

# Prevalence of dyslipidaemia in patients treated with lipid-modifying drugs in the Netherlands

## Part of the Dyslipidaemia International Study

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### ABSTRACT

**Background:** Patients at risk for cardiovascular disease require medical treatment to optimise their lipid profile. Failure to reach optimal lipid levels contributes significantly to the residual cardiovascular risk in treated patients. In the DYSIS-Netherlands study, residual lipid profile abnormalities in patients on stable statin therapy in the Netherlands were assessed.

**Methods:** As part of a multinational cross-sectional cohort study conducted in Canada and Europe, 1212 patients were included in the Netherlands. Patients aged 45 years and older were included if they had taken statins for at least three months. Data on demographics, cardiovascular history and cardiovascular risk profile were recorded, and compared using European Society of Cardiology (ESC) risk classification.

**Results:** In 1139 patients, total lipid profile was measured. In this population ESC LDL-cholesterol normal levels were not achieved in 33.3% (n=379), whereas 71.7% (n=817) did not reach the three-normal level: for LDL cholesterol, plus they had low HDL cholesterol and/or elevated triglycerides. In the high-risk group (n=1036), LDL-cholesterol levels were not at goal in 33.3% (n=345). In the entire cohort, only 28.3% (n=322) of patients receiving statin therapy reached normal levels for all lipid parameters.

**Conclusion:** The majority of patients receiving statin therapy fail to reach normal levels for lipid parameters. Although the final results of ongoing outcome trials using combinations of lipid-altering treatments should be awaited, optimisation of lipid management is still amenable to improvement in the Netherlands.

### KEYWORDS

Cardiovascular disease prevention, DYSIS, HDL cholesterol, LDL cholesterol, triglycerides

### INTRODUCTION

Cardiovascular disease (CVD) was a leading cause of mortality in the Netherlands in 2008 with a total of 40,000 CVD deaths.<sup>1</sup> The incidence of CVD is expected to increase in the Netherlands as well as in other countries due to the rising prevalence of obesity and diabetes mellitus. Dyslipidaemia secondary to obesity and diabetes mellitus plays a central role in the development of CVD. During the last decades, the use of cholesterol-lowering drugs has increased substantially due to their beneficial impact on cardiovascular risk. Particularly statins (HMG-CoA reductase inhibitors) have been associated with a profound reduction in CVD risk. As a consequence, more than 1,500,000 patients in the Netherlands were taking statins in 2007.<sup>2</sup> Statin use is expected to increase even further due to improved identification of patients at risk as well as the lower thresholds used for initiating statin therapy. Statins reduce CVD risk by approximately 23% per every 1 mmol/l (~39 mg/dl) low-density lipoprotein (LDL) cholesterol lowering. This proportional reduction is largely independent of the LDL cholesterol prior to statin initiation.<sup>3</sup> Besides LDL cholesterol, low high-density lipoprotein (HDL) cholesterol levels and high triglyceride (TG) levels also are predictors of CVD risk.<sup>4,5</sup> Even if LDL cholesterol is lowered to levels below 2 mmol/l (~77 mg/dl), HDL cholesterol and TG levels remain independent predictors of CVD risk.<sup>6,7</sup> In men and women, a TG

increase of 1 mmol/l (~89 mg/dl) is associated with a 12 and 37% increase in risk of coronary heart disease (CHD) respectively.<sup>8</sup> For HDL cholesterol, an increase of 0.03 mmol/l (~1 mg/dl) is associated with a 1.9 to 2.3% decrease in risk of CHD for men and 3.2% risk reduction in women.<sup>9</sup>

In an attempt to fight the CVD risk arising from dyslipidaemia, the European Society of Cardiology (ESC) recently published their fourth, adapted guidelines on cardiovascular prevention in clinical practice.<sup>10</sup> These guidelines were produced to promote higher quality of care to prevent CVD in Europe. In order to achieve this goal, objectives were formulated for individuals after attributing them to a risk class based on their demographic characters using the ESC Systematic Coronary Risk Evaluation (SCORE).

The present study, conducted in Canada and Europe, is called the Dyslipidemia International Study (DYSIS).<sup>11</sup> Data gathered in the Netherlands were extracted from the international database in order to assess the lipid profile abnormalities in patients on stable statin therapy in the Netherlands. The ESC guidelines accompanied with the SCORE was used to illustrate discrepancy between the initiated therapy and the pursued goal of that therapy.

