To stop or not to stop : deprescribing preventive cardiovascular medication in low-risk general practice patients

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door Clare Helen Luymes, geboren te Haarlem in 1987

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CHAPTER 1

General introduction

GENERAL INTRODUCTION

Approximately 27% of global mortality is caused by cardiovascular disease (CVD).[1] Furthermore, ischemic heart disease is the leading cause of years of life lost, both globally and in the Netherlands.[1] As a result of more effective treatment options and an increase in preventive measures and surveillance, the worldwide age-standardized death rate has decreased with a median percentage of 22 from 1990 onwards, and years of life lost due to CVD have decreased about two- to four-fold.[1, 2] Reduction of hypertension and hypercholesterolemia on a population-level can (cost-)effectively prevented new cases of CVD and death from CVD, resulting in a reduction of Disability Adjusted Life Years (DALYs).[2, 3] Hence, the impact of preventive strategies on reducing CVD is evident. Because of the importance of CVD prevention, many countries have guidelines with recommendations on prevention of CVD in adults with as well as without a history of CVD.[4-10] Although these guidelines have the same goal, there is no consensus about the screening methods, which prediction models to apply, and what thresholds to use regarding initiation of drug treatment in patients in order to prevent CVD.[11] The European Society of Cardiology, for example, recommends to initiate anithypertensive drugs based on a combination of total cardiovascular risk and blood pressure, whereas the guideline from the Centers of Disease Control and Prevention/American Heart Association recommends to start treatment based on a combination of blood pressure level and the presence of chronic kidney disease or diabetes mellitus.[11]
Medical science continuously investigates the optimal way to prevent CVD in individuals, which is the reason for regular revision and further refinement of guidelines in the area of prevention of CVD.[5, 6, 12-19]

1. THIS THESIS

This thesis addresses a problem that was raised, predominantly in Dutch general practice, as a result of revisions of guidelines in the area of primary prevention of CVD and that expands into the area of further individualizing preventive interventions during lifetime. This thesis concerns the practical problem of general practitioners (GPs) on how to deal with patients using antihypertensive and/or lipid-lowering drugs (preventive cardiovascular medication) in whom guideline changes, changing insights in risk assessment or changing individual circumstances, result in losing the strict indication for initiation and further use of these drugs.

To illustrate this problem, first the history of the Dutch guidelines in the area of primary prevention of CVD will be discussed. Next, two vignets of patients will be introduced (miss Bremer and mister Aalbers), to exemplify the issues that GPs encounter in general practice. Finally, the aims of the thesis are presented.

2. THE DUTCH SITUATION

In the Netherlands, the first guidelines in the area of primary prevention of CVD were the guidelines "Hypertensie" [Hypertension] and "Cholesterol", launched by the Dutch College of General Practitioners (Nederlands Huisartsen Genootschap, NHG) in 1993. These guidelines recommended opportunistic screening of blood pressure and cholesterol in patients at risk of hypertension, hypercholesterolemia, or patients at increased risk of developing CVD (e.g., in case of diabetes mellitus). Recommendations in these two former guidelines differ from the recommendations in the current Cardiovascular Risk Management (CVRM) guideline with respect to, for example, definition of hypertension, preferred prescribed medications, and thresholds for initiation of medication.
As of 2003, the Dutch hypertension guideline advocated for the assessment of total (or: global) cardiovascular risk, using a 10-year risk of cardiovascular morbidity essentially based on the Framingham Risk Score to evaluate whether drug treatment should be initiated. In 2006, the guidelines on hypertension and on hyperlipidaemia were integrated into one CVRM guideline advocating for the assessment of total (or: global) cardiovascular risk, based on all traditional risk factors. However, the 2006 CVRM guideline refrained from using the Framingham Risk Score, and started using a 10-year risk of CVD morbidity and mortality (10-year CVD risk) score based on the SCORE equation to evaluate drug treatment initiation.[20] In the CVRM guideline that was established in 2012, this 10-year CVD risk score was based on the SCORE equation for low-risk European countries and improved for the Dutch population with help of data of the Dutch MORGEN-cohort and a Dutch cohort from the ERGO study.[4, 16, 21] Five determinants currently define a patient's 10-year CVD risk: systolic blood pressure (range 120 to 180 mmHg), total cholesterol/high-density lipoprotein cholesterol (TC/HDL) ratio (range 4 to 8), age (range 40 to 70 years; 15 years are added to age in the presence of diabetes mellitus or rheumatoid arthritis), sex (male or female), and smoking status (yes or no). In case a patient has a low risk, i.e. 10-year CVD risk <10%, the guideline recommends physicians to discuss lifestyle when necessary. In case a patient has a medium risk, i.e. 10-year CVD risk 10% to 20%, the recommendation for initiation of

drug treatment depends on the presence of additional determinants that could increase CVD risk, such as family history of CVD, physical activity level, body mass index, and kidney function. This means that, if there are no or few risk increasing factors, these medium-risk patients are considered low-risk patients and initiation of drug treatment is not recommended (and vice versa: with many risk increasing factors, drug treatment is recommended). In case a patient has a high risk, i.e. 10-year CVD risk ≥20%, initiation of drug treatment is recommended under all context circumstances.

2.1. Consequences of a guideline revision for clinical practice

Guideline revisions resulting in different thresholds for initiation of drug treatment compared to previous guidelines, as described above, can have implications for clinical practice. This is because guideline recommendations do not only refer to 'new patients', but also to patients who are already being treated for their specific disease or risk factor(s). However, these implications are often not considered by physicians, policy makers and guideline committees, and most guidelines lack recommendations for physicians on how to deal with the consequences of guideline revisions.[22]
In Part 1 of this thesis we describe the effects of the last revision of the Dutch CVRM guideline on a population- and an individual patient-level.

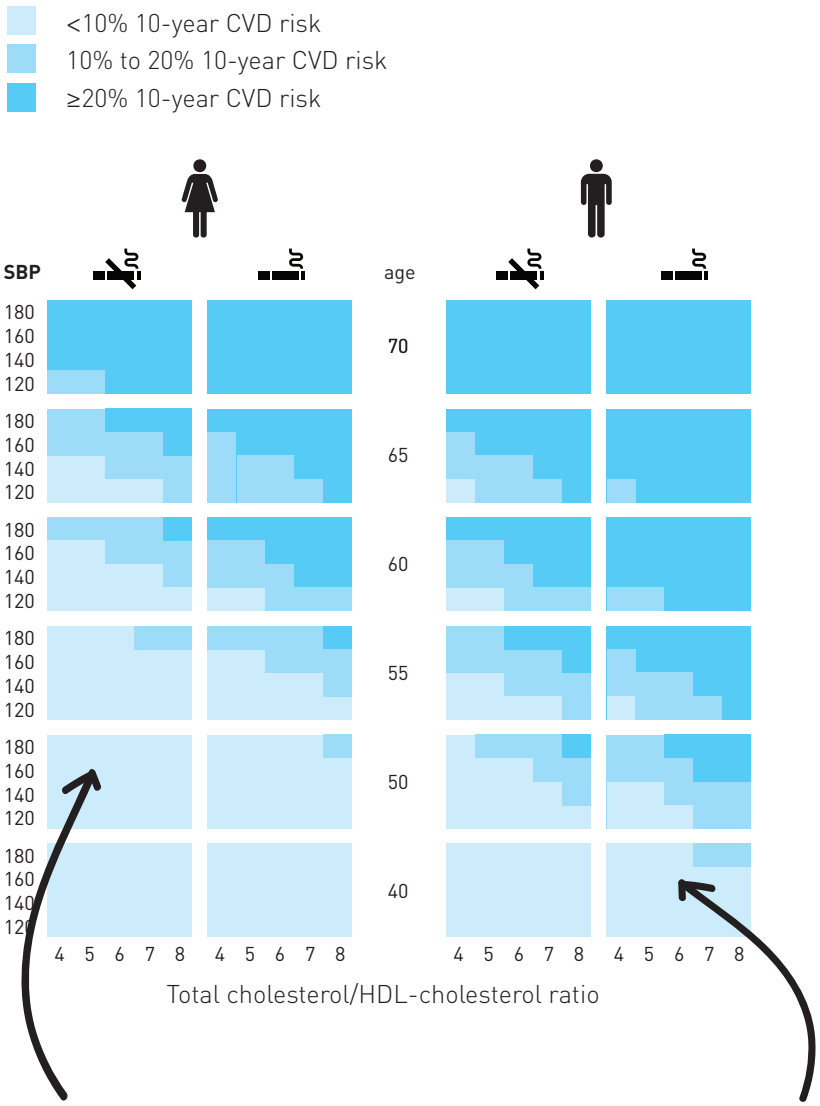
3. ILLUSTRATION OF THE PROBLEM WITH PATIENT CASES

To illustrate the problem that is addressed in this thesis we describe the cases of miss Bremer and mister Aalbers who both did not experience a cardiovascular event and have a low overall CVD risk. They both visit the same GP. The most recent CVRM guideline does not recommend initiation of drug treatment in low-CVD-risk patients such as miss Bremer and mister Aalbers, and drug treatment in low-CVD-risk could be considered as overtreatment. However, they are already using preventive cardiovascular medication, because in earlier days antihypertensive and/or lipid-lowering drugs were prescribed following guidelines that were in force at the time. Both patients present themselves to their GP because of the routine preventive check-up, which is recommended when patients use preventive cardiovascular medication. How should the GP deal with the possible overtreatment in these patients?

Just after the revision of the CVRM guideline, miss Bremer visits her GP for her routine preventive check-up. She is 50 years old and uses an ACE-inhibitor (enalapril 5 mg once daily) for three years now. Her antihypertensive drugs were initiated during a period in which she had headache complaints and a relatively high systolic as well as diastolic blood pressure found repeatedly during consultations in the past (160/90 mmHg). She has never smoked, her TC/HDL ratio is 5, her current systolic blood pressure is 135 mmHg, and she has no additional risk increasing factors (no elevated body mass index, normal kidney function, no family history of CVD, and a good physical activity level). She sees her GP during the yearly preventive check-up. Her headache has faded since, and the general practitioner questions herself whether miss Bremer could stop her antihypertensive drugs.

Just after the revision of the CVRM guideline, mister Aalbers visits his GP for his routine preventive check-up. He is 40 years old and uses antihypertensive and lipid-lowering drugs for two years now (hydrochlorothiazide 12.5 mg, enalapril 5 mg, and simvastatin 40 mg, all once daily). At the time, the GP had advised him to start medication because of his risk factors for developing a cardiovascular disease. He is a smoker, has a TC/HDL ratio of 5 (it was 6 at the time he started his medication), an LDL-cholesterol of 2.4 mmol/L (it was 4.1 mmol/L at the time he started his medication), and his systolic blood pressure is 136 mmHg (it was 155 mmHg at the time he started his medication). Furthermore, he has a body mass index of 37 kg/m^2, he has a sedentary lifestyle, and his kidney function is 55 ml/min/1.73m^2. His brother was 48 when he had a heart attack and his mother suffered from a stroke at the age of 62. Mister Aalbers visits his GP and asks her if he could stop his medication because he does not see or feel any benefits of it and dislikes use of medication.

Figure 1 shows miss Bremers' and mister Aalbers' 10-year CVD risk score, based on their pre-treatment levels of blood pressure (miss Bremer), and LDL-cholesterol (mister Aalbers), as if they would currently not be using preventive cardiovascular medication. Because there is a lack of evidence to judge overtreatment and to guide the decision whether or not to deprescribe in these cases, assessing the 10-year CVD risk score as if patients do not use preventive cardiovascular medication is used here to inform the decision-making process.
The general discussion of this thesis will address recommendations for the GP on how to deal with the potential overtreatment in these two patients, based on the findings of the studies discussed in this thesis.



10-year CVD risk score of miss Bremer. Based on her pre-treatment systolic blood pressure level, current cholesterol levels, smoking status, age and sex.

10-year CVD risk score of mister Aalbers. Based on his pre-treatment systolic blood pressure and cholesterol levels, smoking status, age and sex.

Figure 1. 10-year CVD risk score table

3.1. Potentially inappropriate prescribing

As illustrated by the cases of miss Bremer and mister Aalbers, for patients who are already using preventive cardiovascular medication based on former guideline recommendations, a revision of the guideline may question the need to continue preventive cardiovascular medication. In these two low-CVD-risk patients the guideline revision may change the feeling of urgency for treatment in hindsight and potentially results in inappropriate prolonging of prescription, where potential risks of the medication (e.g., side effects) outweigh their potential benefits.[23-25]

The question whether or not to continue the preventive cardiovascular medication will probably lead to a physician-patient discussion about deprescribing. Deprescribing has been defined as the process of withdrawal (or dose reduction) of medication that became inappropriate following evaluation, supervised by a healthcare professional.[26] GPs seem to be reluctant to advise about deprescribing, since evidence to change a supposedly "winning team" is lacking and the impact of deprescribing preventive cardiovascular medication on a low-CVD-risk patient's health actually is unknown. Is it safe to deprescribe? And, if it is safe, should GPs invite all low-CVD-risk patients in a structured way for a deprescribing consultation to discuss whether to withdraw preventive cardiovascular medication? Time and costly efforts should be balanced against the impact of the guideline revision on patients' health to assess whether such a structured deprescribing strategy is an effort that should be made. In Part 2 of this thesis we have investigated the safety, effectiveness, and cost-effectiveness of a structured deprescribing strategy, to evaluate whether active invitations for deprescribing consultations in possibly overtreated, low-CVD-risk patient populations in general practice are recommended.

3.2. The deprescribing consultation

The deprescribing consultation, in which patients like miss Bremer and mister Aalbers discuss with their GP whether or not to withdraw their preventive cardiovascular medication, may play a big role in the (cost-)effectiveness of the overall deprescribing strategy; if none of the patients, as outcome of a shared decision with their GP, would decide to stop the medication, the deprescribing strategy would definitely not be (cost-) effective. Because the (cost-)effectiveness of a structured deprescribing strategy could be highly influenced by the course of the deprescribing consultation, it is worthwhile to find out more about the course of these conversations and what factors have a bearing on its outcome (deprescription or continuation). In addition, knowledge of the factors that play a role in the decision-making process can aid the physician-patient communication in future deprescribing consultations

In Part 3 of this thesis we have discussed the factors influencing the outcome of the deprescribing consultation.

3.3. Predictors of successful deprescribing

Regardless of the risks and benefits of a deprescribing strategy for the total population of low-CVD-risk patients, there will always be individual low-CVD-risk patients that embrace the idea to stop their medication. The other way around, some GPs will always question the necessity of preventive cardiovascular medication in some low-CVD-risk patients. In these cases, information about the patient's individual probability to successfully stop the medication could be helpful in the decision-making process. In addition, this information can be used to screen the electronic medical records of general practices for patients who have a high probability of successful stopping.
In Part 3 we have investigated predictors of successful stopping preventive cardiovascular medication.

4. AIMS OF THIS THESIS: SUMMARY

The overall aim of this thesis is to improve cardiovascular preventive care in general practice for low-CVD-risk patients, aged 40 to 70 years, and with a changed indication or without a strict indication for preventive cardiovascular medication.
The aim of Part 1 is to investigate the implications of the revision of the Dutch CVRM guidelines on a population- and an individual patient-level.
Part 2 aims to evaluate the safety, the effectiveness, and the cost-effectiveness, of a structured deprescribing strategy in patients aged 40 to 70 years and using preventive cardiovascular medication, but without a history of CVD and with low risk of future CVD, and (therefore) losing a strict indication for prolonged preventive cardiovascular medication in general practice.
The aim of Part 3 is two-fold. The first aim is to identify the factors that influence the outcome (deprescription or continuation of preventive cardiovascular medication) of the deprescribing consultation in which patient and GP discuss deprescribing. The second aim is to identify predictors of successful stopping preventive cardiovascular medication.

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PART 1

Current practice

CHAPTER 2

Change in calculated cardiovascular risk due to guideline revision: A cross-sectional study in the Netherlands

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ABSTRACT

Background
Guidelines and accompanying risk charts concerning cardiovascular risk management (CVRM) are regularly revised worldwide.

Objective
To evaluate whether revision of the Dutch CVRM guideline has led to the reclassification of patients and, accordingly, to changes in drug recommendations.

Methods
All medical records (year 2011) of patients aged 40 – 65 years with no history of cardiovascular disease (CVD) but using antihypertensive and/or lipid-lowering drugs, were selected from the Registration Network of General Practices associated with Leiden University Medical Center. Multiple imputation techniques for missing determinants were used. The individual cardiovascular risk was calculated and the resulting drug recommendation was assessed according to both the 2006 and 2012 versions of the guideline.

Results
In total, 2075 patients were selected, of whom 1248 fulfilled the guideline criteria (systolic blood pressure 115 – 180 mmHg and total cholesterol/high-density-lipoprotein-cholesterol ratio 3.5 – 8). According to the 2012 guideline, 58.2% of the patients had low risk and 249 patients (20.0%) shifted to a different risk category. For 150 of these patients (12.0%), this category shift implied a shift in drug recommendation. The probability of shifting in drug recommendation increased with increasing age, cholesterol level, and blood pressure, and by being male.

Conclusion
Guideline revision may have important implications: based on identical values for risk factors, according to the latest revision of the Dutch CVRM guideline 20% of patients shifted in risk category and 12% of the patients shifted in drug recommendation.

INTRODUCTION

In primary preventive cardiovascular disease (CVD) care, risk classification — based on a patient's absolute risk of developing CVD as calculated by combining several risk factors — is widely used.[1-12] Increasing knowledge about the underlying assumptions and calculations of these risk classification systems, and about the effects of interventions, leads to regular revisions of guidelines.[1-14]

Like in many other countries, the first Dutch guidelines on the prevention of CVD introduced by the Dutch College of General Practitioners, had a 'single risk factor approach', i.e. they looked at either blood pressure, or cholesterol levels, or at diabetes as a risk factor, but the risk factors were not combined into an integrated approach of risk management.[15-17] In 2006, the first comprehensive guideline on cardiovascular risk management (CVRM) was introduced.[18] Five risk factors for CVD, i.e. age, sex, smoking status, systolic blood pressure (SBP) and total cholesterol/high-density-lipoprotein cholesterol (TC/HDL) ratio, were integrated into one risk chart depicting absolute cardiovascular risk. This risk chart was based on the SCORE risk function, as described in the European guideline developed by the Third Joint Task Force 2003.[19] A patient's 10-year risk of cardiovascular mortality was calculated, and the need for preventive medication was assessed accordingly, using a 10%, 10-year risk on cardiovascular mortality as threshold for entering the high-risk category.

The latest European guideline on CVD prevention was published in 2012, presenting a risk chart for high CVD risk countries and low CVD risk countries.[8] In the Netherlands, a new guideline on CVRM was launched in 2012 as well, presenting a risk chart based on the European risk chart for low CVD risk countries.[20] This new guideline included some differences regarding the calculation of CVD risk; differences that are also seen in recent updates of other CVD prevention guidelines.[1, 2, 7, 8, 11, 12] The first difference is that the age range now is set at 40 – 70 years instead of 40 – 65 years; second, cardiovascular risk assessment is now based on both cardiovascular mortality and morbidity; third, a 20% 10 – year risk of cardiovascular mortality and morbidity was now chosen as the threshold for entering the high-risk category; and finally, the additional risks by diabetes mellitus and rheumatoid arthritis were quantified into the risk chart.

At first glance, this 2012 guideline identifies more patients requiring preventive medication than the 2006 guideline. However, due to other differences between the two versions (especially the weight of additional risk-increasing factors) the exact implications of the 2012 revision on an individual level are not known.

Although the CVRM guidelines in other countries are also regularly revised and most of them present risk charts,[1, 2, 5-10] to our knowledge the effects of a change of guidelines

at the population level have not yet been examined. Therefore, we used data from 19 general practices in the western part of the Netherlands to assess whether patients using preventive cardiovascular medication would shift in risk category according to the most recent revision of the Dutch CVRM guideline, and whether these patients would shift in drug recommendation.

METHODS

Study population

A cross-sectional study was performed with data from the Registration Network of General Practices associated with Leiden University (RNUH — LEO); this is a longitudinal database of electronic medical records (EMRs) of all patients (approximately 30 000) enlisted with 19 regular general practitioners (GPs) (located in four healthcare centres) in the western part of the Netherlands.[21]

Medical records of patients aged 40 – 65 years who were using antihypertensive treatment (anatomical therapeutic chemical codes C02*, C03*, C07*, C08*, C09*) and/or lipid-lowering drugs (C10*) during the whole year 2011 were selected.[22] All medical records of patients with previous atherothrombotic CVD (international classification of primary care (ICPC) codes K75, K76*, K89, K90*, K91, K92*, K99*) and not using platelet aggregation inhibitors excluding heparin (anatomical therapeutic chemical code B01AC), providing an undisputed indication for medication, were excluded.[23] Medical records of patients with diabetes mellitus (T90*) or rheumatoid arthritis (L88*) were also excluded, as inclusion of medical records of these patients would lead to an overestimation of reclassifications because only the 2012 guideline takes these two diseases into account as quantifiable risk-increasing factors. With these criteria, 2075 medical records of patients were selected.

Classification in risk charts

Based on data in the medical records, we calculated the patient's 10-year cardiovascular risk before start of treatment according to the 2006 and 2012 risk charts respectively, using age, sex, smoking status, pre-treatment SBP and pre-treatment TC/HDL ratio, and assessed the risk category and drug recommendation for each patient according to both guidelines. Pre-treatment values were selected closest to the date the medication was started, up to one year before the start of medication. The same was done for smoking status, except that when the patient was registered as a non-smoker or a former smoker longer than one year ago, we considered the patient a current non-smoker.

To calculate the risk according to both the 2006 and 2012 guidelines, we used the same values of the determinants. Supplementary Appendix 1 to be found online at http://informahealthcare.com/doi/abs/10.3109/13814788.2015.1064389 shows the 2006 risk chart and Supplementary Appendix 2 to be found online at http://informahealthcare.com/doi/abs/10.3109/13814788.2015.1064389 the currently used 2012 risk chart. The Dutch College of General Practitioners provided us with the underlying algorithms of the risk charts of both guidelines. These algorithms were used to calculate cardiovascular risk and are being used by the college itself for their online implementation support; subsequently, patients were divided into the three risk categories (low-, medium- and high-risk) for each of both guidelines.

In both guidelines, drug recommendations depend on a patient's 10-year cardiovascular risk. In low-risk patients, lifestyle changes are advised and in high-risk patients with hypertension and/or hypercholesterolemia, preventive medication is advised. However, in the medium-risk group, drug recommendations also depend on weighing several additional risk factors, including family history, renal function, overweight and physical activity.

Patients in the medium-risk group are regarded either as low-risk patients or as high-risk patients taking into account these additional risk factors and are treated accordingly.

Because the additional risk-increasing factors listed in the 2006 guideline differ from those in the 2012 guideline, we made some assumptions to harmonize these two sets of additional risk factors (Table 1).

When patients were classified in a different risk category according to the 2012 guideline than according to the 2006 guideline, we reported this as a 'shift in risk category'. When the 2012 guideline recommended a different drug treatment for a certain patient than the 2006 guideline, we reported this as a 'shift in drug recommendation'. Thus, patients could shift in risk category but not in drug recommendation (e.g. from low-risk category in 2006 to medium-risk category without additional risk factors in 2012), but also vice versa (e.g. in both guidelines in medium-risk category, but in 2012 requiring a different drug recommendation than in 2006, based on a different weighing of the additional risk factors).

Statistical analysis

Patients' shifts in the risk category and drug recommendation were described using frequency tables. Using an independent t -test, mean cardiovascular risk was compared between the group shifting in risk category and the non-shifting group, as well as for the group shifting in drug recommendation versus the group not shifting in drug

recommendation. The odds ratios of risk factors for shift in risk category or drug recommendation were calculated with logistic regression analysis to explore further the differences between these groups. We rounded to whole patient numbers in all our analyses.

Missing patient data

Data on SBP were missing in 48.3% of the patients, TC/HDL ratio in 50.2% and smoking status in 48.1%. To deal with missing data, we used multiple imputation techniques generating 10 imputed datasets, all presenting different values of imputed variables because of the between-imputation component of variability.[24] The imputation model included the following variables: sex, age, smoking status, SBP, TC/HDL ratio, low density lipoprotein (LDL) cholesterol, antihypertensive medication use, lipid-lowering drug use, family history, exercise, kidney function, and body mass index. The range for imputed values of SBP was set at 50 – 250 mmHg, and for TC/HDL ratio at 1 – 15 to avoid clinically impossible values. After multiple imputation probabilities of variables, shifts in risk category and drug recommendation were calculated based on the population fulfilling the guideline criteria; as the risk charts use a range for SBP (120 – 180 mm Hg) and for TC/HDL ratio (4 – 8), patients with a SBP 115 – 180 and a TC/HDL ratio 3.5 – 8 fulfilled guideline criteria, making risk calculation possible. Age, SBP and TC/HDL ratio were quantified using the means and standard deviations; sex and smoking status were quantified as percentages and its ranges.

Sensitivity analysis

Shifts in risk category as described above were compared with the original dataset and with a set with imputed data without range restrictions. All analyses were performed with the IBM SPSS version 20.

RESULTS

Patient characteristics

Mean age of the patients was 55.4 years (SD 3.9), 50.2% were men (range: 49.2 – 51.2), 16% were smokers (range: 15 – 18%), mean SBP was 153 mmHg (SD 16.7), and the mean TC/HDL ratio was 5.0 (SD 1.0).
Due to the different values of SBP and TC/HDL ratio in the imputed datasets, the number of patients fulfilling guideline criteria differed per dataset. On average 827 (range: 792 – 841) out of 2075 patients did not fit the guideline, leading to an eligible study population of on average 1248 patients (range: 1234 – 1283).

Shifts in risk category and drug recommendation

The percentage of patients remaining in the same risk category was 80% [(999/1248) * 100]. Furthermore, 726 patients (58.2% of all patients) had a low risk according to the 2012 guideline despite being treated with preventive medication (Table 2).

Table 2. Patients (n=205) distributed over the risk categories as well as drug recommendation (yes or no) according to the 2006 and 2012 version of the cardiovascular risk management guidelines (in %)

			2012					
		Risk	**Low**		**Medium**		**High**	
	Risk	Drug recommendation	yes	no	yes	no	yes	no
2006	**Low**	yes	-	-	-	-	-	-
		no	-	50.2%	5.4%	8.8%	-	-
	Medium	yes	-	0.5%	8.8%	2.4%	5.4%	-
		no	-	-	-	8.3%	3.4%	-
	High	yes	-	-	-	-	6.8%	-
		no	-	-	-	-	-	-

In total, 249 patients (20.0%) shifted in risk category due to the new guidelines. In these latter patients, the mean cardiovascular risk according to the 2006 and 2012 guidelines was increased compared with the patients that did not shift in risk category

(both P < 0.0001). Of those 249 patients, 150 (12.0% of all patients) shifted in drug recommendation. These 150 patients showed a higher cardiovascular risk according to the 2006 and 2012 guideline compared with the group that did not shift in drug recommendation (both P < 0.0001). In 126 of these 150 patients (10.1% of all patients) drugs were not recommended according to the 2006 guideline but were recommended according to the 2012 guideline; in the other patients vice versa (Table 2).

Predictors of shift in drug recommendation

Table 3 shows the differences between the group shifting in drug recommendation and the group not shifting in drug recommendation. Differences were found for age, SBP and TC/HDL ratio: i.e. the higher the age, SBP or the TC/HDL ratio, the greater the probability that a patient would shift in drug recommendation. Moreover, being male also increased the probability of shifting in drug recommendation.

Table 3. Determinants of change in drug recommendation between the 2006 and 2012 guideline.

	Change in drug recommendation			
	Yes (n=24)	**No (n=181)**	**Odds Ratio[a] (CI 95%)**	**P value**
Determinant			3.170 (1.203 to 8.354)	0.020
Male	18 (75.0)	88 (48.6)		
total no. (%)			0.520 (0.147 to 1.835)	0.309
Smoker	3 (12.5)	39 (21.5)		
total no. (%)			1.091 (1.009 to 1.180)	0.029
Age (per year)	58.7	55.5		
Mean	52 to 65	40 to 65		
Range			1.224 (0.929 to 1.612)	0.151
SBP (per 10 mmHg)	160.5	155.1		
Mean	122 to 180	116 to 180		
Range			1.712 (1.129 to 2.596)	0.011
TC/HDL ratio	5.3	4.7		
Mean	3.8 to 7.4	3.5 to 7.6		
Range				

No., number; SBP, systolic blood pressure; TC, total cholesterol; HDL, HDL-cholesterol.

[a] Odds ratios are shown for change in drug recommendation compared to no change in drug recommendation

Sensitivity analysis

When we imputed data without range restrictions, there was no difference in the percentage of shifts in risk category compared to the shifts in risk category mentioned above (data not shown). The same results emerged from the complete case analysis (n = 236).

