Time trends in statin use and incidence of recurrent cardiovascular events in secondary prevention between 1999 and 2013: a registry-based study

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Abstract

Objectives: To evaluate time trends of statin use and incidence of recurrent cardiovascular diseases (CVD) in secondary prevention from 1999 to 2013 and to investigate which factors are associated with the underuse of statins in secondary prevention.

Design: Retrospective registry-based study on Intego data from January 1st 1999 to December 31st 2013.

Setting: Primary care registration network with 111 general practitioners (GPs) working in 48 practices sending routinely collected patient data.

Participants: Patients aged 50 years or older with a history of CVD (myocardial infarction (MI), stroke, transient ischemic attack (TIA), ischemic disease with or without angina and peripheral arterial disease (PAD)).

Main outcome measures: The time trends of statin use and incidence of recurrent CVD in secondary prevention were determined by using a joinpoint regression analysis. Multivariable mixed-effect logistic regression analysis was used to assess factors associated with statin underuse in patients in secondary prevention in 2013.

Results: The overall prevalence of statin use increased and showed two trends: a sharp increase from 1999 to 2005 (annual percentage change (APC) 25.4%) and a weaker increase from 2005 to 2013 (APC 3.7%). The average increase in statin use was the highest in patients aged 80 and older. People in the age group 70-79 years received the most statins. Men used more statins than women, but both genders showed similar time trends. The incidence of CVD decreased with an APC of -2.2%. There were no differences between males and females and between

different age groups. In 2013, 60.7% of the patients in secondary prevention did not receive a statin. Statin underuse was most importantly associated with the absence of other preventive medication (OR 33.99, 25.15 and 48 in age groups 50-59 years, 60-79 years and 80+, respectively). Other factors associated with statin underuse in secondary prevention were female gender, age and comorbidity.

Conclusions: The prevalence of statin use in secondary prevention increased strongly from 1999 to 2013. Despite this increase, there was only a small decrease in the incidence of recurrent CVD. In 2013, less than 50% of the patients with a history of CVD received a statin. An important gap remains between the guidelines and the current clinical practice.

1. Introduction

Cardiovascular diseases (CVD) are the leading cause of death in Europe: in 2012 they were responsible for 47 % of all deaths (1, 2). Due to improvements in treatment and prevention of CVD in the last decades, the survival after CVD has increased and cardiovascular mortality has decreased (1, 2). However, because of the better survival after CVD, the rising prevalence in cardiovascular risk factors and the aging of the population, the prevalence of CVD is rising and it is expected that it will remain the main cause of death (1, 3). Therefore, cardiovascular prevention remains a priority in healthcare.

Individuals with established CVD have a high risk of recurrence of any type of CVD (2). To reduce this risk and to reduce mortality, guidelines recommend secondary prevention (4-6). Secondary prevention consists of non-pharmacologic and pharmacologic interventions. The non-pharmacologic interventions are smoking cessation, regular physical activity, losing weight and healthy diet. The recommended pharmacological intervention is a combination of antithrombotic therapy, statins and in some cases antihypertensive agents. These recommendations are independent of age, gender or any other factors.

HMG-CoA reductase inhibitors, i.e. statins, came on the market in 1989 for the treatment of primary hypercholesterolemia (7). Ever since, the prevalence of statin use increased because its indications were broadened as a result of growing evidence from many randomized controlled trials (RCT) (8-10). Statins have proven to reduce the risk of recurrent CVD and of cardiovascular and total mortality in secondary prevention (4, 5, 9, 11, 12). Therefore, every individual with established CVD should receive a statin (4, 5, 13-16).

Nevertheless, there remains a large gap between evidence based recommendations and clinical practice: previous studies reported that only a minority of patients with a history of CVD receives statins (17-39). However, no study described time trends of statin use in secondary

prevention in combination with the evolution of recurrent CVD in the general population. Our hypothesis was that, although statin underuse is very prevalent, the use of statins in secondary prevention has increased enormously and that this would coincide with a lower incidence of recurrent CVD. Furthermore, factors associated with statin underuse like gender, age, race, comorbidity (diabetes, heart failure), smoking, cholesterol level, time after diagnosis and type of CVD have been described (17, 18, 20, 23, 31, 34, 40-44). However, a recent evaluation of statin underuse in secondary prevention and a description of factors related to statin underuse in a real world population are lacking.

Therefore, this retrospective registry-based study was performed. The first aim of this study was to evaluate time trends of statin use and incidence of recurrent CVD in secondary prevention from 1999 to 2013. The second aim was to investigate which factors are associated with the underuse of statins in secondary prevention.

2. Methods

2.1 Study design and study population

Data were obtained from Intego, a Flemish general practice-based morbidity registration network at the Department of General Practice at the University of Leuven. The Intego procedures were approved by the ethical review board of the Medical School of the Catholic University of Leuven (N° ML 1723) and by the Belgian Privacy Commission (no SCSZG/13/079). In 2013, 111 general practitioners (GPs), all using the medical software program Medidoc, collaborated in the Intego project (45). These 111 GPs worked in 48 practices evenly spread over Flanders, Belgium. GPs applied for inclusion in the registry. Before acceptance of their data, registration performance was audited using a number of algorithms that compared their results with all other applicants. Only the data of the practices with an optimal registration performance were included in the database. The Intego GPs prospectively and routinely registered all new diagnoses together with new drug prescriptions, as well as laboratory test results and some background information (including gender and year of birth), using computer-generated keywords internally linked to codes. Using specially framed extraction software, new data were coded and collected from the GPs' personal computers and entered into a central database. Registered data were continuously updated and historically accumulated for each patient. New diagnoses were classified according to a very detailed thesaurus automatically linked to the International Classification of Primary Care (ICPC-2). Drugs were classified according to the WHO's Anatomical Therapeutic Chemical (ATC) classification system.

The current study is a retrospective cohort study that used Intego data from January 1st 1999 till December 31st 2013. In every yearly contact group (JCG) between 1999 and 2013, we selected all patients aged 50 years or older with a history of CVD (myocardial infarction (MI), stroke, transient ischemic attack (TIA), ischemic disease without angina, ischemic disease with angina

and peripheral arterial disease (PAD)). Recurrent CVD was defined as an incident case of MI, stroke or TIA in all selected patients, or an incident diagnosis of ischemic disease with or without angina or PAD in patients without a previous diagnosis of the incident illness. The prevalence of statin (ATC code C10AA) use (at least 2 prescriptions in the selected year) was registered for each year.

2.2 Clinical characteristics

Comorbidity

The medical history of all patients in secondary prevention in 1999 and in 2013 was registered. Besides the history of CVD as defined above, also other comorbidities were registered like atrial fibrillation, hypercholesterolemia, hypertension and mental disorders (anxiety, depression or surmenage). Furthermore, the comorbidities in order to construct the modified Charlson Comorbidity Index (mCCI) were registered (46, 47). Therefore, the presence of the following diagnoses was also collected: heart failure, dementia, chronic obstructive pulmonary disease (COPD) or asthma, a history of peptic ulcer, liver disease, hemiplegia, a history of cancer, a history of leukemia, a history of lymphoma, HIV or AIDS and renal insufficiency. For the presence of renal insufficiency, the glomerular filtration rate (GFR) was estimated (MDRD equation) based on the last creatinine measurement in the two years before 1999 or 2013. All included patients were checked whether or not they received an LDL measurement in the three years before 1999 or 2013.

Pharmacotherapy

The prescription of cardiovascular medication was registered for all patients in secondary prevention in 1999 and in 2013. Data on the prescription of aspirin (ATC code B01AC06), agents acting on the renin-angiotensin system (RAS) (ATC code C09), non-RAS antihypertensive agents (ATC codes C03, C07 and C08) and other lipid lowering medication

(LLD) (ATC code C10 except C10AA) were collected. The use of medication was considered positive when at least two prescriptions were made in the respective year.

2.3 Statistical analysis

To analyse the trend in age-standardised rates between 1999 and 2013, a joinpoint regression analysis was performed (48). A joinpoint is a point in the trend curve where a statistically significant change in trend over time is observed. A minimum number of 3 observations from a joinpoint to either end of the data, and a minimum number of 4 observations between two joinpoints were required. The age-standardised rates were computed taken the Flemish population in Belgium as the standard population, using 10-years age groups until 79 years, and 80 years and older as the last age group for the standardisation. The reference year for the standard population was 1999. From the joinpoint regression model, the annual percentage change (APC) and the average annual percentage change (AAPC) were extracted. APC is calculated for each significant trend from a piecewise log-linear model on the logarithm of the age-standardised rate versus the year. AAPC represents the average of APC estimates per significant trend weighted by the corresponding trend length (number of years in the trend). The trend analysis using the joinpoint regression model was performed using the SEER*Stat software (Joinpoint Trend Analysis software from the Surveillance Research Program of the US National Cancer Institute (available at http://surveillance.cancer.gov/joinpoint)).

