

# Adherence to guidelines to prevent cardiovascular diseases: The LifeLines cohort study

J.W. Balder<sup>1,3</sup>, S. Scholtens<sup>2</sup>, J.K. de Vries<sup>3</sup>, L.M. van Schie<sup>1,3</sup>, S.M. Boekholdt<sup>4</sup>, G.K. Hovingh<sup>5</sup>, P.W. Kamphuisen<sup>3</sup>, J.A. Kuivenhoven<sup>1\*</sup>

Departments of <sup>1</sup>Pediatrics, Section Molecular Genetics, <sup>2</sup>Epidemiology, <sup>3</sup>Vascular Medicine, University of Groningen, University Medical Centre Groningen, Groningen, the Netherlands, Departments of <sup>4</sup>Cardiology, <sup>5</sup>Vascular Medicine, Academic Medical Centre, University of Amsterdam, Amsterdam, the Netherlands, \*corresponding author: tel.: +31(0)50-3632687, fax: +31(0)50-3638971, email: j.a.kuivenhoven@umcg.nl

## ABSTRACT

**Background:** Cardiovascular disease (CVD) is the leading cause of death worldwide. While there is indisputable evidence that statin treatment reduces the burden of CVD, undertreatment remains a concern for primary and secondary prevention. The aim of this study was to assess the use of lipid-lowering drugs (LLD) among 70,292 individuals in the Netherlands as a proxy of adherence to the national guideline for prevention and treatment of CVD.

**Methods:** LifeLines is a population-based prospective cohort study in the three Northern provinces of the Netherlands. At baseline, all participants completed questionnaires, and underwent a physical examination and lab testing. The national guidelines were used to assess how many participants were eligible for LLD prescription and we analysed how many indeed reported LLD use.

**Results:** For primary prevention, 77% (2515 of 3268) of those eligible for LLD treatment did not report using these drugs, while for secondary prevention this was 31% (403 of 1302). Patients with diabetes mellitus were treated best (67%) for primary prevention. Notably, of the patients with stroke, only 47% (182 of 386) reported LLD treatment.

**Conclusion:** Despite clear guidelines and multiple national initiatives to improve CVD risk management, adherence to guidelines for the treatment of CVD in the Netherlands remains a major challenge. This study calls out for improving public awareness of CVD and to improve primary and secondary prevention to prevent unnecessary CVD-related morbidity and mortality.

## KEYWORDS

Cardiovascular risk, primary prevention, secondary prevention, statins, undertreatment, underuse, risk assessment

## INTRODUCTION

In the early 1990s, several landmark trials unequivocally showed that HMG-CoA reductase inhibitors, i.e. statins, reduce cardiovascular morbidity and mortality in secondary as well as primary prevention through lowering low-density lipoprotein cholesterol (LDL-c) levels.<sup>1,2</sup>

There are to date only very few reports on the use of statins for primary prevention. Data from the Oslo Health Study (collected in 2000-2001) showed that most participants with diabetes were not treated, especially women.<sup>3</sup> In 2003, it was shown that over 95% of the population eligible for pharmacological treatment of hypercholesterolaemia were untreated or uncontrolled in a Dutch population-based cohort study.<sup>4</sup> It was subsequently shown that the use of cardiovascular drugs increased over time in the Netherlands,<sup>5</sup> but recent figures on the implementation of cardiovascular disease (CVD) guidelines for the use of lipid-lowering drugs (LLD) for primary and secondary prevention are lacking. The need for continuous awareness was recently illustrated by the observation in the USA that only 20% of individuals with a ten-year CVD risk > 20% were treated with statins.<sup>6</sup>

For patients who suffered from CVD (secondary prevention), several studies in the late 1990s highlighted

that undertreatment was also common.<sup>7</sup> In a representative survey of the US population, it was recently shown that only 58% of patients with coronary artery disease were treated with statins.<sup>8</sup>

