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Received 28 March 2013; revised 19 July 2013; accepted 15 August 2013; online publish-ahead-of-print 17 September 2013

Background

Methods and results
The PHARMO database was used for record linkage of drug dispensing, hospitalization, and population data to identify drug use between 1998 and 2010 in 1,203,290 persons ≥25 years eligible for primary prevention, 84,621 persons hospitalized for an acute coronary syndrome (ACS), and 15,651 persons eligible for secondary prevention. The use of cardiovascular drugs increased over time in all three settings. In primary prevention, the proportion of women that used lipid-lowering drugs was lower than men between 2003 and 2010 (5.7 vs. 7.3% in 2010). The higher proportion of women that used blood pressure-lowering drugs for primary prevention, compared with men, attenuated over time (15.1 vs. 13.8% in 2010). During hospital admission for an ACS, the proportion of women that used cardiovascular drugs was lower than men. In secondary prevention (36 months after hospital discharge), drug use was lowest in young women. The proportion receiving lipid-lowering drugs declined after the age of 75 in all three settings. This age difference attenuated over time.

Conclusion
Age differences in drug use tended to attenuate over time, whereas gender differences persisted. Areas potentially for improvement are in the hospital treatment of ACS in young women, in secondary prevention among young women and the elderly, and in the continuity of drug use in secondary prevention.

Keywords
Cardiovascular drugs • Coronary heart disease • Trends • Prevention • Age • Gender

Introduction
Coronary heart disease (CHD) is a largely preventable disease.1 Yet, it remains one of the major causes of disability and death.2 Recent guidelines on primary and secondary prevention of CHD emphasize, apart from lifestyle changes, the use of cardiovascular drugs, in particular platelet aggregation inhibitors, lipid-lowering drugs (mostly statins), and blood pressure-lowering drugs [including beta-blockers, angiotensin-converting enzyme inhibitors (ACE-Is), angiotensin receptor blockers (ARBs), calcium channel blockers (CCBs) and diuretics].3–6
Several studies have indicated that in secondary prevention, age and gender inequalities exist in the use of preventive drugs.7–11 These point towards less lipid-lowering drug use at older ages and in women. Data for primary prevention are much more limited and seem to point towards differences in cardiovascular drug use with increasing age, in particular lipid-lowering drugs lagging behind blood pressure-lowering drugs.12 Insight into time trends in cardiovascular
drug use for the prevention and treatment of CHD may provide important information on how much progress has been made in different settings, which is vital information for future strategies. As evidence on recent time trends in age and gender differences in cardiovascular drug use is scarce, we set out to assess time trends in age–gender-specific cardiovascular drug use for primary prevention, secondary prevention, and in-hospital treatment of CHD.

Methods

Data source
We conducted a population-based analysis on the PHARMO database network, a record linkage system containing drug-dispensing records from community and hospital pharmacies linked with hospital discharge records, as described in detail previously. Cardiovascular drug dispensions between 1998 and 2010 were identified in a dynamic cohort of over 1.4 million residents aged 25 years and over in the Netherlands. Members of a dynamic cohort can leave or can be added over time to the cohort. In our study, individuals could have moved in or moved out of the PHARMO area, could have died, could have turned 25 years of age, or could have been institutionalized. These aspects all lead to inclusion or exclusion out of the study population every year. In order to estimate population-based treatment uptakes of cardiovascular drug use, we used cross-sectional samples of each year, drawn from the number of inhabitants of the well-defined 48 geographical areas of the PHARMO area. The number of inhabitants over 25 years in the PHARMO area increased from 1.0 million in 1998 to 1.2 million in 2010. In the total study period, data from more than 1.4 million unique individuals were analysed. The inhabitants of the PHARMO population are representative for the total Dutch population of that year. The clustering of community pharmacies within the PHARMO areas resulted in drug-dispensing information that contained >95% of all prescriptions dispensed to all the community-dwelling residents.

