Prevalence of dyslipidaemia in statin-treated patients in South Africa: results of the DYSlipidaemia International Study (DYSIS)

FREDERICK J RAAL, DIRK J BLOM, SHANIL NAIDOO, PETER BRAMLAGE, PHILIPPE BRUDI

Abstract

Introduction and objectives: Cardiovascular disease (CVD) is the leading cause of mortality worldwide and increased levels of low-density lipoprotein cholesterol (LDL-C) are an important modifiable risk factor. Statins lower LDL-C levels and have been shown to reduce CVD risk. Despite the widespread availability of statins, many patients do not reach the lipid targets recommended by guidelines. We evaluated lipid goal attainment in statin-treated patients in South Africa and analysed variables contributing to poor goal attainment as part of the DYSlipidaemia International Study (DYSIS).

Methods: This cross-sectional, observational study enrolled 1 029 consecutive South African patients consulting office-based physicians. Patients were at least 45 years old, had to be treated with a stable dose of statins for at least three months and had been fasting for 12 hours. We evaluated lipid goal attainment and examined variables associated with residual dyslipidaemia [abnormal levels of LDL-C, high-density lipoprotein cholesterol (HDL-C) and/or triglycerides (TG)].

Results: We found that 50.3% of the patients overall did not achieve target LDL-C levels and 73.5% of patients were at very high cardiovascular risk. In addition, 33.7% had low levels of HDL-C, while 45.3% had elevated TG levels despite statin therapy. Asian and mixed-ancestry patients but not black (vs Caucasian ethnicity), as well as obese individuals in South Africa were more likely to still have dyslipidaemia involving all three lipid fractions.

Conclusions: We observed that many patients in South Africa experienced persistent dyslipidaemia despite statin treatment, supporting the concept that there is a need for more intensive statin therapy or the development of novel treatment strategies. Measures aimed at combating obesity and other lifestyle-related risk factors are also vital for effectively controlling dyslipidaemia and reducing the burden of CVD.

Keywords: cardiovascular disease (CVD), dyslipidaemia, lipid abnormalities, statins, low-density lipoprotein cholesterol (LDL-C)

Cardiovascular Journal of Africa 2013; 24: 330–338
DOI: 10.5830/CVJA-2013-071

Cardiovascular disease (CVD) is the leading cause of mortality worldwide. In 2008, World Health Organisation (WHO) estimates suggested that 30% (17.3 million) of all deaths worldwide could be attributed to CVD. In 2008 and 2009, the two most recent years for which South African data are available, CVD was responsible for 13.7 and 14.0% of total deaths, respectively. However, CVD mortality rates are expected to rise in South Africa as unhealthy lifestyle trends associated with urbanisation spread to the countryside, and the population of people surviving life-threatening infections continues to grow.

Well-known risk factors for CVD include age, gender, dyslipidaemia, tobacco smoking, high blood pressure and diabetes mellitus (DM). Other lifestyle behaviours such as excessive alcohol consumption, sedentary lifestyle and poor diet with resultant obesity further contribute to CVD risk. The WHO 2008 estimates indicated that the prevalence of obesity, tobacco smoking and physical inactivity in South Africa were 31.3 (≥ 20 years old), 14 and 51.1%, respectively. Furthermore, in 2010 the prevalence of DM was 4.5% for individuals ≥ 15 years old, and the WHO estimated the rate of high blood pressure at 42.2% in 2008. As the prevalence of these risk factors rise in South Africa, so will the rate of CVD.

The main effect of statins is to lower LDL-C levels and they are used extensively in both primary and secondary prevention of CVD. Importantly, several large clinical trials have indicated that for every 1-mmol/l reduction in LDL-C levels there is a 23% reduction in CVD risk. In a further meta-analysis of studies comparing high and low statin doses, more intensive lowering of LDL-C (0.51 mmol/l additional reduction) in the high-dose statin arm was associated with a further 15% reduction in CVD risk. In the most recently published statin cardiovascular outcomes trial (JUPITER study: men and women free of overt cardiovascular disease over the ages of 50 and 60 years, respectively; baseline LDL-C < 3.37 mmol/l and high-sensitivity C-reactive protein of 2 mg/l or more; randomised to rosvuavatin 20 mg/day or placebo), statin treatment was associated with a 39% reduction in primary endpoints (myocardial infarction, stroke, admission to hospital for unstable angina, arterial revascularisation or CV death) in patients with at least one risk factor for DM.

The results of these and other studies have resulted in treatment guidelines recommending progressively lower LDL-C levels.
targets. However, studies from all over the world have demonstrated that many patients on lipid-lowering therapy do not reach their recommended lipid targets. The South African Heart Association (SA Heart) together with the Lipid and Atherosclerosis Society of Southern Africa (LASSA) therefore recently emphasised that intensive management of dyslipidaemia could significantly reduce the South African CVD health burden.

The DYSlipidaemia International Study (DYSIS) is a cross-sectional, observational study that has examined the efficacy of lipid-lowering therapies in patients from various regions of the world, including Canada and Europe (11 countries), in order to better characterise predictive factors for dyslipidaemia and CVD. Here, as part of DYSIS, we have analysed residual dyslipidaemia in statin-treated South African patients.

Methods

As part of DYSIS, this epidemiological, observational, cross-sectional study was conducted in South Africa between 1 November and 9 December 2011. Data for the study were collected in the South African private healthcare sector by 16 physicians; 50% were primary-care physicians and 50% were specialised office-based physicians (e.g. cardiologists).

Prior to study initiation, the relevant local ethical review committees approved the study protocol and all patients gave written informed consent before enrolling in the study. Key eligibility criteria were: (1) age of at least 45 years, (2) receiving stable statin therapy for at least 3 months, and (3) fasting for at least 12 hours at the time of visit while on statin therapy. Participating physicians were instructed to include all eligible and consenting patients consecutively.