## METHODS

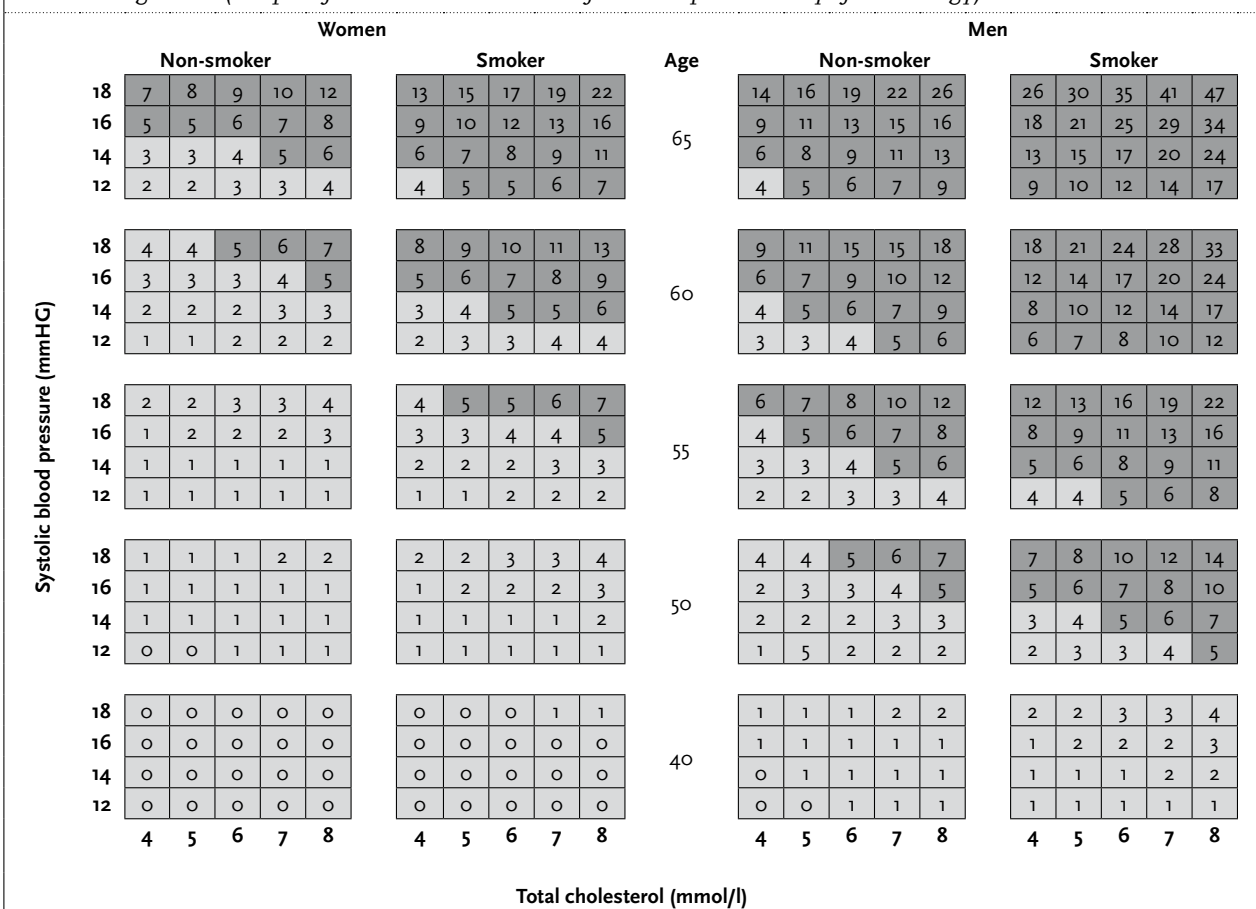
### Study design and patient population

The DYSIS-Netherlands study is an epidemiological multicentre cross-sectional cohort study and is part of a multinational study conducted in Canada and Europe, where approximately 21,000 patients have participated. In the Netherlands, 1208 patients were included if aged 45 or older and taking statins for at least three months. Patients were recruited randomly from primary and secondary care centres. All patient data were collected from clinical examination and medical charts from single consecutive visits over a two-month recruitment period between April 2008 and February 2009. Data on demographics, cardiovascular history, cardiovascular risk profile and lipid-modifying therapy were recorded. For 69 (5.7%) of the included patients, lipid parameters were inappropriate or missing. These patients were not included in the lipid analyses.

