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# Statins: The case for higher, individualized starting doses

## ABSTRACT

If patients with hypercholesterolemia were started on higher doses of statins tailored to their lipid levels and risk, more of them would achieve their low-density lipoprotein cholesterol (LDL-C) goals, possibly leading to fewer cardiovascular events and deaths.

## KEY POINTS

Statin therapy reduces the risk of a first or repeat cardiovascular event in patients at moderate to high short-term risk.

Undertreatment of hypercholesterolemia remains a problem, especially as guidelines have extended the eligible patient population.

An initial statin dose should be prescribed according to a patient's risk, baseline LDL-C level, and degree of LDL-C reduction needed to attain his or her goal.

The risk of liver toxicity or myopathy with statin use is very low, even at high doses, and is far outweighed by the benefits of therapy.

**M**OST PATIENTS on statin therapy aren't receiving high enough doses to get their low-density lipoprotein cholesterol (LDL-C) down to recommended goal levels. I believe that instead of starting with a low dose and titrating upward, we would do better by starting at a higher dose if the patient has a higher baseline LDL-C level or is otherwise at higher risk of coronary heart disease (CHD).

*See related editorial, page 751*

This article aims to increase awareness of undertreatment of hypercholesterolemia and to recommend a starting dose commensurate with a patient's global CHD risk.

## STATINS PREVENT CHD EVENTS

Therapy for preventing CHD and its complications focuses on controlling modifiable risk factors, including dyslipidemia—a major cardiovascular risk factor identified in epidemiologic studies.<sup>1</sup>

The development of statins (3-hydroxy-3-methylglutaryl coenzyme A [HMG-Co A] reductase inhibitors) was a significant advance. Multiple studies have shown that statins improve clinical outcomes in patients with a broad range of baseline cholesterol levels both with and without established CHD.<sup>2,3</sup>

The benefit was first demonstrated in the Scandinavian Simvastatin Survival Study (4S),<sup>4</sup> in which a statin reduced the incidence of cardiovascular events and total mortality in patients with established CHD (angina pectoris or previous myocardial infarction). Most recently, the Anglo-Scandinavian Cardiac Outcomes Trial—Lipid-Lowering Arm (ASCOT-LLA)<sup>5</sup> found that patients with hypertension but with-

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out CHD had significantly fewer cardiovascular events with statin therapy regardless of their baseline total cholesterol levels.

These studies highlight the safety and benefit of statin therapy in patients at moderate-to-high short-term risk. LDL-C goals can also be achieved by drugs that inhibit cholesterol absorption, taken alone or combined with statins. However, not all such therapies have demonstrated clinical benefit.

### ■ TOUGHER GOALS FOR THOSE AT HIGHER RISK

Organizations in the United States and other countries have developed specific guidelines for estimating cardiovascular risk and for decreasing it. The guidelines focus on lowering serum LDL-C; secondary goals are to raise low levels of high-density lipoprotein cholesterol and to lower high levels of serum triglyceride.

The Third Report of the Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (ATP III),<sup>6</sup> published in 2001 and updated in 2004,<sup>7</sup> sets the current standard for testing and managing cholesterol in the United States.

The ATP III guidelines set a lower LDL-C goal for patients with documented CHD and for those at equally high risk due to noncoronary atherosclerotic disease, type 2 diabetes mellitus, or a 10-year CHD risk of greater than 20% according to Framingham risk prediction charts. This concept of “CHD risk equivalents” was new in the ATP III report and it substantially increased the number of patients who qualify for the most intensive LDL-C target (< 100 mg/dL).<sup>6</sup> The 2004 update included an even lower target (< 70 mg/dL) as an option for patients at very high risk.<sup>7</sup>

The Third Joint European Task Force<sup>8,9</sup> uses a different system for estimating cardiovascular risk, but for people at high risk the goals are similar to those in the 2001 ATP III guidelines: an LDL-C concentration of 100 mg/dL or less and a total cholesterol concentration of 175 mg/dL or less.

