Clinical Use and Effectiveness of Lipid Lowering Therapies in Diabetes Mellitus—An Observational Study from the Swedish National Diabetes Register

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Abstract

Objectives: To describe the use and evaluate the effectiveness of different lipid lowering therapies in unselected patients with type 1 and type 2 diabetes in clinical practice.

Design: Observational population-based study using the personal identification number to link information from the National Diabetes Register, the Prescribed Drug Register and the Patient register in Sweden. All patients in the NDR aged 18–75 years with diabetes more than one year were eligible, but only patients starting any lipid lowering treatment with at least three prescriptions 1 July 2006–30 June 2007 were included (n = 37182). The mean blood lipid levels in 2008 and reductions in LDL cholesterol were examined.

Results: Blood lipid levels were similar in patients treated with simvastatin, atorvastatin and rosuvastatin, showing similar lipid lowering effect as currently used. Users of pravastatin, fluvastatin, ezetimib and fibrate more seldom reach treatment goals. Moderate daily doses of the statins were used, with 76% of simvastatin users taking 20 mg or less, 48% of atorvastatin users taking 10 mg, 55% of pravastatin users taking 20 mg, and 76% of rosuvastatin users taking 5 or 10 mg.

Conclusions: This observational study shows that the LDL-C levels in patients taking simvastatin, atorvastatin or rosuvastatin are very similar as currently used, as well as their LDL-C lowering abilities. There is potential to intensify lipid lowering treatment to reduce the remaining high residual risk and achieve better fulfilment of treatment goals, since the commonly used doses are only low to moderate.

Introduction

Recent randomized clinical trials and a major meta-analysis have emphasized the importance of LDL-cholesterol (LDL-C) lowering for cardiovascular risk reduction in diabetes mellitus [1–3]. Therefore the current treatment guidelines advocate aggressive multifactorial risk factor intervention in patients with diabetes [4,5]. The European guidelines promote lifestyle changes and lipid lowering therapy in order to reach a lower LDL-C value than 2.5 mmol/L, or 1.8 mmol/L or lower if overt cardiovascular disease (CVD) is present [5]. The pharmacological treatment should be based on HMG CoA reductase inhibitors, also known as statins, but other options are to be considered if the treatment goals are not reached.

The LDL-C lowering effects of the different statins in clinical trials have recently been reviewed [6]. A small or moderate dose of statins could decrease LDL-C by 20–40%, with small differences between the different agents. These conclusions are in agreement with the CURVES and the STELLAR studies, in which atorvastatin and rosuvastatin, respectively, showed similar effects as other statin [7,8]. At higher doses, however, atorvastatin and rosuvastatin are the only agents that can lower LDL-C more than 40% [6]. There have not been any randomized clinical trials or observational epidemiological studies with head to head comparisons of the cholesterol lowering effect by different statins in patients with diabetes.

The aim of this observational study linking data from the Swedish National Diabetes Register (NDR), a quality register with nation-wide coverage, with two other national population-based registers, was to describe the use and evaluate the LDL-C lowering effects of different lipid lowering therapies in 37 182 unselected patients with type 1 and type 2 diabetes in clinical practice.
Methods

This is a population-based study using the personal identification number to link information from three national registers. NDR was initiated in 1996 as a tool for quality improvement in diabetes care, and has been described previously [9,10]. Physicians and nurses in hospital outpatient clinics and primary health care clinics report to the NDR at least once every year, either online or by direct transfer of data from medical records databases. The Swedish Prescribed Drug Register contains information about dispensed prescribed drugs in the entire Swedish population of 9.4 million inhabitants [11]. The Swedish Patient Register contains information on dates of hospital admission and discharge, codes for all surgical procedures and discharge diagnoses [12,13]. The Regional Ethical Review Board of the University of Gothenburg approved the study, and all included patients have agreed to be reported.

All patients aged 18–75 years in the NDR with diabetes for more than one year were eligible, but only patients who had not purchased any lipid lowering medicine 1 July 2005–30 June 2006 and thereafter filled at least three prescriptions 1 July 2006–30 June 2007 were included in the study (n = 37,182). These criteria were chosen based on the Swedish Pharmaceutical Benefits Scheme where the patients normally fill a prescription for 90 days of supply, and can refill again when two thirds of the theoretical consumption time has passed. In some cases the first filled prescription encompasses only a small start package for 30 days of supply. Thus, those included in the study would have purchased lipid lowering drugs corresponding to seven months of use or more. Clinical characteristics including mean blood lipid values on treatment (2008) were studied in this group. We also performed a subgroup analysis of patients who also had a known LDL-C value before 1 July 2005 and 30 June 2006, i.e., before the initiation of lipid lowering therapy (n = 10,456).

