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# Use of cholesterol lowering drugs could be improved further:

## Results from the National FINRISK 2007 Study

### Background

The aim of this study was to assess the changes in serum cholesterol levels since 1982 among the general population and in different patient groups in Finland, and to evaluate actual use of prescribed cholesterol lowering medication, its use in specific patient groups, and the achievement of therapeutic levels.

### Methods

The subject material consisted of people from six areas in Finland who had participated in the National FINRISK Study since 1982. The sample comprised the population between the ages of 25 and 64 years. In addition, in the last study year, 2007, people aged 65 to 74 were included.

### Results

In patients with a history of myocardial infarction, the total serum cholesterol level decreased by 32% from 1982 to 2007, while in the total population the decrease was 15%. Twenty percent of 35 to 75 year-old men and 17% of women of the same age used cholesterol lowering medication in 2007. Of patients with coronary heart disease, 70% used cholesterol lowering medication. Use of cholesterol lowering medication was most common among those who had undergone bypass surgery (92%). About one in four patients on cholesterol lowering medication had serum cholesterol levels higher than 5 mmol/l. As the medication was estimated to lower cholesterol levels on average by 25%, 67% of men with no coronary heart disease and taking cholesterol lowering medication would have a higher than 10% risk of developing coronary heart disease or having a stroke within the next ten years, the corresponding rate in women being 33%.

### Conclusions

There are still patient groups among the general population that would benefit from starting cholesterol lowering medication. Existing medication should be intensified to achieve therapeutic levels and thus to prevent arterial disease events as effectively as possible. Estimation of total risk would help to direct medication to those who would benefit most.

According to statistics kept by the Social Insurance Institution of Finland (Kela), the use of cholesterol lowering drugs, particularly statins, has increased clearly within the last few years. Kela statistics from 2006 show that 516,745 people received reimbursement from health insurance either for statins or for other cholesterol lowering drugs (1). Due to their clearly proved health benefits, these drugs have been recommended for secondary prevention for practically all patients with arterial disease as well as for primary prevention for high-risk patients (2). The most recent meta-analysis (3) confirms former data showing that statins also benefit women, the elderly, and people with diabetes, even if they would not have clinically manifest arterial disease yet. The National FINRISK Study per-

formed in 2007 makes it possible to assess the use of pharmacotherapy in various patient groups and the realization of therapeutic recommendations at the population level in Finland.

### Material and methods

Since 1982, representative samples of people ranging in age from 25 to 64 years have been studied every five years in the provinces of North Karelia and Kuopio and in the Turku and Loimaa regions. Studies were started in the Helsinki-Vantaa region in 1992 and in the province of Oulu in 1997. The sample was stratified by age and gender. In each study region, 125–500 representatives of each ten-year age cohort of men and women were included in the sample. In 2007, 61% of the men and 71% of the women invited in-

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#### Literature

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to the study participated. In that year, the subject group was extended to cover people ranging from 65 to 74 years of age. As the use of statins is extremely rare in the 25 to 34 year-old age group, most of the analyses concerning medication were made for subjects 35 to 74 years of age.

Questionnaires and attached letters of invitation to a health examination at the nearest health center were sent to subjects at their home address. The subjects were asked to take the completed questionnaire with them to the examination. The cholesterol and HDL-cholesterol levels contained in blood samples drawn during the examination were analyzed at the National Public Health Institute Laboratory of Analytical Biochemistry. An enzymatic method was used to de-

termine cholesterol levels and a direct enzymatic method to determine HDL-cholesterol levels. Information on diseases and medication was obtained by the questionnaire. People who had taken antihypertensive medication during at least the preceding week were classified as hypertensive, and those who took insulin or other antidiabetic medication were classified as diabetics. The study methods are described in more detail elsewhere (4). The total risk was calculated using the FINRISK calculator (5).

## Results

The serum cholesterol levels of people with a history of myocardial infarction have decreased greatly over the last few decades. In 1982, the average cholesterol level of patients with a history of myocardial infarction was 6.78 mmol/l, while in 2007 it was only 4.58 mmol/l (Figure 1). In people with no history of infarction, the serum cholesterol levels declined from 6.30 mmol/l in 1982 to an average of 5.36 mmol/l in 2007.

