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Author: Peet, Petra van

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Chapter 2

Drug prescription rates in secondary cardiovascular prevention in old age: do vulnerability and severity of the history of cardiovascular disease matter?

Petra G. van Peet¹, Jacobijn Gussekloo¹, Wendy P.J. den Elzen¹,
Jeanet W. Blom¹, Margot W.M. de Waal¹, Wouter de Ruijter¹.

¹ Department of Public Health and Primary Care, Leiden University Medical Center, Leiden,
The Netherlands

ABSTRACT

Objective

To assess the influence vulnerability and severity of cardiovascular disease (CVD), on prescription rates of secondary cardiovascular preventive drugs in old age

Design

Population based observational study within the ISCOPE study

Setting

General practices in the Netherlands

Subjects

1350 patients with a history of CVD (median age 81 years, 50% female)

Main outcome measures

One year prescription rates of lipid-lowering drugs and antithrombotics were obtained from the electronic medical records of 46 general practitioners (GPs). Prescription of both drugs for ≥ 270 days per year was considered optimal. GPs made a judgement of vulnerability. Severity of CVD was expressed as major (myocardial infarction, stroke, or arterial surgery) versus minor (angina, transient ischemic attack or claudication).

Results

GPs considered 411 (30%) participants vulnerable and 619 (55%) participants had major CVD. Optimal treatment was prescribed to 680 (50%) participants, whereas 370 (27%) received an antithrombotic drug only, 53 (4%) a lipid-lowering drug only, and 247 (18%) received neither. Optimal treatment was lower in participants aged ≥ 85 years [OR 0.37(95% CI 0.29-0.48)], in females [OR 0.63(0.50-0.78)], in vulnerable persons [OR 0.79(0.62-0.99)] and in participants with minor CVD [OR 0.65(0.53-0.81)]. Multivariate ORs remained similar whereas vulnerability lost its significance [OR 0.88(0.69-1.1)].

Conclusion

In old age, GPs' judgement of vulnerability is not independently associated with lower treatment rates of both lipid-lowering drugs and antithrombotics, whereas a history of minor CVD is. Individual proactive re-evaluation of preventive treatment in older (female) patients, especially those with a history of minor CVD, is recommended.

INTRODUCTION

In ageing societies cardiovascular disease (CVD) is an important cause of disability and mortality.¹² Secondary preventive treatment is effective up to high age³⁻⁸, and lifelong lipid-lowering drugs and antithrombotics are recommended in all guidelines for secondary prevention.⁹⁻¹² However, although prescription of preventive treatment has generally increased in the last decades, treatment in older age groups still lags behind.¹³⁻¹⁶

Decreasing life expectancy, in combination with the lag time to benefit¹⁷, may influence physicians and older persons when deciding not to start or to stop secondary cardiovascular preventive treatment in old age. The START criteria do not recommend starting of statin therapy in patients aged 85 years and over, because of lack of evidence based on randomized controlled trials (RCTs) in this age group. However, the STOPP criteria do not advise stopping these medications in very old age.¹⁸ In (very) old age, medical care is often more personalised, taking into account all comorbidities and individual patient preferences. The eventual prescription of secondary cardiovascular preventive treatment is the result of this complex interaction between physician and patient.

As the general practitioner's (GP's) judgement of vulnerability may affect treatment decisions¹⁹, more data on the influence of vulnerability on the intensity of secondary cardiovascular preventive medication is required.²⁰ In general, vulnerable patients might receive fewer preventive drugs than fit older people^{21,22}, although, ultimately, vulnerability should not be viewed as a reason to withhold care, but rather as a means of delivering it in a more patient-centred fashion.²³ For secondary cardiovascular preventive medication this topic is not well studied.

