RESEARCH ARTICLE

LDL-cholesterol lowering efficacy of atorvastatin® in primary prevention. Real-world experience in a developing country; a program based on evidence, personalization, and empowerment.

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Abstract

Despite the iconoclasts of the LDL-centric principle and the net benefit of statins, the plurality, quantity, and especially the scientific quality of the evidence that supports the causal role of low-density lipoprotein cholesterol (LDL-C) in atherosclerosis, as well as the net benefit of statins in its prevention, make these two concepts, universal principles accepted by all guidelines worldwide.

The efficacy, safety, and cost-effectiveness of statins have been confirmed in multiple randomized and controlled clinical trials. However, paradoxically, and especially in developing countries like Mexico, the use of this therapeutic class is suboptimal. The reasons to explain this paradox are multiple and are analyzed in this article, which has the purpose of confirming the efficacy, safety, and significant potential impact of statins in the "real developing world." To fulfill this purpose, this article presents our center experience using statins, especially atorvastatin®, in patients without atherosclerotic cardiovascular disease (ASCVD). Founded on an evidence-based, personalization, and empowerment program, our results in almost four hundred patients in primary cardiovascular prevention are as follows. In intermediate-risk patients, atorvastatin® 10 mg/day with a baseline LDL-C of 111.6 mg/dL (±25.1), reduced LDL-C by 38.0% (±13.9); atorvastatin® 20 mg/day with a baseline LDL-C of 124.4 mg/dL (±25.3), reduced LDL-C by 44.9% (±15.0) ($p < 0.005$ for both). In the atorvastatin® 10/20 mg/day cohort (a total of 294 patients), 87.7% (258 patients) achieved a ≥30% LDL-C reduction, and 36.7% (108 patients) a ≥50% reduction. In the atorvastatin 10/20 mg/day cohort, with an average baseline LDL-C of 122.6 mg/dL (±25.6), 92.5 and 55.7% achieved LDL-C of ≤100 and ≤70 mg/dL, respectively. In high-risk patients, atorvastatin® 40 mg/day with a baseline LDL-C of 151.7 mg/dL (±31.6), there was an LDL-C average reduction of 54.7% (±12.2). Atorvastatin 80mg/day with a baseline LDL-C of 160.2 mg/dL (±41.5) produced an LDL-C average reduction of 62.5% (±10.8) ($P < 0.005$ for both). In the atorvastatin® 40/80 mg/day cohort (89 patients), 98.8% (88 patients) achieved a ≥30% LDL-C reduction, and 76.4% (68 patients) achieved a ≥50% reduction. In the atorvastatin 40/80 mg/day cohort, with an average baseline LDL-C of 153.0 mg/dL (±33.2), 95.8 and 62.9% achieved LDL-C of ≤100 and ≤70 mg/dL, respectively.

INTRODUCTION

Driven by the urgent need to mitigate the growing incidence of cardiovascular risk factors and cardiovascular diseases in Latin America and Mexico,[1,2,3,4,5,6] our center has implemented a 360-degree primary cardiovascular prevention program that we called a "structured, evidence-based, personalization, and empowerment program."[7] The program objective is the optimal diagnosis, treatment, and control of the three main cardiovascular risk factors (hypercholesterolemia, hypertension, and diabetes). In addition to the behavioral recommendations, our program is based on the preferential use of brand-name drugs and their prescription based on the scientific evidence of RCTs and cost-effectiveness, especially from the American guidelines. The program is also constructed on personalization, based on complete medical history and physical examination, complemented with lab tests guided by clinical judgment, and finally, in the informed therapeutic recommendation or empowerment, based on the principle of net therapeutic benefit.[8] Our center has adhered to the AHA/ACC /+10 guidelines[9] for its philosophy based on RCTs results and cost-effectiveness analysis.

In this article, we report the results with the referred program in patients without ASCVD and with inappropriate levels of LDL-C. The results confirm the real-world high efficacy of statins®. Furthermore, these results projected to the adult population of a country like Mexico would translate into a very significant and cost-efficient reduction of fatal and non-fatal cardiovascular outcomes.

