Safety and Effectiveness of Statins for Prevention of Recurrent Myocardial Infarction in 12,156 Typical Older Patients: A Quasi-Experimental Study

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ABSTRACT

Background

There is limited evidence on statin risk and effectiveness for patients aged 80+. We estimated risk of recurrent myocardial infarction (MI), muscle-related and other adverse events, and statin-related incremental costs in 'real-world' older patients treated with statins vs. no statins.

Methods

We used primary care electronic medical records from the UK Clinical Practice Research Datalink. Sub-hazard ratios (SHR, competing risk of death) for MI recurrence (primary endpoint), falls, fractures, ischemic stroke, and dementia and hazard ratios (Cox) for all-cause mortality were used to compare older (60+) statin users and 1:1 propensity-score-matched controls (n=12,156). Participants were followed-up for 10 years.

Results

Mean age was 76.5±9.2 years; 45.5% were women. Statins were associated with near significant reduction in MI recurrence (SHR=0.84, 0.69-1.02, p=0.073), with protective effect in the 60-79 age group (0.73, 0.57-0.94) but a non-significant result in the 80+ group (1.06, 0.78-1.44; age interaction p=0.094). No significant associations were found for stroke or dementia. Data suggest an increased risk of falls (1.36, 1.17-1.60) and fractures (1.33, 1.04-1.69) in the first two years of treatment, particularly in the 80+ group. Treatment was associated with lower all-cause mortality. Statin use was associated with healthcare cost savings in the 60-79 group but higher costs in the 80+ group.

Conclusions

Estimates of Statins effectiveness for recurrent MI prevention in patients aged 60-79 were similar to trial results, but more evidence is needed in the older group. There may be an excess of falls and fractures in very old patients, which deserves further investigation.

Key words: statins, myocardial infarction, falls, fractures, older, electronic medical records.

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Introduction

Statins are cholesterol-lowering drugs commonly used to prevent myocardial infarction (MI), ischemic stroke (ST), and other cardiovascular conditions(1). Despite their widespread use in older people evidence of efficacy and risks is limited for the very old and older people with significant comorbidities(1, 2).

In the US from 2004 to 2009, 27% of people 55-79 years old and 24% of those aged 80 and older received statins(3). These figures are expected to rise significantly according to recommendations from current guidelines(1, 4). While statin safety and efficacy have been consistently shown in randomised clinical trials (RCTs) of middle-aged and generally healthy younger old people(5-8), evidence in the very old and in older patients with greater burden of disease is poor. RCTs on statins enrolled a relatively low proportion of individuals aged 75 and over (1), very few patients with significant comorbidity and no patient 85 and older(2). Therefore results of available RCTs should not be extrapolated to the general older population and additional research is needed.

RCTs in real-world older patients are practically and ethically challenging, particularly for established treatments in high-risk populations, therefore observational studies evaluating the statin risk and effectiveness might help clarify the risk-to-benefit ratio in this group. To our knowledge, only one relatively small study investigated the effect of statins in preventing MI recurrence in 'real-world' patients(9). This work did not account for major confounders, explore the competing risk of death, or investigate concurrent adverse events(9).

Moreover, RCTs are often based on too small samples and too short follow-ups to provide robust evidence on adverse events. For this reason, the US Food and Drug Administration, for example, support the use of electronic medical record data to provide active surveillance of regulated medications (http://www.fda.gov/Safety/FDAsSentinelInitiative/ucm149340.htm).

The present study was aimed to investigate the effectiveness of statins for MI recurrence prevention in a large sample of 'typical' older patients with incident MI, accounting for many potential

confounders and the competing risk of death. We also explored the risk of a number of conditions leading to disability in older age (ST, severe falls, fragility fractures, and dementia) and all-cause mortality, and estimated the effect of older age (80+) and burden of diseases on the association between statins and relevant endpoints. Finally, we investigated the incremental costs of statins. This was accomplished using a very-large database of GP medical records linked to hospital records and death certificates.

Although the presence of residual confounding from unmeasured factors can never be entirely excluded in observational research, results of this study will help increase the evidence base on statin risks and effectiveness in typical older people and support future interventional studies in this section of the population.