Patient demographic, lifestyle and clinical characteristics were documented. Lipid levels (total cholesterol, LDL-C, HDL-C and triglycerides) were measured using the CardioChek device (http://www.cardiocheck.com) at the time of patient enrollment to reliably collect lipid measurements uniformly at all sites. The LDL-C test strip provided measures LDL-C directly across a range of 1.29–5.18 mmol/l in about two minutes. Additionally, the lipid-lowering regimen at the time of the most recent blood sample was recorded for each patient (in particular, statin type and daily dose) as well as any information regarding other lipid-modifying therapies. The potency of different types of statins was normalised using a calculation that allows benchmarking against six different simvastatin dose levels (5, 10, 20, 40, 80 and 160 mg/day), with potency scores ranging from 1 (5 mg/day simvastatin) to 6 (160 mg/day simvastatin).

The 2011 ESC guidelines were used to classify CV risk, LDL-C level treatment goals, and sub-optimal HDL-C and triglyceride levels. Variables independently associated with dyslipidaemia were evaluated with logistic regression modelling using the following variables: age (≥ 70 years), female gender, family history of premature coronary heart disease (CHD), current tobacco smoker, sedentary lifestyle, alcohol consumption (> 2 units/week), body mass index (BMI) ≥ 30 kg/m², large waist circumference (> 102 cm in men, > 88 cm in women), hypertension, DM, coronary heart disease, cerebrovascular disease, heart failure, peripheral artery disease, systolic/diastolic blood pressure ≥ 140/90 mmHg, simvastatin equivalent dose of either 20 to 40 versus 10 mg/day, or > 40 mg versus 10 mg/day, ezetimibe use, and physician’s specialty (cardiologist, endocrinologist, diabetologist, internal medicine or other).

Statistical analysis

To estimate the sample size needed for South Africa we assumed a prevalence of residual lipid abnormalities between 20 and 60% in patients fulfilling the entry criteria for this study and a design effect of 20% (variance inflation due to cluster sampling design). We calculated that, within this range, a sample size of 1,000 would be sufficient to estimate the prevalence of residual dyslipidaemia with a given precision of ± 3.4% (range of 95% confidence interval: 6.8%). Furthermore we determined that this size guaranteed enough information for estimating the prevalence in smaller subgroups (representing one-quarter or more of the population) with a precision of ± 6.8% (95% CI: 13.6%).

Following data collection, patient information was entered into a central web-based database housed and managed at the Institut für Herzinfarktforschung, Ludwigshafen, Germany. Real-time quality control (internal logic checks) occurred during web-based data entry. Continuous variables are presented as means with standard deviations or medians with 25th and 75th percentiles [interquartile range (IQR)] as indicated, and categorical variables are reported as absolute numbers and percentages.

Kernel density estimation was used to analyse the distribution of total cholesterol, LDL-C, HDL-C and triglyceride levels. The value of a kernel density and its slope at the lipid value equal to the ESC goal provides a crude indicator of the change in the proportions of patients meeting the goal from a small improvement or deterioration in lipid level starting from the ESC goal. This approach thus provides a sensitivity analysis for either changes in the ESC goals or changes in lipid levels for people whose levels are near the goals.

Multiple logistic regression analyses with backward selection (α = 0.05) were used to identify variables independently associated with LDL-C, HDL-C and triglyceride irregularities. Two-tailed statistical comparisons were used (p < 0.05 was significant) and patients lacking the appropriate lipid parameters were not included within the analyses. All analyses were performed using SAS v 9.1 (SAS Institute Inc, USA).

Results

Patient characteristics, risk categories and lipid parameters are presented in Table 1. The study enrolled 1,029 patients (429 men, 600 women). The mean age of patients was 65.4 years, and 58.3% were female. The study population was of mixed ethnic (multi-racial) origin, including Caucasians (56.6%), blacks (22.0%), Asians (9.5%) and patients of mixed ancestry (12.0%).

Patient characteristics and cardiovascular risk profile differed by ethnic group. A family history of premature CVD was reported by 34% of Caucasian patients while the diabetes prevalence of 25.6% was the lowest of all the ethnic groups studied. Hypertension was found in 69.8% and CVD in 41.1% of Caucasian patients. Black patients were least likely (1.8%) to report a family history of premature CHD and had the lowest (5.3%) smoking rates. However, hypertension was almost universal (93.3%) and diabetes and obesity were highly prevalent at 71.2 and 61.9%, respectively. Despite the high prevalence
of hypertension and obesity, only 9.7% of black patients had clinically overt CVD. Asian patients had the highest rates of CVD (51.5%) among all ethnic groups studied and also the highest reported rate of a family history of premature CVD (44%). Diabetes was highly prevalent at 44.4% while the hypertension prevalence of 64.6% was similar to that observed in Caucasian patients. Mixed-ancestry patients had the highest smoking rates (18%) while the diabetes and hypertension prevalences were 50.8 and 89.3%, respectively. CVD was documented in 49.2% of mixed-ancestry patients.

CVD was almost twice as common in men (49.9%) than women (26.3%). DM was more common in men than women (45.7 vs 36.7%), while obesity was more frequent in women (46.8 compared with 35.7%). Additionally, using the 2011 ESC criteria, 73.5% of patients (83.9% men and 66.0% of women) met the IDF criteria, 73.5% of patients (83.9% men and 66.0% of women) (46.8 compared with 35.7%). Additionally, using the 2011 ESC criteria, 73.5% of patients (83.9% men and 66.0% of women) were classified as very high risk for CV complications [defined as having CVD, DM and/or an ESC systematic coronary risk evaluation (SCORE) risk of ≥ 10% on chronic statin therapy].