The clinical characteristics analysed at baseline were age, sex, diabetes duration, BMI, smoking, blood pressure, HbA1c, total cholesterol (TC), HDL-C, and serum triglycerides. The patients were screened using local methods, but guidelines were available to ensure the use of similar methodology. A smoker was defined as a patient smoking one or more cigarettes per day, or a pipe dally, or who had stopped smoking within the past three months. Renal disease was defined as a history of acute, chronic, and any or unspecified renal insufficiency.

Laboratory analyses, including TC and HDL-C levels, were carried out at local laboratories. HbA1c analyses are quality assured in Sweden by regular calibration with Mono-S, a HPLC method. In this study, all HbA1c values were converted to the DCCT (Diabetes Control and Complications Trial) standard levels: HbA1c (DCCT) = 0.923 × HbA1c (Mono-S)+1.345; R² = 0.996 [14]. LDL-C was calculated using Friedewald’s formula [15] if serum TG levels were lower than 4.0 mmol/L [16].

History of CVD recorded at hospital discharge was retrieved from the Swedish Patient Register. CVD was defined as diagnosis of myocardial infarction, angina pectoris, intracerebral haemorrhage, cerebral infarction or unspecified stroke before the survey, but peripheral vascular disease was not included.

Statistical methods

General linear modelling was used to compare clinical characteristics and reductions in LDL-C. The relative risks of reaching LDL-C ≥2.5 mmol/L were estimated by using generalized linear modelling and simvastatin as the reference. When adjusting for potential confounding factors, we categorised the numeric variables: age (<30 years, 30–39 years, 40–49 years, 50–59 years, ≥60 years), diabetes duration (<10 years, ≥10 years), LDL-C level before taking statin (<2.5 mmol/L, ≥2.5 mmol/L). Median doses of the lipid lowering agents were used as cut-offs in these calculations (high dosages: simvastatin ≥20 mg, pravastatin ≥40 mg, fluvastatin ≥40 mg, atorvastatin ≥20 mg, rosuvastatin ≥10 mg as high dosage, fibrates ≥0.5 mg; all used 10 mg ezetimib). In order to avoid a substantial reduction of the number of subjects, we accepted ‘missing value’ of LDL-C as a single category in our main analyses. All statistical analyses were performed by use of SAS statistical software version 9.2 (SAS Institute, Cary, NC, USA).

Results

Table 1 gives the clinical characteristics of the patients on any lipid lowering treatment in 2008. Of all patients around 75% used simvastatin, 14% used atorvastatin, 4% used pravastatin, 3% used a statin plus ezetimib combination and 2% used a statin plus fibrate combination. Fluvastatin, rosuvastatin and ezetimib were used by 1% or less of the patients, respectively. The mean age was around 62 years with almost 15 years of mean diabetes duration. The proportion of men in the cohort was around 60%, circa 10% had type 1 diabetes and 13% were smokers. Mean BMI was almost 30 kg/m², mean blood pressure was 135/75 mm Hg and HbA1c 6.4%. There were statistically significant differences between mean values and proportions of all risk factors (except diastolic blood pressure) in the different treatment groups and also between the users of the different statins (except systolic and diastolic blood pressure). A history of CVD was most common in patients on pravastatin, fluvastatin or rosuvastatin. In patients on simvastatin, a fibrate or combination therapy, a history of renal disease was less common.

The numbers of patients and the proportion of patients reaching LDL-C < 2.5 mmol/L on the different doses of the statins are given in Table 2. In patients with LDL-C < 2.5 mmol/L the distribution of doses were the same as in the overall cohort. Only ezetimib 10 mg was used. In patients on fibrates, a daily dose of 600 mg was the most common dose, used in 44% of these patients. In statin plus ezetimib or fibrate combination therapy, simvastatin was used in 64%, atorvastatin in 26%, pravastatin in 5% and rosuvastatin in 4%.

In Table 3 blood lipid values are given and the proportion of patients achieving the current treatment goals. Figures 1, 2, 3, 4, 5, 6 presents the distribution of LDL-C values in patients on different lipid lowering treatments. TC, LDL-C were lower and the proportion of subjects, we accepted ‘missing value’ of LDL-C as a single category in our main analyses. All statistical analyses were performed by use of SAS statistical software version 9.2 (SAS Institute, Cary, NC, USA).
Table 1. Clinical characteristics of the patients on lipid lowering treatment 2008.

