CONTROVERSY

The Pleiotropic Effect is Essential for the Benefit of Treatment with Statins

Agonist

ALCEO R. BARRIOS[MTSAC, 1]

The first isolated statins were lovastatin and mevastatin, obtained as from *Asperfillus* fungi in the late 70'. As from then, new molecules were developed and at present we can find two types: 1) natural (by fermentation): simvastatin and pravastatin and 2) synthetic: fluvastatin, atorvastatin and rosuvastatin. These drugs were initially used to reduce plasma cholesterol levels and they work on the liver by the competitive inhibition of the 3-hydroxy-3-methylglutaryl coenzyme A (HMG-Co-A) reductase. This enzyme is responsible for the production of mevalonate, a sterols precursor, cholesterol is one of them. But this is not the only inhibition that they cause; they also participate in the production of isoprenoids, responsible for the activation of G proteins such as Rho and Ras, which intervene in inflammatory and endothelial dysfunction, and that together with thrombosis are the main mechanisms that interact in acute coronary syndromes (ACS).

Lipid reduction was the only known mechanisms for years, but we should open our minds to pleitropy. First, let's define pleitropy, a word originated in genetics, and that was then adopted by pharmacology: condition under which a gene has multiple effects on the life of an organism.

So far, the known pleitropic effects in ACS are three: 1) anti-inflammatory, 2) anti-thrombotic, 3) endothelial anti-dysfunction. These are key effects in the acute phase of ACS as inflammation, the prothrombotic status, and endothelial dysfunction lead to instability to the atherosclerotic plaque and therefore to the formation of the thrombus and vice versa, causing a vicious circle, of difficult control most of the times.

Anti-inflammatory effect: I am going to address the evidences shown by two clinical trials which enrolled a significant number of patients and showed these effects: MIRACL and PROVE-IT TIMI 22 (1, 2). PROVE-IT showed in 4,000 patients a significant reduction in an anti-inflammatory marker such as PCR, with a beneficial effect even greater in patients with LDL cholesterol < 70 mg/dl with the administration of atorvastatin 80 mg (interventional branch) versus pravastatin 40 mg (conservative branch). The study was design to show the non inferiority of pravastatin over atorvastatin in ACS, but during its performance, the dose of pravastatin had to be increased due to the evident superiority of the atorvastatin dose. However, a reduction of 25% in the endpoints was obtained. The benefit was accompanied by PCR reduction, but the relation between PCR reduction and decreased LDL was very weak: 0.13.

The other considered study, MIRACL, that enrolled 2,000 patients, showed not only a significant reduction in PCR, but in other inflammatory markers such as the ligand CD 40 and serum amiloid A. Another trial performed in Argentina (3) showed that with atorvastatin 40 mg significant PCR reductions were achieved independently of cholesterol reduction, as shown also by the PROVE-IT and also with reduction in the speed of globular eritro-sedimentation. Although PCR specificity is low, the REVERSAL study (4) showed a strong relation between PCR reduction and plaque regression assessed by intra-coronary ultrasound.

Anti-thrombotic effect: I would like to highlight an experimental study (5) that showed a clear reduction in the expression of plasma tissular factor and endothelial cells in the presence of simvastatin. This was not related either to the levels in cholesterol reduction. Another ACS trial in patients treated with 10 mg atorvastatin and mean total cholesterol in the population of 210 mg/dl showed a significant reduction in ATIII, Va factor and von Willbrand's in regards to those receiving placebo (6).

Endothelial anti-dysfunction: an experimental trial in mice where rosuvastatin was administered to one group and saline solution to another showed a significant increase in plasma nitric oxide in the rosuvastatin group, the counter test with a substance that inhibits the NO synthetase reduced NO plasma levels in both groups (7). It is interesting to comment on another study with simvastatin and ezetimibe. Both drugs reduced LDL cholesterol levels in 15% compared to baseline values, but when the arm test was performed and by measuring post ischemic vasodilatation, the ezetimibe group did not show differences with baseline values after 16 weeks of treat-

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ment, whereas the simvastatin group showed a significant flow increase following administration (8).