Methods

Data source

We used data from the UK Clinical Practice Research Datalink (CPRD), a database of anonymised electronic medical records collected by UK general practitioners (GPs)(10). Only data from practices linked to Hospital Episode Statistics (HES, for hospital records) and Office for National Statistics (ONS, for health certificates) databases(10) were used. The CPRD has been granted Multiple Research Ethics Committee approval (05/MRE04/87) to undertake purely observational studies and this study was approved by the Independent Scientific Advisory Committee for MHRA database research under protocol numbers 15_192R.

Study design and study sample

This is a quasi-experimental study designed as a retrospective parallel-cohorts study. Quasi-experiments are studies that aim to evaluate interventions but that do not use randomization(11). All participants were hospitalised for first MI between 1st April 1997 (first HES data collection) and

31st March 2014 (latest HES data collection date in the available dataset), aged 60+ years at the time of, and alive 4 weeks after the acute event (CONSORT diagram with participant selection criteria in Supplementary Figure S1).

Treatment groups

Statins (atorvastatin, fluvastatin, pravastatin, rosuvastatin and simvastatin), regardless of strength and treatment duration, represented the exposure. Lovastatin (not commercialised in the UK), cerivastatin (withdrawn from the market) and the association simvastatin/ezetimibe were not included in the analysis. Statins were coded according to Chapter 2.12 of the British National Formulary(12) and prescriptions derived from GP records.

The treatment group included all participants never treated with statins before their incident MI who had records of statin prescription within 56 days after the acute event. The control group included people never treated with statins before their first MI who did not receive a prescription of statins in the 56 after the acute event. According to previous research(13), including 'late' statin users in the control group, allows both to simulate situations encountered during RCTs and avoid a biased comparison only with controls never "at risk" of being prescribed a statin. The study groups were followed-up from the date of incident MI (baseline), until the occurrence of the event of interest, death, study end (i.e. 10 years after baseline or 31st March 2014, whichever came first) or, only for 'late statin users', until statin prescription.

For the purpose of exploring drug persistence in people treated with statins, duration of treatment was assessed only in people alive for the entire 10-year period, as the time spanning between the first and the last prescription refill.

Endpoints

Primary endpoint was a composite of fatal MI (MI followed by death within 28 days(14)) or non-fatal MI. We used only episodes of MI leading to hospitalisation and reported in HES records, to minimise misclassification given the low specificity of MI diagnosis in CPRD(15).

Secondary endpoints were ST, severe falls (requiring hospital admission), fragility fractures (spine, hip, wrist, humerus, pelvis, and ribs, requiring hospitalisation), dementia, and all-cause mortality. These conditions were coded using ICD-10 for ST and severe falls and ICD-10 + OPCS-4 codes for fractures and derived from HES database. Dementia was coded using GP ("Read codes" adapted for CPRD) and/or HES records (ICD-10). All-cause mortality was ascertained using a combination of both ONS and GP records. Analyses of all secondary endpoints were hypothesis generating and excluded people with the relevant condition at baseline.

Covariates

We used a set of 73 characteristics/conditions including enrolment period, demographics, traditional risk factors, diseases, drugs, and measures of healthcare utilisation (those included in table 1) as covariates to ensure an adequate control of confounding, according to previous work(16).
Covariates were coded by combining GP and HES data to reduce misclassification.
Healthcare costs, including statins and other medications(17), relevant monitoring tests(4), GP visits recorded(18), outpatient(18) and inpatients(19) hospital attendances were calculated based on GP and HES recorded events. Drugs were coded using the British National Formulary(12) and prescriptions derived from GP records.

Statistical analysis

Baseline differences of both non-matched and matched samples were reported as mean and standard deviation (SD) or percentages and compared using analysis of variance (ANOVA) or chi-square test as appropriate.
Groups were matched 1:1 using propensity score, based on 60 of the 73 covariates initially listed (those independently associated with exposure and/or primary outcome plus a few variables included regardless their lack of association because of their potential confounding effect).

Endpoint analyses used survival analysis with competing risk models(20), to account for the high frequency of death within this age group, and results were reported as Sub-hazard ratios (SHR) and 95% confidence intervals (95%CI), according to Fine and Gray(21). Cox proportional hazard models (using practice ID as strata) were used to analyse all-cause mortality and results were displayed as hazard ratios (HR) and 95%CIs.