Medical history can influence a GP's judgement of vulnerability, but has also been related to prescription rates themselves: a history of less severe CVD, such as angina, transient ischaemic attack or claudication, as opposed to myocardial infarction, stroke or arterial surgery, can be associated with reduced prescription rates.^{24,25}

It is unknown whether GPs' judgement of vulnerability, or the severity of the CVD history, might (in part) explain the observed low prescription rates of secondary cardiovascular preventive medication in (very) old age.

We hypothesised that vulnerability and less severe CVD might be associated with lower prescription rates of cardiovascular preventive drugs in old age, and investigated the associations of prescription rates of lipid-lowering drugs and antithrombotics with age, sex, GPs' judgement of vulnerability and the severity of CVD, in a population-based sample of participants aged ≥ 75 years with a history of CVD.

METHODS

The present study is embedded in the ISCOPE (Integrated Systematic Care for Older Persons) study. The ISCOPE study is a cluster randomised trial among persons aged ≥ 75 years from 59 general practices in and around the city of Leiden (the Netherlands), who were invited to participate (inclusion period September 2009 to September 2010).²⁶ The aim was to evaluate the effectiveness of a tailored care plan carried out by the GP for older persons with complex health problems, using a functional approach for older people.

Informed consent was obtained from each patient and the study protocol conforms to the ethical guidelines of the 1975 Declaration of Helsinki. The Medical Ethics Committee of the Leiden University Medical Centre approved the study. The study is registered in the Netherlands Trial Register (Registration number: 1946).

Cardiovascular disease history

The history of cardiovascular disease in the electronic medical records (EMR) was defined by the presence of International Classification of Primary Care (ICPC) codes K74, K75, K76, K89, K92 (excluded K92.2 and K92.3 and text words M. Raynaud and M. Buerger) and K99.01, or an episode with the text words angina, myocardial infarction (MI), ischemic heart disease, transient ischemic attack (TIA), stroke, (intermittent claudication), peripheral arterial disease (PAD) or aneurysm, respectively. An episode with text words coronary artery bypass grafting (CABG) or percutaneous coronary intervention (PTCA) or surgery for peripheral arterial disease was coded as surgery for arterial disease.

Medication use

The Anatomical Therapeutic Chemical (ATC) code C10 was used to select lipid-lowering drugs, and ATC codes B01AA (anticoagulants) and B01AC (antiplatelet drugs) to select antithrombotics. All participants with prescriptions for ≥ 270 days during the year after study entrance were considered current users of this type of drug. Optimal treatment was defined as the prescription of both a lipid-lowering drug and an antithrombotic drug; suboptimal treatment was defined as the current prescription of only one of these two types of drugs; and poor treatment was defined as the current use of neither.

Additional parameters

Age

Participants were divided in two age groups: those aged 75-84 years (old age) and those aged ≥ 85 years (very old age).

GPs' judgement of vulnerability

Before inviting the older people to participate, we asked GPs to classify all enlisted older people into three categories according to their own perception: i) not vulnerable, ii) possibly vulnerable, and iii) vulnerable. To include only those participants that were with certainty considered to be vulnerable in the vulnerable group, we combined the 'not vulnerable' or 'possibly vulnerable' participants and compared them with the vulnerable participants.

Severity of cardiovascular disease history

The participants were classified according to the severity of their CVD history. Minor CVD included angina, transient ischaemic attack or peripheral arterial disease without surgery, whereas major CVD included myocardial infarction, stroke, or surgery for arterial disease. In addition, we created groups according to the number and type of cardiovascular beds involved: cardiac bed (angina, MI or ischaemic heart disease), cerebral bed (TIA or stroke), and peripheral artery bed (intermittent claudication or aneurysm).

Statistical analysis

Categorical variables were expressed in percentages. Differences between groups in categorical variables were analyzed using Pearson's Chi-square test.

Associations between the percentage of prescriptions (prescription rates) and age groups, sex, GPs' judgement of vulnerability and severity of CVD, were investigated with logistic regression models. Univariate and multivariate odds ratios (OR) with 95% confidence intervals (CIs) were estimated for the relation between these variables and prescription rates; a possible interaction between age and the other variables was also tested. No additional adjustments were made for depressive symptoms, cognition, functional status and other comorbidities, because these latter characteristics are included in the GPs' judgement of vulnerability.