DISCUSSION

Main findings

In our primary care cohort, revision of the guideline on cardiovascular risk management led to a shift in risk category in one in five patients (20%) and to a concomitant shift in drug recommendation in 12% of the patients.
In addition, the finding that about 60% of the patients use preventive medication whilst having a low risk suggests considerable overtreatment of low-risk patients.

Strengths and limitations

Data for the present study were based on patients' EMRs because, in the Netherlands, CVRM is predominantly primary care based, and all Dutch citizens are enlisted with a general practice. This ensures that our cohort is a representative sample from the general population that is eligible for primary preventive cardiovascular care. Sampling from a large cohort of patients strengthens the external validity of our results. Moreover, over 96% of the problems registered in the EMRs of the healthcare centres of RNUH — LEO are coded with an ICPC code (which is higher than in the average Dutch general practices), ensuring a reliable selection of our study participants.[25]
We imputed 48.1 – 50.2% of the SBP, TC/HDL ratio and smoking status-values in the dataset to be able to calculate 10-year cardiovascular risk. This may be a true reflection of the incompleteness of relevant data before deciding on the prescription of preventive medication, but can also be due to the incomplete registration of data in the EMRs. However, the imputed dataset showed the same percentage of shifts in the risk category as the complete case analysis.

Comparison with existing literature

In an earlier study, we found that 61.4% of the patients had a predicted low cardiovascular 10-year risk according to the 2006 Dutch CVRM guideline before start of medication, compared with 70.6% (based on the 2006 version) in the present study.[26] Besides this confirmation in a new patient population, the present study reports on the implications of a guideline revision at a population level with regard to shifts in risk categories and drug recommendations.
Scheltens et al., compared the Framingham risk score with the SCORE risk function with regard to the number of patients assigned to treatment; a difference with our study is that we examined an actually revised guideline, making the present study less hypothetical.[27] Another additional aspect of this study is that we report the determinants of the patients who shifted in drug recommendation, which can be helpful in daily

practice.
In this study, we observed that about 60% of the patients use preventive medication whilst having a low risk. This can be explained by former guidelines (before the guideline on integrated CVRM was issued) recommending preventive medication based on a single risk factor ('hypertension' or 'hypercholesterolemia', etc.) without taking other risk factors (e.g. age, sex and smoking status) into account and not integrating the risk. It is likely that also a considerable number of low-risk patients in other European countries are unnecessarily treated as well. For example in Germany, as in the Netherlands, the concept of starting treatment based on the total burden of risk was adopted only recently,[9, 17] although the European guideline adopted this idea much earlier.[28]

Implications for research and practice
GPs should be aware that a revised guideline in the area of primary prevention of CVD could have consequences for their patients: it is advisable to re-evaluate drug recommendations in patients assessed according to the former guideline and not yet using preventive treatment.
Then again, a large proportion of patients seem to use medication without a clear indication, irrespective of the version of the guideline used. It remains unclear how to proceed when a revised guideline has a higher threshold for starting preventive medication, resulting in situations where patients may well be advised to stop taking preventive medication they have been using, sometimes for years on a row. Obviously, it is important to establish whether withdrawal of medication in patients with low risk is safe in the long run, and whether this is efficacious and cost effective.

CONCLUSION

Revision of a guideline in the area of primary prevention of CVD may have a considerable impact on patient care since it may lead to shifts in risk categories and, accordingly, to shifts in drug recommendation. Professional medical organizations in countries with guidelines for primary preventive CVD care, especially when using risk charts, should be aware of these consequences and develop protocols for healthcare professionals on how to cope with these reclassifications.

KEY MESSAGE

- Revising the Dutch guideline on cardiovascular risk management implied a shift in drug recommendation in 12% of the patients.

- GPs should be aware of the possible consequences of guideline revisions for patients.

- Professional medical organizations should develop policies on how to cope with these consequences.

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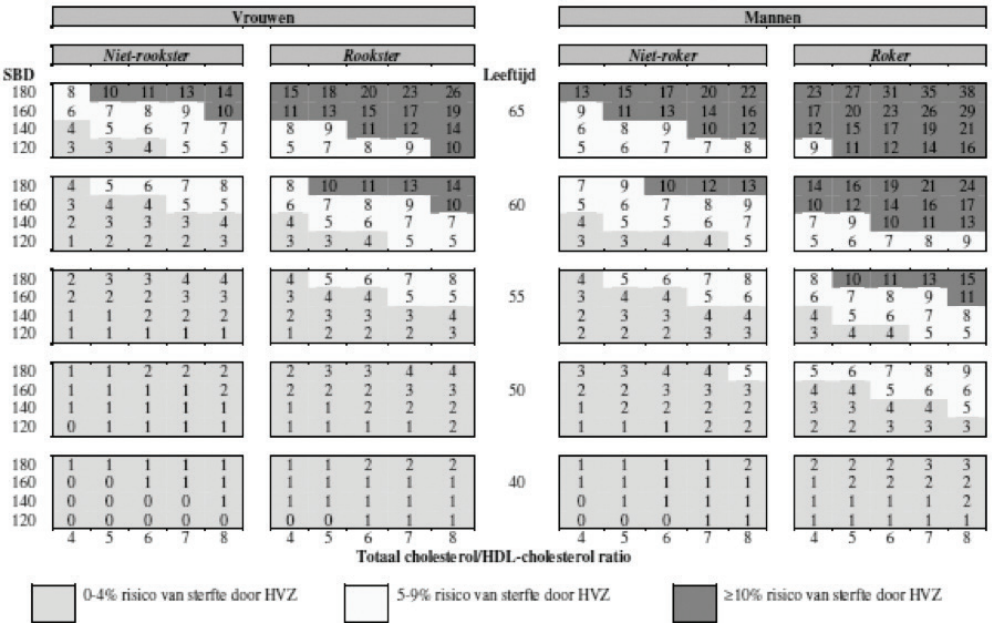
Table 1. Differences in additional risk factors, used for determining recommendations for medication in medium-risk patients, between the two Dutch guidelines on cardiovascular risk management (2006[18] and 2012[20]) and conversion of the determinants registered in the electronic medical record (EMR).

	Additional risk factor		Conversion of EMR registration to be able to assess drug recommendation	
Additional risk factors	2006 guideline	2012 guideline	Registration EMR 2006	Converted to 2012
Family History	CVD in a first degree relative <60 years	CVD in a first degree relative <65 years	CVD in a first-degree relative <60 years	Not converted
		CVD in ≥2 first degree relatives <65 years CVD in ≥1 first degree relatives <60 years 30-35 kg/m^2	No CVD in a first-degree relative <60 years	No CVD in a first-degree relative <65 years
Body mass index (BMI)	>30 kg/m^2	30-35 kg/m^2 ≥35 kg/m^2	BMI	Not converted
Vascular outcome	Kidney function disorders: eGFR <60 ml/min/1.73m^2	<65 years: eGFR >60 ml/min/1.73m^2 Or ≥65 years: >45 ml/min/1.73m^2 <65 years: eGFR 30-60 ml/min/1.73m^2 Or ≥65 years: 30-45 ml/min/1.73m^2	MDRD	Not converted
	Left ventricle hypertrophy		Not assessed	Not assessed
	Intima thickening carotid artery		Not assessed	Not assessed
	Excessive atherosclerosis		Not assessed	Not assessed
Physical activity		Sedentary lifestyle <30 min/d, ≤5 d/wk ≥30 min/d, ≥5 d/wk	Less than ADL ADL More than ADL Healthy	Sedentary lifestyle Sedentary lifestyle <30 min/d, ≤5 d/wk ≥30 min/d, ≥5 d/wk

CVD, cardiovascular disease; eGFR, estimated glomerular filtration rate; MDRD, modification of diet in renal disease; ml, millilitre; min, minute; m^2, square metre; d, day; wk, week; ADL, activities of daily living.

SUPPLEMENTARY DATA

Supplementary Appendix 1.
Risk chart of the Dutch 2006 guideline on cardiovascular risk management.[18]



Supplementary Appendix 2. Risk chart of the Dutch 2012 guideline on cardiovascular risk management.[20]

Tabel 1. Risicotabel: 10-jaarsrisico op ziekte of sterfte door HVZ voor patiënten zonder HVZ

SBD	Vrouwen: Niet-rookster					Vrouwen: Rookster				
180	35	38	41	43	44	47	50	>50	>50	>50
160	28	31	33	35	36	38	41	44	46	48
140	22	24	26	28	29	31	33	36	38	39
120	18	19	21	22	23	25	27	29	30	32
180	14	17	20	24	30	27	32	37	45	>50
160	10	12	14	17	21	19	22	27	32	39
140	7	8	10	12	15	14	16	19	23	28
120	5	6	7	9	11	10	11	14	17	20
180	10	12	15	18	23	20	23	28	34	42
160	7	8	11	13	16	14	17	20	24	30
140	5	6	7	9	12	10	12	14	17	21
120	4	4	5	7	8	7	8	10	12	15
180	5	6	8	10	12	10	12	15	18	22
160	4	4	5	7	9	7	8	10	13	16
140	3	3	4	5	6	5	6	7	9	11
120	2	2	3	3	4	4	4	5	6	8
180	2	3	4	5	6	5	6	7	9	11
160	2	3	3	3	4	3	4	5	6	8
140	1	1	2	2	3	2	3	3	4	6
120	1	1	1	2	2	2	2	2	3	4
180	1	1	1	1	1	1	1	1	2	2
160	<1	<1	1	1	1	1	1	1	1	2
140	<1	<1	<1	1	1	<1	<1	1	1	1
120	<1	<1	<1	<1	<1	<1	<1	1	1	1
	4	5	6	7	8	4	5	6	7	8
	Ratio totaal cholesterol/HDL									

Leeftijd	Mannen: Niet-roker					Mannen: Roker				
70	>50	>50	>50	>50	>50	>50	>50	>50	>50	>50
	45	48	>50	>50	>50	>50	>50	>50	>50	>50
	37	40	42	44	46	49	>50	>50	>50	>50
	30	32	34	36	38	40	43	45	48	50
65	25	30	36	44	>50	45	>50	>50	>50	>50
	18	21	26	32	40	33	39	47	>50	>50
	12	15	18	23	29	23	28	34	42	>50
	9	11	13	16	21	17	20	24	30	38
60	22	26	32	40	50	40	48	>50	>50	>50
	15	19	23	29	36	29	35	42	>50	>50
	11	13	16	20	26	20	25	30	38	47
	8	9	12	15	19	14	18	22	27	34
55	13	16	20	26	32	25	31	38	47	>50
	10	12	15	18	23	18	22	27	34	43
	7	8	10	13	17	13	16	19	24	31
	5	6	7	9	12	9	11	14	17	22
50	8	10	12	15	20	15	18	23	28	36
	6	7	9	11	14	11	13	16	20	26
	4	5	6	8	10	7	9	12	15	19
	3	3	4	6	7	5	7	8	10	13
40	3	3	4	6	7	5	6	8	10	13
	2	2	3	4	5	4	4	6	7	9
	1	2	2	3	4	3	3	4	5	7
	1	1	2	2	3	2	2	3	4	5
	4	5	6	7	8	4	5	6	7	8
	Ratio totaal cholesterol/HDL									

< 10% risico op ziekte of sterfte door HVZ; leefstijladviezen indien daar aanleiding voor is, zelden medicamenteuze behandeling.

10% tot 20% risico op ziekte of sterfte door HVZ: leefstijladviezen, medicamenteuze behandeling alleen bij risicoverhogende factoren en SBD > 140 mmHg en/of LDL > 2,5 mmol/l.

≥ 20% risico op ziekte of sterfte door HVZ; leefstijladviezen, medicamenteuze behandeling als SBD > 140 mmHg en/of LDL > 2,5 mmol/l.

Het risico bij patiënten met DM of RA kan worden geschat door bij de actuele leeftijd van de patiënt 15 jaar op te tellen.

PART 2

(Cost)-effectiveness and safety of deprescribing

CHAPTER 3

Deprescribing Preventive Cardiovascular Medication in Patients with Predicted Low Cardiovascular Disease Risk in General Practice – The ECSTATIC Study: A Cluster Randomised Non-inferiority Trial

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ABSTRACT

Background

Use of cardiovascular medication for primary prevention of cardiovascular disease (CVD) is potentially inappropriate when potential risks outweigh the potential benefits. It is unknown whether deprescribing preventive cardiovascular medication in patients without a strict indication for such medication is safe and cost-effective in general practice.

Methods

In this pragmatic cluster randomised controlled non-inferiority trial we recruited 46 general practices in the Netherlands. Patients, aged 40-70 years, using antihypertensive and/or lipid-lowering drugs without CVD and with low risk of future CVD, were followed for two years. The intervention was an attempt to deprescribe preventive cardiovascular medication. The primary outcome was the difference in the increase in predicted (10-year) CVD risk in the per-protocol (PP) population with a non-inferiority margin of 2.5 percentage points. An economic evaluation was performed in the intention-to-treat (ITT) population. We used multilevel (generalised) linear regression with multiple imputation of missing data.

Results

Of 1067 participants recruited between November 7, 2012 and February 18, 2014 72% were female; mean age was 55 years; mean predicted CVD risk at baseline was 5%. Of 492 participants (ITT intervention group), 319 (65%) quit the medication (PP intervention group); 135 (27%) of those participants were still not taking medication after two years. The predicted CVD risk increased by 2.0 percentage points in the PP intervention group compared to 1.9 percentage points in the usual care group. The difference of 0.1 (95% CI -0.3 to 0.6) fell within the non-inferiority margin. Compared to the usual care group, the SBP was 6 mmHg higher after two years in the PP intervention group, DBP was 4 mmHg higher, and the total cholesterol and LDL-cholesterol levels were both 7 mg/dl higher (all $P<0.05$). Cost and quality-adjusted life-years did not differ between the groups.

Conclusions

The results of the ECSTATIC study show that an attempt to deprescribe preventive cardiovascular medication in low-CVD-risk patients is safe when blood pressure and cholesterol levels are monitored after stopping. An attempt to deprescribe medication can be considered, taking patient preferences into consideration.

Trial Registration

This study was registered with Dutch trial register at June 20, 2012, NTR3493.

BACKGROUND

Cardiovascular disease (CVD) remains a leading cause of mortality and morbidity worldwide and is associated with a loss of quality of life and high costs.[1, 2] Physicians use their clinical judgement as well as clinical practice guidelines to determine whether treatment with antihypertensive and lipid-lowering drugs is necessary in individual patients. Recommendations concerning initiation of drug treatment in patients with hypertension or hypercholesterolemia, but without established CVD, are subject to change and are still under debate. Currently, guideline recommendations concerning initiation of drug treatment are often based on composite risk scores.[3-7] However, recommendations to start medication in previous guidelines used to be based on single risk factors, such as increased blood pressure or cholesterol levels, or diabetes, and thus lacked an integrated approach to risk management[8-10] which resulted in drug prescription to patients that are now considered low-CVD-risk patients. Over time, these evolving recommendations have resulted in the potentially inappropriate use of antihypertensive and lipid-lowering drugs, namely, in situations where potential risks (e.g., side effects) outweigh the potential benefits.[11-14] Although physicians are aware that medication use in low-CVD-risk patients is of little benefit, fear of negative consequences and lack of evidence for withdrawal keep them from stopping the medication.[15] A study investigating the positive (e.g., quality of life) and negative effects (e.g., increase in CVD risk, experiencing inconvenient symptoms) of deprescribing preventive cardiovascular medication in low-CVD-risk patients may improve the knowledge of the physician on this point. Depending on the outcome, this may lead to a more positive or negative attitude towards deprescribing in this patient population amongst physicians. Therefore, the aim of the Evaluating Cessation STatins and Antihypertensive Treatment In primary Care (ECSTATIC) study was to evaluate whether an attempt to deprescribe preventive cardiovascular medication in low-CVD-risk patients using these medications without indication according to current guidelines is safe and cost-effective.

METHODS

Study design

The ECSTATIC study was designed and carried out as a cluster randomised non-blinded parallel-group active-control non-inferiority study, including patients from 46 general practices in the western part of the Netherlands from November 7, 2012, with a follow-

up period lasting until November 20, 2015 (Dutch Trial Register, NTR3493). To reduce contamination of the participants in the control group, the unit of randomisation and analysis was the general practice. The primary outcome was the difference in the increase in the predicted 10-year CVD risk in the two years after the first visit. Our choice for a non-inferiority trial design was based on the expectation that the attempt to deprescribe preventive cardiovascular medication in low CVD risk patients would increase CVD risk to some extent, but, at the same time, would lead to fewer side effects, less cost and the disutility of daily medication use, together tipping the risk-benefit ratio into its favour.

The study protocol was approved by the medical ethics committee of the Leiden University Medical Center. The study was conducted in accordance with the Declaration of Helsinki. The study received external funding from ZonMw, The Netherlands Organisation for Health Research and Development (reference number 200320017). The funder of the study had no role in the study design, data collection, data analysis, or interpretation to the data.

To avoid allocation bias and imbalance in the number of general practices allocated to the study groups, we used computer-generated block randomisation in a 1:1 ratio, with random block sizes consisting of 10 or 12 general practices.

General practices and participants

All general practices in our network were invited. Before randomisation, general practitioners (GPs) of the practices selected possibly eligible patients who were 40 to 70 years old without established CVD, using potentially inappropriate antihypertensive or lipid-lowering drugs for at least one year based on their electronic medical record (EMR) (Figure 1). Patients aged below 40 years old or over 70 years old were excluded, because the SCORE risk function (recalibrated for the Dutch population), that we used to assess eligibility for inclusion, is only available for patients aged 40 to 70 years old.[4] Subsequently, the participating general practices were randomised. GPs sent a written invitation for trial participation to their patients who had already been declared eligible before randomisation. We used a complete-double consent design in which informed consent was sought in both the intervention group and usual care group, mentioning the use of the other comparison group. To avoid contamination of the usual care group, the invitation letter sent to the usual care group did not specify the exact intervention. The letter sent to the intervention group explained the intervention and mentioned the use of a control group that was given care as usual.[16]

After obtaining informed consent of the patients, the researchers re-assessed the patients for eligibility using the SCORE risk function recalibrated for the Dutch

population as used in the Dutch guideline for Cardiovascular Risk Management (Figure 2).[4] An overview of all patient inclusion and exclusion criteria is listed in Additional file 1.

Inclusion criteria
- Age 40 to 70 years
- Using antihypertensive and/or lipid-lowering drugs for ≥ 12 months
- No recommendation for drug treatment according to Dutch guideline cardiovascular risk management

Exclusion criteria
- History of cardiovascular disease

Figure 2. Inclusion and exclusion criteria ECSTATIC trial

We assessed the pre-treatment CVD risk based on current (i.e., at first visit) age, sex, and smoking behaviour (smoking yes/no), in combination with reported pre-treatment systolic blood pressure (SBP) and total cholesterol/HDL-cholesterol ratio levels in general practice EMRs. If these values were not available up to one year before the start of drug treatment, pre-treatment SBP was conservatively estimated at 180 mmHg, and low-density lipoprotein (LDL) and high-density lipoprotein (HDL) cholesterol levels were estimated based on current levels of total cholesterol, HDL-cholesterol, and LDL-cholesterol measured by local laboratories (Additional file 1).
The Dutch College of General Practitioners provided us with the underlying algorithm for CVD risk estimation. We used these algorithms to estimate predicted 10-year CVD risk. All patients willing to participate who had a predicted low 10-year risk of CVD morbidity and mortality, without additional risk increasing factors (further reported as 'low CVD risk'), i.e., patients for whom drug treatment was not recommended according to the Dutch guideline for Cardiovascular Risk Management, were included in the trial.[4]

Interventions
GPs and (when applicable) practice nurses in intervention practices received a two-hour workshop providing information about the background, the aim and the intervention of the ECSTATIC study. The workshop was carried out in the Leiden University Medical

Center and led by a GP with special interest in cardiovascular risk management and the researcher of this project (CL).

At the first visit, the research nurse advised participants in the intervention practices to consult their GP to discuss deprescribing their preventive cardiovascular medication. For more details about the factors influencing this decision-making process we refer to an earlier study we performed.[17] When deprescribing was attempted, GPs followed our predefined deprescribing guideline for gradual dose reduction and monitoring of blood pressure and cholesterol levels (Additional file 2). Furthermore, they were advised to follow the recommendations of the Dutch guideline for Cardiovascular Risk for (re-) initiation of medication (Additional file 2).

There was no intervention planned for the GPs, practice nurses, and participants in the usual care group.

Outcome measures

For all participants, we aimed for a follow-up period of two years. The primary outcome assessed for non-inferiority was the increase in participants' predicted 10 year CVD risk in the two years after the first visit. Non-inferiority would be declared if the upper limit of the 95% confidence interval of the difference between the mean increase in CVD risk in the intervention group and the mean increase in the CVD risk in the usual care group was below +2.50 percentage points (on an absolute scale). The non-inferiority margin was set at 2.50 percentage points, because we believed this difference in the increase in the 10-year CVD risk between the intervention group and usual care group was clinically acceptable.

Secondary outcomes assessed for superiority were SBP, diastolic blood pressure (DBP), total cholesterol, HDL-cholesterol and LDL-cholesterol levels, body mass index (BMI: body weight kg / height in meters squared), waist circumference, body weight, smoking behaviour, physical activity, fruit and vegetable intake, and alcohol consumption; all were assessed at three months and two years after the first visit. These variables were assessed as outcomes, because we hypothesized that the intervention could induce lifestyle changes that could affect these variables. Other secondary outcomes were negative effects of deprescribing (in the intervention group) and side effects of antihypertensive and lipid-lowering drugs (in the usual care group) reported by GPs during trial follow-up, and incidence of CVD, assessed for superiority two years after the first visit.

We performed three post-hoc analyses to investigate differences between the intervention group and the usual care group after two years of follow-up, using a generalised logistic mixed linear model to assess the relative risk (RR) of: 1) having a mean increase in CVD risk >2.50 percentage points; 2) having hypertension, defined by a SBP >140 mmHg; and 3) having hypercholesterolemia, defined by a LDL-cholesterol level >96.5 mg/dl (=2.5 mmol/L). We did not adjust for the baseline values in order to calculate RR based on the observed odds ratio (OR) [18].

Measurements

Participants were visited at baseline (first visit), after three months and after 24 months by trained research nurses at the general practice of their GP. During these visits, smoking behaviour was registered, and SBP and DBP were measured twice with a five-minute interval on the arm where SBP at baseline was highest after at least five minutes of seated rest[4] (Omron HEM-907); additionally, body weight in kilograms (seca 762), height in centimetres (seca 213), and waist circumference in centimetres (seca 201) were measured and registered. The research nurse registered the total cholesterol, HDL-cholesterol, and LDL-cholesterol values that local laboratories reported to the general practices.

If research nurses measured a mean SBP >180 mmHg, or registered a total cholesterol level >308.9 mg/dl (8 mmol/l) or a LDL-cholesterol level >193.1 mg/dl (5 mmol/l) the participant's GP was notified.

Two weeks before each visit, participants were asked to prospectively keep a 7-day diary of their alcohol consumption[19] and to complete questionnaires concerning: 1) ethnicity and education level (only at baseline); 2) physical activity (short questionnaire to assess health-enhancing physical activity (SQUASH)[20-22]); and 3) fruit and vegetable intake (standard nutrition questionnaire of Dutch common health services[23]). The research nurse collected and checked the completed questionnaires during the visit.

At 24 months of follow-up, participants in the intervention group were asked to describe their 'deprescribing status' of preventive cardiovascular medication by choosing one of five options: 1) currently not using medication, 2) currently using fewer or lower doses of medications, 3) restarted some medications, 4) restarted all medications, or 5) never stopped or tried to stop. In case participants did not complete the deprescribing status questionnaire, we used the reported negative effects of deprescribing by the GP to search for information about their deprescribing status, and registrations of the participants' deprescribing status by the research nurse during follow-up.

Safety

GPs in the intervention group were asked to report negative effects of deprescribing to the researchers during trial follow-up, and GPs in the usual care group were asked to report side effects of antihypertensive and lipid-lowering drugs. Although assessment of negative effects of deprescribing in the control group would improve comparison of the safety profile of the intervention this was not possible for practical reasons (e.g., to avoid contamination).

The incidence of CVD in participants was determined, using corresponding ICPC codes for angina pectoris (K74), acute myocardial infarction (K75), other/chronic ischaemic heart disease (K76), transient ischaemic attack (K89), cerebrovascular accident (K90.03), atherosclerosis (K91), vascular claudication (K92.01), and aortic aneurysm (K99.01), as registered by the GP in the EMR (standard care) during follow-up.

Economic evaluation

Costs were estimated in the intention-to-treat (ITT) population from a societal perspective at the price level from 2015.[24] Costs are reported in pounds (based on purchasing power parities of 08-08-2016). Primary care specific costs included costs for periodically carried out patient selection (Additional file 3), general practice consultations, antihypertensive and lipid-lowering drug use, and cardiovascular management related laboratory measurements; all of these were based on the EMR from the general practices. Total healthcare costs also included specialist and physical therapist consultations, use of home care, and hospitalisations, all reported by the participants in a cost questionnaire with a three-month recall period that was administered at 3, 6, 12 and 24 months in the follow-up period (months in between were interpolated). Cost-effectiveness acceptability curves were used to relate the difference in costs to the difference in 2-year quality-adjusted life years (QALYs), as assessed with the Dutch tariff for the EQ-5D-3L questionnaire.[25] Hypothetically, QALYs would be higher in the intervention group compared to the usual care group because of the reduction of the burden of daily medication use and side effects but would be lower because of an increase in the 10-year CVD risk. Acceptability curves show the probability that the intervention has better net benefit (NB = WTP x QALY – Costs) than the usual care, depending on the willingness to pay (WTP) for one QALY.[26]

The economic evaluation was limited to the 2-year trial period, because no reliable information is available to extrapolate the long-term impact on medication use and the balance between side effects, CVD risk and costs in this low-risk population.

Statistical analysis

For sample size calculation, we set the expected difference in the increase in the 10-year CVD risk at 1.50 percentage points and the standard deviation (SD) at 3.5, and we estimated the number of participating patients per general practice attempting to have their medication deprescribed at 10 (per-protocol population) based on data from a previous study concerning deprescribing preventive cardiovascular medication in low CVD risk patients.[12] We assumed an intraclass correlation coefficient of 0.05, taking into account differences between the participating general practices that could influence study outcomes. The prespecified non-inferiority margin of 2.50 percentage points was based on both statistical reasoning (sample size) and clinical judgement and was set as the maximum allowed upper limit of the 95% confidence interval (one-sided alpha of 5%) of the difference in the increase in the 10-year CVD risk.[27] Assuming that two-thirds of the participants would attempt to have their medication deprescribed, we estimated that 464x1.5=696 participants from 46 general practices needed to undergo randomisation. Recruitment of general practices was stopped after the number of 46 included general practices was reached.

During the trial, the proportion of participants attempting to have their medication deprescribed was less than the expected 67% (approximately 55%), while the number of eligible patients per general practice was higher than expected. We therefore decided to increase the number of included patients per general practice, allowing us to decrease the planned one-sided alpha from 5% to 2.5%. At the end of the inclusion period we again had to randomly exclude patients from invitation, because the number of possibly eligible patients per general practice was even higher than anticipated early on in the trial (Figure 1).

The primary outcome was evaluated in the per-protocol (PP) population, defined as all patients who were included at the first visit and were allocated to the usual care group, and all patients who were included at the first visit in the intervention group who had (attempted to have) their preventive cardiovascular medication stopped based on their self-reported deprescribing status. In non-inferiority trials an ITT analysis tends to bias towards making the intervention and usual care look similar. Therefore, we chose to evaluate the primary outcome in a PP analysis, as this analysis is more likely to reflect differences between two treatments.[28] Secondary outcomes were evaluated in the PP population as well. All analyses were repeated for the ITT population; the ITT population is defined as all usual care and intervention group patients who were included at the first visit. Furthermore, we evaluated the primary outcome, SBP, DBP and LDL-cholesterol levels in the 'quitters' population, defined as all usual care group patients and all intervention group patients who were able to permanently stop their medication based

on their self-reported deprescribing status. The intervention group patients are defined as ITT intervention group; the intervention group patients who had (attempted to have) their preventive cardiovascular medication stopped are defined as PP intervention group; and the intervention group patients who persisted without cardiovascular medication two years after the first visit are defined as the quitters intervention group.
We used multiple imputations to deal with missing values of primary and secondary outcomes and predictors in 15 imputation sets.[29] The following baseline predictors, without any missing values, were used to build the imputation model: allocation group, sex, age, SBP, total cholesterol, HDL-cholesterol, and the utility value of the EQ-5D-3L questionnaire. The clusters were not included as predictors to avoid instability of the model. The imputation model for symmetrically distributed continuous variables was based on linear regression, for skewly distributed continuous variables (skewness statistic >1 or <-1) predictive mean matching was used. The imputation model for dichotomous variables was based on logistic regression. For missing values of height at baseline, we used the value reported at the end of follow-up and vice versa. For age, we calculated the patient's age at median date of the assessments at 24 months of other patients coming from the same general practice. One intervention group patient, who never attempted to have her preventive cardiovascular medication deprescribed, died of an unknown cause, and was left out of our intention-to-treat analyses at 24 months.
To compare continuous and binary outcomes, linear mixed and generalised (logistic) mixed linear models were used, respectively, to adjust for cluster randomization and baseline values of the outcome that was evaluated. Given the low incidence of CVD estimation of a clustereffect would be unreliable, therefore CVD incidence was analysed with Fisher's Exact test. SPSS Statistics for Windows, version 23 was used for all analyses.