FINRISK Studies have inquired into the use of cholesterol lowering medication since 1992. In patients with a history of infarction and taking medication, the cholesterol levels have decreased considerably, from 5.7 mmol/l in 1992 to 4.39 mmol/l in 2007. In those with a history of infarction but not taking cholesterol lowering medication, the cholesterol levels changed in the same way as in those with no history of infarction.

The average cholesterol levels in the population were 6.11 mmol/l in 1982 and 5.22 mmol/l in 2007. The decrease amounted to 0.89 mmol/l, i.e., 15%. Assuming that statins have lowered cholesterol levels by 25% in all those taking the medication, the average cholesterol level in the 25 to 64 year-old population not taking cholesterol lowering medication would now be 5.32 mmol/l. Cholesterol lowering medication in its current form has thus reduced the average cholesterol level in the population by 0.10 mmol/l.

Serum cholesterol levels were below 5 mmol/l in slightly less than 80% of those with a history of myocardial infarction or who had undergone either bypass surgery or balloon angioplasty (Table 1), and in 63% of those taking insulin or oral antidiabetic medication. The situation was worst in patients with hyperten-

FIGURE 1

### Serum cholesterol levels in patients with a history of myocardial infarction and in other people aged 35–65.

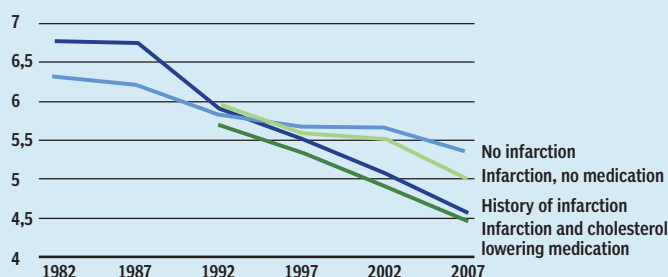


TABLE 1.

### Distribution (%) of 35 to 74 year-old patients with cardiovascular disease and diabetes according to serum cholesterol level in the National FINRISK 2007 Study.

| Disease background          | n     | Serum cholesterol level, mmol/l |         |         |      |
|-----------------------------|-------|---------------------------------|---------|---------|------|
|                             |       | < 5 %                           | 5–5.9 % | 6–6.9 % | 7– % |
| Myocardial infarction       | 138   | 73                              | 18      | 8       | 1    |
| Bypass operation            | 82    | 79                              | 17      | 4       | 0    |
| Balloon angioplasty         | 79    | 77                              | 19      | 4       | 0    |
| Effort angina               | 172   | 60                              | 28      | 10      | 2    |
| Antidiabetic medication     | 219   | 63                              | 27      | 6       | 4    |
| Antihypertensive medication | 1,253 | 45                              | 36      | 15      | 4    |
| Total study population      | 5,232 | 37                              | 38      | 19      | 6    |

sion, of whom only 45% had cholesterol levels below 5 mmol/l.

Among those participating in the study, 20% of 35 to 74 year-old men and 17% of women of the same age used cholesterol lowering medica-

tion (Table 2). Cholesterol lowering medication was more commonly used by working-age men than women. In the oldest age cohort, the difference in the use of cholesterol lowering medication between men and women was slight. Of those taking such medication, 37% had serum cholesterol levels of 5 mmol/l or higher.

Cholesterol lowering medication was taken very much as prescribed by those who had a history of myocardial infarction or who had undergone balloon angioplasty or bypass operation (Table 3). In this group, the mean serum cholesterol level was 4.4 mmol/l, and the level exceeded 5 mmol/l in only about 20%. Half of the patients with diabetes and 38% of those with hypertension took cholesterol lowering medication.

