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

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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

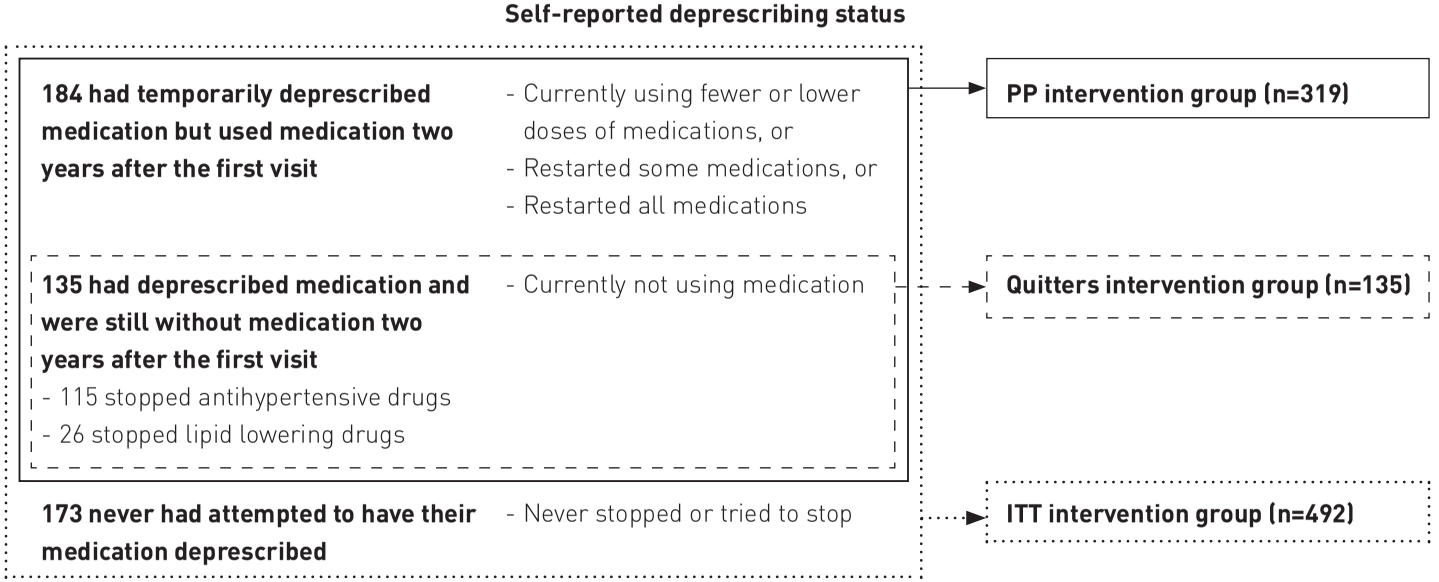

Figure 3. Deprescribing status of preventive cardiovascular medication of the 492 participants in the intervention group

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).