### ■ MOST PATIENTS ARE UNDERTREATED

Although the consensus guidelines have been broadly disseminated, most patients at risk for

CHD are not attaining the defined LDL-C goals, owing to undertreatment.<sup>10–13</sup>

The European Action on Secondary Prevention Through Intervention to Reduce Events (EUROASPIRE) study<sup>14</sup> showed that 67% of CHD patients who were surveyed in 1995 to 1996 required more intensive cholesterol-lowering treatment than they were receiving, and only 33% were receiving lipid-lowering drugs. The follow-up survey in 1999 to 2000 found that the percentage of CHD patients who were receiving lipid-lowering drugs had increased to 63%, although most still had not attained the recommended cholesterol targets.<sup>11,12</sup>

Most physicians agree with the guidelines—they just don’t follow them aggressively enough,<sup>15</sup> and they prescribe statin doses that are too low.<sup>16–19</sup> Irish pharmacy reimbursement claims show that although prescriptions for lipid-lowering drugs (92% of which were statins) increased by 263% (from 35,590 to 129,324) from 1994 to 1997, most patients received the lowest dose, ie, 10 mg of either simvastatin or pravastatin.<sup>13</sup>

In a study in Norway, physicians in general practice who were provided with clear information about the new guidelines still failed to modify the starting statin dose, such that only 17% of primary prevention patients (ie, without CHD) and 44% of secondary prevention patients (ie, with CHD) reached their lipid goals.<sup>16</sup>

Although some coaching and counseling programs improve adherence and achievement of goals, a substantial number of patients still receive a suboptimal statin dose, regardless of LDL-C profile.<sup>20</sup> National prescription data show that commonly prescribed statin doses are substantially lower than those used in the landmark statin trials, eg:

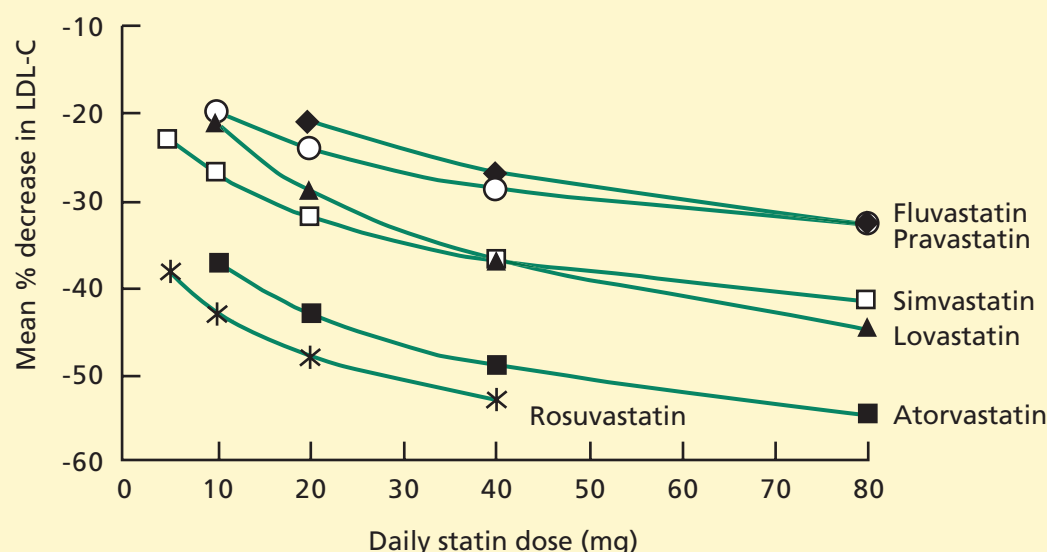
- Simvastatin 20 to 40 mg (used in the 4S study<sup>4</sup>) or 40 mg (used in the Heart Protection Study<sup>21</sup>)
- Pravastatin 40 mg (used in the Cholesterol and Recurrent Events study,<sup>22</sup> the Long-Term Intervention With Pravastatin in Ischaemic Disease,<sup>23</sup> and the West of Scotland Coronary Prevention study<sup>24</sup>).