Continuous data were summarized using median [P_{25}; P_{75}], and categorical data using proportions. Factors associated with statin underuse in patients who were in secondary prevention in 2013 were assessed using mixed effects logistic regression, which belongs to generalized linear mixed models (GLMM). Each GP practice was treated as a random effect to explore the variability between GP practices in addition to the individual patient observations themselves, by age group (50-59 years, 60-79 years, 80+ years). The log-likelihood was estimated using the Laplace approximation. All variables in univariate analysis were candidate

for the multivariable model. A stepwise approach was then used to select the best multivariable model. The goodness of fit of the model was assessed using the Akaike information criteria (AIC), Hosmer-Lemeshow test, c-index of the receiver operating characteristic (ROC) curve and the Somers' D_{xy} rank correlation. The c-index assesses the predictive performance of the model and the Somers' D_{xy} is an estimate of the rank correlation of the observed binary outcome and the predicted probabilities. In addition, at each step, the maximum variance inflation factor value associated with each parameter in the model must be less than 10 for the model to be chosen. A p-value < 0.05 was considered statistically significant. Statistical analyses of the factors associated with an underuse of statin in patients who are in secondary prevention were performed using R Software Version 3.0.3 (Free Software Foundation Inc., Boston, MA, USA) (lme4, pgirmess, gof and ROCR packages) (49).

3. Results

The prevalence of statin use in secondary prevention increased from 8.4% in 1999 to 39.3% in 2013. Table 1 shows the trends in the prevalence of statin use between 1999 and 2013, according to age and gender. The overall prevalence of statin use showed two trends: there was a sharp increase from 1999 to 2005 and a weaker, but also statistical significant increase from 2005 to 2013 (APC resp. 25.4%, 95%CI (21.8; 29.0) and 3.7%, 95%CI (1.7; 5.6)). Figure 1 shows the prevalence of statin prescription in secondary prevention according to age groups. The average increase in statin use was the highest in the group 80+ (AAPC 23.2% and 28.0% in resp. women and men) and differed significantly with other age groups. In 2013, people in the age group 70-79 years received the most statins (51%). While patients of 69 years or younger reached a plateau after 2005, the statin use of patients aged 70 years or older raised further, but less strongly than before. Men used more statins in secondary prevention than women, but the time trends were similar in both genders (AAPC resp.12.3% and 12.6%, AAPC difference -0.3, 95%CI (-2.6; 2.0)).

Table 2 shows the time trends for the incidence of CVD among individuals aged 50 years and older in secondary prevention: the incidence of CVD was 52/1000 patient years in 1999, did not show a significant trend till 2001, after which a significant decrease was observed with an APC of -2.2%, 95%CI (-3.8; -0.6). Figure 2 shows the incidence of CVD in secondary prevention according to age groups. There were no significant differences in AAPC between males and females and between different age groups.

The first part of table 3 shows the main characteristics of patients in secondary prevention in 1999 (n=4007) and in 2013 (n=6295). The mean age (73 and 74 years, respectively), the gender distribution (45.9% and 45.6% women, respectively) and the prevalence of different CVD were similar. The prevalence of statin underuse in secondary prevention decreased sharply from 92.6% in 1999 to 60.7% in 2013. In 2013 more people received other secondary preventive

medications (aspirin, RAS- and non-RAS-antihypertensive agents) than in 1999. In terms of comorbidity, there was an increase of hypercholesterolemia, hypertension, COPD, diabetes and cancer between 1999 and 2013.

In the second part of table 3 the 2013 study population was split in different age groups (50-59 years, 60-79 years and 80+), because important differences in prevalence of statin underuse were observed (67.2%, 49.7% and 74.3%, respectively). The age groups 60-69 years and 70-79 years were combined because the prevalence of statin underuse was similar. In every age group, the prevalence of statin underuse was compared in subjects with and without specific clinical characteristics. In all age groups, women, subjects with an LDL-measurement in the past 3 years, subjects with no history of hypercholesterolemia, MI or ischemic disease with angina, subjects with heart failure, and subjects with no GFR estimated or not receiving any other preventive medication, showed a higher prevalence of statin underuse. People in the oldest age group with a history of stroke, TIA or dementia received less often a statin than people without these conditions. At younger age (50-79 years), individuals with cancer were less likely to receive a statin than peers without cancer, whereas the opposite was observed for patients with diabetes. The youngest patients (50-59 years) with a history of PAD or ischemic disease with angina received less statins than young patients without these conditions.

Table 4 shows the results of the multivariable mixed-effect logistic regression analysis. In all age groups, statin underuse was most importantly associated with the absence of other preventive medication: patients who did not receive aspirin, RAS- or non-RAS-antihypertensive agents showed an OR of 33.99, 95%CI (17.94; 67.78), 25.15, 95%CI (18.36; 34.77) and 48, 95%CI (29.65; 79.36), in age groups 50-59 years, 60-79 years and 80+, respectively. Despite the fact that few individuals received other LLD than statins, this decreased the chance of having a statin prescribed. In all age groups, women were less likely to receive statins in secondary prevention than men. In the 60-79 age group, age was a protective

factor: every year increase was associated with a 20% lower risk of not receiving a statin (OR 0.80, 95%CI (0.66; 0.98)). On the other hand, in the oldest age group, age was a risk factor for not receiving a statin (OR 5.31, 95%CI (3.43; 8.36)). In some age groups, the presence of coronary disease (MI, ischemic heart disease without or with angina) was associated with a lower risk of statin underuse. In all age groups, hypertension was a risk factor for statin underuse, whereas hypercholesterolemia was a protective factor. Diabetes was associated with a lower statin underuse in the 60-79 age group (OR 0.66, 95%CI (0.53; 0.82)). In the youngest age group, subjects with a paralysis had a lower risk for statin underuse, and subjects with a history of cancer had a higher risk for statin underuse.

The c-index of the full model was 0.86, 0.84 and 0.90 in the respective age groups (50-59 years, 60-79 years and 80+), demonstrating a good total discriminant ability to identify patients with statin underuse. The c-index of the model that included only co-medication was 0.83, 0.80 and 0.86, respectively. The c-index of the model without the medication was 0.76, 0.73 and 0.80, respectively. The Somers' D_{xy} rank correlation of the full model between the predicted probabilities and the observed outcome was respectively 0.72, 0.68 and 0.80. Finally, the p-values associated with the Hosmer and Lemeshow test of the full model were 0.62, 0.10 and 0.73, respectively, demonstrating that the predicted values from the model fit the observed values.

4. Discussion

4.1 Major findings

This large registry-based study showed that the prevalence of statin use in secondary prevention increased dramatically from 1999 to 2005, and more slightly from 2005 to 2013. Despite the strong increase in statin use in secondary prevention, there was rather a modest decline in the incidence of CVD. In 2013, less than 50% of the patients with a history of CVD received a statin. The strongest associated factor of statin underuse was not receiving other secondary preventive medication. Gender, age and comorbidity (especially hypercholesterolemia and hypertension) were to a lesser degree associated with statin underuse.

4.2 Time trends in prevalence of statin use

We found, like previous studies, that the prevalence of statin use in secondary prevention increased during the last decades (17-26, 28, 29, 31-44, 50-52). The rise in statin use has been linked to progressive evidence of statins, guideline changes, increased awareness of the benefits of statins in GPs, promotions by the pharmaceutical industry, media reports, reimbursement conditions, patent expiry, entrance of generic medication and reductions of the price (18, 20, 23, 25, 26, 29, 32, 33, 36, 40, 41, 50, 51, 53).

This study was the first to compute the AAPC of the prevalence of statin use in secondary prevention, which showed two trends: there was a sharp increase from 1999 to 2005 and a weaker, but also statistical significant increase from 2005 to 2013. This suggests that the steep increase in statin use in secondary prevention in the first time period was mainly linked to the growing evidence of statins and to guideline changes, rather than to the change in its costs or reimbursement conditions. After 2005, when the reimbursement and cost of statins in Belgium started to change, the prevalence of statin use in secondary prevention rather seemed to reach a plateau. This finding is in line with previous studies (22, 23, 29, 32, 34, 35, 41, 44). However, these studies also showed that the intensity of statin therapy is on the rise: more patients

received the recommended dose of statins for secondary prevention. The current study did not investigate the prescribed dose of statins.