Other studies, such as OPUS TIMI 16, (9) GUSTO IIb (10) and PURSUIT, (11) showed a significant reduction in cardiovascular mortality in patients treated with statins. Although the analyses were post-hoc, results deserve to be taken into consideration.

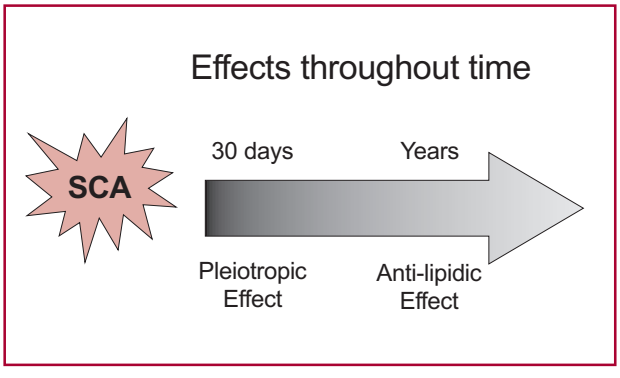
The time of initiating therapy with statins in the ACS is also important. According to the evidences shown in the MIRACL and PROVE-IT trials, early administration – no later than the 96 hours – is advisable. The ARMYDA 1 (12) study also showed a reduction in enzyme infarction in acute patients with indication of coronary angioplasty that were receiving statins previously.

A sub study of the MIRACLS trial showed that the reduction in absolute risk for an event such as STROKE after 16 weeks of therapy was similar to that of the CARE (13) and LIPID (14) after five years! What happened was that in MIRACL patients were acute and received early therapy with high doses, contrary to the other two mentioned studies where patients were chronic and received late therapy in regards to the initial event.

Therefore, I believe that the pleitropic mentioned effects are predominant in the benefit that acute patients receive during the first thirty days; the antilipidic effect – predominant during the chronic phase – starting to overlap later for the prevention of late effects throughout the years.

We are at the early stages concerning these concepts and so many others new to medicine. There are publications still that do not consider these effects that were assessed in chronic patients or with late therapy, outside the 96 mentioned hours. Maybe my opponent will refer to them in order to define his position.

I finalize with a graphic that summarizes this presentation so far.



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Antagonist

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In the title of this controversy there are two fundamental words that I believe should be clearly defined. "Pleiotropic" effect and "essential". The former is a term derived from the English language which in turn derives from the Greek *pleiôn*, besides, and *tropos*, turn or twist, that do not exist in the "Diccionario de la Real Academia Española". The original term, "pleiotropic", was used in genetics to explain the multiple phonotypical expression "*pleiotropic gene*". An extension of its meaning would be "that causes more than one effect". In regards to statins, it could be understood as "the other effects", besides the decrease in plasma cholesterol caused by these drugs.

The other key word is "essential", a term derived from the Latin (*primordiâlis*) (which definition is: primitive, first). It is said about the fundamental principle of any thing.

As from these definitions, I believe that pleiotropic effects exist, but no randomized controlled studies showing that "the other effects of statins" are "the essential principle" by which these drugs are beneficial in the reduction of cardiovascular events have been published. At present there is no doubt about them being the most potent and efficacious hypolipemiant drugs available. As from the publication of the 4S study up to date, numerous controlled and randomized studies have shown that different statins reduce the major cardiovascular events. The pleiotropic effects of these dugs have been bound to their action over the pathway of isoprenyls, geranyl diphosphate and pharnesyl diphosphate that modulate intra cellular proteins such as Rho and Ras that participate in different intra cellular processes related with the expression of nitric oxide, adhesion molecules and cellular proliferation. As from these experimental findings, many in *vitro studies* have been performed showing anti-inflammatory, anti-proliferative actions, modulating the expression of different adhesion, anti oxidant molecules. Also, different studies have shown the effect of these drugs on the endothelial function. Considering that inflammatory mechanisms, oxidative processes, release of different kinins, adhesion molecules, cellular migration and proliferation are involved in atherogenesis, the pleiotropic effects have been associated to the anti-atherosclerotic statins effect. However, it is fundamental to understand that in the initial genesis of atherosclerosis, the increase in LDL cholesterol level- in fact, the term is atherosclerosis, "fatty accumulation" – is essential.