| Variable                  | Simvastatin | Pravastatin | Fluvastatin | Atorvastatin | Rosuvastatin | Ezetimib | Fibrate | Statin + ezetimib | P-values overall: \(<0.0001\) | P-values overall: \(<0.0001\) |
|---------------------------|-------------|-------------|-------------|--------------|--------------|----------|---------|-------------------|-----------------------------|-----------------------------|
| Number of patients        | N           | 28025       | 940         | 159          | 5098         | 355      | 208     | 536               | 754                         | 1107                        |
| Age (Mean ± SD)           |             |             |             |              |              |          |         |                   |                             |                             |
|                           |             | 62.8±8.6    | 64.7±7.4    | 64.3±7.9     | 62.6±8.2     | 60.8±8.7 | 62.9±8.2 | 62.2±8.5         | 62.1±8.2                    | 61.7±8.6                    |
| Duration (Mean ± SD)      |             | 28025       | 940         | 159          | 5098         | 355      | 208     | 536               | 754                         | 1107                        |
|                           |             | 12.8±11.5   | 14.2±12.0   | 15.5±13.7    | 14.5±12.1    | 12.5±11.4| 15.5±13.2| 12.8±8.8         | 11.9±8.6                    | 13.2±12.1                   |
| Men N                     |             | 8444        | 102         | 3078         | 194          | 104      | 336      | 513               | 645                         |                             |
|                           |             | 58.7        | 55.2        | 64.2         | 60.4         | 54.6     | 50.0     | 67.2               | 68.0                        | 58.3                        |
| Type 1 diabetes N         |             | 2536        | 73          | 24           | 522          | 33       | 26       | 17                | 15                          | 115                         |
|                           |             | 9.0         | 7.8         | 15.1         | 10.2         | 9.3      | 12.5     | 3.2               | 2.0                         | 10.4                        |
| Type 2 diabetes N         |             | 23594       | 793         | 126          | 4148         | 291      | 167      | 465               | 671                         | 897                         |
|                           |             | 84.2        | 84.4        | 79.2         | 81.4         | 82.0     | 80.3     | 86.8               | 89.0                        | 81.0                        |
| Systolic blood pressure   |             | 27543       | 929         | 156          | 5011         | 348      | 204     | 530               | 736                         | 1089                        |
|                           |             | 136±16      | 137±16      | 137±17       | 136±16       | 135±16   | 136±16   | 138±17            | 135±16                      |                             |
| Diastolic blood pressure  |             | 27543       | 929         | 156          | 5011         | 348      | 204     | 530               | 736                         | 1089                        |
|                           |             | 75±9        | 75±9        | 75±10        | 75±9         | 75±10    | 76±9     | 76±10             | 75±9                        |                             |
| BMI N                     |             | 26569       | 883         | 148          | 4814         | 335      | 198     | 502               | 714                         | 1047                        |
|                           |             | 29.6±5.1    | 29.6±5.0    | 29.3±4.8     | 29.9±5.1     | 30.0±5.0 | 29.4±4.9 | 30.2±5.0         | 30.8±4.8                    | 30.1±4.9                    |
| Smokers N                 |             | 3659        | 121         | 13           | 676          | 44       | 19       | 68                | 127                         | 152                         |
|                           |             | 13.0        | 12.9        | 8.2          | 13.3         | 12.4     | 9.1      | 12.7               | 16.8                        | 13.7                        |
| HbA1c N                   |             | 27836       | 935         | 158          | 5072         | 354      | 208     | 531               | 748                         | 1099                        |
|                           |             | 6.4±1.2     | 6.3±1.1     | 6.5±1.3      | 6.5±1.3      | 6.5±1.4  | 6.3±1.2  | 6.4±1.3            | 6.5±1.3                     | 6.6±1.3                     |
| CVD N                     |             | 5567        | 258         | 44           | 1153         | 97       | 46       | 86                | 143                         | 195                         |
|                           |             | 19.9        | 27.4        | 27.7         | 22.6         | 27.3     | 22.1     | 16.0               | 19.0                        | 17.6                        |
| Renal disease N           |             | 2472        | 107         | 39           | 641          | 48       | 29       | 37                | 63                          | 99                          |
|                           |             | 8.8         | 11.4        | 24.5         | 12.6         | 13.5     | 13.9     | 6.9               | 8.4                         | 8.9                         |

CVD, history of cardiovascular disease; Renal disease, history of renal disease. SD, standard deviation.
doi:10.1371/journal.pone.0018744.t001

expected, with higher mean HDL-C and lower TG levels, while LDL-C (2.4±0.7 mmol/L) was numerically almost the same, as the overall cohort (2.3±0.7 mmol/L). In the patients with type 1 diabetes on simvastatin or atorvastatin, a history of CVD was less common but a history of renal disease clearly more prevalent (22.8% in simvastatin-treated patients and 32.4% in patients taking atorvastatin) than the overall cohort, which mainly consisted of patients with type 2 diabetes (79–89% in the different treatment groups).

The mean effects on LDL-C levels after starting a lipid lowering treatment in a subgroup of patients with an LDL-value both before and during treatment are given in Table 4. The clinical characteristics of these patients did not differ markedly from the data presented in Table 1 and 3 (data not shown). The most pronounced effects were seen in patients starting on simvastatin, rosuvastatin, ezetimib or statin plus ezetimib combination. Compared with the LDL-C levels before treatment, all changes were statistically significant except for pravastatin and fluvastatin.