OBJECTIVE AND METHODS

We conducted a retrospective, systematic, and consecutive review of the clinical records of our center to know the LDL-C-lowering therapeutic efficacy of statin treatment in patients without ASCVD. This review included all the records from January 2013 to June 2021 at Aguascalientes's Cardiometabolic Research Center (CRC). The inclusion criteria comprised the records of first-time patients without ASCVD and without prior lipid-modifying therapy, with a baseline lipid profile (total cholesterol, low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, and triglycerides), with complete information for estimating atherosclerotic cardiovascular risk (ASCVD-R) using the AHA/ACC/+10 algorithm,[9] and at least one LDL-C measurement between 4 and 12 weeks after the start of the statin® treatment (control). Records of patients who did not meet the mentioned inclusion criteria and those participating in clinical research trials were excluded.

Evaluation of statins therapeutic efficacy

Based on the AHA/ACC/+10 guidelines,[9] we assessed the therapeutic efficacy of statins according to the percentage reduction of LDL-C after 4 to 12 weeks of stable treatment; ≥30% reduction for moderate-intensity statins and ≥50% reduction for high-intensity statins. As a standardized procedure and to ensure a therapeutic efficacy similar to that reported in clinical trials, since 2012, our center has prescribed statins in three ways: a) first option, atorvastatin® 10, 20, 40, or 80 mg/day; b) second option, rosuvastatin® 10, 20, or 40 mg/day; c) third option, other statins. Likewise, we have standardized the beginning and upgrading of statin intensity depending on the baseline ASCVD-R estimated with the population cohort equation[9] and LDL-C

reduction reached between weeks 4 and 12 of treatment.

Therapeutic structuring based on evidence, personalization, and empowerment

In our center, every patient between 40 and 75 years with diabetes mellitus (DM) or without DM with intermediate ASCVD-R (7.5% to <20.0%) and in some cases without DM with borderline ASCVD-R (5% to <7.5% plus ≥1 risk-enhancer) receives a moderate-intensity statin to reduce 30% or more the baseline LDL-C; if the goal is not reached, it is upgraded to a high-intensity statin. Any patient between 40 and 75 years with or without DM with high ASCVD-R (≥20.0%) receives a high-intensity statin to reduce 50% or more the baseline LDL-C; if the goal is not reached, ezetimibe 10 mg/day might be added after evaluation. Statins recommendation in patients under 40 or over 75 is defined by the individual clinical situation (not analyzed in this study).

Besides these procedures based on RCTs and cost-effectiveness, included in the AHA/ACC/+10,[9] we practice personalization based on the clinical history findings, physical examination, and lab tests recommendations guided by clinical and physical findings. With this information on evidence and personalization, we complement our therapeutic structure with an informed prescription based on the net therapeutic benefit principle, that is, we inform the patient, and, if necessary, the family, the relationship between benefit and risk, and savings and expenditure of the recommended therapy.[8] We call this strategy patient-family empowerment; with it, we try to increase acceptance, adherence, and persistence to prescribed treatments.[7] Finally, in each follow-up consultation, we carry out a physical assessment of the containers (boxes) of each patient's treatments. This is a complementary strategy to the previous ones, which allows us to monitor if the patient is taking the prescribed treatment, especially important given the frequent change of prescriptions to generic or "similar" drugs with unstandardized quality, which often happens in our country when the patient goes to the pharmacy.[10]

RESULTS

Use of statins® at Aguascalientes´s CRC

Epidemiology: From January 2013 to June 2021, 2,696 new records were generated in our center, 383 complied with the inclusion criteria, without exclusion criteria for this analysis. The patients included were treated with atorvastatin as our first therapeutic option: 338 with atorvastatin® Pfizer (88.2%), 34 with atorvastatin® Sandoz (8.8%), and 11 with generic atorvastatin (2.8%). In the 10, 20, 40, and 80 mg/day atorvastatin group, 43 (16/27 men/women), 251 (104/147 men/women), 75 (29/46 men/women), and 14 (7/7 men/women) patients were included, respectively. The average age was 61.0 ± 10.8, 60.7 ± 11.3, 61.5 ± 9.2, and 65.1 ± 8.6 years, respectively.