The general aim of guidelines is to assist physicians in selecting the best treatment strategy for an individual patient. The indication to prescribe LLD in the Netherlands is based on the national CardioVascular Risk Management (CVRM), written by the Dutch Institute of Health Care Improvement and the Dutch College of General Practitioners (NHG).<sup>9</sup> Concerning primary prevention, the Dutch CVRM uses dedicated prediction charts, based on Dutch prospective cohort studies, to calculate the ten-year risk of cardiovascular morbidity or mortality (ten-year CVD risk). This ten-year CVD risk is stratified as low (< 10%), medium (10-19%), or high ( $\geq$  20%) risk. Patients at high risk with LDL-c levels > 2.5 mmol/l and patients with a total cholesterol/high-density lipoprotein cholesterol (TC/HDL-c) ratio > 8 are all eligible for LLD prescription. LLD treatment is only recommended for patients at medium risk when they present with LDL-c levels > 2.5 mmol/l and one or more additional risk factors (sedentary lifestyle, positive family history of premature CVD, obesity and renal failure). Concerning secondary prevention, patients with myocardial infarction and those who have undergone coronary surgery should be treated. The same holds true for those who have suffered from stroke or peripheral vascular disease and have LDL-c levels > 2.5 mmol/l (table 1).

International guidelines were recently compared by Saraf *et al.*<sup>10</sup> Overall, the Dutch guidelines are quite similar to the international guidelines; however, there are some differences. While most international guidelines recommend statin treatment if LDL-c levels are  $\geq$  4.9 mmol/l,

the Dutch CVRM does not include this. The CVRM guideline is unique in its recommendation for treatment in patients with a medium ten-year CVD risk in combination with additional risk factors.

To tackle undertreatment, the NHG is dedicated to improving implementation of these guidelines through developing e-learning modules, organising courses, and generating protocols for nurse practitioners, brochures and websites for patients. The Dutch Heart Foundation has also developed standards for managing cardiovascular risk factors to improve implementation. To improve the awareness of cardiovascular risk in the general population a National Cholesterol test was initiated in 2014.

In the current study, we evaluated the use of LLD in both primary and secondary prevention in a large sample of the Dutch general population (LifeLines study).

## METHODS

### Study design and participants

LifeLines is an observational population-based study of the Northern provinces of the Netherlands.<sup>11</sup> The study protocol was approved by the medical ethics committee of the University Medical Centre Groningen. All participants provided written informed consent.

For the current study, baseline data were available of 70,292 participants who were recruited between 2006 and 2012. Participants were excluded if data to calculate the ten-year CVD risk were missing or when medication use was not verified. Individuals who reported a myocardial infarction, stroke, or coronary revascularisation procedures, defined as coronary angioplasty or bypass,

**Table 1.** Indication to prescribe lipid-lowering drugs based on the Dutch Cardiovascular Risk Management guideline

Patient characteristic	LDL-c level threshold	Additional criteria
<b>Primary prevention</b>		
Medium 10-year CVD risk	> 2.5 mmol/l	Additional risk factors*
High 10-year CVD risk	> 2.5 mmol/l	All
TC/HDL-c ratio > 8	All	All
<b>Secondary prevention</b>		
Coronary surgery	All	All
Myocardial infarction	All	All
Stroke	> 2.5 mmol/l	All
Peripheral vascular disease	> 2.5 mmol/l	All

\* Additional risk factors are classified as renal failure, sedentary lifestyle, obesity, and positive family history of premature CVD. TC/HDL-c ratio = total cholesterol/high-density lipoprotein cholesterol ratio.

were classified as secondary prevention. The remainder were classified as primary prevention. Peripheral vascular disease was not addressed in the LifeLines questionnaires and could unfortunately not be evaluated.

### Questionnaires and physical examination

Baseline questionnaires included questions on demographics, family structure, medical history, lifestyle factors and medication use. For the current study, statins and ezetimibe were grouped as LLD. The use of fibrates was not taken into consideration for the current study because fibrates are not the first-choice treatment to lower LDL-c levels. All participants visited the LifeLines research site for physical examination, which included measurement of blood pressure (ten times using an automated blood pressure monitor; Dinamap), body height and weight. Hypertension was defined as systolic or diastolic blood pressure higher than 140 or 90 mmHg, respectively. Positive family history was defined as a parent or sibling who suffered from premature CVD (before the age of 50 years). Sedentary lifestyle was defined as less than 30 minutes of physical activity a day. Estimated glomerular filtration rate (eGFR) was determined using the Cockcroft-Gault formula. Fasting blood samples were collected. Total cholesterol and LDL-c levels were measured with a direct assay (Roche Modular P, Mannheim, Germany). High-density lipoprotein cholesterol (HDL-c) was measured via a direct quantitative assay (Roche Modular P, Mannheim, Germany). Triglycerides were measured using an enzymatic colorimetric test (Roche Modular P, Mannheim, Germany).