One aspect that should be considered is the differences that exist between the basic experiments that are developed in isolated models at the laboratories and the biological processes in humans. In the first case, it is possible to isolate the phenomenon to be examined and therefore modify a single variable, which is the subject of the research. In the human being, when a drug is administered, as with statins, multiple changes appear that operate at different levels. Of all the modifications induced by these drugs, cholesterol decrease has been associated with decrease in cardiovascular events.

In the medical literature there are different situations where the results of experimental studies do not apply to the clinical practice. Two recent examples that could be considered due to their association with atherosclerosis are:

– Oxidative processes: in laboratory studies it has been shown that oxidation causes from modifications in the different lipoproteins, particularly LDL, up to changes in the endothelial function. However, the controlled, randomized studies that used antioxidative drugs or vitamins did not show decrease in cardiovascular events.
– The inflammatory processes: it is known and widely publicized that they are intimately related to atherosclerosis, as previously discussed. Again, neither that inflammatory markers such as the ultra sensitive, reactive protein C (uRPC) supply benefits over the traditional risk scales (Framingham), nor that non steroid anti-inflammatory drugs decrease cardiovascular risk have been shown. In the systematic review and meta-analysis carried out by Mc Gettigan and Henry, the authors observed that robecoxib increased event risk in 33%, diclofenac in 40%, piroxicam and ibuprofen were neutral and only naproxen decreased it in 3%. Considering the methodological limitations in this study, it can be concluded that inflammation control, with potent drugs for the control of these types of processes, do not decrease the risk of vascular events and also could increase them. In these situations we observe that experimental laboratory data leads to a physiopathological rationale that has not found correlation in the evidences supplied by clinical studies. Therefore, it is possible to enunciate that the finding of physiopathological processes or mechanisms of action shown in experimental studies do not always apply in clinical practice.

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Based on the previous examples, it is interesting to examine some questions:

Is it possible to dissect in the human being (*in vivo*) the hypolipemiant effect of statins from its other actions? Is it possible to enunciate that pleiotropism is "essential" in the benefit that statins provide?

The answer to these questions takes us to a fascinating world, and generally hardly known by physicians that are not specialized on lipidic disorders: the control of the severe stages by means of aggressive, non pharmacological strategies such as the surgical techniques and LDL aphaeresis.

In 1982 the POSCH study, that included 838 patients randomized to partial ileac *bypass* or control was published. LDL cholesterol reduction was 37,7% and combined events (myocardial infarction- cardiovascular death) were 35%. In the angiographic follow up at 3, 5, 7 and 10 years a significant decrease in the progression of coronary atherosclerosis was observed. This study showed that cholesterol reduction decreased vascular events and coronary atherosclerosis.

However, it did not assess other parameters related to the pleiotropic effects of statins such as the action on the endothelial function, adhesion molecules, etc.

An interesting matter is to know if the reduction of cholesterol *per se* improves or has other actions. In this field of research, a study by Tamai et al opens a scarcely publicized spectrum of knowledge. The author used a technique known as LDL aphaeresis, which consists in performing an extraction of high density proteins by means of a procedure similar to plasmapheresis. With this technique, the author showed that endothelial dysfunction measured by forearm pletismography increases rapidly when LDL plasma cholesterol is drastically reduced. With similar procedures, improvement of the coronary endothelial dysfunction, increased coronary flow, and decreased ischemia by positron emission tomography were shown, and a very important aspect was that benefit was observed at 20 and 24 hours after aphaeresis finalized. Besides these effects on endothelial dysfunction, it has also been shown that abrupt reductions in total cholesterol of about 44.6% and LDL cholesterol in 54.6% are associated with significant decreases in the following molecules: von Willebrand's factor (38,6%), sE-selectin (22,6%), sICAM-1 (14%) and sVCAM-1 (15,5%). In a recent review, Koga explains that cholesterol reductions by aphaeresis also cause atherosclerosis plaque stabilization and regression. All these effects were achieved without drugs or techniques that work by inhibiting the pathway of geranyls and/or pharnesyls , postulated mechanism by which the pleiotropic actions of statins are produced. From the published evidence emerges the concept that the simple cholesterol reduction improves the endothelial function, modulates the expression of the inflammatory and adhesion molecules, and decreases the progression of atherosclerosis plaques.