Results with moderate-intensity atorvastatin®

Baseline and on-treatment LDL-C: In the 10 mg/day group, baseline LDL-C was 111.6 mg/dL (±25.1), and on-treatment 68.7 mg/dL (±20.9), with an average reduction of 38.0% (± 13.9). In the 20 mg/day group, baseline LDL-C was 124.4 mg/dL (±25.3) and on-treatment 68.2 mg/dL (± 21.9) with an average reduction of 44.9% (± 15.7). The average baseline LDL-C with atorvastatin® 10/20 mg/day

was 122.6 mg/dL (±25.6) and on-treatment 68.3 mg/dL (±21.7), with an average reduction of 43.9% (±15.0), with P value <0.005 for all baseline versus treatment comparisons (Figure 1).

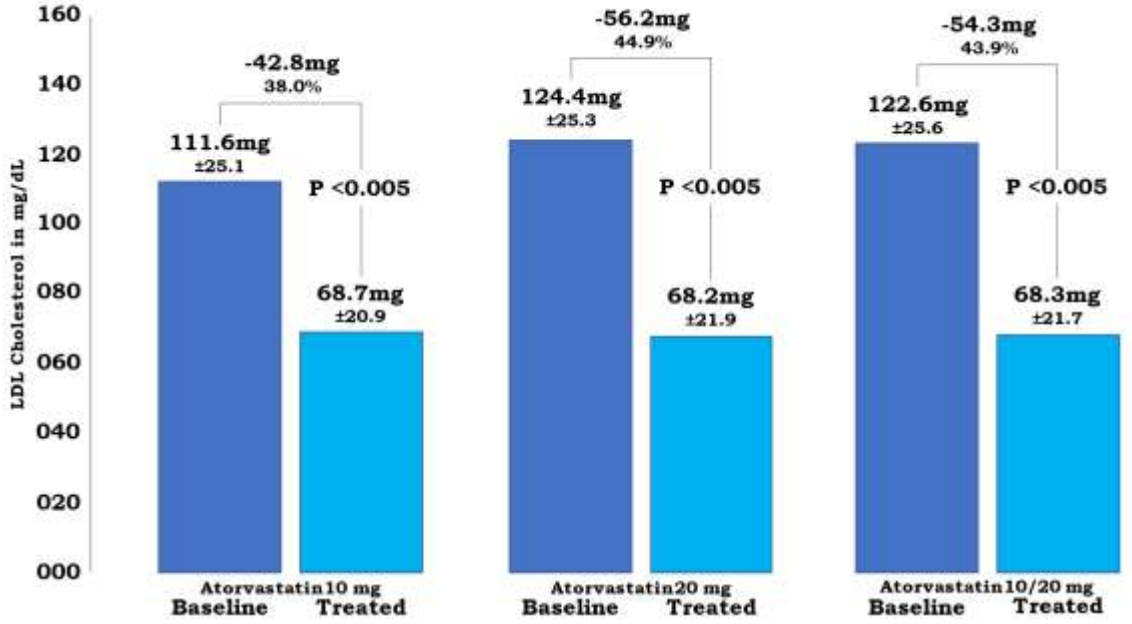


Figure 1: This graph shows the mg/dL and percentage LDL-C reduction with atorvastatin® 10, 20, and 10/20 mg/day

Achievement of ≥30 and ≥50% reduction: With atorvastatin® 10/20 mg/day (294 patients), 87.7% (258 patients) reached a ≥30% LDL-C reduction (76.7% with atorvastatin 10 mg/day and 89.6% with atorvastatin 20 mg/day) and 36.7% (108 patients) reached a ≥50% LDL-C reduction (23.2% with atorvastatin 10 mg/day and 39.0% with atorvastatin 20 mg/day) (Figure 2 and 3).