Table 5 gives the relative risks (and 95% confidence interval) of achieving a LDL-C level ≥2.5 mmol/L in patients taking other lipid lowering agents than simvastatin with those using simvastatin as reference category. Without adjustment for covariates, dose and LDL-C levels before the lipid lowering treatment, only atorvastatin and rosuvastatin showed no difference in relative risk. The relative risks were significantly higher than 1 in all other treatment groups. An identical pattern was seen also after adjustment for the covariates separately or all simultaneously, including doses of the lipid lowering treatment and LDL-C before the treatment.
This observational study examining clinical use and the effects on LDL-C levels of lipid lowering therapies shows that blood lipid levels are very similar in patients treated with simvastatin, atorvastatin and rosuvastatin in clinical practice in Sweden. These three agents have also shown similar LDL-C lowering effects as currently used. A combination with a statin and ezetimib or a fibrate also shows similar effects, while users of pravastatin, fluvastatin, ezetimib and fibrate more seldom reach recommended TC and LDL-C levels. However, only moderate doses of the different statins are used, with 76% of the patients on simvastatin taking 20 mg or less daily, 48% of atorvastatin users taking 10 mg daily, 55% of pravastatin users taking 20 mg daily, and 76% of rosuvastatin users taking 5 or 10 mg daily.

The subgroup of patients with type 1 diabetes was characterized by more renal disease but less history of CVD than the overall cohort. These patients were mostly treated with simvastatin or atorvastatin.

### Table 2. Distribution of mean doses of the statins in patients on statins.

| Substance | Number (N) and proportion (%) | Dose | 5 mg | 10 mg | 20 mg | 40 mg | 80 mg | Total N |
|-----------|-------------------------------|------|------|------|------|------|------|-------|
| Simvastatin | N/%                          | n.a. | 5457 (19.5%) | 15874 (56.6%) | 6592 (23.5%) | 102 (0.4%) | 28025 |
| % with LDL-C<2.5 mmol/L | n.a.                          | 3292 (18.4%) | 10220 (57.2%) | 4319 (24.1%) | 50 (0.3%) | 17881 |
| Pravastatin | N/%                          | n.a. | 515 (54.8%) | 425 (45.2%) | n.a. | 940 |
| % with LDL-C<2.5 mmol/L | n.a.                          | 218 (51.4%) | 206 (48.6%) | n.a. | 424 |
| Fluvastatin | N/%                          | n.a. | 60 (37.7%) | 47 (29.6%) | 52 (32.7%) | 159 |
| % with LDL-C<2.5 mmol/L | n.a.                          | 16 (26.2%) | 16 (26.2%) | 29 (47.6%) | 61 |
| Atorvastatin | N/%                          | n.a. | 2466 (48.4%) | 1713 (33.6%) | 415 (8.1%) | 504 (9.9%) | 5098 |
| % with LDL-C<2.5 mmol/L | n.a.                          | 1606 (48.9%) | 1103 (33.6%) | 252 (7.7%) | 319 (9.8%) | 3280 |
| Rosuvastatin | N/%                          | 17 (4.8%) | 254 (71.5%) | 75 (21.1%) | 9 (2.5%) | n.a. | 355 |
| % with LDL-C<2.5 mmol/L | 13 (5.5%)                      | 174 (73.1%) | 47 (19.7%) | 4 (1.7%) | n.a. | 238 |

N.a., not applicable.

