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Achievement of LDL-C goals depends on baseline LDL-C and choice and dose of statin: An analysis from the VOYAGER database*

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Abstract

Background: Reducing low-density lipoprotein cholesterol (LDL-C) levels decreases cardiovascular risk in direct proportion to the decrease in LDL-C.

Design: The aim of this study was to assess the importance of baseline LDL-C and choice and dose of statin in achievement of LDL-C goals of 100 and 70 mg/dl, using a novel statistical model. The analysis included 30,102 patient exposures to rosuvastatin 10–40 mg or atorvastatin 10–80 mg from 31 direct comparative trials in the VOYAGER database.

Methods: For each statin dose, percentage goal achievement was plotted for 20 equally large subgroups defined by baseline LDL-C. Logistic regression analysis was then performed for each statin dose to estimate the percentage of patients reaching target. Best-fit logistic regression curves were plotted 'pair-wise', comparing each rosuvastatin dose with equal or higher doses of atorvastatin.

Results: LDL-C <100 mg/dl was achieved by 53.7–85.5% of patients on rosuvastatin 10–40 mg and 43.3–80.0% of those on atorvastatin 10–80 mg, whereas LDL-C <70 mg/dl was achieved by 4.5–44.0% of rosuvastatin-treated patients and 6.5–41.4% of those on atorvastatin. Similar differences in efficacy favouring rosuvastatin over equal or double doses of atorvastatin were observed across the range of baseline LDL-C levels for both LDL-C goals, being more pronounced at higher baseline values.

Conclusions: Baseline LDL-C and choice and dose of statin are important for LDL-C goal achievement. The present analysis may allow prediction of individual patient response to different statins at different doses.

Keywords

Low-density lipoprotein cholesterol, LDL-C, treatment goals, rosuvastatin, atorvastatin

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Introduction

There is extensive evidence that high levels of low-density lipoprotein cholesterol (LDL-C) are associated with increased risk of cardiovascular events,[1–3] and that reductions in LDL-C are associated with a decreased cardiovascular risk.[4–6] The recently updated Cholesterol Treatment Trialists' Collaboration meta-analysis of data from 170,000 patients included in 26 randomised trials of statin therapy, showed that the size of reduction of major cardiovascular events is proportional to the reduction in LDL-C. For every 1.0 mmol/l (~40 mg/dl) reduction in LDL-C, there was a

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corresponding 22% reduction in major cardiovascular events.[6]

Treatment guidelines for dyslipidaemia recommend LDL-C targets based on estimates of global cardiovascular risk, including baseline LDL-C levels and other risk factors.[7–9] Baseline LDL-C levels have often been grouped into broad intervals: optimal, <100 mg/dl (2.56 mmol/l); near optimal, 100–129 mg/dl (2.56–3.30 mmol/l); borderline high, 130–159 mg/dl (3.33–4.07 mmol/l); high, 160–189 mg/dl (4.10–4.84 mmol/l); and very high, ≥190 mg/dl (4.87 mmol/l).[7] In the USA, LDL-C treatment goals have been defined as <100 mg/dl (~2.6 mmol/l), <130 mg/dl (~3.3 mmol/l) and <160 mg/dl (~4.1 mmol/l), respectively, in patients considered to be at high, medium and low risk.[7] For very high-risk patients (i.e. those with established cardiovascular disease [CVD] plus multiple major risk factors, severe and poorly controlled risk factors, metabolic syndrome or acute coronary syndromes), the recommended LDL-C goal was later lowered to <70 mg/dl based on evidence from more recent clinical trials.[8] These US guidelines are expected to be updated in the near future.

