Prescribing behaviour according to Dutch and European guidelines on the management of hypercholesterolaemia (1992–1999)

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Keywords

guideline adherence, hydroxymethylglutaryl-CoA reductase inhibitors, hypercholesterolaemia

Received

10 May 2005

Accepted

12 December 2005

Published OnlineEarly

20 February 2006

Background

The success of the full implementation of a new guideline may depend on the observed discrepancy between daily medical practice developed before the release of the guideline and new treatment recommendations issued by the guideline.

Aim

To assess whether the initiation of statin treatment for primary prevention of cardiovascular disease in an elderly population was in agreement with guidelines.

Methods

Data were obtained from the Rotterdam Study, a prospective population-based cohort study consisting of 7983 subjects aged ≥ 55 years. In the period 1992–1999, all patients starting statins for primary prevention were selected. Treatment eligibility was established according to Dutch guidelines based on considerations of cost effectiveness (1998) and European guidelines based on clinical effectiveness (1998 and 2003).

Results

Only 5.7% [95% confidence interval (CI) 3.1, 8.3] of the 299 subjects starting statins for primary prevention met the eligibility criteria of the Dutch guidelines. Most patients (92.0%, 95% CI 88.9, 95.1) met the criteria of the 2003 European guidelines. Patients who did not meet any eligibility criteria were female and had one or less cardiovascular risk factor, except for two patients with total cholesterol levels < 5 mmol L⁻¹ prior to start of statin therapy.

Conclusions

The use of statins was in agreement with the most recent European guidelines in over 90% of elderly patients who started statins for primary prevention, but in only 6% of these patients according to the Dutch guidelines. As long as existing guidelines are as discrepant as they are now, variation in agreement between physicians' prescribing and guideline recommendations is unavoidable.

Introduction

Statins have proven to be safe and effective in reducing cardiovascular disease and total mortality [1]. In 2003, around 25 million people were treated with statins worldwide [2] and the economic burden associated with their use is considerable. Global statin sales are estimated at \$22 billion per year and will increase in future. In 2002, €286 million (£196 million) was spent on statins in the Netherlands, accounting for 7.7% of the total amount spent on pharmaceutical care [3].

The decision to start drug therapy is usually based on available clinical guidelines, a patient's needs, a physician's personal experience and new evidence emerging from clinical trials. In the case of the pharmacological treatment of hypercholesterolaemia, new and compelling evidence of the beneficial effects of statins has been published during the 1990s [4–10]. Revised guidelines on the management of hypercholesterolaemia including this new evidence are generally released after a few years' lag time. In the meantime, physicians may have adapted a certain prescribing behaviour that is not in accordance with these forthcoming guidelines.

Recently, two similar Dutch guidelines released in 1998 [11] and 1999 [12] and two European guidelines released in 1998 [13] and 2003 [14] were issued to guide the prescribing and use of lipid-lowering drugs. These guidelines differ substantially, not only because of the time lag between them, but also because Dutch guidelines include considerations of cost effectiveness and restrict lipid-lowering drug use to middle-aged high-risk patients [11, 12]. The success of the full implementation of any of these guidelines may depend on the observed discrepancy between adapted prescribing practice and recommended treatment eligibility by these guidelines.

The aim of the present study was to assess whether the start of statin therapy in an elderly population during the period 1992–1999 was in agreement with current Dutch and European guidelines on the management of hypercholesterolaemia in order to establish the extent to which physicians' prescribing behaviour would need to change to attain adherence to current guidelines. The treatment eligibility of patients with established cardiovascular diseases is barely questioned, unless their serum total cholesterol (Tc) level is $<5 \text{ mmol l}^{-1}$. Therefore, we restricted our analyses to primary prevention in people without a history of cardiovascular events.