Data were analysed by censoring follow-up time of 'late users' (control group only) when statin prescription was issued according to previous research(13). Alternate results obtained without this censoring were also presented as supplementary material.

Analyses on MI, ST, dementia, and all-cause mortality excluded events occurring the first two years of follow-up. Exclusion of the first two years of follow-up was based on exploratory analyses (data not shown) and meant to *i*) reduce "reverse causation' issues (people more likely to die in the short period were less likely to be treated and patients more likely to have immediate MI recurrence were more likely to receive statins), *ii*) reduce the confounding effect of early non-atherosclerotic coronary events (i.e. restenosis or late stent thrombosis) and *iii*) account for the timing of statin effect on cardiovascular outcomes that is likely to be apparent many years after treatment initiation(5). The main model for falls and fractures included the first two years of follow-up based on considerations regarding the shorter timing of statins effects on skeletal muscle. Results from alternate models including first two years of follow-up for MI, ST, dementia and all-cause mortality and excluding the first two years of follow-up for falls and fractures were also presented as supplementary material.

To investigate the effect of age and burden of disease on outcomes, using interactions terms, participants were divided into age (60-79 and 80+) and disease burden groups. The Charlson Comorbidity Index was used to assess disease burden since as this tool was adapted and validated in the CPRD(22). Patients divided into two disease burden groups (Charlson Index: <5, fist three quartiles, and ≥5, last quartile(22)). Age and disease burden analyses were not data-driven but pre-specified in the approved protocol, as one of the main objects of the present research.

A similar analysis investigated the effect of post-MI revascularisation procedures (percutaneous transluminal coronary angioplasty or coronary artery by-pass graft) on the association between statins and recurrent MI.

Numbers needed to treat were calculated using a published formula(23).

An alpha level of 0.05 was chosen as the threshold for statistical significance for the primary endpoint and a 0.10 level for interaction terms. All secondary endpoint analyses were considered exploratory.

Data were analysed using the Stata 13 (StataCorp. 2013. Stata Statistical Software: Release 13. College Station, TX: StataCorp LP).

Results

Sample characteristics

After propensity score matching, the study sample included 12,156 people (6,078 per group). Mean age at baseline was 76.5 (SD: 9.2), ranging from 60 to 105.4 years, women comprised 45.5% of the sample.

In the treatment group, 78.1% of patients received one statin, 18.9% two, and the remaining three or four. Of those who received one statin, 65% were treated with simvastatin, 28.9% with atorvastatin, and the remaining with pravastatin, fluvastatin, or rosuvastatin. In the control group, 42.6% of the patients received statin treatment ≥57 days after the acute event. Of these 'late' statin users, 29.8% received statins within the first 3 months, 34.5% within the first year, and the remaining 36.1% from 1 to 10 years after the first MI.

Eighty percent of participants aged 60-79 years and 58% of those aged 80+ and over who were alive for the entire 10-year follow-up were still on statins two years after the incident MI; these proportions decreased to 67.6% and 35.2% at year 4 and to 58.6 and to 20.9 respectively at year 6.

After matching, study groups did not differ for any of the 73 measured baseline characteristics (Table 1).

Primary endpoint

Figure 1 shows SHRs and 95% CI for recurrent MI for the whole study sample and by age and disease burden group. Patients were followed-up for 43,314 person-years. The rate of MI recurrence was 19.2 per 1,000 person-years (831 MIs). People treated with statins were less likely to have MI recurrence, although the association was only marginally significant in the whole sample. Statins showed a significant benefit in the 60-79 but not in the 80+ group. Disease burden did not affect the estimates.

Number needed to treat for MI recurrence was 154.6 (104.5-248.2); Undergoing revascularisation was associated with better statin effectiveness (revascularisation: SHR=0.41, 95%CI=0.27-0.51, p<0.001; no revascularisation: 0.95, 0.76-1.19, p=0.685; p for interaction=0.003).

When the first two years of follow-up were included in the analysis (Supplementary Table S1), statins were associated with a greater MI risk, particularly in older people (60-79: 0.99, 0.81-1.21, p=0.976; 80+: 1.46, 1.18-1.81, p<0.001; p for interaction=0.025).