RESULTS

A total of 1067 participants at 46 general practices (16% of invited general practices) were included between November 2012 and February 2014 (Figure 1 and Table 1). The median follow-up period was 23 months (range 17 to 32 months), and the intraclass correlation coefficient for the primary outcome was <0.01. The ITT intervention group consisted of 492 participants; the PP intervention group consisted of 319 (65% of the ITT intervention group), and had (temporarily) deprescribed medication; the quitters intervention group consisted of 135 participants (27% of the ITT intervention group), and persisted without cardiovascular medication two years after the first visit (Figure 3). At baseline, there were some differences between the usual care group, and the PP and ITT intervention groups (Table 1).

Baseline CVD risk in the PP intervention group was 4.7% compared to 5.3% in the 173 intervention group participants who continued their medication or had unknown de-prescribing status. The total cholesterol/HDL-cholesterol ratio at baseline was lower in participants who had (temporarily) deprescribed medication. However, there was no difference in age, sex, smoking behaviour, SBP, or LDL-cholesterol levels.

In 15% of the participants levels of SBP, total cholesterol/HDL-cholesterol ratio, or smoking status to determine the primary outcome at the end of follow-up were missing and were imputed

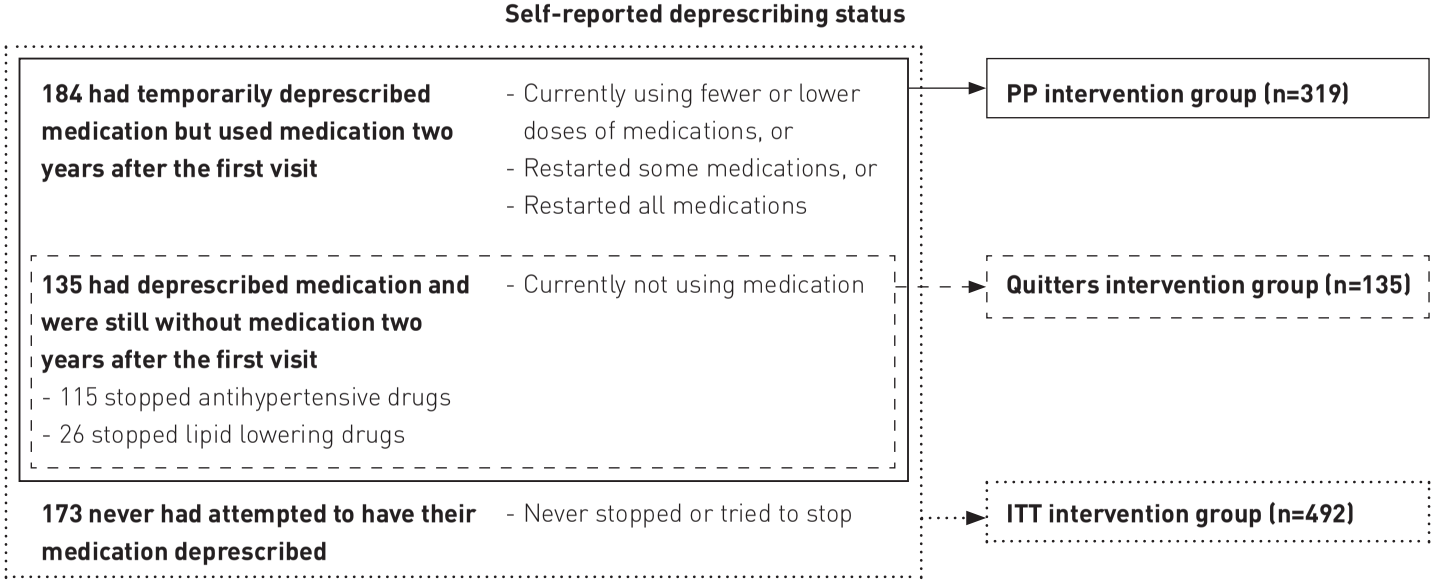

Figure 3. Deprescribing status of preventive cardiovascular medication of the 492 participants in the intervention group

Abbreviations: PP denotes per-protocol; ITT denotes intention-to-treat.

Primary outcome

The PP analysis showed a two-year increase in CVD risk in both the intervention group and usual care group, from 4.7% to 6.7% (+2.0 percentage points) and from 5.1% to 7.0% (+1.9 percentage points), respectively. The mean increase in CVD risk was +0.1 percentage points higher in the deprescribing group, with a 95% CI of -0.3 to 0.6 percentage points, establishing non-inferiority (Figure 4). The ITT analysis showed similar results; CVD risk increased from 4.9 to 6.9% (+2.0 percentage points) in the intervention group, with a mean difference in the increase of 0.1 percentage points (95% CI -0.4 to 0.7).

Secondary outcomes

Figure 5 shows SBP, LDL-cholesterol levels, and predicted 10-year CVD risk at the first visit, and three and 24 months after the first visit. At the end of follow-up, SBP, DBP, total cholesterol, and LDL-cholesterol levels were higher in the PP intervention group compared to the usual care group (all $P<0.01$, Table 2). Smoking behaviour and BMI were similar in both groups. Physical activity level, fruit and vegetable intake, and alcohol consumption were also similar in both groups. The ITT analysis showed similar results on the secondary outcomes.

Cardiovascular events and other negative effects

In the usual care group eight participants developed CVD during follow-up, and zero developed CVD in the PP intervention group ($P=0.03$). In the ITT intervention group two participants developed CVD ($P=0.12$ compared to the usual care group). CVD incidence could not be identified in 61 participants because of withdrawn informed consent (29 in the usual care group, 5 in the PP intervention group, and 32 in the ITT intervention group).

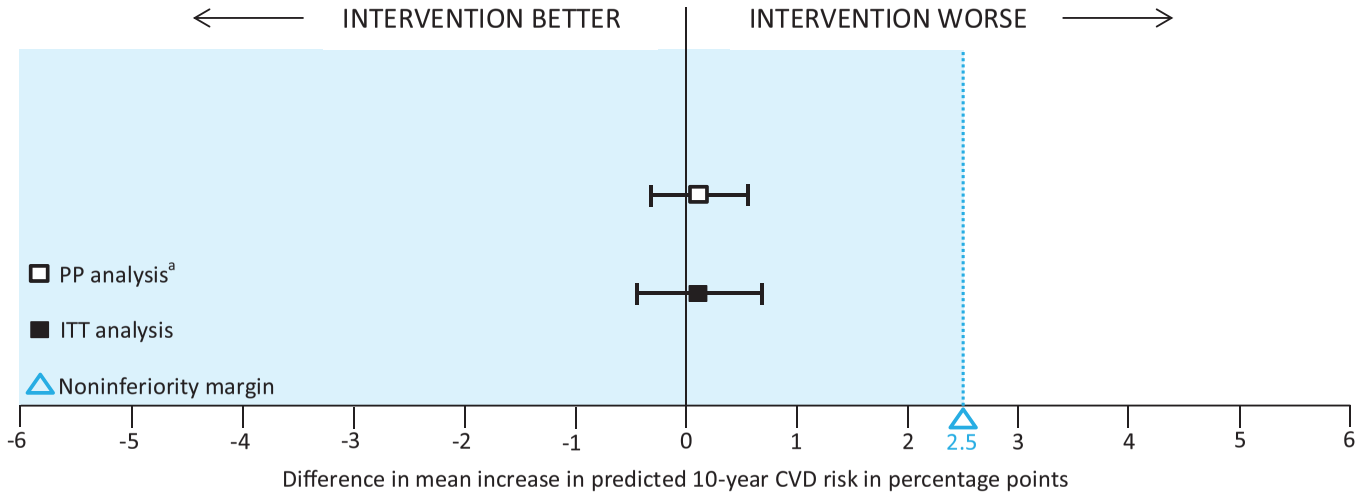

Figure 4. Intention-to-treat and per-protocol analysis of the difference in mean increase in predicted 10-year CVD risk.

Abbreviations: CVD denotes cardiovascular disease; PP denotes per-protocol; ITT denotes intention-to-treat.

The error bars depict the 95% CI of the estimated difference in increase of 10-year CVD risk between the usual care and intervention group two years after the first visit.

[a] PP analysis includes only the 319 participants in the intervention group who had (temporarily) deprescribed their preventive cardiovascular medication.

In the PP intervention group, GPs reported 76 negative effects because of deprescribing in 42 of 319 participants (13.2%) (Table 3). Antihypertensive and/or lipid-lowering drugs were restarted in 34 of these 42 participants. GPs in the usual care group reported no side effects of antihypertensive or lipid-lowering drugs during follow-up.

Table 3. Negative effects of deprescribing reported to the researchers by GPs in the intervention group[a]

Negative effects	**Participants (n= 42)**	**Only restarted participants (n= 34)**
	Times reported	**Times reported**
Hypertension/increased blood pressure	24	21
Headache or migraine	18	11
Nervous or stressed feeling	7	5
Palpitations	7	5
Ankle edema/fluid buildup	4	3
Hypercholesterolemia	4	4
Pressure sensation on chest	2	2
Dizziness	2	2
Not feeling well	2	2
Tachycardia	1	1
Systolic cardiac souffle	1	1
Dyspnea	1	1
Fatigue	1	1
Nausea	1	1
Hot flushes	1	1
Total	**76**	**61**

Abbreviations: GP denotes general practitioner

[a] GPs in the usual care group did not report any side effect of antihypertensive or lipid-lowering drugs to the researchers during follow-up.

Quitters

Analysis of 135 participants who were still not taking medication two years after the first visit (Figure 3), showed a two-year increase in CVD risk from 4.3% to 6.6% (+2.3 percentage points). This increase was a +0.4 percentage points higher compared to the usual care group, with a 95% CI of -0.3 to 1.1 percentage points, establishing non-inferiority. Two years after the first visit, the difference in SBP between the quitters intervention group and the usual care group was 10 mmHg (146 vs. 136 mmHg, respectively); the difference in DBP was 7 mmHg (87 vs. 80 mmHg, respectively); and the difference in LDL-cholesterol was 13 mg/dl (141 vs. 128 mg/dl, respectively); all were P<0.01.

The difference in SBP between the 115 participants who had their antihypertensive drugs deprescribed (Figure 3) compared to the 479 participants using antihypertensive drugs at baseline in the usual care group was 13 mmHg two years after the first visit (149 vs. 136 mmHg, respectively, P<0.01). The difference in LDL-cholesterol of the 26 participants who had their lipid-lowering drugs deprescribed (Figure 3) compared to the 163 participants using lipid-lowering drugs at baseline in the usual care group was 56 mg/dl (178 vs. 122 mg/dl, respectively, P<0.01).

Individual follow-up

The RR of having a mean increase in CVD risk >2.5 percentage points after two years of follow-up for the PP intervention group versus the usual care group was 1.29 (95% CI 1.01 to 1.61, based on a baseline risk of 0.222 and a OR of 1.40). The RR of having a SBP >140 mmHg and the RR of having a LDL-cholesterol level >96.5 mg/dl for the PP intervention group versus the usual care group was 1.41 (95% CI 1.18 to 1.64, based on a baseline risk of 0.372 and a OR of 1.87) and 1.10 (95% CI 1.04 to 1.15, based on a baseline risk of 0.807 and a OR of 1.96), respectively. The ITT analysis showed similar results for having a SBP >140 mmHg and having a LDL-cholesterol level >96.5 mg/dl, as the RR and 95% CI in the ITT analysis were comparable to the RR and 95% CI resulting from the PP analysis. In the ITT analysis, the RR of having mean increase in CVD risk >2.5 percentage points for the PP intervention group versus the usual care group was 1.21 (95% CI 0.97 to 1.49).

Economic evaluation

In the first year, intervention costs and GP consultation costs were higher in the ITT intervention group by £86 per participant (Additional file 3: Table S3, P<0.01). In both years, medication costs were lower in the ITT intervention group by £28 (P<0.01). Total 2-year healthcare costs and primary care costs did not differ between the two groups

(P=1.00 and P=0.19, respectively). In addition, no difference was found in QALYs (P=0.45) (Additional file 3: Table S3). Whether an attempt to deprescribe preventive cardiovascular medication is cost-effective depends on how much one is willing to pay for one QALY. Figure S2 in Additional file 3 shows the probability that an attempt to deprescribe preventive cardiovascular medication in general practice is cost-effective compared with usual care. An attempt to deprescribe preventive cardiovascular medication is 70% to 80% likely to be cost-effective for a willingness to pay between £20,000 and £30,000.

DISCUSSION

The ECSTATIC study revealed that an attempt to deprescribe preventive cardiovascular medication in patients in general practice with predicted low 10-year CVD risk was safe in the short term compared to usual care based on a minimal difference in the increase in predicted 10-year CVD risk. After two years of follow-up, the mean blood pressure was 6 mmHg higher, and the total cholesterol and LDL-cholesterol levels were both on average 7 mg/dl higher compared to usual care in the intervention group. The risk of having hypertension after two years of follow-up was approximately 20% to 60% higher in the intervention group and the risk of having hypercholesterolemia was approximately 5% to 15% compared to the usual care group. Only 27% of participants persisted without medication two years after the first visit. In the intervention group, 1-year primary care costs were higher, but 2-year primary care costs and total healthcare costs were similar and there was no difference in QALYs.
Based on our findings, an attempt to deprescribe preventive cardiovascular medication in low CVD risk patients is safe when blood pressure and cholesterol levels are monitored after stopping, but does not improve the quality of life or reduce healthcare costs.

Strengths and weaknesses of study

Study strengths include the large sample of general practices and patients, and the pragmatic trial design; both of these reflect the results of implementing such an intervention in daily practice.
The ECSTATIC study was not designed to answer questions about efficacy, but was designed as a pragmatic trial, to answer the question whether a structured deprescribing strategy in low-CVD-risk patients is (cost-)effective when implemented in general practice.[30] The pragmatic choice to leave the decision to deprescribe to the patient and their GP and the choice to use an active control group may have resulted

in an underestimation of the effect of the intervention on CVD risk, blood pressure and cholesterol levels.[31] A PP analysis gave information on the potential effects of an attempt to deprescribe preventive cardiovascular medication.
The differences at baseline between the intervention group and the usual care group may be the consequence of the different invitation letters that both groups received. We minimised the effect of these differences by correcting all analyses (except for the post-hoc analyses) for baseline values.
Our choice to include participants in the trial based on their predicted 10-year CVD risk was practice-driven. Although current debate questions the use of population-based prediction models for drug treatment in individuals, these models seem to predict individual CVD risk better in low risk than in high risk populations.[32, 33] The predicted 10-year CVD risk score is designed to assess risk while off treatment, however, the predictions of this risk assessment tool are partly based on cohorts of patients using cardiovascular medication, justifying its use in our patient population.[34] Additionally, our choice to include participants based on their 10-year CVD risk was based on the best available evidence as aggregated in the current Dutch guideline for cardiovascular risk management. The long-term incidence of CVD would have been the optimal primary outcome measure for our trial; however, time and budgetary restrictions kept us from using this endpoint. We would encourage future studies to compare a deprescribing strategy with usual care in low-CVD-risk patients based on long-term incidence of CVD.
In 15% of the participants we had to impute for missing data to be able to analyse the primary outcome. This number of missing data may lead to less reliable results. However, we used rigorous imputation methods to ensure the validity of our data and the precision of our results.[29] It was hard to verify based on the EMR whether a medication was stopped after two years of follow-up, or whether it was just not yet prescribed again. Therefore, self-reported deprescribing status seemed more reliable. The self-reported deprescribing status may have led to incorrect allocation to ITT intervention group, PP intervention group, and the quitters intervention group. However, SBP and LDL-cholesterol levels in the PP intervention group and the quitters intervention were higher than in the ITT intervention group, suggesting that the allocation was quite reliable.
Because adequate registration of cardiovascular events in the EMR is usual practice and its extraction based on ICPC-codes was protocolised, we believe the lack of blinding in these cases was not prohibiting objective registration and collection of events.

Comparison with other studies and interpretation

The ECSTATIC study adds new information to the body of knowledge concerning preventive cardiovascular drug treatment in primary prevention of CVD because of its

pragmatic design, carried out in a primary care population with low average CVD risk. It has been known that the preventive effects of antihypertensive and lipid-lowering drugs in low CVD risk populations are less than in intermediate and high risk populations.[35-39] The HOPE-3 investigators found that treatment with 16 mg of candesartan and 12.5 mg of hydrochlorothiazide per day in intermediate risk patients did not result in a significant lower risk of major cardiovascular events compared to a placebo.[37] Antihypertensive therapy reduced CVD risk only in intermediate risk patients with higher baseline SBP (>143.5 mmHg).[37] Furthermore, the meta-analysis of the Cholesterol Treatment Trialists' (CTT) Collaborators found that a statin induced LDL-cholesterol reduction of 1 mmol/l (38.6 mg/dl) in patients without vascular disease with a 5-year major vascular event risk <5%, did lower the rate ratio of vascular events, though not the rate ratio of vascular death.[35] The findings of these studies are consistent with the similar and low incidence of CVD (although underpowered) in the usual care group and intervention group and the non-inferiority of an attempt to deprescribe in the ECSTATIC population (which had a mean SBP of 140 mmHg at baseline, and a mean 10-year CVD risk of 5%).

With a mean 10-year CVD risk of 5%, the ECSTATIC population has lower risk compared to populations in other trials. Based on their reports of baseline characteristics, study populations of recent trials, such as the JUPITER Study (approximately 15% 10-year CVD risk), the HOPE-3 trial (approximately 17% 10-year CVD risk), and the SPRINT trial (approximately 24% 10-year CVD risk), have higher risks at baseline, predominantly because of higher ages and fewer female participants.[37, 40-43] The findings from these trials can therefore not directly be compared with the ECSTATIC population. With a mean 10-year CVD risk of approximately 6%, mean age of 58.3 years and inclusion of 68% women, the total Asian population in the MEGA Study is most comparable to the ECSTATIC population.[44] The MEGA Study showed that statins reduce relative risk of coronary heart disease in a subgroup of patients with LDL-cholesterol levels >4.01 mmol/l (155 mg/dl).[44] This suggests that the 26 ECSTATIC participants who had their lipid-lowering drugs deprescribed two years after the first visit, with a mean LDL-cholesterol level of 178 mg/dl, may have beneficial preventive effects of statin use. However, other evidence suggests that the increase in total life expectancy and CVD-free life expectancy may be too small to justify long-term statin use at all, especially in an ageing population.[45]

It is remarkable that 35% of the participants in the intervention group ofthe ECSTATIC study did not do an attempt to have their medication deprescribed. Based on the findings of two of our previous studies, possible reasons for not doing an attempt are, for example, fear of the consequences of deprescribing, fear of cardiovascular events, the

lack of negative effects of the medication participants experienced, or the GPs' doubts about deprescribing.[17, 46] Furthermore, only 27% of the participants in the intervention group persisted in quitting, while 65% of the participants did an attempt to have their medication deprescribed. Reasons for restarting medication were scarcely reported by GP, as reasons were reported in only 34 restarted participants (18% of all restarted participants). However, hypertension, headache, nervousness/stress, and palpitations were most frequently mentioned by GPs as reasons for restarting medication.

CONCLUSIONS

The results of the ECSTATIC study show that an attempt to deprescribe preventive cardiovascular medication in patients with predicted low CVD risk is safe in the short term, but does not necessarily improve quality of life or reduce healthcare costs. Moreover, less than one third of participants persisted without cardiovascular medication after two years of follow-up. Therefore, we do not recommend implementation of a structured deprescribing strategy for all patients with low CVD risk in general practice as was implemented in the intervention group of the ECSTATIC study. However, an attempt to deprescribe may be considered in low CVD risk patients, e.g., during their routine (yearly) cardiovascular check-up and as the result of a shared decision between a doctor and his/her patient. In an earlier study we found that low-CVD-risk patients and their GPs may doubt the appropriateness of medication use, fear side effects, dislike medication use, and consider alternative prevention options.[17] Although an attempt to deprescribe medication increases the risk of developing hypertension with approximately 20% to 60% and the risk of developing hypercholesterolemia with approximately 5% to 15%, the balance of the risks of (future) side effects and benefits for individual patients (e.g., no burden of daily medication use), together with patients' preferences, may drift in the direction of an individual attempt to deprescribe medication. When an attempt to deprescribe preventive cardiovascular medication in low-CVD-risk patients is made, it is important to monitor blood pressure and cholesterol levels, especially in the first three months after withdrawal, and to assess whether drug treatment should be re-initiated. Combining deprescribing with a lifestyle intervention could possibly restrict increases in blood pressure and cholesterol levels and lower CVD risk.[47-49]

In conclusion, a structured deprescribing strategy for all patients with low CVD risk in general practice is not recommended because of its low adherence (27% persistent quitters) and low gains in quality of life, but an attempt to deprescribe for those willing

to, is safe in the short term when blood pressure and cholesterol levels are monitored after stopping and can therefore be considered in low CVD risk patients during routine visits.

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Table 1. Baseline characteristics of general practices and participants[a]

Abbreviations: PP denotes per-protocol; ITT denotes intention-to-treat; GP denotes general practitioner; CVD denotes cardiovascular disease; HDL-cholesterol denotes high density lipoprotein cholesterol; LDL-cholesterol denotes low density lipoprotein cholesterol.

[a] Plus-minus values are means ±SD; all continuous variables were adjusted for cluster randomisation with multilevel linear models.

[b] University (of Professional Education) level

[c] $P<0.05$ compared to the usual care group

[d] 10-year CVD risk score estimated for inclusion with baseline values of age, sex, and smoking status, and pre-treatment systolic blood pressure and pre-treatment total cholesterol/HDL-cholesterol ratio as if participants did not use preventive cardiovascular medication.

[e] 10-year CVD risk score estimated at baseline with baseline values of age, sex, smoking status, systolic blood pressure, and total/cholesterol/HDL-cholesterol ratio

Characteristic	Usual care group	PP intervention group	ITT intervention group
General practices			
No. of general practices	23	23	23
Years of working experience (as GP) of GP – median (range)	14 (4-36)	21 (1-36)	21 (1-36)
Participants			
No. of participants	575	319	492
Caucasian – no. (%)	543 (94.4)	297 (93.1)	451 (91.7)
High education level – no. (%)[b]	168 (29.2)	124 (38.9)[c]	180 (36.6)[c]
10-year CVD risk score for inclusion – %[d]	7.0 (±5.6)	6.5 (±4.8)	6.7 (±4.2)
Cardiovascular risk factors			
10-year CVD risk score – %[e]	5.1 (±3.7)	4.7 (±4.0)	4.9 (±3.7)
Age – years	54.9 (±9.2)	54.5 (±8.0)	54.5 (±7.8)
Female – no. (%)	420 (73.0)	229 (71.8)	347 (70.5)
Smokers – no. (%)	66 (11.5)	19 (6.0)[c]	38 (7.7)[c]
Systolic blood pressure – mm Hg	139.8 (±16.3)	140.4 (±17.2)	140.9 (±20.8)
Total cholesterol/HDL-cholesterol ratio	3.7 (±1.4)	3.7 (±1.0)	3.8 (±1.0)
LDL-cholesterol – mg/dl	126.8 (±55.1)	126.4 (±38.8)	127.2 (±42.5)
Medication use at baseline			
Using antihypertensive drugs – no. (%)	479 (83.3)	280 (87.8)	431 (87.6)
- Agents acting on the renin-angiotensin system – no. (%)	300 (52.2)	163 (51.1)	276 (56.1)
- Diuretics – no. (%)	267 (46.4)	136 (42.6)	216 (43.9)
- Beta blocking agents – no. (%)	154 (26.8)	83 (26.0)	125 (25.4)
- Calcium channel blockers – no. (%)	62 (10.8)	37 (11.6)	61 (12.4)
- Other antihypertensive drugs – no. (%)	3 (0.5)	1 (0.3)	2 (0.5)
- Using antihypertensive drugs from ≥2 classes– no. (%)	58 (10.1)	20 (6.3)[c]	44 (8.9)
Using lipid-lowering drugs – no. (%)	163 (28.3)	65 (20.4)[c]	105 (21.3)
-HMG CoA reductase inhibitors – no. (%)	162 (28.2)	62 (19.4)[c]	101 (20.5)[c]
-Other lipid-lowering drugs – no. (%)	10 (2.0)	8 (2.5)	11 (2.2)
Using both antihypertensive and lipid-lowering drugs – no. (%)	67 (11.7)	27 (8.5)[c]	44 (8.9)[c]

Table 2. Secondary outcomes after 24 months[a]

Abbreviations: PP denotes per-protocol; ITT denotes intention-to-treat; HDL-cholesterol denotes high densitiy lipoprotein cholesterol, and LDL-cholesterol low density lipoprotein cholesterol

[a] Plus-minus values are means ±SE from linear mixed models.

[b] Only participants who had (temporarily) deprescribed their preventive cardiovascular medication were analysed in the PP intervention group.

[c] One participant who died of unknown cause during follow-up without having attempted to have her preventive cardiovascular medication deprescribed was left out in the analyses at 24 months in the ITT population of the intervention group.

[d] Compared to the usual care group at 24 months.

[e] To change value to mmol/l multiply by 38.61033861.

[f] Using a generalised logistic mixed linear model adjusting for cluster randomisation did not result in a pooled estimate, therefore we calculated estimates for the 15 imputation sets and reported the lowest p value in this table.

[g] For patients <55 years old only activities with a MET-score (Metabolic Equivalent score) ≥4 kcal/kg/hour executed ≥60 minutes on one or more days were taken into account to assess physical activity level[12]; for patients ≥55 years old only activities with a MET-score ≥3 kcal/kg/hour executed ≥30 minutes on one or more days were taken into account to assess physical activity level12.

Outcome	**Usual care group** (n=575)	**PP intervention group** (n=319[b])		**ITT intervention group** (n=492[c])	
	t=24	t=24	P value[d]	t=24	P value[d]
Systolic blood pressure – mm Hg	136.0±0.8	142.4±0.9	<0.01	140.9±0.8	<0.01
Diastolic blood pressure – mm Hg	80.7±0.5	84.8±0.6	<0.01	84.2±0.5	<0.01
Total cholesterol/HDL-cholesterol ratio	3.83±0.04	3.89±0.05	0.22	3.90±0.05	0.35
Total cholesterol – mg/dl [e]	210.0±1.4	217.2±1.8	<0.01	214.1±1.6	0.05
HDL-cholesterol– mg/dl [e]	58.4±0.5	59.1±0.6	0.75	58.3±0.5	0.84
LDL-cholesterol– mg/dl [e]	128.2±1.3	135.1±1.7	<0.01	133.1±1.5	0.01
Smokers – no. (%)f	59 (10.3)	18 (5.6)	>0.31	35 (7.1)	>0.25
Body mass index – kg/height in meters^2	28.0±0.1	27.6±0.1	0.26	27.9±0.1	0.57
Body weight – kg	81.5±0.3	80.4±0.3	0.18	81.1±0.3	0.35
Waist circumference – cm	96.1±0.4	96.2±0.5	0.54	96.5±0.4	0.53
Physical activity level – minutes per day[g]	137±5	127±6	0.18	130±6	0.36
Fruit and vegetable consumption – grams per day	329±5	335±7	0.41	333±6	0.62
Alcohol consumption – glasses per day	0.97±0.05	0.90±0.06	0.29	0.87±0.05	0.10

Figure 1. Trial profile

Abbreviations: EMR, electronic medical records, GP, general practitioner; CVD, cardiovascular disease; FH, familial hypercholesterolemia.

[a] The number of patients who declined to participate did not differ between intervention and usual care group adjusting for cluster randomisation (P=0.28).

[b] At the measurement three months after the first visit 459 participants had complete data available for calculation of the 10-year CVD risk score; at the measurement 24 months after the first visit 403 participants had complete data available for calculation of the 10-year CVD risk score.

[c] At the measurement three months after the first visit 546 participants had complete data available for calculation of the 10-year CVD risk score; at the measurement 24 months after the first visit 499 participants had complete data available for calculation of the 10-year CVD risk score.