Methods

Setting

Data were obtained from the Rotterdam Study, a population-based prospective cohort study, which started in March 1990. All 10 275 residents of the suburb

Ommoord in Rotterdam aged ≥ 55 years were invited to participate, of whom 7983 (78%) subjects participated in the baseline examination. Baseline examination during 1990–1993 included a home interview on demographics, current health status, medical history, cardiovascular risk factors and current use of medication. Height, weight and blood pressure were measured at the research centre and blood was drawn for DNA extraction and laboratory measurements, including serum total cholesterol and high-density lipoprotein cholesterol (HDL-C). The design of this study has been described in more detail elsewhere [15]. Second and third examination rounds were conducted between 1993 and 1995 and 1997 and 1999, respectively.

Validated data on stroke were available until March 1999 and major coronary events [myocardial infarction (MI), coronary artery bypass grafting (CABG) and percutaneous transluminal coronary angioplasty (PTCA)] and vital status were available until 31 December 1999. Pharmacy records were available for approximately 99% of the cohort as of 1 January 1991. Additionally, all outpatient serum cholesterol measurements ordered by physicians in the Rotterdam area were available as of 25 April 1997 via the Stichting Trombosedienst & Artsenlaboratorium Rijnmond (STAR).

Study population

All starters of statins, defined as subjects who had not received a lipid-lowering drug for at least 1 year before the first dispensing of a statin in our database, were identified in the period 1 January 1992 to 31 December 1999. Patients receiving statins for secondary prevention were excluded from the study population. This comprised subjects reporting a previous MI at baseline, subjects with a MI, CABG, PTCA or stroke during follow-up but prior to the start of statins, a history of two or more nitrate prescriptions as a marker for angina pectoris [16] and patients using a loop diuretic combined with an ACE inhibitor or angiotensin-II receptor blocker, indicating the presence of heart failure, which may be the consequence of prior coronary heart disease (CHD). For the remaining patients, we reviewed available hospital discharge letters and general practitioners' files for additional information on cardiovascular diseases, including peripheral arterial disease. Subjects were also excluded based on any relevant information obtained from these files.

The most recent Tc and HDL-C measurements prior to start of statin therapy were obtained for every patient from any of our available data sources (laboratory or examination rounds). Information on date of birth, gender, educational level, insurance and a family history of

cardiovascular disease was obtained from the baseline interview. Smoking status and body mass index were obtained from the closest examination which preceded the start of statin therapy. Diabetes mellitus was based on the use of insulin or oral antidiabetics and the self-reporting of diabetes during the examination rounds. Similarly, hypertension was based on the use of antihypertensive medication, and systolic and diastolic blood pressure as measured during the most recent visit to the research centre before starting statin therapy was obtained.

Guidelines on the management of hypercholesterolaemia
Treatment eligibility at the start of statin therapy was established according to two different guidelines. First, we used the Dutch national guidelines [11, 12], which indicate pharmacological treatment for primary prevention:

- 1 In case of familial hypercholesterolaemia (FH), which is suspected if Tc levels exceed 8 mmol l^{-1} . Patients with $\text{Tc} > 8 \text{ mmol l}^{-1}$ should be referred to a lipid clinic for further diagnostics and individual treatment strategies.
- 2 when $\text{Tc} > 5 \text{ mmol l}^{-1}$ and the absolute level of 10-year CHD risk exceeds an age- and gender-specific cut-off point, ranging from 25 to 40%. These cut-off points are based on considerations of cost effectiveness with a maximum expenditure of approximately €18 000 (£12 300) per life year saved. Restricted use of statins in elderly patients is advocated, because start of statin therapy is considered not to be cost-effective in men over 70 years of age and women older than 75 years.

The Framingham risk function is used to estimate the 10-year risk of CHD (consisting of MI and CHD death plus angina pectoris and coronary insufficiency) for persons aged 30–74 years. The Framingham risk function includes gender, age (years), systolic blood pressure (SBP) (mmHg), the Tc/HDL-C ratio, diabetes (yes/no), smoking (yes/no) and ECG-left ventricular hypertrophy (ECG-LVH; yes/no) [17]. Since we had no valid information on ECG-LVH, all patients were considered not to have ECG-LVH. Pharmacological treatment for hypercholesterolaemia is indicated for those aged between 40 and 60 years if the absolute 10-year risk is $> 25\%$, for those aged between 60 and 70 years if the 10-year risk is $> 30\%$ and above age 70 if the 10-year risk is $> 40\%$ (men) or $> 35\%$ (women). These levels are 5% lower in patients with diabetes mellitus or a family history of CHD (CHD in parents < 60 years).