### Recommendation for treatment and assessment of CVD risk

The CVRM guideline was used to decide whether or not participants were eligible for using LLD. The ten-year risk of cardiovascular morbidity or mortality of each participant was calculated using a risk prediction score according to the CVRM guideline.<sup>9</sup> This algorithm used gender, age, smoking status, systolic blood pressure and TC/HDL-c ratio as the main risk determinants. The risk of participants with rheumatoid arthritis and diabetes mellitus was calculated by adding 15 years to the actual age.<sup>9</sup> The ten-year risk of cardiovascular morbidity or mortality was stratified as low (< 10%), medium (10-19%), or high (≥ 20%) risk.

### Statistical analyses

For statistical analysis PASW Statistics (Version 20, IBM, Armonk, NY, USA) was used. Participants' baseline characteristics were presented by mean, standard deviation (SD) and ranges or by percentages in case of categorical variables. We assessed which individuals should receive LLD according to the CVRM guideline. Recommended treatment was compared with the self-reported treatment.

For both primary and secondary prevention, differences between those reporting and not reporting LLD treatment were compared using a Student's t test or Mann-Whitney U test. We further explored undertreatment in different subgroups. All statistically significant subgroups in univariate logistic regression (data not shown) were assessed in subsequent multivariate logistic regression, adjusted for sex and age, to analyse independent predictors of not reporting LLD.

## RESULTS

### Baseline characteristics of study cohort

The study population consisted of 70,292 participants. Baseline characteristics are shown in *table 2*. Briefly, the

**Table 2.** Baseline characteristics of study cohort

Baseline characteristics of 70,292 participants	
Classical risk factors, mean (SD) and [range] or n (%)	
Age (years)	45 (12) [18 – 93]
Total cholesterol (mmol/l)	5.0 (1.0) [1.8 – 14]
Low-density lipoprotein cholesterol (mmol/l)	3.2 (0.9) [0.3 – 11.4]
High-density lipoprotein cholesterol (mmol/l)	1.5 (0.4) [0.1 – 4.0]
Triglycerides (mmol/l)	1.2 (0.8) [0.01 – 23]
Systolic blood pressure (mmHg)	126 (15) [71 – 258]
Gender (male)	31,439 (45)
Current smoker	15,206 (22)
Diabetes mellitus	1209 (1.7)
Rheumatoid arthritis	1263 (1.8)
Additional risk factors, mean (SD) or n (%)	
Body mass index (kg/m <sup>2</sup> )	26 (4.2) [14 – 60]
Positive family history of cardiovascular disease	4002 (8.6)
Sedentary lifestyle	2758 (3.9)
Other characteristics, n (%)	
Hypertension	13,138 (19)
Statin treatment	3172 (4.5)
Coronary revascularisation	744 (1.1)
Self-reported myocardial infarction	586 (0.8)
Self-reported stroke	422 (0.6)

Positive family history is defined as a parent or sibling who suffered from CVD before age of 50. Sedentary lifestyle is defined as less than 30 minutes of physical activity a day. SD = standard deviation.

mean age of the participants was 45 (18-93) years and 45% were male. Of the participants, 22% smoked or had stopped smoking in the six months preceding completion of the questionnaire, while 19% of the participants had hypertension. A total of 68,954 participants did not report CVD or stroke. Of these, 92% (n = 63,393) were at low ten-year CVD risk, and 4.2% (n = 2926) and 3.8% (n = 2635) were at medium and high risk, respectively. A total of 1338 participants reported a previous CVD event, i.e. 744, 586 and 386 reported coronary surgery or suffered from myocardial infarction or stroke, respectively. Of note, some patients reported to have suffered from several forms of CVD and therefore the numbers do not add up directly.