4.3 Incidence of recurrent CVD

To our knowledge, the current study was the first to compare the evolution over time of statin use in secondary prevention with the evolution of recurrent CVD in the general population. The incidence of recurrent CVD did not decrease much compared to the strong increase in the prevalence of statin use and the use of other preventive medications. Possible explanations are a higher prevalence of other cardiovascular risk factors and an inadequate control of other risk factors. The current study also showed an increase in prevalence of diabetes, hypertension and hypercholesterolemia between 1999 and 2013. Unfortunately, insufficient data on the body mass index (BMI) and smoking status are available in the Intego registry. However, the Intego registry is representative for the Flemish population and the Belgian Health Interview Survey showed that the prevalence of overweight and smoking status in the age group 55+ years in Flanders didn't change much from 1997 to 2013 (from 56.3% to 59% and from 17.6% to 16.9%, respectively) (66).

Furthermore, the Euroaspire surveys described time trends in lifestyle, risk factor control and use of evidence-based medications in patients with coronary heart disease in Europe (22). This study concluded that there is an increase of obesity and diabetes and that the proportion of smokers and the level of physical activity remained stable from 1999 to 2013. The study showed that a majority of patients had the intention to quit smoking after a coronary event, but that a minority of these patients got support and/or drugs for this. Other studies showed similar results of cardiovascular risk factor control in secondary prevention (30, 36, 63-65).

4.4 Factors associated with statin underuse

Despite the large increase in statin use in secondary prevention, the current study confirmed, in line with the results of previous studies, that less than 50% of patients in secondary prevention received a statin in 2013 (17-26, 28, 29, 31-44, 50-52).

The most important associated factor with statin underuse in secondary prevention was the concomitant underuse of other secondary preventive medications (aspirin, RAS and non-RAS antihypertensive agents). This study was the first to show this association. Possible explanations of these findings could be doctor-related factors such as a poor knowledge and application of the guidelines and patient-related factors such as poor adherence to therapy.

Béjot et al. found also an association between the use of statins, aspirin and antihypertensive agents, but their study population consisted of patients with established recurrent CVD (19). The association between these medications was also seen in the study by Tonstad et al., but this study was conducted in 2001 and focused on primary and secondary prevention (31).

Women were less likely to receive statins in secondary prevention than men. This finding is also in line with previous studies (17, 20, 23, 27, 31, 37, 39-42). Some of these studies showed that women also received less intensive statin therapy (17, 35, 42). Possibly doctors think that women are more susceptible for adverse effects of statins or assume that female gender lowers the cardiovascular risk.

In the age group 60-79 years, higher age was a protective factor, whereas it was a risk factor for statin underuse in the oldest age group. This pattern of age-related statin use was seen in other studies (20, 23, 29, 40, 41). In general, age is a cardiovascular risk factor, and therefore it’s logic that this factor is associated with higher statin use in secondary prevention. A possible explanation for the lower statin use in the oldest age group is that there has been no evidence about the benefits of the initiation or continuation of statins in this group (40). The most recent

guidelines do not recommend age limitations for the use of statins in secondary prevention, but it is known that changing the clinical practice after adjusting the guidelines needs time (3, 5, 6). Possibly doctors have the intention to give elderly less statins because they think this group has a higher risk for adverse effects and drug-drug interactions.

The current study showed several comorbidities or cardiovascular risk factors were to a lesser degree associated to statin underuse. First, a history of coronary artery disease was inversely associated with statin underuse. On the other hand, we found no association between statin underuse and other atherosclerotic diseases (stroke, TIA and PAD). This could be explained by the fact that the evidence for coronary heart diseases exists longer than the evidence for stroke/TIA and PAD. Second, hypercholesterolemia was inversely associated with statin underuse in secondary prevention. This probably suggests that physicians prescribe statins in function of cholesterol levels, despite the fact that statins should be prescribed in secondary prevention independently of cholesterol level (27, 28, 33, 40). Third, diabetes was a protective factor for statin underuse in the age group 60-79 years. A possible explanation for this is the entrance of a diabetes care program in Belgium, which involves a better follow-up of these patients and an increased awareness of the higher risk on recurrent CVD among diabetics. Fourth, hypertension was a risk factor for statin underuse. Possibly because patients take already antihypertensive agents and are reluctant to polypharmacy. Xi et al. found that patients with hypertension after stroke are more likely to receive a statin (33). No other studies examined the role of hypertension in the underuse of statins in secondary prevention. Fifth, the current study was the first to examine the role of cancer in statin underuse. We found that a history of cancer was associated with statin underuse in the age group 50-59 years. Possibly doctors think that statins won't have a beneficial effect anymore because of the bad life expectancy, or because they are afraid of the side effects in already weakened patients, or because they want to avoid polypharmacy and optimize the quality of life.

Future research should focus on the reason behind the finding that less than 50% of patients in secondary prevention use a statin. This qualitative research should focus on doctor- and patient-related factors.

4.5 Strengths and limitations

The major strengths of the current study are inclusion of a large real-world study population, representative for the general Flemish population, and the long follow-up period. This study was the first to examine the prevalence of statin use parallel with the incidence of recurrent CVD in the same population. Furthermore, we were able to examine multivariable models to explain statin underuse in different age groups and have included a broad range of factors that were possibly associated with statin underuse.

However, this study has also a few limitations. First, there is no data available on mortality in Intego. Second, we defined statin use as receiving at least two statin prescriptions within a year, however, it's not because patients get a prescription that they also take the medication. Third, we did not investigate the dose and type of statin patients used and have insufficient data on actual cholesterol levels. Last, no information on smoking status, BMI, race, socio-economic status and time after diagnosis of the first CVD was available. However, the Intego registry well represents the Flemish population and the Belgian Health Interview Survey showed no important changes in smoking status and overweight in Flanders from 1997 to 2013 (66).

5. Conclusion

The prevalence of statin use in secondary prevention increased strongly from 1999 to 2013. Despite this increase, there is only a small decrease in the incidence of recurrent CVD. In 2013, less than 50% of the patients with a history of CVD received a statin. So, there remains an important gap between the guidelines and the current clinical practice. The major factor associated with statin underuse was not using other preventive medications. Other factors influencing the statin underuse were age, gender, type of CVD and comorbidity.

Funding

Intego is funded on a regular basis by the Flemish Government (Ministry of Health and Welfare) and by the Belgian National Institute for Health and Disability Insurance on a contractual basis (ACHIL project). This work would not have been possible without the collaboration of all general practitioners of the Intego network. We hereby state the independence of researchers from funders.

Competing interests

None.

Provenance and peer review

Not commissioned; externally peer reviewed.

Data sharing statement

All authors had full access to all of the data (including statistical reports and tables) in the study and can take responsibility for the integrity of the data and the accuracy of the data analysis.

References

1. <EU-cardiovascular-disease-statistics-2012.pdf>.
2. Bansilal S, Castellano JM, Fuster V. Global burden of CVD: focus on secondary prevention of cardiovascular disease. Int J Cardiol. 2015;201 Suppl 1:S1-7.
3. <ab_cardiovasculair_risicobeheer.pdf>.
4. De Backer G, Ambrosioni E, Borch-Johnsen K, Brotons C, Cifkova R, Dallongeville J, et al. European guidelines on cardiovascular disease prevention in clinical practice: third joint task force of European and other societies on cardiovascular disease prevention in clinical practice (constituted by representatives of eight societies and by invited experts). Eur J Cardiovasc Prev Rehabil. 2003;10(4):S1-S10.
5. Stone NJ, Robinson JG, Lichtenstein AH, Bairey Merz CN, Blum CB, Eckel RH, et al. 2013 ACC/AHA guideline on the treatment of blood cholesterol to reduce atherosclerotic cardiovascular risk in adults: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. J Am Coll Cardiol. 2014;63(25 Pt B):2889-934.
6. Graham I, Atar D, Borch-Johnsen K, Boysen G, Burell G, Cifkova R, et al. European guidelines on cardiovascular disease prevention in clinical practice: executive summary. Fourth Joint Task Force of the European Society of Cardiology and other societies on cardiovascular disease prevention in clinical practice (constituted by representatives of nine societies and by invited experts). Eur J Cardiovasc Prev Rehabil. 2007;14 Suppl 2:E1-40.
7. Illingworth DR, Bacon S. Hypolipidemic effects of HMG-CoA reductase inhibitors in patients with hypercholesterolemia. Am J Cardiol. 1987;60(12):33G-42G.
8. <kce_141a_statines_in_belgië.pdf>.
9. Ong HT. The statin studies: from targeting hypercholesterolaemia to targeting the high-risk patient. QJM. 2005;98(8):599-614.
10. Walley T, Folino-Gallo P, Stephens P, Van Ganse E. Trends in prescribing and utilization of statins and other lipid lowering drugs across Europe 1997-2003. Br J Clin Pharmacol. 2005;60(5):543-51.
11. Randomised trial of cholesterol lowering in 4444 patients with coronary heart disease: the Scandinavian Simvastatin Survival Study (4S). Lancet. 1994;344(8934):1383-9.
12. Descamps OS, De Backer G, Annemans L, Muls E, Scheen AJ. [New European guidelines for the management of dyslipidaemia in cardiovascular prevention]. Rev Med Liege. 2012;67(3):118-27.
13. Levine GN, Bates ER, Blankenship JC, Bailey SR, Bittl JA, Cercek B, et al. 2015 ACC/AHA/SCAI Focused Update on Primary Percutaneous Coronary Intervention for Patients With ST-Elevation Myocardial Infarction: An Update of the 2011 ACCF/AHA/SCAI Guideline for Percutaneous Coronary Intervention and the 2013 ACCF/AHA Guideline for the Management of ST-Elevation Myocardial Infarction: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines and the Society for Cardiovascular Angiography and Interventions. Circulation. 2016;133(11):1135-47.
14. Rooke TW, Hirsch AT, Misra S, Sidawy AN, Beckman JA, Findeiss L, et al. Management of patients with peripheral artery disease (compilation of 2005 and 2011 ACCF/AHA Guideline Recommendations): a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. J Am Coll Cardiol. 2013;61(14):1555-70.
15. Kernan WN, Ovbiagele B, Black HR, Bravata DM, Chimowitz MI, Ezekowitz MD, et al. Guidelines for the prevention of stroke in patients with stroke and transient ischemic