Since we had no additional information on a patient's genetic profile, we could not distinguish between 'true'

FH and those who had high Tc levels from other causes. We therefore chose to perform multiple analyses. First, we assumed that none of the patients with Tc levels $> 8 \text{ mmol l}^{-1}$ had FH and treatment eligibility was established using the risk charts for all patients. Then we conducted a second analysis assuming that statin therapy was also appropriate in all patients with Tc levels $> 8 \text{ mmol l}^{-1}$.

We also established treatment eligibility according to the European guidelines as published in 1998 [13] and 2003 [14]. The 1998 guidelines promote statin therapy in high-risk individuals whose 10-year risk of nonfatal or fatal CHD exceeds 20%. These guidelines use Tc levels instead of the Tc/HDL-C ratio as do the Dutch guidelines. SBP is presented as a continuous variable and no specific categories exist for patients already using antihypertensive drugs. In patients using antihypertensive medication at the time of blood pressure measurement, we assumed that they had a drug-free SBP of 180 mmHg (the maximum blood pressure used in the chart). No restrictions were set on age in these guidelines. The 2003 guidelines recommend statin therapy in subjects with multiple risk factors and a 10-year risk of fatal cardiovascular disease exceeding 5%, in persons with a markedly raised level of a single risk factor (i.e. total cholesterol $\geq 8 \text{ mmol l}^{-1}$) and in all patients with diabetes mellitus. Although the cardiovascular risk function is derived from the Systematic Coronary Risk Evaluation (SCORE) database, it includes the same cardiovascular risk factors as the Framingham risk function.

Statistical analysis

The proportion of patients starting statin treatment was established in each calendar year. To calculate this proportion, the number of patients starting statin treatment was divided by the number of patients alive and without a history of statin treatment in the study cohort.

Prevalences of statin use in agreement with different guidelines and their 95% confidence intervals (CI) were calculated. The distribution of patient characteristics was compared between those eligible for statin use and those non-eligible according to any guideline. The Mann–Whitney *U*-test was used to compare mean age and mean serum cholesterol levels and a χ^2 test was used to compare frequency distributions. Additionally, treatment eligibility was assessed in different strata. A χ^2 test was used to test for significant differences within strata.

Results

In the period 1992–1999, 789 elderly patients started statin therapy. Figure 1 shows the proportion of patients

Figure 1

Incidence of statin treatment per calendar year (1992–1999). Primary prevention (■), secondary prevention (□)

starting statin treatment in each calendar year. In secondary prevention, an increase in treatment was observed especially after the publication of landmark trials in 1994 and 1995, whereas treatment for primary prevention increased gradually throughout the study period.

Of the 789 subjects starting statin therapy, 410 (52.0%) patients received statins for secondary prevention, 40 patients had used nonstatin lipid-lowering drugs prior to the start of statin therapy, in 23 subjects we lacked information on cholesterol levels, and 17 patients started statin therapy before their first visit to the research centre. Therefore, 299 patients remained for the analyses. Characteristics of these patients at the start of statin therapy are shown in Table 1. More women (71.9%) than men (28.1%) started statins for primary prevention. Average Tc levels were high, but only 14.4% had a Tc/HDL-C ratio >8.0 . Cholesterol measurements ordered by specialists within the clinic were not available and outpatient measurements were available only as of March 1997. Therefore, we had to rely on laboratory measurements during the examination rounds in many cases, which led to relatively long periods between measurements and start of therapy. The median for the period between the measurement of serum lipid levels and the start of statins was 477 days (range 1–3288) and 87 patients (29.1%) had a cholesterol measurement within 90 days before the start of statin therapy.