Drug-dispensing records from hospital pharmacies were linked to hospital discharge records of the same patient from the national hospital discharge register. Hospital discharge records included information concerning primary and secondary diagnoses, performed procedures, and dates of hospital admission and discharge. Hospital discharge diagnoses were coded according to the International Classification of Diseases version 9 (ICD-9). The number of inhabitants over 25 years in the PHARMO area increased from 1.0 million in 1998 to 1.2 million in 2010. In the total study period, data from more than 1.4 million unique individuals were analysed. The inhabitants of the PHARMO population are representative for the total Dutch population of that year. The clustering of community pharmacies within the PHARMO areas resulted in drug-dispensing information that contained >95% of all prescriptions dispensed to all the community-dwelling residents.

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Primary prevention
We studied the use of blood pressure-lowering drugs (beta-blockers, ACE-I/ARBs, CCBs, and diuretics) and lipid-lowering drugs (statins and others) in the eligible population for primary prevention by a previously described method. In brief, we used information on filled prescriptions from community pharmacies to estimate drug use by a point prevalence at one time point in each index year (for primary prevention at 1 October). An individual was defined as user if this time point fell between the dispensing date and theoretical end date of a prescription. The calculated theoretical duration of a prescription was multiplied with 1.1 to correct for early and irregular drug collection from the pharmacy as detailed previously.

To distinguish individuals with established cardiovascular disease from those in the primary prevention population, persons with a cardiovascular-related hospital admission within 5 years and 9 months prior to 1 October in the index year (ICD-9 401–459 or an admission with PCI, CABG, or diagnostic cardiac catheterization performed), or those that were on nitrates (C01DA), digitalis glycosides (C01AA), or antithrombotic drugs (B01) in the index year, were excluded from the primary prevention population. The latter were considered as asymptomatic individuals. The primary prevention population was defined from the total dynamic PHARMO cohort each year separately. We had data available from January 1998 to December 2010. Since 5 years were needed to make sure that no hospital admission for cardiovascular disease had taken place to identify asymptomatic individuals, time trends in cardiovascular drug use for primary prevention were based on the time period between 2003 and 2010.

In-hospital treatment
We studied cardiovascular drug use during hospital stay in individuals from the dynamic PHARMO cohort admitted to the hospital for an acute myocardial infarction (AMI, ICD-9 code 410) and for unstable angina (UA, ICD-9 code 411 or 413). These individuals were identified by linking hospital discharge and hospital pharmacy records. Primary discharge diagnoses were used to select AMI and UA hospital admissions. Recurrent admissions within 3 months in the same individual were excluded. To ensure enrolment status, individuals were required to have at least one filled prescription from the hospital pharmacy during their hospitalization. Drug use was defined as at least one prescription within a drug class during hospital stay. Drugs evaluated were antithrombotic drugs (heparin, aspirin, thienopyridines), vasodilators, blood pressure-lowering drugs (beta-blockers, CCBs, ACE-I/ARBs, diuretics), and lipid-lowering drugs. Time trends in in-hospital treatment were studied for the period between 1998 and 2010.

Secondary prevention
We followed closed cohorts of individuals admitted for ACSs (i.e. AMI or UA) in 1998, 2003, and 2007 with respect to drug use 3 months (T3), 12 months (T12), and 36 months (T36) after the date of hospital discharge (T0). These time points were specifically chosen to make optimal use of the available data (1998–2010), enabling us to study time trends in drug use between the beginning, middle, and end of the study period, and at shorter and longer intervals from hospital discharge. The denominator was based on patients who were alive at hospital discharge. Individuals were excluded from the denominator at their discharge from the database, which could be due to moving out of the PHARMO area, death, or institutionalization. Information on drug dispensings at T3, T12, and T36 was obtained from community pharmacy data and presented at cohort level. We used the same definition of drug use as in primary prevention, with T3, T12, and T36 as time points for the estimation of drug use in secondary prevention of CHD.