The FINRISK calculator was used to assess the risk of coronary heart disease or stroke within the next ten years in people taking cholesterol lowering medication and with no history of coronary heart disease (Table 4). For risk calculation, their cholesterol levels were increased by 25%, which was considered to be

TABLE 2

**Shares of people on cholesterol lowering medication by age group, their average cholesterol levels, and shares of patients on medication with cholesterol level 5 mmol/l or higher.**

|                                | Age, years |       |       |       | Total |
|--------------------------------|------------|-------|-------|-------|-------|
|                                | 35-44      | 45-54 | 55-64 | 65-74 |       |
| <b>Men (n = 2,683)</b>         |            |       |       |       |       |
| On medication, %               | 4          | 10    | 27    | 34    | 20    |
| Mean cholesterol level, mmol/l | 5.0        | 4.8   | 4.7   | 4.5   | 4.6   |
| ≥ 5 mmol/l, %                  | 41         | 33    | 37    | 25    | 31    |
| <b>Women (n = 2,941)</b>       |            |       |       |       |       |
| On medication, %               | 1          | 4     | 17    | 31    | 14    |
| Mean cholesterol level, mmol/l | 5.8        | 5.3   | 5.1   | 4.9   | 5.0   |
| ≥ 5 mmol/l, %                  | 75         | 57    | 52    | 37    | 44    |
| <b>Total (n = 5,624)</b>       |            |       |       |       |       |
| On medication, %               | 3          | 7     | 22    | 33    | 17    |
| Mean cholesterol level, mmol/l | 5.2        | 4.9   | 4.9   | 4.7   | 4.8   |
| ≥ 5 mmol/l, %                  | 50         | 41    | 43    | 31    | 37    |

TABLE 3.

**Distribution (%) of 35- to 74-year-old patients with cardiovascular disease according to cholesterol lowering medication and serum cholesterol level in the National FINRISK 2007 Study.**

| Disease background                  | n     | On cholesterol lowering medication % | On cholesterol lowering medication |                     | No cholesterol lowering medication |                     |
|-------------------------------------|-------|--------------------------------------|------------------------------------|---------------------|------------------------------------|---------------------|
|                                     |       |                                      | S-Chol mean mmol/l                 | S-Chol ≥ 5 mmol/l % | S-Chol mean mmol/l                 | S-Chol ≥ 5 mmol/l % |
| Myocardial infarction               | 153   | 80                                   | 4.4                                | 20                  | 5.3                                | 53                  |
| Bypass operation                    | 88    | 92                                   | 4.3                                | 18                  | 5.0                                | 60                  |
| Balloon angioplasty                 | 89    | 89                                   | 4.4                                | 20                  | 5.1                                | 50                  |
| Effort angina                       | 172   | 61                                   | 4.6                                | 29                  | 5.3                                | 58                  |
| Coronary heart disease <sup>1</sup> | 348   | 70                                   | 4.4                                | 21                  | 5.3                                | 53                  |
| No coronary heart disease           | 4,914 | 13                                   | 4.9                                | 42                  | 5.5                                | 68                  |
| Stroke                              | 172   | 51                                   | 4.5                                | 23                  | 5.5                                | 72                  |
| Diabetes                            | 247   | 51                                   | 4.3                                | 23                  | 5.2                                | 51                  |
| Hypertension                        | 1,366 | 38                                   | 4.7                                | 30                  | 5.5                                | 70                  |

<sup>1</sup> coronary heart disease = myocardial infarction or bypass operation or balloon angioplasty or effort angina

TABLE 4.

**Risk of myocardial infarction or stroke within the next ten years in people with cholesterol lowering medication but no coronary heart disease or stroke.**

To calculate the risk, the cholesterol level was increased by the estimated average effect of medication, 25%.