**Lipid-modifying regimens and statin potency**

Prior to enrollment in DYSIS, patients had been treated with various lipid-lowering therapies. The most commonly prescribed statin was simvastatin (64.6%), followed by atorvastatin (22.2%), rosuvastatin (10.9%), pravastatin (1.6%), fluvastatin (0.6%) and lovastatin (0.2%). Other lipid-lowering agents were used by only 2% of patients, including ezetimibe (1.2%), fibrates (0.9%) and bile acid sequestrants (0.2%).

The most frequently used statin dose potency was 3 (equivalent to 20 mg simvastatin per day) for both very high-risk patients (40.2%) and non-very high-risk patients (47.6%), while the second most-frequent dose potency was 2 (equivalent to 10 mg simvastatin per day) in 25.6% of very high-risk patients and non-very high-risk patients, respectively (Fig. 1). While a statin dose potency of 3 was most frequently used in Caucasian, Asian and mixed-ethnicity patients, a dose potency of 2 was most common in black patients.

**Lipid abnormalities**

Data on the frequency of lipid abnormalities, including sub-analyses by CVD risk level, are provided in Table 2 and 3. Among all patients (n = 1 029), 50.3% had LDL-C levels not at goal. We defined ‘not at LDL-C goal’ as LDL-C ≥ 1.8 mmol/l and LDL-C reduction of ≥ 50% for patients with CVD, DM and/or a SCORE risk of ≥ 10% (very high risk), and as ≥ 2.5 mmol/l and ≥ 3 mmol/l for patients with a SCORE risk of 5 to 9% (high risk) and 1 to 4% (moderate risk), respectively. Elevated TG levels (defined as ≥ 1.7 mmol/l) were seen in 45.3% of patients, and 33.7% had low HDL-C levels (defined as < 1.0 mmol/l for men and < 1.2 mmol/l for women).

---

**TABLE 1. PATIENT CHARACTERISTICS, RISK CATEGORIES AND LIPID PARAMETERS IN DIFFERENT ETHNIC GROUPS**

|                               | All patients (n = 1 029) | Caucasian (n = 582; 56.6%) | Black (n = 226; 22.0%) | Asian (n = 99; 9.6%) | Mixed ancestry (n = 122; 11.9%) |
|------------------------------|--------------------------|----------------------------|------------------------|---------------------|-------------------------------|
| Age (years) (mean ± SD)       | 65.4 ± 10.8              | 69.0 ± 11.0                | 60.0 ± 8.9             | 61.8 ± 9.0          | 60.9 ± 7.4                    |
| Family history of premature CHD (%) | 26.7                     | 34.0                       | 1.8                    | 4.4                 | 23.0                          |
| Current smokers (%)           | 10.7                     | 11.2                       | 5.3                    | 11.1                | 18.0                          |
| Hypertension (%)              | 76.8                     | 69.8                       | 93.3                   | 64.6                | 89.3                          |
| Systolic BP (mmHg) (mean ± SD) | 134.4 ± 20.0             | 134.9 ± 20.4               | 135.2 ± 19.4           | 129.0 ± 17.1        | 134.9 ± 20.7                  |
| Diastolic BP (mmHg) (mean ± SD) | 79.7 ± 11.0              | 79.6 ± 11.1                | 79.6 ± 11.5            | 78.3 ± 9.6          | 81.2 ± 10.5                   |
| Waist circumference (cm) (mean ± SD) | 100.7 ± 15.1            | 99.5 ± 16.5                | 105.0 ± 13.4           | 96.1 ± 9.6          | 101.8 ± 12.5                  |
| BMI (kg/m²) (mean ± SD)       | 29.6 ± 6.4               | 28.6 ± 6.4                 | 32.8 ± 6.5             | 27.0 ± 4.5          | 30.4 ± 5.6                    |
| BMI > 30 kg/m² (%)            | 42.2                     | 36.8                       | 61.9                   | 22.2                | 47.5                          |
| CVD (%)                      | 36.2                     | 41.1                       | 9.7                    | 51.5                | 49.2                          |
| Diabetes mellitus (%)         | 40.4                     | 25.6                       | 71.2                   | 44.4                | 50.8                          |
| Metabolic syndrome (IDF) (%)  | 67.2                     | 59.8                       | 83.2                   | 59.8                | 78.7                          |
| ESC risk level (2011)*        |                          |                            |                        |                     |                               |
| Very high-risk patient (%)    | 73.5                     | 69.9                       | 77.9                   | 73.7                | 82.0                          |
| High-risk patient (%)         | 8.9                      | 11.2                       | 4.0                    | 11.1                | 5.7                           |
| Moderate-risk patient (%)     | 13.5                     | 15.6                       | 11.5                   | 9.1                 | 10.7                          |
| Low-risk patient (%)          | 4.1                      | 3.3                        | 6.6                    | 6.1                 | 1.6                           |
| South African guidelines      |                          |                            |                        |                     |                               |
| Very high-risk patient (%)    | 68.6                     | 61.2                       | 77.9                   | 73.5                | 82.8                          |
| High-risk patient (%)         | 9.2                      | 11.7                       | 6.2                    | 8.2                 | 3.3                           |
| Moderate-risk patient (%)     | 21.6                     | 26.6                       | 15.9                   | 15.3                | 13.9                          |
| Low-risk patient (%)          | 0.6                      | 0.5                        | 0.0                    | 3.1                 | 0.0                           |
| Lipids (mmol/l) (mean ± SD)   |                          |                            |                        |                     |                               |
| LDL-C                        | 2.3 ± 1.1                 | 2.2 ± 1.0                   | 2.1 ± 1.0              | 2.6 ± 1.2           | 2.7 ± 1.1                     |
| HDL-C                        | 1.3 ± 0.4                 | 1.3 ± 0.4                   | 1.4 ± 0.4              | 1.3 ± 0.4           | 1.3 ± 0.5                     |
| Total cholesterol             | 4.4 ± 1.3                 | 4.4 ± 1.2                   | 4.4 ± 1.4              | 4.7 ± 1.6           | 4.7 ± 1.3                     |
| Triglycerides [median (IQR)]  | 1.6 (1.1–2.3)            | 1.5 (1.1–2.2)              | 1.7 (1.2–2.4)          | 1.7 (1.2–2.7)       | 1.5 (1.1–2.4)                 |
| Blood glucose                 |                          |                            |                        |                     |                               |
| FBG (mmol/l) [median (IQR)]   | 4.9 (4.3–6.4)            | 4.6 (4.2–5.4)              | 6.2 (4.7–9.0)          | 5.3 (4.2–7.0)       | 5.6 (4.7–7.2)                 |
| HbA1c (%) [median (IQR)]      | 7.4 (6.6–8.8)            | 7.1 (6.0–8.0)              | 8.2 (6.8–9.9)          | 7.8 (7.0–8.7)       | 7.4 (7.0–8.8)                 |

