Variability of low-density lipoprotein cholesterol response with different doses of atorvastatin, rosuvastatin, and simvastatin: results from VOYAGER

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Aims
Patient response to statin treatment is individual and varied. As a consequence, when using a specific-dose approach, as recommended in the 2013 American College of Cardiology/American Heart Association guideline, there will be a range of reductions in the concentration of low-density lipoprotein cholesterol (LDL-C). The aim of this study was to use individual patient data from the VOYAGER meta-analysis to determine the extent of the variability in LDL-C reduction in response to treatment across the recommended doses of different statins.

Methods and results
The percentage change from baseline in LDL-C was calculated using individual subject data collected from 32,258 patients treated with atorvastatin 10–80 mg, rosuvastatin 5–40 mg, or simvastatin 10–80 mg. The percentage change in LDL-C for each patient was then used to generate waterfall plots that demonstrated the extent of the variability in response to treatment at all doses of the three statins. The standard deviation of LDL-C reduction for all statins and doses ranged from 12.8 to 17.9%. The percentage of patients experiencing a suboptimal response (<30% reduction in LDL-C) ranged from 5.3 to 53.3%.

Conclusion
These results indicate that there is considerable individual variation in the LDL-C reduction at all doses of simvastatin, atorvastatin, and rosuvastatin.

Keywords
Atorvastatin • Low-density lipoprotein cholesterol • Rosuvastatin • Simvastatin • Variability

Introduction
One of the aims of the 2013 American College of Cardiology (ACC)/American Heart Association (AHA) guideline was to simplify treatment decisions for physicians and ensure that all patients at higher risk of atherosclerotic cardiovascular disease (ASCVD) receive appropriate statins at appropriate doses. For example, it is suggested that essentially all patients at high cardiovascular risk are treated with high-intensity statins, which are defined as atorvastatin 40 and 80 mg and rosuvastatin 20 and 40 mg (Table 1). These high-intensity statins are expected to reduce low-density lipoprotein cholesterol (LDL-C) by at least 50%. Moderate-intensity statins, such as atorvastatin 10–20 mg, rosuvastatin 5–10 mg, and simvastatin 20–40 mg, are recommended for patients at moderate risk of ASCVD, those aged >75 years, or those who are unable to tolerate high-intensity statins. These statins are expected to reduce LDL-C levels by 30 to <50%.

However, patient response to statin treatment is individual and varied, and by using a specific-dose approach and not monitoring LDL-C and patient response, it may be unclear how many patients are experiencing inadequate lowering of LDL-C and thereby inadequate risk reduction, and which patients could consequently
benefit from treatment modification. There are a large number of studies on LDL-C reduction with different statins and comparisons between statins; however, most studies compare average LDL-C reductions, which give limited information about how common poor response is. A previous meta-analysis, based on eight single studies, showed the wide variation in response to single statins and single doses.

Therefore, the aim of this study was to use individual patient data from the VOYAGER (an indiVidual patient data meta-analysis Of statin therapY in At risk Groups: Effects of Rosuvastatin, atorvastatin and simvastatin) meta-analysis database to describe the variability in LDL-C reduction following treatment with different statins at different doses.

Methods
Study design
VOYAGER is an individual patient database of 32,258 patients from 37 clinical trials comparing the lipid-modifying effects of atorvastatin 10, 20, 40, or 80 mg, rosuvastatin 5, 10, 20, or 40 mg, and simvastatin 10, 20, 40, or 80 mg. Patients were not permitted to receive any other lipid-modifying medications in any of the 37 randomized clinical trials. The patient population included in the meta-analysis and the methods have been reported previously.

Objective
The objective of this study was to use the VOYAGER database to determine the variability in LDL-C reduction following treatment with different statins and doses.

Statistical analyses
The percentage change from baseline in LDL-C was calculated for each patient, and the distribution of percentage change in LDL-C was plotted for each statin at each dose.

The percentage of patients experiencing a suboptimal response was also calculated. In the absence of a standard definition, an LDL-C reduction of <15% from baseline was defined as suboptimal based on clinical experience.

Results
Patients
Baseline characteristics and lipid parameters of the 32,258 patients in the VOYAGER database are summarized in Table 2. Overall, 51% of the patients had ASCVD and 29% had diabetes.

Efficacy
The lowest mean percentage LDL-C reduction was (standard deviation [SD]) 28.4% (13.8) with simvastatin 10 mg, and the highest mean percentage LDL-C reduction was 55.5% (14.8) with rosuvastatin 40 mg (Table 3). Atorvastatin 10–80 mg reduced LDL-C by a mean (SD) of 35.7% (16.0) to 49.2% (17.3). Rosuvastatin 5–40 mg reduced LDL-C by a mean (SD) of 41.4% (12.8) to 55.5% (14.8). Simvastatin 10–80 mg reduced LDL-C by a mean (SD) of 28.4% (13.8) to 45.7% (13.1). The SD of LDL-C reduction for all statins and doses ranged from 12.8 to 17.9% (Table 3). Variability did not appear to be related to statin or dose.