Recently updated European guidelines recommend LDL-C targets of <3 mmol/l (~115 mg/dl) in moderate-risk patients, <2.5 mmol/l (~100 mg/dl) in high-risk patients and <1.8 mmol/l (~70 mg/dl) and/or a reduction in LDL-C of at least 50% in patients at highest risk, including those with established CVD, diabetes or moderate-to-severe chronic kidney disease.[10]

The importance of baseline LDL-C levels for reaching a treatment goal is often not taken into consideration, for example, when comparing results of treatments in different studies. Differences in baseline LDL-C levels may explain a lot of the observed variability between studies in terms of LDL-C goal achievement rates, even in patients treated with the same statin and with the same dose.[11–13] In previous studies that have investigated the relationship between baseline LDL-C level and goal achievement rate, patients were divided into the broad and somewhat arbitrary baseline LDL-C categories described above, such as those with LDL-C <130 mg/dl, those with LDL-C 130–160 mg/dl and those with LDL-C >160 mg/dl.[14–16]

For the present analysis, it was hypothesized that the relationship between baseline LDL-C and achievement of treatment goals with statins may be described in more detail by assessing achievement of LDL-C goals according to a continuum of baseline LDL-C levels. This is a novel approach that will allow a more explicit characterization of the relationship between baseline LDL-C levels and the effects of different statins and doses on LDL-C goal achievement. Such information can be important for difficult-to-treat patients and for their physicians in making optimal treatment choices.

The VOYAGER (An Individual Patient Meta-analysis of Statin Therapy in At Risk Groups: Effects of Rosuvastatin, Atorvastatin and Simvastatin) database[16] was therefore used to undertake an analysis of LDL-C <100 mg/dl and <70 mg/dl goal achievement with rosuvastatin 10–40 mg and atorvastatin 10–80 mg across the continuous range of baseline LDL-C values.

Methods

The methods employed in developing the VOYAGER database have been described previously.[16] Briefly, individual patient data were obtained from 37 studies that employed fixed-dose comparisons of rosuvastatin with either atorvastatin or simvastatin, and recorded lipid levels at baseline and on therapy. The present analysis compared the effects of rosuvastatin and atorvastatin on LDL-C goal achievement, as they are often considered to be the most effective statins. Six of the studies in the VOYAGER database were excluded from the present analysis: five because they were not direct comparisons of rosuvastatin and atorvastatin, and one because the patients had heterozygous familial hypercholesterolaemia, and their extremely high baseline LDL-C levels were outside the range of baseline values observed in all the other studies in the VOYAGER database. Inclusion of the results from the latter study would have had an undue influence on the results of the statistical analysis. Patients with baseline LDL-C ≤100 mg/dl were also excluded from the analysis. Finally, it should be noted that, in seven studies (e.g. ANDROMEDA), patients were force-titrated to higher statin doses regardless of lipid levels; these studies therefore provided additional exposures for some comparisons. Titration occurred at 8 weeks in ANDROMEDA, and at 6-week intervals in the remaining six studies. Studies in which patients were titrated to higher doses based on lipid goal attainment were excluded from the present analysis.

Therefore, this analysis included data from 30,102 patient exposures to daily treatment with rosuvastatin 10–40 mg or atorvastatin 10–80 mg among 24,901 hypercholesterolaemic patients included in 31 direct, randomized comparative trials of these agents that were included in the VOYAGER database.

For each comparison between a dose of rosuvastatin and an equal or higher dose of atorvastatin, only those trials that randomly compared the two statins were used. For each statin and dose, the percentage goal achievement values were plotted for 20 subgroups defined by baseline LDL-C, with equal or nearly equal numbers of patients in each subgroup. Logistic regression analysis was performed for each statin dose to estimate the percentage of patients in each patient group achieving LDL-C treatment targets of <100 mg/dl and

<70 mg/dl, across the range of baseline values. Best-fit logistic regression curves were plotted 'pair-wise', comparing each rosuvastatin dose with equal or higher doses of atorvastatin.

For descriptive purposes only, percentage goal achievement values were calculated and plotted for each statin dose in all the trials employing that dose.

Results

Across all the paired comparisons, LDL-C <100 mg/dl was achieved by 53.7–85.5% of patients treated with rosuvastatin 10–40 mg and by 43.3–80.0% of those treated with atorvastatin 10–80 mg. Logistic regression curves for the pairwise comparisons for achievement of the LDL-C goal of <100 mg/dl for the overall population are shown in Figure 1 for each dose comparison of rosuvastatin and atorvastatin. The number of studies directly comparing each dose is indicated in the figure legend. Observed data were well fit by the logistic regression curves. Goal achievement was shown to be better across the range of baseline LDL-C with rosuvastatin 10 mg versus atorvastatin 10 mg. For all equal-dose comparisons, the difference in achievement of goal was consistently in the same direction between the two statins, and with a possibly greater magnitude at higher baseline LDL-C values. The same was true, but with smaller differences, for comparisons of rosuvastatin with double doses of atorvastatin.