### Lipid-lowering drugs and primary prevention

Of the participants without CVD (n = 68,954), 3268 (4.7%) were eligible for LLD. The baseline characteristics of these patients are shown in *table 3*. Of these, 77% (n=2515) did not report LLD, which was associated with significantly higher median TC (5.9 vs. 4.5 mmol/l; p < 0.001) and median LDL-c (3.9 vs. 2.6 mmol/l; p < 0.001) levels, compared with those reporting LLD use. Those who reported use of LLD had a higher BMI (29 vs. 28 kg/m<sup>2</sup>; p < 0.001) whereas systolic blood pressure was not statistically different (143 vs. 144 mmHg; p = 0.07). These results thus indicate that 2515 of 68,954 (3.6%) participants were not using LLD while the guidelines recommended this. Thus, eight out of ten patients eligible for LLD did not report using LLD.

**Table 3.** Lipid-lowering treatment for primary prevention

Characteristics	Recommended to use LLD n = 3268	Reported use of LLD n = 753 (23%)	Reported not using LLD n = 2515 (77%)	P-value
<b>Classical risk factors, mean (SD) or n (%)</b>				
Age (years)	67 (10)	69 (7.3)	67 (11)	<0.001
Total cholesterol (mmol/l)	5.6 (1.2)	4.5 (1.0)	5.9 (1.0)	<0.001
LDL-c (mmol/l)	3.6 (1.0)	2.6 (0.9)	3.9 (0.9)	<0.001
HDL-c (mmol/l)	1.4 (0.4)	1.4 (0.4)	1.4 (0.4)	ns
Triglycerides (mmol/l)	1.8 (1.7)	1.6 (1.2)	1.8 (1.9)	<0.01
Systolic blood pressure (mmHg)	144 (18)	143 (17)	144 (18)	0.07
Male	2079	420 (20)	1659 (80)	<0.001
Female	1189	333 (28)	856 (72)	<0.001
Current smoker	717	126 (18)	591 (82)	<0.001
Diabetes mellitus	506	341 (67)	165 (33)	<0.001
Rheumatoid arthritis	401	79 (20)	322 (80)	ns
<b>Additional risk factors, mean (SD) or n (%)</b>				
Body mass index (kg/m <sup>2</sup> )	28 (4.3)	29 (4.6)	28 (4.1)	<0.001
Positive family history CVD	312	50 (16)	262 (84)	<0.01
Sedentary lifestyle	156	27 (17)	129 (83)	0.08
<b>Other characteristic (n (%))</b>				
Hypertension	2046	460 (22)	1586 (78)	ns
<b>Individuals with low, medium and high risk, n (%)</b>				
Low CVD risk	247	9 (3.6)	238 (96)	<0.001
Medium CVD risk	518	109 (21)	409 (79)	ns
High CVD risk	2503	635 (25)	1868 (75)	<0.001
Positive family history is defined as a parent or sibling who suffered from CVD (before age of 50). Sedentary lifestyle is defined as less than 30 minutes of physical activity a day. LLD = lipid-lowering drugs; LDL-c = low-density lipoprotein cholesterol; HDL-c = high-density lipoprotein cholesterol; CVD = cardiovascular disease; SD = standard deviation.				

Subgroup analyses showed that 80% of the males and 72% of the females were not treated according to the CVRM guidelines. The percentage of undertreatment of patients with diabetes mellitus was much lower, namely 32% (figure 1).

#### Lipid-lowering drugs and secondary prevention

A total of 1338 participants reported to have suffered from CVD or stroke. Of these, 36 patients suffered from stroke but had LDL-c levels  $\leq 2.5$  mmol/l and therefore had no indication for using LLD. Thus 1302 individuals were eligible for treatment. Of these patients, 403 (31%) did not report use of LLD. Table 4 shows the baseline characteristics of the patients with CVD, who according to the guidelines should receive LLD. The use of LLD in this group was again associated with a significantly lower median TC (5.3 vs. 4.2 mmol/l;  $p < 0.001$ ) and median LDL-c (3.5 vs. 2.4 mmol/l;  $p < 0.001$ ) levels, compared with those who did not report LLD, respectively. Thus, out of ten patients eligible for LLD, three did not use LLD.