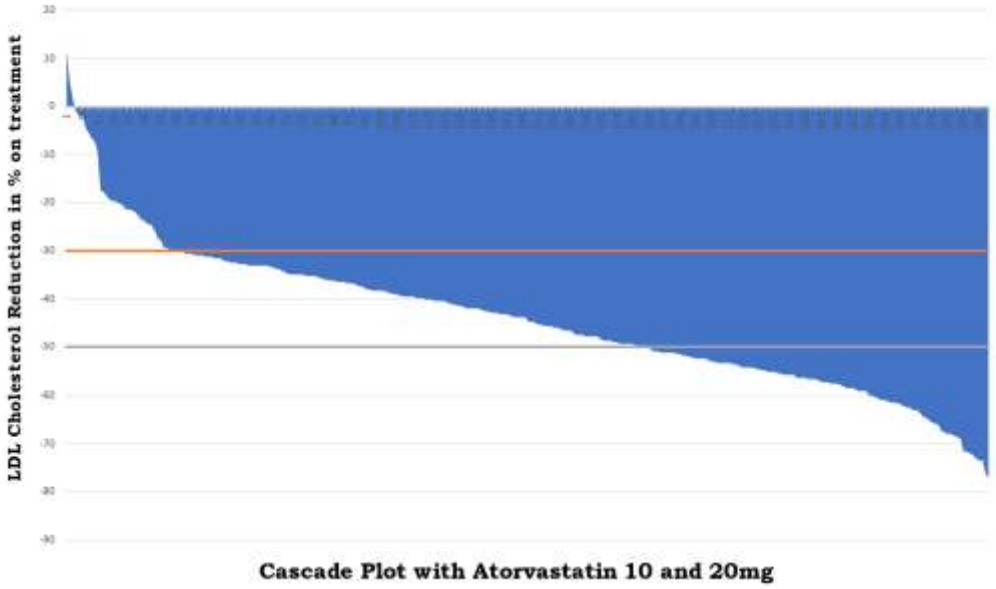


Figure 2: This graph shows the "cascade" distribution of LDL-C reduction patient by patient with atorvastatin® 10/20 mg/day.

Achievement of LDL-C ≤100, ≤90, and ≤70 mg/dL: In the atorvastatin® 10 mg/day group with an average baseline LDL-C of 111.6 mg/dL (±25.1), 93.0, 90.6, and 60.4% reached on-treatment LDL-C levels of ≤100, ≤90, and ≤70 mg/dL, respectively. In the atorvastatin® 20 mg/day group with an average baseline LDL-C of 124.4 mg/dL (±25.3), 92.4, 86.8, and 54.9% reached on-treatment LDL-C levels of ≤100, ≤90, and ≤70 mg/dL, respectively. In the atorvastatin® 10/20 mg/day cohort, with an average baseline LDL-C of 122.6 mg/dL (±25.6), 92.5, 87.4, and 55.7% reached on-treatment LDL-C levels of ≤100, ≤90, and ≤70 mg/dL, respectively (Figure 3).