|              | Risk of disease by age group |               |               |         |
|--------------|------------------------------|---------------|---------------|---------|
|              | 35-54 years %                | 55-64 years % | 65-74 years % | Total % |
| <b>Men</b>   |                              |               |               |         |
| Risk 0-4.9%  | 63                           | 3             | 0             | 14      |
| Risk 5-9.9%  | 26                           | 33            | 1             | 19      |
| Risk 10+%    | 11                           | 64            | 99            | 67      |
| Total        | 100                          | 100           | 100           | 100     |
| n            | 65                           | 122           | 146           | 312     |
| <b>Women</b> |                              |               |               |         |
| Risk 0-4.9%  | 86                           | 56            | 8             | 33      |
| Risk 5-9.9%  | 14                           | 30            | 40            | 34      |
| Risk 10+%    | 0                            | 14            | 51            | 33      |
| Total        | 100                          | 100           | 100           | 100     |
| n            | 35                           | 103           | 179           | 317     |

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**Financial ties:**

Erkki Vartiainen, Tiina Laatikainen, Veikko Salomaa, Pekka Jousilahti have not reported any financial ties. Timo Strandberg has made presentations at events organized by pharmaceutical companies, has participated in congresses abroad at the expense of pharmaceutical companies, and has received research grants from pharmaceutical companies.

the average effect of cholesterol lowering medication. The risk of disease was higher than 10% in 67% of men and 33% of women.

**Discussion**

Among Finns, serum cholesterol levels have decreased since the early 1970s. The decrease from 1982 amounts to 0.89 mmol/l. If we assume that cholesterol lowering medication lowers the levels by about 25%, medication (mostly statins) can be estimated to have decreased cholesterol levels among the 25 to 64 year-old population by 0.10 mmol/l. Most of the cholesterol level reduction in this age group has been due to changes in diet. This effect has been highly significant. In the older age group, those 65 to 74 years of age where the use of cholesterol lowering medication is more common than among those in younger age groups, the significance of medication is higher than can be estimated on the basis of population samples available since 1982. If we assume that the change in the 65 to 74 age group would have been similar to that in the 25 to 64 year-old age group, the effect on average cholesterol level would be 0.17 mmol/l in the 25 to 74 year-old age group 0.38 mmol/l and in the oldest age group, those 65 to 74 years old.

Little data are available on how much statins reduce cholesterol levels in normal clinical situations. The general impression is that, for several reasons (patient motivation, low doses), they are clearly less effective than in clinical studies and even in such studies the effects of statins vary widely, depending on dose and medicine (6). The average effect of 25% used for calculations is therefore only an estimate. The effect of the medication and, consequently, the effect on population level cholesterol values may be either greater or lower. This analysis aims to provide an estimate of effects at the population level and cannot be used to deduce that the effects of statins on the Finnish population are precisely these.

The effects on population level cholesterol values found in the present study appear modest, but it must be remembered that the usefulness of statins against slowly developing arterial changes is not determined only by how much cholesterol levels decrease but also by how systematic and how long the treatment is. According to a Finnish register study, the ten-year per-

sistence with statin therapy is as low as 44% (7), which undoubtedly reduces the benefits of the treatment. Evidence that focused statin therapy truly does have significant effects on end points at the population level is gradually beginning to accumulate. A recent Dutch analysis shows that the risk of myocardial infarction in patients with familial hypercholesterolemia (and probably good compliance) treated with a statin for up to about 20 years is no longer significantly different from that for the rest of the population (8). It would thus seem possible to eliminate a harmful genetic effect by means of statin therapy. A population-level cohort study performed within the Israeli health care system suggests that total mortality among those taking statins as prescribed is lower in both primary and secondary prevention than among those taking less medicine than prescribed (9).

According to the present study, Finnish patients with coronary heart disease take their cholesterol lowering medication pretty much as prescribed, but in a notable proportion of them the cholesterol levels do not meet the targets defined in therapeutic guidelines to stop the atherosclerotic process. If a target level of below 4.0 mmol/l is applied for such high-risk patients, the situation appears even worse. There are still groups of patients that would benefit from secondary prevention, in particular, with cholesterol lowering medication. Therapeutic cholesterol levels should be achieved in a greater proportion of those taking medication. The results are very similar to those obtained in the EUROASPIRE III Study (10) and in a study based on the Hospital Discharge Register and Kela's Drug Reimbursement Register (11). Most patients (about 75%) taking cholesterol lowering medication are patients other than those with coronary heart disease. Even in this group, the FINRISK calculator shows that medication appears to be quite well targeted to those with high risk. In younger age groups, the absolute ten-year risk of disease is naturally small and the need for medication should be assessed on the basis of relative risk or risk at the age of 60.