CHD, coronary heart disease; BP, blood pressure; BMI, body mass index; CVD, cardiovascular disease; DM, diabetes mellitus; IDF, International Diabetes Federation.
The most prevalent lipid disorder (either alone or in combination) in very high-risk patients was above-target LDL-C levels (60.1%), followed by elevated TG levels (45.8%), and low HDL-C levels (36.0%). By contrast, in both high- and moderate-risk patients, elevated TG levels were observed more frequently (46.7 and 40.1%, respectively in the two risk groups) than above-target LDL-C levels (33.3 and 24.1%, respectively). We next performed a sub-analysis of lipid abnormalities for only very high-risk patients (756 of all patients, Table 3), which we stratified as indicated. Of those with CVD and DM, 57.9% displayed off-target LDL-C levels (≥1.8 mmol/l and a decrease in LDL-C levels of <50%), 39.7% showed low HDL-C levels, and 54.2% had elevated TG levels. In comparison, patients in the CVD without DM group showed a higher rate of LDL-C not at target (68.0%), decreased rates of low HDL-C levels, and elevated TG levels (38.2%). Interestingly, the ESC SCORE group with risk of ≥10% showed a lower proportion of patients with low HDL-C and elevated TG levels. Overall, we found that LDL-C not at goal was the most common lipid abnormality observed in each of the four sub-sets.

Additionally, we analysed patient lipid abnormalities using kernel density curves for the empirical distributions of very high-risk patients (Fig. 2). Overall, we found that the density curves were unimodal and positively skewed, and the data indicated that the very high-risk group showed slightly lower overall LDL-C levels than non-very high-risk patients. Moreover, we observed that women maintained higher overall HDL-C levels than men in both the very high and non-very high-risk groups, while TG levels were similar between the two risk groups.

### Distributions of lipid abnormalities

Distributions of single and multiple combined lipid abnormalities for our study are shown in Figs 3–5. Here, we present the joint...
distribution of lipid abnormalities for the entire sample and then for sub-samples of very high-risk and non-very high-risk patients. Additionally, joint distributions that either include or exclude patients with no lipid abnormalities are provided for each patient group.

Fig. 3 shows that in 39.4% of patients with a total lipid profile, there was only one single-lipid abnormality, 32.8% had two abnormalities, and the remaining 7.3% had abnormalities in all three assessed components of the lipid profile. Among statin-treated patients, the most common abnormality was high LDL-C levels (18.8% of all cases), accounting for 47.7% of all single-lipid abnormalities. Among the 983 patients, 20.4% had no lipid abnormalities.

Figs 4 and 5 present the joint distribution for non-very high-risk and very high-risk patients, respectively, and indicate different patterns of prevalence for these sub-groups. For the 261 non-very high-risk patients with at least one abnormality depicted in Fig. 4, 37.2% had only one lipid abnormality, 21.5% had two lipid abnormalities and the remaining 4.2% had all three lipid abnormalities.

By contrast, for the 826 very high-risk patients depicted in Fig. 5, the majority, 45.4%, had two or more lipid abnormalities (40.2% had one, 37.0% had two, and the remaining 8.4% had all three). For non-very high-risk patients, elevated triglycerides were the largest single abnormality present, appearing in 42.2% of all non-very high-risk patients. By contrast, among very high-risk patients, high LDL-C level was the most frequent abnormality, at 60.1% of all very high-risk patients.

Variables independently associated with dyslipidaemia

Multivariate logistic regression analyses indicated that among the 19 risk factors incorporated into the model, mixed ancestry, along with history of hypertension, DM and cerebrovascular disease were among the risk factors strongly, positively and...
Fig. 4. Distribution of no, single and multiple combined lipid abnormalities in non-very high-risk patients (ESC 2011, SCORE < 10%). TG, triglycerides; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; thresholds for LDL-C are based on the ESC guidelines (2011): SCORE risk 1–4%: LDL-C ≥ 3.0 mmol/l; patients with SCORE risk 5–9%: LDL-C ≥ 2.5 mmol/l; patients with CVD, DM, and/or SCORE risk ≥ 10%: LDL-C ≥ 1.8 mmol/l.

Fig. 5. Distribution of no, single and multiple combined lipid abnormalities in very high-risk patients (ESC 2011, SCORE ≥ 10%). TG, triglycerides; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; proportions add up to 100.1% because of rounding; thresholds for LDL-C are based on the ESC guidelines (2011): SCORE risk 1–4%: LDL-C ≥ 3.0 mmol/l; patients with SCORE risk 5–9%: LDL-C ≥ 2.5 mmol/l; patients with SCORE risk ≥ 10%: LDL-C ≥ 1.8 mmol/l.