[d] Missing values of (systolic blood pressure and/or total cholesterol/HDL-cholesterol ratio and/or smoking status) of 88 participants in the intervention group and 76 in the usual care were imputed; one participant in the intervention group died of unknown cause without having attempted to have her medication deprescribed and was not included in the analysis

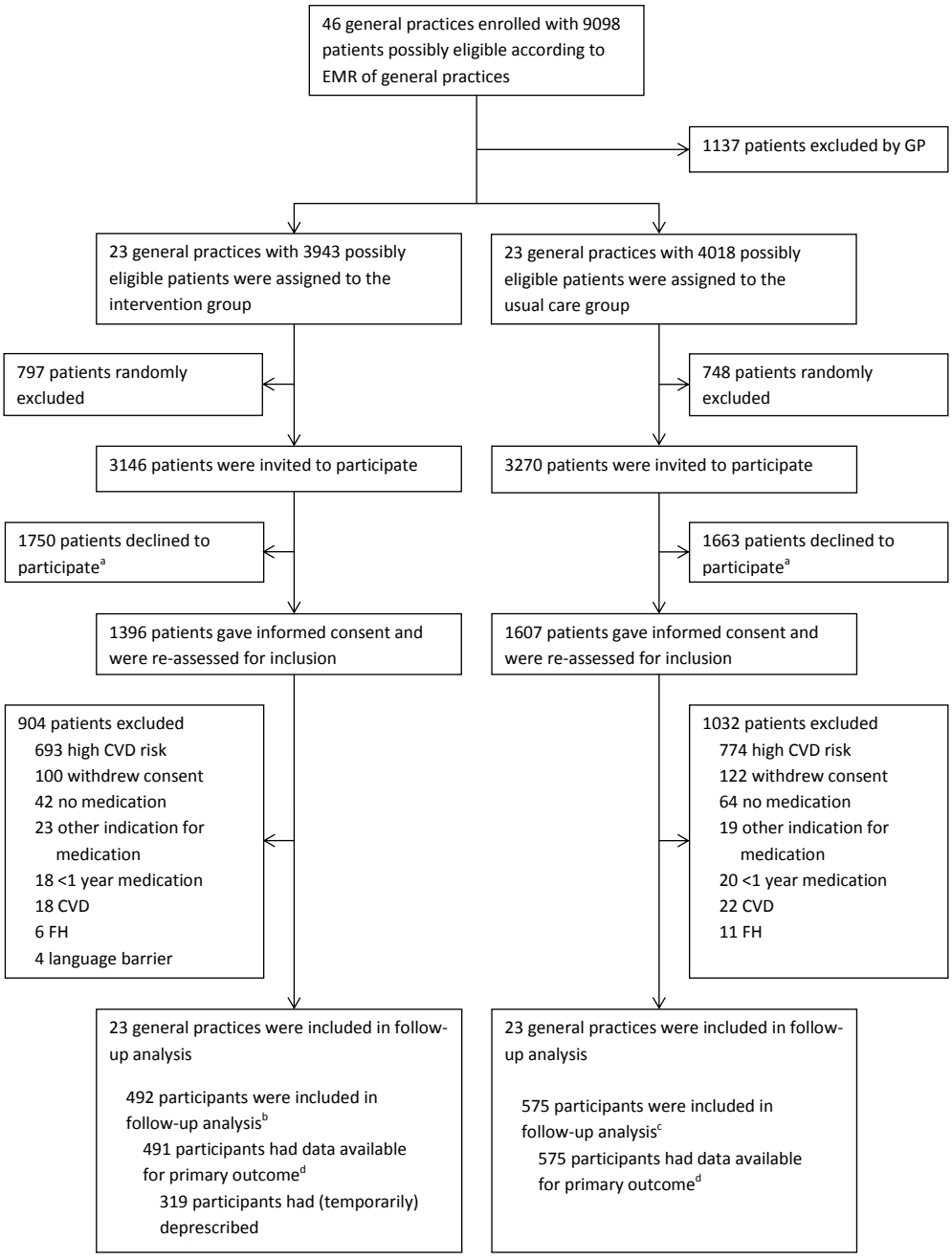
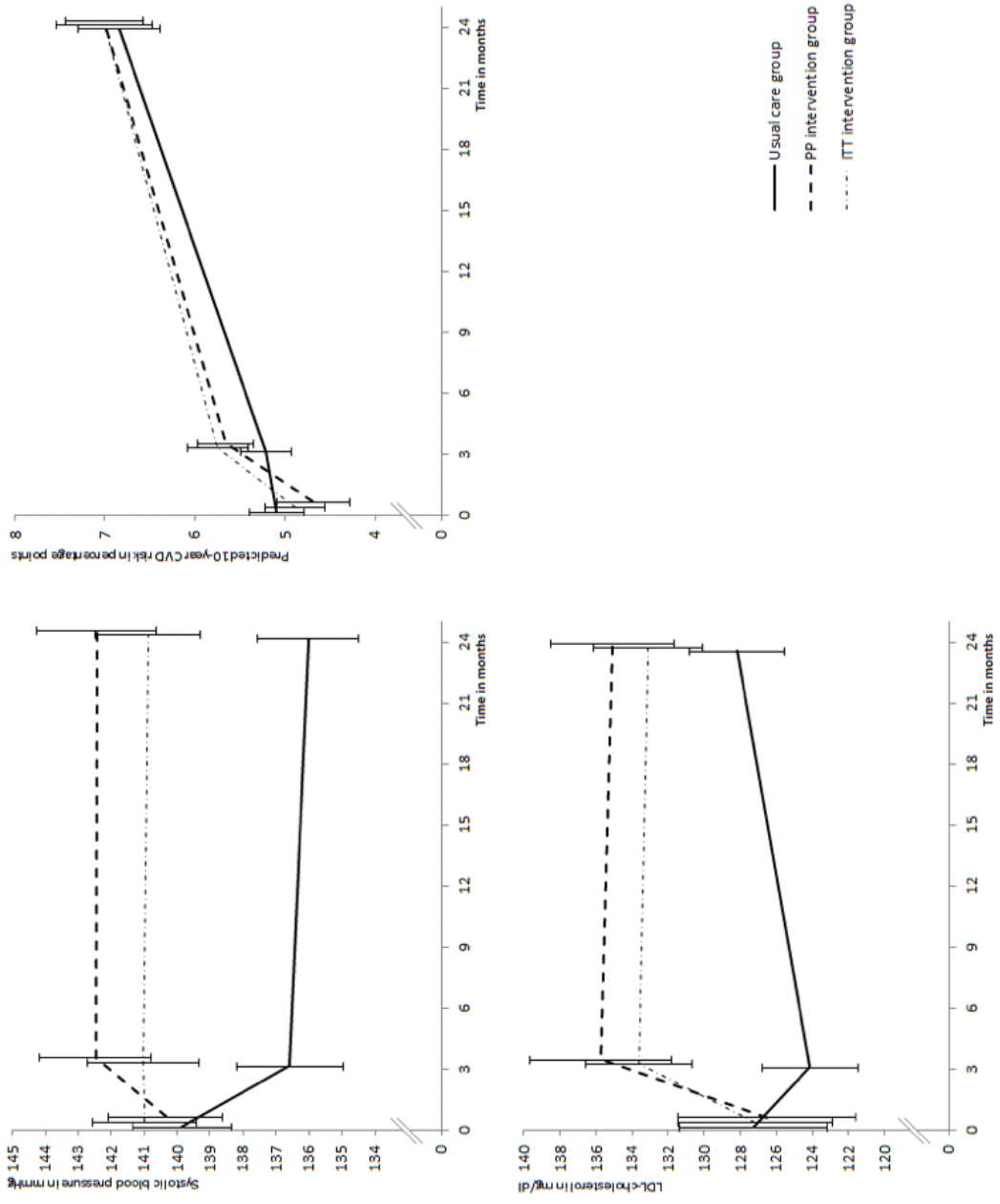

46 general practices enrolled with 9098 patients possibly eligible according to EMR of general practices
1137 patients excluded by GP
23 general practices with 3943 possibly eligible patients were assigned to the intervention group
23 general practices with 4018 possibly eligible patients were assigned to the usual care group
797 patients randomly excluded
748 patients randomly excluded
3146 patients were invited to participate
3270 patients were invited to participate
1750 patients declined to participate[a]
1663 patients declined to participate[a]
1396 patients gave informed consent and were re-assessed for inclusion
1607 patients gave informed consent and were re-assessed for inclusion
904 patients excluded
693 high CVD risk
100 withdrew consent
42 no medication
23 other indication for medication
18 <1 year medication
18 CVD
6 FH
4 language barrier
1032 patients excluded
774 high CVD risk
122 withdrew consent
64 no medication
19 other indication for medication
20 <1 year medication
22 CVD
11 FH
23 general practices were included in follow-up analysis
492 participants were included in follow-up analysis[b]
491 participants had data available for primary outcome[d]
319 participants had (temporarily) deprescribed
23 general practices were included in follow-up analysis
575 participants were included in follow-up analysis[c]
575 participants had data available for primary outcome[d]

Figure 5. Systolic blood pressure, LDL-cholesterol level and predicted 10-year CVD risk over time in the usual care and intervention group

Abbreviations: CVD denotes cardiovascular disease; PP denotes per-protocol; ITT denotes intention-to-treat.

Measurements at t=0 were performed at the first visit. Error bars depict the 95% CI of the mean.


Predicted 10-year CVD risk in percentage points
Systolic blood pressure in mmHg
LDL-cholesterol in mg/dl
Time in months
Usual care group
PP intervention group
ITT intervention group

SUPPLEMENTARY DATA

Additional file 1. Inclusion and exclusion criteria of the Evaluating Cessation of STatins and Antihypertensive Treatment In primary Care trial, as approved by the Medical Ethics Committee of the Leiden University Medical Center

Inclusion criteria

Patients in general practice are included in the study if they meet the following criteria:

- Age 40 to 70 years;
- Prescription and use of antihypertensive medication and/or lipid-lowering drugs for hypertension and/or hypercholesterolemia during the last 12 months (using ATC codes: C02, C03, C07, C08, C09, C10).

Exclusion criteria

Patients with the following criteria are excluded:

- Cardiovascular disease (ICPC codes: K74, K75, K76, K89, K90.03, K91, K92.01 and K99.01)[1];
- Use of platelet aggregation inhibitors (heparin excluded) (ATC code: B01AC);
- Use of antihypertensive medication for another reason than prevention of CVD;
- Familial hypercholesterolemia/lipidemia (ICPC code: T93.04)[a];
- Patients with a current SBP[b] >180 mmHg, or a SBP >180 mmHg before the start of medication;
- Patients with a current TC/HDL ratio >8, or a TC/HDL ratio >8 before the start of medication;
- Patients with a 10-year CVD risk >16%[c]
- 10-year CVD risk of 10-16% based on the 2011 risk table, in combination with **at least one additional major risk-increasing factor:**
    - Family history with ≥2 first degree family members with CVD <65 years or ≥1 first degree family member with CVD <60 years;
    - Physical activity: sedentary lifestyle;
    - Obesity: BMI >35 kg/m^3;
    - Kidney function: eGFR <30 ml/min/1.73m^2;
    - DM and poor metabolic control;
    - DM and (micro)albuminuria;
    - DM and microvascular complications;
    - RA with high disease activity.

- 10-year CVD risk of 10-16%, based on the 2011 risk table, in combination with **two or more additional minor risk-increasing factors:**
    - Family history: 1 first degree family member with CVD <65 years;
    - Physical activity: <30 min/day ≤5 days per week (but not sedentary);
    - Obesity: BMI >30-35 kg/m^3 (or waist circumference >80 cm in women, >94 cm in men;
    - Kidney function: eGFR <65 years 30-60 ml/min/1.73m^2, eGFR ≥65 years 30-45 ml/min/1.73m^2.
- 10-year CVD risk of 10-16%, based on the 2011 risk table, in combination with **one additional minor risk-increasing factor:**
    - Family history: 1 first degree family member with CVD <65 years;
    - Physical activity: <30 min/day ≤5 days per week (but not sedentary);
    - Obesity: BMI >30-35 kg/m^3 (or waist circumference >80 cm in women, >94 cm in men;
    - Kidney function: eGFR <65 years 30-60 ml/min/1.73m^2, eGFR ≥65 years 30-45 ml/min/1.73m^2;

AND

- SBP >140 mmHg and/or LDL >2.5 mmol/L.
- Patients <50 years with a repeatedly measured SBP >160 mmHg who do not reach their target SBP with help of lifestyle adjustments after 3 months.[d]

Abbreviations: SBP, systolic blood pressure; TC, total cholesterol; HDL, HDL-cholesterol; CVD, cardiovascular disease; BMI, body mass index; eGFR, estimated glomerular filtration rate; DM, diabetes mellitus; RA, rheumatoid arthritis; LDL, LDL-cholesterol.

[a] URL: http://www.kith.no/upload/2705/icpc-2-english.pdf

[b] SBP was measured once at both arms, and twice at the arm with highest SBP at the first measurement after at least 5 minutes sitting rest; mean SBP of the two measurements at the same arm was noted as current SBP and SBP at baseline.

[c] Patients with a 10-year CVD risk >16.99% (≥17%) were excluded.

[d] This exclusion criterion appeared to be infeasible in practice.

Calculation of pre-treatment 10-year CVD risk

Pre-treatment CVD risk was based on current age, sex, and smoking behaviour (smoking yes/no), in combination with reported pre-treatment systolic blood pressure (SBP) and total cholesterol/HDL-cholesterol ratio levels in general practice EMRs. If these values were not available up to one year before the start of drug treatment, pre-treatment SBP was conservatively estimated at 180 mmHg; to estimate the pre-

treatment total cholesterol ratio, 72 mg/dl (2.0 mmol/l) was added to the current total cholesterol level and 4 mg/dl (0.1 mmol/l) was subtracted from the current HDL level. In case patients were using only antihypertensive drugs, the current total cholesterol/HDL-cholesterol ratio was used to estimate the pre-treatment CVD risk; in case patients were using only lipid-lowering drugs, current SBP was used to estimate pre-treatment CVD risk. The algorithm for the CVD risk calculation can be requested from the Dutch College of General Practitioners (Nederlands Huisartsen Genootschap, Utrecht, the Netherlands). Current SBP was measured with an automated sphygmomanometer (Omron HEM-907) once on both arms and twice on the arm with highest SBP at the first measurement, with an interval of five minutes after at least five minutes of seated rest. The mean SBP of the two measurements on the same arm was used as the current SBP to estimate the pre-treatment CVD risk. Local laboratories measured current levels of total cholesterol, HDL-cholesterol, and LDL- cholesterol.

We used an SBP of 120 mmHg for a mean SBP <120 mmHg to estimate CVD risk; an SBP of 180 mmHg, for a mean SBP >180 mmHg; a total cholesterol/HDL-cholesterol ratio of 4, when total cholesterol/HDL-cholesterol ratio <4; and a total cholesterol/HDL-cholesterol ratio of 8, when total cholesterol/HDL-cholesterol ratio was >8.

In addition, for patients with intermediate pre-treatment CVD risk, to determine whether a patient met the inclusion criteria, current glomerular filtration rate (estimated using the Modification of Diet in Renal Disease Study equation measured by local laboratories) was used, together with current body mass index (BMI), physical activity level, and family history of CVD in accordance with the Dutch guideline.[4]

Additional file 2. Deprescribing guideline

The following examples of dose-lowering schemes (Table S1) were available for the general practitioners (GPs) to provide guidance when withdrawal of medication was attempted.

Table S1. Examples of dose-lowering schemes

Medication	Example of dose-lowering scheme (in mg, per week)
Lipid-lowering drugs (in general)	Stop at once
Hydrochlorothiazide	25 – 12.5 – 0
Chlorthalidone	25 – 12.5 – 0
Nifedipine	120 – 60 – 30 – 0
Amlodipine	10 – 5 – 0
Metoprolol	100 – 50 – 25 – 0
Enalapril	40 – 20 – 10 – 5 – 0
Lisinopril	30 – 20 – 10 – 5 – 0
Losartan	100 – 50 – 5

According to the research protocol, the GP or practice nurse monitored the patient when withdrawal of medication was attempted. In case antihypertensive drugs were deprescribed, blood pressure monitoring occured after four and 12 weeks and after six months; in case lipid-lowering drugs were deprescribed, lipid level monitoring was conducted after 12 weeks. After medication was stopped and monitoring had taken place according to the research protocol, patients were monitored according to the Dutch guideline for Cardiovascular Risk Management.
When monitoring patients according to the research protocol, in addition to blood pressure and lipid level measurement, the GP or practice nurse asked whether the patient experienced adverse effects. The GP or practice nurse always asked whether shortness of breath, oedema, or weight gain had occurred. The pulse was assessed to determine pace and regularity. According to the research protocol, the practice nurse had to consult the GP in case the patient: 1) did not feel well; 2) experienced symptoms

of heart failure (shortness of breath, oedema); 3) gained >2 kg in body weight; 4) had a systolic blood pressure >180 mm Hg; 5) had a pulse rate >100/minute; 6) had an irregular pulse; 7) (possibly) experienced an adverse effect of withdrawal. The data safety monitoring board added a total cholesterol level >308.9 mg/dl (8 mmol/l) and a LDL-cholesterol level >193.1 mg/dl (5 mmol/l) to this list.

Additional file 3. Cost-effectiveness analysis

Table S2. Costs (in £) for the preparation of the intervention, per selected patient[a]

Activity	Time investment (in minutes)	Costs per 10 minutes[b]	Costs
Workshop GP	150	28	420
Workshop practice nurse	150	9	140
Patient group selection by GP	120	28	336
Group costs per GP practice	420		896
Group costs per selected patient (n=160)[a]	3		6
Individual preparation of invitation/consultation	10	28	28
Costs per selected patient			**34**

Abbreviations: GP denotes general practitioner.

[a] Based on the number of patients invited to participate in the ECSTATIC trial, with an estimated GP practice size of 2168 (NZa 2016, URL: https://www.lhv.nl/uw-beroep/over-de-huisarts/kerncijfers-huisartsenzorg).

[b] Obtained from Dutch guidelines for economic evaluations, at the price level of 2015.[21]

Table S3. Costs (in £) and QALYs per patient in usual care group and intervention group

	Usual care group (n=575)	**ITT intervention group** (n=492[a])	P value
Preparation for intervention			
Year 1	0	34	-
Year 2	0	0	-
General practice consultations			
Year 1	170	222	<0.01
Year 2	179	171	0.58
Preventive cardiovascular medication			
Year 1	36	20	<0.01
Year 2	33	21	<0.01
Laboratory[b]			
Year 1	32	33	0.67
Year 2	31	29	0.34
Other healthcare[c]			
Year 1	508	472	0.55
Year 2	617	606	0.93
Total primary care specific costs[d]			
Year 1	239	309	<0.01
Year 2	243	220	0.19
Total primary care specific costs over two years[e]	482	528	0.19
Total healthcare costs[f]			
Year 1	742	787	0.49
Year 2	861	824	0.77
Total healthcare costs over two years[e]	1607	1607	1.00
QALYs			
Year 1	0.870	0.879	0.38
Year 2	0.874	0.879	0.58
Total QALYs[e]	1.743	1.759	0.45

Abbreviations: QALYs denotes quality-adjusted life years; ITT denotes intention-to-treat.

[a] One patient who died of unknown cause during follow-up without having attempted to have her preventive cardiovascular medication deprescribed was left out in the analyses at 24 months.

[b] Only cardiovascular management related

[c] Costs of specialist and physical therapist consultations, use of home care, and hospitalisations.

[d] Sum of costs of implementation of the intervention, general practice consultations, preventive cardiovascular medication, and laboratory.

[e] Sum of costs and QALYs in year 1 and year 2 do not exactly add up to the total costs over two years due to adjustment for cluster randomization in the analyses.

[f] Primary care specific costs plus other costs.

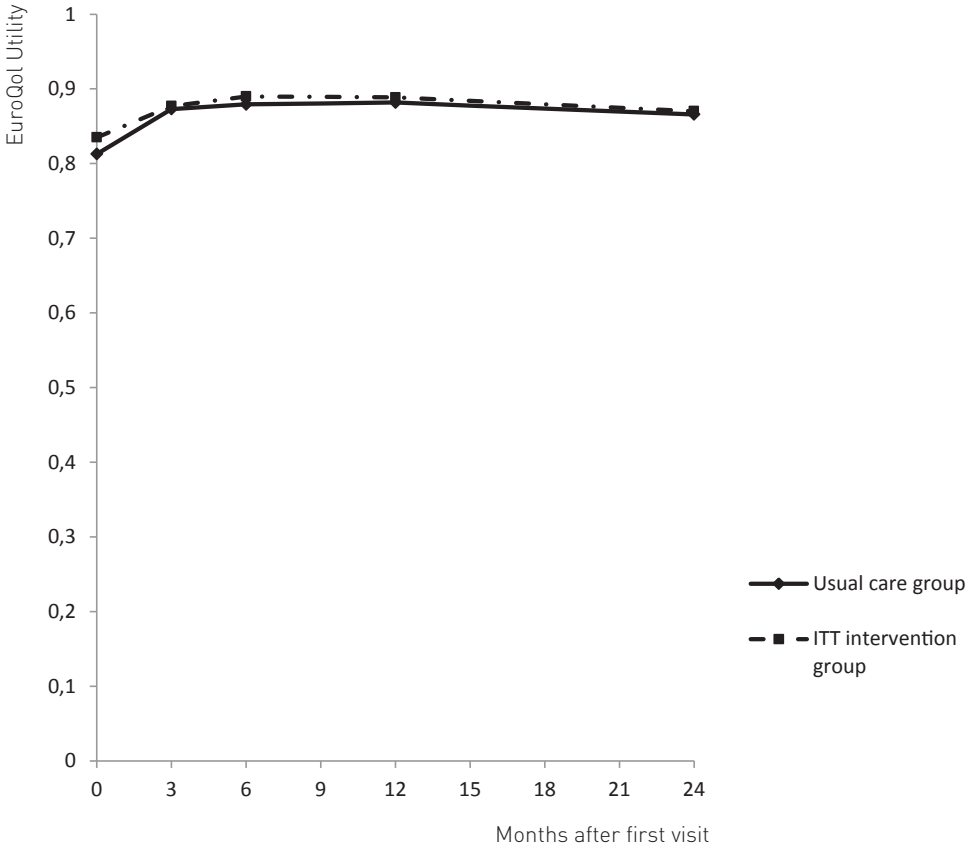


Figure S1. EuroQol Utility at t=0, t=3, t=6, t=12, and t=24 in the usual care group and the intention to treat population of the intervention group.

Abbreviations: ITT denotes intention-to-treat.

Measurements at t=0 were performed at the first visit.

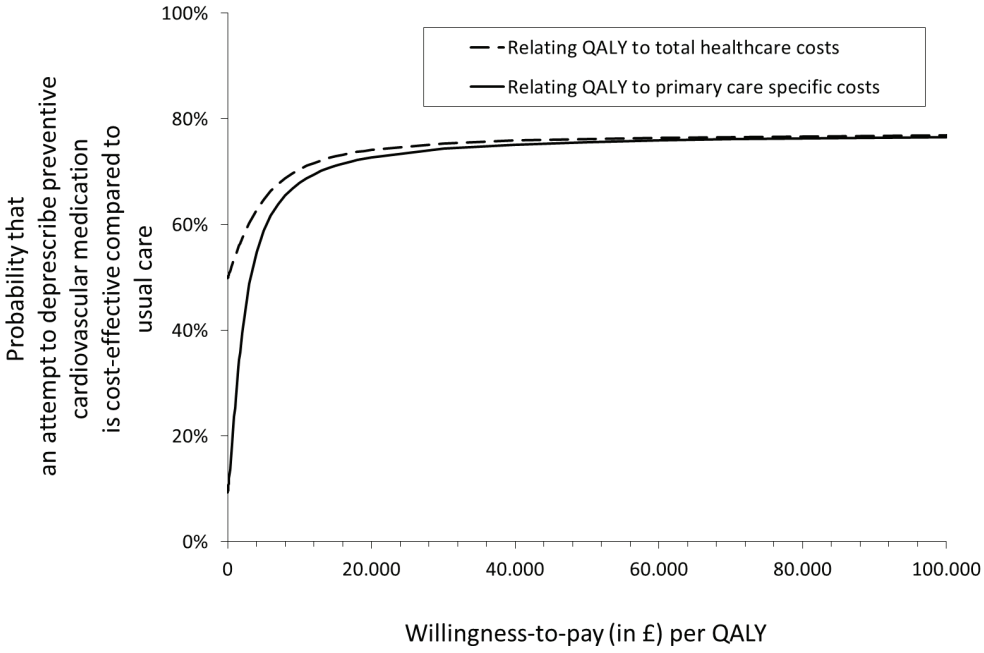
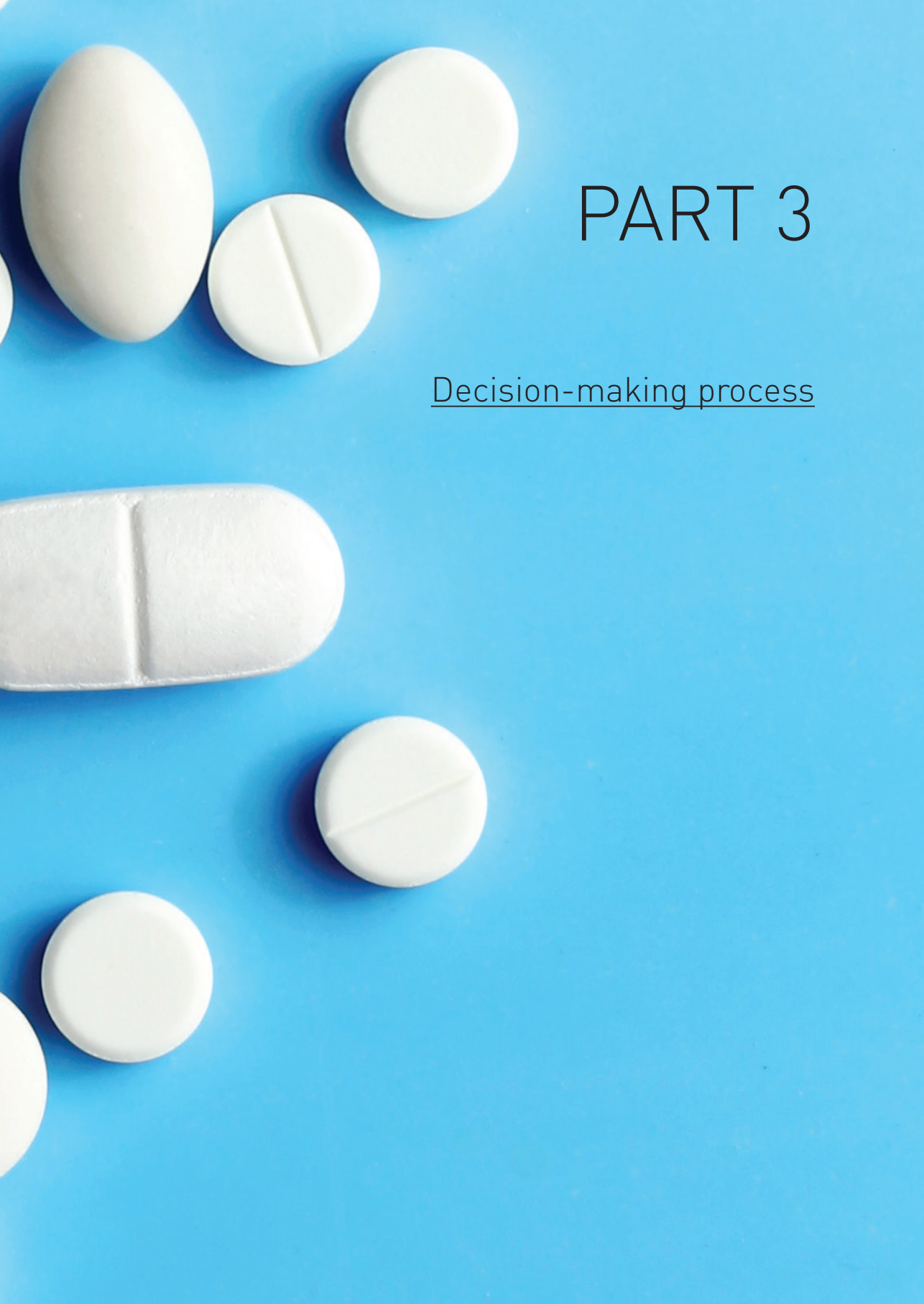


Figure S2. Cost-effectiveness acceptability curve showing the probability that an attempt to deprescribe preventive cardiovascular medication is cost-effective compared to usual care.



PART 3

Decision-making process

CHAPTER 4

Deprescribing Potentially Inappropriate Preventive Cardiovascular Medication: Barriers and Enablers for Patients and General Practitioners

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ABSTRACT

Background
The use of preventive cardiovascular medication by patients with low cardiovascular disease (CVD) risk is potentially inappropriate.

Objective
The aim of this study was to identify barriers to and enablers of deprescribing potentially inappropriate preventive cardiovascular medication experienced by patients and general practitioners (GPs).

Methods
A total of 10 GPs participating in the ECSTATIC trial (Evaluating Cessation of STatins and Antihypertensive Treatment In primary Care) audiotaped deprescribing consultations with low-CVD-risk patients. After initial conventional content analysis, 2 researchers separately coded all barriers to and enablers of deprescribing medication using framework analysis. We performed a within-case and cross-case analysis to explore barriers and enablers among both patients and GPs.