Finally, it is interesting to analyze the effect of reducing cholesterol beyond the effect provided by a statin. In the randomized controlled study known as postCABG a single dose of lovastatin was used in both groups and cholestyramine was associated with the objective of achieving LDL cholesterol plasma level higher or lower than 100 mg/dl. The group with levels of 93-97 mg/dl had less progression of the coronary disease (angiography) compared with the group that reached levels of 136 mg/dl. With the analyzed evidence it is possible to conclude that:

The experimental findings not always are correlated with the results in studies that included patients.

Cholesterol decrease causes reduction of coronary events and has anti-atherosclerotic effects expressed over the endothelial function and different molecules related to the genesis of atherosclerosis.

Cholesterol decreases over those reached by statins, with the addition of other drugs such as ezetimibe or cholestyramine, reduce atherosclerosis and inflammatory parameters such as URPC. After analyzing the pool of doses, Sager observed in 668 patients that received simvastatin alone in doses of 10 to 80 mg *versus* simvastatin plus ezetimibe 10 mg that the reductions in LDL cholesterol were of 37,15% *versus* 51% and for the higher quartile of URPC, of 34,4% *versus* 51,3%, respectively. This finding is interesting because ezetimibe works at the enterocyte membrane level and has no systemic effects, which supports the concept that cholesterol reduction "alone" has anti-inflammatory effects.

Recently, a study performed by Bleske et al in non ischemic heart failure patients treated with high doses of atorvastatin (80 mg/dl), where the effect over the brain natriuretic peptide, URPC and TNF alpha, the anti-LDL oxidase antibodies, VAM2, p selectin and intracellular adhesion molecules was assessed. The authors did not observe significant changes in any of these molecules compared with the placebo group.

From the data presented, it can be concluded that:

- There are no randomized, controlled studies in human beings that were able to show the isolated "pleiotropic" effect of statins.
- There is evidence on the effect of decreasing *only* cholesterol with other techniques and/or drugs that do not have systemic action: reduce atherosclerosis, inflammation and molecules related to atherogenesis.

Therefore, it cannot be sustained that pleiotropic effects are *essential* (in accordance with the meaning accepted by the Real Academia Española) to justify the benefit that is observed with statins and that part of the findings on inflammation, adhesion, etc. are not only due to cholesterol reduction.

Finally, beyond this analysis, I feel that it is important to rescue the concept that statins are the most effective hypolipemiant drugs to reduce coronary morbi-mortality and general mortality and therefore should be used independently of the molecular mechanism/s that allow their action.

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AGONIST REPLY

The word pleiotropy, not yet included in the Diccionario de la Real Academia Española (RAE) (Royal Spanish Academy) and therefore without the corresponding meaning, is used in genetics. Undoubtedly, the Academy will include it as it has done in the past with other scientific terms.

In regards to the presence or not of pleiotropic effects, medicine in general has been reluctant to the early consideration of different drug effects that were introduced for a specific purpose. One example is aspirin, which for a long time was used as anti-pyretic, analgesic, and anti-inflammatory, and that almost after a century its beneficial effects in cardiovascular pathology, i.e. a pleiotropic effect, were discovered and accepted.