**Table 3. Blood lipid values of the patients on lipid lowering treatment 2008.**

| Variable | Simvastatin | Pravastatin | Fluvastatin | Atorvastatin | Rosuvastatin | Ezetimib | Fibrate | Statin + fibrate | Statin + ezetimib |
|----------|-------------|-------------|-------------|--------------|--------------|----------|---------|-----------------|------------------|
| TC       | N           | 27887       | 933         | 158          | 5065         | 351      | 207     | 534             | 751              |
| Mean±SD  | 4.4±0.8     | 4.7±0.8     | 4.8±0.9     | 4.4±0.8      | 4.4±1.1      | 5.3±1.0  | 4.9±1.0 | 4.5±0.9         | 4.5±1.2          |
| TC<4.5   | N           | 15758       | 367         | 59           | 2938         | 201      | 44      | 185             | 378              |
| %        | 56.5        | 39.3        | 37.3        | 58.0         | 57.3         | 21.2     | 34.6    | 50.3            | 53.7             |
| LDL-C    | N           | 28025       | 940         | 159          | 5098         | 355      | 208     | 536             | 754              |
| Mean±SD  | 2.3±0.7     | 2.7±0.7     | 2.7±0.7     | 2.3±0.7      | 2.3±1.0      | 3.1±0.8  | 2.9±0.9 | 2.4±0.9         | 2.4±1.0          |
| LDL-C<2.5 | N           | 17881       | 424         | 61           | 3280         | 238      | 58      | 182             | 433              |
| %        | 63.8        | 45.1        | 38.4        | 64.3         | 67.0         | 27.9     | 34.0    | 57.4            | 63.0             |
| LDL-C≤1.8 with history of CVD | N | 1526 | 30 | 4 | 310 | 33 | 2 | 7 | 39 | 67 |
| %        | 25.9        | 32.2        | 25.0        | 25.7         | 28.9         | 25.0     | 12.1    | 21.08           | 20.3             |
| HDL-C    | N           | 27769       | 927         | 159          | 5052         | 347      | 206     | 533             | 748              |
| Mean±SD  | 1.3±0.4     | 1.3±0.4     | 1.3±0.4     | 1.3±0.4      | 1.3±0.4      | 1.3±0.4  | 1.1±0.4 | 1.1±0.3         | 1.2±0.4          |
| HDL-C>1.0 (men) | N | 10752 | 326 | 56 | 1819 | 117 | 65 | 136 | 196 | 381 |
| %        | 38.7        | 35.2        | 35.2        | 36.0         | 33.7         | 31.6     | 25.5    | 26.2            | 35.0             |
| HDL-C>1.3 (women) | N | 5849 | 194 | 28 | 898 | 66 | 54 | 61 | 59 | 205 |
| %        | 21.1        | 20.9        | 17.6        | 17.8         | 19.0         | 26.2     | 11.4    | 7.9             | 18.8             |
| TG       | N           | 27661       | 924         | 159          | 5036         | 346      | 207     | 533             | 749              |
| Mean±SD  | 1.7±0.9     | 1.7±0.8     | 1.8±0.9     | 1.8±0.9      | 1.9±1.0      | 1.8±1.0  | 2.1±1.2 | 2.4±1.3         | 2.1±1.2          |
| TG<1.7   | N           | 16309       | 493         | 82           | 2624         | 171      | 103     | 241             | 229              |
| %        | 59.0        | 53.4        | 51.6        | 52.1         | 49.4         | 49.8     | 45.2    | 30.6            | 44.4             |

SD, standard deviation; TC, total cholesterol; LDL-C, LDL cholesterol; HDL-C, HDL cholesterol; TG, triglycerides.

doi:10.1371/journal.pone.0018744.t002
doi:10.1371/journal.pone.0018744.t003
Figure 1. Histogram for the LDL-C values in patients on simvastatin.
doi:10.1371/journal.pone.0018744.g001

Figure 2. Histogram for the LDL-C values in patients on atorvastatin.
doi:10.1371/journal.pone.0018744.g002
Figure 3. Histogram for the LDL-C values in patients on pravastatin.
doi:10.1371/journal.pone.0018744.g003

Figure 4. Histogram for the LDL-C values in patients on rosuvastatin.
doi:10.1371/journal.pone.0018744.g004
Figure 5. Histogram for the LDL-C values in patients on a fibrate.
doi:10.1371/journal.pone.0018744.g005

Figure 6. Histogram for the LDL-C values in patients on a statin and ezetimib combination.
doi:10.1371/journal.pone.0018744.g006
Table 4. LDL cholesterol values of patients on lipid lowering treatments before and on treatment in 2008.

| Variable | Simvastatin | Pravastatin | Fluvastatin | Atorvastatin | Rosuvastatin | Ezetimib | Fibrate | Statin + ezetimib | Statin + ezetimib |
|----------|-------------|-------------|-------------|--------------|--------------|----------|---------|------------------|------------------|
| Number of patients | N           | 7975        | 260         | 33            | 1398         | 83       | 64      | 138              | 215              |
| LDL-C before lipid lowering treatment (mmol/L) Mean±SD | 2.6±0.9 | 2.7±0.7 | 2.7±0.8 | 2.4±0.8 | 2.6±1.0 | 3.3±0.9 | 3.0±0.9 | 2.5±0.9 | 2.8±1.1 |
| LDL-C on lipid lowering treatment (mmol/L) Mean±SD | 2.3±0.7 | 2.7±0.7 | 2.7±0.7 | 2.3±0.7 | 2.3±1.0 | 3.1±0.8 | 2.9±0.9 | 2.4±0.9 | 2.4±1.0 |
| Change (mmol/L) Mean (95% CI) | 0.24 (0.22–0.26) | 0.05 (−0.02–0.13) | −0.002 (−0.18–0.17) | 0.064 (0.02–0.10) | 0.34 (0.12–0.56) | 0.34 (0.10–0.59) | 0.14 (0.01–0.27) | 0.18 (0.07–0.29) | 0.37 (0.25–0.49) |
| Change (%) Mean | 9.2 | 1.9 | 0.1 | 2.7 | 13.1 | 10.3 | 4.7 | 7.2 | 13.2 |
| P-value | <0.0001 | 0.1654 | 0.9754 | <0.0031 | <0.0024 | 0.0063 | 0.0270 | 0.0009 | <0.0001 |