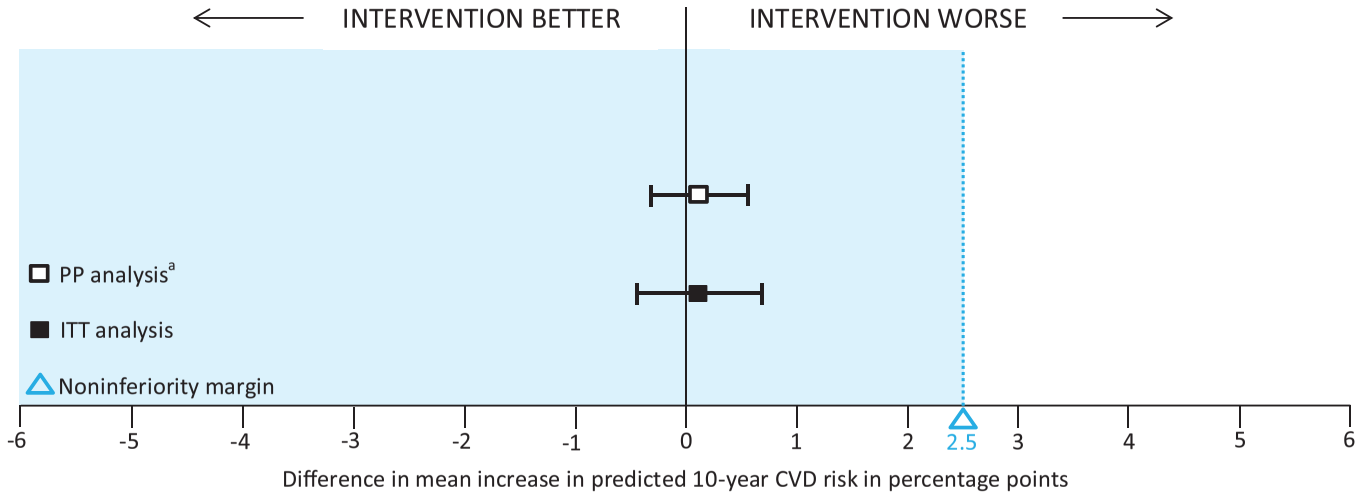

Figure 4. Intention-to-treat and per-protocol analysis of the difference in mean increase in predicted 10-year CVD risk.