Results
Patients (n = 49) and GPs (n = 10) expressed barriers and enablers with regard to the appropriateness of the medication and the deprescribing process. A family history for CVD was identified as a barrier to deprescribing medication for both patients and GPs. Patients feared possible consequences of deprescribing and were influenced by the opinion of their GP. Additionally, a presumed disapproving opinion from specialists influenced the GPs' willingness to deprescribe medication.

Conclusions
Patients appreciated discussing their doubts regarding deprescribing potentially inappropriate preventive cardiovascular medication. Furthermore, they acknowledged their GP's expertise and took theiropinion toward deprescribing into consideration. The GPs' decisions to deprescribe were influenced by the low CVD risk of the patients, additional risk factors, and the alleged specialist's opinion toward deprescribing. We recommend deprescribing consultations to be patient centered, with GPs addressing relevant themes and probable consequences of deprescribing preventive cardiovascular medication.

INTRODUCTION

According to many international guidelines on the prevention of cardiovascular disease (CVD), patients with low CVD risk should be given lifestyle advice and do not require treatment with antihypertensive and/or lipid-lowering drugs.[1-6] Nevertheless, it has been shown that drugs are frequently prescribed and used on a long-term basis by low-CVD-risk patients. More or less depending on the reason for prescription, use of these drugs is considered potentially inappropriate because their potential risks (eg, side effects) outweigh their potential benefits.[8-10] Deprescribing medication after long-term use is preferable for (subgroups of) patients with low CVD risk for whom deprescribing is found to be a safe and effective procedure.

Two recent systematic reviews based on studies concerning deprescribing medications identified several categories of barriers and enablers for patients and for prescribers to deprescribe potentially inappropriate medication.[8, 11] Both reviews included studies of hypothetical deprescribing of various kinds of medication (eg, benzodiazepines, antidepressants, psychotropic medications).

We hypothesized that the barriers and enablers of deprescribing in general might differ from the factors playing a role in the decision concerning deprescribing preventive cardiovascular medication. Regarding implementation of a deprescribing policy, knowledge of these factors would be valuable. Therefore, the aim of our study was to identify the barriers and enablers encountered in real-life discussions between patients and their general practitioners (GPs) considering deprescribing preventive cardiovascular medication.

METHODS

The study population was selected from the ECSTATIC trial (started in 2012, end of follow-up December 2015). In the ECSTATIC trial (NTR3493), we evaluate whether it is cost-effective and safe to deprescribe antihypertensive and lipid-lowering drugs in primary care patients to whom medication is not recommended, according to the current Dutch guideline Cardiovascular Risk Management (Box 1).[1]

Box 1. ECSTATIC Trial

ECSTATIC Trial

The ECSTATIC trial evaluates whether it is cost-effective and safe to deprescribe antihypertensive and lipid-lowering drugs inprimary care patients to whom medication is not recommended according to the current Dutch guideline Cardiovascular Risk Management. Patients without cardiovascular disease (CVD) were included in the ECSTATIC-trial when having low CVD risk and using antihypertensive and/or lipidlowering drugs. GPs in the intervention practices received a training providing information about this guideline and its differences with respect to the former guideline. In preparation of the deprescribing consultations they were presented cases of fictional low-CVD-risk patients and they discussed these patients' suitability to have their medication deprescribed. GPs participating in the trial sent a written invitation to their patients without CVD, using potentially inappropriate antihypertensive and/or lipid-lowering drugs. After obtaining informed consent, the researchers determined eligibility on the basis of the patients' pre-treatment 10-year risk of morbidity and mortality of CVD, using the SCORE risk function as well as their (possible) additional risk increasing factors (positive family history for CVD, obesity, decreased kidney function, and sedentary lifestyle).[1] When, based on the combination of the risk score and additional risk increasing factors for CVD, medication was not recommended according to the current guideline Cardiovascular Risk Management, patients were considered eligible for inclusion and were advised to make an appointment for a deprescribing consultation with their GP.

In the intervention practices, patients knew in advance that, if found eligible (from here on referred to as low-risk patients), they would be offered a consultation with their GP discussing deprescribing and deciding whether to deprescribe or continue the medication.

Participants

Through purposeful sampling,[12] we included 9 general practices that were in the process of organizing deprescribing consultations in the course of their participation in the ECSTATIC trial. The GPs of the included practices selected the patients based on opportunity (having an appointment for a deprescribing consultation) and on the patient's informed consent to audiotape their consultation with their GP. The GPs did not receive additional training in communication skills, and the deprescribing consultations did not follow a predefined format. The patients signed a written informed consent before the consultation was audiotaped. The study was approved by the Medical Ethics Committee of the Leiden University Medical Center (P12.095/SH/gk).

General Description of the Deprescribing Consultations

All audiotaped consultations were transcribed verbatim. The transcripts were used to describe the characteristics of the consultation and the sequence of barriers to and enablers of deprescribing.

Analysis of Barriers and Enablers

To identify barriers to and enablers of deprescribing preventive cardiovascular medication for both patients and GPs, transcripts were analyzed using a conventional content analysis.[13] This analysis revealed that emerging themes matched the theoretical framework of Reeve et al.[8] This framework consists of 6 categories of barriers and enablers: (1) appropriateness, (2) fear, (3) process, (4) influences, (5) dislike, and (6) other (Table 1). To ensure that no themes were missed, we performed an additional round of coding using a framework approach based on Reeve et al,[8] which allowed deductive and inductive coding. All coding was performed by 2 researchers (CHL and RMJJvdK), and differences in codes assigned were resolved by discussion. The codes identified inductively were added to Reeve's framework (Table 1).[8] We also described whether themes were intertwined when separate codes were assigned to the same citation. Within-case and cross-case analyses were then conducted, as described by Miles and Huberman.[14] We performed an indepth exploration of both patient and GP barriers and enablers for each consultation using the within-case analysis. This allowed us to properly interpret all mentioned barriers and enablers per consultation as we

investigated each consultation separately. We then used the cross-case analysis to evaluate whether barriers and enablers occurred in patterns across cases, intending to explore commonly mentioned barriers and enablers during the consultations. In addition, we specifically compared barriers and enablers mentioned in consultations in which the outcome was "deprescribing of medication" with consultations where the outcome was "continuation of medication". The outcome of the consultation was deduced from the conclusion of the consultation itself by noting whether medication was continued or deprescribed. The barriers and enablers discussed in consultations were compared depending on the type(s) of medications the patient used (antihypertensive medication, lipid-lowering drugs, or both). If any inconsistencies in themes were found during the crosscase analysis, transcript information was consulted for verification.

RESULTS

Table 2 shows the characteristics of the patients (mean age = 55.4 years) and the outcome of the consultation. We included 49 deprescribing consultations of 10 different GPs from 9 general practices. In 42 of the 49 consultations, the outcome was deprescribing of medication. Median time for all consultations was 6½ minutes.

Table 2. Characteristics of the participating patients (n=49)

	Patients
Male – no. (%)	14 (29)
Age in years – mean (SD)	55.4 (5.5)
Using antihypertensive medication – no. (%)	42 (86)
Using lipid-lowering drugs – no. (%)	12 (25)
Outcome of the consultation deprescribing of medication (%)	42 (86)
Outcome of the consultation continuation of medication (%)	7 (14)

Course of the Deprescribing Consultation

Table 3 shows the characteristics of the GPs and their deprescribing consultations. The GP often started the consultations by explaining the reason for consultation: the patient was included in the ECSTATIC trial and had a low risk.

Four GPs specifically mentioned that the decision whether or not to deprescribe the medication was a joint decision that needed to be made by both the patient and GP. Additionally, regardless of the outcome of the deprescribing consultation (deprescribing/continuation), 6 out of 10 GPs discussed a healthy lifestyle with their patients as an alternative to medication.

Table 3. Characteristics of the participating GPs (n=10) and their deprescribing consultations

	Gender of GP	Age of the GP	Years of working experience as GP	Number of audiotaped consultations	Duration of consultation (range in minutes)	Consultations with the outcome 'deprescribing of medication' (%)
GP-1	Male	35	3	11	4-25	10 (91)
GP-2	Female	60	28	6	5-29	4 (67)
GP-3	Male	52	9	3	1-2	1 (33)
GP-4	Male	58	28	10	3-7	10 (100)
GP-5	Male	60	30	5	1-4	5 (100)
GP-6	Male	56	24	5	5-8	5 (100)
GP-7	Female	53	25	1	10	0 (0)
GP-8	Male	58	19	3	5-10	3 (100)
GP-9	Female	60	32	2	4-12	1 (50)
GP-10	Female	48	14	3	8-14	3 (100)

GP, general practitioner.

Barriers and Enablers

Barriers were more frequently cited by patients than by GPs, and patients also mentioned more diverse barriers than GPs (Table 1). Irrespective of the outcome of the consultation, barriers to deprescribing were cited by both patients and GPs. Although the number of enablers mentioned by patients and GPs differed, in general, both cited the same enablers. The enablers cited by patients and GPs were similar regardless of the outcome of the consultation. However, GPs mentioned fewer and different barriers in consultations in which the outcome was to deprescribe medication. Furthermore, in a majority of consultations, the GP mentioned an enabler after a patient mentioned a barrier.

When the GP expressed doubts about deprescribing, the barriers mentioned were often personalized and directed toward the consulting patient. In contrast, the GPs more frequently brought a general, nonpersonalized barrier forward when they were positive toward deprescribing medication.

'The ophthalmologist can tell that that you have a high blood pressure based on the examination of your eyes . . . and that's why we need to ask ourselves whether it would be wise to stop your medication.' (GP-2 consulting a patient whose outcome was continuation)

'And to some patients we say that their [CVD] risk is really too high, and that they have to continue their medication.' (GP-10 consulting a patient whose outcome was deprescribing)

When comparing consultations of patients using antihypertensive medication, lipid-lowering drugs, or both, we found no differences in the barriers and enablers mentioned by both patients and GPs.

Appropriateness

We found that 9 of 49 patients and 7 out of 10 GPs mentioned that medication was currently necessary or beneficial. This reason to continue intertwined with other themes in patients, such as (1) the GP's advice to take preventive medication, (2) fear-related themes, and (3) mistrust or scepticism of the recommendation to deprescribe.

'We were always told that there would be so much damage done to heart and blood vessels by high blood pressure.' (52-year-old woman whose outcome was deprescribing)

In GPs, this theme was intertwined with the patient having an unhealthy lifestyle and/or having several risk factors for developing CVD:

'As a doctor, I feel your smoking behaviour argues against withdrawal.'
(GP-2 consulting a patient whose outcome was continuation)

When explaining the reason for the consultation or when the patient asked for advice, all GPs expressed that medication was not (medically) ecessary, implying a general positive attitude toward deprescribing — for example, when the patient had a low risk or when the revised recommendations concerning the use of preventive cardiovascular medication indicated that the medication was unnecessary for a certain patient.

'So according to the current guidelines you would not need lipid-lowering drugs.'
(GP-10 consulting a patient whose outcome was deprescribing)

Patients expressed doubts regarding the necessity for medication use; they stated that they were "unsure about their (continuous) need" for it.

'I used these [medications] for two years now, [or rather] one and a half years, maybe even longer. This makes me think, well, is it necessary? And . . . shouldn't we stop it?' (53-year-old man whose outcome was deprescribing)

Patients sometimes assumed that at the time their medication was initiated, stress had induced their hypertension. In that case, their rationale for having a well-controlled blood pressure at this moment in time was the absence of stressful events.
We found that 20 of 49 patients and 4 of 10 GPs expressed
a general positive attitude toward deprescribing, which makes it a dominant theme among patients:

'That [deprescribing] would be fantastic.' (61-year-old woman whose outcome was deprescribing)

Fear
Both patients and GPs cited the fear of the return of the previous condition for which the medication was started/prescribed:

'I don't know if we take one [of the medications] off, whether my blood pressure will rise again.' (61-year-old woman whose outcome was continuation)
'Also, how over the past few years we struggled to get that blood pressure under control, makes me say like, no, we're not going to withdraw that medication now.' (GP-7 consulting a patient whose outcome was continuation)

Patients feared the return of hypertension or hypercholesterolemia and feared the dangers that might accompany these conditions (CVD/death). Two of the 3 GPs who forwarded fear of return of the previous condition advised to continue medication. Only patients expressed fear for the unknown consequences of deprescribing:

'However, maybe I will have side effects [of deprescribing], such as dizziness or something?' (64-year-old woman whose outcome was deprescribing)

Process
Both patients and GPs encountered problems with the timing or with the complexity of

the process of deprescribing. However, these problems were always solved: when timing was the issue, the deprescribing was postponed, and in the case of complexity, the GP wrote a dose-lowering scheme for the medications. Patients and GPs appreciated the availability of a follow-up scheme for the blood pressure and cholesterol levels after deprescribing and noted the possibility of restarting medication:

'However, I can always return to have my blood pressure measured again and restart the pill?' (59-year-old female whose outcome was deprescribing) 'Yes, yes.' (GP-5)
'If your blood pressure rises above 180 [mm Hg], yes, then there is an indication again to restart medication.' (GP-6 consulting a patient whose outcome was deprescribing)

Five of 10 GPs reassured patients that deprescribing would be safe by stressing that the medication would be deprescribed step-by-step.

Influences

In the analysis, several themes emerged as important factors in the decision-making process. The patient's decision was strongly determined by the GP's voiced opinion, which we deduced by noting whether the GP said it was justified to deprescribe the medication. The outcome of these consultations then was very likely to be deprescribing medication, and vice versa:

'That doesn't feel right with me, honestly speaking.' (GP-2)
'Then, we just don't do it [name of GP].' (61-year-old woman whose outcome was continuation)

This quote was derived from 1 of 2 consultations in which the GP's arguments seem to change the patient's initial thoughts about deprescribing. In this particular consultation, the patient expressed her desire to have her medication deprescribed. The GP had reservations because of the patients smoking behavior. The patient acknowledged the hesitations of the GP and decided to persist using the medication. They continued discussing smoking cessation.
In the other consultation where the patient and GP had discordant views, the patient was afraid of getting agitated after stopping. The GP addressed her low risk that would justify deprescribing her medication, after which they decided to lower the dose. He indicated that medication was not necessary to lower her blood pressure. However, the GP did forward that the dose-lowering might prove the medication's supposed necessity to keep her from getting agitated.

When patients had earlier bad experiences with stopping their medication, they tended to decide to continue medication.

'According to me, we stopped them once, but then it rose again . . . according to me . . . and then you prescribed it again, so . . .' (52-year-old woman whose outcome was continuation)

Both patients and GPs cited a family history of CVD explicitly as a barrier to deprescribing.

'I have a father who . . . got 5 bypasses. His youngest sister died of a stroke. So also in my family there are examples . . . of which I think, well . . .' (58-year-old woman whose outcome was continuation)
'So we have just gone through all your risk factors and we came to the conclusion that we won't stop the medication. Predominantly based on your family history [being positive for CVD].' (GP-3 consulting a patient whose outcome was continuation)

GPs considered the patient having an unhealthy lifestyle and the specialist's opinion that the patient needed medication as serious barriers to deprescribing.

'And then you went to see the specialist, isn't it? . . . and he also advised to continue [the medication] isn't it?' (GP-7 consulting a patient whose outcome was continuation)

Dislike
Both patients and GPs expressed a general dislike of taking (or prescribing) medication.

'The less [medication] the better.' (51-year-old woman whose outcome was deprescribing)

'Well, that means that someone who was used to taking medication, suddenly doesn't need medication anymore, which is quite nice of course.' (GP-6 consulting a patient whose outcome was deprescribing)

Other enablers for patients within the dislike theme were the following: (1) removing the stigma of "being a patient," (2) psychological benefits of deprescribing, (3) lowering costs for society, and (4) easier access to a mortgage once off medication.

Other

A lack of fear of the consequences of deprescribing medication was cited by 7 of 10 GPs.

'When your systolic blood pressure is above 180 [mm Hg], or when you get all kinds of complaints [of deprescribing], but, well, you didn't have that much complaints back then [before medication was started], so that's not to be expected.' (GP-6 consulting a patient whose outcome was deprescribing)

GPs stated that they had positive expectations of deprescribing because no serious adverse events occurred in a previous study, or they assumed that patients might only experience light complaints after deprescribing.

DISCUSSION

Summary

Our study showed that patients were generally positive toward deprescribing preventive cardiovascular medication and that they relied on the information and expertise of their GP to determine whether deprescribing was justified. Patients also mentioned that they feared the consequences of deprescribing. However, knowing follow-up care was available and that medication could be restarted facilitated the patients' agreement to deprescribe.

The main reason for GPs to advise deprescribing was the low CVD risk of patients when recalculated following the current guideline. The GPs also considered the impact of additional risk factors such as a positive family history for CVD, unhealthy lifestyle, and earlier advice of the specialist to continue/start medication.

Strengths and Limitations

One of the strengths of this study is its unique nonhypothetical setting. We believe that this led to the emergence of themes reflecting those themes that in day-to-day clinical practice play a role in the patient's and GP's decision to deprescribe/continue. In contrast to other deprescribing studies that focused on older adults with polypharmacy, as a result of the prerequisite of having low CVD risk to be included in the ECSTATIC trial, our study investigated a relatively young population (mean age = 55.4 years). This adds new information to the current knowledge of the deprescribing process. Furthermore, deprescribing of a specific kind of medication (ie, cardiovascular medication) is studied. This knowledge could be useful when designing implementation

plans to facilitate deprescription policies in general practice in patients with low CVD risk.

Two GPs (GP-1 and GP-4) together audiotaped 21 consultations of which the outcome was deprescription in 20 consultations. This suggests a strong positive attitude of these GPs toward deprescription, which possibly affected the statements of their patients. All GPs participating in the ECSTATIC trial were informed about their patient's (low) CVD risk. We asked GPs to select patients themselves for our study, which may have led to an underestimation of patients with a presumed negative attitude toward deprescribing. Furthermore, the patients in our study agreed to and were, therefore, willing to have a deprescribing consultation. This selection bias may in turn have led to an incomplete overview of barriers to deprescribing. Despite these methodological limitations, in our opinion, the large sample of 49 patients from 10 GPs allowed the emergence of a generalizable framework of barriers and enablers.

Comparisons With Individual Studies in Patients

Our study showed many similarities between the mentioned barriers and enablers of patients and GPs. Anderson et al[11] also concluded that there were similarities in the cited barriers and enablers in prescribers and patients when comparing their results (of barriers and enablers of prescribers) with the outcomes of the review by Reeve et al[8] (of barriers and enablers of patients). However, in our study, we found even more similarities when comparing the barriers and enablers mentioned by GPs with the barriers and enablers that Reeve et al[8] identified in patients. This discrepancy is probably caused by the fact that in our study, patients and GPs discussed real deprescribing of medication, and they were able to react to the barriers and enablers mentioned, whereas both reviews included studies regarding (hypothetical) medication deprescribing/continuation. Additionally, we believe that having investigated nonhypothetical consultations, our findings are more close to day-to-day clinical practice.

Our study supports earlier findings that patients value the opinion of their physician when considering deprescribing.[7, 15, 16] Our findings are also consistent with a study on the deprescribing of selective serotonin reuptake inhibitors; this study included patients who had actually tried or discussed deprescribing with their GP and highlighted the importance of being monitored and knowing that there was a possibility to restart their medication.[17]

The health care system in the Netherlands is funded by a combination of taxes and a state-controlled mandatory insurance for all people. Payments to physicians are combined per capita for service and are paid out-of pocket by patients themselves. A health care allowance is provided by the government for patients with lower incomes.

Patients aged 18 years and older have to pay for their own health care costs up to 350 euro a year (2013). In our study, however, reducing individual costs was never mentioned as an enabler for deprescribing, in keeping with a study by Benson and Britten[18] concerning deprescribing antihypertensive drugs. This is possibly caused by the low prices of the most commonly prescribed generic antihypertensive and lipid-lowering drugs.

Comparisons With Individual Studies in Physicians

Most GPs take preventive measures, such as blood pressure monitoring in response to a positive family history of CVD, obesity, smoking, and other risk factors.[19] Thus, it is not remarkable that in our study, GPs mentioned these patient characteristics as barriers to deprescribing.

Several themes emerging from the analysis that we added to the patient perspectives-based framework of Reeve et al[8] were actually described by Anderson et al.[11] For example, themes such as the influence of the specialist and the positive attitude of physicians toward deprescribing were already present in the framework of Anderson et al.[11] However, knowledge or skill deficits seemed to be less of a barrier to deprescribing in our study. This is probably a consequence of the fact that GPs were informed about suitability for deprescribing (ie, low CVD risk) by the researchers.

Anderson et al[11] argued that physicians needed to discuss rather than assume the patients' attitudes toward deprescribing. In this study, the GPs discussed the views of their patients adequately.

Possible Implications for Practice

In the context of implementation of a deprescribing policy of preventive cardiovascular medication in general practice, we believe, on the basis of our results, that a consultation aiming at deprescribing is not necessarily time-consuming and should be a patient-centered discussion. Based on their specific cardiovascular risk management expertise and individual knowledge of the patient involved, GPs should address all probable consequences of deprescribing, ensuring that patients make an informed decision. If necessary, they should stress that regular follow-up and the possibility of restarting medication is available, which will potentially reduce patients' fears.

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Table 1. Framework of Reeve et al[8] including the added barriers and enablers

Category	Theme	Barrier (-) or enabler (+)
Appropriateness	Medication is currently necessary/ beneficial for condition	-
	Medication is necessary/beneficial for condition in the short term[d]	-
	Blood pressure well-controlled in the end[b]	-
	Hope for future benefit[s]	-
	Many risk factors and therefore hope for future benefits when taking medicationd	-
	Psychological benefits of taking the medication (empowerment)[b]	-
	Lack of suitable alternative/unwillingness to try alternatives[c]	-
	Beliefs about lack of ability to continue/sustain alternative treatments	-
	Desire for increased dose of medication[c]	-
	Mistrust/scepticism of recommendation to cease	-
	Acceptance of medical condition and therefore need for medication[b]	-
	Lack of negatives[b]	-
	Experiencing side effects	+
	Fear for side effects	+
	Medication is not necessary	+
	Limited number of risk factors	+
	Nonsmoker[d]	+
	Good activity level[d]	+
	Blood pressure well-controlled	+
	Lack of efficacy	+
	Fear of addiction/dependency[b]	+
	Considering alternative treatment option	+
	Advising alternative treatment option[d]	+
	Preference for lifestyle intervention over medication[d]	+
	Unsure about continued need	+

	Mistrust of prescriber who started the medication[c]	+
	General positive attitude toward ceasing	+
	Benevolent toward goal of research[b]	+
	Mistrust of pharmaceutical industry[d]	+
Fear	Psychological issues related to cessation/ non-specific fears	-
	Fear of return of condition	-
	Fear of withdrawal effects[b]	-
	Fear for CVD/death[b]	-
Process	Lack of primary care physician support/time[b]	-
	Unknown how to cease/conflicting information	-
	Lack of ongoing support needed[c]	-
	Need for appropriate timing for cessation	-
	Knowledge that there are possibilities to handle negative effects[d]	+
	Knowledge that they could restart medication	+
	Follow-up/primary care physician support available	+
	Other support available (family or processes)	+
	External factors relating to ability to cease removed[d]	+
	External factors causing hypertension removed[b]	+
	Action planning[b]	+
	Withdrawing medication step-by-step	+
Influences	Previous bad experiences with stopping	-
	Influence of primary care physician/family/friends[b]	-
	Influence specialist	-
	Family history positive for condition	-
	Family history negative for condition[d]	+
	Primary care physician[b]	+
	Other advice[c]	+

Dislike	Psychological benefits of ceasing[b]	+
	Inconvenience (including cost)[c]	+
	Feeling of unfairness having to take medication[b]	+
	General dislike of taking medication	+
	General dislike of prescribing medication[d]	+
	General dislike of taking tablets	+
	Medications are unnatural[b]	+
	Stigma associated with taking medication[b]	+
	Beliefs about costs for society[b]	+
	Problem getting a mortgage[b]	+
Other	Pragmatic considerations[b]	-
	Habit[b]	-
	Not wanting to have one's mind occupied with tapering[c]	-
	Guilt related to depriving loved ones of something that might work[c]	-
	Inconvenience (including cost)[b]	-
	Lack of fear of consequences of stopping	+
	Concern about compatibility of drugs[c]	+

Barriers and enablers written in italics were added to the existing framework of Reeve et al. [8]; * barriers and enablers not mentioned by patients in this study; ** barriers and enablers not mentioned by GPs in this study; *** barriers and enablers both patients and GPs did not mention in this study.

CHAPTER 5

Understanding deprescribing of preventive cardiovascular medication: a Q-methodology study in patients

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ABSTRACT

Background

Patients with low cardiovascular disease (CVD) risk potentially use preventive cardiovascular medication unnecessarily. Our aim was to identify various viewpoints and beliefs concerning the preventive CVD management of patients with low CVD risk using pre¬ventive cardiovascular medication. Furthermore, we investigated whether certain viewpoints were related to a preference for deprescription or the continuation of preventive cardiovascular medication.

Methods

In 2015, we purposively sampled patients from the intervention arm of the Evaluating Cessation of STatins and Antihypertensive Treatment In primary Care (ECSTATIC) trial in the Netherlands for this study. Participants made Q-sorts by ranking 43 statements concerning preventive CVD management from "totally disagree" to "totally agree". These Q-sorts were analyzed using PQMethod 2.35 software. A varimax procedure presented the distinguishing viewpoints that were favored by our participants. We used group discussion quotations to underline our findings. For validation purposes, we asked participants how well each viewpoint fitted them.

Results

Of 291 invited patients, 33 participated. Thirty-one Q-sorts were analyzed. The following three viewpoints were found: 1) a controlling viewpoint, in which patients held the belief that monitoring blood pressure and cholesterol levels is important (n=13, of which seven had their medication deprescribed and six continued their medication); 2) an autonomous viewpoint, in which patients showed a dislike of medication (n=8, of which seven had their medication deprescribed and one had it continued); and 3) an afraid viewpoint, in which patients were fearful of developing CVD (n=8, of which two had their medication deprescribed and six had it continued). Seventy-four percent of the participants believed that the viewpoint to which they were assigned was a good fit.

Conclusion

Three well-discriminating viewpoints about preventive CVD management were determined. Knowing and recognizing these viewpoints is effective for general practitioners when discussing the deprescribing of preventive cardiovascular medications with patients and may be used to promote implementation of deprescription.

INTRODUCTION

According to the guidelines of many countries, patients with predicted low cardiovas¬cular disease (CVD) risk do not require medication to prevent CVD.[1-6] Nonetheless, preventive cardiovascular medication is often prescribed and used by patients with lower levels of predicted CVD risk than the actual guideline thresholds, because recommendations for drug initiation have been revised after treatment has been started.[7, 8] Deprescribing these potentially inappropriate medications can reduce unnecessary adverse reactions in patients and undue medical costs. In an earlier study, we identified the barriers and enablers that patients and general practitioners (GPs) mention during consultations in which the deprescribing of preventive cardiovascular medication is discussed.[9] Patients expressed doubts about the appropriateness of their medication and seemed to rely on the information and expertise of their GP in determining whether deprescribing was justified. This finding was also observed in other studies.[10-12] Furthermore, a general dislike of medication and knowing that follow-up care was available and medication could be restarted are known to be enablers of deprescribing.[9, 13] Patients' expectations of the long-term medications they use play a role in their willingness to have their preventive medication deprescribed. Dohnhammar et al[14] reported that patients use medication to care for them¬selves above and beyond lifestyle changes alone and that they tend to overestimate the risk-lowering effects of preventive medication. Furthermore, patients and doctors balance risks and benefits of medication in a different way. For example, benefits in the short term are identified as more important to patients compared with doctors.[14] Patients' views on depre¬scribing their medication can thus be different than their physicians' views, but patient viewpoints could influence the implementation of preventive CVD management. Therefore, our objective was to identify various viewpoints and beliefs in patients with low CVD risk using preventive cardiovascular medication concerning preventive CVD management. Hence, we performed a Q-methodological study in patients with low CVD risk who had discussed deprescribing their preventive cardiovascular medication with their GP.

METHODS

Q-methodology

To investigate the viewpoints of patients with low CVD risk concerning their preventive CVD management, a Q-methodological study was conducted. Q-methodology combines the strengths of both qualitative and quantitative methods, which enables the conversion

of subjective perspec-tives into an objective outcome.[15] Although Q-methodology does not claim to identify viewpoints that are consistent within individuals across time, it is expected that viewpoints should show some degree of consistency over time. Hence, for the possible future implementation of a deprescribing policy, Q-methodology seems to be an appropriate way to investigate whether certain viewpoints are related to a preference for deprescription or for the continuation of preventive cardiovascular medication.[15] In contrast to quali¬tative analyses, Q-methodology focuses on groups instead of individuals, and therefore on the variety of viewpoints instead of on the viewpoint of the majority. It focuses on similarities and differences in a study population, resulting in various viewpoints or patterns of thought that specify a given population. The method consists of the following four steps, which we will further describe: 1) the determination of the concourse and generation of a Q-set, 2) the generation of a P-set (study population), 3) performing the Q-sorts, and 4) factor analysis and interpretation.