Discussion

In the DYSIS South Africa study we observed marked ethnic differences in cardiovascular risk profiles and the primary indication for statin therapy. While about half of Asian and mixed-ancestry patients had clinically overt CVD, the rate in black patients was less than 10%. The major indication for statin therapy in black patients was diabetes, which was present in 71.2% of patients. A family history of premature CVD was very uncommon (1.8%) in black patients.

These data are reflective of the epidemiological transition, which the South African black population is currently undergoing, with increasing urbanisation and transition to a

Table 4. Factors Independently Associated With LDL-C, HDL-C and TG Abnormalities: Results from Multiple Regression Analyses (OR, 95% CI)

| Age ≥ 70 years | LDL-C not at target*† (≥ 1.8/2.5/3.0 mmol/l) | Low HDL-C* (< 1.0 (m)/1.2 (w) mmol/l) | Elevated TG* (> 1.7 mmol/l) | LDL-C not at target, low HDL-C, elevated TG* |
|----------------|---------------------------------------------|---------------------------------------|-----------------------------|---------------------------------------------|
| ns             | ns                                          | 0.57 (0.43–0.77)                      | ns                          | ns                                          |
| Female         | ns                                          | 0.43 (0.32–0.58)                      | 1.33 (1.02–1.74)            | ns                                          |
| ns             | ns                                          | ns                                    | 2.48 (1.19–5.16)            | ns                                          |
| Asian vs Caucasian | ns                                   | ns                                    | ns                          | ns                                          |
| Black vs Caucasian | ns                                   | ns                                    | ns                          | ns                                          |
| Mixed ancestry vs Caucasian | 2.12 (1.36–3.32) | ns                                    | ns                          | 2.78 (1.50–5.19) |
| Alcohol consumption > 2 units/week | ns | ns | ns | ns |
| BMI ≥ 30 kg/m² (obesity) | ns | ns | 1.74 (1.33–2.29) | 2.11 (1.27–3.50) |
| WC > 102 (m)/88 (w) (cm) | ns | 1.71 (1.26–2.32) | ns | ns |
| Hypertension | 1.55 (1.12–2.13) | ns | ns | ns |
| Diabetes mellitus | 1.36 (1.01–1.82) | 1.58 (1.17–2.15) | 1.49 (1.12–1.98) | ns |
| Cerebrovascular disease | 1.89 (1.39–2.57) | ns | ns | ns |
| Peripheral artery disease | ns | ns | 2.35 (1.09–5.07) | ns |
| Specialist (Cardiologist, Endocrinologist, Diabetologist, Int = internist, Oth = other specialty, ns = not significant (p > 0.05), OR = odds ratio, CI = confidence interval) | ns | 2.01 (1.46–2.76) | ns | ns |

*Models contained the following variables: age, gender, ethnicity, 1st-grade family history of premature CVD, current smoker, sedentary lifestyle, alcohol consumption > 2 units/week, BMI ≥ 30 kg/m² (obesity), waist circumference > 102 cm in men/88 cm in women, hypertension, diabetes mellitus, coronary heart disease, cerebrovascular disease, heart failure, peripheral artery disease, RR ≥ 140/90 mmHg (systolic/diastolic), 20–40 vs 10 mg/day simvastatin equivalent, ≥ 80 vs 10 mg/day simvastatin equivalent, ezetimibe.

† Patients with SCORE risk 1–4%: LDL-C ≥ 3.0 mmol/l; patients with SCORE risk 5–9%: LDL-C ≥ 2.5 mmol/l; patients with CVD, DM, and/or SCORE risk ≥ 10%: LDL-C ≥ 1.8 mmol/l.

Card = cardiologist, Endo = endocrinologist, Dia = diabetologist, Int = internist, Oth = other speciality, ns = not significant (p > 0.05), OR = odds ratio, CI = confidence interval.
Westernised lifestyle. Hypertension, obesity and diabetes are highly prevalent in black patients while CVD, which results from prolonged exposure to cardiovascular risk factors, is still relatively uncommon. With further progression of the epidemiological transition, CVD rates in black patients are likely to rise and may well match or exceed those observed in the other ethnic groups if cardiovascular risk factors are not addressed intensively, both on a population and an individual level.

The DYSIS South Africa study identified a group of patients at high cardiovascular risk, with 73.5% of statin-treated patients assessed to be at very high risk for CVD. Within this very high-risk group, despite statin therapy, 85.6% had at least one lipid abnormality, of which a majority had two or more lipid abnormalities. The most common lipid abnormality was high LDL-C levels, which was diagnosed in 60.1% of all very high-risk patients.

Moreover, for all patients in the study, 50.5% had LDL-C levels not at goal, which is comparable with the findings from the recently published CEPHEUS-SA study and the Canadian-European cohort of the DYSIS study, and below the levels found in the Middle Eastern cohort (62%). Not surprisingly, the metabolic syndrome was present in 67.2% of the sample, since its components also contribute to elevated CVD risk.

Statistically significant factors associated with high LDL-C levels included ethnicity, hypertension, DM, and the presence of coronary and cerebrovascular heart disease. Factors associated with low HDL-C levels were a high waist circumference, DM and being treated by a specialist. Elevated TG was associated with female gender, obesity, DM and peripheral artery disease. However, the only statistically significant factors independently associated with the presence of all three lipid abnormalities were obesity and Asian as well as mixed-ancestry ethnicity.

Based on the current data, it is unclear whether the findings with regard to ethnicity are biologically or sociologically determined. Even though this study was conducted exclusively in the private healthcare sector in South Africa, Asian or mixed-ancestry ethnicity most likely still correlates partially with social deprivation, which has been shown to be a risk factor for cardiovascular disease. Social deprivation may also affect access to medical care, with less access to specialist care and a bias towards less aggressive treatment. Studies from other countries have shown that ethnic minorities or immigrants often receive less aggressive cardiovascular care, as also observed in this study, with black patients receiving lower-dose potency of statins, despite the majority of patients being at high risk.