Data analyses
Treatment uptakes of cardiovascular drugs were presented as the percentage of users of the different drug classes within the patient groups and population groups, and plotted using yearly intervals. In secondary prevention, we analysed combination therapy by the number of drugs that was used from the four preventive drug classes (i) antithrombotics,
We age-standardized treatment uptakes for primary prevention to the asymptomatic population of 2010 aged 25 years and over, using a direct method with 10-year age groups. Treatment uptakes during in-hospital treatment and secondary prevention were standardized to the age distribution of the ACS population in 2010.

Differences in the use of cardiovascular drugs by age, gender, and over time were evaluated by using generalized estimating equation (GEE) models. These models were used to account for the correlation in treatment uptakes over time within individuals. We adjusted for differences in age, gender, and calendar year and in secondary prevention and in-hospital treatment also for the diagnosis of the hospital admission (AMI or UA). Interaction terms between calendar year and age or gender were added to the models to assess the presence of changes in age and gender differences over time. All analyses were performed using PROC GENMOD in SAS Enterprise Guide version 4.3 (SAS Institute, Cary, NC, USA).

Results

Primary prevention
From the dynamic PHARMO population, we identified 1,203,290 eligible persons for primary prevention in the total period, of which 55.3% were women. We considered 84.7% in 2003 and 77.2% of the population in 2010 as asymptomatic individuals.

Overall use in time
In 2003, 3.3% of the population used lipid-lowering drugs and 11.1% used any blood pressure-lowering drug. In 2010, these percentages were 6.5 and 14.6%. The use of all cardiovascular drugs increased over time (all P-values < 0.001, Supplementary material online, File 2).

Differences by age and gender
Cardiovascular drug use increased with increasing age, up to the age of 75 years for lipid-lowering drugs and up to the age of 85 years for blood pressure-lowering drugs (Figure 1). The use of blood pressure-lowering drugs at old age (≥75 years) was at least three times that of lipid-lowering drugs (38.2 vs. 12.0% in 2010, P < 0.001). The age-standardized proportion that used lipid-lowering drugs was lower in women than men (5.7 vs. 7.3% in 2010, P < 0.001). Women received lipid-lowering drugs, on average, at later age than men. The lower proportion of lipid-lowering drug users in women than men was present in all up to the age of 65 years (3.8 vs. 5.9% in 2010, P < 0.001), whereas the proportion of elderly (≥65 years) that used lipid-lowering drugs was higher in women than men (15.5 vs. 14.3% in 2010, P < 0.001). The proportion that used any blood pressure-lowering drug was higher in women (15.1 vs. 13.8% in 2010, P < 0.001), most pronounced at higher ages (Figure 1).

Age- and gender-specific time trends
Lipid-lowering drug use increased over time in all age groups, yet most pronounced aged ≥75 years (Figure 1, P < 0.001). The use of lipid-lowering drugs for primary prevention increased in the age group of 75–84 years from 5.0% in 2003 to 14.7% in 2010 and in the age group of 85–94 years from 0.9 to 4.7%. The gender difference in the use of lipid-lowering drugs did not significantly change over time (P = 0.28). The difference between men and women in the use of blood pressure-lowering drugs attenuated over time (P < 0.001).

In-hospital treatment
We identified 32,043 AMI and 52,578 UA hospital admissions between 1998 and 2010, of which 32.9 and 38.2% were women, respectively. The mean age was 64.8 (SD 13.3) years for AMI patients and 64.5 (SD 12.1) years for UA patients.