Q-set

The Q-set consisted of statements representing the concourse, the full range of contributions in the qualitative debate, on preventive CVD management. Statements were based on the literature,[10, 11, 13] expert opinion and data from our previous study concerning the barriers and enablers that patients mention during deprescribing consultations with their GPs.[9] Researchers (CHL, NLB, and RKEP) formulated 44 statements to cover the concourse. After testing the Q-set with four patients to determine the clarity of the statements and their sufficiency in displaying different viewpoints, a final Q-set of 43 statements was established. These were randomly numbered and printed on cards.

P-set

The study population was purposively sampled from the Evaluating Cessation of STatins and Antihypertensive Treatment In primary Care (ECSTATIC) trial (NTR3493). In the ECSTATIC trial (a randomized controlled trial that started in 2012, with follow-up ending in November 2015), we evaluated whether it is cost-effective and safe to deprescribe antihypertensive and lipid-lowering drugs in primary care patients for whom medication is not recommended according to the current Dutch guideline on Cardiovascular Risk Management (Box 1). Participants from the intervention practices were offered a consultation with their GP to discuss whether to deprescribe their preventive cardiovascular medication.

Box 1. ECSTATIC trial

The ECSTATIC trial evaluates whether it is cost-effective and safe to deprescribe antihypertensive and lipid-lowering drugs in primary care patients to whom medication is not recommended according to the current Dutch guideline on Cardiovascular Risk Management. Patients without CVD were included in the ECSTATIC trial when having low CVD risk and using antihypertensive and/or lipid-lowering drugs. GPs in the intervention practices received a training providing information about this guideline and its differences with respect to the former guideline. In preparation of the deprescribing consultations, there were presented cases of fictional low CVD risk patients and they discussed these patients' suitability to have their medication deprescribed.
GPs participating in the trial sent a written invitation to their patients without CVD, using potentially inappropriate antihypertensive and/or lipid-lowering drugs. After obtaining the informed consent, the researchers determined eligibility on the basis of the patients' pretreatment 10-year risk of morbidity and mortality of CVD, using the SCORE risk function as well as their (possible) additional risk increasing factors (positive family history for CVD, obesity, decreased kidney function, and sedentary lifestyle).[1]
When, based on the combination of the risk score and additional risk increasing factors for CVD, medication was not recommended according to the current guideline Cardiovascular Risk Management, patients were considered eligible for inclusion and were advised to make an appointment for a deprescribing consultation with their GP.

We sent written invitations to all patients from the intervention practices of the ECSTATIC trial (n=291) living in and around the cities of Leiden and Alphen aan den Rijn. Based on the preferred dates, we organized five sessions: three with patients who stopped their preventive cardiovascular medication 2 years ago and who still received no preventive cardiovascular medication (the deprescription group) and two with patients who had continued or restarted preventive cardiovascular medication or who had lowered their dose of their medication during the 2-year follow-up period (the continuation group).

Q-sorts

The sorting board that patients used to rank statements followed the Q-convention of a "forced normal distribution" (Figure S1).

Individual patients were given a pile of 43 statement cards and made piles containing statements with which they agreed, disagreed, or were neutral (no opinion or irrelevant). Next, each patient ordered the statements. On the extreme left, they placed the statements they disagreed with most. Next to those statements, they placed statements they disagreed with to a lesser extent, and so on. They did the same with the statements they agreed with most, except that these were placed on the right end of the sorting board. Finally, neutral statements were ordered and placed on the empty spots of the sorting board.

Factor analysis and interpretation

We analyzed the Q-sorts with PQMethod 2.35 software and used the varimax procedure to reveal the range of viewpoints that were favored by our study population.[15] An algorithm was used to calculate how high the correlation coefficient must be and how much the correlation coefficient of the factor must differ from the correlation coefficient of the other factors to state that a person loads on to that specific factor. The patients loading on a specific factor are the patients with the most representative Q-sorts for this factor.[16] Only the Q-sorts of patients loading on a specific factor were used for subsequent calculations. For each specific factor, an "ideal Q-sort" was created, showing how a hypothetical patient loading 100% on the factor would have ranked the statements. To interpret and name the factor, we used the Z-scores of the statements in these ideal Q-sorts, as well as the presented distinguishing and consensus statements of the factors. We reported statements distinguishing between any pair of factors with a P-value <0.01 (distinguishing statements) and statements not distinguishing between any pair of factors with a P-value >0.01 (consensus statements).

After patients ranked their statements on the sorting board and their informed consent was audiotaped, we asked them to reflect on their rank ordering. Their reflections and

the following group discussions were audiotaped and used for the further interpretation of the factors. Due to a technical problem in one of the sessions, we had to leave one group discussion from the desprescription group out of our analysis.
We identified the distribution of patients from the deprescription and continuation group across the factors. A chi-square test was used to examine the significance of this distribution.
To validate the factors that resulted from the Q-methodology, we made factor descriptions highlighting the important distinguishing characteristics of the different factors. This validation questionnaire was sent to the patients. We asked them how well each factor description fitted them, using a five-point Likert scale ranging from "totally not" to "very well". The study was approved by the Medical Ethics Committee of the Leiden University Medical Center.

RESULTS

Of the 291 invited patients, 33 were willing to participate. There were no statistically significant differences between the respondents and nonrespondents with regard to age or gender. Two patients were excluded from the analysis of the Q-sorts (incomplete Q-sort and language barrier). The characteristics of the patients who performed the Q-sort (n=31) and of those who participated in the group discussions (n=28) are shown in Table 1.

Table 1. Characteristics of the patients that performed the Q-sort and of the patients that participated in the focus groups

	Q-sort patients (n=31)	Focus group patients (n=28) Netherlands Februari and March 2015=28)
Male – no. (%)	9 (29.0)	9 (32.1)
Age in years – mean (SD)	57.1 (6.8)	57.7 (6.8)
Using/used antihypertensive medication – no. (%)	18 (58.1)	16 (57.1)
Using/used lipid-lowering drugs – no. (%)	7 (22.6)	7 (25.0)
Using/used both medications – no. (%)	6 (19.4)	5 (17.9)
Deprescription group – no. (%)	17 (54.8)	13 (46.4)
Continuation group – no. (%)	14 (45.2)	15 (53.6)

Table 2 shows the consensus and distinguishing statements in the Q-set. All patients had the idea that they could do something to reduce their CVD risk, even if CVD ran in their families (statement 5). Patients placed importance on a GP with good communication skills who explained their treatment options clearly (statement 12).

'I feel that she shows interest in me as a patient and I always get a good advice, that is medically substantiated.' (60-year-old female in the continuation group)

Another patient said:

'When I go there [to the GP] I feel heard, and he takes time to explain things, and when he explains things to me, in the end, most of the time I don't even need medication, so, that's just really important to me.' (66-year-old woman in the continuation group)

They did not feel medications were unnatural (statement 6), and all patients regarded hypertension management as one of the GPs' job responsibilities (statement 7).
In addition, three distinguishable factors emerged from the Q-sorts (Table 2), explaining 52% of the variance in our data. The patients from the description and con¬tinuation groups were unequally distributed across these factors (P=0.04).

Factor 1: controlling (n=13; seven from the deprescription group and six from the continuation group)
Patients loading on this factor placed great importance on the periodical monitoring of blood pressure and cholesterol levels by their GP, whether they were using medication or not (statement 19). During group discussions, these patients expressed dissatisfaction with their GP on this point:

'For years, I've been getting these repeated prescriptions, but no one [in the general practice] has ever said to me: let's measure your blood pressure [...] well, I think that is regrettable.' (56-year-old woman in the continuation group)

If CVD ran in their families, they were more inclined to start using medication (statement 35):

'I think that when it [blood pressure] is always really high and it is familial, you are more inclined to just continue tak¬ing that medication because in that case, it is different than just having [high blood pressure], well, yes.' (66-year-old woman in the continuation

group)

For patients loading on this factor, maintaining a healthy lifestyle was something obvious.

'Being aware of what you eat, a bit of exercising, just the normal things.' (62-year-old woman in the deprescription group)

Hence, they felt that nobody should smoke (statement 34). In addition, they easily maintained a healthy lifestyle, and they never sought professional help to live (even) healthier (statements 23 and 36, respectively).

Factor 2: autonomous (n=8; seven from the deprescription group and one from the continuation group)
These patients would really appreciate living a long life without using medication, and they did not feel physically better when using medication (statements 33 and 21, respectively). Hence, they disagreed that using more and more medications comes along with growing old (statement 15). They disliked medication:

'Throw it [medication] in the dustbin, that crap.' (50-year-old woman in the deprescription group)

Furthermore, they were interested in the way that the medication worked, and they knew exactly why they did or did not use medication to lower their blood pressure or cholesterol levels (statements 18 and 13, respectively).

'I Googled like crazy, especially when it was suggested to start medication, why is that necessary, what is the matter, what are the effects [of the medication], I did it [Google] far less when stopping it [the medication] was discussed.' (54-year-old man in the deprescription group)

Having a high blood pressure did not scare them, whereas having a low cardiovascular risk was a reason for them to deprescribe preventive cardiovascular medica¬tion, even if CVD ran in their families (statements 20 and 35, respectively). In contrast to the other factors, patients loading on this factor did not have that much confidence in the decisions their GP made for them (statement 32). These patients decided for themselves whether they would or would not use medication.

'It was me [who made the decision to deprescribe]. The GP then checked whether it [deprescribing] was justified, and he said it was justified. Then I said, well, in that case I'll stop [the medication].' (64-year-old woman in the depre¬scription group)

Factor 3: afraid (n=8; two from the deprescription group and six from the continuation group)

Patients loading on this factor felt relieved when their blood pressure or cholesterol test result was in order and were afraid to develop a stroke or heart attack (statements 14 and 26).

'I'm scared I'll get a heart attack or a stroke, although I use medication, I will always have that fear.' (68-year-old woman in the continuation group)

In contrast to the other factors, these patients did not hesi¬tate to turn to professionals to help improve their lifestyle (statement 36). However, it was hard for them to change and maintain a healthy lifestyle (statement 23).

'There is nothing as hard as changing your lifestyle.' (53-year-old man in the continuation group)

They were afraid of the negative effects of the long-term use of antihypertensive and lipid-lowering drugs (statement 10).

'You take them [medications] because you think they will help you [...] what would be the negative effect in the long term, concerning my cholesterol pills that is not that clear to me.' (47-year-old man in the deprescription group)

Furthermore, they always read the information leaflet of their medications (statement 25).

Validation questionnaire

The validation questionnaire was sent to 31 patients. A total of 29 patients responded. Of these, 27 loaded onto one of three factors (Table 3). In 74% (20/27) of the cases, patients self-selected the factor they loaded on, indicating that this factor fitted them "well" or very well. Seven patients reported that more than one factor description contained elements matching their ideas.

Table 3. Patients' (n=31) reports on whether or not the three distinguishable factors that emerged from the Q-sorts fitted[a] them

Patients	Loading on factor 1 (n=13)	Loading on factor 2 (n=8)	Loading on factor 3 (n=8)	Not loading on any factor (n=2)
Fitting factor 1	10	3	2	1
Fitting factor 2	3	6	2	1
Fitting factor 3	1	0	4	0
Fitting just one factor	9	5	4	0
Fitting two factors	1	2	2	1
Non-respondents	0	1	1	1

[a]'well' or 'very well'.

DISCUSSION

With our Q-methodology study, we aimed 1) to identify the viewpoints of patients with low CVD risk concerning preventive CVD management and 2) to investigate whether certain viewpoints were related to a preference for either the deprescription or continuation of preventive cardiovas¬cular medication. We found the following three viewpoints: 1) controlling, 2) autonomous, and 3) afraid viewpoints. Patients who had their preventive cardiovascular medica¬tion deprescribed were differentially distributed across these viewpoints relative to patients who continued their medi-cation. Most of the patients loading onto the autonomous viewpoint had their medication deprescribed, and most of the patients loading onto the afraid viewpoint had it continued. Several group discussion statements reinforced the findings of our Q-methodology, and in 74% of the cases, patients self-selected the factor they loaded on as fitting them well.

Strengths and limitations

Using Q-methodology and postsort group discussions led to profound understanding of the factor arrays. The inclusion of patients who had deprescribed their medication and patients who had continued their medication ensured that different viewpoints were represented in our data. The participation grade of the study was fairly low, probably because of the fixed dates we offered for our sessions, combined with our working class population. However, as discussed by Watts and Stenner,[15] our sample size was considered sufficiently large for a Q-methodological study to reveal some of the main viewpoints that were favored by our specific study population. Moreover, our study population was similar to the nonrespondents in terms of age and gender. Because of their participation in the ECSTATIC trial, it is possible that our study population had more negative views toward preventive cardiovascular medication use than patients generally have. The outcomes might therefore not be generalizable in that respect. The goal of this Q-methodological study, however, was to identify different patterns of thought in our specific population. One of the strengths of this study is that the study population had previously discussed deprescribing with their GPs. We believe that this ensured that their views and opin¬ions were well thought-out, resulting in balanced outcomes. Furthermore, it enabled us to link the patients who had deprescribed or continued their medication with the factors we found, revealing a more defined image of the viewpoints of patients loading on these factors. This information may be helpful for implementation purposes. In addition, by asking all patients how well each factor fitted them, we were able to show that our factor description indeed represented the viewpoints of the patients within the study population.

Comparison with existing literature

Results from our Q-methodology overlap with the outcomes of several other studies. For example, similar observations had been made previously regarding the importance patients place on monitoring blood pressure and cholesterol[10, 13] (controlling and afraid), the role of stress as a cause of hypertension[10] (controlling), the search for aides in chang¬ing one's lifestyle to reduce the effects of modifiable factors that influence blood pressure and cholesterol,[10] and the fear of developing CVD[17] (afraid). It is known that a dislike of medication and a lack of confidence in its prescriber are enablers of deprescribing.[13, 18] These characteristics were shared by the patients loading on the autonomous viewpoint, and these patients were indeed more likely to have their medi¬cation deprescribed. However, the fear of side effects is also known as an enabler of deprescribing,[13] but patients loading onto the afraid viewpoint were more likely to continue their medication. This is likely because they feared CVD even more than the side effects, or because they were not able to change their lifestyle.[14]

Morecroft et al[10] found that about half of the patients with hypertension believed that appropriate antihyperten¬sive treatment involved leaving medical decisions to their GPs. Interestingly, all patients in our study population appreciated being involved in the general decision-making process. Considering the comparable age groups of both study populations, this may represent changing medical attitudes or cultural differences between patients in the UK and the Netherlands.

Practice implications

Knowing which views and thoughts patients have concerning preventive CVD management may be helpful for GPs when discussing this topic with a patient in daily practice. Furthermore, when planning to implement a deprescription strategy for inappropriate preventive cardiovascular medication, it seems appropriate to start implementation in patients who have an autonomous viewpoint because deprescribing is most likely to be successful in this group of patients. We believe that this approach to start implementation will not be very time-consuming because most GPs can clearly identify the patients who fit this profile.

CONCLUSION

The three well-discriminating viewpoints concerning preventive CVD management that emerged from our Q-methodological study (controlling, autonomous, and afraid) can be used for implementation and communication purposes in deprescribing. Table 4 shows some suggestions on how to detect patients with certain viewpoints and how to optimally communicate with them.

Table 4. Suggested approaches for general practitioners to discuss preventive cardiovascular management

Factor	Main features of the patient	Communication advice
Factor 1: Controlling	Having a healthy lifestyle is something obvious	Discuss (treatment) options and explain why and how
	Periodical monitoring of blood pressure/cholesterol is important	Focus the information on monitoring of blood pressure/cholesterol
	No strong opinion regarding medication use	When the patient is indecisive, give your (expert) opinion
Factor 2: Autonomous	Knows a lot about medication and healthy lifestyles	Discuss (treatment) options and explain why and how
	Little fear for cardiovascular disease	Focus the information on pro's and cons of medication use
	Negative towards medication use	Let the patient decide for themselves, eventually
Factor 3: Afraid	Changing and maintaining a (healthy) lifestyle is hard	Discuss (treatment) options and explain why and how
	Fears cardiovascular disease	Focus the information on a healthy lifestyle and suggest professional help
	No strong opinion regarding medication use	When the patient is indecisive, give your (expert) opinion

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Table 2. Consensus and distinguishing statements in the Q-set and the values of the ideal Q-sort per factor

No	Statements	Q-sort value factor 1: Controlling	Q-sort value factor 2: Autonomous	Q-sort value factor 3: Afraid
Consensus statements				
1.	A healthy lifestyle is important to keep my CVD risk as low as possible*	3	2	4
2.	My individual CVD risk can change over time*	1	1	0
3.	My own experiences and the ones from people around me were the most important in my decision whether or not to deprescribe the medication for my blood pressure/ cholesterol level*	0	-1	-1
4.	Medications for blood pressure/ cholesterol level are very safe in comparison to other kinds of medications*	-1	-1	0
5.	If CVD runs in your family, you can do very little to prevent developing CVD yourself**	-2	-2	-2
6.	Medications are unnatural**	0	0	-1
7.	I feel a bit ashamed when I come to my GP for my blood pressure; he does not have much time and should help patient who are really ill**	-2	-3	-4
8.	I fear(ed) for side effects of blood pressure/cholesterol level lowering medication*	-1	0	-1

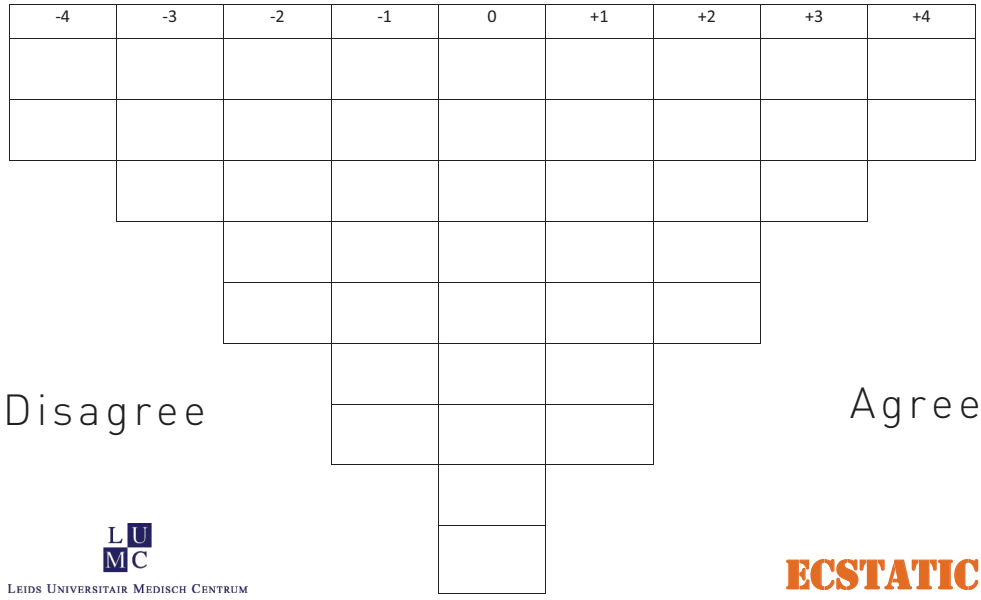
9.	I would rather use medication than change my lifestyle to reduce my CVD risk*	-4	-4	-3
10.	I am afraid that long-term use of medication for my blood pressure/ cholesterol level will have negative effects on me*	0	0	1
11.	It is important that I can communicate well with my GP*	2	3	2
12.	It is important that my GP clearly explains why I need a certain treatment, what the options are and how the medication works**	4	3	3
Distinguishing statements				
13.	I understand well why I do or do not use medication for high blood pressure/cholesterol level	2	4***	1
14.	I feel relieved when my cholesterol level is ok when it is checked	1	1	4***
15.	Using more and more medications just accompanies getting older	-2	-3	0***
16.	I know which food is healthy and will help me lowering my cholesterol level	1	4***	1
17.	If I experience less stressful events my blood pressure will be lower as well	2	2	0***
18.	I am interested in the mechanisms of different medications for high blood pressure	0	1	-1***
19.	It is important that my GP keeps monitoring my blood pressure, whether I use medication or not	4***	0***	2***
20.	It is scary to walk around having a high blood pressure	3***	-2***	2***

21.	I feel physically better when I use medication for my blood pressure or cholesterol level	0	-4***	0
22.	I do not make decisions concerning medication use alone, but together with my partner/family/friends	-2	0	-2***
23.	It is hard to maintain a healthy lifestyle	-3***	1	2
24.	I would rather increase the dose of one medication than us a combination of two medications in a lower dose	0	-1	-2***
25.	I always read the information leaflet before I start using medication	1	1	3***
26.	I am afraid of developing a heart attack or stroke	-1	0	2***
27.	Whether medication is reimbursed plays a role in my decision to use them or not	-3	-2***	-4
28.	Doctors prescribe medication too easily	-2	0***	-1
29.	Using medication for my high blood pressure gives me a feeling of control	0***	-1	-2
30.	If I have a low risk of developing CVD I do not have to use medication to prevent it	1	2***	0
31.	It is just a small effort to take medication	2	0***	1
32.	I trust my GP in making the right decisions for me	1	-1***	0
33.	My wish is to become a 100-years old without using medication	0***	3***	-1***
34.	Nobody should smoke	3***	1	1

35.	If CVD runs in my family I am more inclined to take medication	2	-1***	1
36.	I have searched for help in order to achieve a healthier lifestyle (e.g., help to stop smoking, dietary advice, advice of a sports instructor)	-3***	0***	3***
Remainder statements				
37.	Medications that lower blood pressure or cholesterol level are expensive	-1	-1	-2
38.	If my partner or good friend/colleague would advise me to continue my medication then I would definitely do that	-1	-2	-3
39.	I would appreciate it more if my GP decides for me whether or not I should use medication than I would appreciate deciding that myself	-1	-2	-1
40.	If my GP explains things to me, I am able to retell it when I am home	1	2	0
41.	Use of medications should be prevented or restricted as much as possible	0	2	1
42.	I would want to reduce my CVD risk with alternative medicine such as homeopathy or acupuncture	-1	1	0
43.	If I can stop my medication for high blood pressure/cholesterol level, I will continue until the package is empty, otherwise it would be a waste	-4	-3	-3

Notes: *Consensus statement that does not distinguish between any pair of factors with a p-value >0.01; **Consensus statement that does not distinguish between any pair of factors with a p-value >0.05; ***Distinguishing statement (the marker is placed at the Q-sort value of the factor for which the statement is a distinguishing between any pair of factors with a p-value <0.01).
Abbreviations: CVD, cardiovascular disease; GP, general practitioner.

SUPPLEMENTARY DATA



Appendix 1. Score sheet Q-methodology; the Netherlands, 2015

CHAPTER 6

Reduction of cardiovascular medication when guidelines change: personalized prediction of who will be able to stop successfully

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Submitted

ABSTRACT

Background

Patients whose indication for the use of antihypertensive and/or lipid-lowering drugs changes, may want to stop their medication. We aimed to develop a decision rule for successfully stopping preventive cardiovascular medication, thus providing the physician with individualised information and enhancing decision making concerning deprescription.

Methods

We re-analyzed data from the intervention group of our own previously published Evaluating Cessation of STatins and Antihypertensive Treatment In primary Care (ECSTATIC) study, a controlled trial in primary care in which we assessed the (cost-) effectiveness and safety of an attempt to deprescribe antihypertensive and/or lipid-lowering drugs in a population with low cardiovascular disease risk. Potential determinants of successful deprescription were found in literature and expert opinion. We assessed demographic factors, physical examination measures, laboratory results, and information from questionnaires. Potential determinants showing a univariable association with a $P<0.2$ were tested in a multivariable prediction model with generalised estimating equations in SPSS version 23. We used cross-validation for internal validation of the model.

Results

Among those in the intervention group (N=492) 135 patients successfully stopped medication (27%). We found a systolic blood pressure (SBP) ≤140, using preventive cardiovascular medication ≤10 years, using either an antihypertensive or a lipid-lowering drug, and using ≤1 class of antihypertensive drugs to predict successful stopping independently. Discrimination and calibration were reasonable, with an area under the curve of 0.70 (95% CI 0.65 to 0.75), reduced to 0.65 in cross-validation (95% CI 0.60 to 0.71). The decision rule derived from our model showed that the probability of successfully stopping medication was 45% if all four predictors were positive.

Conclusion

The highest probability of successful stopping (redundant) preventive cardiovascular medication is approximately 50% for patients who show all four factors when the decision is taken. If one of these factors is absent, probability is substantially lower. This information will help GPs to inform their patients and to improve decision making during deprescribing consultations.

INTRODUCTION

Hypertension and hypercholesterolemia are known risk factors for cardiovascular diseases (CVD).[1] Over time, the recommendations for initiation of drug treatment for hypertension and hypercholesterolemia have been subject to change.[2-7] Change of recommendations can lead to under- or overtreatment in specific populations. Overtreatment occurs for example in patients with predicted low CVD risk according to current guidelines, who are using antihypertensive or lipid-lowering drugs based on former recommendations.[8] Our previously published Evaluating Cessation of STatins and Antihypertensive Treatment In primary Care (ECSTATIC) study showed that low risk patients without a strict indication for the use of antihypertensive or lipid-lowering drugs can stop their medication safely in the short term.[9] Of all the study participants who were advised to consult their general practitioner (GP) to discuss deprescribing of their preventive cardiovascular medication however, only 27% (135/492) successfully persisted in not using the medication after two years of follow-up.[9] Known predictors of normotension after withdrawal of antihypertensive drugs and of long-term stopping of antihypertensive drugs are low systolic blood pressure (SBP), monotherapy, using antihypertensive drugs for less than 5 years, low dosage of antihypertensive drugs, and young age.[10-12] To the best of our knowledge, some studies reported predictors for short term discontinuation of lipid-lowering drugs, but no studies have looked into predictors of successful long-term withdrawal after stopping lipid-lowering drugs that might be helpful for physicians wanting to embark on a deprescribing trajectory with individual patients.[13-15]

Therefore, our aim was to develop a practical decision rule that can be easily used in daily general practice and can help patients and GPs in the decision making process by providing individualised information about the probability of successfully stopping preventive cardiovascular medication.

METHODS

We re-analyzed the data from the intervention group among participants of our own previously published ECSTATIC study. The ECSTATIC study is a cluster randomised non-inferiority controlled clinical trial in general practice in the Netherlands, with a two-year follow-up, conducted between 2012 and 2015.[9] The results of the ECSTATIC study show that an attempt to deprescribe preventive cardiovascular medication in patients with predicted low CVD risk according to the Dutch guideline for cardiovascular

risk management in general practice is safe in the short term.[3,9] The participants of the ECSTATIC study were 40 to 70 years old, using antihypertensive and/or lipid-lowering drugs ≥1 year, without a history of cardiovascular events and with a recalculated low risk of future CVD, resulting in the absence of a strict indication for preventive cardiovascular drug treatment. The intervention group of the ECSTATIC study consisted of 492 participants from 23 practice centres, who were all included in the present study. At 24 months of follow-up, participants in the intervention group self-reported whether or not they were 'currently not using medication'. Reporting 'currently not using medication' was defined as persistent successfully stopping preventive cardiovascular medication. As this was a self-reported outcome by the participants, it was blinded to information about potential predictors of successful stopping. Further methods used in the ECSTATIC study were extensively described elsewhere.[9]

Predictors

Potential determinants of successful depresciption, were found in literature, in the results of our qualitative study in the intervention group of the ECSTATIC study and in expert opinion.[10-12,16] In developing our prediction model and the resultant decision rule, we used the following variables for each patient, extracted from the electronic medical records (EMR) of the general practices at inclusion: age, sex, duration of preventive cardiovascular medication use, use of both antihypertensive and lipid-lowering drugs, and number of antihypertensive drugs used. The results of laboratory tests that were also extracted from the EMR at inclusion were: low-density-lipoprotein (LDL) cholesterol, total cholesterol, and glomerular filtration rate. All variables considered as potential determinants of successful deprescription are summarized in Table 1.

