

Does the Conduct of Argentine Physicians Adjust to Clinical Guideline Recommendations for Statin Control of Cardiovascular Risk?

¿Se ajusta la conducta de los médicos argentinos a la recomendada por las guías clínicas para el control del riesgo cardiovascular mediante la utilización de estatinas?

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Cardiovascular (CV) diseases are currently the worldwide leading cause of death. (1) They account for over 24% of all deaths and it is estimated that about 23 million people/year will die for this cause within 15 years. (2) Nine per cent of health expenditure in Europe is assigned to CV disease (3) and it is estimated that in the next 3 decades the money directed towards this goal is expected to triple in the United States. (4) Eliminating the responsible risk factors, including cholesterol, 80% of these diseases could be prevented. (5) Thus, the optimization of blood cholesterol levels with statins is one of the pillars of CV disease prevention. However, although lifestyle and treatment goals are well-defined, control of blood cholesterol levels is still far from optimal. (6, 7) For this reason, studies such as the EUROASPIRE surveys (6, 7) (performed in several European countries) or the COFEMA study (8) (carried out in Argentina and published in this same issue) are necessary to analyze the conduct of physicians regarding the use of statins, allowing the identification of existing weaknesses and thus improving the strategies to be followed in order to better achieve blood cholesterol targets indicated by clinical guidelines (CG).

Blood cholesterol targets are one of the discrepant points that we find among CG and analyzed both by the EUROASPIRE surveys (6, 7) and the COFEMA study. (8) The American guidelines (9) do not identify specific LDL levels, but rather identify four risk groups in whom to start statins directly. Among these four risk groups are diabetic patients, who are recommended direct initiation of pharmacological treatment. However, only 79% of Argentine physicians surveyed in the COFEMA study complied with this recommendation. (8) And this is because it is not a globally accepted recommendation; the recently presented European guidelines (10) maintain target LDL levels for each risk group which, in the case of diabetic patients, would be <70-100 mg/dL in most cases, rec-

ommending direct initiation of statin therapy only in type I diabetics with microalbuminuria or associated kidney damage. This lack of consensus may contribute to the fact that not all physicians treat patients with similar characteristics in the same way.

Besides knowing when to start statins, it is also important to know the most suitable dose. Although the 2013 AHA (9) guidelines mainly emphasize the recommendation of high statin doses on secondary prevention, European studies also make it clear that the greater the intensity of treatment, the greater the percentage of patients achieving LDL target levels. (6) Despite the clinical evidence, only 37.6% of patients suffering from a CV event in Europe are discharged from hospital with high-intensity statins. (6). Likewise, the COFEMA study revealed that slightly over half (65%) of Argentine physicians used statins at high doses.

The cause?: fear of adverse effects. A US survey revealed that up to 62% of patients discontinued statins on their own for fear of side effects. (11) In the same line, most Argentine doctors recognized routine monitoring of liver enzymes, although it is not a precaution recommended by any CG.

It is possible, therefore, that the low percentage of physicians prescribing a high-statin therapy (40-80 mg atorvastatin, 20-40 mg rosuvastatin) is related to the fear of adverse effects, despite existing clinical evidence.

It is also significant that in most of the results (33% in both studies) of both the COFEMA study (8) and the EUROASPIRE IV survey (6), doctors reduced the dose or discontinued treatment with statins once the desired targets were achieved. However, the contrary approach does not happen. Among all patients participating in the EUROASPIRE IV survey (6) who did not receive adequate statin treatment despite its indication, only in 12.3% of cases the treatment was initiated or intensified.

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However, we can confirm that statins are the main weapon we have against dyslipidemia, albeit not the only one. Ezetimibe is an inhibitor of intestinal cholesterol absorption that has been shown to improve the reduction of LDL levels associated with statins. (12) That is why its use is recommended by European guidelines (10) associated with statins in those cases where the desired LDL targets are not achieved, or alone in case of intolerance to statins. The American guidelines (9) do not share this recommendation, as there is no thorough evidence of the efficacy of this drug despite existing publications. The attitude of Argentine doctors is consistent with this premise, using ezetimibe in less than 20% of cases.

The analysis on the use of statins in controversial situations could not be missing in a study of such relevance as COFEMA. For example, there has been much debate about the risk of using statins in patients with chronic kidney disease (CKD). The 2013 American guidelines (9) avoided any recommendation regarding the use of statins in the absence of evidence. The 2016 European guidelines, (10) however, set a clear position based on the different clinical trials available in patients with CKD and statins: patients with CKD are patients at very high CV risk in whom statin use is indicated, except those on hemodialysis free of known atherosclerotic disease. Accordingly, 90% of Argentine physicians surveyed in the COFEMA study indicated statins in secondary prevention in patients with CKD.