Because of undertreatment, the at-risk population is unlikely to receive the same

**Most physicians agree with the guidelines but do not follow them aggressively enough**



## How much do statins lower LDL-C?



**FIGURE 1.** Percent reduction in low-density lipoprotein cholesterol (LDL-C) after 8 weeks of treatment with different statins in multiple trials. Data reflect effects observed up to the maximum approved dose for each drug.

DATA FROM LAW MR, WALD NJ, RUDNICKA AR. QUANTIFYING EFFECT OF STATINS ON LOW DENSITY LIPOPROTEIN CHOLESTEROL, ISCHAEMIC HEART DISEASE, AND STROKE: SYSTEMATIC REVIEW AND META-ANALYSIS. *BMJ* 2003; 326:1423–1429. BY PERMISSION OF THE BRITISH MEDICAL JOURNAL.

level of cardioprotective benefits as demonstrated in these trials.

For example, the Greek Atorvastatin and Coronary Heart Disease Evaluation (GREACE) study<sup>18</sup> compared morbidity and mortality rates in patients with CHD and high cholesterol who were given either usual medical care as provided by a primary care physician (which may have included drug treatment) or structured care with open-label atorvastatin provided by a specialist. In the structured-care group, 95% of patients achieved their LDL-C goals vs 3% of usual-care patients, a particularly low number considering that 14% received hypolipidemic drug treatment, mostly statins, at a dose considered appropriate by the primary care physician. The rates of recurrent CHD-related events and deaths were half as high in patients who received structured care as in those who received usual care. This trial highlights that usual care is not optimal and that lipid reductions in line with guidelines are necessary for clinical benefits.

### ■ A TARGETED DOSING STRATEGY

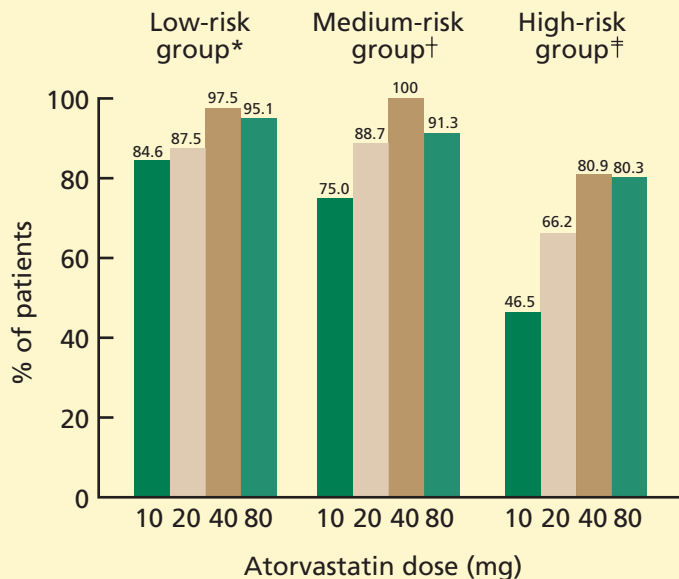
An alternative to the traditional “start-low-and-titrate” strategy is to choose the initial statin dose according to a patient’s baseline LDL-C level, global CHD risk profile, and percent reduction needed to attain his or her treatment goal. The ATP III update recommends that statins be prescribed at a dose capable of reducing LDL-C levels by at least 30% to 40%.<sup>7</sup>

All of the statins available in the United States and in some European countries come in a range of doses that permit a higher starting dosage.

The dose-response curves for statins are not linear: most of the LDL-C reduction occurs at the lowest dose, and each doubling in dose yields incremental reductions in LDL-C of 5% to 7% (FIGURE 1).<sup>25</sup> Clinicians can tailor therapy appropriately if they know approximately how much the six available statins reduce LDL-C at what dose.