Only 17 of the 299 patients starting statin therapy met the eligibility criteria of the Dutch guidelines (5.7%; 95% CI 3.1, 8.3). If use of statins was also considered appropriate in all patients with Tc levels >8 mmol L^{-1}

(because of possible FH), 44.1% of the starters with statin therapy met the eligibility criteria (Table 2). In approximately two-thirds of the study population (64.5%) the start of statin therapy was justified by the European guidelines as released in 1998. Finally, in 92.0% the start of statin therapy was in agreement with the most recent European guidelines on the management of hypercholesterolaemia. When we restricted all our analyses to patients with serum cholesterol measurements within a 90-day period before the start of statin therapy, we observed similar results compared with the main analyses.

A total of 24 patients (8.0%) starting statin therapy did not meet the eligibility criteria of any guideline according to our data. Two patients (8.3%) had many cardiovascular risk factors but Tc levels ≤ 5.00 mmol L^{-1} (or ≤ 4.50 mmol L^{-1} in case of diabetes, according to the 2003 European guidelines). All of the non-eligible patients with Tc >5.00 mmol L^{-1} were women and none of these patients had diabetes mellitus or hypertension (Table 3). Compared with those eligible according to the 2003 European guidelines, these 22 patients were younger ($P = 0.006$) and had lower Tc levels ($P = 0.003$). There was a tendency to lower Tc/HDL-C ratios ($P = 0.16$) and less frequent current smoking ($P = 0.18$) in these patients.

In Table 4, the proportion of use in agreement with the Dutch guidelines and the most recent European guidelines (2003) is stratified by different baseline characteristics. The proportion of appropriate use was higher in men than in women, although this was not statistically significant when applying the Dutch guidelines

Table 1

Characteristics of elderly patients starting statin therapy for primary prevention between 1992 and 1999 ($n = 299$)

Characteristic	<i>n</i> (%) [*]
Female	215 (71.9%)
Age, mean (SD)	67.4 (6.3)
Highest education level	
– primary school	94 (32.0%)
– secondary school	167 (56.8%)
– college/university	33 (11.2%)
Statin used at start of therapy	
– simvastatin	214 (71.6%)
– pravastatin	33 (11.0%)
– fluvastatin	26 (8.7%)
– atorvastatin	25 (8.4%)
– cerivastatin	1 (0.3%)
Insurance	
– sick fund	168 (56.4%)
– private	130 (43.6%)
Total cholesterol level, mean (SD), mmol l ⁻¹	8.1 (1.4)
– ≤5.0	2 (0.7%)
– 5.1–8.0	159 (53.2%)
– >8.0	138 (46.2%)
HDL-cholesterol level, mean (SD), mmol l ⁻¹	1.4 (0.4)
– ≤1.0	45 (15.1%)
– 1.1–1.4	146 (48.8%)
– >1.4	108 (36.1%)
Tc/HDL ratio, mean (SD)	6.3 (2.1)
– ≤5.0	72 (24.1%)
– 5.1–8.0	184 (61.5%)
– >8.0	43 (14.4%)
Hypertension	159 (53.2%)
– Use of antihypertensive medication	138 (86.8%) [†]
Diabetes mellitus	28 (9.4%)
– Diet only	5 (17.9%) [‡]
Family history of CHD§	91 (30.4%)
Smoking status	
– current smoker	65 (21.7%)
– former smoker	124 (41.5%)
– never smoked	100 (36.8%)
BMI, kg m ⁻²	
– ≤25	95 (32.9%)
– >25	194 (67.1%)

^{*}Unless otherwise specified. SD, Standard deviation; HDL, high-density lipoprotein; Tc, total cholesterol; CHD, coronary heart disease; BMI, body mass index. [†]Percentage of those with hypertension. [‡]Percentage of those with diabetes mellitus. [§]CHD in parents, siblings or offspring ≤65 years.

($P = 0.21$). We did not observe any differences between calendar years. Patients with college or university education were more often appropriately treated compared with patients with lower education, but only when using

the Dutch guidelines. Patients with a high Tc/HDL-C ratio, patients with diabetes mellitus and current smokers were more frequently appropriately treated with statins when using these guidelines. The same trend was observed for the European guidelines, but differences within strata were no longer statistically significant. When applying these European guidelines, patients with hypertension were more likely to be appropriately treated compared with patients without hypertension.