For additional analyses regarding age, we calculated ORs with dichotomisation on the median age and for tertiles of age. With respect to vulnerability, all analyses were repeated with the exclusion of the 'possibly vulnerable' participants. Concerning the severity of CVD status, prescription rates were calculated for participants with only one cardiovascular bed involved, and for participants with more than one cardiovascular bed involved.

For sensitivity analysis, prescription rates were also calculated stratified for participants with a cardiovascular disease within two years before the start of the ISCOPE study, and participants with an event longer ago.

Data analyses were performed using SPSS 20 for Windows (SPSS Inc., Chicago, IL, USA).

RESULTS

Of the 11,476 eligible persons, 7,285 (63%) from 59 general practices, participated in the screening phase of the study. (Additional online file: Flow chart of participants in the study). After one year, complete electronic medical records (EMR) were available for 4,361 (38%) participants (EMR of participants who gave consent and were not lost to follow up, from the 46 general practices with an EMR compatible with extraction of data for our research question). Of these 4,361 participants, 1,350 participants (33%) had a history of CVD, according to their EMR. Complete data on drug prescriptions from the EMRs were available from study entrance until one-year follow-up for all these 1,350 participants.

Baseline characteristics

The median age of the 1,350 participants with a history of CVD in the ISCOPE study was 81 years (interquartile range 78-85 years, age range 75-101 years), 26% was aged ≥ 85 years, and 50% was female (Table 1). GPs considered 411 (30%) participants to be vulnerable. Minor CVD was present in 619 (46%) of the participants.

Current prescription of lipid-lowering drugs was seen in 54% of the participants, and current prescription of antithrombotics in 78%. Optimal prescription of both drugs was seen in 50% of the participants. Suboptimal treatment was seen in 31%: 27% used an antithrombotic drug only and 4% a lipid-lowering drug only. Poor treatment was observed in 18% of the participants.

Determinants of prescription rates

Table 2 and Figure 1 present the optimal prescription rates of lipid-lowering drugs and antithrombotics according to age, sex, GPs' judgement of vulnerability, and severity of the CVD history. Participants aged ≥ 85 years, females, vulnerable participants, and participants with minor CVD, all had lower optimal prescription rates (33%, 45%, 46% and 45%, respectively) compared with participants aged 75-84 years, males, non-vulnerable participants or participants with major CVD [57% ($p < 0.01$), 56% ($p < 0.01$), 52% ($p < 0.05$) and 55% ($p < 0.01$), respectively].

In contrast, prescription of antithrombotics only (no lipid-lowering drugs) was more often observed in participants aged ≥ 85 years, in females, and in vulnerable participants. In the age group ≥ 85 years, about 25% was receiving none of the two drugs.

Table 3 presents univariate and multivariate ORs for age ≥ 85 years, female sex, minor CVD and GPs' judgement of vulnerability, with regard to the prescription of both drugs. Age was the strongest predictor [OR for age ≥ 85 years 0.37 (0.29-0.48)], followed by female sex [0.63 (0.50-0.78)], minor CVD [0.65 (0.53-0.81)], and GPs' judgement of vulnerability [0.79 (0.62-0.99)]. In the multivariate analyses, associations remained similar,

although GPs' judgement of vulnerability lost its significance [multivariate OR 0.88 (0.69-1.1)]. There was no interaction between age and the other three variables (data not shown).