There were similar findings for achievement of the <70 mg/dl LDL-C goal, as shown in Figure 2. Across the paired comparisons, LDL-C <70 mg/dl was achieved by 4.5–44.0% of patients treated with rosuvastatin 10–40 mg and by 6.5–41.4% of those treated with atorvastatin 10–80 mg. The results again show that baseline LDL-C and choice and dose of statin are important for LDL-C goal achievement. The results of the statistical analyses of LDL-C goal achievement rates across the baseline LDL-C range for the individual dose comparisons are shown in Table 1 and Figure 3.

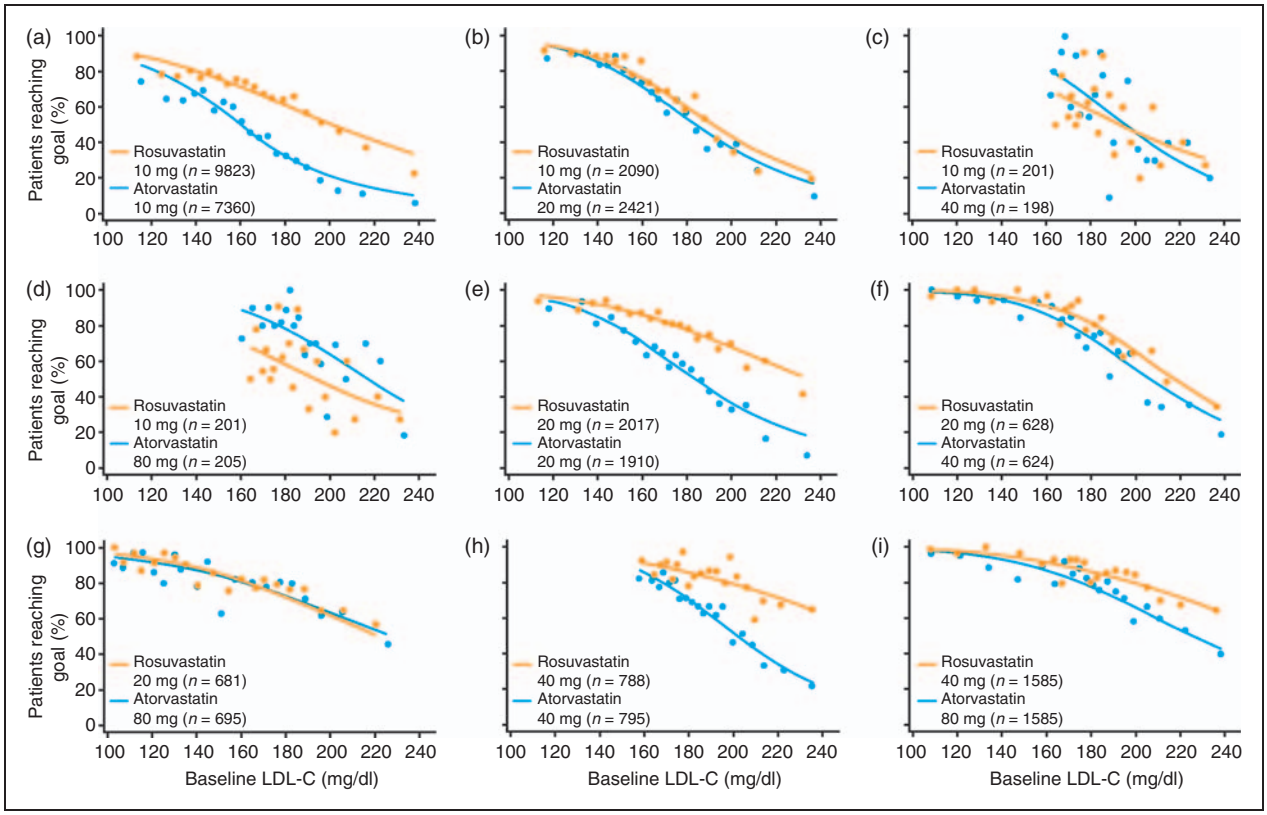

Figure 1. Achievement of low-density lipoprotein cholesterol (LDL-C) goal <100 mg/dl according to baseline LDL-C level. Logistic regression curves for pair-wise comparisons of different doses of rosuvastatin and equal or higher doses of atorvastatin: (a) rosuvastatin 10 mg vs atorvastatin 10 mg in 24 direct studies; (b) rosuvastatin 10 mg vs atorvastatin 20 mg in nine direct studies; (c) rosuvastatin 10 mg vs atorvastatin 40 mg in two direct studies; (d) rosuvastatin 10 mg vs atorvastatin 80 mg in two direct studies; (e) rosuvastatin 20 mg vs atorvastatin 20 mg in nine direct studies; (f) rosuvastatin 20 mg vs atorvastatin 40 mg in five direct studies; (g) rosuvastatin 20 mg vs atorvastatin 80 mg in four direct studies; (h) rosuvastatin 40 mg vs atorvastatin 40 mg in four direct studies; (i) rosuvastatin 40 mg vs atorvastatin 80 mg in seven direct studies.