Discussion

In this study, the start of statin therapy for primary prevention in elderly patients during the period 1992–1999 was compared with eligibility criteria of Dutch and European guidelines which were released at the end of the study period and after the study period, respectively. The start of statins was frequently not in accordance with the Dutch guidelines on the management of hypercholesterolaemia. Even when we considered statin use appropriate in all patients with Tc levels >8 mmol l⁻¹, less than half of patients starting statins were eligible for treatment. However, over 90% of patients were eligible for the treatment of hypercholesterolaemia according to the European guidelines as issued in 2003. Patients not eligible according to any guideline included only a few patients with Tc levels ≤5.00 mmol l⁻¹ (or ≤4.50 mmol l⁻¹ in case of diabetes mellitus) and women with 0 or 1 cardiovascular risk factor.

The clinical implications of the results of the present study could be considerable for the current and future prescribing of statins for primary prevention in elderly patients. During the 1990s, physicians may have focused on initiating statin therapy in patients with high cholesterol levels but with a limited number of other cardiovascular risk factors, as was advocated by previous Dutch guidelines [18]. However, current Dutch guidelines are based on considerations of cost effectiveness, excluding men >70 years and women >75 years from therapy and restricting lipid-lowering therapy to younger patients at high 10-year risk of CHD. Even when we assumed that all patients with Tc levels >8 mmol l⁻¹ had FH, the start of statin therapy was in agreement with Dutch guidelines in less than half of the patients in our study population. However, this proportion will have been overestimated, because the prevalence of FH is only 1 in 400 [19]. Full implementation of current Dutch guidelines would therefore require a significant change in physicians' prescribing behaviour. The continuation of the medical practice as observed during our study period in more recent years would lead to a substantial overtreatment of elderly patients for primary prevention.

Table 2

Appropriateness of statin therapy in primary prevention in elderly patients according to different guidelines

	All patients (<i>n</i> = 299) % appropriate use (95% CI)	Patients with a recent cholesterol measurement* (<i>n</i> = 87) % appropriate use (95% CI)
Dutch guidelines 1998/1999 [11,12]		
1. Main analysis	5.7% (3.1, 8.3)	4.6% (0.2, 9.0)
2. First analysis + use appropriate in all patients with Tc >8 mmol l ⁻¹	44.1% (38.5, 49.8)	32.2% (22.4, 42.0)
European guidelines 1998 [13]	64.5% (59.1, 70.0)	67.8% (58.0, 77.6)
European guidelines 2003 [14]	92.0% (88.9, 95.1)	92.0% (86.2, 97.7)

*Cholesterol measurements within 90 days before start statin therapy. CI, Confidence interval; Tc, total cholesterol.

Table 3Patient characteristics of patients with serum total cholesterol levels >5.00 mmol l⁻¹ not meeting the eligibility criteria for lipid-lowering therapy according to any guideline on the management of hypercholesterolaemia (*n* = 22)

Characteristic	<i>n</i> (%)*
Female	22 (100%)
Age, mean (SD)	64.1 (5.6)
Total cholesterol level, mean (SD), mmol l ⁻¹	7.5 (0.4)
HDL-cholesterol level, mean (SD), mmol l ⁻¹	1.4 (0.4)
Tc/HDL ratio, mean (SD)	5.6 (1.5)
Hypertension	0 (0%)
Diabetes mellitus	0 (0%)
Family history of CHD†	7 (31.8%)
Smoking status	
– current smoker	2 (9.1%)
– former smoker	10 (45.5%)
– never smoked	10 (45.5%)

*Unless otherwise specified. SD, Standard deviation; HDL, high-density lipoprotein; Tc, total cholesterol; CHD, coronary heart disease. †CHD in parents, siblings or offspring ≤65 years.