Table 1. Sociodemographics and clinical characteristics of participants with a history of cardiovascular disease from the ISCOPE study (n=1350)

	n (%)
Sociodemographics	
Age in years (median (interquartile range))	81 (78-85)
Male	678 (50)
GPs' judgement of vulnerability^a	
Vulnerable	411 (30)
Possibly or not vulnerable	927 (69)
Cardiovascular disease history^b	
Severity	
Minor cardiovascular disease ^c	619 (46)
Major cardiovascular disease ^d	731 (54)
Type of vascular bed	
Cardiac	834 (62)
Angina	428 (32)
Myocardial infarction	377 (28)
Ischaemic heart disease	122 (9)
Cerebral	494 (37)
Transient ischaemic attack	246 (18)
Stroke	257 (19)
Peripheral	253 (19)
Intermittent claudication	195 (14)
Aneurysm	68 (5)
Cardiovascular preventive treatment: lipid-lowering/antithrombotic drugs	
Type	
Lipid-lowering drug ^e	733 (54)
Antithrombotic drugs (aspirin or oral anticoagulant)	1050 (78)
Completeness of treatment	
Optimal treatment: both lipid-lowering drug and antithrombotic drug ^f	680 (50)
Suboptimal treatment: lipid-lowering drug only	53 (4)
Suboptimal treatment: anti-thrombotic drug only	370 (27)
Poor treatment: no lipid-lowering or antithrombotic drug	247 (18)

^a assessed before screening (12 missing values); vulnerable participants versus possibly vulnerable (n=360), not vulnerable (n=513) or don't know (n=54)

^b obtained from EMR general practitioners

^c history of angina, transient ischaemic attack, or intermittent claudication

^d history of myocardial infarction, stroke or arterial surgery

^e use of statins (n=1336) or other lipid-lowering drugs (n=14)

^f use of both drugs during more than 270 days during the first year of the ISCOPE study

Table 2. Prescription rates (%) of lipid-lowering and/or antithrombotic drugs ^a in participants with a history of cardiovascular disease from the ISCOPE study (n=1350)

	Age		Sex		Vulnerability ^b		CVD history ^c	
	≥ 85 n=347	75-84 n=1003	female n=678	male n=672	yes n=411	no n=927	minor n=619	major n=731
Optimal treatment (both drugs)	33	57**	45	56**	46	52*	45	55**
Suboptimal treatment								
antithrombotic drug only	40	23**	32	23**	30	26*	29	26
lipid-lowering drug only	2	5	5	3	3	4	5	3
Poor treatment (none of the two)	25	16**	19	18	21	17	21	16*

CVD: cardiovascular disease

^a more than 270 days prescription of Lipid-lowering and/or antithrombotic drugs in the year after start of ISCOPE study

^b assessed before screening (12 missing values); vulnerable ('yes') versus possibly vulnerable, not vulnerable participants or do not know (together 'no')

^c minor CVD: history of angina, transient ischaemic attack, and/or claudication; major CVD: history of myocardial infarction, stroke and/or arterial surgery;

** Pearson Chi-Square $p < 0.01$ (as compared to ≥ 85 years, female, vulnerable or minor CVD, respectively)

* Pearson Chi-Square $p < 0.05$ (as compared to vulnerable, and as compared to minor CVD, respectively)