I would like to address now some of aspects mentioned by my opponent: although is true that it is impossible to isolate the effect of these drugs in the context of the human being, there are some evidences lately that support my position. The REVERSAL study showed RPC reduction which caused also a regression in the atherosclerotic plaque. This RPC reduction was independent of cholesterol levels. If it is considered that RPC is very unspecific, then let us assess other more specific marker of inflammation and platelet activation such as the CD-40 ligand, which was significantly reduced with the use of atorvastatin in the MIRACL trial. The PROVE-IT study showed that RPC and LDL cholesterol reduction is not parallel with the use of statins either; its correlation is weak: 0.13 by the end of the follow up period.

In regards to other interventions to reduce cholesterol, such as ileac bypass or bile acids sequestrants, it is noted that at least three years are necessary to obtain a benefit that is similar to statins after four weeks.

If there is any doubt in regards to the results of randomized studies, then we can rely on patient registries, which are closer to the "real" medicine: the GRACE registry enrolled 15,693 patients with acute coronary syndrome. Patients were divided in groups, according to aspirin, clopidogrel, and statins combinations; the group that included statins had less mortality and re-hospitalizations after 6 months

On the other hand, cholesterol reduction, with any other drug does not have the same effect on the endothelial function, in the study by Landmesser et al in a group of patients with heart failure ezetimibe was used in one of the study branches and statins in the other; in both, cholesterol was equally reduced, but in the arm test it showed beneficial effect only in the statins branch. These were patients with normal LDL cholesterol levels of less than 130. The beneficial effect of statins in patients with normal choles-

terol levels, with acute or chronic coronary disease, is not explained only by cholesterol reduction, except if it is assumed that the presence of cholesterol is bad and should be decreased to minimum levels, to explain my opponent's position. Studies where cholesterol levels do not have a fundamental role – as with heart failure - are being carried out. In these studies, CORONA and GISSI-HF, statins are used.

As in Hamlet, "to be or not to be", "to believe or not to believe" will always be present. But I think that the number of believers in regards to pleiotropic effects (word that in due time will be included in the RAE dictionary), is growing on a daily basis.

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ANTAGONIST REPLY

I agree with Dr. Alceo Barrios in some of the discussed matters. In the description of the origin of statins and the description of the cellular mechanisms that justify pleiotropic effects (PE). However, I have not found answers to the controversy based on that PE is essential for the benefit provided by statins, centre of the present discussion. Dr. Barrios has focused his presentation in two acute studies. The first one, MIRACL, in its original hypothesis did not address the demonstration that EP were fundamental for the beneficial effect of statins. Results provided evidence that after 6 weeks, atorvastatin 80 mg daily caused a very important LDL cholesterol decrease and that it was correlated with the decrease in combined events. In regards to stroke, the difference was statistically significant in non fatal cases, after including all strokes, p value was 0.45. I think that to extrapolate these results to the concept that the reduction of cerebral events, assessed at 3 months, should be due "essentially" to a PE more than to LDL cholesterol decrease or to the multiplicity of other intervening factors, is asking too much to the existing data.

The second mentioned study is PROVE-IT. It is important to know that patients were included with a mean of 7 days after the event (not within the first hours or on the first day) and that the initial data were collected after 30 days. Therefore, we can observe that the effect was not initiated so acutely given that the drug was administered after one week, nor were the initial results obtained early. The 51% LDL cholesterol reduction with atorvastatin has *per se* effects on the ultrasensitive PCR. The benefit in the reduction of events is not immediate; when analyzing the results it can be observed that the statistical significance is reached only after 180 days. These results were obtained at the primary endpoint, which was combined (death of any origin + cardiovascular events). In the analysis of the separate events there were no significant differences, including in stroke. Another important matter is related to the baseline lipidic profile. Patients that before initiating statin had LDL cholesterol values equal or higher than 125 obtained increased benefits in regards to those that initiated it with lower values (34% *versus* 7%, respectively).

Beyond all these theoretical speculations elaborated as from the *sui generis* interpretation of the data obtained from these studies, it is not possible to ensure that PE are "essential" for the benefit provided by statins. To analyze this matter from a point of view based on a "linear system" leads to conceptual errors. Maybe we should allow ourselves to think on which models based on the "systemic theory" could better explain the interaction between lipoprotein changes, PE, athero-thrombosis, and cardiovascular events.

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