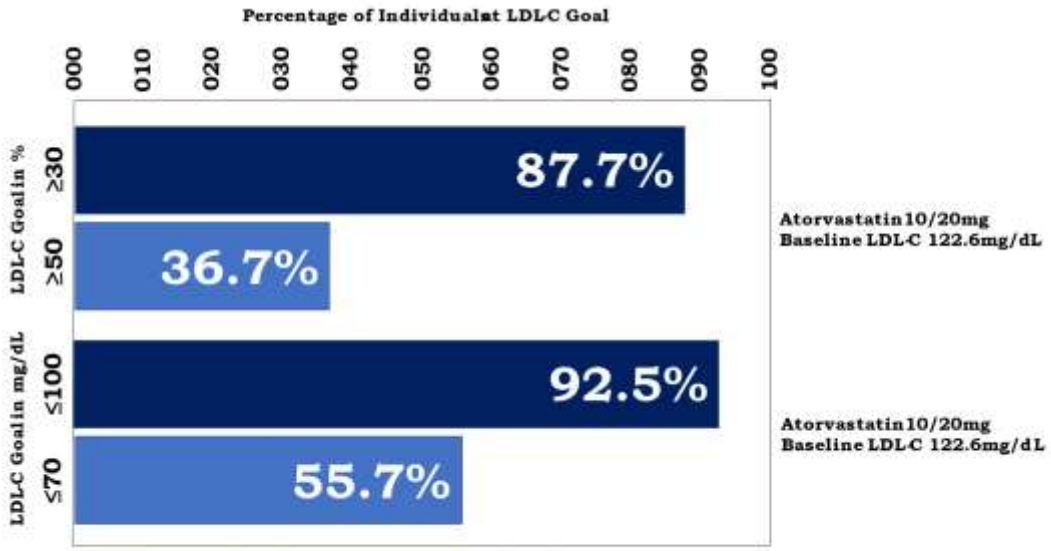


Figure 3: This graph shows the percentage of individuals at LDL-C goal in percentage of reduction (≥30 and ≥50%) and in absolute value (≤100 and ≤70 mg/dL) with atorvastatin® 10/20 mg/day.

Results with high-intensity atorvastatin®

Baseline and on-treatment LDL-C: In the atorvastatin® 40 mg/day group, baseline LDL-C was 151.7 mg/dL (±31.6) and on-treatment 67.9 mg/dL (±21.9) with a 55.2% (±12.2) average reduction. In the atorvastatin® 80mg/day group, baseline LDL-C was 160.2 mg/dL (±41.5) and on-treatment 58.9 mg/dL (±14.1) with a 62.5% (±10.8) average reduction. Thus, the average baseline LDL-C with atorvastatin® 40/80 mg was 153.0 mg/dL (±33.2) and on-treatment 66.5 mg/dL (±21.1) with an average reduction of 56.5% (±14.6) with a P value <0.005 for all baseline versus treatment comparisons (Figure 4).

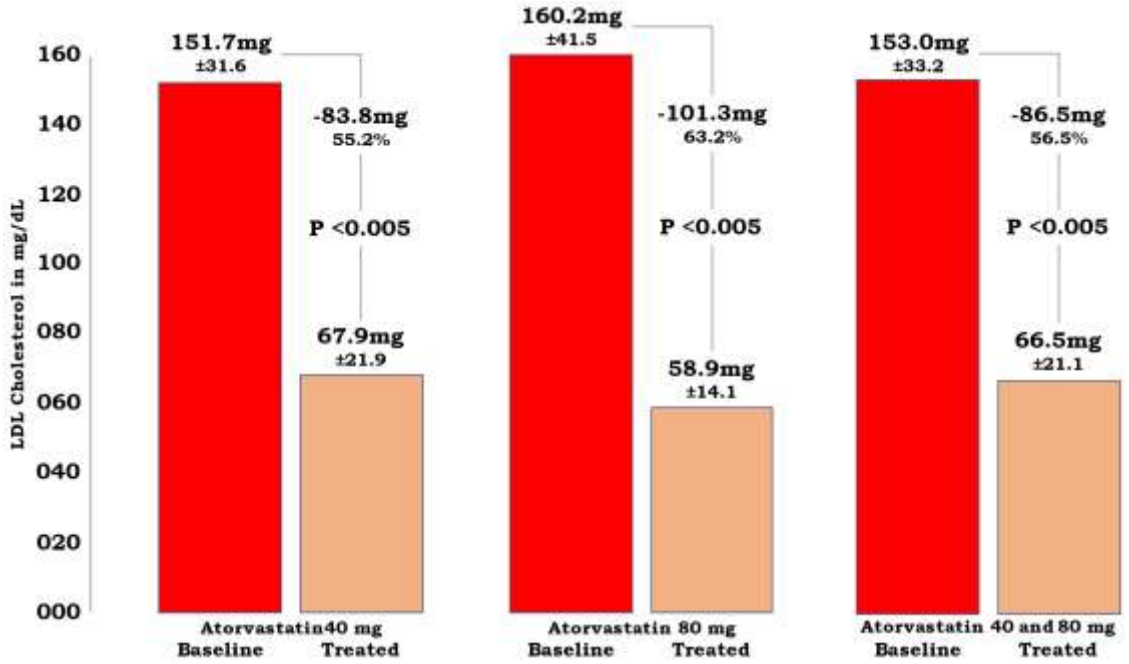


Figure 4: This graph shows the mg/dL and percentage LDL-C reduction with atorvastatin® 40, 80, and 40/80 mg/day.