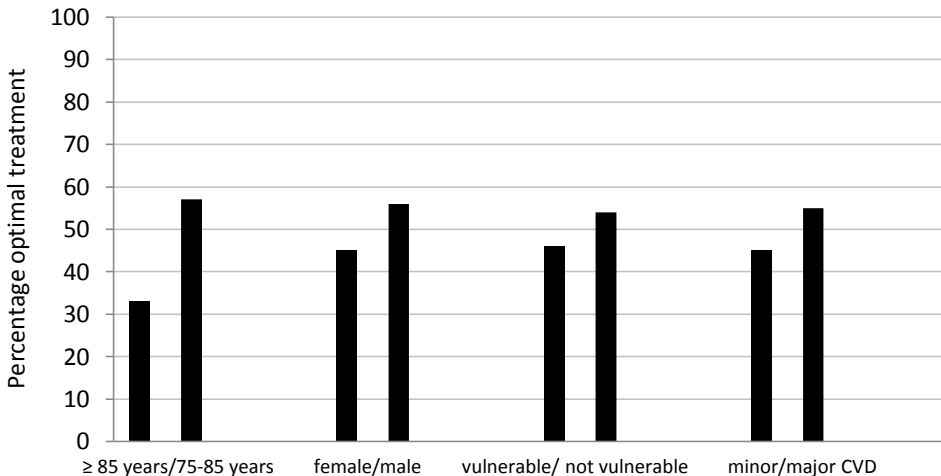


Figure 1. Optimal prescription rates (both lipid-lowering- and antithrombotic drugs) depending on age, sex, GPs' judgement of vulnerability, and severity of cardiovascular disease (n=1350, p all < 0.05)

Table 3. Relation of age, sex, GPs' judgement of vulnerability, and severity of cardiovascular disease with optimal^a prescription rates of cardiovascular preventive treatment in participants with a history of cardiovascular disease from the ISCOPE study (n=1350)

	Age ≥ 85 years		Female sex		Vulnerable ^b		Minor CVD ^c	
	OR	95% CI	OR	95% CI	OR	95% CI	OR	95% CI
Univariate	0.37	0.29-0.48	0.63	0.50-0.78	0.79	0.62-0.99	0.65	0.53-0.81
Multivariate^d	0.39	0.30-0.50	0.71	0.57-0.89	0.88	0.69-1.1	0.67	0.53-0.83

CVD: cardiovascular disease

^a both lipid lowering and antithrombotic drug

^b patient considered vulnerable by their GP, 12 missing values

^c history of angina, transients ischaemic attack, or claudication without arterial surgery

^d adjusted for age, gender, vulnerability and disease severity

Additional analyses

For additional analyses with regard to age, we dichotomised the participants into two groups according to the median age of 81 years. In the high age group, 42% of the participants was treated optimally compared to 58% in the low age group [OR 0.50 (95% CI 0.40-0.62); multivariate OR 0.53 (0.42-0.66)]. When making tertiles of age, we observed optimal treatment in 36% in the highest tertile (age > 83.5 years), in 54% in the middle tertile, and in 61% in the low age tertile (age ≤ 79.0 years) ($p_{\text{trend}} < 0.01$), indicating that the influence of age on prescription rates is dose-dependent and robust.

Analyses with regard to vulnerability, excluding the 'possibly vulnerable' participants, did not substantially change the results [univariate and multivariate OR for GPs' judgement of vulnerability 0.74 (95% CI 0.57-0.96) and 0.86 (0.65-1.1), respectively].

The severity of CVD expressed as involvement of more than one vascular bed (n=214) was positively associated with optimal treatment (optimal prescription in 63% versus 48% for one vascular bed, $p < 0.01$). Univariate OR for one vascular bed was 0.54 (95% CI 0.40-0.73) and multivariate OR (including age, sex, and GPs' vulnerability judgement) was 0.54 (0.39-0.74).

Stratified analyses performed in the group with a recent cardiovascular disease (< 2 years before the start of the ISCOPE study, n=280) and a cardiovascular disease longer ago showed similar rates of optimal, suboptimal and poor treatment in both subgroups (data not shown).

DISCUSSION

This study on current prescription rates in secondary cardiovascular prevention in older persons in the Dutch general population shows that half of all participants with a history of CVD received optimal treatment, with a combination of a lipid-lowering drug and an antithrombotic drug. Another quarter received an antithrombotic only, indicating that especially statin use is still limited in old age.

GPs' judgement of vulnerability was not independently associated with lower prescription rates, whereas age itself, female sex, and the severity of CVD history were. In view of increasing research on the influence of vulnerability on medical decision-making in old age this is an intriguing finding, indicating that age, sex, and disease severity are essential constituents of the judgement of vulnerability. In other words when taking age, sex and disease severity into account, GPs judgement of vulnerability does not independently influence prescription rates. This might be seen as a positive finding, indicating that GPs do not a priori withhold treatment in vulnerable patients.