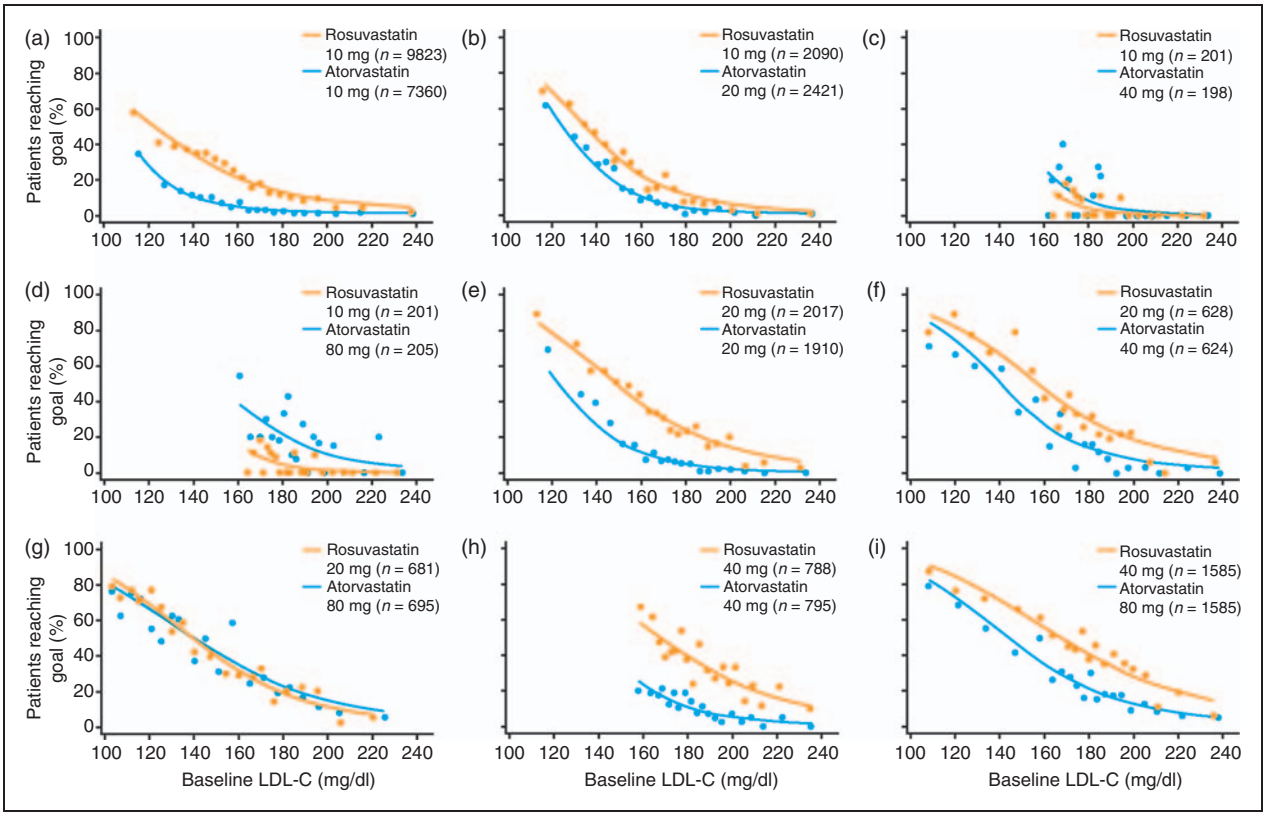

Figure 2. Achievement of low-density lipoprotein cholesterol (LDL-C) goal <70 mg/dl according to baseline LDL-C level. Logistic regression curves for pair-wise comparisons of different doses of rosuvastatin and atorvastatin: (a) rosuvastatin 10 mg vs atorvastatin 10 mg in 24 direct studies; (b) rosuvastatin 10 mg vs atorvastatin 20 mg in nine direct studies; (c) rosuvastatin 10 mg vs atorvastatin 40 mg in two direct studies; (d) rosuvastatin 10 mg vs atorvastatin 80 mg in two direct studies; (e) rosuvastatin 20 mg vs atorvastatin 20 mg in nine direct studies; (f) rosuvastatin 20 mg vs atorvastatin 40 mg in five direct studies; (g) rosuvastatin 20 mg vs atorvastatin 80 mg in four direct studies; (h) rosuvastatin 40 mg vs atorvastatin 40 mg in four direct studies; (i) rosuvastatin 40 mg vs atorvastatin 80 mg in seven direct studies.