### Risk classification

In order to define treatment goals for the included patients, the ten-year risk of fatal CVD was assessed using the Systemic Coronary Risk Evaluation (SCORE) risk chart (figure 1). In this chart, risk estimation is based

**Figure 1.** SCORE chart, ten-year risk of fatal CVD in the Netherlands by gender, age, systolic pressure, total cholesterol and smoking status (adapted from the SCORE chart of the European Society of Cardiology)



on age, sex, smoking habits, systolic blood pressure and total cholesterol level. Patients with an ESC-SCORE risk of 5% or more, presence of established CVD, presence of diabetes mellitus type 2 or 1 with microalbuminuria, or patients with a markedly elevated single risk factor were ascribed to a high-risk class. Patients with an ESC-SCORE risk less than 5% were attributed to a non-high-risk class (figure 2). For the two risk classes, treatment goals were determined, based on the ESC guidelines. For the high-risk class, normal levels of total cholesterol and LDL cholesterol are below 4.5 mmol/l (~174 mg/dl) and 2.5 mmol/l (~97 mg/dl), respectively. In the ESC guidelines, normal levels are not defined for HDL cholesterol and TG levels, but HDL levels of 1.0 mmol/l (~38 mg/dl) and lower for men and 1.2 mmol/l (~46 mg/dl) and lower for women and fasting TG levels of 1.7 mmol/l (~151 mg/dl) are markers of increased CVD risk. For the non-high-risk class, total cholesterol and LDL cholesterol targets are below 5 mmol/l (~193 mg/dl), 3 mmol/l (~116 mg/dl) respectively. TG and HDL cholesterol levels as mentioned above are the same markers of increased CVD risk as for the high-risk class.

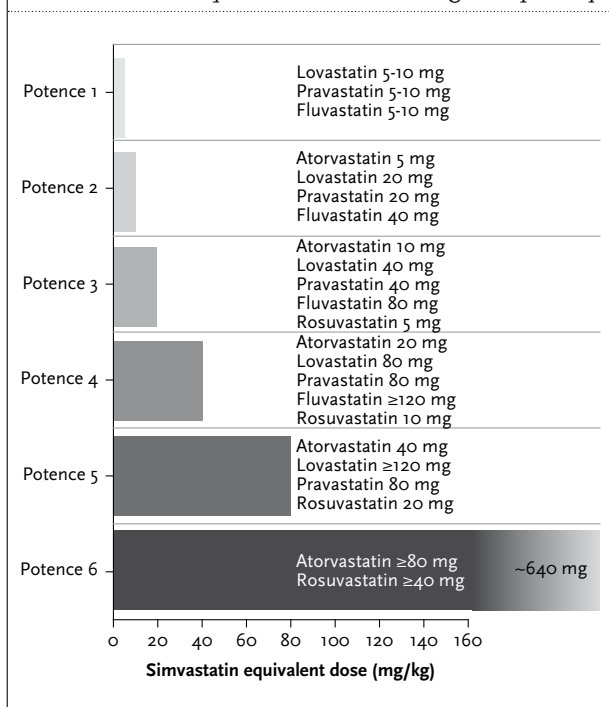
#### Statistical analysis

Of all data, means, medians and standard deviations (SD) were calculated with SPSS v16.0 (SPSS Inc.). Data are shown in Kernel density curves and overlap diagrams, with percentages calculated with SPSS v16.0 (SPSS Inc.).

#### Statin potency

Statin doses were classified into groups with comparable statins because of differences in efficacy between statin dose potencies. With data extracted from Roberts and more recent data from Grundy and co-workers from Adult Treatment Panel III (ATPIII) guidelines, six groups were defined (table 1).<sup>12-14</sup>