According to the 2013 ACC/AHA guideline, the expected LDL-C reduction with moderate-intensity statin treatment is in the range of 30 to <50%, and with high-intensity statins is

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>N = 32,258</th>
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<tbody>
<tr>
<td>Age [years, mean (SD)]</td>
<td>60.0 (11.1)</td>
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<tr>
<td>Men, %</td>
<td>56.7</td>
</tr>
<tr>
<td>Race, %</td>
<td></td>
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<tr>
<td>White</td>
<td>79.9</td>
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<tr>
<td>Black</td>
<td>5.1</td>
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<td>Hispanic</td>
<td>4.1</td>
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<tr>
<td>Asian</td>
<td>8.3</td>
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<tr>
<td>Other</td>
<td>2.6</td>
</tr>
<tr>
<td>Body mass index [kg/m², mean (SD)]</td>
<td>28.8 (5.5)</td>
</tr>
<tr>
<td>Baseline lipid levels [mg/dL, mean (SD)]</td>
<td></td>
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<tr>
<td>LDL-C</td>
<td>170.9 (38.7)</td>
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<td>HDL-C</td>
<td>48.7 (12.7)</td>
</tr>
<tr>
<td>Non-HDL-C</td>
<td>205.2 (41.8)</td>
</tr>
<tr>
<td>TG, median (interquartile range)</td>
<td>162.2 (120.4, 215.0)</td>
</tr>
<tr>
<td>ApoB</td>
<td>159.3 (37.2)</td>
</tr>
<tr>
<td>ApoA-I</td>
<td>148.8 (28.7)</td>
</tr>
<tr>
<td>ASCVD, %</td>
<td>51</td>
</tr>
<tr>
<td>Diabetes, %</td>
<td>29</td>
</tr>
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</table>

Apo, apolipoprotein; ASCVD, atherosclerotic cardiovascular disease; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; SD, standard deviation; TG, triglycerides.
The waterfall plots in Figures 1–3 show the variability in response to treatment with different doses of atorvastatin, rosuvastatin, and simvastatin.

When atorvastatin was given at a dose of 10 mg, 10.2% of patients failed to achieve a 15% reduction in LDL-C, 27.2% failed to achieve a 30% reduction, and 85.9% failed to achieve a 50% reduction. At the 20-mg dose, the percentages of patients failing to achieve 15, 30, and 50% reductions were 4.3, 12.8, and 67.7%, respectively. At the 40-mg dose of atorvastatin, the respective proportions failing to achieve 15, 30, and 50% reduction were 2.8, 7.6, and 52.6%. In the case of 80 mg atorvastatin, the respective percentages failing to achieve the reductions were 4.7, 11.3, and 42.5% (Figure 1).

When rosuvastatin was given, the proportions failing to achieve a reduction in LDL-C of 15, 30, and 50% were, respectively, 4.9, 14.7, and 76.5%, at the 5-mg dose, 7.8, 17.5, and 59.6% at the 10-mg dose, 4.8, 9.4, and 42.7% at the 20-mg dose, and 2.7, 5.3, and 26.2% at the 40-mg dose (Figure 2).

In the case of simvastatin, the proportions failing to achieve a reduction in LDL-C of 15, 30, and 50% were, respectively, 12.7, 53.3, and 98.8%, at the 10-mg dose, 10.7, 32.8, and 90.2% at the 20-mg dose, 4.4, 17.7, and 78.6 at the 40-mg dose, and 4.2, 9.0, and 56.9 at the 80-mg dose (Figure 3).

Discussion

The 2013 ACC/AHA guideline recommends specific statins and doses based on an individual patient’s risk of ASCVD. The intent of the guideline was to use the wealth of available evidence to simplify the treatment of blood cholesterol in patients at perceived risk of ASCVD for clinicians and to help ensure that patients who will experience a net benefit with high- or moderate-intensity statin

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Table 3  Mean (SD) percent change in LDL-C in response to atorvastatin 10–80 mg, rosuvastatin 5–40 mg, and simvastatin 10–80 mg

<table>
<thead>
<tr>
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<th>LDL-C reduction (%)</th>
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<tr>
<td></td>
<td>Mean (SD)</td>
<td>Median (IQR)</td>
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<tr>
<td></td>
<td>n</td>
<td>ATV 10 mg (N = 7804)</td>
<td>ATV 20 mg (N = 3896)</td>
<td>ATV 40 mg (N = 1324)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Mean (SD)</td>
<td>Median (IQR)</td>
<td>Mean (SD)</td>
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<tr>
<td></td>
<td>n</td>
<td>7804</td>
<td>3896</td>
<td>1324</td>
</tr>
<tr>
<td></td>
<td>ATV 10 mg (N = 7804)</td>
<td>−35.7 (16.0)</td>
<td>−38.3 (−46.1, −28.8)</td>
<td>−47.9 (13.8)</td>
</tr>
<tr>
<td></td>
<td>ATV 20 mg (N = 3896)</td>
<td>−43.1 (14.5)</td>
<td>−45.5 (−52.0, −37.2)</td>
<td>−47.9 (13.8)</td>
</tr>
<tr>
<td></td>
<td>ATV 40 mg (N = 1324)</td>
<td>−47.9 (13.8)</td>
<td>−49.6 (−56.1, −42.4)</td>
<td>−49.4 (17.5)</td>
</tr>
<tr>
<td></td>
<td>ATV 80 mg (N = 2070)</td>
<td>−49.2 (17.3)</td>
<td>−52.6 (−59.7, −43.4)</td>
<td>−52.5 (−59.8, −43.4)</td>
</tr>
</tbody>
</table>

IQR, interquartile range; LDL-C, low-density lipoprotein cholesterol; SD, standard deviation.