Secondary endpoints

The incidence rate for ST was 7.1 per 1,000 person-years (n=196 cases), for dementia was 16.7 (n=446); for severe falls was 24.8 (n=1,026 episodes); for fragility fractures was 7.6 (n=322) and all-cause mortality rate was 115.1 (n=5,165) per 1,000 person-years.

Figure 2 shows SHR and 95%CI for ST, dementia, falls and fractures. No association was found between ST and dementia. People treated with statins were at greater risk of severe falls and fragility fractures.

The risk of falls (60-79: 1.13, 0.91-1.40, p=0.260; 80+: 1.82, 1.45 to 2.30, p<0.001; p for interaction=0.012) and fractures (60-79: 1.00, 0.70-1.41, p=0.993; 80+: 1.91, 1.36-2.67, p<0.001; p for interaction=0.019) was greater in people 80+ then in their younger counterparts.

Although the estimates were not significant, SHRs for ST were lower in the 60-79 than in the 80+ group (60-79: 0.73, 0.42-1.14, p=0.168; 80+: 1.37, 0.81-2.33; p for interaction=0.098).

No interaction with age was found for dementia. Burden of diseases did not affect the estimates of ST, dementia, falls and fractures (data not shown).

When events occurring during the first two years of follow-up were excluded from the analysis, people in the treatment group were less likely to fall than those in the control group (0.73, 0.64 to 0.85, p<0.001) (Supplementary Table S2).

Participants in the statin group had lower risk for all-cause mortality (HR=0.62, 0.57 to 0.68, p<0.001). Increasing age (60-79: 0.62, 0.55 to 0.72, p<0.001; 80+ and over: 0.77, 0.67 to 0.89, p<0.001; p for interaction=0.010), but not burden of disease, affected the association between statins and all-cause mortality. When follow-up of statin-treated controls was not censored at the time of statin initiation, the benefit of statins on all-cause mortality was substantially attenuated (HR=0.83, 0.78 to 0.90; p<0.001).

Costs

Over 10 years, mean total cost per patient in the statin group was £24,011 (~$36,000, at exchange rate of 1.50 $ per 1 £). For the control group the mean total cost was £23,094 (~$34,700). The mean cost difference between the groups was £917 (-3,930-5,630) (~$1,400) per patient per annum. In the 60-79 age group, statins resulted in cost savings of -£13,234 (-35,122-2,287) (~$20,000) but increased costs in the 80+ group £6,729 (5,099-8,265) (~$10,000).

Same associations but lower estimates were found when follow-up of people taking statins in the control group was not censored at the time of statin prescription. Overall mean cost difference was -£176 (-2,299-1,789) reflecting a cross-over use of statins by 42% (2564/6078) of subjects in the control group after the start of the observation period. The mean cost difference between the groups was £92 per patient per annum. In the 60-79 age group, statins resulted in cost savings of £-3,962 (-8,012- -175) but increased costs in the 80+ group £3,377 (1,319-5,077).

Discussion

To our knowledge, this is the first study investigating statin effectiveness for the prevention of MI recurrence in a large sample of 'real-world' older people with incident MI, accounting for a large number of covariates and exploring the competing risk of death. Results showed that statins were effective in younger old people in reducing recurrent MI, with similar effect sizes to those from RCTs. In testing for interactions with advanced age, we found evidence of more modest protective effects in the older group, but confidence intervals were wide and more evidence will be needed to clarify the effect sizes. Burden of disease did not affect the estimates. Undergoing post-MI revascularisation was associated with greater statin benefit.

Risk of falls and fractures might be higher, particularly in the very old during the first years of treatment. No association with ST or dementia was found. Finally, people treated with statins were at lower risk of all-cause mortality and yet, the benefit was lower in the very old. Statin treatment was associated with cost-savings in the 60-79 but higher costs in the 80+ group.

Data on older people have been provided in RCTs on statins including both primary and secondary prevention patients(24-26) and results are not easy to directly compare. Overall, our estimates for the primary endpoint (MI) are similar to those of RCTs on statins in the age group (60-79) usually enrolled in RCTs (5). To the best of our knowledge, only one observational study has evaluated the effectiveness of statins on the prevention of MI recurrence in 'real-world' older patients(9). In this study, conducted in a relatively small sample (n=1,410) of older patients, the authors found that, after adjusting for age, smoking habit, hypertension, diabetes, and LDL and HDL cholesterol levels, people in the statin group were less likely to develop fatal and non-fatal MI than people in the control group (Relative Risk=0.49, 0.43-0.57)(9). Given the limited number of potential confounders included in the analysis, the risk of residual confounding, particularly 'reverse causation', cannot be excluded in this study.