**Table 1.** Overview of statin potency groups, substantiated with simvastatin equivalent dose, in milligrams per day

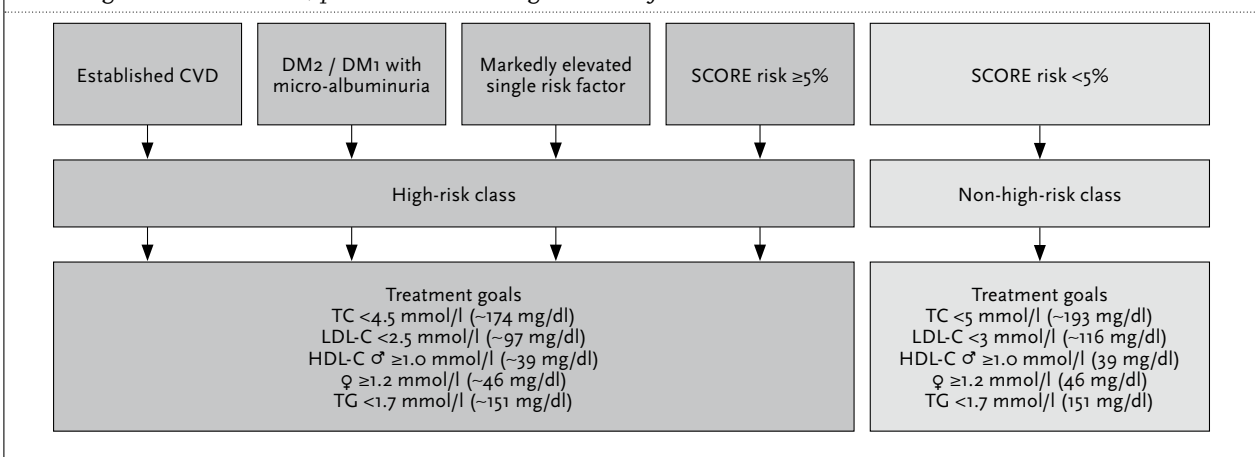


## RESULTS

#### Patient characteristics

The patient characteristics, risk categories, and lipid parameters are listed in table 2. Ninety-one percent of patients were attributed to the high-risk class, mainly because of the presence of established CVD. Seven percent of patients were attributed to the high-risk class based on the estimated ESC-SCORE risk without evidence of established CVD or diabetes mellitus. The remaining 9% of the patients had an ESC-SCORE risk of less than 5% (non-high-risk class).

**Figure 2.** Flow chart for determining treatment goals. Depending on cardiovascular medical history and the estimated risk using the SCORE chart, patients' treatment goals are defined



**Table 2.** Patient characteristics, risk categories and lipid parameters

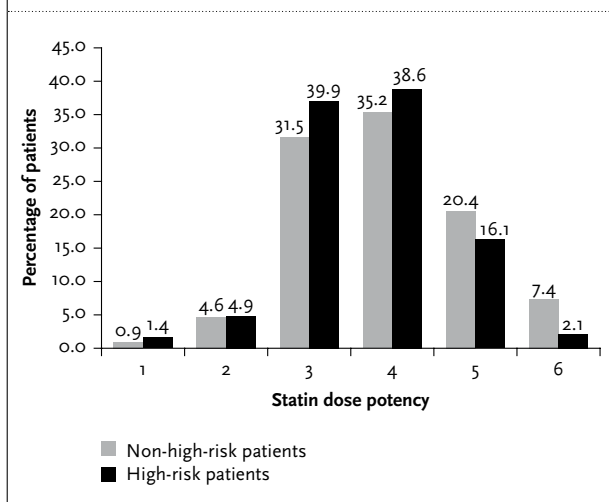
	All patients (n=1208)
<b>Patient characteristics</b>	
Age (years) [mean±SD]	65.6±9.7
Caucasian (%)	95.2
Family history of premature CHD (%)	39.4
Current smokers (%)	20.0
Hypertension (%)	69.0
Systolic BP (mmHg) [mean±SD]	138.9±18.7
Diastolic BP (mmHg) [mean±SD]	79.0±9.7
Waist circumference (cm) [mean±SD]	101.9±13.0
BMI (kg/m <sup>2</sup> ) [mean±SD]	28.5±4.7
BMI ≥30 kg/m <sup>2</sup> (%)	30.9
<b>ESC risk parameters</b>	
High risk (CVD, diabetes and/or SCORE risk ≥5%) (%)	91.0
CVD (%)	59.8
Diabetes mellitus (%)	46.4
SCORE risk ≥5% (%) without CVD and diabetes	7.0
SCORE risk <5% (%) without CVD and diabetes	9.0
<b>Lipid parameters</b>	
Total cholesterol (mmol/l) [mean±SD]	4.4±1.0
LDL-C (mmol/l) [mean±SD]	2.4±0.9
HDL-C (mmol/l) [mean±SD]	1.2±0.4
Triglycerides (mmol/l) [median (IQR)]	1.4 (1.0-2.1)
<b>Statin treatment</b>	
Simvastatin (%)	32.7
Atorvastatin (%)	34.8
Rosuvastatin (%)	21.4
Pravastatin (%)	8.8
Fluvastatin (%)	2.3
Lovastatin (%)	0.0
<b>Other lipid-lowering treatment (%)</b>	
Ezetimibe (%)	11.7
Fibrate (%)	2.0
Nicotinic acid (%)	0.7
Bile acid sequestrant (%)	0.1
CHD = coronary heart disease; BP = blood pressure; BMI = body mass index; CVD = cardiovascular disease, DM = diabetes mellitus.	