Socio-economic status has also been associated with statin adherence, as has ethnicity. In the South African context, lower socio-economic status would, for instance, often correlate with membership of a medical scheme option that restricts lipid-lowering treatment to less-potent (and less-costly) options. Lower income may also influence the willingness and ability to pay ‘co-payments’ that are often required to access more potent lipid-lowering therapy. However, factors such as provider bias, access to treatment and differential adherence do not completely explain the observed ethnic differences, as black patients generally still experience the highest level of socio-economic deprivation as a legacy of South Africa’s past history.

Lesser goal attainment may also in part be due to differences in baseline lipids. In the Heart of Soweto study, there were significant differences in untreated lipid profiles by ethnicity in patients presenting for cardiovascular care at a tertiary referral centre. The odds ratio (compared to black patients) for elevated LDL-C levels in Asian and mixed-ancestry patients was 4.66 and 2.44, respectively. Indian and mixed-ancestry patients also had higher median TG levels (1.8 and 1.4 mmol/l, respectively) than black patients (1.1 mmol/l).

In addition to identifying factors that are associated with dyslipidaemia in statin-treated patients, DYSIS in South Africa (along with previous DYSIS studies) also highlights the deficiencies of lipid-lowering therapy in clinical practice. Other researchers analysing the efficacy of lipid-lowering therapies have supported this conclusion, including another recent study analysing statin-treated South African patients. Together, these findings suggest that there is a need to improve upon existing treatment strategies (e.g. combination of current therapies for optimal patient efficacy, utilisation of more-potent statins, improving adherence) while also developing novel therapeutic approaches.

Combination therapies were evaluated in the Austrian Cholesterol screening and Treatment (ACT) II study, which evaluated the effect of lipid-lowering therapies in high-risk, statin-treated patients with elevated LDL-C levels. Interestingly, combination therapy consisting of simvastatin and ezetimibe (used for 73% of patients in the ACT II study) resulted in 40.3% of patients meeting their LDL-C goals, with a decline in LDL-C levels from a baseline of 31.3% following 12 months of intensified therapy.

High-dose statins are another option to achieve LDL-C targets in high-risk patients. Improving adherence is a challenge that physicians face every day, and some strategies that have shown promise include regular phone calls by a practice nurse, regular review by a community pharmacist and providing a medication calendar when patients filled their first prescription. There is likely no single strategy that will work for all patients but studies show that adherent patients have much better cardiovascular outcomes than non-adherent patients, although some of the improvement may also be ascribed to the correlation between adherence and other healthy behaviours.

According to a mathematical model of statin use in a population, increasing statin adherence from 50 to 75% at five years would prevent more events than lowering the risk threshold for prescribing statins. Lastly, novel LDL-C-lowering therapies may be necessary for patients with very high baseline LDL-C levels, such as is seen in familial hypercholesterolaemia, and when patients are unable to tolerate adequate doses of potent statins.

In South Africa, the modal statin dose potency prescribed to patients was 3, which was prescribed to 42.2% of the individuals. Interestingly, although the very high-risk patients had a disproportionately high share of the statin prescriptions with a potency of 4 and 5, they also had a disproportionately high amount of prescriptions with a potency of 2, and a disproportionately low share of the prescriptions with a potency of 6. In addition, although combination therapies may have the potential to benefit some patients, we found that the use of combination treatment with lipid-lowering therapies was rare in South Africa. Only seven patients were co-prescribed statins and ezetimibe in this study.

DYSIS-South Africa had several limitations, including its cross-sectional design, which did not permit follow up to assess
the effects of statins over time in either reducing CVD risk factors or their ultimate effects in reducing CVD. In addition, the cross-sectional nature of the study precludes us from drawing conclusions of temporality based on observed associations. The study was also only conducted in the private sector and does not therefore provide any information on the care provided in the public sector, which accounts for about 80% of patients in South Africa. As this study was conducted in the private sector, the ethnic make-up of the DYSIS study cohort is not representative of the South African population at large.

Furthermore physicians were aware of the study purpose, possibly making the results prone to a selection bias towards patients with better-than-average lipid goal attainment. DYSIS by its design is also unable to provide data on the important public patients with better-than-average lipid goal attainment. DYSIS by possibly making the results prone to a selection bias towards conclusions of temporality based on observed associations. The study was also only conducted in the private sector and does not therefore provide any information on the care provided in the public sector, which accounts for about 80% of patients in South Africa. As this study was conducted in the private sector, the ethnic make-up of the DYSIS study cohort is not representative of the South African population at large.

Conclusions

The DYSIS study for South Africa, like the DYSIS studies in other countries and regions, indicates that large proportions of statin-treated patients have persisting lipid abnormalities, which place them at ongoing risk for CVD. While some observations with regard to co-morbid conditions and demographics associated with lipid goal attainment were expected, observations also demonstrate a decreased likelihood of obtaining lipid goals among two ethnic minority groups, independent of treatment, demographics and other co-morbidities. These findings deserve further attention. As statins remain among the most effective agents for preventing CVD, the findings of this study emphasise the necessity for more aggressive therapy in order to achieve recommended lipid targets, so as to reduce the burden of cardiovascular disease, which is on the increase not only in South Africa but worldwide.

The authors thank Dr Claus Jünger and Dr Steffen Schneider, Stiftung Institut für Herzinfarktforschung, Ludwigshafen, Germany, for performing the statistical analyses, Dr Myrga Zankel (MSD International) for general support of the study, and Dr Lori D Bash (Merck, Sharp & Dohme Corp) for critical content review. We are indebted to all investigators and patients in South Africa who participated in DYSIS. This study was funded by Sharp & Dohme Corp, a subsidiary of Merck & Co, Ltd (New Jersey, USA).