attack: a guideline for healthcare professionals from the American Heart Association/American Stroke Association. Stroke. 2014;45(7):2160-236.
16. Anderson JL, Adams CD, Antman EM, Bridges CR, Califf RM, Casey DE, Jr., et al. 2012 ACCF/AHA focused update incorporated into the ACCF/AHA 2007 guidelines for the management of patients with unstable angina/non-ST-elevation myocardial infarction: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. J Am Coll Cardiol. 2013;61(23):e179-347.
17. Dodhia H, Kun L, Logan Ellis H, Crompton J, Wierzbicki AS, Williams H, et al. Evaluating quality and its determinants in lipid control for secondary prevention of heart disease and stroke in primary care: a study in an inner London Borough. BMJ Open. 2015;5(12):e008678.
18. Wallach Kildemoes H, Vass M, Hendriksen C, Andersen M. Statin utilization according to indication and age: a Danish cohort study on changing prescribing and purchasing behaviour. Health Policy. 2012;108(2-3):216-27.
19. Bejot Y, Zeller M, Lorgis L, Troisgros O, Aboa-Eboule C, Osseby GV, et al. Secondary prevention in patients with vascular disease. A population based study on the underuse of recommended medications. J Neurol Neurosurg Psychiatry. 2013;84(3):348-53.
20. Jorgensen CH, Gislason GH, Ahlehoff O, Andersson C, Torp-Pedersen C, Hansen PR. Use of secondary prevention pharmacotherapy after first myocardial infarction in patients with diabetes mellitus. BMC Cardiovasc Disord. 2014;14:4.
21. Park JH, Ruiz MC, Shields D, Orr DJ. Socioeconomic deprivation does not affect prescribing of secondary prevention in patients with peripheral arterial disease. Int Angiol. 2013;32(6):593-8.
22. Kotseva K, De Bacquer D, Jennings C, Gyberg V, De Backer G, Ryden L, et al. Time Trends in Lifestyle, Risk Factor Control, and Use of Evidence-Based Medications in Patients With Coronary Heart Disease in Europe: Results From 3 EUROASPIRE Surveys, 1999-2013. Glob Heart. 2016.
23. DeWilde S, Carey IM, Bremner SA, Richards N, Hilton SR, Cook DG. Evolution of statin prescribing 1994-2001: a case of agism but not of sexism? Heart. 2003;89(4):417-21.
24. Subherwal S, Patel MR, Kober L, Peterson ED, Jones WS, Gislason GH, et al. Missed opportunities: despite improvement in use of cardioprotective medications among patients with lower-extremity peripheral artery disease, underuse remains. Circulation. 2012;126(11):1345-54.
25. Fitzgerald TN, Popp C, Dardik A, Federman DG. Lipid goal achievement and trends in lipid-lowering therapy in veterans undergoing carotid endarterectomy. Vasc Med. 2009;14(1):21-7.
26. Tu JV, Gong Y. Trends in treatment and outcomes for acute stroke patients in Ontario, 1992-1998. Arch Intern Med. 2003;163(3):293-7.
27. Ovbiagele B, Schwamm LH, Smith EE, Hernandez AF, Olson DM, Pan W, et al. Recent nationwide trends in discharge statin treatment of hospitalized patients with stroke. Stroke. 2010;41(7):1508-13.
28. Lemaitre RN, Furberg CD, Newman AB, Hulley SB, Gordon DJ, Gottdiener JS, et al. Time trends in the use of cholesterol-lowering agents in older adults: the Cardiovascular Health Study. Arch Intern Med. 1998;158(16):1761-8.
29. Whincup PH, Emberson JR, Lennon L, Walker M, Papacosta O, Thomson A. Low prevalence of lipid lowering drug use in older men with established coronary heart disease. Heart. 2002;88(1):25-9.
30. Young F, Capewell S, Ford ES, Critchley JA. Coronary mortality declines in the U.S. between 1980 and 2000 quantifying the contributions from primary and secondary prevention. Am J Prev Med. 2010;39(3):228-34.

31. Tonstad S, Rosvold EO, Furu K, Skurtveit S. Undertreatment and overtreatment with statins: the Oslo Health Study 2000-2001. J Intern Med. 2004;255(4):494-502.
32. Deambrosis P, Saramin C, Terrazzani G, Scaldaferri L, Debetto P, Giusti P, et al. Evaluation of the prescription and utilization patterns of statins in an Italian local health unit during the period 1994-2003. Eur J Clin Pharmacol. 2007;63(2):197-203.
33. Li X, Gao Y, Li J, Feng F, Liu JM, Zhang HB, et al. Underuse of statins in patients with atherosclerotic ischemic stroke in China. Chin Med J (Engl). 2012;125(10):1703-7.
34. Di Martino M, Degli Esposti L, Ruffo P, Bustacchini S, Catte A, Sturani A, et al. Underuse of lipid-lowering drugs and factors associated with poor adherence: a real practice analysis in Italy. Eur J Clin Pharmacol. 2005;61(3):225-30.
35. Shalev V, Weil C, Raz R, Goldshtein I, Weitzman D, Chodick G. Trends in statin therapy initiation during the period 2000-2010 in Israel. Eur J Clin Pharmacol. 2014;70(5):557-64.
36. Girot M, Mackowiak-Cordoliani MA, Deplanque D, Henon H, Lucas C, Leys D. Secondary prevention after ischemic stroke. Evolution over time in practice. J Neurol. 2005;252(1):14-20.
37. Balder JW, Scholtens S, de Vries JK, van Schie LM, Boekholdt SM, Hovingh GK, et al. Adherence to guidelines to prevent cardiovascular diseases: The LifeLines cohort study. Neth J Med. 2015;73(7):316-23.
38. Sheppard JP, Fletcher K, McManus RJ, Mant J. Missed opportunities in prevention of cardiovascular disease in primary care: a cross-sectional study. Br J Gen Pract. 2014;64(618):e38-46.
39. Shah NS, Huffman MD, Ning H, Lloyd-Jones DM. Trends in myocardial infarction secondary prevention: The National Health and Nutrition Examination Surveys (NHANES), 1999-2012. J Am Heart Assoc. 2015;4(4).
40. Wallach-Kildemoes H, Stovring H, Holme Hansen E, Howse K, Petursson H. Statin prescribing according to gender, age and indication: what about the benefit-risk balance? J Eval Clin Pract. 2016;22(2):235-46.
41. Rasmussen JN, Gislason GH, Abildstrom SZ, Rasmussen S, Gustafsson I, Buch P, et al. Statin use after acute myocardial infarction: a nationwide study in Denmark. Br J Clin Pharmacol. 2005;60(2):150-8.
42. Cho L, Hoogwerf B, Huang J, Brennan DM, Hazen SL. Gender differences in utilization of effective cardiovascular secondary prevention: a Cleveland clinic prevention database study. J Womens Health (Larchmt). 2008;17(4):515-21.
43. Mohammed MA, El Sayed C, Marshall T. Patient and other factors influencing the prescribing of cardiovascular prevention therapy in the general practice setting with and without nurse assessment. Med Decis Making. 2012;32(3):498-506.
44. Kildemoes HW, Stovring H, Andersen M. Driving forces behind increasing cardiovascular drug utilization: a dynamic pharmacoepidemiological model. Br J Clin Pharmacol. 2008;66(6):885-95.
45. Truyers C, Goderis G, Dewitte H, Akker M, Buntinx F. The Intego database: background, methods and basic results of a Flemish general practice-based continuous morbidity registration project. BMC Med Inform Decis Mak. 2014;14:48.
46. Vaes B, Beke E, Truyers C, Elli S, Buntinx F, Verbakel JY, et al. The correlation between blood pressure and kidney function decline in older people: a registry-based cohort study. BMJ Open. 2015;5(6):e007571.
47. Charlson ME, Pompei P, Ales KL, MacKenzie CR. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. J Chronic Dis. 1987;40(5):373-83.