As expected, statin treatment immediately after MI was probably driven by a combination of better short-term prognosis (~4-fold greater first-year mortality rates in controls, data not shown) and greater risk of imminent MI recurrence (increased MI risk associated with statins when events occurred in the first years were included).

The fact that statin benefit might decrease in older age has been considered biologically plausible and previously reported in studies on statins and mortality(27). Of note, age also markedly affects the association between cholesterol levels and mortality for ischemic heart disease(28). However, we cannot exclude that the observed reduced benefit in people 80+ might result from poor treatment persistence.

All secondary endpoint analyses of this study should be considered exploratory.

Our results showed that statin was not associated with dementia risk. This is in line with a recent Cochrane review(29). The lack of association with ischemic stroke requires consideration. Although not significant, estimates obtained in the 60-79 group are similar to those of RCTs and our study was not powered to capture such an effect with small number of events.

We found increased risk in falls and fractures, especially in people 80+ during the first treatment years. Statins can cause myopathy, from subclinical to life-threatening forms and age and comorbidity are important risk factors (30). Its consequences in vulnerable older people can potentially be more dangerous than in younger/healthier older patients. While statin use has been associated with lower energy and greater muscle exertion(31), longitudinal decrease in muscle performance, and increased risk of falls in small studies of older people(32), other authors found no association(33), or even benefit on skeletal muscle(34). The fact that statins are protective from falls after the first two years, when follow-up time in statin-prescribed controls was not censored, is not easy to explain. This might result from a combination of fall rate reduction in the treatment group after the second year of follow up (discontinuation of treatment in case of adverse reactions and/or timing of muscle damaging effect) and concurrent fall rate increase among ‘late statin users’ (once

they start receiving treatment) in the control group that could not be captured when 'late statin users' follow-up time was censured. Alternatively, when taken for longer periods, statins might reduce the fall risk by slowing the decline of cardiovascular function.

A number of studies have investigated the association between statin use and all-cause mortality (27) in older people with previous cardiovascular disease. Our estimates were remarkably consistent with those of most published reports (27). The fact that estimates of statin benefit for all-cause mortality is greater than that for MI recurrence might be explained by long-term non-cardiovascular beneficial statin effects such as those on cancer(35); however, we cannot exclude the presence of residual confounding.

Previous modelling studies (36) found that statin therapy for secondary prevention is associated with increased costs to the health care system. In contrast, this analysis presents evidence from 10 years observational follow-up that statins may result in cost savings in people aged 60-79 but increased costs in 80+. These results warrant further cost-effectiveness analysis that accounts for the accrual of healthcare costs and quantity and quality of life benefits to patients.

There are inevitably limitations in the analysis presented. While statin prescription and the main conditions studied are likely to be accurately ascertained in the combination of primary care and hospital inpatient records used, there may be some under-diagnosis of dementia and under-recording of falls, but there is no apparent reason why these limitations would be associated with statin receipt after MI. The propensity scoring approach models effects only in those cases and controls that have overlapping scores, reducing the sample size analysed, although the patients included in analyses are those for whom clinical decisions about adding in statins varied after myocardial infarction in apparently similar cases.

Observational analyses like the one presented here are always limited in not being able to definitively exclude the existence of residual confounding that might have resulted from unmeasured factors, although the very high number of variables used in our propensity scoring

should have minimised such biases. Given that the statin treated group enjoyed lower mortality rates during the up to 10 year follow-up, the observed associations with injurious falls and fractures are unlikely to have been driven by a general excess morbidity in the statins group, but appear to be a specific effect that is difficult to explain by residual negative health difference between the statin treated patients and their controls, after matching. The main analysis for the primary endpoint (MI recurrence) excluded the first two years of follow-up and therefore the results obtained cannot be generalisable to the early period of treatment. However, since the beneficial effect of statins for cardiovascular prevention occurs 1-3 years after treatment start(5) we are confident that this exclusion, while helpful to address reverse causation, did not significantly bias the primary endpoint estimates. Finally, a number of unmeasured factors might have contributed to the high "noise-to-signal" ratio reflected by the large variability and confidence intervals in our real-world older people. While an "a priori" sample size calculation was performed based on the point estimates obtained by Baigent and colleagues(5), given the greater proportion of older patients in our sample and higher heterogeneity seen in this group, we cannot exclude that the overall primary endpoint analysis was slightly underpowered.