Overall use in time
Cardiovascular drug use during ACS hospitalization increased over time (Supplementary material online, File 3). The most pronounced increases were observed in the use of thienopyridines (from 2.2 to 77.0%), ACE-Is or ARBs (from 30.3 to 58.3%), and lipid-lowering drugs (from 25.3 to 85.4%). Decreases were observed in the use of vasodilators (from 74.8 to 54.0%) and CCBs (from 42.7 to 32.2%) (all P-values < 0.001). Trends in the use of combination therapy during hospitalization are presented in Supplementary material online, File 4.
Differences by age and gender
In elderly ACS patients ≥75 years, compared with younger patients, the proportion using lipid-lowering drugs was lower (79.1 vs. 92.8% in 2010, P = 0.02, Figure 2). For antithrombotics and beta-blockers, no differences were seen (P = 0.16 and P = 0.77). The proportion using other blood pressure-lowering drugs than beta-blockers was higher in those ≥75 years (84.8 vs. 72.0% in 2010, P < 0.001). Women were less likely to use antithrombotics (P = 0.02), lipid-lowering drugs (P < 0.001), and beta-blockers (P = 0.03) than men over the total study period (Figure 2), most pronounced at younger ages. Especially in UA patients, a lower proportion of users in women than men was observed (in 2010: antithrombotics 93.0 vs. 95.6%, lipid-lowering drugs 77.5 vs. 85.4%, beta-blockers 80.6 vs. 83.3%, and other blood pressure-lowering drugs than beta-blockers 72.3 vs. 74.6%).

Age- and gender-specific time trends
The age difference in the use of lipid-lowering drugs attenuated over time (P = 0.03); however, a marked decline after the age of 85 years remained in 2010 (50.1% ≥85 years vs. 87.6% <85 years, Figure 2). The higher use of other blood pressure-lowering drugs than beta-blockers in patients ≥75 years compared with younger patients did not significantly change over time (P = 0.49). The differences between men and women did not significantly change for the use of antithrombotics (P = 0.73), lipid-lowering drugs (P = 0.45), and beta-blockers (P = 0.96).

Secondary prevention
We followed 15,651 men and women after hospital discharge for ACS for cardiovascular drug use in the secondary prevention setting at 3, 12, and 36 months after discharge. Loss to follow-up at 3, 12, and 36 months after hospital discharge was 258 (1.6%) persons after 3 months, 867 persons (5.5%) at 12 months, and 2359 persons (15.1%) at 36 months from hospital discharge.

Overall use in time
The use of recommended drugs in secondary prevention increased between the cohorts of 1998, 2003, and 2007 (P < 0.001). Three months after discharge in 1998, 64.6% of the patients used antithrombotics, 25.6% lipid-lowering drugs, 47.4% a beta-blocker, and 52.7% an ACE-I, ARB, CCB, or diuretic (Supplementary material online, File 5). Three months after discharge in 2007, these percentages were 73.1, 61.7, 62.1, and 61.0%. Thirty-six months after hospital discharge in 1998, 63.2% used antithrombotics, 36.1% lipid-lowering drugs, 40.9% a beta-blocker, and 50.0% other blood pressure-lowering drugs than beta-blockers. These percentages were 64.7, 53.1, 50.1, and 57.4% for patients admitted in 2007. In 2001, 25.4% of the patients used none of the four recommended drugs, 35.9% drugs from one or two drug classes, and 38.6% drugs from three or all four drug classes. In 2010, these percentages were 26.3, 22.3, and 51.3% (Figure 3).

Differences by age and gender
The use of antithrombotic drugs increased with age in a gradual manner (Figure 4). A similar pattern was found for beta-blockers and other blood pressure-lowering drugs. Lipid-lowering drug use seemed stable up to the age of 85 years after which the use of lipid-lowering drugs declined (28.2% ≥85 years vs. 53.0% <85 years in 2010, Figure 4). Women were less likely to use antithrombotic drugs than men (60.5 vs. 67.0% in 2010). For lipid-lowering drugs, a similar trend was seen, especially in 2010 (48.1 vs. 55.8%). Under the age of 65 years, women were also less likely to use combination therapy than men (drugs from three or four drug classes, P < 0.001, Figure 3).

Age- and gender-specific time trends
The age differences in the use of the recommended drug classes did not significantly change over time (all P > 0.18). The gender differences in the use of lipid-lowering drugs and antithrombotic drugs in secondary prevention of CHD also did not significantly change over time (P = 0.32 and P = 0.28). An overview of all trends in cardiovascular drug use is presented in Table 1.