48. Kim HJ, Fay MP, Feuer EJ, Midthune DN. Permutation tests for joinpoint regression with applications to cancer rates. Stat Med. 2000;19(3):335-51.
49. Dean CB, Nielsen JD. Generalized linear mixed models: a review and some extensions. Lifetime Data Anal. 2007;13(4):497-512.
50. de Ruijter W, de Waal MW, Gussekloo J, Assendelft WJ, Blom JW. Time trends in preventive drug treatment after myocardial infarction in older patients. Br J Gen Pract. 2010;60(570):47-9.
51. Appelros P, Jonsson F, Asberg S, Asplund K, Glader EL, Asberg KH, et al. Trends in stroke treatment and outcome between 1995 and 2010: observations from Riks-Stroke, the Swedish stroke register. Cerebrovasc Dis. 2014;37(1):22-9.
52. Ko DT, Mamdani M, Alter DA. Lipid-lowering therapy with statins in high-risk elderly patients: the treatment-risk paradox. JAMA. 2004;291(15):1864-70.
53. Fraeyman J, Van Hal G, De Loof H, Remmen R, De Meyer GR, Beutels P. Potential impact of policy regulation and generic competition on sales of cholesterol lowering medication, antidepressants and acid blocking agents in Belgium. Acta Clin Belg. 2012;67(3):160-71.
54. Sacks FM, Pfeffer MA, Moye LA, Rouleau JL, Rutherford JD, Cole TG, 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(14):1001-9.
55. Miettinen TA, Pyorala K, Olsson AG, Musliner TA, Cook TJ, Faergeman O, et al. Cholesterol-lowering therapy in women and elderly patients with myocardial infarction or angina pectoris: findings from the Scandinavian Simvastatin Survival Study (4S). Circulation. 1997;96(12):4211-8.
56. Hebert PR, Gaziano JM, Chan KS, Hennekens CH. Cholesterol lowering with statin drugs, risk of stroke, and total mortality. An overview of randomized trials. JAMA. 1997;278(4):313-21.
57. Hirsch AT, Haskal ZJ, Hertzer NR, Bakal CW, Creager MA, Halperin JL, et al. ACC/AHA Guidelines for the Management of Patients with Peripheral Arterial Disease (lower extremity, renal, mesenteric, and abdominal aortic): a collaborative report from the American Associations for Vascular Surgery/Society for Vascular Surgery, Society for Cardiovascular Angiography and Interventions, Society for Vascular Medicine and Biology, Society of Interventional Radiology, and the ACC/AHA Task Force on Practice Guidelines (writing committee to develop guidelines for the management of patients with peripheral arterial disease)--summary of recommendations. J Vasc Interv Radiol. 2006;17(9):1383-97; quiz 98.
58. Pyorala K, De Backer G, Graham I, Poole-Wilson P, Wood D. Prevention of coronary heart disease in clinical practice. Recommendations of the Task Force of the European Society of Cardiology, European Atherosclerosis Society and European Society of Hypertension. Eur Heart J. 1994;15(10):1300-31.
59. Wood D, De Backer G, Faergeman O, Graham I, Mancia G, Pyorala K. Prevention of coronary heart disease in clinical practice: recommendations of the Second Joint Task Force of European and other Societies on Coronary Prevention. Atherosclerosis. 1998;140(2):199-270.
60. van der Harst P, de Boer RA. Statins in the treatment of heart failure. Circ Heart Fail. 2010;3(3):462-4.
61. Rysz J, Gluba-Brzozka A, Banach M, Wiecek A. Should we use statins in all patients with chronic kidney disease without dialysis therapy? The current state of knowledge. Int Urol Nephrol. 2015;47(5):805-13.

62. Preiss D, Campbell RT, Murray HM, Ford I, Packard CJ, Sattar N, et al. The effect of statin therapy on heart failure events: a collaborative meta-analysis of unpublished data from major randomized trials. Eur Heart J. 2015;36(24):1536-46.
63. Steinberg BA, Bhatt DL, Mehta S, Poole-Wilson PA, O'Hagan P, Montalescot G, et al. Nine-year trends in achievement of risk factor goals in the US and European outpatients with cardiovascular disease. Am Heart J. 2008;156(4):719-27.
64. Wong ND, Patao C, Wong K, Malik S, Franklin SS, Iloeje U. Trends in control of cardiovascular risk factors among US adults with type 2 diabetes from 1999 to 2010: comparison by prevalent cardiovascular disease status. Diab Vasc Dis Res. 2013;10(6):505-13.
65. Tang L, Patao C, Chuang J, Wong ND. Cardiovascular risk factor control and adherence to recommended lifestyle and medical therapies in persons with coronary heart disease (from the National Health and Nutrition Examination Survey 2007-2010). Am J Cardiol. 2013;112(8):1126-32.
66. https://his.wiv-isp.be/nl/SitePages/Rapporten.aspx

Tables and figures

Table 1. Age-standardised prevalence rate of statin use.

Group	ASPR of statin use in 1999	Summary	Trend 1		Trend2		Trend3	
		AAPC	Years	APC	Years	APC	Years	APC
Total	8.4%	12.5 [10.9; 14.1]*	1999-2005	25.4 [21.8; 29.0]*	2005-2013	3.7 [1.7; 5.6]*		
Females	6.5%	12.6 [10.9; 14.3]*	1999-2005	25.0 [21.3; 28.8]*	2005-2013	4.1 [2.1; 6.2]*		
50-59	7.6%	8.3 [5.7; 10.8]*	1999-2005	21.0 [15.5; 26.9]*	2005-2013	-0.4 [-3.4; 2.6]		
60-69	13.6%	7.3 [5.1; 9.6]*	1999-2006	15.2 [11.4; 19.2]*	2006-2013	-0.1 [-3.4; 3.3]		
70-79	6.6%	14.0 [12.1; 16.0]*	1999-2004	31.0 [27.7; 34.4]*	2004-2008	11.2 [5.0; 17.8]*	2008-2013	1.3 [-1.3; 3.9]
80+	1.2%	23.2 [17.3; 29.4]*	1999-2005	40.0 [26.8; 54.5]*	2005-2013	11.9 [5.0; 19.3]*		
Males	10.0%	12.3 [10.7; 13.9]*	1999-2005	25.4 [21.8; 29.0]*	2005-2013	3.4 [1.5; 5.3]*		
50-59	18.3%	6.5 [4.7; 8.4]*	1999-2005	17.2 [13.2; 21.4]*	2005-2013	-0.8 [-3.0; 1.5]		
60-69	12.7%	10.7 [9.0; 12.4]*	1999-2005	24.9 [21.2; 28.8]*	2005-2013	1.0 [-0.9; 3.1]		
70-79	7.6%	15.5 [13.7; 17.4]*	1999-2005	29.2 [25.1; 33.3]*	2005-2013	6.2 [4.1; 8.4]*		
80+	0.8%	28.0 [22.8; 33.3]*	1999-2005	59.1 [46.5; 72.9]*	2005-2013	8.7 [3.0; 14.6]*		

* p < 0.05; ASPR: age-standardized prevalence rate

Table 2. Age-standardised incidence rate of CV/heart diseases.

Group	ASIR of CV/heart disease in 1999	Summary	Trend 1		Trend2	
		AAPC	Years	APC	Years	APC
Secondary prevention						
Total	51.7‰	-3.9 [-7.4; -0.4]*	1999-2001	-13.7 [-34.4; 13.5]	2001-2013	-2.2 [-3.8; -0.6]*
Females	50.3‰	-2.8 [-4.5; -1.1]*	1999-2013	-2.8 [-4.5; -1.1]*		
50-59	34.5‰	-1.2 [-6.5; 4.4]	1999-2013**	-1.2 [-6.5; 4.4]		
60-69	33.2‰	-0.7 [-3.8; 2.5]	1999-2013	-0.7 [-3.8; 2.5]		
70-79	50.5‰	-3.3 [-6.7; 0.1]	1999-2013	-3.3 [-6.7; 0.1]		
80+	66.6‰	-3.7 [-5.4; -2.1]*	1999-2013	-3.7 [-5.4; -2.1]*		
Males	52.8‰	-3.3 [-5.1; -1.5]*	1999-2013	-3.3 [-5.1; -1.5]*		
50-59	33.5‰	-1.1 [-4.9; 2.9]	1999-2013	-1.1 [-4.9; 2.9]		
60-69	51.4‰	-3.3 [-5.4; -1.1]*	1999-2013	-3.3 [-5.4; -1.1]*		
70-79	58.0‰	-3.7 [-6.3; -1.1]*	1999-2013	-3.7 [-6.3; -1.1]*		
80+	64.1‰	-3.2 [-5.5; -0.8]*	1999-2013	-3.2 [-5.5; -0.8]*		

* p < 0.05; **without 2002 because it was 0; ASIR: age-standardized incidence rate

Table 3. Characteristics of patients on secondary prevention.