Benefits of statins have now been demonstrated across a wide range of patient subpopulations [9, 10, 20]. The European guidelines as released in 1998 were based on evidence as accumulated during our study period. In approximately two-thirds of the elderly patients starting statins for primary prevention, statins

were used in accordance with these guidelines. Although statins have proven to be effective in over 90% of patients starting statins in our population according to the most recent European guidelines, most of these pivotal trial results were published after 1999. Only a slight change in physician prescribing behaviour would be needed to obtain full adherence to these European guidelines, i.e. start of statin therapy in women with moderately raised cholesterol levels but with a minimal number of additional cardiovascular risk factors should be carefully considered. Setting priorities, however, is necessary to avoid the unrealistic and undesirable alternative: infinite healthcare costs [21], and future Dutch guidelines will probably again include some considerations of cost effectiveness. In addition, resources are urgently needed for the treatment of patients at high risk of cardiovascular disease. Undertreatment of hypercholesterolaemia is a widespread phenomenon in the Netherlands, as in other countries [22, 23].

Physicians may perceive a variety of barriers keeping them from adherence to guidelines [24]. Lack of agreement with the concept of a specific guideline is one of the barriers that may undermine physician adherence. This could be the case for guidelines including considerations of cost effectiveness, because this concept remains controversial. Therefore, medical doctors may not rigidly apply these recommendations in daily medical practice. They often consider the personal physician–patient relationship as most important, which may add to the prescribing of statins to patients with high cholesterol levels regardless of considerations of cost effectiveness. Physicians might feel that it is not ethical to apply cost-effectiveness criteria to individual patients

Table 4

Proportion of appropriate statin use according to the Dutch guidelines (1998) and the most recent European guidelines (2003) among elderly patients starting statin therapy for primary prevention, stratified by different baseline characteristics

Baseline characteristic	Dutch guidelines % (95% CI)	European guidelines % (95% CI)
Overall	5.7% (3.1, 8.3)	92.0% (88.9, 95.1)
Gender		
– male	8.3% (2.4, 14.2)	98.8% (96.5, 100)*
– female	4.7% (1.8, 7.5)	89.3% (85.2, 93.4)*
Calendar year		
– 1992–95	4.8% (1.3, 8.3)	93.2% (89.1, 97.2)
– 1996–99	6.5% (2.6, 10.5)	90.8% (86.3, 95.4)
Education		
– primary school	2.1% (0–5.0)*†	95.7% (91.7, 99.8)
– secondary school	5.4% (2.0–8.8)*†	90.4% (86.0, 94.9)
– college/university	18.2% (5.0, 31.3)*	90.9% (81.1, 100)
Insurance		
– sick fund	3.6% (0.8, 6.4)	89.9% (85.3, 94.4)
– private	8.5% (3.7, 13.2)	94.6% (90.7, 98.5)
Tc/HDL ratio		
– ≤8	3.9% (1.5, 6.3)*	91.0% (87.5, 94.5)
– >8	16.3% (5.2, 27.3)*	97.7% (93.2, 100)
Diabetes mellitus		
– no	1.8% (0.2, 3.4)*	91.5% (88.2, 94.8)
– yes	42.9% (24.5, 61.2)*	96.4% (89.6, 100)
Smoking status		
– current smoker	13.8% (5.4, 22.2)*	95.4% (90.3, 100)
– former smoker	4.0% (0.6, 7.5)*‡	91.9% (87.1, 96.7)
– never smoked	2.7% (0, 5.8)*‡	90.0% (84.4, 95.6)
Hypertension		
– no	5.0% (1.4, 8.6)	84.3% (78.3, 90.3)*
– yes	6.3% (2.5, 10.1)	98.7% (97.0, 100)*
Family history of CHD§		
– no	3.8% (1.2, 6.5)*	92.3% (88.7, 95.9)
– yes	9.9% (3.8, 16.0)*	91.2% (85.4, 97.0)
BMI, kg m ⁻²		
– ≤25	3.2% (0, 6.7)	93.7% (88.8, 98.6)
– >25	6.2% (2.8, 9.6)	91.2% (87.3, 95.2)

CI, Confidence interval; Tc, total cholesterol; HDL, high-density lipoprotein; CHD, coronary heart disease; BMI, body mass index. *Significant difference ($P < 0.05$) in the proportions appropriate use within the stratum. †No significant difference between 'primary school' and 'secondary school'. ‡No significant difference between 'former smoker' and 'current smoker'. §CHD in parents, siblings or offspring ≤65 years.

for whom the effectiveness of lipid-lowering drug use has been established. Moreover, recommended pharmacotherapeutic handbooks and the formal product information mostly endorse the treatment of hypercholesterolaemia regardless of concomitant cardiovascular risk factors. Interventions to implement guidelines based on cost-effectiveness considerations should take these important considerations into account.