**Doubling the statin dose lowers LDL-C by 5%–7%**

### More patients at high risk achieve LDL-C goals with higher starting doses of statin



\* 0 - 1 risk factors, n = 144

† 2 or more risk factors, n = 184

‡ Coronary heart disease (CHD) or CHD risk equivalent (n = 584)

**FIGURE 2.** Percent of patients who attained the low-density lipoprotein cholesterol goals specified in the Third Report of the Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (ATP III) after being randomized to receive different doses of atorvastatin in the New Atorvastatin Starting Doses: A Comparison (NASDAC) study.

ADAPTED FROM JONES PH, MCKENNEY JM, KARALIS DG, DOWNEY J. COMPARISON OF THE EFFICACY AND SAFETY OF ATORVASTATIN INITIATED AT DIFFERENT STARTING DOSES IN PATIENTS WITH DYSLIPIDEMIA. *AM HEART J* 2005; 149:e1. WITH PERMISSION FROM ELSEVIER.

For example, if a patient needs to have his or her LDL-C level reduced by 40% from baseline to meet the goal, one should start with a statin dose expected to lower LDL-C by at least that much (eg, rosuvastatin 10 mg/day or atorvastatin 20 mg/day). This strategy reduces the number of follow-up visits and repeat laboratory tests necessary in the titration process, increases compliance and convenience for the patient, and minimizes management costs.

#### Studies of individualized statin dosing

The Atorvastatin Matrix study<sup>26</sup> tested a strategy of choosing the appropriate statin

dose to attain LDL-C goals. Patients with hypercholesterolemia who did not achieve European Atherosclerosis Society lipid-lowering targets received open-label treatment for 12 weeks with atorvastatin 10, 40, or 80 mg/day. The dosage was determined by baseline LDL-C levels and other CHD risk factors. More than 85% of the patients at low or moderate risk without existing CHD achieved their cholesterol goal with this strategy, as did 69% of the patients at high risk (who had CHD, peripheral vascular disease, or familial hypercholesterolemia).

Two newer trials undertaken specifically to determine the optimum starting atorvastatin dose also support the use of higher doses for achieving LDL-C goals.

In the New Atorvastatin Starting Doses: A Comparison (NASDAC) study,<sup>27</sup> 919 patients with CHD or at risk for it were randomized to receive atorvastatin 10, 20, 40, or 80 mg/day.

The Atorvastatin Goal Achievement Across Risk Levels (ATGOAL) study<sup>28</sup> also evaluated atorvastatin 10, 20, 40, or 80 mg/day. However, instead of being randomized, patients (N = 1,295) were assigned a starting dose according to an algorithm based on their risk factors and baseline LDL-C levels. After 4 weeks the dose was titrated upward until patients reached either their goal or the highest dose.

In both studies, atorvastatin produced dose-dependent reductions in LDL-C (36%–52%), and each of the higher doses significantly reduced LDL-C levels vs all lower doses. Patients were more likely to achieve ATP III LDL-C goals with a higher starting dose, regardless of CHD risk level (FIGURE 2, FIGURE 3).

#### ■ RISKS OF HIGH STATIN DOSES ARE LOW

The primary clinical concerns with higher doses of statins are liver toxicity and myopathy.

The available statins have a strong record of safety and tolerability across the range of approved doses. More than 70,000 people have participated in controlled randomized statin trials, with no serious morbidity or mortality attributed to drug treatment.<sup>3</sup>



After cerivastatin was withdrawn from the market in 2001 because of reports of myopathy, the American College of Cardiology, the American Heart Association, and the National Heart, Lung, and Blood Institute produced a clinical advisory report to update recommendations about the use and safety of statins.<sup>29</sup> The report emphasized the lifesaving potential of statins, stating that the benefits of therapy in at-risk patients greatly outweigh the risks of adverse effects. It concluded that improved safety monitoring can limit adverse effects and alleviate physician and patient concerns.