Table 1. Results of the statistical analyses of target low-density lipoprotein cholesterol (LDL-C) goal achievement rates (<100 mg/dl and <70 mg/dl) across the baseline LDL-C range for each of the paired dose comparisons

	Target goal LDL-C <100 mg/dl			Target goal LDL-C <70 mg/dl		
Dose comparison	Odds ratio[a]	95% CI	*p*-value	Odds ratio[a]	95% CI	*p*-value
RSV 10 mg vs ATV 10 mg	2.65	2.48–2.83	<0.001	4.22	3.78–4.70	<0.001
RSV 10 mg vs ATV 20 mg	1.34	1.18–1.53	<0.001	1.93	1.65–2.26	<0.001
RSV 10 mg vs ATV 40 mg	0.87	0.59–1.30	0.507	0.50	0.22–1.15	0.102
RSV 10 mg vs ATV 80 mg	0.49	0.32–0.73	<0.001	0.21	0.10–0.45	<0.001
RSV 20 mg vs ATV 20 mg	2.92	2.52–3.37	<0.001	4.12	3.45–4.93	<0.001
RSV 20 mg vs ATV 40 mg	1.83	1.40–2.41	<0.001	2.43	1.86–3.18	<0.001
RSV 20 mg vs ATV 80 mg	1.18	0.90–1.55	0.234	1.03	0.83–1.29	0.772
RSV 40 mg vs ATV 40 mg	2.77	2.19–3.49	<0.001	4.65	3.54–6.10	<0.001
RSV 40 mg vs ATV 80 mg	1.81	1.50–2.17	<0.001	2.16	1.85–2.52	<0.001

ATV: atorvastatin; RSV: rosuvastatin; CI: confidence interval.; [a]Odds ratio >1 favours rosuvastatin.