The severity of the history of CVD proved to be relevant, since older persons with major CVD (MI, stroke, arterial surgery) were more often optimally treated. This leaves room for improvement of preventive therapy in relatively fit patients with only minor CVD, in whom prevention of major events might help preserve their independence.

Age itself was most strongly associated with prescription rates: only a third of participants aged ≥ 85 years received optimal treatment compared to more than half of those aged 75-84 years. This might partly be due to the START criteria¹⁸ and the relative lack of RCT evidence for secondary preventive treatment with statins in patients aged ≥ 85 years²⁷, lag time to benefit, and/or an increasing number of comorbidities.

Our data do not allow to conclude whether the observed low prescription rates are the result of appropriate patient-centred medical decision-making, as opposed to forgetfulness or lack of attention from physicians and patients for cardiovascular preventive measures. Therefore, we recommend that GPs regularly monitor their older patients with a history of CVD (especially those with minor CVD) and individually discuss possible preventive treatments.

Strengths and weaknesses

A strength of our study in a population-based sample of CVD patients in general practice is that it reflects current prescription rates in the general older population in the Netherlands. The GP practices in our study were randomly chosen and there were no predefined cardiovascular criteria. Therefore, the observed prescription rates are representative for current general practice. Moreover, including all atherothrombotic CVD (cardiac, cerebral and peripheral) also allowed to observe the prescription rates for the whole secondary prevention population and not for a specific vascular bed only.

It is well known that drug prescription rates after incident cardiovascular disease decline over time.¹⁵ However, in our sensitivity analysis in participants with a recent cardiovascular disease (as compared to those with cardiovascular disease longer ago), prescription rates were similar, indicating that the low prescription rates observed in older people are most likely not caused by the fact that cardiovascular disease in general presented itself longer ago in this old population.

Various tools have been developed to screen for vulnerability. GPs' assessment of vulnerability is an easily available parameter in general practice. Since the goal was to assess patient vulnerability as defined by GPs themselves, GPs were not provided with a specific definition of vulnerability. It could be questioned, as to which constituents GPs' judgement of vulnerability is based. Therefore, an in depth validation study on the vulnerability assessment by GPs within the ISCOPE study was performed by Drewes et al..²⁸ This study concluded that somatic and psychological problems were uniformly taken into account in GPs' judgement of vulnerability.

Another weakness may be that we used routine clinical data and that not all diagnoses were validated by a team of experts. Also, information on the frequency of consultations for secondary cardiovascular prevention in the GP practices was not available, and a possible influence of consultation frequency on prescription rates, could therefore not be studied.

A further weakness is that we have no qualitative information on physicians and patients and do not know the reasons for not prescribing medication; moreover, due to small numbers, GP-specific analyses were not possible. Furthermore, it is unknown whether some patients had been prescribed statins in the past and had discontinued taking them, e.g. because of side-effects. Also, the use of a more complex and validated frailty or vulnerability instrument might have yielded different results. However, it is still unknown which instrument is best and, in routine practice, GPs use their general and intuitive judgement of vulnerability. Finally, 60% of all eligible patients aged ≥ 75 years in general practices in the Netherlands that were invited to participate in the ISCOPE study, participated. However, in the non-response analysis of the ISCOPE study, median age of non-responders was 81 years, and 25% was considered vulnerable by their GP. Therefore we think including these non-responders would not substantially have changed our results.