Discussion
We found that (i) the use of cardiovascular drugs increased between 1998 and 2010 in primary prevention, secondary prevention, and in-hospital treatment of CHD; (ii) cardiovascular drug use generally increased with increasing age; however, this pattern was different for lipid-lowering drug use, which declined after the age of 75 years; (iii) young women were substantially less likely to use
lipid-lowering drugs and antithrombotics than men in all three settings; (iv) gender differences in cardiovascular drug use persisted over time, whereas age differences generally attenuated.

**Primary prevention**

Our data confirm the finding among general practitioners in 2009 in the UK that at older age (i.e. ≥75 years) the use of lipid-lowering drugs is much lower than that of blood pressure-lowering drugs. This was found despite the fact that trials consistently showed beneficial effects of these drugs up to the age of 80 years. We expand on the findings of the UK study by showing that the absolute use of cardiovascular drugs in primary prevention increased over time. The guideline of the Dutch College of General Practitioners (NHG) for prescription of lipid-lowering drugs has recently removed the previous upper age limit—70 years in men and 75 years in women, in the guideline of 2006. Persons ≥75 years showed the largest increase in lipid-lowering drug use between 2003 and 2010. The difference between the use of lipid-lowering...
and blood pressure-lowering drugs highlights the need for a stronger evidence base and clearer guidelines for the elderly.

In contrast to the UK study, we found differences between men and women in the use of lipid-lowering drugs (lower in women) and blood pressure-lowering drugs (higher in women). Gender differences in drug use could be a consequence of differences in the prescription attitude of physicians or differences in attitude in taking the drugs by patients. In primary prevention, however, the most likely underlying cause for gender differences is differences in indications for prescriptions. Since women have a lower absolute risk for cardiovascular events, at least in younger age ranges, a lower use of lipid-lowering drugs in women might be a result of adherence to guidelines.

In-hospital treatment
As reported in other hospital-based studies, ACS patients are generally treated well pharmacologically during hospital stay. Yet, gender differences persisted, especially in UA patients. A study from Sweden performed between 1995 and 1999 among 1744 patients hospitalized for ACS patients showed no gender differences. We observed that especially young women used, compared with young men, less antithrombotics, lipid-lowering drugs, and beta-blockers during ACS hospitalization. A Japanese study observed lower use of aspirin in young women compared with young men, and higher use of lipid-lowering drugs in older women compared with older men. Age and gender differences in drug use during hospitalization could, to some extent, be related to differences in the severity of the ACS and comorbidities. However, one would expect that women with an ACS receive the same treatment with respect to antithrombotics and lipid-lowering drugs in-hospital as men.

Secondary prevention
Our study, like most other studies, showed increases over time in the use of cardiovascular drugs in secondary prevention. Furthermore, we confirm that the use of cardiovascular drugs substantially declined soon after hospital discharge, and continued to decline in the following years. Low continuation rates of cardiovascular drugs are worrisome and need attention of both physicians and patients. Quitters when compared with compliant individuals are at increased risk of future events.

With respect to age and gender differences in secondary prevention, two British studies reported persistent lower use of lipid-lowering drugs in older age. Underuse of lipid-lowering drugs and beta-blockers in angina patients in Scotland was most pronounced in older women. Gender differences in the use of cardiovascular drugs in secondary prevention increased over time in Scotland, whereas age differences attenuated. A recent Italian study showed that the improvement over time in prescription of evidence-based treatment was less in the elderly and most pronounced in the young. These studies all reported lower use of lipid-lowering drugs in secondary prevention in elderly patients. We expanded this by showing that drug use was more worrisome in young women, which showed the lowest use of antithrombotics, lipid-lowering drugs, beta-blockers, and other blood pressure-lowering drugs in secondary prevention. Whereas age differences attenuated in primary prevention and in-hospital treatment, these age—gender differences persisted in secondary prevention.