Whether used for secondary or primary prevention, statins have been shown to affect morbidity in every significant subgroup of men and postmenopausal women and in patients with or without arterial disease and with or without di-

### What was known before

- More than half a million Finns use cholesterol lowering drugs.

### What the study taught

- Use of medication for secondary prevention has been fairly successful even though therapeutic cholesterol levels have not always been achieved.
- In patients with coronary heart disease, serum cholesterol levels have decreased considerable over the decades.
- Some patients with coronary heart disease do not take cholesterol lowering medication even though they might benefit from it.
- By intensifying the assessment of total risk, medication could be targeted at those benefitting most from it.

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abetes (2,3). The benefit appears to be related to the total risk. At very low risk levels, it is rarely justified to start medication, but this should always be considered individually. Cholesterol lowering medication could be better targeted by using the FINRISK calculator (5) or the European SCORE table (12) to estimate the total risk; however, the latter only considers sex, age, blood pressure, cholesterol, and smoking and uses only cardiovascular death as an end point. The FINRISK calculator has the significant advantage of considering nonfatal cardiovascular events in addition to death. It also includes the HDL-cholesterol level, diabetes, and family history (myocardial infarction or stroke in a parent) as risk factors. A 5% risk according to SCORE is equivalent to a 10% risk according to the FINRISK calculator.

With time, losses have increased even though the participation percentage is still quite high in international comparison. Poor participation among young men is the greatest problem. In the present material, however, the youngest age group was excluded because there were few people using medication in that group. Even so, participation in this material, too, has been more active in the older age groups. For biological risk factors, the estimated changes may thus be conservative, as risk factors may change with age and with clinical and subclinical diseases associated with aging. When losses were analyzed in 1992, there were more smokers among those not participating

in the study. Taking this into account, the share of smokers in the general population is estimated to be 1-3 percentage points higher than reported here, varying with age and gender. It is not possible to make equivalent estimates of other risk factors. As risk factors have changed in different directions, particularly as regards weight, changes in cholesterol levels can hardly be explained by increased losses. In future, home measurement of risk factors should perhaps be considered, at least if the subject has not come to the research site for that purpose. There are no data available for any other sociodemographic variables for the lost group.

It has at times been speculated that cholesterol lowering medication may be used 'unnecessarily', but in Finland it would rather appear to be used insufficiently, particularly in relation to the target cholesterol levels. Even though patients with coronary heart disease are now relatively well treated, there are still important groups with high risk of arterial disease (such as patients with diabetes or hypertension) in need of more intensive treatment. As the proven health benefits are significant and treatment is largely safe and cheap at present, correctly targeted and individually effective cholesterol lowering medication is important for the health of high-risk groups in the population. In addition to medication, the significant effects of dietary and other habits on blood lipid levels and the risk of arterial disease must naturally be taken into consideration. ■

## ENGLISH SUMMARY

### Use of cholesterol lowering drugs in FINRISK 2007

The aim of this study was to assess the changes in serum cholesterol levels among the general population and in different patient groups in Finland. We also evaluated the use of cholesterol lowering drugs in specific patient groups and in primary prevention. The data are based on the National FINRISK Studies carried out in men and women aged 25-64 years in six different areas every five years since 1982. In the latest survey in 2007 persons aged 65-74 years were also included. Among patients with ischaemic heart disease the serum cholesterol level had decreased by 32%. In the total population, the corresponding decrease was 15%. Among participants aged 35-74 years 20% of men and 17% of women were using cholesterol lowering drugs. Seventy percent of patients with coronary heart disease were using statins. One quarter of statin users had a total cholesterol higher than 5 mmol/l. In primary prevention 67% of men and 33% of women had an absolute risk of coronary heart disease or stroke during the next 10 years of 10% or more.