#### Lipid-modifying treatment and statin dose potency

Atorvastatin was the most commonly used statin (34.8%), followed by simvastatin (32.7%) and rosuvastatin (21.4%). Other statins used by the patients were pravastatin (8.8%) and fluvastatin (2.3%). Non-statin lipid-lowering treatment on top of statins was used by 13.6% of the patients, including ezetimibe (11.7%), fibrates (2.0%), nicotinic acid (0.7%) and bile acid sequestrants (0.1%).

In figure 3, patients' statin regimen classified according to potency for the high-risk patients and non-high-risk

**Figure 3.** Statin dose potency according to patients' risk status



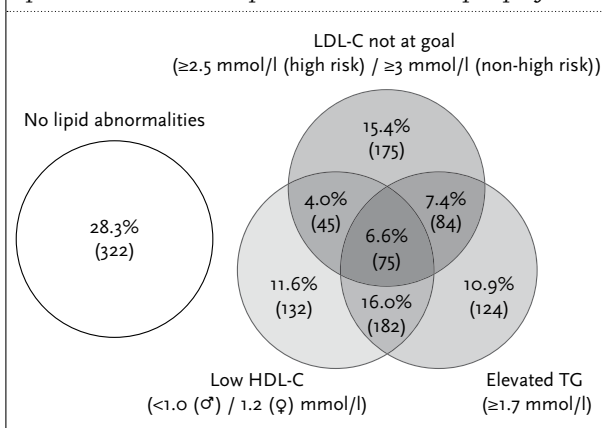
patients is shown. The majority of patients used a regimen with potency 3 and 4, which is equivalent to simvastatin 20 mg/day and 40 mg/day respectively. Interestingly, in the non-high-risk class a higher percentage of the patients used a more potent (5 and more) statin regimen compared with the high-risk class, whereas the less potent regimens (4 and below) were more frequent in the high-risk groups. Of patients from both risk categories, 6.1% use statin regimens with a potency of 2 and less, which is equivalent to a maximum dosage of 10 mg simvastatin and less.

#### Achievement of normal lipid levels

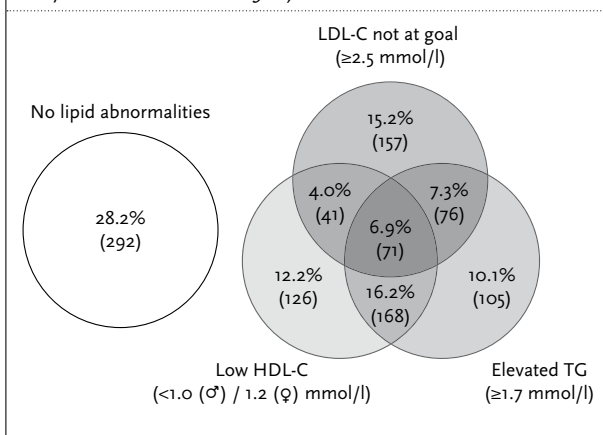
One third of all patients (33.3%) had an LDL cholesterol not at goal (≥2.5 mmol/l; 79 mg/dl in high-risk patients and ≥3.0 mmol/l; 116 mg/dl in non-high risk patients) according to ESC guidelines. In 35% total cholesterol was not at goal (≥4.5 mmol/l; 174 mg/dl in high-risk patients and ≥5.0 mmol/l; 193 mg/dl in non-high-risk patients). Low HDL cholesterol (<1.0 mmol/l; 39 mg/dl in men and <1.2 mmol/l; 46 mg/dl in women) and elevated triglycerides (>1.7 mmol/l; 151 mg/dl) were seen in 38.1 and 40.8% of patients (figure 4). Strikingly, the same proportion of patients at high risk (defined as presence of CVD, diabetes and/or ESC-SCORE ≥5%) fail to reach goals for total and LDL cholesterol, had low HDL cholesterol and elevated triglycerides as patients at non-high risk (ESC-SCORE <5%, see figures 5 and 6).