Achievement of ≥30 and ≥50% reduction: With atorvastatin® 40/80 mg/day (89 patients), 98.8% (88 patients) reached a ≥30% LDL-C reduction, and 76.4% (68 patients) achieved a ≥50% LDL-C reduction (Figures 5 y 6).

Figure 5: This graph shows the "cascade" distribution of LDL-C reduction patient by patient with atorvastatin® 40/80 mg/day.

Achievement of LDL-C ≤100, ≤90, and ≤70 mg/dL: In the atorvastatin® 40 mg/day group with an average baseline LDL-C of 151.7 mg/dL (±31.6), 94.6, 89.3, and 60.0% reached on-treatment levels of ≤100, ≤90, and ≤70 mg/dL, respectively. In the atorvastatin® 80 mg/day group with an average baseline LDL-C of 160.2 mg/dL (±41.5), 100, 100, and 78.5% reached on-treatment LDL-C levels of ≤100, ≤90, and ≤70 mg/dL, respectively. In the atorvastatin® 40/80 mg/day cohort, with an average baseline LDL-C levels of 153.0 mg/dL (±33.2), 95.8, 91.0, and 62.9% reached on-treatment LDL-C levels of ≤100, ≤90, and ≤70 mg/dL, respectively (figure 6).

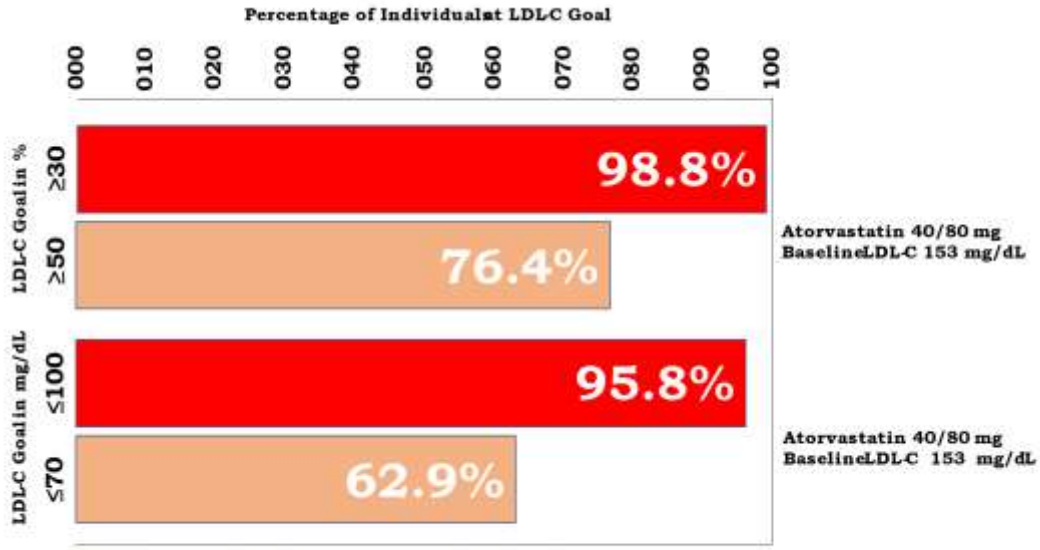


Figure 6: This graph shows the percentage of individuals at LDL-C goal in percentage of reduction (≥30 and ≥50%) and in absolute value (≤100 and ≤70 mg/dL) with atorvastatin® 40/80 mg/day.

DISCUSSION

In a country like Mexico with a per-capita income of less than 10,000 USD (<20% and <10% compared to the United States or Switzerland, respectively),[11] and with a galloping increase in atherosclerotic cardiovascular risk factors, and as a consequence, in the incidence of atherosclerotic cardiovascular disease, the leading cause of premature death, disability and health costs,[2,3,4,5,6] it is urgent to reassess the net therapeutic benefit of cost-efficient preventive strategies such as statins; drugs studied with the highest scientific rigor since the 1970s, since the discovery of the LDL receptor by Goldstein and Brown and of compactin by Endo.[12,13,14,15,16,17,18,19,20,21]