While 26% of the men were not treated according to guidelines, this percentage was significantly higher in females (42%;  $p < 0.001$ ). Remarkably, 53% of the patients with stroke and LDL-c levels  $> 2.5$  mmol/l did not report the use of LLD. In contrast, diabetes mellitus, coronary revascularisation and myocardial infarction were associated with the most frequent use of LLD (80-85%) (figure 1).

#### Multivariate logistic regression analysis

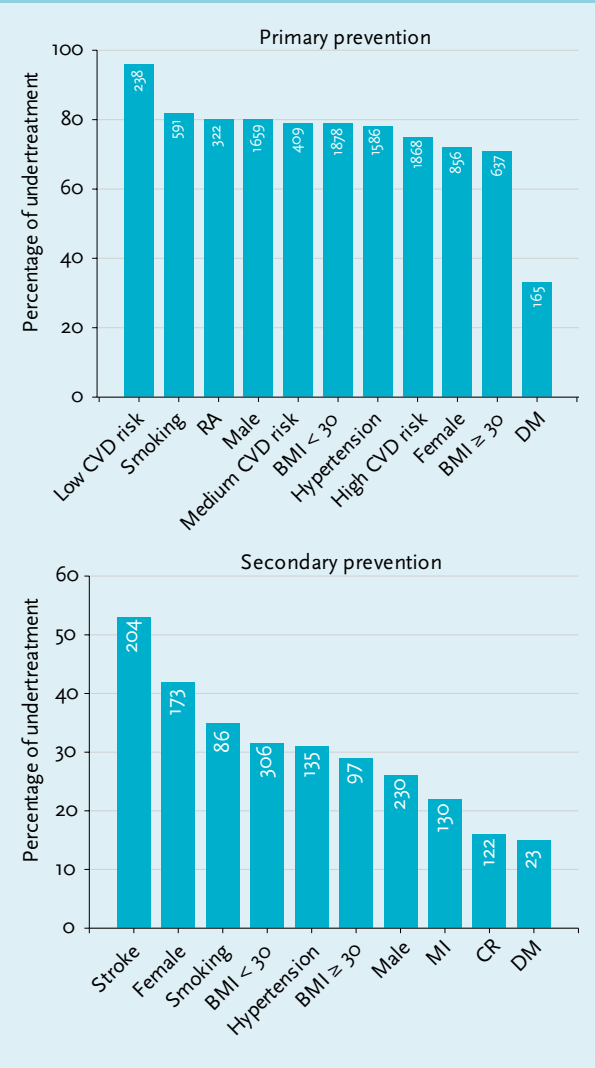
The risk factors for undertreatment of LLD, based on multivariate logistic regression analysis, for primary and secondary prevention are shown in table 5. The strongest predictor of not reporting LLD use was a low ten-year CVD risk (OR = 2.4;  $p = 0.03$ ). These were individuals with TC/HDL-c ratio  $> 8$ . Patients with diabetes mellitus, females, older patients and those with higher BMI were more likely to receive LLD (OR  $< 1.0$ ;  $p < 0.05$ ).

For secondary prevention, the strongest predictor of undertreatment was being female (OR = 1.63;  $< 0.01$ ). Predictors of LLD treatment following the guidelines are coronary revascularisation, diabetes mellitus, myocardial infarction, higher BMI and higher age (OR  $< 1.0$ ;  $p < 0.05$ ).

## DISCUSSION

This general population study in the Netherlands showed that, despite clear recommendations, 77% of subjects at high risk of CVD (primary prevention) and 31% with CVD (secondary prevention) did not report receiving LLD. Although these rates of undertreatment have been reported previously, this large and recent study indicates that better action should be taken by healthcare providers and policy makers in the Netherlands.

**Figure 1.** Percentage of undertreatment of individuals eligible for LLD treatment in different subgroups for primary (top) and secondary (bottom) prevention. Numbers on top of the bar are the total number of participants undertreated in the subgroup. LLD = lipid-lowering drug; RA = rheumatoid arthritis; MI = myocardial infarction; CR = coronary revascularisation