The same happens with heart failure (HF) and the use of statins. The 2013 AHA guidelines (9) did not consider that there was enough evidence to make any recommendation in this regard, although the 2016 ESC guidelines (10) point out that while the routine use of statins in patients with HF is not indicated, there is neither evidence of damage, and therefore of their discontinuation in patients with HF and indication to use them for another reason. In this line, 81% of COFEMA study respondents chose to indicate statins on secondary prevention in patients who also presented HF.

Hence, does the conduct of Argentine doctors adjust to CG recommendations? The results of the COFEMA study demonstrate, as we have previously analyzed, that it does. Perhaps the greatest deficiency is observed in the low number of Argentine doctors prescribing high doses of statins, similar to that observed in the EUROASPIRE surveys. Given the evi-

dence in favor of high intensity statin therapy, it would be interesting to carry out future studies to confirm the causes of this attitude in order to redirect it, thus increasing the percentage of patients that reach the blood cholesterol targets indicated by CG.

Conflicts of interest

None declared.

(See authors' conflicts of interest forms in the website/Supplementary material).

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Challenging the Right Ventricle: The Ups and Downs and Ins and Outs of Strain

Desafiando al ventrículo derecho: los altibajos y pormenores del strain

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The left ventricle (LV) may be perceived as the dominant heart chamber but, as is often the case, bulk is often associated with simpleness. The left ventricular chamber can simply be modelled as a prolated ellipse - or a bullet. Left ventricular remodelling is divided simply into volume loaded or eccentrically remodelled as in aortic and mitral regurgitation vs. pressure loaded, with concentric remodelling as in aortic stenosis or systemic hypertension. Either way, with the exception of a varying degree of sphericity, the basic shape does not dramatically change.

The right ventricle (RV), on the other hand, while displaying far less brawn than the LV is actually infinitely more complex. It must eject the same volume as the LV (in the absence of shunt), yet only has one fifth of the mass. Adding to the complexity, due to the right ventricular shape, its remodeling process is geometrically far less simple. (1) Of course, it hypertrophies and dilates, but the pattern is considerably challenging to predict or describe. Add to this the shared inter-ventricular septum and the muscle fibers that the LV wraps around the right ventricular apex and we have a mathematical modeler's life challenge. (2)

So, how can we describe the RV when it is faced with pathology? The first thing to recognize is the difference between normal and abnormal. This was the main goal of establishing "cut-off" values through guideline documents. (3) But here again we see, as was demonstrated in Del Castillo et al.'s paper published in this issue of the Journal, (4) as well as in others, there is considerable overlap between so-called normal values and abnormal values. (5) Cut-off points are best viewed as values to suggest abnormality, as opposed to confirm normalcy. The next thing is to recognize that not all conditions will provoke the same kind of reaction. We know that clinically, volume overload conditions such as atrial septal defect (ASD), behave differently clinically than pressure-loaded conditions such as pulmonary hypertension, so it is likely their effects on the heart should be different.

With that in mind, Del Castillo et al. approached both these goals by describing the different ways of adaptation or maladaptation in a significant sample of volume-loaded patients with ASDs and pressure loaded patients with pre-capillary pulmonary hypertension secondary to schistosomiasis, comparing them with normal subjects. A number of interesting observations were made through their results. Firstly, they demonstrated that the LV is compromised physically by the dilated RV through compression and that its systolic function is somewhat reduced - not by considering LVEF- but when global longitudinal strain is used, likely because of the shared septum. As such, the RV-LV interaction is more than just compression from inter-chamber pressure gradients. Second, they demonstrated that the pressure overloaded ventricles demonstrated more severe dilatation than the volume loaded ones, as well as more significant systolic dysfunction when traditional parameters of tricuspid annular plane systolic excursion (TAPSE), S' wave and fractional area change (FAC) are used. The authors point out what was stated above: despite significant remodeling and dysfunction, many right ventricular pressure overload (RVPO) subjects had values within normal limits. They suggest that this might be related to presence of significant tricuspid regurgitation (TR) (data not shown), but in pulmonary arterial hypertension (PAH), the basal segments are often the last to fail. The finding of a small LV, reduced FAC and severely elevated systolic pulmonary artery pressure (sPAP) suggest clinically advanced PAH. In other words - normal does not connote normal, but abnormal is very bad.

There are few data comparing right ventricular remodeling and function with differing etiologies of pulmonary hypertension. Anecdotally, post-capillary etiologies result in a relatively preserved right ventricular shape, with dysfunction presenting only very late, or with concomitant pulmonary artery reactivity as in mitral stenosis. In addition, Grapsa et al., studied right

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