Unfortunately, statins' tremendous net therapeutic benefit has been overshadowed by multiple facts that limit their optimal use and, therefore, their potential benefit. Among these factors, the following stand out: a) the lack of information of patients at risk[5]; b) the distorted information disclosed by non-specialized media, which favors the nocebo effect or anticipated perception of damage[22,23,24]; c) statin phobia created by

the "iconoclasts" of the LDL-centric principle and the benefit of statins[25,26]; d) attraction to new strategies such as monoclonal antibodies (mAbs) or antisense oligonucleotides (ASOs) and small interfering RNAs (siRNAs), many of them still in the research phase and many others, although already approved for clinical use, with inappropriate balances between saving and spending, especially in primary cardiovascular prevention or in patients with LDL-C <100 mg/dL in treatment with statins[27]; the latter, the main limitation to access these new strategies, even in countries like the United States[28]; e) and finally, the proliferation of so-called generic and "similar" statins whose therapeutic efficacy is presumed by a single bioequivalence study (generic) or by the active ingredient included in the label (similar), without any other pharmacokinetic or pharmacodynamic evaluation.[29] In addition, the use of some naturopathic products that have been approved by the Federal Commission for the Protection of Sanitary Risks in Mexico.[30]

In this retrospective, systematic, and consecutive study of a population of almost four hundred adult patients in primary cardiovascular prevention, the therapeutic efficacy of atorvastatin® is demonstrated in its moderate and high intensities. The first prescribed to patients with intermediate ASCVD-R and the second to patients with high ASCVD-R, and less frequently, to patients with intermediate ASCVD-R with an insufficient response (LDL-C reduction <30%) to a moderate-intensity statin.

Atorvastatin® 10 mg/day achieved an average LDL-C reduction of 38.0%, while atorvastatin® 20 mg/day achieved an average of 44.9%. Atorvastatin® 10/20 mg/day achieved the goal of reducing LDL-C ≥30% in 87.7% of cases and even ≥50% in 36.7% of cases, with atorvastatin 20 mg/day being superior. Likewise, moderate-intensity atorvastatin® achieved the LDL-C goals of <100 and <70 mg/dL in 92.5 and 55.7% of cases. Atorvastatin® 40 mg/day achieved an average 54.7% LDL-C reduction, while atorvastatin® 80 mg/day achieved 62.5%. Atorvastatin® 40 and 80 mg/day achieved the goal of reducing LDL-C ≥30% in 98.8% of cases and ≥50% in 76.4%. In absolute numbers, high-intensity atorvastatin® achieved the LDL-C goals of <100 and <70 mg/dL in 95.8 and 62.9% of cases.

In primary cardiovascular prevention, following the AHA/ACC/+10 guidelines,[9] atorvastatin® prescribed under an evidence-based therapeutic program (RCT and cost-effectiveness), personalization, and empowerment is a highly effective tool. With all the limitations that this has, extrapolating to the EAS/ESC 2019 guidelines recommendations,[31] in intermediate-risk patients, 92.5% and 95.8% would reach the absolute goal of LDL-C <100 mg/dL with moderate-intensity and high-intensity atorvastatin®, respectively. In high-risk patients, 62.9% would reach the absolute goal of LDL-C <70 mg/dL with high-intensity atorvastatin®.

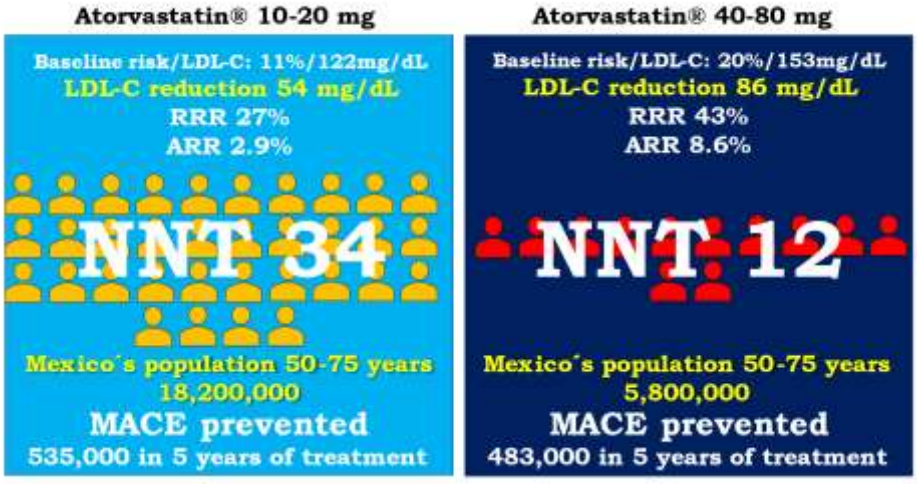
Although this analysis was not focused on assessing the tolerance and safety of statins, the retrospective, systematic, and consecutive review of almost four hundred patients treated with statins only detected two cases of true muscle intolerance (without myositis) to atorvastatin®. In addition, one patient is currently on ezetimibe 10 mg/day after presenting myalgias with both lipophilic and