Along with the limitations, it is worth noting that the analysis includes all eligible patients in the dataset (i.e. the equivalent of a 100% response rate) and likely negligible loss to follow-up in hospital and death certificate data during our up to ten year analysis of outcomes. The estimates produced are therefore likely to represent 'real world' outcomes in typical clinical practice during the period studied. Also worth noting is that we have not excluded frail or dependent groups including those in nursing and residential homes.

Further work, including RCTs, is needed to replicate these findings in independent populations and to clarify the mechanisms of the excess falls and fractures, establishing whether these are driven by the well-known effects of statins on muscle or through other mechanisms in older people.

In conclusion, our quasi-experimental analysis of effectiveness of statins for secondary prevention of myocardial infarction produced estimates in line with results of RCTs for patients aged 60 to 79, but more evidence is needed in the older groups. We found evidence of excess falls and fractures in very old patients, which deserve further investigation. If these results are confirmed, higher falls and fracture rates need to be considered in judgements about the appropriateness of statin use in older patients. Very old patients in our analysis were less likely to stay on treatment for a period long enough to provide benefit but long enough to risk serious adverse reactions.

Table 1: Characteristics of the matched sample at baseline by treatment group

Characteristic	***Controls***	***Statins***	***p-value***
Number	6,078	6,078	
Enrolment year (%)			0.797
1997-2001	34.7	35.5	
2002-2005	25.0	24.9	
2006-2009	18.2	17.9	
2010-2014	22.2	21.7	
Demographics			
Age at baseline [years, mean (SD)]	76.4 (9.4)	76.5 (8.9)	0.555
Age category (%)			0.312
60-79	61.8	62.6	
80+	38.3	37.4	
Gender (%, women)	45.5	45.5	0.956
Ethnicity (%)			0.888
White	82.9	82.7	
Non-white	2.1	2.2	
Undisclosed/Unreported	15.0	15.1	
Index of multiple deprivations (%)			0.978
First quintile (least deprived)	19.7	19.5	
Second	24.3	24.4	
Third	21.2	21.6	
Fourth	20.5	20.0	
Fifth quintile (most deprived)	14.1	14.4	
Undisclosed/Unreported	0.20	0.20	
Cardiovascular risk factors			
Smoking status (%)			0.845
Never	33.1	33.1	
Former	25.4	25.7	
Current	39.2	39.2	
Undetermined	2.3	2.0	
Drinking habit (%)			0.978
Never	13.7	13.9	
Current normal amount	42.2	41.6	
Current, unknown amount	1.0	1.0	
Current, heavy drinker	8.3	8.4	
Former	2.4	2.5	
Undetermined	32.5	32.6	
Body Mass Index (%)			0.869
18.4 or below	1.9	1.7	
18.5-24.9	20.9	20.9	