	1999	2013	Age group in 2013								
	Total (n=4007)	Total (n=6295)	50-59 years (n=1077)			60-79 years (n=3211)			80+ years (n=2077)		
Variables	**n (%) or Median [P25; P75]**	**n (%) or Median [P25; P75]**	**n (%) or Median [P25; P75]**	**Underuse cat. %**	**Underuse ref. cat. %**	**n (%) or Median [P25; P75]**	**Underuse cat. %**	**Underuse ref. cat. %**	**n (%) or Median [P25; P75]**	**Underuse cat. %**	**Underuse ref. cat. %**
Statin underuse	3712 (92.6)	3818 (60.7)	677 (67.2)			1597 (49.7)			1544 (74.3)		
Baseline characteristics											
Age, years	73 [66; 79]	74 [64; 82]	55 [52; 57]			70 [65; 75]			85 [82; 89]		
Gender: Females vs males	1839 (45.9)	2871 (45.6)	448 (44.5)	75.9***	60.3	1280 (39.9)	58.4***	44.0	1143 (55)	79.6***	67.9
LDL measurements in the past 3 years: yes vs no	1559 (38.9)	2405 (38.2)	421 (42.0)	76.7***	60.4	1040 (32.4)	61.3***	44.2	944 (45.5)	85.4***	65.1
Type of heart/CV disease history											
Myocardial infarction	848 (21.2)	1507 (23.9)	331 (32.9)	63.7*	68.9	786 (24.5)	41.0***	52.6	390 (18.8)	69.0**	75.6
Stroke	831 (20.7)	1496 (23.8)	248 (24.6)	70.2	66.3	672 (20.9)	53.7**	48.7	576 (27.7)	79.5***	72.4
TIA	631 (15.7)	963 (15.3)	67 (6.7)	58.2	67.9	414 (12.9)	50.7	49.6	482 (23.2)	78.2**	73.2
Isch. Dis. Without angina	754 (18.8)	1147 (18.2)	144 (14.3)	57.6**	68.8	648 (20.2)	38.7***	52.5	355 (17.1)	66.8***	75.9
Isch. Dis. With angina	1582 (39.5)	1809 (28.7)	173 (17.2)	53.2***	70.1	938 (29.2)	45.9**	51.3	698 (33.6)	72.5	75.3
Peripheral arterial illness	1011 (25.2)	1669 (26.5)	242 (24.0)	72.7**	65.5	873 (27.2)	54.1	48.1	554 (26.7)	72.6	75.0
Comorbidities											
Atrial fibrillation	430 (10.7)	870 (13.8)	24 (2.4)	54.2	67.5	359 (11.2)	46.2	50.2	487 (23.4)	78.9**	73.0
Hypercholesterolemia	1040 (26.0)	2075 (33.0)	292 (29.0)	49.3***	74.5	1134 (35.3)	39.4***	55.4	649 (31.2)	65.8***	78.2
Hypertension	1396 (34.8)	2772 (44.0)	344 (34.2)	63.4*	69.2	1422 (44.3)	48.3	50.9	1006 (48.4)	75.2	73.5
Mental health disorder	625 (15.6)	1310 (20.8)	289 (28.7)	67.5	67.1	627 (19.5)	54.9**	48.5	394 (19.0)	82.5***	72.4
Co-medications											
Aspirin and antihypertensive agents											
Reference: Aspirin + RAS and Non-RAS antihypertensive agents											
Aspirin + (RAS or Non-RAS antihypertensive agents)	220 (5.5)	757 (12.0)	83 (8.2)	19.3	26.5	501 (15.6)	19.0**	26.3	173 (8.3)	29.2	37.0
Aspirin alone	68 (1.7)	226 (3.6)	45 (4.5)	19.3	31.1	147 (4.6)	19.0***	41.5	34 (1.6)	29.2**	55.9
RAS and/or Non-RAS antihypertensive agents	702 (17.5)	1808 (28.7)	256 (25.4)	19.3***	61.3	1014 (31.6)	19.0***	39.6	538 (25.9)	29.2***	55.2

None of these 3 categories	2942 (73.4)	2797 (44.4)	535 (53.1)	19.3***	87.3	1091 (34.0)	19.0***	83.9	1171 (56.4)	29.2***	95.4
Other lipid modifying agent		237 (3.8)	37 (3.7)	51.4**	67.8	164 (5.1)	56.7*	49.4	36 (1.7)	69.4	74.4
Charlson comorbidity index											
CCI index[a]	5 [3; 6]	5 [4; 7]	3 [2; 4]			5 [4; 6]			7 [6; 8]		
Acute myocardial infarction/ ischaemic heart disease w/o angina	1395 (34.8)	2364 (37.6)	442 (43.9)	63.6**	70.1	1269 (39.5)	40.7***	55.7	653 (31.4)	67.7***	77.4
Heart failure	364 (9.1)	500 (7.9)	20 (2.0)	45.0**	67.7	156 (4.9)	40.4**	50.2	324 (15.6)	80.9**	73.1
Atherosclerosis/ PVD	1011 (25.2)	1669 (26.5)	242 (24.0)	72.7**	65.5	873 (27.2)	54.1**	48.1	554 (26.7)	72.6	75.0
Transient cerebral ischemia/ stroke/ cerebrovascular accident	1333 (33.3)	2283 (36.3)	305 (30.3)	68.2	66.8	1014 (31.6)	53.4**	48.1	964 (46.4)	78.9***	70.4
Dementia	94 (2.3)	301 (4.8)	17 (1.7)	76.5	67.1	87 (2.7)	59.8*	49.5	197 (9.5)	85.3***	73.2
Chronic obstructive pulmonary disease/ asthma	579 (14.4)	1580 (25.1)	276 (27.4)	68.1	66.9	862 (26.8)	51.6	49.0	442 (21.3)	75.3	74.1
Duodenal ulcer/ peptic ulcer other	471 (11.8)	647 (10.3)	65 (6.5)	69.2	67.1	331 (10.3)	50.5	49.7	251 (12.1)	78.1	73.8
Liver disease NOS	110 (2.7)	361 (5.7)	52 (5.2)	59.6	67.6	200 (6.2)	52.0	49.6	109 (5.2)	79.8	74.0
Diabetes insulin dependent/ non-insulin dependent	644 (16.1)	1587 (25.2)	235 (23.3)	61.3**	69.0	855 (26.6)	41.1***	52.9	497 (23.9)	72.6	74.9
Paralysis/ weakness	122 (3.0)	141 (2.2)	18 (1.8)	44.4**	67.6	65 (2.0)	56.9	49.6	58 (2.8)	84.5*	74.0
Cancer CCI	382 (9.5)	1207 (19.2)	191 (19.0)	79.1***	64.5	631 (19.7)	56.7***	48.0	385 (18.5)	76.6	73.8
Leukaemia	9 (0.2)	40 (0.6)	10 (1.0)	80.0	67.1	15 (0.5)	53.3	49.7	15 (0.7)	66.7	74.4
Hodgkin's disease/ lymphoma	12 (0.3)	44 (0.7)	6 (0.6)	83.3	67.1	27 (0.8)	59.3	49.7	11 (0.5)	63.6	74.4
HIV-infection/ aids	NA	NA	NA								
Renal insufficiency											
Yes vs no	468 (11.7)	665 (10.6)	14 (1.4)	62.3	50.0	192 (6.0)	45.4	50.5	459 (22.1)	68.1**	74.7
Not measured vs measured	755 (18.8)	970 (15.4)	214 (21.3)	62.3***	86.4	372 (11.6)	45.4***	80.4	384 (18.5)	68.1***	94.0

[a]Missing kidney function is treated as a score of 0; Underuse cat.: statin underuse in the category of interest; Underuse ref. cat.: statin underuse in the category of reference

***: p<0.001; **: p<0.05; *: p<0.10 (p-values are derived from a simple logistic regression model)

Renal insufficiency: the last value of the creatinine was taken if it was measured in the last three years; the eGFR was computed using the MDRD formula. If eGFR<45 => renal insufficiency

Table 4. Determinants of statin underuse in secondary prevention.