References

1. Cardiovascular diseases (CVDs) Fact sheet no. 317: World Health Organization; September 2012. Available from: http://www.who.int/mediacentre/factsheets/fs317/en/index.html.
2. Mortality and causes of death in South Africa, 2009: Findings from death notification: Statistics South Africa; November 2011. Available from: http://www.statssa.gov.za/default.asp.
3. Mortality and causes of death in South Africa, 2008: Findings from death notification: Statistics South Africa; November 2010. Available from: http://www.statssa.gov.za/default.asp.
4. Mortality and causes of death in South Africa, 1997 to 2003: Findings from death notification.: Statistics South Africa; November 2010. Available from: http://www.statssa.gov.za/default.asp.
5. Maredza M HK, Tollman SM. A hidden menace: Cardiovascular disease in South Africa and the costs of inadequate policy response. SA Heart J 2011; 8(1): 48–57.
6. Mayosi BM, Fisher AJ, Lailoo UG, Sitas F, Tollman SM, Bradshaw D. The burden of non-communicable diseases in South Africa. Lancet 2009; 374(9693): 934–947. PubMed PMID: 19709736.
7. Gaziano TA, Bitton A, Anand S, Abrahams-Gessel S, Murphy A. Growing epidemic of coronary heart disease in low- and middle-income countries. Current problems in cardiology. 2010; 35(2): 72–115. PubMed PMID: 20109979. Pubmed Central PMCID: 2864143. Epub 2010/01/30. eng.
8. Gersh BJ, Sliwa K, Mayosi BM, Yusuf S. Novel therapeutic concepts: the epidemic of cardiovascular disease in the developing world: global implications. Eur Heart J 2010; 31(6): 642–648. PubMed PMID: 20176800. Epub 2010/02/24. eng.
9. South Africa: World Health Organization; 2011. Available from: http://www.who.int/nmh/countries/zaf_en.pdf.
10. Shaw JE, Sicree RA, Zimmet PZ. Global estimates of the prevalence of diabetes for 2010 and 2030. Diabetes Res Clin Pract 2010; 87(1): 4–14. PubMed PMID: 19896746. Epub 2009/11/10. eng.
11. Brashard D, Norman R, Pieterce D, Levitt NS. Estimating the burden of disease attributable to diabetes in South Africa in 2000. South Afr Med J 2007; 97(8 Pt 2): 700–706. PubMed PMID: 17952227. Epub 2007/10/24. eng.
12. Taylor F, Ward K, Moore TH, Davey Smith G, Casas JP, et al. Statins for the primary prevention of cardiovascular disease. Cochrane Database Syst Rev 2011 (1): CD004816. PubMed PMID: 21249663. Epub 2011/01/21. eng.
13. Mamdoo FFR. Statins: targeting cardiovascular disease. South Afr Heart J 2008; 5(2): 66–69.
14. Zhou Q, Liao JK. Statins and cardiovascular diseases: from cholesterol lowering to pleiotropy. Curr Pharmacuet Des 2009; 15(5): 467–478. PubMed PMID: 19199975. Pubmed Central PMCID: 2896785. Epub 2009/02/10. eng.
15. Baigent C, Keech A, Kearney PM, Blackwell L, Buck G, Pollicino C, et al. Efficacy and safety of cholesterol-lowering treatment: prospective meta-analysis of data from 90,056 participants in 14 randomised trials of statins. Lancet 2005; 366(9493): 1267–1278. PubMed PMID: 16214597. Epub 2005/10/11. eng.
16. Deedwania P, Barter P, Carmena R, Fruchart JC, Grundy SM, Haffner S, et al. Reduction of low-density lipoprotein cholesterol in patients with coronary heart disease and metabolic syndrome: analysis of the Treating to New Targets study. Lancet 2006; 368(9539): 919–928. PubMed PMID: 16962881. Epub 2006/09/12. eng.
17. Kearney PM, Blackwell L, Collins R, Keech A, Simes J, Petro R, et al. Efficacy of cholesterol-lowering therapy in 18,686 people with diabetes in 14 randomised trials of statins: a meta-analysis. Lancet 2008; 371(9607): 117–125. PubMed PMID: 18191683. Epub 2008/01/15. eng.
18. Wilt TJ, Bloomfield HE, MacDonald R, Nelson D, Rutks I, Ho M, et al. Effectiveness of statin therapy in adults with coronary heart disease. Arch Int Med 2004; 164(13): 1427–1436. PubMed PMID: 15249352. Epub 2004/07/14. eng.
19. Cholesterol treatment trialists, Baigent C, Blackwell L, Emberson J, Holland LE, Keith C, et al. Efficacy and safety of more intensive lowering of LDL cholesterol: a meta-analysis of data from 17,000 partici- pants in 26 randomised trials. Lancet 2010; 376(9753): 1670–1681. PubMed PMID: 21067804. Pubmed Central PMCID: 2988224.
20. Ridker PM, Pradhan A, MacFadyen JG, Libby P, Glynn RJ. Cardiovascular benefits and diabetes risks of statin therapy in primary prevention: an analysis from the JUPITER trial. Lancet 2012; 380(9841): 565–571. PubMed PMID: 22883507. Epub 2012/08/14. eng.
21. Klug E. South African dyslipidaemia guideline consensus statement. South Afr Med J 2012; 102(3 Pt 2): 178–187. PubMed PMID: 22380916. Epub 2012/03/03. eng.
22. Perk J, De Backer G, Gohlke H, Graham I, Reiner Z, Verschuren
WM, et al. European Guidelines on cardiovascular disease prevention in clinical practice (version 2012): The Fifth Joint Task Force of the European Society of Cardiology and Other Societies on Cardiovascular Disease Prevention in Clinical Practice (constituted by representatives of nine societies and by invited experts). Atherosclerosis 2012; 223(1): 1–68. PubMed PMID: 22698795. Epub 2012/06/16. eng.

