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

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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.

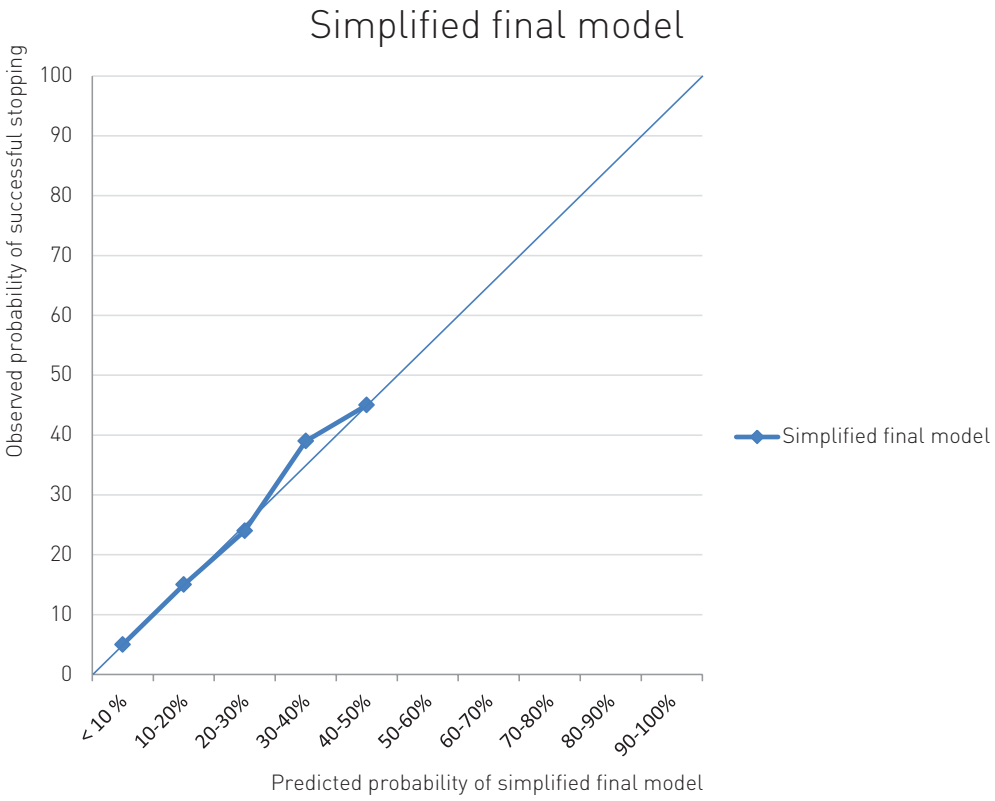

Table 3. Probability of successful stopping per category of the decision rule of the simplified final model

	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).