hydrophilic statins, and another patient was switched to rosuvastatin 40 mg/day without recurrence of myalgias.

Implications: The preferential use of a brand-name statin (in 88% of the cases, it was the same used in RCTs) allows us to reproduce the results of those trials in our "real world" clinical scenario, which, to date, are the gold standard to guide our treatment recommendations.

Knowing that, in 5 years of treatment, an LDL-C reduction of 1 mg/dL decreases the risk of an atherosclerotic cardiovascular event by 0.5%, and that the absolute benefit is directly proportional to the LDL-C reduction and the ASCVD-R,[18,19,20] in a population like the one studied, we could make the following extrapolations. In the intermediate-risk population (294 patients or 76.7%) with an estimated average ASCVD-R of 11%, the reported LDL-C reduction of 54.3 mg/dL with a moderate-intensity statin would decrease the relative risk of a major atherosclerotic cardiovascular event by 27%; a number equivalent to an absolute risk reduction of 2.9%, which represents a number needed to treat (NNT) of 34 in 5 years of treatment. In the high-risk population (89 patients or 23.2%) with an estimated average ASCVD-R of 20%, the reported LDL-C reduction of 86.5 mg/dL with a high-intensity statin would decrease the relative risk of a major atherosclerotic cardiovascular event by 43.2%; a number equivalent to an absolute risk reduction of 8.6%, which represents an NNT of 12 in 5 years of treatment.

Considering that most of the population included in our study was between 50 and 75 years, and if said population could represent the adults of our country (24 million adults between 50 and 75 in Mexico),[32] using statins® as described in this study would prevent approximately one million fatal and non-fatal major cardiovascular events (535,000 in an intermediate-risk population and 485,000 in a high-risk population) in 5 years of treatment (Central figure 6).



Central figure 6: This graph shows a hypothetical projection of benefit [Major adverse cardiovascular events (MACE) prevented] in the Mexican population (24 million between 50-75 years) using statins® as described in this study. Approximately one million fatal and non-fatal major cardiovascular events (535,000 in an intermediate-risk population and 485,000 in a high-risk population) in 5 years of treatment might be prevented.
RRR = Relative risk reduction, ARR = Absolute risk reduction

CONCLUSIONS

In our center, in a population of primary cardiovascular prevention and according to the AHA/ACC/+10 guidelines, a treatment plan with preferential use of brand-name statins and based on evidence, personalization, and empowerment is a high-efficacy tool. Atorvastatin® 10/20 mg/day in intermediate-risk patients (baseline LDL-C 122.6 mg/dl and average ASCVD-R 11%) achieves the therapeutic goal (LDL-C reduction ≥30%) in 87.7% of cases and the absolute therapeutic goal (LDL-C <100 mg/dL) in 92.5%. In high-risk patients (baseline LDL-C 153.2 mg/dL and average ASCVD-R 20%), atorvastatin® 40/80 mg/day achieves the goal (LDL-C reduction ≥50%) in 76.4% of cases and the absolute therapeutic goal (LDL-C <70 mg/dL) in 62.9%. The above with a very low incidence of true muscle intolerance to statins. These results extrapolated to the Mexican population between 50 and 75 would represent a significant net therapeutic benefit. These results cannot be extrapolated to generic or "similar" statins, for which it is a priority to evaluate their efficacy, tolerance, and safety in the medium and long term.

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