	Multivariable analysis (50-59 years)		Multivariable analysis (60-79 years)		Multivariable analysis (80+ years)	
Variables	**OR [95%CI]**	**p-value**	**OR [95%CI]**	**p-value**	**OR [95%CI]**	**p-value**
Baseline characteristics						
Standardized age, years			0.80 [0.66; 0.98]	0.030	5.31 [3.43; 8.36]	<0.001
Gender: Females vs males	1.69 [1.19; 2.40]	0.003	1.55 [1.30; 1.86]	<0.001	1.48 [1.12; 1.94]	0.005
LDL measurements in the past 3 years: yes vs no			1.55 [1.20; 2.03]	0.001	1.99 [1.48; 2.72]	<0.001
Type of heart/CV disease history						
Myocardial infarction			0.71 [0.57; 0.87]	0.001		
Ischemic Heart disease without angina			0.71 [0.57; 0.89]	0.001	0.67 [0.48; 0.95]	0.022
Ischemic Heart disease with angina	0.63 [0.41; 0.96]	0.030			0.74 [0.56; 0.98]	0.033
Comorbidities						
Atrial fibrillation					1.51 [1.09; 2.09]	0.013
Hypercholesterolemia	0.28 [0.19; 0.41]	<0.001	0.42 [0.34; 0.51]	<0.001	0.34 [0.25; 0.46]	<0.001
Hypertension	1.54 [1.05; 2.30]	0.030	1.72 [1.43; 2.08]	<0.001	1.54 [1.17; 2.04]	0.002
Mental health disorder					1.58 [1.10; 2.30]	0.015
Co-medications						
Aspirin and antihypertensive agents						
Reference: Aspirin + RAS and Non-RAS antihypertensive agents						
Aspirin + (RAS or Non-RAS antihypertensive agents)	1.60 [0.74; 3.51]	0.236	1.63 [1.17; 2.27]	0.004	1.49 [0.90; 2.50]	0.126
Aspirin alone	2.09 [0.84; 5.19]	0.110	4.37 [2.79; 6.85]	<0.001	3.31 [1.42; 7.82]	0.006
RAS and/or Non-RAS antihypertensive agents	6.63 [3.59; 12.81]	<0.001	2.79 [2.11; 3.74]	<0.001	2.67 [1.75; 4.12]	<0.001
None of these 3 categories	33.99 [17.94; 67.78]	<0.001	25.15 [18.36; 34.77]	<0.001	48.0 [29.65; 79.36]	<0.001
Other lipid modifying agent	2.60 [1.14; 6.00]	0.024	4.12 [2.85; 5.99]	<0.001	5.30 [2.38; 12.54]	<0.001
Charlson comorbidity index						
CCI index[a]			1.13 [1.05; 1.21]	<0.001		
Liver disease NOS					1.86 [1.00; 3.53]	0.054
Diabetes, insulin dependent/ non-insulin dependent			0.66 [0.53; 0.82]	<0.001		
Paralysis/ weakness	0.20 [0.06; 0.66]	0.009				
Cancer CCI	1.58 [0.99; 2.57]	0.059				
Renal insufficiency						
No						

Yes	0.53 [0.15; 1.88]	0.318	1.02 [0.69; 1.53]	0.90
Not measured	2.96 [1.80; 5.02]	<0.001	2.59 [1.81; 3.75]	<0.001

Mixed-effect logistic regression, patients on secondary prevention

[a]Missing kidney function is treated as a score of 0

Figure 1. Age-adjusted prevalence of statin prescription, by age group, for people in secondary prevention.

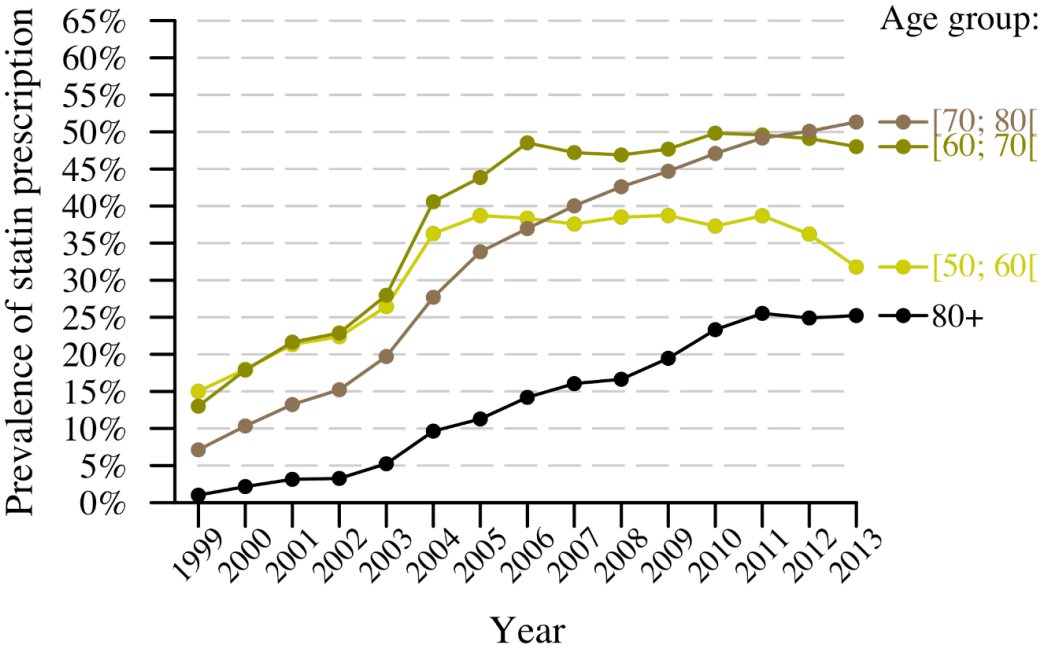
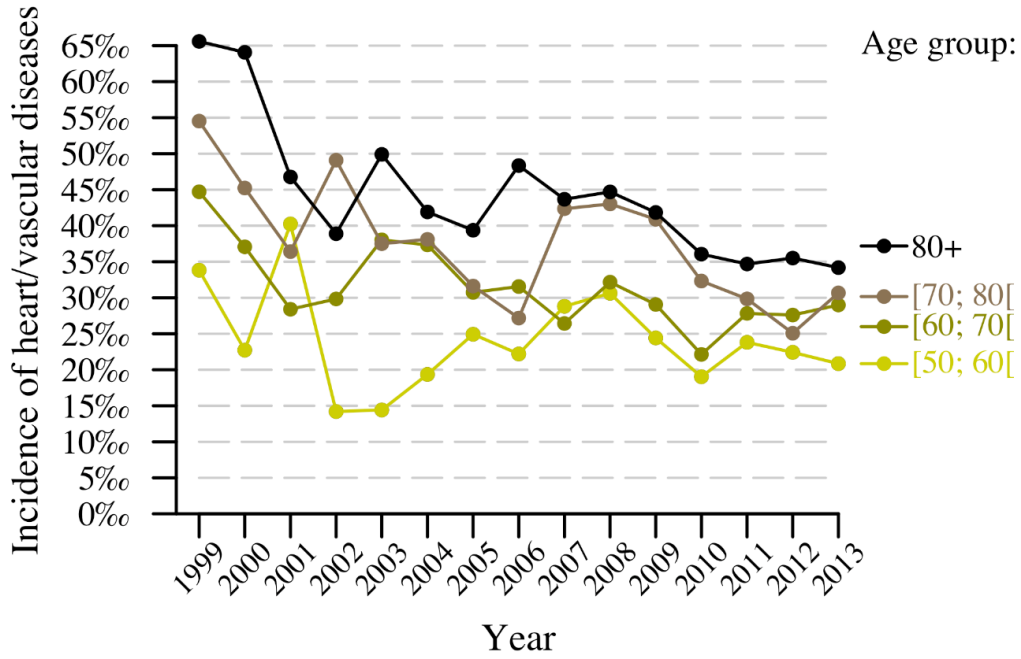


Figure 2. Age-adjusted incidence rate of HD/CV diseases, by age group, for people in secondary prevention.



Appendices

Appendix 1: protocol Ethics Committee

Masterproef: Statinebeleid bij 80-plussers

1. Inleiding

1.1 Probleemstelling: wat is er gekend? Algemene setting en epidemiologische gegevens.

Hart- en vaatziekten vormen een verzamelnaam voor cerebrovasculaire (CVA en TIA), coronaire (AMI) en perifeer arteriële aandoeningen. Deze groep aandoeningen is verantwoordelijk voor 37% van de totale mortaliteit in België en is daarmee de belangrijkste doodsoorzaak. Meer dan de helft van de sterfgevallen tgv. hart- en vaatziekten treedt op bij patiënten die 65 jaar of ouder zijn. De incidentie van hart- en vaatziekten kende in de voorbije decennia een gunstige evolutie met een daling er van in de leeftijdsgroepen onder 69 jaar. Door de toenemende vergrijzing wordt verwacht dat 10% van de Belgische bevolking in 2050 tachtig jaar of ouder zal zijn, wat maakt dat hart- en vaatziekten echter toch de belangrijkste doodsoorzaak zullen blijven.

