EDITORIAL

New Cholesterol Targets of SBC Guidelines on Dyslipidemia

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Evidence from clinical trials and meta-analysis have demonstrated that the most effective LDL (low-density lipoprotein) cholesterol–lowering treatment is associated with unequivocal benefits for reducing atherosclerotic cardiovascular disease (ASCVD) events.[1] More recently, clinical trials concluded that the addition of ezetimibe and of a new class of drugs, inhibitors of proprotein convertase subtilisin/kexine type 9 (iPCSK9), to statins, were able to reduce LDL-C to levels not previously achieved with the available therapy so far.[2-4]

Is this context, the results of the IMPROVE-IT study - *Improved Reduction of Outcomes: Vytorin Efficacy International Trial*,[2] with statins plus ezetimibe compared to statin monotherapy, achieved strict lipid control (LDL-c of 53.7 vs. 69.5 mg/dL, respectively) in patients with acute coronary syndrome, that is, individuals at high cardiovascular risk. In this study, patients achieving LDL-cholesterol levels less than 50 mg/dL had a significantly lower risk of major cardiovascular events compared to patients with LDL cholesterol levels above this value. The risk category was proportionally lower as the level of LDL-C decreased.[2] Although at modest levels, there was an incremental cardiovascular event risk reduction, except mortality.

More recent clinical trials, also in subjects at high cardiovascular risk, on secondary prevention of atherosclerotic disease with PCSK9 inhibitors, notably with evolocumab (The Fourier study - *Further Cardiovascular Outcomes Research with PCSK9 Inhibition in Subjects with Elevated Risk*)[3] and with bococizumab (Spire 1 and Spire 2 trials - *Studies of PCSK9 Inhibition and the Reduction of Vascular Events*,),[4] in combination with high-dose statin treatment regimens, have also shown major cardiovascular events reduction (except cardiovascular and general mortality). In the Fourier study,[3] LDL cholesterol levels decreased to a median of 30 mg per deciliter (with LDL-C reduction of 59% from baseline in 48 weeks) and reduced by 15% the risk of the composite primary outcome (cardiovascular death, myocardial infarction, stroke, hospitalization for unstable angina and coronary revascularization). However, only the Spire 2 study showed a significant benefit associated with the use of bococizumab.[4] It is worth noting that, in the joint analysis of the SPIRE 1 and 2 trials, LDL-C had decreased by 56% by the 14th week of the study. The findings are in line with those observed with the evolocumab in the *Global Assessment of Plaque Regression with a PCSK9 Antibody as Measured by Intravascular Ultrasound* (GLAGOV)[5] trial, which evaluated the volume of atherosclerotic plaque, and showed that the cardiovascular benefits persisted even when LDL-C levels were reduced to 20-25 mg/dL. The study showed an average reduction of 1% in atheroma volume after 18 months of treatment and about two-thirds of patients showed plaque regression.[5]

On the other hand, Mendelian randomization studies involving more than 300,000 carriers of more than 50 genetic variants had already consistently demonstrated that lower LDL-C levels throughout life were associated with a decreased risk of ASCVD development. This not only demonstrated the causal relationship between LDL-C and ASCVD, but also a consistent dose-dependent log-linear association between the magnitude of LDL-C reduction and the risk of developing ASCVD.[6]

Due to these evidences, the Department of Atherosclerosis of the Brazilian Society of Cardiology (SBC-DA) released, in 2017, the Update of the Brazilian Dyslipidemias Directive and Prevention of Atherosclerosis,[7] in accordance with the major international Guidelines on the subject,[8]

Keywords

Atherosclerosis; Cholesterol / standards; Dyslipidemias; Risk Factor; Reference Standards.

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DOI: 10.5935/2359-4802.20170090

and created the "very high cardiovascular risk category" for individuals with severe atherosclerotic coronary, cerebrovascular or peripheral vascular disease. For these subjects, targets for LDL-C were reduced to < 50 mg/dL (or a percentage reduction of at least 50% from baseline) and < 80 mg/dL for non-HDL (Non-high-density lipoprotein) cholesterol, maintaining the recommendation of achieving LDL-C goals as the primary target and non-HDL-C as a secondary treatment target.[7]

Table 1 shows the criteria for the analysis of lipid variables. The levels of TC, HDL-C and triglycerides remain interpreted as reference values, and only triglycerides are influenced by the metabolic state before collection (fasting and nonfasting), while LDL-C and non-HDL cholesterol must be interpreted according to individual health-risk category, estimated by the Global Risk Score (GRS)[6]. The Update of the Guidelines provided an application for calculating the GRS on the SBC-DA website (Risk Calculator 2017).[6]

Thus, aggressive reduction guidelines and, as a result, the inclusion of new LDL-C targets in the SBC-DA Update of the Guidelines of Dyslipidemia for high cardiovascular risk patients are based on the following rational:

- LDL-C plays an important role in the pathogenesis and perpetuation of ASCVD.
- Elevated levels of LDL-C are related to increased risk of ASCVD events and the reduction of LDL-C is associated with reduction of these events, continuously and incrementally. Therefore the higher the cardiovascular risk, the lower should be the level of LDL-C.
- Studies of Mendelian randomization have shown that individuals with low levels of LDL-C throughout life have a much lower risk of developing ASCVD.
- Randomized clinical trials with lipid-lowering drugs, notably statins, ezetimibe and PCSK9 inhibitors have shown a reduction of ASCVD events.

Table 1 – Reference values and therapeutic target, according to the cardiovascular risk assessment estimated for adults aged 20 years and over

Lipids	With fasting (mg/dL)	Without fasting (mg/dL)	Referential category
Total cholesterol†	< 190	< 190	Desirable
HDL-c	> 40	> 40	Desirable
Triglycerides	< 150	< 175 ‡	Desirable
	Risk category		
LDL-c	< 130	< 130	Low
	< 100	< 100	Intermediary
	< 70	< 70	High
	< 50	< 50	Very high
Non HDL-c	< 160	< 160	Low
	< 130	< 130	Intermediary
	< 100	< 100	High
	< 80	< 80	Very high

**According to the cardiovascular risk assessment estimated by the prescribing physician; Total cholesterol > 310 mg/dL: consider the likelihood of familial hypercholesterolemia; When the triglyceride levels are above 440 mg/dL (without fasting), the prescribing physician must request a new triglycerides measurement after 12-hour fasting and the laboratory should consider this as a new triglycerides test.*

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