Statistical analysis

We used the data of all participants in the intervention group of the ECSTATIC study (N=492) to develop the decision rule. We assumed that at least 10 occurrences per candidate predictor in the population, were necessary to prevent overestimation of the performance of the prediction model.[17] We performed a complete case analysis, as the amount of missing data was very low (missingness for all variables was 0 % to 6.5%). We explored nonlinear relationships of all the continuous variables, by fitting quadratic, logarithmic, hyperbolic, and exponential curves. Based on R^2, a linear model provided the best fit in all cases. Interactions were unexpected and were not assessed, reducing the chance of overfitting of the prediction model.[18] We used Generalised Estimating Equations (GEEs) in SPSS version 23 to develop a multivariable prediction model, based on all variables showing a univariable association with the outcome with a $P<0.1$ and

with a P<0.2 succeedingly. One advantage of GEE models over mixed models is that the resulting decision rule can be applied to new independent single individuals, i.e. there is no cluster specific effect in the model.
We compared the discrimination of the prediction model built with all variables showing an association with a P<0.1 with that of the prediction model with all variables showing an association with a P<0.2. If variables showed strong co-linearity, they were separately assessed in different models with otherwise the same variables. Eventually, we continued with the model that performed best, based on the Area Under the Curve (AUC).
Because our aim was to develop a practical decision rule, the effect of categorisation of continuous variables on the AUC was assessed. If reduction in the AUC was believed to be small, we would continue with a dichotomised continuous variables in our final model. We further assessed our model building strategy, by applying a backward stepwise selection to our final model.
Our decision rule was derived from a further simplified final model. This simplified model was calibrated to assess how closely the predicted probability of successfully stopping of the simplified final model agreed with the observed probabilities as given by frequencies of affection status in bins of the risk score. We used cross-validation to assess the internal validity of the simplified final model. The simplified final model was tested in 23 folds (because the data consisted of 23 clusters/general practices) by leaving out each of the clusters once. In each of these folds, the model was first fitted based on data of 22 clusters and then used to calculate the predicted probabilities for the participants in the cluster that was left out. Each cluster was therefore predicted once as a hold-out sample, and these cross-validated predicted probabilities were used to calculate the cross-validated AUC in order to assess potential overfitting of the simplified final model. This procedure resulted in a decision rule with the same variables as the simplified final model, for supporting the decision to deprescribe in practice.

RESULTS

In the intervention group (N=492) 135 participants (27%) persisted in successfully stopping their preventive cardiovascular medication after two years. Of those 135 participants 115 participants had stopped antihypertensive drugs (85.2%) and 26 participants had stopped lipid-lowering drugs (19.3%), so 6 stopped both. Most participants were female (N=374, 72%) and the mean age was 55 years (Table 1). Among the 18 predictors that were considered, five showed missing values ranging from 1.0% to 6.5% with 133 to 134 participants per predictor who succeeded to successfully stop medication.

A systolic blood pressure (SBP) ≤140 mmHg, lower education level (negatively), higher education level (positively), relatively short (1 to 5 years) as well as <10 years of preventive cardiovascular medication use, using only an antihypertensive or a lipid-lowering drug (and not both), and using ≤1 class of antihypertensive drug, all were univariably associated (P<0.02) with successful deprescription (Table 2) and moved to the final model. Prediction of successful stopping with only dichotomous variables did not show a clinically relevant difference with prediction making use of both continuous (nonlinear) and dichotomous variables (AUC 0,71 versus 0,73 with a 95% CI 0.66 to 0.76, and a 95% CI 0.68 to 0.78, respectively). Sensitivity analysis using backward stepwise selection did not further improve our final model.

Based on the final model we produced a simplified final model with a AUC of 0.70 (95% CI 0.65 to 0.75) (Table 2). Participants who had a SBP ≤140 mmHg, who used preventive cardiovascular medication ≤10 years, who used either an antihypertensive of a lipid-lowering drug, and who used ≤1 class of antihypertensive drug had the highest probability of successful stopping. Internal validation using cross-validation showed a decrease in the AUC from 0.70 to 0.65 (95% CI 0.60 to 0.71) of the simplified final model (Figure 1). A practically usable decision rule with the four remaining characteristics was derived from the simplified final model and predicted successful deprescription (Table 3). Eight points or higher indicate a probability of successful stopping higher than the probability of 27% of successful stopping in general. Of 492 participants 91 (18%) had a total score ≤5 points, indicating a 0% to 10% probability of successful stopping. The highest probability of successful stopping according to the decision rule was 45%, which was present in 107 of 492 (22%) participants with a total score of 11 points.

Figure 1. Calibration plot of the simplified final model.

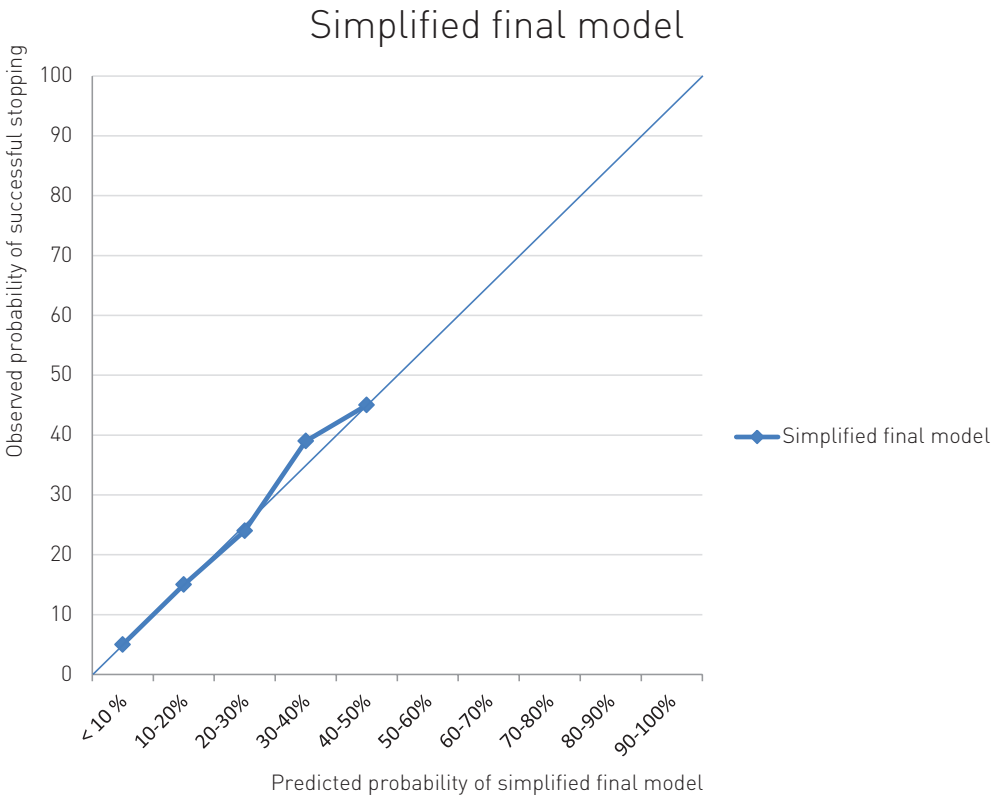

Table 3. Probability of successful stopping per category of the decision rule of the simplified final model

	Points	Probability of successful stopping
Systolic blood pressure ≤ 140 mmHg	1	
Using preventive cardiovascular medication ≤10 years	3	
Using either an antihypertensive or a lipid-lowering drug	3	
Using ≤ 1 class of antihypertensive drug	4	
Total points	≤5	0% to 10%
Total points	6 to 7	20%
Total points	8 to 10	30% to 40%
Total points	11	45%

DISCUSSION

Based on our study the four strongest predictors for successfully stopping medication in low-CVD-risk patients in general practice are: 1) having a SBP ≤140; 2) using preventive cardiovascular medication ≤10 years; 3) using either an antihypertensive or a lipid-lowering drug; and 4) using ≤1 class of antihypertensive drugs. When all four predictors are positive the probability of successfully stopping medication is almost half.

Strengths and weaknesses of study

Data of our study were very complete and close to real life practice. Other strengths of this study included the relatively large total number of participants and the number of participants who successfully stopped their preventive cardiovascular medication.
Our predicted outcome was stopping for either antihypertensive or lipid-lowering drugs (or both). Combining these two events into a single one is motivated by the fact that clinically these two different drug regimens are often discussed together during a single consultation concerning prevention of CVD. GPs can now use the developed decision rule to assess the overall prospect of stopping during such a consultation. The number of participants who persisted successfully in stopping lipid-lowering drugs was relatively low, which would make our results less reliable if we would have analysed successful stopping of lipid-lowering drugs as a separate group. However, this small number of participants also suggests that the decision rule may be less appropriate for low-CVD-risk patients only using lipid-lowering drugs.
Although participants were included based on the Dutch CVD risk score which is derived from the CVD risk score of the European guideline, the developed decision rule may not adequately predict successful stopping of preventive cardiovascular medication in patients with low CVD risk according to other CVD risk prediction calculations. Our decision rule should be further assessed in new populations and therefore should preferably only be used and documented in controlled situations first. However, AUC decreased from 0.70 to 0.65 after cross-validation, which suggests little or no overfitting and our model showed good calibration.[13] Furthermore, three of four predictors we found are known predictors for successfully stopping antihypertensive drugs.[2-4] Therefore, we do believe that we built a simple, ready-to-use tool that can be helpful in the decision-making process concerning deprescribing of preventive cardiovascular medication in low-CVD-risk patients in general practice.

Comparison with other studies and interpretation

Having a SBP ≤140, using preventive cardiovascular medication ≤10 years, and using ≤1 class of antihypertensive drugs were already recognized as potential predictors for successfully stopping antihypertensive drugs in other projects.[2-4] To the best of our knowledge, our study is the first to investigate also predictors of successful stopping lipid-lowering drugs (albeit for a small number of participants stopping lipid-lowering drugs). Predictors for discontinuation of lipid-lowering drugs have been reported, however, discontinuation is a process that in these studies is initiated by the patient, whereas we studied successful stopping after a deprescribing consultation in which patient and physician discuss whether it is appropriate to stop the medication. Despite this difference, there could be some overlap of predictors for discontinuation of lipid-lowering drugs and of successful stopping of these drugs. In fact, we found that using either an antihypertensive or a lipid-lowering drug was a predictor of successful stopping preventive medication, and using no concurrent antihypertensive drugs was already known to be a predictor of discontinuation of statin treatment.[5] Other known predictors of discontinuation of lipid-lowering drugs are for example: 1) experiencing side effects; 2) not being satisfied with their doctor's explanation of treatment; 3) age <55 years; 4) female sex; and 5) lower socio-economic status.[5-7] Although we did not measure experienced side effects, nor whether patients were satisfied with their doctor's explanation, it is not plausible that these would be predictors of successful stopping in our study, because all patients in our study used their medication ≥1 year. The chance that patients would have been included in our study if one of these predictors was positive is very low, because of the high probability that they would have already stopped the medication. We did not find that age ≤55 years and female sex were predictors for successfully stopping. Interestingly, lower socio-economic status as a predictor for discontinuation of lipid-lowering drugs on patients' own initiative seems to be in contradiction with our results concerning successfully stopping after a deprescribing consultation, where we found that a low education level was negatively associated with the probability of successfully stopping. Apart from discontinuation and successfully stopping being something different, this is probably the result of inclusion of different patient populations as well (e.g., duration of medication use at baseline). As a result of the ECSTATIC study, a structured deprescribing strategy in the overall low-CVD-risk population was not recommended because of its low gains in quality of life and costs, and because of its low effectiveness (only 27% of persistent quitters).[9] However, because of the better effectiveness in the low-CVD-risk patients in whom all four predictors of the decision rule are positive (45% persistent quitters), a structured deprescribing strategy in this population may well be cost-effective, and may be worth

further investigation.

Implications

Having a SBP ≤140, using preventive cardiovascular medication ≤10 years, using either an antihypertensive or a lipid-lowering drug, and using ≤1 class of antihypertensive drugs were all positively related with successfully stopping antihypertensive and lipid-lowering drugs.

The decision rule we developed from this simplified final model can be used by physicians and may be helpful in supporting the decision-making process during deprescribing consultations in daily practice: if all four predictors are positive, the patient has about 50% chance to successfully stop preventive cardiovascular medication over a two-year period; if one or more predictors are negative the chance of success is less than 50%.

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Table 1. Patient characteristics (n=492) and used research measurements and questionnaires

Characteristic	Missing Values, n (%)	Value	Instrument
Patients who attempted to stop their preventive cardiovascular medication	0 (0)	319 (64.8%)	
Patients who stopped preventive cardiovascular medication	0 (0)	135 (27.4%)	
10-year CVD risk score for inclusion – %[a]	0 (0)	6.7 (±4.2)	
Medication use at baseline			
Using antihypertensive drugs – no. (%)	0 (0)	431 (87.6%)	EMR, confirmed by self-report
Agents acting on the renin-angiotensin system – no. (%)	0 (0)	276 (56.1%)	EMR, confirmed by self-report
Diuretics – no. (%)	0 (0)	216 (43.9%)	EMR, confirmed by self-report
Beta blocking agents – no. (%)	0 (0)	125 (25.4%)	EMR, confirmed by self-report
Calcium channel blockers – no. (%)	0 (0)	61 (12.4%)	EMR, confirmed by self-report
Other antihypertensive drugs – no. (%)	0 (0)	2 (0.5%)	EMR, confirmed by self-report
Using lipid-lowering drugs – no. (%)	0 (0)	105 (21.3%)	EMR, confirmed by self-report
HMG CoA reductase inhibitors – no. (%)	0 (0)	101 (20.5%)	EMR, confirmed by self-report
Other lipid-lowering drugs – no. (%)	0 (0)	11 (2.2%)	EMR, confirmed by self-report

Variables assessed for prediction model			
Age – years	0 (0)	54.5 (±7.8)	EMR, confirmed by self-report
Female – no. (%)	0 (0)	347 (70.5%)	EMR, confirmed by self-report
Systolic blood pressure – mm Hg	0 (0)	140.9 (±20.8)	Omron HEM-907
LDL-cholesterol – mmol/L	3 (1.0)	3.3 (±1.1)	Local laboratory (EMR)
Total cholesterol – mmol/L	0 (0)	5.5 (±1.4)	Local laboratory (EMR)
Glomerular filtration rate (MDRDb) – ml/min/1.73m^2	16 (3.3)	77.6 (±29.5)	Local laboratory (EMR)
Body mass index – kg/height in meters^2	0 (0)	28.3 (±5.2)	seca 762 and 213
Body weight – kg	0 (0)	81.9 (±19.2)	seca 762
Smokers – no. (%)	0 (0)	38 (7.7%)	Defined by self-reporting in a questionnaire
Education level	0 (0)		Defined by self-reporting in a questionnaire
Low		79 (16.1%)	
Middle		198 (40.2%)	
High		215 (43.7%)	
Duration of preventive cardiovascular medication use	0 (0)		EMR, confirmed by self-report
1 to 5 years		180 (36.6%)	
5 to 10 years		166 (33.7%)	
>10 years		146 (29.7%)	
Alcohol consumption – glasses per day	15 (3.0)	0.95 (±1.85)	Defined by self-reporting in a questionnaire in a 7-day diary[19]
Physical activity level – minutes per day[c]	5 (1.0)	129 (±119)	short questionnaire to assess health-enhancing physical activity (SQUASH)20-22

Fruit and vegetable consumption – grams per day	0 (0)	319 (±150)	standard nutrition questionnaire of Dutch common health services[23]
Positive family history of CVD – no. (%)	32 (6.5)	207 (42.1%)	Defined by self-reporting in a questionnaire
Caucasian descent – no. (%)	0 (0)	451 (91.7%)	Defined by self-reporting in a questionnaire
Using either an antihypertensive or a lipid-lowering drug – no. (%)	0 (0)	448 (91.1%)	EMR, confirmed by self-report
Using ≤ 1 class of antihypertensive drug – no. (%)	0 (0)	290 (58.9%)	EMR, confirmed by self-report

Abbreviations: CVD denotes cardiovascular disease; EMR denotes electronic medical record.

[a] 10-year CVD risk score estimated for inclusion with baseline values of age, sex, and smoking status, and pre-treatment systolic blood pressure and pre-treatment total cholesterol/HDL-cholesterol ratio as if participants did not use preventive cardiovascular medication.

[b] Modification of Diet in Renal Disease Study equation

[c] For patients <55 years old only activities with a MET-score (Metabolic Equivalent score) ≥4 kcal/kg/hour executed ≥60 minutes on one or more days were taken into account to assess physical activity level[22]; for patients ≥55 years old only activities with a MET-score ≥3 kcal/kg/hour executed ≥30 minutes on one or more days were taken into account to assess physical activity level.[22]

Table 2. Univariable associations with successful stopping preventive cardiovascular medication and derived final models for predicting successfully stopping preventive cardiovascular medication

Characteristic	Beta	Odds ratio	95% CI	p value
Age ≤ 55 years		1.12	0.77 to 1.62	0.57
Systolic blood pressure ≤ 140 mmHg		1.41	0.97 to 2.06	0.07
LDL-cholesterol ≤ 2.5 mmol/L		1.15	0.71 to 1.86	0.57
Total cholesterol ≤ 6.5 mmol/L		1.42	0.68 to 2.99	0.35
MDRD ≤ 60 ml/min/1.73m^2		1.06	0.45 to 2.47	0.90
Body mass index (kg/height in meters^2) ≤ 27 points		1.19	0.84 to 1.69	0.33
Body weight ≤ 85 kg		0.98	0.62 to 1.55	0.93
Alcohol consumption ≤ 2 glasses per day		1.26	0.81 to 1.96	0.31
Physical activity level ≤ 150 minutes per day [a]		1.10	0.75 to 1.62	0.63
Fruit and vegetable consumption ≤ 250 grams per day		0.96	0.58 to 1.59	0.88
Female sex		0.90	0.56 to 1.43	0.65
Smoker		0.69	0.35 to 1.34	0.27
Education level				
Low		0.57	0.33 to 1.01	0.05
Middle		1.03	0.78 to 1.36	0.84
High		1.28	1.00 to 1.64	0.05
Duration of preventive cardiovascular medication use				
1 to 5 years		2.04	1.42 to 2.93	<0.01
5 to 10 years		1.07	0.70 to 1.63	0.76
>10 years		0.37	0.22 to 0.61	<0.01
Positive family history of CVD		1.12	0.71 to 1.77	0.62
Caucasian descendence		1.62	0.65 to 4.00	0.30
Using either an antihypertensive or a lipid-lowering drug		2.56	1.23 to 5.32	0.01

Using ≤ 1 antihypertensive drug		3.63	2.03 to 6.50	<0.01
Final model[b]				
Intercept	-2.534			
Systolic blood pressure ≤ 140 mmHg	0.351	1.42	0.93 to 2.17	0.10
Low education level	-0.529	0.59	0.27 to 1.27	0.18
High education level	0.002	1.00	0.74 to 1.36	0.99
1 to 5 years of preventive cardiovascular medication use	0.272	1.31	0.87 to 1.99	0.20
Using preventive cardiovascular medication ≤10 years	0.712	2.04	1.44 to 3.63	0.02
Using either an antihypertensive or a lipid-lowering drug	0.801	2.23	1.16 to 4.29	0.02
Using ≤ 1 class of antihypertensive drug	1.164	3.20	1.71 to 5.98	<0.01
Simplified final model[c]				
Intercept	-3.422			
Systolic blood pressure ≤ 140 mmHg	0.332	1.39	0.92 to 2.12	0.12
Using preventive cardiovascular medication ≤10 years	0.849	2.34	1.36 to 4.01	<0.01
Using either an antihypertensive or a lipid-lowering drug	0.913	2.49	1.35 to 4.61	<0.01
Using ≤ 1 class of antihypertensive drug	1.185	3.27	1.79 to 5.97	<0.01

Abbreviations: CVD denotes cardiovascular disease.

[a] For patients <55 years old only activities with a MET-score (Metabolic Equivalent score) ≥4 kcal/kg/hour executed ≥60 minutes on one or more days were taken into account to assess physical activity level[22]; for patients ≥55 years old only activities with a MET-score ≥3 kcal/kg/hour executed ≥30 minutes on one or more days were taken into account to assess physical activity level.[22]

[b] The predicted probability of successful stopping preventive cardiovascular medication can be calculated as follows with the final model: 1/(exp(-(-2.534 + 0.351*SBP ≤140 mmHg - 0.529*Low education level + 0.002*High education level + 0.272*1 to 5 years of preventive cardiovascular medication use +

0.712*Using preventive cardiovascular medication ≤10 years + 0.801*Using either an antihypertensive or a lipid-lowering drug + 1.164* Using ≤ 1 class of antihypertensive drug))+1).

[c] The predicted probability of successful stopping preventive cardiovascular medication can be calculated as follows with the simplified final model: 1/(exp(-(-3.422 + 0.322*SBP ≤140 mmHg + 0.849*Using preventive cardiovascular medication ≤10 years + 0.913*Using either an antihypertensive or a lipid-lowering drug + 1.185*Using ≤ 1 class of antihypertensive drug))+1).

CHAPTER 7

General discussion

GENERAL DISCUSSION

In this chapter the findings within this thesis will be discussed, mainly aiming at improving preventive cardiovascular care in patients aged 40-70 years with a relatively low cardiovascular disease (CVD) risk. Based on these findings, we will appeal to policy makers revising the Cardiovascular Risk Management (CVRM) guideline, and we will present some tools to help general practitioners (GPs) in dealing with possible overtreatment with antihypertensive and/or lipid-lowering drugs (preventive cardiovascular medication) in low-CVD-risk patients. Specific findings will be illustrated using the cases presented in the introduction.

1. The strengths of a mixed methods approach to investigate deprescribing

Deprescription of medication is a process where quantitative evidence about deprescribing (if available) is discussed in the light of more qualitative views and opinions of the patient and the physician (and sometimes also of the pharmacist). Hence, studies investigating deprescribing are often pragmatic in origin.[1-3] The goal of these pragmatic studies is to investigate the effect of deprescribing compared with an alternative strategy (e.g., usual care) within the 'real world', giving free rein to qualitative reasoning in the decision whether or not to deprescribe medication.[4, 5] The discourse of the process of deprescribing, as well as the pragmatic designs used to investigate deprescribing, cause the combination of both quantitative and qualitative research, the so-called mixed methods approach, to be very valuable in investigating deprescribing. The addition of qualitative findings to quantitative results may help to reveal why an attempt to deprescribe is or is not carried out when a certain deprescribing strategy is implemented in clinical practice.

This thesis is an example of a mixed methods approach in deprescribing research. Chapter 3 of this thesis aimed at improving the evidence in favour or against deprescribing preventive cardiovascular medication in a quantitative way. The outcome was clear, but also led to some new questions that could not be answered with the collected quantitative data. With help of two studies, one study using qualitative data of audiotaped deprescribing consultations (Chapter 4) and one study 'mixing' qualitative and quantitative methods using Q-methodology and group discussions (Chapter 5), questions that arose concerning willingness to have medication deprescribed of both patient and GP could be answered. Subsequently, the quantitative study in Chapter 6 resulted in a practical decision rule that can be used to improve the decision-making process of deprescribing. The following paragraphs in the general discussion show that these four studies together provide a broad perspective on deprescribing preventive

cardiovascular medication, and that especially the (more) qualitative Chapters 4 and 5 enrich the quantitative findings of Chapter 3 and Chapter 6.

2. No indication for initiating medication

We found that approximately 60% of the patients using antihypertensive and/or lipid-lowering drugs to prevent a first cardiovascular event, strictly speaking have no indication for using this medication according to the current Dutch CVRM guideline (Chapter 2). One of the explanations for this observation may be that former guidelines based their treatment recommendation solely on a single risk factor (hypertension or hypercholesterolemia), and that the approach of calculating total cardiovascular risk, as used in the current guidelines, is more conservative in its recommendations to start medication.[6-8] Another explanation for the possible overtreatment in low-CVD-risk patients is that GPs not only take absolute CVD risk into account, but also consider other factors that increase (relative) CVD risk in their opinion, when evaluating the need for preventive cardiovascular medication (Chapter 4). Or, maybe, GPs consider overtreatment in low-CVD-risk patients, but are hesitant to discuss deprescribing with the patient, because there is no evidence that deprescribing is safe.

2.1. Safety of deprescribing

The possible overtreatment in the low-CVD-risk population raised the question whether their preventive cardiovascular medication could be stopped safely in general practice. Our results show that deprescribing preventive cardiovascular medication in low-CVD-risk patients is safe in the short term as long as adverse effects, as well as blood pressure and cholesterol levels are monitored by the GP after stopping (Chapter 3). The reported increase in SBP of 6 mmHg and an increase of LDL-cholesterol of 0.2 mmol/L in the intervention group compared to the usual care group, are in keeping with reductions in SBP and LDL-cholesterol that medication can achieve.[9, 10] This resulted in a difference in mean increase in CVD risk between intervention and usual care group of 0.1 percentage points (95% CI -0.3 to 0.6) after two years of follow-up, implying that deprescribing is safe in the short term (non-inferiority margin 2.5 percentage points). Time and budgetary restrictions kept us from using the difference in cardiovascular event rate as primary outcome, although this would have provided us with better data to assess the safety question. Cluster randomisation and pre-randomisation were necessary to avoid contamination of the usual care group, and for this reason we also used a complete-double consent design. These choices may have led to the discrepancies in the baseline values between the usual care and the intervention group. However, had we not undertaken these measures, the risk of contamination would

have been too high, leading to the intervention being (partly) carried out in the usual care group as well. Introduction of a type 2 error leading to the flawed conclusion that deprescribing is safe, would then have been a likely threat. We tried to minimise the bias introduced by the baseline differences, by adjusting for the baseline values in the analyses.

In patients who stopped antihypertensive drugs SBP increased on average 13 mmHg, and in patients who stopped lipid-lowering drugs LDL-cholesterol increased on average 1.5 mmol/L (56 mg/dl). Most patients who stopped their medication will probably be recommended to restart the medication about 5-10 years later, because by that time they have a high-CVD-risk based on their age according to the guideline. It is not clear to what extent a rise of 13 mmHg in SBP and/or 1.5 mmol/L in LDL-cholesterol level (during about 5 to 10 years) increase the risk of developing CVD in the future in individual patients.

Unfortunately, because of the risk of contamination and poor reports of side-effects to the researchers as well as in the electronic medical records, it was impossible to collect a reliable overview of all side-effects of medication use and of deprescribing. However, serious adverse effects of deprescribing (e.g., heart failure) were not reported by the GPs, and (although underpowered) there was no difference in the number of cardiovascular events between the intervention and usual care group.

2.2. Effectiveness of deprescribing

Approximately 65% of the low-CVD-risk patients in the intervention group did an attempt to have their medication deprescribed, and a total of 27% persisted without medication after two years of follow-up (Chapter 3). Apparently, about 35% of the patients did not try to stop their preventive cardiovascular medication when a deprescribing consultation was offered to them. The findings of our qualitative study and our Q-methodology study suggest this may be explained by fear of the consequences of deprescribing, e.g. fear of hypertension, of hypercholesterolemia, and of cardiovascular events (Chapter 4 and 5). Another explanation may be the GPs' doubts about deprescribing in some cases, and the lack of negative effects of the medication patients experienced (Chapter 4).

At baseline, all included patients were using their medication for one year or longer, and, had they experienced side-effects, they probably would have changed or stopped medication already before entering the study. More than half of the patients who did an attempt to deprescribe, restarted their medication within two years. The GPs of 34 restarted patients (18% of all restarted patients) reported that hypertension, headache, nervousness/stress, and palpitations were the most common reasons for restarting medication.

2.3. Cost-effectiveness of deprescribing

Although the intervention was 70% to 80% likely to be cost-effective for a willingness-to-pay between €20,000 and €50,000[11], we would not recommend implementation of a structured deprescribing strategy in a low-CVD-risk population in general practice (Chapter 3). The main reason for our recommendation is that costs and QALYs did not differ between intervention group and usual care group after two years of follow-up, and that the effectiveness of the intervention was low (27% persistent quitters).

The cost-analysis (Table S3, Additional file 3) suggests that the intervention was indeed carried out in the intervention practices. Costs for general practice consultations in the intervention group were higher in the first year, reflecting the protocolised deprescribing consultations and follow-up consultations after stopping the medication. In addition, costs for preventive cardiovascular medication for total follow-up were lower in the intervention group, suggesting withdrawal of medication. Although there is a reduction of approximately 40% in preventive cardiovascular medication costs, this reduction is small on an absolute scale (approximately 2%), because it predominantly concerns inexpensive, off-patent medication. Furthermore, the reduction in medication costs achieved by the intervention are evened out by the extra costs for general practice consultations.

In addition, the cost-analysis clearly shows that primary care specific (i.e. general practice) costs comprise about 30% of total healthcare costs in our study population. Because the general practice care costs, nationwide, are only a small part of total healthcare costs (approximately 6 %[12]), an intervention in general practice should at least have considerable effect on healthcare costs in general practice itself, but preferably also lead to a reduction of healthcare costs outside general practice. Our study shows that a structured deprescribing strategy of preventive cardiovascular medication in low-CVD-risk patients does not result in these effects.

2.4. Factors influencing the outcome of the deprescribing consultation

When considering deprescribing of preventive cardiovascular medication, all low-CVD-risk patients take more or less the same factors into account, however, individual patients weigh these factors differently (Chapter 4 and 5). The appropriateness of medication use, fear, process (especially knowledge that medication could be restarted and that follow-up care was available), influences, and dislike all played a role in the decision-making process of deprescribing preventive cardiovascular medication as was earlier described by Reeve et al.[13] for deprescribing in general (Chapter 4). We added some new barriers and enablers of deprescribing for both patients and GPs that were specific for deprescribing of preventive cardiovascular medication in a low-

CVD-risk population. These added barriers and enablers could be roughly divided into three topics: 1) presence of risk factors for CVD (barrier or enabler of deprescribing); 2) positive attitude towards ceasing of medication (enabler); and 3) the influence of the (alleged opinion of) the specialist (barrier). In 42 of 49 (86%) of the audiotaped deprescribing consultations an attempt to deprescribe the medication was made versus 65% in the total intervention group of the ECSTATIC study. Although we asked the GPs to audiotape every deprescribing consultation, GPs were probably more inclined to ask patients to participate in this qualitative study in case they thought it was likely that the outcome of the deprescribing consultation would be confirmative. This may be reflected by the general positive attitude towards ceasing expressed during the deprescribing consultation by both patients and GPs.