### Liver toxicity

In early clinical trials of statins, alanine aminotransferase and aspartate aminotransferase levels increased to more than three times the normal values in approximately 1% of participants.<sup>4,22,24,30</sup>

In the Prospective Pravastatin Pooling (PPP) project,<sup>31</sup> which combined data from three trials involving more than 19,000 subjects, pravastatin 40 mg/day did not affect the incidence of elevated hepatic transaminase levels compared with placebo.

In pooled safety data from 44 completed clinical trials involving more than 9,400 patients treated with atorvastatin, fewer than 1% had persistently elevated hepatic transaminase levels across the full dosage range, which was not significantly different from the incidence in the placebo groups.<sup>32</sup>

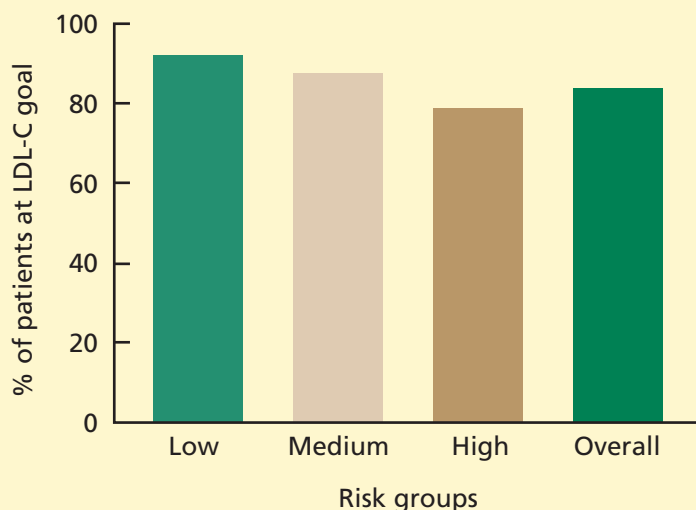
### Myopathy

Myopathy is an important adverse event: in rare cases, it leads to acute rhabdomyolysis and irreversible renal failure.<sup>33</sup>

With simvastatin treatment, the incidence of myopathy, rhabdomyolysis, or both has been reported as 0.02% at 20 mg/day, 0.07% at 40 mg/day, and 0.3% at 80 mg/day.<sup>34,35</sup>

Rosuvastatin, the newest statin approved

## Most patients can achieve their LDL-C goal



**FIGURE 3.** Attainment of ATP III goals with single-dose atorvastatin treatment according to risk in the Atorvastatin Achievement Across Risk Levels (ATGOAL) study.

DATA FROM MCKENNEY J, DAVIDSON M, SAPONARO J, THOMPSON P, BAYS H, FOR THE ATGOAL INVESTIGATORS. EFFICACY AND SAFETY OF ATORVASTATIN INITIATED AT OPTIMAL STARTING DOSES IN ACHIEVING LDL-C GOALS IN PATIENTS WITH DYSLIPIDEMIA [ABSTRACT]. PRESENTED AT THE 74TH EUROPEAN ATHEROSCLEROSIS SOCIETY CONGRESS; 2004; SEVILLE, SPAIN. WWW.DRUGSTUDY.MD/ATGOAL.HTML. REPRINTED BY PERMISSION OF THE AUTHORS.

in the United States, has the same low, dose-related incidence of myopathy.<sup>36</sup>

With atorvastatin, a pooled safety analysis of 44 trials revealed no cases of myopathy or rhabdomyolysis, and the incidence of muscle-related side effects was low and no different from that of placebo.<sup>32</sup>

In a meta-analysis of patients treated with fluvastatin 20 to 80 mg per day, the frequency of elevated creatine phosphokinase levels was similar in the treatment and placebo groups.<sup>37</sup>

These data for the clinically established statins confirm good tolerability and impressive safety across their approved doses.

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