#### Primary prevention

According to the CVRM guideline, 4.7% ( $n = 3268$ ) of the LifeLines subjects without CVD, but with high cardiovascular risk, should have been treated with LLD. Only 23% actually reported using LLD. In a previous study of the general Dutch population, published in 2003, (MORGEN project,  $n = 61,918$ ; aged 20-59 years), 3.8% were eligible to use LLD.<sup>4</sup> Since LDL-c and TC levels increase with age, the higher percentage in our study can be attributed by the inclusion of participants over 59 years of age. In addition, we studied individuals at overall risk of CVD, whereas the MORGEN project focused on hypercho-

**Table 4.** Lipid lowering treatment in patients for secondary prevention

Characteristics	Recommended to use LLD n = 1302	Reported use of LLD n = 899 (69%)	Reported not using LLD n = 403 (31%)	P-value
<b>Classical risk factors, mean (SD) or n (%)</b>				
Age (year)	63 (12)	65 (10)	58 (15)	<0.001
Total cholesterol (mmol/l)	4.5 (1.0)	4.2 (0.8)	5.3 (0.9)	<0.001
LDL-c (mmol/l)	2.8 (0.9)	2.4 (0.7)	3.5 (0.8)	<0.001
HDL-c (mmol/l)	1.3 (0.4)	1.3 (0.4)	1.4 (0.4)	<0.001
Triglycerides (mmol/l)	1.4 (0.8)	1.4 (0.8)	1.4 (0.8)	ns
Systolic blood pressure (mmHg)	133 (18)	133 (17)	134 (19)	ns
Male	890	660 (74)	230 (26)	<0.001
Female	412	239 (58)	173 (42)	<0.001
Current smoker	249	163 (65)	86 (35)	ns
Diabetes mellitus	152	129 (85)	23 (15)	<0.001
Rheumatoid arthritis	72	51 (71)	21 (29)	ns
<b>Additional risk factors, mean (SD) or n (%)</b>				
Body mass index (kg/m <sup>2</sup> )	28 (4.1)	28 (3.9)	27 (4.4)	<0.01
Positive family history CVD	67	49 (73)	18 (27)	ns
Sedentary lifestyle	46	30 (65)	16 (35)	ns
<b>Other characteristics, n (%)</b>				
Hypertension	437	302 (69)	135 (31)	ns
Myocardial infarction	586	456 (78)	130 (22)	<0.001
Stroke	386	182 (47)	204 (53)	<0.001
Coronary revascularisation	744	622 (84)	122 (16)	<0.001
Positive family history is defined as a parent or sibling who suffered from CVD before the age of 50. Sedentary lifestyle is defined as less than 30 minutes of physical activity a day. LLD = lipid-lowering drugs; LDL-c = low-density lipoprotein cholesterol; HDL-c = high-density lipoprotein cholesterol; CVD = cardiovascular disease; SD = standard deviation.				

lesterolaemia. It is interesting to note, however, that in the MORGEN project, adherence to guidelines was 20% compared with 23% in the current study, which indicates only a slight improvement over the last ten years.

The most obvious reason for the marked undertreatment in our study is the possibility that participants may have never been tested for ten-year CVD risk. Since the most important parameters needed to assess CVD risk (i.e. age, smoking habits, blood pressure, and gender) are easy to obtain, insufficient awareness on the part of the individuals and/or their physicians of CVD risk likely contributed to the observed undertreatment.<sup>12</sup>

We further assessed whether we could identify subgroups that were prone to undertreatment. Of the patients with diabetes mellitus, 67% reported LLD which is probably related due to the more intense medical care, thus

monitoring of plasma lipid levels, in these individuals. In the USA, 52% of individuals with diabetes older than 40 years reported statin use.<sup>8</sup> Multivariate logistic regression analysis showed that undertreatment in the LifeLines study was most apparent in younger participants, males, those with lower BMI, and low ten-year CVD risk.

### Secondary prevention

Of the patients who suffered from CVD and had a clear indication for LLD, only 69% reported to be actually treated. In EUROASPIRE III,<sup>13</sup> very similar data but on a much smaller dataset were reported: 115 out of 167 (69%) Dutch participants reported LLD. Other data collected in the Netherlands in 2007 showed that 53% of the CVD patients were undertreated,<sup>14</sup> suggesting a small improvement.