25-29.9	21.1	20.5	
30 or over	9.6	9.9	
Unmeasured	46.5	47.0	
Total cholesterol level [(in mmol/l), %]			0.643
lower than 6.2 (=240 mg/dl)	27.4	28.2	
6.2 or higher	8.4	8.2	
Unmeasured	64.1	63.6	
Health care utilisation and measures of disease burden			
Flu vaccination (%)			0.514
Received (in the previous year)	48.4	49.4	
Not received (in the previous year)	35.1	34.7	
Never received	16.4	15.9	
Number of drugs (%)			0.256
0-1	21.1	20.3	
2-4	19.2	18.3	
5-9	26.9	27.8	
more than 10	32.7	33.6	
Charlson Index (%)			0.947
0	30.5	30.2	
1-2	33.4	33.2	
3-4	14.8	15.1	
5 or more	21.3	21.5	
Nursing home visits [(previous year), %]	0.3	0.3	1.000
Residential home visits [(previous year), %]	0.4	0.3	0.375
More than 4 GP consultations [(previous year), %]	51.6	52.2	0.502
Any hospitalisation [(previous year), %]	15.8	16.2	0.553
Any geriatrics referral [(previous year), %]	0.9	1.1	0.311
Any cardiology referral [(previous year), %]	1.4	1.5	0.445
Revascularisation procedures before MI [(non-myocardial-infarction reason reasons, previous year), %]	0.3	0.3	0.862
Diseases at baseline			
Hypertension (%)	40.0	40.7	0.437
Diabetes (%)	5.3	5.7	0.248
Stroke/Transient ischemic attack (%)	8.1	8.1	0.973
Congestive heart failure (all stages, %)	43.7	43.8	0.869
Atrial fibrillation (%)	8.5	8.9	0.479
Heart failure (%)	7.7	8.1	0.479
Asthma (%)	11.1	10.6	0.414
Chronic Obstructive Pulmonary Disease (%)	9.1	8.9	0.704
Chronic Kidney Diseases (stage 3-5, (%)	6.5	6.8	0.513
Cancer (%)	9.0	9.2	0.614
Dementia (%)	1.7	1.8	0.682
Depression (%)	14.2	14.7	0.470
Mental health condition (%)	1.2	1.3	0.742

Epilepsy (%)	1.4	1.4	0.938
Hypothyroidism (%)	6.6	6.7	0.856
Incontinence (%)	5.7	5.9	0.669
Osteoporosis (%)	5.3	5.3	0.903
Osteoarthritis (%)	26.3	26.7	0.608
Falls (%)	18.4	18.6	0.833
Fractures (%)	4.7	4.5	0.603
Cirrhosis (%)	0.2	0.3	0.563
Drugs at baseline			
Angiotensin converting enzyme inhibitors (%)	11.3	11.6	0.512
Angiotensin Receptors Blockers (%)	2.6	3.1	0.103
Renin inhibitors (%)	0.0	0.0	0.317
Calcium channel blockers (%)	6.6	6.9	0.406
Beta-blockers	9.6	10.6	0.071
Alpha-adrenoceptor blocking drugs (%)	2.1	2.2	0.573
Centrally acting antihypertensive drugs (%)	0.2	0.2	0.835
Non-loop Diuretics (%)	6.9	7.2	0.457
Potassium sparring agents (%)	3.0	2.7	0.254
Loop diuretics (%)	16.5	17.2	0.265
Anti-platelets (%)	22.3	23.5	0.142
Oral anticoagulants (%)	2.6	2.9	0.315
Nitrates (%)	9.3	10.1	0.133
Digoxin (%)	3.3	3.5	0.726
Anti-arrhythmic drugs (%)	0.9	0.8	0.493
Insulin (%)	1.6	1.5	0.770
Sulphonylureas (%)	2.8	3.1	0.286
Metformin (%)	2.9	3.0	0.708
Other antidiabetic drugs	0.2	0.2	0.414
Corticosteroids (including topical and inhaled) (%)	26.6	27.3	0.347
Oestrogens (%)	0.9	0.9	0.923
Testosterone (%)	0.0	0.1	0.414
Proton pump inhibitors (%)	16.6	17.8	0.071
H2-receptor antagonists (%)	3.9	4.0	0.852
First generation antipsychotic drugs (%)	4.8	5.2	0.262
Second generation antipsychotic drugs (%)	0.5	0.6	0.709
Tricyclic antidepressants (%)	5.2	5.0	0.622
Selective Serotonin Reuptake Inhibitors (%)	4.0	4.5	0.209
Other antidepressants (%)	1.1	1.1	0.861
Anti-cholinesterase drugs (%)	0.3	0.4	0.876
Cytochrome P450 inhibiting drugs (%)	13.2	13.8	0.34
Anti-Parkinson's drugs (%)	2.0	2.0	0.948
Drugs for incontinence (%)	3.4	3.7	0.303

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Authors' disclosures

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Figure legends

Figure 1:

Effectiveness of statins for prevention of recurrence of MI in the whole sample (60+) and by age and disease burden group (competing risk of death, excluding first 2 years' events)

Figure 2:

Risk of disabling conditions of older age in the whole sample (60+, competing risk of death, excluding first 2 years' events for ischemic stroke and dementia)