SD, standard deviation; TC, total cholesterol; LDL-C, LDL cholesterol.

doi:10.1371/journal.pone.0018744.t004

Table 5. Relative risks and 95% confidence interval of lipid level ≥ 2.5 mmol/L in patients taking other lipid lowering agents than simvastatin compared to taking simvastatin.

| Variable | Simvastatin | Pravastatin | Fluvastatin | Atorvastatin | Rosuvastatin | Ezetimib | Fibrate | Statin + ezetimib | Statin + ezetimib |
|----------|-------------|-------------|-------------|--------------|--------------|----------|---------|------------------|------------------|
| Model | RR (95% CI) | RR (95% CI) | RR (95% CI) | RR (95% CI) | RR (95% CI) | RR (95% CI) | RR (95% CI) | RR (95% CI) | RR (95% CI) |
| Not adjusted | Referent | 1.52 (1.43–1.61) | 1.70 (1.50–1.93) | 0.99 (0.95–1.03) | 0.91 (0.78–1.06) | 1.99 (1.83–2.17) | 1.82 (1.71–1.94) |
| Adjusted for: | Age | Referent | 1.54 (1.45–1.63) | 1.69 (1.50–1.91) | 0.98 (0.94–1.02) | 0.90 (0.77–1.04) | 1.96 (1.80–2.13) | 1.79 (1.69–1.91) |
| | Sex | 1.50 (1.42–1.60) | 1.71 (1.52–1.94) | 0.99 (0.95–1.03) | 0.91 (0.78–1.05) | 1.97 (1.81–2.15) | 1.83 (1.72–1.95) |
| | Diabetes duration | 1.52 (1.43–1.62) | 1.71 (1.51–1.93) | 0.99 (0.95–1.03) | 0.90 (0.78–1.05) | 2.02 (1.85–2.19) | 1.84 (1.73–1.96) |
| | Smoking | 1.52 (1.43–1.61) | 1.71 (1.51–1.93) | 0.98 (0.95–1.02) | 0.91 (0.78–1.06) | 2.00 (1.83–2.18) | 1.82 (1.71–1.94) |
| | Doses | 1.48 (1.39–1.57) | 1.69 (1.49–1.91) | 0.96 (0.92–1.00) | 0.92 (0.79–1.07) | - | 1.77 (1.66–1.89) |
| | LDL-C levels before treatment | 1.49 (1.41–1.57) | 1.68 (1.50–1.88) | 1.01 (0.97–1.05) | 0.90 (0.78–1.04) | 1.73 (1.61–1.86) | 1.68 (1.59–1.78) |
| | CVD | 1.53 (1.44–1.63) | 1.72 (1.52–1.94) | 0.99 (0.95–1.03) | 0.92 (0.79–1.07) | 2.00 (1.84–2.18) | 1.79 (1.69–1.91) |
| | Renal disease | 1.52 (1.43–1.61) | 1.75 (1.54–1.97) | 0.99 (0.95–1.03) | 0.91 (0.78–1.06) | 2.01 (1.84–2.18) | 1.81 (1.70–1.93) |
| | Several variables* | 1.55 (1.47–1.65) | 1.75 (1.55–1.97) | 1.00 (0.96–1.04) | 0.90 (0.78–1.05) | 2.01 (1.85–2.18) | 1.78 (1.67–1.89) |
| | Several variables# | 1.52 (1.43–1.61) | 1.74 (1.54–1.95) | 0.98 (0.94–1.02) | 0.91 (0.78–1.06) | - | 1.73 (1.62–1.84) |

CVD, history of cardiovascular disease; Renal disease, history of renal disease. SD, standard deviation; RR, Relative risk; CI, Confidence intervals.

*Adjusted for age, duration of diabetes, smoking, CVD, renal diseases.

#Adjusted for age, duration of diabetes, smoking, LDL-level before the treatment, CVD, renal diseases.

doi:10.1371/journal.pone.0018744.t005

atorvastatin, and exhibited very similar LDL-C levels as the overall cohort but had higher mean HDL-C and lower TG levels, as expected.