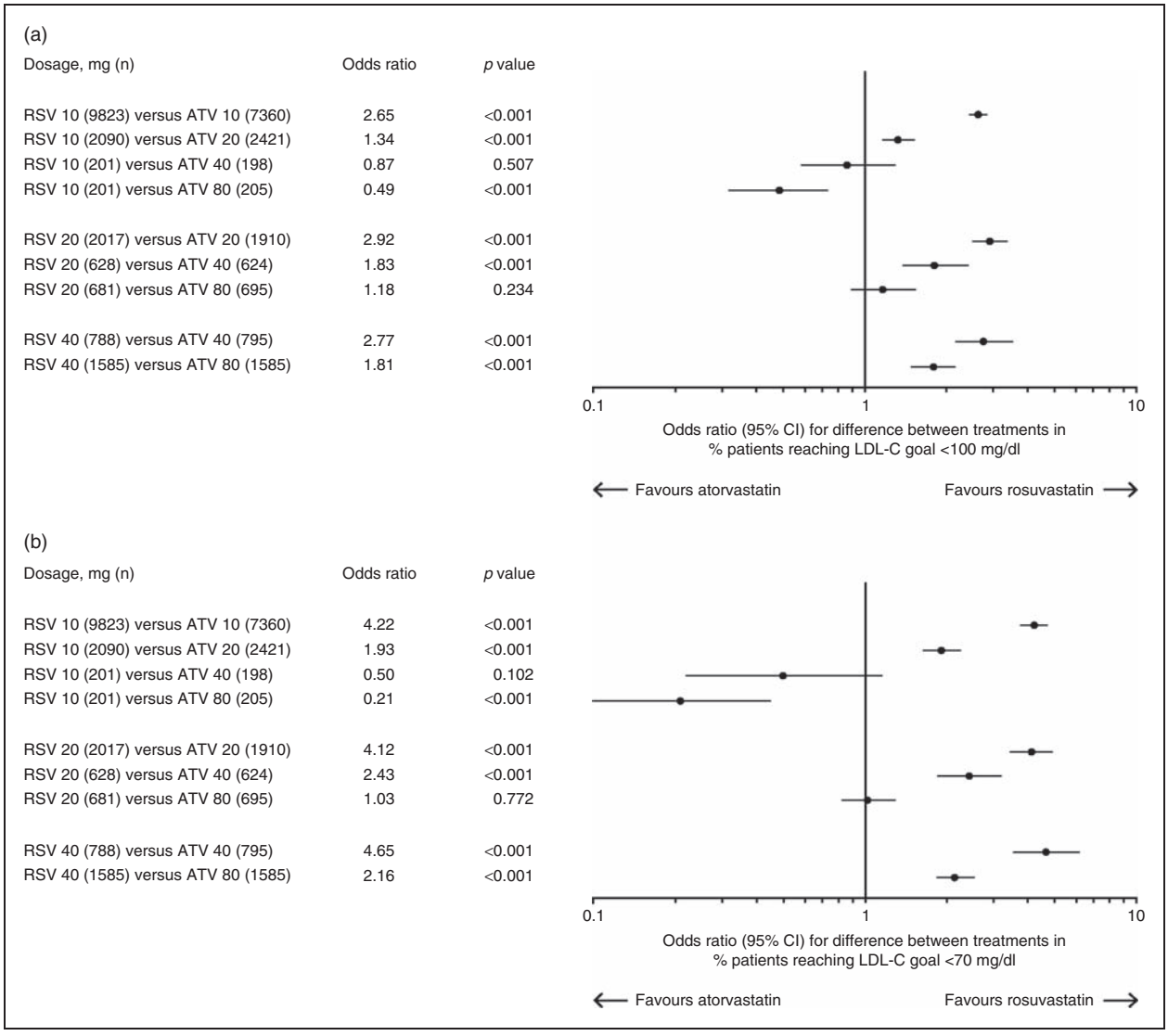

Figure 3. Results of the statistical analyses of target low-density lipoprotein cholesterol (LDL-C) goal achievement across the baseline LDL-C range for each of the paired dose comparisons: (a) LDL-C goal <100 mg/dl; (b) LDL-C goal <70 mg/dl.

LDL-C goal achievement rates were found to vary between the studies included in the analysis, even when the same statin dose was used (Supplementary Table). Mean baseline LDL-C levels were also found to vary between these studies (Supplementary Table).

Figures 4 and 5 show the analysis of percentage goal achievement with rosuvastatin and atorvastatin (LDL-C <100 mg/dl and <70 mg/dl in each case) across the range of baseline values with each statin dose in all the trials employing those doses. This is a descriptive analysis only, and the direct study data shown in Figures 1 and 2 should be used to make valid dose comparisons.

Discussion

These analyses of LDL-C 100 mg/dl and 70 mg/dl goal achievement rates in the VOYAGER population show that baseline LDL-C and choice and dose of statin are all-important determinants of goal achievement. The graphic representation of the data may allow clinicians to estimate their individual patients' chances of achieving their LDL-C goal at a particular dose of each statin. The obvious difficulty in reaching goal for patients at the higher end of the baseline LDL-C continuum, and the increasing difference between the compared statins with increasing baseline LDL-C, may guide clinicians in their choice of statin and dose titration. In the present analysis, a greater proportion of patients achieved lipid goals with increasing statin dose across the spectrum of baseline LDL-C levels, and this supports using appropriate doses of effective statins. Because the trials in the VOYAGER database included high-risk patients, such as those with diabetes or chronic kidney disease, the findings should be applicable to the general population.