Findings in relation to other studies

To our knowledge this is the first study to investigate the association between GPs' judgement of vulnerability and prescription rates of secondary cardiovascular preventive drugs in old age. An association between lower prescription rates of statins and depression/cognitive decline was reported in a retrospective cohort study with a mean age of 74 years.²⁹

The association between secondary preventive drug treatment and the severity of CVD has seldom been examined. In the EURASPIRE surveys prescriptions of statins increased over time but there was a tendency towards lower prescription rates in participants with ischemia as compared to patients with CABG, PTCA or acute MI.³⁰ However, this was not the main objective of this study, mean age was much younger (around 60 years old), and the study population was confined to cardiac disease patients from specialists' cardiac centers, not representing the general population. Also in a younger age group (mean age 70 years), Bangalore et al. observed reduced secondary preventive treatment in participants with TIA as compared to participants with stroke.²⁵ As major CVD is associated with poorer prognosis³¹, these results may reflect GPs' awareness of this.

With regard to the observed lower prescription rates of secondary preventive medication with increasing age, lower prescription rates after MI have been reported in older age groups.^{14;15;24;32} In a meta-analysis, Naderi et al. showed that prescription rates in secondary prevention in age groups with a mean age of 58-78 year were higher (i.e. 66%) for all cardiovascular preventive treatment³³; this is consistent with our finding that younger age is associated with higher prescription rates. However, the latter authors observed no differences in drug classes in these age groups, whereas in the present study statins were less frequently prescribed than antithrombotics. This might indicate that in very old age statin treatment is not started or is more often discontinued, possibly because of lack of evidence in very old age^{18;27}, (expected) side-effects, or lag time to benefit.

With regard to the observed sex differences, lower prescription rates of lipid-lowering drugs in women, are often mentioned.^{15;24;32} This might be because most evidence regarding the benefits of treatment with statins was collected in men, and physicians have a lower awareness of the comparable risks for women. However, this sex difference is not favourable for the ageing society, in which more women live to higher ages.

Meaning of the study

In the present study in older people in the general population, rates of secondary cardiovascular preventive drug prescriptions were relatively low; this may increase the risks of recurrent CVD. Since an intensive outpatient cardiac rehabilitation program recently showed benefits even in patients aged ≥ 80 years³⁴, optimising secondary preventive measures can be worthwhile, even in old age. The observed low prescription rates, especially of statins, in women and in participants with minor CVD, may be the result of a careful decision process weighing all the pros and cons of preventive treatment; however, it may also reflect forgetfulness or loss of attention for these patients. Patients themselves may also have discontinued treatment without their GPs noticing. Therefore, we recommend that physicians regularly monitor all (very) old patients with established

CVD for current use of secondary preventive medication, make an explicit analysis, discuss this with their patients and adjust the individual treatment accordingly.

Further research

The present study did not investigate the influence of physicians' and patients' preferences on prescription rates. In primary prevention, Fried et al. observed that older persons' willingness to take medication was relatively insensitive to its benefits, but highly sensitive to its adverse effects.³⁵ Qualitative research interviewing patients and physicians regarding their opinions on prescription of secondary preventive medication in very old age, may further elucidate possible reasons for non-prescription or discontinuation of treatment in this age group.

CONCLUSION

In old age, only half of all those patients with an indication for secondary preventive cardiovascular medication receive optimal treatment with both lipid-lowering drugs and antithrombotics. Whereas age, female sex and minor CVD are independently associated with even lower prescription rates, GPs' judgement of vulnerability is not. Because this low treatment uptake may not always be the result of a conscious patient-centred choice, we advocate individual pro-active re-evaluation of preventive treatment in all older patients, especially (female) patients with a history of minor CVD.

KEY POINTS

- Prescriptions of lipid-lowering drugs and antithrombotics in secondary cardiovascular prevention, tend to decline with age
- In this study with median age 81 years, 50% of participants received optimal treatment with both lipid-lowering drugs and antithrombotics
- GPs judgement of vulnerability was not independently associated with optimal treatment
- A history of less severe cardiovascular disease was independently associated with lower prescription rates of lipid-lowering drugs and antithrombotics
- Proactive individual re-evaluation of cardiovascular preventive treatment in older (female) patients, especially patients with less severe cardiovascular disease, is recommended

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ADDITIONAL FLOWCHART