Naast de leeftijd wordt het risico op hart- en vaatziekten ook bepaald door verschillende andere factoren, waaronder geslacht, familiale anamnese, rookgedrag, diabetes, hypertensie en dislipidemie. Adequate aanpak van deze verschillende factoren speelt een belangrijke rol in het voorkomen of het uitstellen van hart- en vaatziekten of een recidief ervan. Met de toenemende vergrijzing wordt verwacht dat de kosten die gepaard gaan met de preventie, de behandeling van hart- en vaatziekten en de complicaties ervan, zullen stijgen. Dit maakt dat cardiovasculaire preventie een belangrijk onderdeel vormt in de gezondheidszorg.

1.2 Cholesterol en statines bij 80-plussers: wat is er gekend? (richtlijnen, reviews, meta-analyses en EBM-bronnen)

Hypercholesterolemie gaat gepaard met een verhoogd risico op hart- en vaatziekten en de behandeling er van met lipidenverlagende statines heeft een bewezen gunstig effect in de primaire en secundaire preventie. Hypercholesterolemie (en andere klassieke risicofactoren) blijken echter minder goede voorspellers van het cardiovasculair risico bij 80-plussers te zijn en dit vnl. in primaire preventie. Dit maakt dat er momenteel geen tools bestaan die het cardiovasculair risico bij 80-plussers kunnen inschatten.

Voor het gebruik van statines in primaire preventie bij 80-plussers bestaat er onvoldoende evidentie in huidige RCTs. De Belgische richtlijnen raden aan om statines enkel te starten bij patiënten met een verhoogd cardiovasculair risico tot de leeftijd van 70 jaar. De Nederlandse, Amerikaanse en Britse richtlijnen raden aan om bij het overwegen van een statinebehandeling rekening te houden met de levensverwachting van de patiënt en om de voor- (verwachte winst op morbiditeit en mortaliteit) en nadelen (bijwerkingen, geneesmiddeleninteracties) ervan af te wegen in overleg met de patiënt.

Voor de secundaire preventie van cardiovasculaire ziekten raden alle richtlijnen aan om ongeacht de leeftijd altijd een statine op te starten omdat er dan een duidelijk gunstig effect bestaat op de cardiovasculaire morbiditeit en mortaliteit en op de totale mortaliteit.

Over het eventueel stopzetten van een behandeling met statines (zgn. quaternaire preventie) bestaan er weinig gegevens. Volgens de Nederlandse en Amerikaanse richtlijnen heeft dit een ongekend effect op het cardiovasculair risico. Zij raden aan om de behandeling verder te zetten als het goed verdragen wordt, aangezien het veilige geneesmiddelen zijn. Terminale situaties (bv. kanker, ernstig hart- en nierfalen…) zijn indicaties om een behandeling met statines stop te zetten.

De belangrijkste bijwerkingen van statines zijn DM type2, musculoskeletale aandoeningen, ALT-stijging en cataract. Statines verhogen het risico op kanker niet en over het effect ervan op cognitieve aandoeningen bestaat geen zekerheid. Of ouderen meer vatbaar zijn voor deze bijwerkingen is tot nu toe ongekend. Het risico op bijwerkingen is groter bij patiënten die meerdere geneesmiddelen nemen door eventuele interacties er mee.

1.3 Wat is er nog niet gekend? Wat willen we weten? Wat zouden we kunnen te weten komen?

- Evidentie van statines in primaire preventie bij 80-plussers?
- Kosten-effectiviteit van statines in primaire en secundaire preventie bij 80-plussers?
- Prevalentie en incidentie van bijwerkingen en interacties van statines bij 80-plussers? Komen deze ongewenste effecten meer voor op oudere leeftijd en wegen de voordelen van een statine dan nog op tegen de eventuele nadelen ervan?
- Wanneer kan overwogen worden om een statine te stoppen?
- Wat is het effect van andere hypolipemiërende geneesmiddelen op het cardiovasculair risico?
- Hoe moeten secundaire oorzaken van hypercholesterolemie (DM, hypothyroïdie, nefrotisch syndroom, bijwerking geneesmiddelen…) aangepakt worden?
- Welke factoren spelen er naast de klassieke risicofactoren nog een rol bij het bepalen van het cardiovasculair risico bij ouderen?

1.4 Wat gaan we doen om daar een antwoord op te geven?

De indicaties om een behandeling met statines op te starten zijn veranderd: daar waar het vroeger werd voorgeschreven voor de behandeling van hypercholesterolemie, wordt het nu voorgeschreven bij een verhoogd cardiovasculair risico. Mochten we nu alle patiënten met hypercholesterolemie behandelen, zou dit betekenen dat meer dan 4 op 5 Belgen een statine zou moeten krijgen.

Leeftijd is de belangrijkste cardiovasculaire risicofactor. Men zou dus verwachten dat statines het meest voordeel bieden en dus ook het meest voorgeschreven worden bij oudere patiënten. Onderzoek toont echter aan dat het voorschrijven van statines vermindert met toenemende leeftijd. Deze behandel-risico-paradox wordt verklaard door verschillende factoren: onzekerheid over de evidentie van statines bij oudere patiënten, verhoogd risico op bijwerkingen (door o.a. geneesmiddeleninteracties, veranderde farmacodynamische eigenschappen, frailty en comorbi-diteit…), onderschatting van de levensverwachting van ouderen…

Om antwoord te krijgen op de vragen uit het vorige puntje, zal een therapeutische retrospectieve observationele studie gebeuren, waarbij de gegevens die verzameld werden in de Leiden 85+- en de Belfrailstudie met mekaar zullen vergeleken worden. De Leiden 85+-studie is een prospectief observationele cohortestudie onder alle inwoners van Leiden die in de periode van 1997 tot 1999 85 jaar werden (n=599). De Belfrail studie is een gelijkaardige studie onder alle inwoners van België die in 2008-2009 80 jaar of ouder waren (n=567). In beide studies werden gedurende minstens 5jaar jaarlijks verschillende variabelen (o.a. welzijn, BD, ECG, labo, medicatie, voorgeschiedenis, datum en oorzaak van overlijden...) van alle deelnemers bepaald. Het doel van beide studies was om meer inzicht te krijgen in de verschillende factoren die een invloed hebben op succesvol verouderen. Het percentage deelnemers die een statine nam, bedroeg in de Leiden 85+- en de Belfrailstudie respectievelijk 1% en 30%. Aangezien beide studies een vergelijkbare populatie bestudeerden en aangezien de studies uitgevoerd werden met een verschil van 10 jaar, laat dit toe om na te gaan waarom statines nu en vroeger werden opgestart en om na te gaan wat het effect ervan is op de cardiovasculaire morbiditeit en mortaliteit. Deze studies laten toe om na te gaan of er andere dan de klassieke cardiovasculaire risicofactoren zijn bij ouderen. De Belfrailstudie laat toe om de prevalentie en de ernst van bijwerkingen van statines bij ouderen te bestuderen.

2. <u>Onderzoeksvraag</u>

Bestaat er evidentie voor statines in de primaire en secundaire preventie van cardiovasculaire ziekten bij 80-plussers? Wanneer wordt besloten om een statine op te starten vroeger en nu en heeft dit effect op de cardiovasculaire morbiditeit en mortaliteit en op de totale mortaliteit? Zijn 80-plussers vatbaarder voor bijwerkingen van statines en wegen deze eventuele nadelen zwaarder door dan de voordelen ervan? Welke conclusies kunnen we hieruit trekken m.b.t. de dagdagelijkse praktijk?

Appendix 2: approval Ethics Committee

Van: An Stockmans <an.stockmans@icho.be>
Onderwerp: Betreft uw aanvraag Ethische begeleiding masterproeven
Datum: 8 april 2015 11:19:32 CEST
Aan: Bert Vaes <Bert.Vaes@med.kuleuven.be>
Kopie: Nele Laleman <nele.laleman@student.kuleuven.be>
Antwoord aan: An Stockmans <an.stockmans@icho.be>

Betreft uw aanvraag Ethische begeleiding masterproeven

Beste student
Dear student

Uw aanvraag werd aanvaard door de ethische commissie van het UZ Leuven. Dit wil zeggen dat de ethische commissie van oordeel is dat uw studie volgens de gangbare ethische normen wordt uitgevoerd.
Indien u van plan bent uw masterproef te publiceren kan u deze mail als bewijs van goedkeuring door een ethische commissie aan het betreffende tijdschrift doorgeven.

Your application was accepted by the Ethics Committee of the University Hospitals Leuven. This means that the Ethics Committee acknowledges that your study is carried out according to the prevailing ethical standards.
If you plan to publish your masterthesis you can use this mail as approval by the ethics committee.

Met vriendelijke groeten

An Stockmans