The most frequent single lipid abnormality in all patients was elevated triglycerides. Regarding combined lipid abnormalities, elevated triglycerides combined with low HDL cholesterol was most frequent (22.6%), followed by elevated triglycerides with LDL cholesterol not at goal (14.0%). Combined lipid abnormalities were approximately 3% more common in patients with a high risk, compared with patients without high risk, which counts for all lipid abnormality

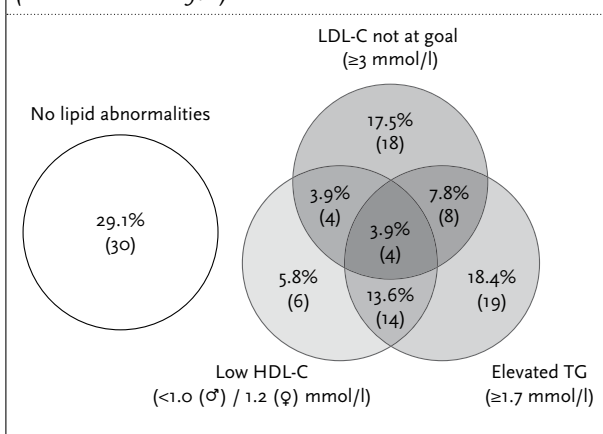
**Figure 4.** Distribution of single and multiple combined lipid abnormalities in patients with total lipid profile



**Figure 5.** Distribution of single and multiple combined lipid abnormalities in high-risk patients (CVD, diabetes and/or ESC SCORE ≥5%)



**Figure 6.** Distribution of single and multiple combined lipid abnormalities in non-high-risk patients (ESC-SCORE <5%)



combinations. As a consequence, single lipid abnormalities were more frequent in non-high-risk patients, with HDL cholesterol excluded. Remarkable is the fact that, despite the inclusion of people with diabetes and established CVD in the

high-risk class, a larger proportion of patients with non-high risk had elevated triglycerides as the sole abnormality (10.1 and 18.4% respectively). More appropriately, isolated low HDL cholesterol is found in a larger proportion of high-risk patients than in non-high-risk patients (12.2 and 5.8%, respectively).

## DISCUSSION

The results of DYSIS-Netherlands, a study of lipid levels in patients receiving stable statin therapy, reveal the failure to achieve normal levels in patients at risk for CVD. To our knowledge, this is the first study using a large dataset focused solely on statin users in both primary and secondary care settings in the Netherlands. This study was conducted after the release of the 2007 ESC guidelines for the prevention of CVD.<sup>10</sup>

Despite stable statin therapy, one third of the patients had LDL-cholesterol levels above normal levels. Similarly, elevated triglycerides and low HDL cholesterol remained despite therapy in approximately 40% per moiety.

### Previous studies

A number of cross-sectional studies have investigated the prevalence of lipid abnormalities and statin use.<sup>15-23</sup> These studies, however, were limited to specific populations such as patients with pre-existing CVD, focused on specific lipid parameters such as LDL cholesterol or HDL cholesterol, or had mixed patients with or without lipid-lowering therapies. DYSIS-Netherlands provides an up-to-date view of statin therapy across primary care and specialist treatment centres. Consistent with published data, the majority of patients in this study (71.7%) showed lipid abnormalities despite lipid-modifying therapy.

### Statin potency and risk class

Figure 3 shows a lower use of highly potent statins in the high-risk class, compared with the non-high-risk class. The apparent discrepancy may be due to the fact that patients at high risk are treated with a combination of statins with lipid-lowering drugs from other classes. Thus, doctors may deliberately use lower doses and less potent statins for instance upon combination therapy with fibrates because of the increased risk of myotoxicity.<sup>24,25</sup> In addition, the non-high-risk group includes young people with inherited dyslipidaemias such as familial hypercholesterolaemia, who are classified in this category using the ESC-risk engine based on their age. However, a diagnosis of primary dyslipidaemia is automatically an indication for the use of aggressive lipid-lowering therapy.