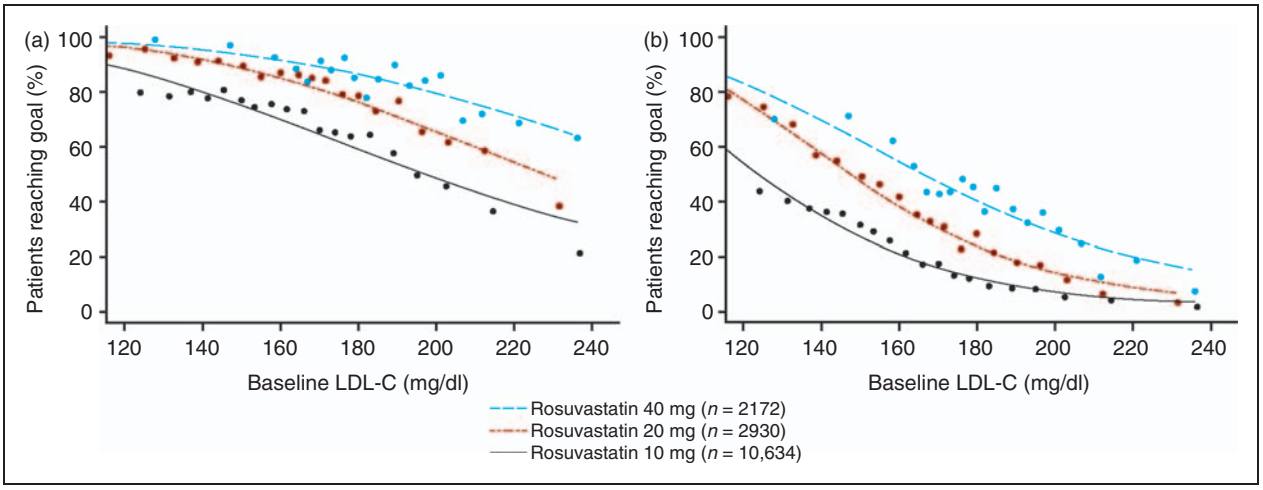

Figure 4. Descriptive analysis: achievement of low-density lipoprotein cholesterol (LDL-C) goals according to baseline LDL-C level with rosuvastatin 10–40 mg in all trials employing these doses: (a) LDL-C goal <100 mg/dl; (b) LDL-C goal <70 mg/dl.