23. Grundy SM, Cleeman JI, Merz CN, Brewer HB, Jr., Clark LT, Hunninghake DB, et al. Implications of recent clinical trials for the National Cholesterol Education Program Adult Treatment Panel III guidelines. Circulation 2004; 110(2): 227–239. PubMed PMID: 15249516. Epub 2004/07/14. eng.

24. Gitt AK, Drexel H, Heely J, Ferrieres J, Gonzalez-Juanatey JR, Thomsen KK, et al. Persistent lipid abnormalities in statin-treated patients and predictors of LDL-cholesterol goal achievement in clinical practice in Europe and Canada. Eur J Prevent Cardiol 2012; 19(2): 221–30. PubMed PMID: 21450576. Epub 2011/04/01. eng.

25. Leiter LA, Lundman P, da Silva PM, Drexel H, Junger C, Gitt AK. Persistent lipid abnormalities in statin-treated patients with diabetes mellitus in Europe and Canada: results of the Dyslipidaemia International Study. Diabetic Med 2011; 28(11): 1343–1351. PubMed PMID: 21679231. Epub 2011/06/18. eng.

26. Raaf F, Schamroth C, Blom D, Marx J, Rajput M, Haus M, et al. CEPHEUS SA: a South African survey on the undertreatment of hypercholesterolaemia. Cardiovasc J Afr 2011; 22(5): 234–240. PubMed PMID: 21922121.

27. Roberts WC. The rule of 5 and the rule of 7 in lipid-lowering by statin medical treatment with beta-blockers and statins after acute myocardial infarction compared with Danish-born residents? A register-based follow-up study. Eur J Clin Pharmacol 2010; 66(7): 735–742. PubMed PMID: 20393695.

28. Chan DC, Shrrank WH, Cutler D, Jan S, Fischer MA, Liu J, et al. Patient, physician, and payment predictors of statin adherence. Med Care 2010; 48(3): 196–202. PubMed PMID: 19890219.

29. Taltyor AH, Schmittfeld JA, Urratsu CS, Mangione CM, Subramanian U. Adherence to cardiovascular disease medications: does patient-provider race/ethnicity and language concordance matter? J Gen Intern Med 2010; 25(11): 1172–1177. PubMed PMID: 20571929. Pubmed Central PMCID: 2947630.

30. Sliwa K, Lyons JG, Carrington MJ, Lecour S, Marais AD, Raal FJ, et al. Different lipid profiles according to ethnicity in the Heart of Soweto study cohort of de novo presentations of heart disease. Cardiovasc J Afr 2012; 23(7): 389–395. PubMed PMID: 22914997.

31. Kotseva K, Stagmo M, De Bacquer D, De Bacquer G, Wood D. Treatment potential for cholesterol management in patients with coronary heart disease in 15 European countries: findings from the EUROASPIRE II survey. Atherosclerosis 2008; 197(2): 710–717. PubMed PMID: 17765905. Epub 2007/09/04. eng.

32. Sudano I, Hess L, Noll G, Arnett D. Persistent dyslipidemia in statin-treated patients: the focus on comprehensive lipid management survey in Swiss patients. Swiss Med Weekly 2011; 141: w13200. PubMed PMID: 21574067. Epub 2011/05/17. eng.

33. Eber B, Lautsch D, Fauer C, Drexel H, Pfeiffer KP, Traindl O, et al. Can LDL-cholesterol targets be achieved in a population at high risk? Results of the non-interventional study ACT II. Curr Med Res Opin 2012; 28(9): 1447–1454. PubMed PMID: 22856551. Epub 2012/08/04. eng.

34. Bandgar TR, Faruqui AA. Managing dyslipidaemia: evolving role of combination therapy. J Indian Med Assoc 2011; 109(8): 549–552. PubMed PMID: 22315861. Epub 2012/02/10. eng.

35. Ito MK. Dyslipidemia: management using optimal lipid-lowering therapy. Ann Pharmacother 2012; 46(10): 1368–1381. PubMed PMID: 23032652. Epub 2012/10/04. eng.

36. Schidlbauer A, Davies P, Fahey T. Interventions to improve adherence to lipid lowering medication. Cochrane Database Syst Rev 2010 (3): CD004371. PubMed PMID: 20238331.

37. Dragonir A, Cote R, White M, Lalonde L, Berard A, et al. Relationship between adherence level to statins, clinical issues and health-care costs in real-life clinical setting. Value Health 2010; 13(1): 87–94. PubMed PMID: 19695008.

38. Ho PM, Magid DJ, Shetterly SM, Olson KL, Maddox TM, Peterson PN, et al. Medication nonadherence is associated with a broad range of adverse outcomes in patients with coronary artery disease. Am Heart J 2008; 155(4): 772–779. PubMed PMID: 18371492.

39. McGinnis BD, Olson KL, Delate TM, Stolcarp RS. Statin adherence and mortality in patients enrolled in a secondary prevention program. Am J Managed Care 2009; 15(10): 689–695. PubMed PMID: 19845421.

40. Wei L, Fahey T, McDonald TM. Adherence to statin or aspirin or both in patients with established cardiovascular disease: exploring healthy behaviour vs. drug effects and 10-year follow-up of outcome. Br J Clin Pharmacol 2008; 66(1): 110–116. PubMed PMID: 18492127. Pubmed Central PMCID: 2485263.

41. Shroufi A, Powles JW. Adherence and chemoprevention in major cardiovascular disease: a simulation study of the benefits of additional use of statins. J Epidemiol Commun Health 2010; 64(2): 109–113. PubMed PMID: 20056964.

42. Wierzbicki AS, Hardman TC, Viljoen A. New lipid-lowering drugs: an update. Int J Clin Pract 2012; 66(3): 270–280. PubMed PMID: 22540447.