Although around two thirds of the patients reach the overall European and Swedish treatment goal of LDL-C<2.5 mmol/L, many patients still have a high residual risk. The majority of patients had HDL-C above target levels and almost half of the population have elevated TG. Furthermore, in patients with a history of CVD, more than 70% do not reach LDL-C<1.8 mmol/L. The treatment targets were thus not sufficiently achieved, particularly in the light of recently updated US and European treatment guidelines from year 2007 with a recommended goal for LDL-C of 2.5 mmol/L in patients with type 2 diabetes in general and 1.8 mmol/L in patients with a history of CVD [4,5]. A slow improvement in overall risk factor control in European and Swedish treatment goal of LDL-C<2.5 mmol/L, in patients with type 2 diabetes and coronary heart disease has been demonstrated, however, including an increased use of lipid lowering agents over time, with a corresponding improvement in blood lipid levels [17].

From 2003 and onwards generic simvastatin has been the first line choice of lipid lowering therapy. Other agents could be used when adverse effects appear, or if the individual treatment goals are not met. In this study there were only minor differences in patient characteristics between users of simvastatin, atorvastatin and rosuvastatin, apart from a slightly higher prevalence of a history of renal disease or CVD in the latter two. It is likely that a history of co-morbidities in the patients was the basis for the choice of statin in some cases, due to the presumed higher efficacy in atorvastatin and rosuvastatin. Still, the LDL-C levels are not lower than in patients taking simvastatin and the doses are low to moderate, suggesting that lipid lowering therapy is currently not consistent, and that a potential extra efficacy of atorvastatin or rosuvastatin has not been made use of [7,8]. Furthermore, the results of the multivariate analysis taking clinical characteristics and LDL-C values before the treatment as well as doses of the statins into account, suggest similar LDL-C lowering effectiveness of these three agents. The weaker effects of pravastatin and fluvastatin in this study are in agreement with previous reports.
[7,8], although our results must be interpreted with caution due to the small sample sizes and possible selection effects. Overall, these results from clinical practice verify a recent meta-analysis of published randomized clinical trials, showing that the different lipid lowering agents are equally efficacious at comparable doses [6].

A possible contributory cause for the results of this study could be the on-going discussion on the value of reaching certain treatment lipid goals vs. standardized treatment with statins in risk groups of patients, which could affect the prescribers. Major clinical trials such as the Heart Protection Study [1] and the Collaborative Atorvastatin Diabetes Study [2], underscored by the results of the recent meta-analysis by the Cholesterol Treatment Trialists’ (CTT) Collaborators [3], have shown secondary preventive risk reduction after statin treatment also in patients without pronounced hypercholesterolaemia. In order to reduce CVD risk, however, the current US guidelines [4] promote statin use in patients with diabetes and overt CVD, or in patients without CVD who are older than 40 years and have one or more CVD risk factors. Alternatively, a reduction in LDL-C of 30–40% could be aimed at in patients not satisfactorily responding to a maximal dose of statin. The European guidelines [5] similarly promote LDL-C<2.5 mmol/L as the general treatment target in patients with type 2 diabetes or type 1 diabetes with nephropathy, but also give an opportunity for the clinician to offer statins in patients with LDL-C<2.6 mmol/L.

The NDR has currently an estimated coverage of more than 90% of all patients in hospital outpatient clinics and more than 70% of all patients in primary care. The patients included in this study are selected only based on completeness of the analysed data, that they are indeed representative. There might be minor errors in the clinical characteristics and risk factor values from clinics where these are reported manually, but more and more clinics transfer data automatically from computerized medical records systems. There were, however, some expected differences in mean levels and proportions of risk factors in the different treatment groups, suggesting possible selection effects.

Therefore the results regarding blood lipid levels as well as the LDL-C lowering effects of the different treatments should be interpreted with some caution and should ideally be confirmed in prospective clinical trials.

All information on the lipid lowering agents is retrieved from Swedish Prescribed Drug Register, which contains complete information about drug utilization in the entire Swedish population [11]. We used strict criteria regarding the use of the lipid lowering treatments, with only patients without former purchases during a certain time period, followed by three purchases during a specified period of time. We used the blood lipid values reported after that period in our study, a technique that could cause some errors. We determined, however, this to be the best method to ensure the maximal number of patients in the study, since blood lipid values are not measured frequently in clinical practice, perhaps not more often than every second year in most patients, and they are not likely to be reported to NDR more than once every year.

In conclusion, this observational study shows that the LDL-C levels in patients taking simvastatin, atorvastatin or rosuvastatin are very similar as currently used, as well as their LDL-C lowering effects. In order to achieve better fulfilment of treatment goals, since the residual risk remains high in a large proportion of the patients, there is a potential to increase the doses of the lipid lowering treatments.

Supporting Information

Table S1 Blood lipid values and history of CVD and renal disease of the patients with type 1 diabetes on lipid lowering treatment 2008.

(DOC)

Author Contributions

Conceived and designed the experiments: BE AMS MM JMJ KAS SG. Performed the experiments: AMS MM JMJ. Analyzed the data: BE AMS MM JMJ KAS. Wrote the paper: BE AMS MM JMJ KEO KAS SG.