Several other issues may explain the observed discrepancies between guideline recommendations and

daily medical practice. After the study period, important information on the effectiveness of lipid-lowering drug use in elderly patients became available [9, 20]. Physicians may have started to treat elderly patients with statins in anticipation of these results. Furthermore, public awareness and understanding of cholesterol as a risk factor, although still far from optimal, has steadily increased [21]. Well-informed patients may put pressure on their physician to initiate statin treatment regardless of considerations of cost effectiveness.

We focused on statin use for primary prevention in the present study, because patients with previous cardiovascular events are all eligible for statin therapy, unless their Tc level is below 5.00 mmol l⁻¹ [11, 13, 14]. Information on cardiovascular disease was obtained from multiple sources. Case identification of patients with major coronary events and stroke during follow-up is virtually complete in the Rotterdam Study, and all case diagnoses have been validated. Pharmacy records were used to establish possible angina pectoris [16] and heart failure. Additionally, we checked available hospital discharge letters and general practitioners' files for further information. Using this strategy, we excluded all patients eligible for secondary prevention.

Treatment eligibility was established according to different guidelines, but all of them used the same cardiovascular risk factors to calculate the 10-year risk of nonfatal or fatal cardiovascular events. Although the mean period between the measurement of serum lipid levels and the start of statins was 708 days, restriction of our analyses to patients with cholesterol measurements within 90 days of start of statins did not change the results of our main analysis. Although the European guidelines specify a markedly raised low-density lipoprotein (LDL)-C (≥ 6 mmol l⁻¹) in asymptomatic subjects as a priority for treatment, we could not establish treatment eligibility according to this criterion because LDL-C measurements were not part of the routine laboratory measurements in the Rotterdam study. In addition, outpatient measurements ordered by physicians seldom included LDL-C because the measurement of a full lipid profile is not recommended by the Dutch guidelines. However, these patients will usually also have a markedly raised level of serum Tc levels.

Pharmacy records were used to establish the presence of hypertension. In patients not using antihypertensive drugs, systolic and diastolic blood pressure were obtained from the cross-sectional examinations at the research centre. In case the time period between the visit to the research centre and the start of statin therapy was long, these blood pressures may no longer be a valid proxy of current blood pressure. However, physicians starting lipid-lowering drug use will frequently also measure a patient's blood pressure and will consider concomitant start of antihypertensive therapy. In patients using antihypertensive drugs, we assumed their pretreatment SBP to be at the upper end of the blood pressure scale. This may have overestimated the number of patients using statins in accordance with both European guidelines.

For the presence of diabetes mellitus, we also mainly relied on pharmacy records. We may have missed some

patients with newly diagnosed diabetes mellitus treated with diet only, although we obtained data on this at baseline and during the second examination. Smoking status was ascertained during each examination round. We may have classified some patients as smokers who had just quit smoking. Misclassification of smoking status would have overestimated the number of patients using statins in accordance with any guideline. Another possible limitation of our study is that it was conducted at only one site, which may limit the generalizability of our results. However, the incidence rate of lipid-lowering drug use in our study population is comparable to the incidence rate as measured in elderly patients in the general Dutch population [25] and in older US adults [26] in the same period of time.

In conclusion, in over 90% of the elderly patients who started statins for primary prevention of cardiovascular disease, use of statins was in accordance with the most recent European guidelines. However, when the Dutch guidelines based on strict considerations of cost effectiveness were applied, appropriateness of statin use decreased to 6%. As long as existing guidelines are as discrepant as they are now, variation in agreement between physicians' prescribing and guideline recommendations is unavoidable. Whether a substantial change in prescribing behaviour is needed depends on which guideline will be preferred by healthcare policy makers.

We gratefully acknowledge J. Heeringa for carefully reading the manuscript.

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