Age—gender differences in secondary prevention are most likely a consequence of differences in the prescription attitude of physicians or differences in attitude in taking the drugs by patients. Furthermore, previous studies have reported that gender differences in secondary prevention may be partly explained by more severe disease in men.
It is important that both patients and physicians are aware of the need for lifelong therapy with cardiovascular drugs in secondary prevention. Physicians might focus more on reduction of risk factors (e.g. high blood pressure) than on the risk for the patient. This might also be reflected in the lower use of cardiovascular drugs in women than men in secondary prevention, the lower use of cardiovascular drugs <75 years, and the relatively high use of blood pressure-lowering drugs compared with the suboptimal use of lipid-lowering drugs in elderly persons.

Study strengths and limitations
The main strength was the availability of large, longitudinal, population-based data sets providing accurate data on hospital admissions and prescription of drugs from hospital and community pharmacies. We were able to follow a well-defined population of over 1.4 million community-dwelling Dutch inhabitants for information up to the year 2010. We included all residents ≥25 years from the PHARMO area, thus also those who rarely consult a general physician or specialist hospital doctor. The use of pharmacy records is commonly considered more complete than medical records. Additionally, pharmacy records bypass the potential recall bias that may arise from interview data, or survey data using self-reported drug use.

Our study also had some limitations. First, we might have misclassified some cardiovascular disease patients as asymptomatic with our restriction of excluding everyone within 5 years and 9 months with a hospital admission for cardiovascular disease. This approach might have led to a small overestimation of cardiovascular drug use in primary prevention. Yet, our method of using information from registries to distinguish cardiovascular disease patients from asymptomatic individuals is well established. A register-based study from Kildemoes et al. reported the impact of applying different run-in periods to capture surviving individuals with prior myocardial infarction in Denmark. About 60% of the AMI patients were captured applying a run-in period of three years, and 74 and 94% were captured with run-in periods of 5 and 10 years, respectively. Second, our relatively tight definition of drug use may have resulted in an underestimation of drug use in primary and secondary prevention. Third, we excluded persons who were lost to follow-up because of death, movement out of the PHARMO area, or institutionalization from the secondary prevention population (15% lost to follow-up after 36 months). We assume that there are no large differences in drug use between the 85% of persons who remained in the PHARMO area and the 15% of persons who disappeared from the PHARMO area. We, therefore, think that bias by survival is unlikely. Yet, if our prevalence estimates in secondary prevention are biased by survival, the estimates probably reflect an overestimation of the truth, as non-compliant patients are most likely to die, so there could be an under-reporting of those who did not use the medication. Fourth, we had no information on the indication for prescription or the contraindication for not prescribing, and thus differences between men and women and between age ranges might be a consequence of differences in risk estimates (primary prevention) or clinical symptoms/presentation of the patient in in-hospital treatment and in secondary prevention. Yet, we would like to stress that our results are meant for descriptive purposes at a population level rather than for use as an indicator of quality of individual care.

Implications
Effective primary prevention and secondary prevention have the capacity to quickly lower the burden of CHD, which makes optimal implementation of cardiovascular drugs in all age and gender groups highly relevant and a necessary and desirable objective. Our study highlights age and gender differences in the use of cardiovascular drugs and provides trends over time, which may trigger further research into the reasons for not adhering to the current guidelines and for the observed age and gender differences.

Conclusions
The use of cardiovascular drugs for prevention and treatment of CHD increased in recent years in the Netherlands. Overall, age differences in cardiovascular drug use for prevention and treatment of CHD tended to attenuate over time, whereas gender differences persisted. There seems to remain opportunity for improvement, especially in the hospital treatment of young women, secondary prevention therapy of young women and the elderly, and the continuity of drug use in long-term secondary prevention.

Supplementary material
Supplementary material is available at European Heart Journal online.

Funding
C.K. was supported by a grant from the Dutch Heart Foundation (grant DHF project ‘Facts and Figures’).

Conflict of interest: none declared.

References