**Table 5.** Risk factors for undertreatment of LLD based on multivariate logistic regression analysis for primary and secondary prevention

Variable	OR	95% CI	P-value
<b>Primary prevention</b>			
Low risk (< 10%)	2.40	1.08-5.27	0.03
Age, per year	0.98	0.96-0.99	<0.01
Body mass index, per kg/m <sup>2</sup>	0.95	0.93-0.98	<0.001
Gender, female	0.80	0.65-0.98	0.02
Diabetes mellitus	0.10	0.08-0.12	<0.001
Positive family history	1.29	0.89-1.86	ns
High risk (> 20%)	0.75	0.55-1.04	ns
<b>Secondary prevention</b>			
Gender, female	1.63	1.23-2.18	<0.01
Age, per year	0.96	0.95-0.97	<0.001
Body mass index, per kg/m <sup>2</sup>	0.96	0.93-0.99	0.01
Myocardial infarction	0.59	0.40-0.85	<0.01
Diabetes mellitus	0.45	0.27-0.74	<0.01
Coronary revascularisation	0.21	0.14-0.31	<0.001
Stroke	0.85	0.53-1.36	ns

In line with other Dutch studies,<sup>5</sup> the current study shows that for secondary prevention 42% of the females did not report LLD, whereas this was only 26% in males. Although CVD is currently the number one cause of death in women in the Netherlands, it appears clear that general practitioners underestimate the risk of CVD in women.<sup>15</sup> Our results furthermore show that of the patients who reported stroke, 53% were not reporting LLD use. Remarkably, undertreatment of patients with stroke is even worse in the Oslo Heart study: only 21% of men and 16% of the women were using LLD at age 60, while at age 70 these numbers increased to 44% and 48%, respectively.<sup>3</sup> In another Dutch population study it was shown that only 10% of patients with cerebrovascular accident/transient ischaemic accident were undertreated.<sup>14</sup> The heterogeneity of these findings may be related to differences in mean age in the respective studies as older people are much more likely to receive a statin. Nevertheless, our observations that both stroke and female gender are associated with undertreatment may need attention in the Netherlands, especially since women generally have a higher overall risk of stroke.<sup>16</sup> Multivariable logistic regression analysis showed that physicians prescribing LLD should additionally focus on females and individuals at a younger age.

### Limitations

The LifeLines questionnaires do not assess peripheral vascular disease, and we could not account for this parameter in our secondary prevention analysis. Next, the information on medication was dependent on the information given by participants. Furthermore, our dataset lacked information on BMI (n = 15), eGFR (n = 262), daily activity (n = 5530) and family history of CVD (n = 23,850). Since these determinants were used in the decision for LLD treatment in the medium ten-year CVD category, this may have resulted in an underestimation of the number of participants with an indication for LLD. We had to decide how to use the guidelines for those patients who had LDL-c levels  $\leq 2.5$  mmol/l and reported LLD use. We have assumed that these participants had LDL-c levels  $> 2.5$  mmol/l before initiation of LLD treatment, which may have led to overestimating the proportion of proper recommended treatment.

The CVRM guideline used in this study was published in June 2011. However, the inclusion of the LifeLines participants started in 2006 indicating that a significant number of participants entered in a time period in which the previous guideline was applicable. Although the differences between the guidelines are small, the CVRM 2011 guidelines do recommend more aggressive treatment of patients with rheumatoid arthritis. As a result, 145 patients with rheumatoid arthritis were wrongly categorised. This did not affect the overall outcome of our primary prevention analysis (this is only 4.4% of total patients eligible for LLD treatment in primary prevention). In line, *table 5* shows that rheumatoid arthritis was not a significant predictor of undertreatment in our multivariate analysis. However, due to the change in the guidelines during the course of our study, the outcome of our study is not applicable for patients with rheumatoid arthritis.

As Lifelines is a population-based study, it should be mentioned that the Dutch CVRM guidelines do not advocate the assessment of a cardiovascular risk profile in all adults. Reasons to assess this are e.g. the presence of hypertension, family history with premature CVD or diabetes. Looking into this specifically, we found however that 90% of participants who were eligible to use LLD, also met criteria for assessing a cardiovascular risk profile (data not shown).

### Conclusions and perspective

This large population-based study showed that 77% of the individuals, without CVD, in the Northern three provinces of the Netherlands did not receive LLD while the CVRM guideline would recommend this. This figure is 31% for secondary prevention. While significant progress in the treatment of CVD has previously been reported, our current data showed no signs of further improvement over the last years in the Netherlands.