The viewpoints we found with our Q-methodology study showed, for example, that for some patients their dislike of medication use resulted in a positive attitude towards deprescribing with a tendency towards deprescription (autonomous viewpoint), whereas for other patients the fear of developing CVD predominated their view, resulting in a negative attitude towards deprescribing with a tendency towards continuation (afraid viewpoint) (Chapter 5). Although 74% of the patients self-selected the viewpoint they loaded on according to our analysis, 7 of 29 (24%) patients made the remark that it was hard to choose which viewpoint fitted them best. They reported that elements of another (or all) viewpoint(s) also matched their views. The separation in the three viewpoints may thus be not that black and white. This shows how individual and complex the decision-making process of deprescribing preventive cardiovascular medication in low-CVD-risk patients is.

2.5. Predictors of successful deprescribing

We found four strong predictors for successful deprescribing over a two-year period. If all four predictors were positive, the probability of successful stopping was approximately 50%. Although this probability was substantially higher than in a random low-CVD-risk patient (who had a 27% probability of successful stopping), this chance of successful stopping was still relatively low, presumably because of reasons described above.

We considered investigating characteristics of patients who developed more extreme values of hypertension (e.g., SBP>160 mmHg) or hypercholesterolemia (e.g., LDL-cholesterol level >4 mmol/L), because this information would be helpful in the decision-making process of deprescribing. However, we believed the sample size of the group of patients in the intervention group that persistently quitted their antihypertensive medication (n=115), or persistently quitted their lipid-lowering drugs (n=26), was too

small to reliably investigate this. Especially, because the number of events in these two groups was very limited, and only a few candidate predictors could be considered.[14] However, we were able to assess the average risk of developing hypertension (SBP≥140 mmHg) and hypercholesterolemia (LDL-cholesterol level ≥2.5 mmol/L) for the total group of patients who did an attempt to have their medication deprescribed in the intervention group, which was approximately 20% to 60% and 5% to 15% higher compared to the usual care group, respectively (Chapter 3).

3. IMPLICATIONS FOR MEDICAL PRACTICE

Following our findings, preventive cardiovascular medication in low-CVD-risk patients can be safely deprescribed in those patients willing to, under surveillance of the GP. However, judgement of overtreatment in low-CVD-risk patients is complex and consists of a mixture of 'evidence about individual risk, prognosis, and treatment benefit-harm calculations, combined with the personal values and preferences inherent in any decision-making' as Moynihan et al. state so nicely.[15] Given the complex nature of defining overtreatment in low-CVD-risk patients, the deprescribing consultation should be patient-centered and different aspects to judge overtreatment should be discussed, to be sure that the patient is able to make an optimally informed decision. A proposed format for the deprescribing consultation based on the findings of this thesis is presented in Figure 1.

PROPOSED FORMAT OF DEPRESCRIBING CONSULTATION

STEP 1 The subject of deprescribing preventive cardiovascular medication is raised by the patient or the GP

STEP 2 Patient-centered consultation
- CVD risk profile
- Explore views towards CVD risk profile, medication use, and lifestyle changes
- Give information and advice when deemed necessary

STEP 3 The patient makes an informed decision about deprecribing

STEP 4 In case of an attempt to deprescribe follow-up consultations are planned

Figure 1. Proposed format for consultations in which a GP discusses deprescribing of preventive cardiovascular medication with a patient with a low 10-year cardiovascular disease risk, based on the findings of this thesis.

Abbreviations: GP denotes general practitioner; SBP denotes systolic blood pressure; LDL denotes low-density lipoprotein.

Additional information based on this thesis that can be used in Step 1:

- 60% of the patients using preventive cardiovascular medication to prevent a first cardiovascular event strictly has no indication for this medication;
- A structured deprescribing strategy in this population is not recommended;
- An attempt to deprescribe preventive cardiovascular medication in individual low CVD-risk patients under surveillance of the GP is safe.

Additional information based on this thesis that can be used in Step 2:

- GPs consider the impact of additional risk factors on the effects of deprescribing.
- Individual patients balance the risks and benefits of deprescribing differently.
- Patients appreciate the availability of follow-up care and the possibility to restart medication.
- Patients rely on the information and expertise of their GP to determine whether deprescribing is justified.
- Compared to usual care, the risk of having a SBP ≥140 mmHg after two years of follow-up was approximately 20% to 60% higher, and the risk of having a LDL-holesterol ≥2.5 mmol/L was approximately 5% to 15% higher in patients who did an attempt to have their medication deprescribed
- Predictors of successful stopping of the medication are:
    1) having a SBP ≤140;
    2) using preventive cardiovascular medication ≤10 years;
    3) using either an antihypertensive or a lipid-lowering drug (not both);
    4) using ≤1 class of antihypertensive drugs.

  When all four predictors are positive the probability of successful stopping is approximately 50%.

Additional information based on this thesis that can be used in Step 4:

- Mean SBP is 6 mmHg higher, and the total cholesterol and LDL-cholesterol levels are both on average 0.2 mmol/L higher in patients who do an attempt to have their medication deprescribed compared to usual care.
- Reasons to restart medication were: hypertension, headache, nervousness/stress, and palpitations.

Topics to discuss during a deprescribing consultation are: the CVD risk profile, assessed in a broader sense than just assessing 10-year CVD risk score according to the guideline; exploration of the patient's view about his or her risk of developing CVD and medication use; and the patient's attitude towards lifestyle changes. In this way, the GP is able to give explanations when necessary, to redress misapprehensions, and to ensure that the patient feels capable to make an informed decision based on those aspects the patient values most. With help of the findings of this thesis, the GP can forward information about the possible negative effects of withdrawal and about the chance of successful deprescribing to the patient during a deprescribing consultation.
When it is decided to attempt deprescribing of the preventive cardiovascular medication, it is advised to plan follow-up consultations. During these follow-up consultations potential adverse effects of withdrawal should be discussed, and blood pressure and cholesterol levels should be measured in order to evaluate the necessity of restarting the medication.
As an attempt to stop preventive cardiovascular medication is currently discouraged by the Dutch guideline for Cardiovascular Risk Management,[8] we would advise the policy makers who are revising the guideline at this moment, to discuss the option to deprescribe preventive cardiovascular medication in low-CVD-risk patients in a paragraph of the guideline with help of this thesis' findings.

3.1. Back to miss Bremer and mister Aalbers

How should the GP of miss Bremer and mister Aalbers deal with the possible overtreatment in these two patients coming to her for their routinely check-up? Cases like the ones of miss Bremer and mister Aalbers were presented to the GPs of the intervention practices during the ECSTATIC-workshop they received (Chapter 3). Given the discussion that followed the presentation of the cases, and based on the findings of our qualitative study, it is likely that the GP's feeling about deprescribing will be more positive in miss Bremers' case, than in mister Aalbers' case. According to the findings of the ECSTATIC study an attempt to deprescribe medication in both these patients can be performed safely, although the results of this thesis also suggest that patients like mister Aalbers are probably underrepresented in the per protocol intervention group of the ECSTATIC study (Chapter 3). However, also for patients like mister Aalbers the chance of successful deprescribing can be assessed with help of the decision rule (Chapter 6).
First we will discuss miss Bremer's case.

Just after the revision of the CVRM guideline, miss Bremer visits her GP for her routine preventive check-up. She is 50 years old and uses an ACE-inhibitor (enalapril 5 mg once daily) for three years now. Her antihypertensive drugs were initiated during a period in which she had headache complaints and a relatively high systolic as well as diastolic blood pressure found repeatedly during consultations in the past (160/90 mmHg). She has never smoked, her TC/HDL ratio is 5, her current systolic blood pressure is 135 mmHg, and she has no additional risk increasing factors (no elevated body mass index, normal kidney function, no family history of CVD, and a good physical activity level). She sees her GP during the yearly preventive check-up. Her headache has faded since, and the general practitioner questions herself whether miss Bremer could stop her antihypertensive drugs.

Things that will probably make the GP more positive towards an attempt to deprescribe in miss Bremers' case are, for example, that deprescribing is safe because of her low-CVD-risk, and that she has no additional risk factors for developing CVD. In addition, she has a relatively high chance (approximately 50%) to successfully stop her medication. Miss Bremer may have questions about the possible short- and long-term negative effects of deprescribing, that could be addressed by the GP. The short-term negative effects of deprescribing can be addressed as a result of the findings of this thesis. The knowledge that GPs gained about deprescribing preventive cardiovascular medication through this thesis, may drift their advice in case of miss Bremer more towards an attempt to have her medication deprescribed than before.
Now, we move over to the case of mister Aalbers.

Just after the revision of the CVRM guideline, mister Aalbers visits his GP for his routine preventive check-up. He is 40 years old and uses antihypertensive and lipid-lowering drugs for two years now (hydrochlorothiazide 12.5 mg, enalapril 5 mg, and simvastatin 40 mg, all once daily). At the time, the GP had advised him to start medication because of his risk factors for developing a cardiovascular disease. He is a smoker, has a TC/HDL ratio of 5 (it was 6 at the time he started his medication), an LDL-cholesterol of 2.4 mmol/L (it was 4.1 mmol/L at the time he started his medication), and his systolic blood pressure is 136 mmHg (it was 155 mmHg at the time he started his medication). Furthermore, he has a body mass index of 37 kg/$m^{2,}$ he has a sedentary lifestyle, and his kidney function is 55 ml/min/1.73m^2. His brother was 48 when he had a heart attack and his mother suffered from a stroke at the age of 62. Mister Aalbers visits his GP and asks her if he could stop his medication because he does not see or feel any benefits of it and dislikes use of medication.

Mister Aalbers brings up the subject of deprescribing himself, suggesting a positive attitude towards an attempt to deprescribe. The fact that he has many risk factors for developing CVD despite his low absolute CVD risk score, probably make the GP of mister Aalbers more reluctant towards deprescribing. The GP may feel she has to 'convince' the patient to continue the medication. Results of our qualitative study showed that the GP is capable to change the initial thoughts of the patient concerning deprescribing, resulting in the GP's preferred outcome (deprescription or continuation) of the deprescribing consultations (Chapter 4). The GP could also emphasize that if it is decided to attempt deprescribing, the chance that he (mister Aalbers) is able to successfully stop his medication is very little, 10% at maximum, based on the decision rule presented in this thesis.

4. FUTURE RESEARCH

Future studies should focus on the long-term effects of an attempt to deprescribe preventive cardiovascular medication in patients without a strict indication for preventive cardiovascular medication use. It would be interesting to investigate in which individuals or group of patients deprescribing is safe in the long-term, and in which individual or group it is not. Hypothetically, long-term safety of deprescribing could be assessed by extending the follow-up of the participants of the ECSTATIC study to investigate a difference in hazard rate of cardiovascular events between usual care patients and intervention group patients. However, an estimation showed that approximately 16000 patients should be followed for 30 years to prove a 5% difference in disease free survival between usual care and intervention group patients. Obviously, with 1067 participants included in the ECSTATIC study, this is not feasible.

An even more important field to focus on, is the field of CVD risk prediction and its usefulness in recommendations for drug treatment initiation. The SCORE equation, for example, on which the Dutch 10-year CVD risk score is based, overestimates risk on average by a factor five across all risk categories (low, medium, high), which may lead to overtreatment of patients.[16, 17] In addition, the SCORE equation was compared to the American College of Cardiology/American Heart Association (ACC/AHA) guidelines in a European cohort, and was found to be inferior to the ACC/AHA guidelines in accurately assigning statin therapy to those who would benefit.[17] Moreover, the use of population-based prediction models for recommendation of drug treatment initiation in individuals without a history of CVD is questioned.[18, 19] It is not even clear whether the use of CVD risk scores in general decreases the number of cardiovascular events.[20]

Hence, research should focus on finding the optimal way to predict development of a first cardiovascular event in individual patients, and search for the way to initiate drug treatment only in patients who really benefit from them. For CVD risk prediction on population-level, it is probably best to examine pre-existing models and recalibrate them in new target populations. In this way the effects of different prediction models can be compared and the best approach per population can be assessed.[21, 22] However, the availability of a risk score not only assessing CVD risk, but also estimating the individual's benefit of treatment, would even be better. The other way around, a similar risk score for patients already using preventive cardiovascular medication, to predict who would benefit from continuation of medication and who would be better off having the medication deprescribed, would improve the judgement of overtreatment and aid the decision-making process concerning deprescribing. Use of routinely registered data could aid the development of such personalised risk scores.[18, 19]

5. CONCLUSION

Based on the findings of this thesis, we believe that an attempt to deprescribe preventive cardiovascular medication under surveillance of the GP in those low-CVD-risk patients willing to do so, is safe in the short term. The GP is advised to monitor adverse effects, blood pressure, and cholesterol levels after withdrawal, to evaluate whether drug treatment should be restarted (Chapter 3). The judgement of overtreatment in low-CVD-risk patients is complex and should be an individualised, patient-centered process (Chapters 4 and 5). We advise the GP to let the patient's views and preferences be leading the course of a deprescribing consultation, and to give information and advice (based on this thesis' findings) when deemed necessary (Chapters 3, 4, 5, and 6).
With this thesis we aimed to improve cardiovascular preventive care in general practice for low-CVD-risk patients aged 40-70 years, in whom changing circumstances or changed guidelines resulted in losing the strict indication for (prolonged) preventive cardiovascular medication use. We trust that our findings provide both practical tools for GPs to improve the judgement of overtreatment in low-CVD-risk patients, as well as valuable information for policy makers appointed to revise the CVRM guideline.

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CHAPTER 8

Summary

SUMMARY

Cardiovascular disease (CVD) contributes highly to mortality and is the leading cause of years of life lost globally. In many countries, recommendations to reduce the prevalence of CVD are integrated in guidelines. However, although the goal of these guidelines is the same, there is no consensus about the optimal preventive care. In search for further optimisation, medical knowledge progresses, resulting in regular revisions of guidelines in this area. The latest revision of the Dutch guideline was in 2012. It was unclear what this new guideline would imply for daily practice. This thesis' research questions relate to the implications the revision of the guideline had in daily practice. To best address these research questions, a combination of quantitative and qualitative research, the so-called mixed methods approach, is used in this thesis.

1. OVERVIEW OF THIS THESIS' FINDINGS

1.1. Part 1

The findings in Chapter 2 show that the revision of the Dutch CVRM guideline had considerable impact on patient care. The revision has led to shifts in risk categories (high, medium, and low risk) in 20% of the patients using preventive cardiovascular medication (antihypertensive and/or lipid-lowering drugs). Furthermore, 12% of the patients shift in drug recommendation, notably: with unchanged initial risk factor values. In the Netherlands, following our estimates, approximately 60% of the patients using cardiovascular medication to prevent a first cardiovascular event, strictly speaking, have no indication for using this medication according to the current Dutch CVRM guideline.

1.2. Part 2

The ECSTATIC study that is described in Chapter 3 shows that, compared to usual care, mean systolic blood pressure (SBP) in patients who did an attempt to have their medication deprescribed (the intervention) is 6 mmHg higher after two years of follow-up. The total cholesterol and low-density lipoprotein (LDL) cholesterol levels are both on average 0.2 mmol/L higher compared to the usual care group. These differences in SBP and LDL-cholesterol level between intervention group and usual care group are already present after three months of follow-up.

Compared to the patients in the usual care group using antihypertensive drugs at baseline, SBP is on average 13 mmHg higher in the patients in the intervention group who had still stopped antihypertensive drugs after two years. The LDL-cholesterol level

of the patients who had stopped lipid-lowering drugs after two years of follow-up, was on average 1.5 mmol/L higher compared to the LDL-cholesterol level of the patients in the usual care group using lipid-lowering drugs at baseline. After an attempt to deprescribe preventive cardiovascular medication is made, the risk of having hypertension (SBP ≥140 mmHg) after two years of follow-up is approximately 20% to 60% higher compared to the usual care group, and the risk of having hypercholesterolemia (LDL-cholesterol level ≥2.5 mmol/L) is approximately 5% to 15% higher.
Predicted CVD risk increased by 2.0 versus in the intervention group and 1.9 percentage points in the usual care group; the difference of 0.1 (95% CI -0.3 to 0.6) fell within the pre-specified non-inferiority margin. Thus the ECSTATIC study reveals that an attempt to deprescribe preventive cardiovascular medication in general practice with predicted low-risk is safe in the short term (two years).
The most frequently reported adverse effects of deprescribing and reasons to restart medication are: hypertension, headache, nervousness/stress, and palpitations. There is no indication of serious adverse effects of deprescribing in the short term.
Furthermore, the ECSTATIC study shows that after implementation of a structured deprescribing strategy in general practice, 65% of the low-risk patients attempt to have their medication deprescribed, and that 27% of the initial intervention group is still without medication after two years.
A structured deprescribing strategy in low-risk patients in general practice is 70% to 80% likely to be cost-effective for a willingness-to-pay for one Quality Adjusted Life Year (QALY) between €20,000 and €50,000. However, implementation of a structured deprescribing strategy is not recommended, because it makes no difference in total healthcare costs, nor in quality of life of the patients. Furthermore, the effectiveness of the deprescribing strategy is fairly low (27% persistent quitters).

1.3. Part 3

Chapter 4 shows that low-risk patients, who discuss deprescribing of preventive cardiovascular medication with their GP during a deprescribing consultation fear the consequences of deprescribing. Therefore, they appreciate the availability of follow-up care and the possibility to restart medication. Chapter 4 and 5 show that patients are generally positive towards deprescribing. They rely on the information and expertise of their GP to help determine whether deprescribing is justified. Individual patients balance the risks and benefits of deprescribing differently and have different preferences with regard to an attempt to deprescribe. One of the reasons for GPs to advise deprescribing is the low-risk of the patients when recalculated following the current guideline. In addition, the GPs base their view concerning deprescribing on the presence of additional

risk factors such as a positive family history of CVD or an unhealthy lifestyle, and on the earlier advice of the specialist to continue/start medication.
Chapter 6 shows that the four strongest baseline predictors for successfully stopping preventive cardiovascular medication in low-risk patients in general practice are: 1) having a SBP ≤140 mmHg; 2) using preventive cardiovascular medication ≤10 years; 3) using either an antihypertensive or a lipid-lowering drug; and 4) using ≤1 class of antihypertensive drugs. When all four predictors are positive, the probability that a patient has still stopped the preventive cardiovascular medication after two years is approximately 50%.

2. CONCLUSION

In conclusion, this thesis shows that an attempt to deprescribe preventive cardiovascular medication in 40 to 70 year old low-risk patients under surveillance of the GP is safe in the short term. The deprescribing consultation should be patient-centered in order to optimally judge overtreatment.
Decision-making could be improved if more personalised risk scores were available, that assess an individual's CVD risk and benefit of treatment. Opportunities for future development of these personalised risk scores lie in the use of routinely registered patient data.
Overall, this thesis' findings provide both practical tools for GPs to judge overtreatment in low-risk patients, as well as valuable information for policy makers revising the CVRM guideline.

CHAPTER 9

SAMENVATTING

Wereldwijd zijn hart- en vaatziekten (HVZ) de belangrijkste oorzaak voor het verlies van levensjaren en is de sterfte aan HVZ hoog. Veelal worden aanbevelingen om het vóórkomen van HVZ te verminderen geïntegreerd in nationale richtlijnen. Ondanks het feit dat het doel van de richtlijnen uit de diverse landen hetzelfde is, is er geen consensus over de weg daar naar toe: wat is optimale preventieve zorg? Doordat de wetenschappelijke zoektocht hiernaar ononderbroken voortgaat, worden richtlijnen op het gebied preventie van HVZ met enige regelmaat herzien. De meeste recente herziening van de Nederlandse richtlijn vond plaats in 2012. Het is onduidelijk welke implicaties deze nieuwe richtlijn heeft gehad voor de dagelijkse praktijk. De onderzoeksvragen van dit proefschrift hebben betrekking op de impact van deze herziening van de richtlijn had op de dagelijkse praktijk. Om deze onderzoeksvragen zo goed mogelijk te beantwoorden is in dit proefschrift gebruik gemaakt van een combinatie van kwantitatief en kwalitatief onderzoek, de zogenaamde mixed methods approach.

1. OVERZICHT VAN DE BEVINDINGEN VAN DIT PROEFSCHRIFT

1.1. Deel 1

Hoofdstuk 2 van dit proefschrift laat zien dat de herziening van de richtlijn gevolgen heeft voor de patiëntenzorg. De herziening heeft geleid tot een verschuiving van risicogroep (hoog-, midden- of laag-risico) bij 20% van de patiënten die preventieve cardiovasculaire medicatie (antihypertensiva en/of lipiden-verlagende medicatie) gebruiken. Tegelijkertijd verandert het medicatieadvies in 12% van de gevallen, uitgaand van gelijkblijvende waarden van de risicofactoren. In Nederland heeft naar schatting ongeveer 60% van de patiënten die preventieve cardiovasculaire medicatie gebruikt, strikt genomen, géén indicatie voor het gebruik van deze medicatie volgens de huidige richtlijn.

1.2. Deel 2

De ECSTATIC studie, beschreven in Hoofdstuk 3, toont aan dat na twee jaar follow-up de systolische bloeddruk (SBD) bij patiënten die een poging doen om hun medicatie te staken (de interventie) gemiddeld 6 mmHg hoger is dan bij de patiënten die de gebruikelijke zorg ontvangen. Het totaal cholesterol en het low-density-lipoprotein (LDL) cholesterol zijn beide ongeveer 0,2 mmol/L hoger in vergelijking met de groep die

de gebruikelijke zorg ontvangt. Deze verschillen in SBD en LDL-cholesterol tussen de interventiegroep en de groep die de gebruikelijke zorg ontvangt zijn al aanwezig vanaf drie maanden follow-up.
In de groep patiënten die bij de start van het onderzoek een anithypertensivum gebruiken is de gemiddelde SBD van patiënten die na twee jaar follow-up nog steeds gestopt zijn met hun antihypertensivum 13 mmHg hoger dan die van patiënten die de gebruikelijke zorg krijgen. Het LDL-cholesterol van de groep patiënten die gestopt is met lipiden-verlagende medicatie is gemiddeld 1,5 mmol/L hoger in vergelijking met het LDL-cholesterol van de patiënten in de groep die de gebruikelijke zorg ontvangt. Indien een poging tot staken wordt gedaan is het risico op het hebben van hypertensie (SBD ≥140 mmHg) na twee jaar follow-up ongeveer 20% tot 60% hoger dan in de groep die de gebruikelijke zorg ontvangt en is het risico op hypercholesterolemie (LDL-cholesterol ≥2,5 mmol/L) ongeveer 5% tot 15% hoger.
Het voorspelde risico om binnen 10 jaar HVZ te ontwikkelen stijgt in twee jaar tijd met gemiddeld 2,0 procentpunt bij de patiënten die een poging doen de medicatie te staken, versus 1,9 procentpunt in de groep die de gebruikelijke zorg ontvangt; het verschil van 0,1 procentpunt (95% CI -0,3 tot 0,6) valt binnen de (door ons vooraf gedefinieerde) non-inferiority marge van 2,5 procentpunt. Daarmee toont de ECSTATIC studie aan dat een poging tot staken van preventieve cardiovasculaire medicatie bij patiënten met een laag risico op HVZ in de huisartspraktijk op de korte termijn (twee jaar) veilig is.
De meest gerapporteerde negatieve effecten van het staken zijn tevens de meest voorkomende oorzaken voor het herstarten van de medicatie, te weten: hypertensie, hoofdpijn, nervositeit/stress en hartkloppingen. Er zijn geen aanwijzingen gevonden voor ernstige negatieve effecten van het staken op de korte termijn.
De ECSTATIC studie laat daarnaast zien dat na implementatie van een gestructureerde *deprescribing* (het staken van medicatie)-strategie in de huisartspraktijk, 65% van de laag-risico patiënten een poging tot staken van de medicatie doet en dat 27% van de totale interventiegroep na twee jaar nog steeds geen medicatie gebruikt.
De kans dat het implementeren van een gestructureerde deprescribing-strategie onder laag-risico patiënten in de huisartspraktijk kosten-effectief is, is 70% tot 80% voor een willingnes-to-pay voor één Quality Adjusted Life Year (QALY) tussen €20.000 en €50.000. Desondanks, zou een gestructureerde deprescribing-strategie niet geïmplementeerd moeten worden, omdat het geen verschil maakt voor de totale zorgkosten en het geen verschil maakt voor de kwaliteit van leven van de patiënten. Bovendien was de effectiviteit van de deprescribing-strategie tamelijk laag (27% definitieve stoppers).

1.3. Deel 3

Hoofdstuk 4 laat zien dat laag-risico patiënten die tijdens een stopconsult het staken van de medicatie bespreken met hun huisarts hun zorgen uitspreken over de mogelijke gevolgen van het staken. Ze vinden het afspreken van vervolgconsulten en de mogelijkheid tot het herstarten van de medicatie om die reden belangrijk. Hoofdstuk 4 en 5 laten zien dat patiënten over het algemeen positieve houding hebben tegenover het staken van hun medicatie. Ze vertrouwen op de informatie en expertise van de huisarts om te bepalen of het verantwoord is om de medicatie te staken. Individuele patiënten wegen de voor- en nadelen van het staken op verschillende manieren tegen elkaar af en staan daarmee ook wisselend tegenover het staken van de medicatie. Eén van de redenen voor huisartsen om het staken van de medicatie te adviseren is het lage risico op HVZ, berekend volgens de meest recente richtlijn. Daarnaast bepalen huisartsen hun advies op basis van de aanwezigheid van additionele risicofactoren, zoals bijvoorbeeld een positieve familieanamnese voor HVZ of een ongezonde leefstijl. Ook het eerdere (of vermeende) advies van een specialist om de medicatie te continueren/starten speelt een rol in het advies dat huisartsen geven.
Hoofdstuk 6 laat de vier sterkste voorspellers voor het succesvol staken van preventieve cardiovasculaire medicatie bij laag-risico patiënten in de huisartspraktijk zien, te weten: 1) huidige bloeddruk <140 mmHg; 2) ≤10 jaar gebruik van preventieve cardiovasculaire medicatie; 3) het gebruiken van óf een antihypertensivum óf een lipiden-verlagend medicijn (en niet beide); en 4) het gebruiken van ≤1 soort antihypertensivum. Indien al deze vier voorspellers aanwezig zijn dan is de kans dat een patiënt na twee jaar nog steeds gestopt is met preventieve cardiovasculaire medicatie ongeveer 50%.

2. CONCLUSIE

Dit proefschrift laat zien dat een poging tot staken van preventieve cardiovasculaire medicatie onder begeleiding van de huisarts bij patiënten van 40 tot 70 jaar met een laag risico op het krijgen van HVZ op de korte termijn veilig is. Het is belangrijk dat de patiënt centraal staat tijdens het stopconsult omdat dit ervoor zorgt dat het beoordelen van mogelijke overbehandeling door de huisarts zo optimaal mogelijk gebeurt. Gepersonaliseerde risicoscores die het individuele HVZ-risico aangeven en inzicht geven in het nut van medicamenteuze behandeling kunnen dit beslisproces nog verbeteren. Patiëntgegevens die routinematig worden geregistreerd bieden een geschikte mogelijkheid om dergelijke gepersonaliseerde risicoscores in de toekomst te ontwikkelen.

Dit proefschrift verschaft praktische handvatten aan huisartsen voor het beoordelen van overbehandeling bij laag-risico patiënten. Daarnaast bevat het waardevolle informatie voor beleidsmakers die de richtlijn Cardiovasculair Risicomanagement herzien.

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CURRICULUM VITAE

Clare Luymes was born on May 27th 1987, in Haarlem, the Netherlands. After graduating her secondary school at Stedelijk Gymnasium Haarlem in 2005, she started studying medicine at the Leiden University Medical Centre (LUMC). In 2011 she finished medical school and started her PhD project at the department of Public Health and Primary Care of the Leiden University Medical Centre (supervisors M.E. Numans, W. de Ruijter, and R.K.E. Poortvliet). In 2013 she started the vocational training for general practitioner at the same department. In 2014 and 2015 she continued working at the general practice of P.S. Ottengraf, who was the supervisor during her first year of the vocational training for general practitioner. During those two years she was also a member and webmaster of the LOVAH Werkgroep Wetenschap. From 2016 onwards, she participated in the Journal Club for general practitioners in training, as one of the supervisors. In 2016 she won the researcher award of the Dutch cardiovascular general practitioners group (HartVaatHAG) and the Dr. Barbara Starfield Award at the North American Primary Care Research Group (NAPCRG) Conference for her research in the ECSTATIC study.