### LDL cholesterol, HDL cholesterol, and triglycerides

Although LDL cholesterol is the best characterised risk factor, one third of the patients taking statins have

LDL-cholesterol levels above their normal level. Failure to achieve normal levels in the majority of patients may not be due to an absolute inability to do so, but rather reflects the use of less potent statins. Since the proportion of patients reaching LDL-C normal levels is very modest, there is a clear need to increase awareness of the relevance of achieving normal levels in order to optimally lower CVD risk.<sup>10</sup>

In parallel, 38.1% of patients presented with HDL-cholesterol levels below the normal level. In this case, it most likely reflects the lack of therapeutic options to selectively increase HDL cholesterol.<sup>26</sup> The effect of statins on HDL cholesterol is fairly modest (2 to 10%), and the clinical relevance of statin-induced HDL-cholesterol changes has never been established.<sup>27</sup> Novel approaches to increase HDL cholesterol have gained a lot of attention. The recent withdrawal of the CETP-inhibitor torcetrapib, which increased HDL cholesterol significantly with a concomitant increase in CVD, has once again fuelled the concept that increasing HDL cholesterol may turn out to be more complicated compared with LDL cholesterol-lowering interventions.<sup>28</sup>

Surprisingly, with a prevalence of 40.8%, elevated triglycerides was the most frequent lipid abnormality. A potential explanation is the inclusion of patients with secondary dyslipidaemias, largely due to metabolic syndrome treated with statins only. Although potent statins such as atorvastatin and rosuvastatin can reduce fasting triglyceride levels by 20 to 40%, less potent statins have little impact on triglyceride levels.<sup>29,30</sup> At the same time, whereas fibrates are valuable in lowering triglyceride levels, the additional impact of fibrates on top of statins on CVD event rate has not been convincingly demonstrated.<sup>31,32</sup> The final verdict awaits the results of the ongoing Action to Control Cardiovascular Risk in Diabetes (ACCORD) study.<sup>33</sup>

### Study limitations

Our study has some limitations that deserve closer attention. First, DYSIS was a cross-sectional (single point) observational study which did not evaluate long-term outcomes. Therefore SCORE risk was calculated based on current or retrospective data, rather than prospectively observed. Second, lipid parameters were those taken from patients' case notes. There was no blood sample collection or core laboratory analysis of the lipid parameters. Notwithstanding this observation, our results are a true reflection of clinical practice. Thirdly, the treatment centres included were those prescribing statins to their patients, given that current statin use was a patient eligibility criterion. This may have introduced a self-selection bias. This implies that, in fact, the present data may over-estimate the use of statins across the CVD population. Finally, the present study did not collect

data on patient lifestyle, genetic predisposition to CVD (although family history was assessed) or treatment compliance.

### Clinical implications

In more than 70% of patients in the DYSIS-Netherlands study, lipids were not at normal levels despite stable statin treatment. Side effects and lack of selective drugs were probably the cause of undertreatment. These data indicate that the awareness of the need to achieve appropriate or normal lipid levels needs close attention. For LDL cholesterol, since the Treating to New Targets (TNT) and Incremental Decrease in End Points through Aggressive Lipid Lowering (IDEAL) trials, it has been demonstrated that lower LDL cholesterol results in lower CVD risk.<sup>34,35</sup> For TG levels, in a recent post hoc analysis of the TNT and IDEAL trial, risk of a cardiovascular event increased as a function of increasing TG levels.<sup>36</sup> This is presumably because TG levels cause an increase of small dense LDL cholesterol and lower HDL cholesterol, thereby causing higher CVD risk. For HDL cholesterol, no evidence has been found that therapeutically increased levels lead to a decreased CVD risk, because of the lack of selective therapeutics.<sup>26</sup> Because of the residual risk, in future, combination therapy of lipid-modifying agents will presumably be used to reach normal levels for all moieties. In the next decade, statins combined with a second drug will be the best regimen in high-risk patients. New agents have to be developed to reach lipid normal levels.

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## FINANCIAL DISCLOSURE

The authors report no potential conflicts of interest.

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