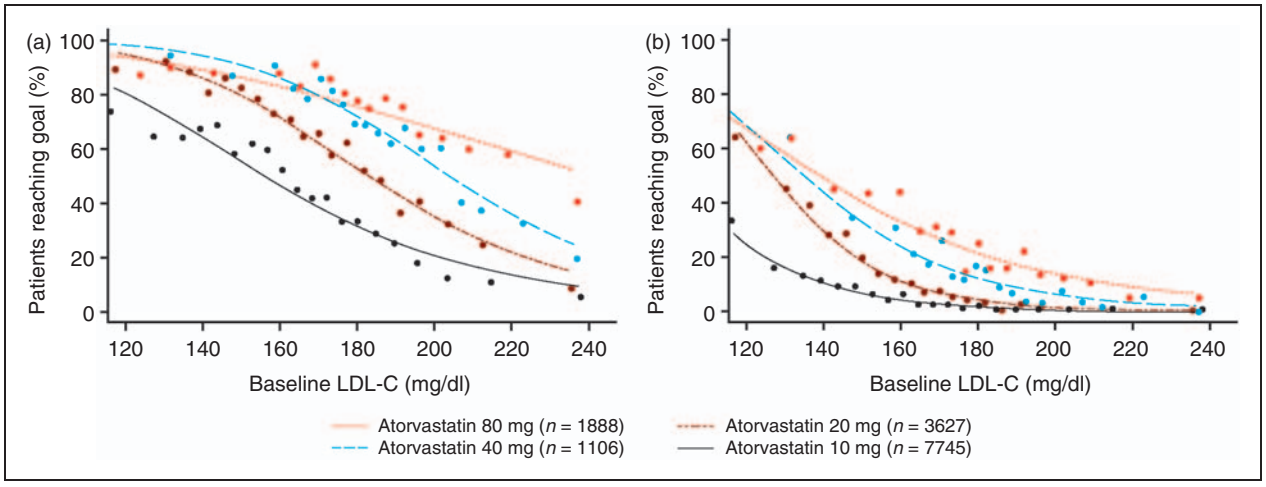

Figure 5. Descriptive analysis: achievement of low-density lipoprotein cholesterol (LDL-C) goals according to baseline LDL-C level with atorvastatin 10–80 mg in all trials employing these doses: (a) LDL-C goal <100 mg/dl; (b) LDL-C goal <70 mg/dl.

Comparison of the trials included in the analysis also demonstrates the variable rates of LDL-C goal achievement with the same statin at the same dose in different trials. Within a trial, it is likely that baseline LDL-C levels are less important when comparing the efficacy of different statins, as randomization is expected to produce two groups with similar baseline LDL-C distributions. When comparing the results from different trials as in the Supplementary Table, for example, the effect of baseline LDL-C should always be taken into consideration by using the type of analysis reported here.

In an observational study assessing determinants of real-world effectiveness of lipid-lowering therapy in outpatients with coronary heart disease, post-treatment LDL-C and LDL-C goal achievement were found to be independently associated with pre-treatment LDL-C.[17] Another observational study of statin-treated patients in clinical practice in Europe and Canada found that nearly half were not at their LDL-C goal, and that predictors of goal achievement included higher statin dose.[18]

A recent meta-analysis has indicated that lower is better for LDL-C, with no evidence that reducing LDL-C to very low levels is associated with increased risk of adverse events.[6] In fact, another recent paper, from the TIMI Study Group, suggests that human adults were genetically designed for very low lipid levels.[19] The Group also suggest that the risk of cardiovascular events might approach zero if LDL-C was lowered to <60 mg/dl in primary prevention and <30 mg/dl in secondary prevention. The updated European treatment guidelines for dyslipidaemia still

stipulate a target LDL-C level of <70 mg/dl for very-high-risk patients, but also recommend at least a 50% reduction from baseline LDL-C when the target cannot be reached.[10]

When statins, including atorvastatin, become generic, there is also a cost consideration to the choice of drug. This efficacy–cost balance is not always obvious, and must take into account total cardiovascular risk. For example, a recent Spanish study employing a statistical model reported that rosuvastatin was more effective than generic atorvastatin in terms of survival and quality-of-life adjusted survival, with incremental cost-effectiveness ratios within the acceptable range in most subpopulations evaluated.[20]

A possible limitation of the present analysis is the use of a logistic regression model. Although it seems to provide good quantitative descriptions of the relationship between target goal achievement and baseline LDL-C, other statistical methods could be considered.

The analysis included patients who were force-titrated to higher statin doses, but not patients who were titrated according to lipid goal achievement. In a post hoc exploratory analysis, evaluation of the data excluding the force-titrated patients revealed a similar pattern of LDL-C goal achievement according to baseline LDL-C and statin dose (data not shown).

It is hoped that this novel method of analysis may allow physicians to optimize the management of their dyslipidaemic patients. Such an approach may also prove useful in other target-driven therapeutic areas.

Conclusions

This study introduces a statistical model that characterizes in a novel and precise way the relationship between baseline LDL-C level and attainment of LDL-C targets. The study shows that baseline LDL-C and choice and dose of statin are important for goal achievement (<100 mg/dl and <70 mg/dl) in patients in need of reducing their LDL-C levels. This analysis may allow prediction of individual patient response to different statins at different doses.

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Conflict of interest

Mike K Palmer has received fees for statistical analysis from AstraZeneca; Stephen J Nicholls has received research support from AstraZeneca; Pia Lundman has received speaker fees from AstraZeneca; Philip J Barter has received speaker fees from AstraZeneca; and Björn W Karlson is an employee of AstraZeneca.

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