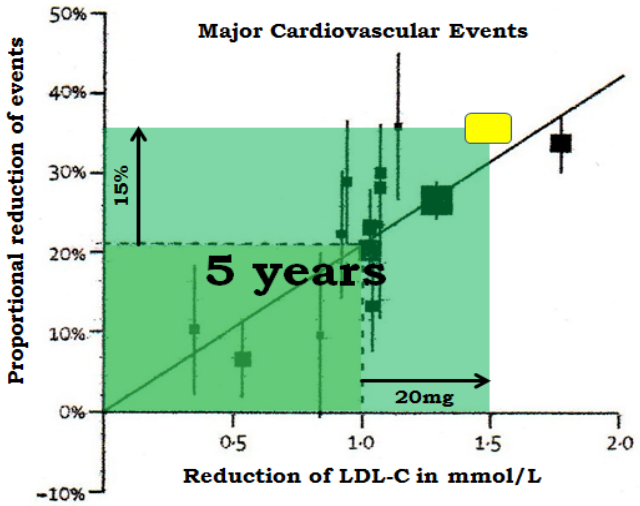

Figure 7: Following the linear relationship, the mean LDL cholesterol reduction of 20 mg/dL (0.5 mmol/L) with a high intensity vs. a moderate intensity statin adds a relative risk reduction of 15% for a cardiovascular event during a 5-year treatment (cardiovascular death, non-fatal myocardial infarction, stroke, or coronary revascularization) [30].

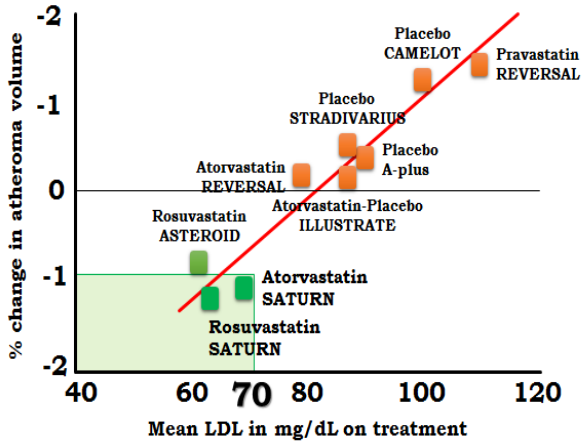

Figure 8: In a linear relationship, LDL-C reduction with statins induces athero-stabilization and even significant athero-regression (> 1%/year) when at high-intensity statins (atorvastatin 80mg or rosuvastatin 40mg-SATURN study) LDL-C levels below 70 mg/dL (green box) are achieved [32].

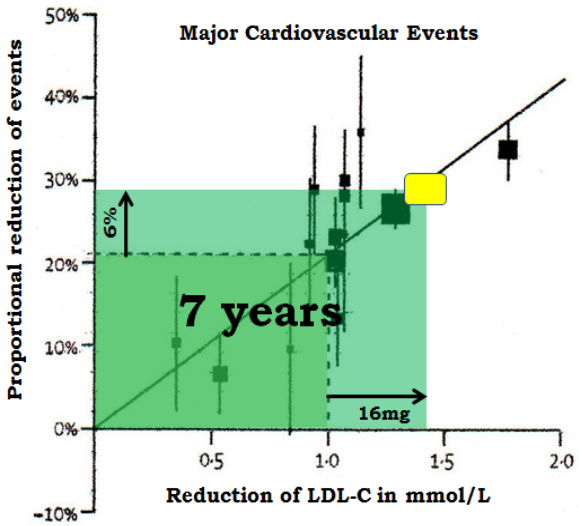

Figure 9: Following the linear relationship, the mean LDL cholesterol reduction of 16 mg/dL with ezetimibe 10 mg+simvastatin 40mg vs. simvastatin 40mg adds a relative risk reduction of 6% for a cardiovascular event during a 7-year treatment (cardiovascular death, non-fatal myocardial infarction, stroke or coronary revascularization) [33].

glance looks modest, it adds to the "LDL-centric" hypothesis, which until recently had only been demonstrated with LDL-C reducing strategies operating through the synthesis, expression and function of the LDLR.

Inhibition of PCSK9

Without a doubt, the 14-year story that began in 2003 with the description by Seidah [34-38] of the protease initially called NARC-1-now PCSK9-and its most advanced saga, the March 2017 publication of the study FOURIER "*Further Cardiovascular Outcomes Research with PCSK9 Inhibition in Subjects with Elevated Risk*" (NCT01764633) [39] with evolocumab is the most fascinating story of current cardiology. Using an approach wich blocks the protein PCSK9 from binding to the LDLR and thus enhancing LDLR recycling, the authors demonstrated a third approach to reducing ASCVD through LDL-C reduction. This story reconfirms Goldstein and Brown's hypothesis that physiological LDL levels are lower than LDL levels prevalent in general population and that strategies wich efficiently enable us to reach physiological levels of LDL are beneficial. This area of research has been updated and extensively reviewed by the author [40-43].

Conclusion

This brief summary corroborates that in the 21st century, we as Cardiologists can aspire to our main goal - eradication or at least a significant reduction of ASCVD - by reducing the gap between the pathological observed values we see in routine clinical practice and the physiological values of LDL-C.

We have reviewed the keys of 40 years of scientific evidence that allow us to consider that the physiological level of LDL range from 25 to 50 mg/dL and that in addition to the utopian option to adopt during the pre- and post-gestational life a Paleolithic lifestyle, we have pharmacological and biological strategies to effectively bridge the gap between the so-called "normal" or average value and the "biologically active" or physiological value of LDL-C. These strategies, operating by different physiological pathways, favor the catabolism of LDL through the increase of the synthesis, expression and function of the receptor for said lipoprotein and have demonstrated, with unquestionable scientific evidence, to reduce the level of circulating LDL-C at a physiological level, to reduce the progression of atherosclerosis and to reduce the incidence of events by ASCVD. As mention at the beginning of this review, certainly the best story in contemporary cardiology.

This story supported by very contemporaneous analyses [44] still continues and we must participate in generating new evidence, among the most important: the incorporation of the "Genetic Risk Score" to the traditional estimate of the cardiovascular risk; to date, the hybrid algorithm (CRS+GRS) has shown significant improvement in prognostic and therapeutic discrimination [45]; likewise, the development of new strategies for the reduction of levels of different atherogenic lipoproteins begins to show promising results [46-49], and finally, perhaps the most fascinating, the new proposals for the application of cost-effective strategies (e.g., statins) in young high-risk populations for ASCVD in the medium and long term [50]. In the author's view, the latter is the most important scenario, in which the hybrid algorithms for the medium-long term estimation of cardiovascular risk will have their greatest application and impact at population and individual levels.

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