The results of this study call for improved awareness and better treatment. The development of simple apps to estimate ten-year CVD risk could be of help. However, unfortunately, several key parameters such as plasma levels of HDL-c and LDL-c as well as systolic blood pressure, are currently needed to accurately estimate ten-year CVD risk. Clearly, our data call for large-scale primary prevention programs to improve awareness and treatment of CVD.

## DISCLOSURES

This work is supported by Foundation LeDucq (Transatlantic Network, 2009-2014), the Netherlands CardioVascular Research Initiative (CVON2011-2016; Genius) and the European Union (Resolve: FP7-305707; TransCard: FP7-603091-2).

## REFERENCES

- Sacks FM, Pfeffer MA, Moya LA, et al. The effect of pravastatin on coronary events after myocardial infarction in patients with average cholesterol levels. Cholesterol and Recurrent Events Trial investigators. *N Engl J Med*. 1996;335:1001-9.
- Downs JR, Clearfield M, Weis S, et al. Primary prevention of acute coronary events with lovastatin in men and women with average cholesterol levels: results of AFCAPS/TexCAPS. Air Force/Texas Coronary Atherosclerosis Prevention Study. *JAMA*. 1998;279:1615-22.
- Tonstad S, Rosvold EO, Furu K, Skurtveit S. Undertreatment and overtreatment with statins: the Oslo Health Study 2000-2001. *J Intern Med*. 2004;255:494-502.
- Mantel-Teeuwisse AK, Verschuren WM, Klungel OH, et al. Undertreatment of hypercholesterolaemia: a population-based study. *Br J Clin Pharmacol*. 2003;55:389-97.
- Koopman C, Vaartjes I, Heintjes EM, et al. Persisting gender differences and attenuating age differences in cardiovascular drug use for prevention and treatment of coronary heart disease, 1998-2010. *Eur Heart J*. 2013;34:3198-205.
- Gamboa CM, Safford MM, Levitan EB, et al. Statin underuse and low prevalence of LDL-C control among U.S. adults at high risk of coronary heart disease. *Am J Med Sci*. 2014;348:108-14.
- Majumdar SR, Gurwitz JH, Soumerai SB. Undertreatment of hyperlipidemia in the secondary prevention of coronary artery disease. *J Gen Intern Med*. 1999;14:711-7.
- Johansen ME, Green LA, Sen A, Kircher S, Richardson CR. Cardiovascular risk and statin use in the United States. *Ann Fam Med*. 2014;12:215-23.
- Wiersma T, Smulders YM, Stehouwer CD, Konings KT, Lanphen J. Summary of the multidisciplinary guideline on cardiovascular risk management (revision 2011). *Ned Tijdschr Geneesk*. 2012;156:A5104.
- Saraf S, Ray KK. Guidelines in the USA, a viewpoint contrary to those guidelines in Europe, Canada, Britain and the International Atherosclerosis Society. *Curr Opin Lipidol*. 2014;25:413-7.
- Stolk RP, Rosmalen JG, Postma DS, et al. Universal risk factors for multifactorial diseases: LifeLines: a three-generation population-based study. *Eur J Epidemiol*. 2008;23:67-74.
- Mosca L, Linfante AH, Benjamin EJ, et al. National study of physician awareness and adherence to cardiovascular disease prevention guidelines. *Circulation*. 2005;111:499-510.
- Kotseva K, Wood D, De Backer G, et al. Cardiovascular prevention guidelines in daily practice: a comparison of EUROASPIRE I, II, and III surveys in eight European countries. *Lancet*. 2009;373:929-40.
- van den Haak P, Heintjes E, Plat AW, et al. Determination of non-treatment with statins of high risk patients in The Netherlands. *Curr Med Res Opin*. 2010;26:271-8.
- Stranges S, Guallar E. Cardiovascular disease prevention in women: a rapidly evolving scenario. *Nutr Metab Cardiovasc Dis*. 2012;22:1013-8.
- Hart RG, Eikelboom JW, Pearce LA. Sex, stroke, and atrial fibrillation. *Arch Neurol*. 2012;69:1641-3.