References

1. MRC/BHF Heart Protection (2002) Study of cholesterol lowering with simvastatin in 20,536 high-risk individuals: a randomised placebo-controlled trial. Lancet 360: 7–22.
2. Colhoun HM, Betteridge DJ, Durrington PN, Hitman GA, Neil HA, et al. (2004) Primary prevention of cardiovascular disease with atorvastatin in type 2 diabetes in the Collaborative Atorvastatin Diabetes Study (CARDS): multicentre randomised placebo-controlled trial. Lancet 364: 685–96.
3. Kearney PM, Blackwell L, Collins R, Keech A, Simes J, et al. (2008) Efficacy of cholesterol-lowering therapy in 18,686 people with diabetes in 14 randomised trials of statins: a meta-analysis. Lancet 371: 117–25.
4. American Diabetes Association (2010) Executive summary: Standards of medical care in diabetes-2010. Diabetes Care 33 Suppl 1: S4–10.
5. Ryden L, Standl E, Bartnik M, Van den Bergh G, Betteridge J, et al. (2007) Guidelines on diabetes, pre-diabetes, and cardiovascular diseases: executive summary. The Task Force on Diabetes and Cardiovascular Diseases of the European Society of Cardiology (ESC) and of the European Association for the Study of Diabetes (EASD). Eur Heart J 28: 88–136.
6. Weng T-C, Kao Yang Y-H, Lin S-J, Tai S-H (2010) A systematic review and method-comparison study. Clin Chem 50: 166–74.
7. Jones P, Kafonek S, Laurora I, Hunninghake D (1998) Comparative dose efficacy study of atorvastatin versus simvastatin, pravastatin, lovastatin, and fluvastatin in patients with hypercholesterolaemia (the CURVES study). Am J Cardiol 81: 502–7.
8. Jones PH, Davidson MH, Stein EA, Bays HE, McNerney JM, et al. (2003) Comparison of the efficacy and safety of rosuvastatin versus atorvastatin, simvastatin, and pravastatin across doses (STELLAR* Trial). Am J Cardiol 92: 62–60.
9. Erg-Olofsson K, Cederholm J, Nilsson PM, Zethelius B, Nunez L, et al. (2009) Risk of cardiovascular disease and mortality in overweight and obese patients with type 2 diabetes: an observational study in 15,087 patients. Diabetologia 52: 63–73.
10. Erg-Olofsson K, Cederholm J, Nilsson PM, Zethelius B, Svensson AM, et al. (2010) Glycemic control and cardiovascular disease in 7454 patients with type 1 diabetes: an observational study from the Swedish National Diabetes Register (NDR). Diabetologia 53: 1614–6.
11. Wettermark B, Hammar N, Fored CM, Leimanis A, Otterblad Olausson P, et al. (2007) The new Swedish Prescribed Drug Register—opportunities for pharmacoepidemiological research and experience from the first six months. Pharmacoepidemiol Drug Saf 16: 729–35.
12. Melo J, Lindblad U, Pessah-Rasmussen H, Hedblad B, Rastam J, et al. (2000) Comparison of different procedures to identify possible cases of myocardial infarction and stroke in two Swedish prospective cohort studies using local and national routine registers. Eur J Epidemiol 16: 235–43.
13. Tunstall-Pedoe H, Kuulasmaa K, Amouyel P, Arveiler D, Raikkangas AM, et al. (1994) Myocardial infarction and coronary deaths in the World Health Organization MONICA Project. Registration procedures, event rates, and case-fatality rates in 38 populations from 21 countries in four continents. Circulation 90: 503–612.
14. Hoelzel W, Weykamp C, Jeppsson JO, Miedema K, Barr JR, et al. (2004) IFCC reference system for measurement of hemoglobin A1c in human blood and the national standardization schemes in the United States, Japan, and Sweden: a method-comparison study. Clin Chem 50: 166–74.
15. Friedewald WT, Levy RI, Fredrickson DS (1972) Estimation of the concentration of low-density lipoprotein cholesterol in plasma, without use of the preparative ultracentrifuge. Clin Chem 18: 499–502.
16. Eriksson M, Erg-Olofsson K, Zethelius B, Cederholm J, Nilsson PM, et al. (2011) Blood lipids in 75048 type 2 diabetic patients: A population-based survey from the Swedish National Diabetes Register. Eur J Cardiovasc Prev Rehabil 18: 97–103.
17. Gudbjornsdottir S, Erg-Olofsson K, Cederholm J, Zethelius B, Eliasson B, et al. (2009) Risk factor control in patients with Type 2 diabetes and coronary heart disease: findings from the Swedish National Diabetes Register (NDR). Diabet Med 26: 53–60.