Figure 1  Waterfall plots showing variability in LDL-C response with atorvastatin 10–80 mg. The horizontal dotted lines in each panel have been drawn to indicate reductions in LDL-C of 15, 30, and 50%. ATV, atorvastatin; LDL-C, low-density lipoprotein cholesterol.
Figure 2. Waterfall plots showing variability in LDL-C response with rosuvastatin 5–40 mg. Horizontal dotted lines have been drawn at reductions in LDL-C of 15, 30, and 50%. LDL-C, low-density lipoprotein cholesterol; RSV, rosuvastatin.

Figure 3. Waterfall plots showing variability in LDL-C response with simvastatin 10–80 mg. Horizontal dotted lines have been drawn at reductions in LDL-C of 15, 30, and 50%. LDL-C, low-density lipoprotein cholesterol; SIM, simvastatin.
treatment will receive it. We have previously described the mean reduction of LDL-C with each high-intensity statin in the four statin benefit groups described by the ACC/AHA guideline, and to what extent the expected 50% reduction is reached in these high-risk patients. Although this guideline highlights the need for moderate- and high-intensity statins in patients at risk of ASCVD, it does not take into account the variability between patients in their response to statin treatment, which is something that needs to be seriously considered when treating patients with statins for dyslipidaemia.

Mean reductions in LDL-C in response to statins have been well documented and although variability in response to statins has been noted in some clinical studies, including a study by Boekholdt et al. that looked at variability with atorvastatin 80 mg and rosuvastatin 20 mg, as far as we are aware, this study is one of the first to evaluate individual variability of response to statin therapy with the three most commonly used statins in clinical practice.

We found that the SD for the mean reduction in LDL-C from baseline was fairly consistent among the different statins and doses, ranging from 12.8 to 17.9%. This suggests that there is substantial individual variability in response with each statin and dose, and highlights the possibility of poor responses in individual patients with these statins and doses and the need to monitor patient response to treatment.

This was confirmed by the finding that clinically significant numbers of patients experienced a suboptimal response (<15% reduction in LDL-C level), ranging from 2.7 to 12.7% of patients. In general, lower-dose statins, e.g. atorvastatin 10 mg and simvastatin 10–20 mg, were associated with higher rates of suboptimal responses. However, even with high-dose statins, e.g. atorvastatin 80 mg and rosuvastatin 40 mg, 4.7 and 2.7% of patients, respectively, experienced a suboptimal response. For these individuals, additional therapy may be required to reduce LDL-C levels and subsequent cardiovascular risk.

It has been found that individual variability is often associated with genetic polymorphisms, with the apolipoprotein E locus found to be involved in LDL-C response variability. In addition, polymorphisms in genes involved in the transport, uptake, and metabolism of lipoproteins in genes involved in the transport, uptake, and metabolism of lipoproteins, dyslipidaemia.

A possible limitation of our analysis is that there is no universally accepted definition for the suboptimal response with statin treatment. The <15% reduction in LDL-C from baseline that we used was therefore based on clinical judgment and is, we feel, a conservative estimate. Perhaps, a more realistic definition when considering moderate- or high-intensity statins would be a <30% reduction in LDL-C from baseline. Using this definition, the percentage of patients in VOYAGER experiencing a suboptimal response ranges from 5.3 to 53.3%. When only moderate- and high-intensity statins are considered (i.e. statins expected to reduce LDL-C levels by >30%; Table 1), the percentage of patients experiencing a <30% reduction in LDL-C still ranges from 5.3 to 27.2%. It is also worth noting that the percentage of patients receiving high-intensity statins (atorvastatin 40–80 mg and rosuvastatin 20–40 mg) and achieving a <50% reduction in LDL-C ranges from 26.2% with rosuvastatin 40 mg to 52.6% with atorvastatin 40 mg. According to the ACC/AHA guideline definition, patients recommended for treatment with high-intensity statins are those at high risk of developing ASCVD; it may therefore be prudent to monitor these patients more closely and ensure that they are achieving clinically significant reductions in LDL-C with statin therapy.

In conclusion, individual variability in LDL-C response observed with different doses of different statins is important to consider in daily clinical practice. This may be especially important when interpreting the ACC/AHA guideline recommendations. In particular, clinicians should be mindful of possible poor responses to treatment in individual patients and amend treatment as appropriate.

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References


Erratum
doi:10.1093/ehjcvp/pvv055

Erratum to:


How European Society of Cardiology guidelines are made [Eur Heart J Cardiovasc Pharmacother (2015) 1(2):82]


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