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

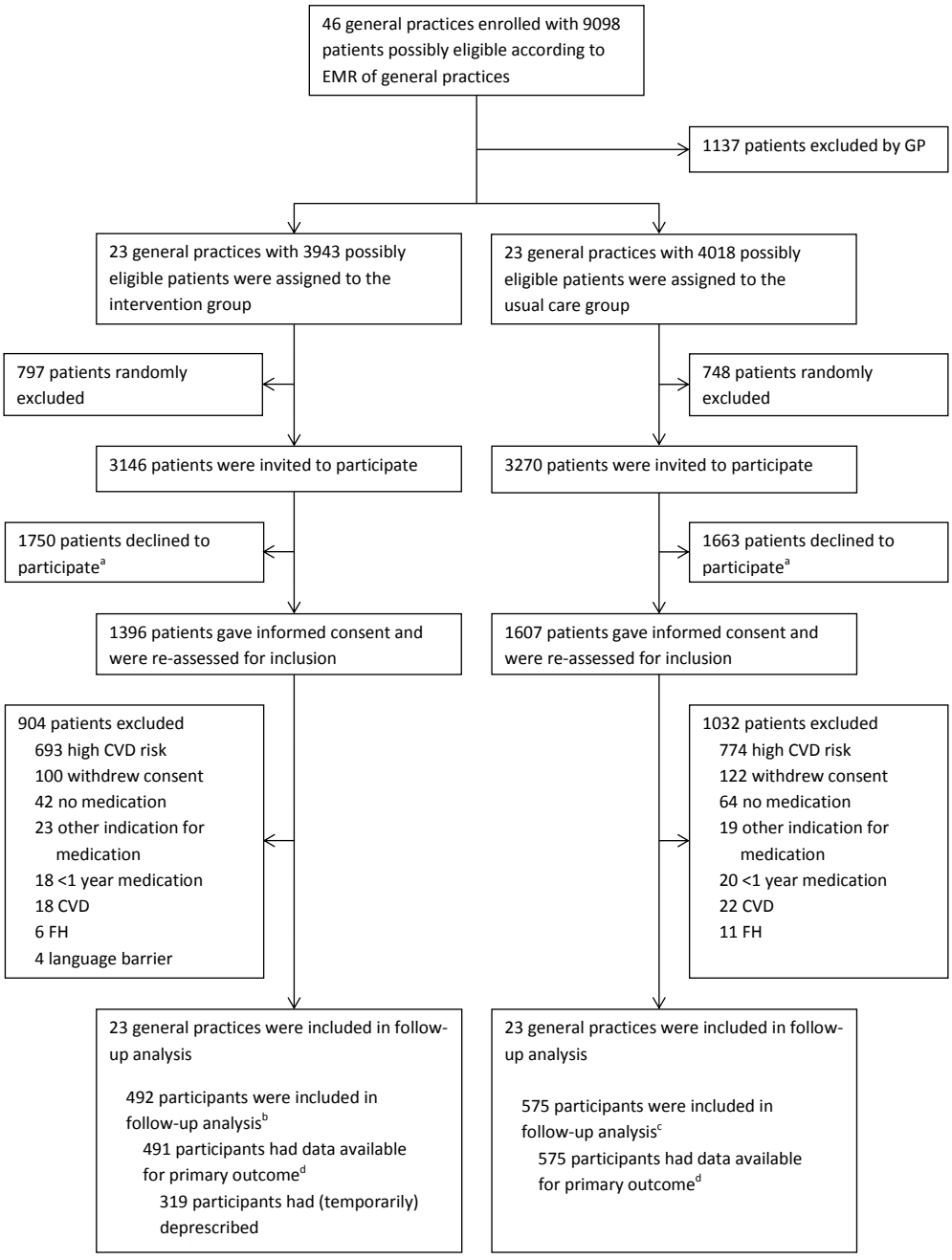
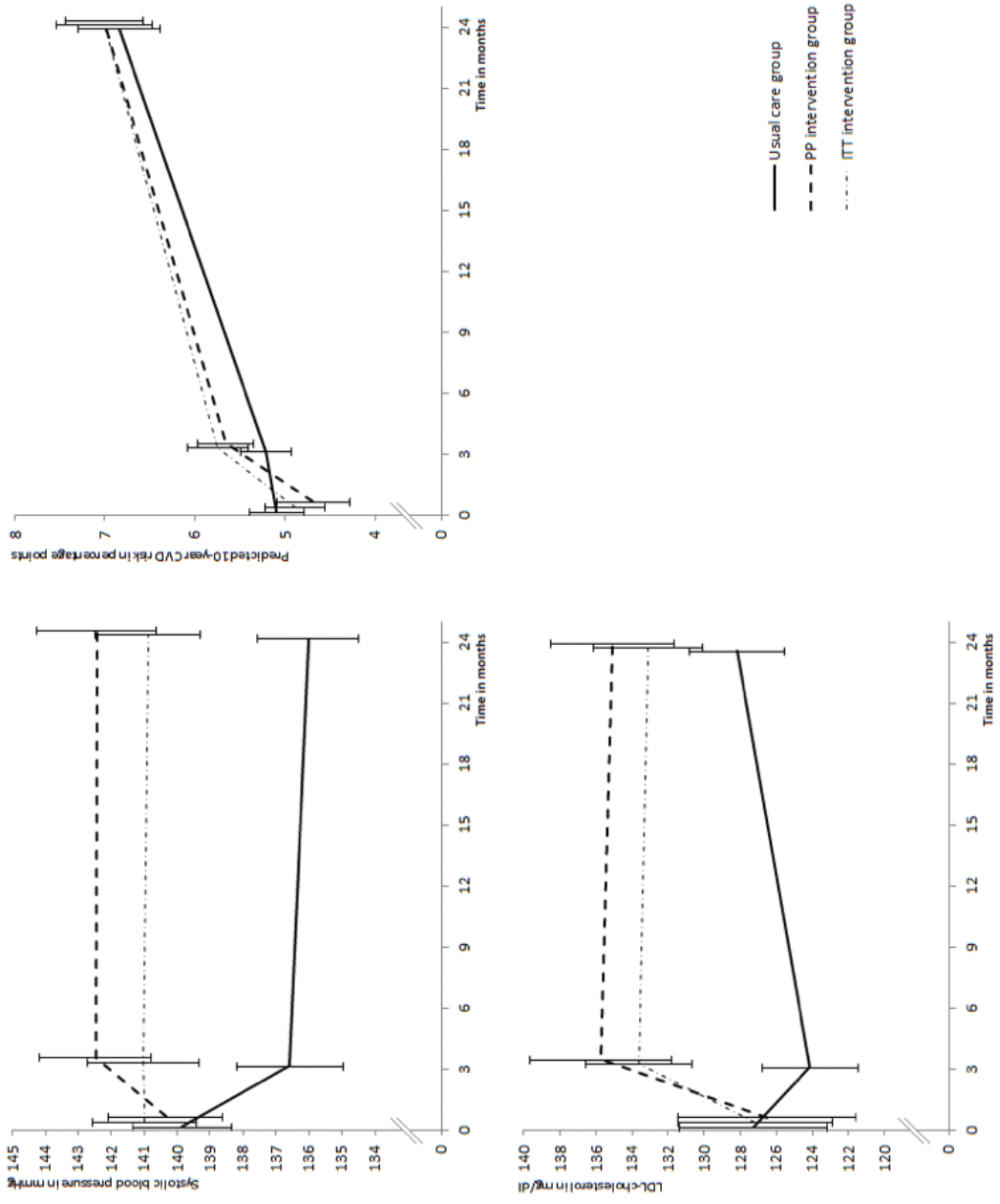

46 general practices enrolled with 9098 patients possibly eligible according to EMR of general practices
1137 patients excluded by GP
23 general practices with 3943 possibly eligible patients were assigned to the intervention group
23 general practices with 4018 possibly eligible patients were assigned 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.

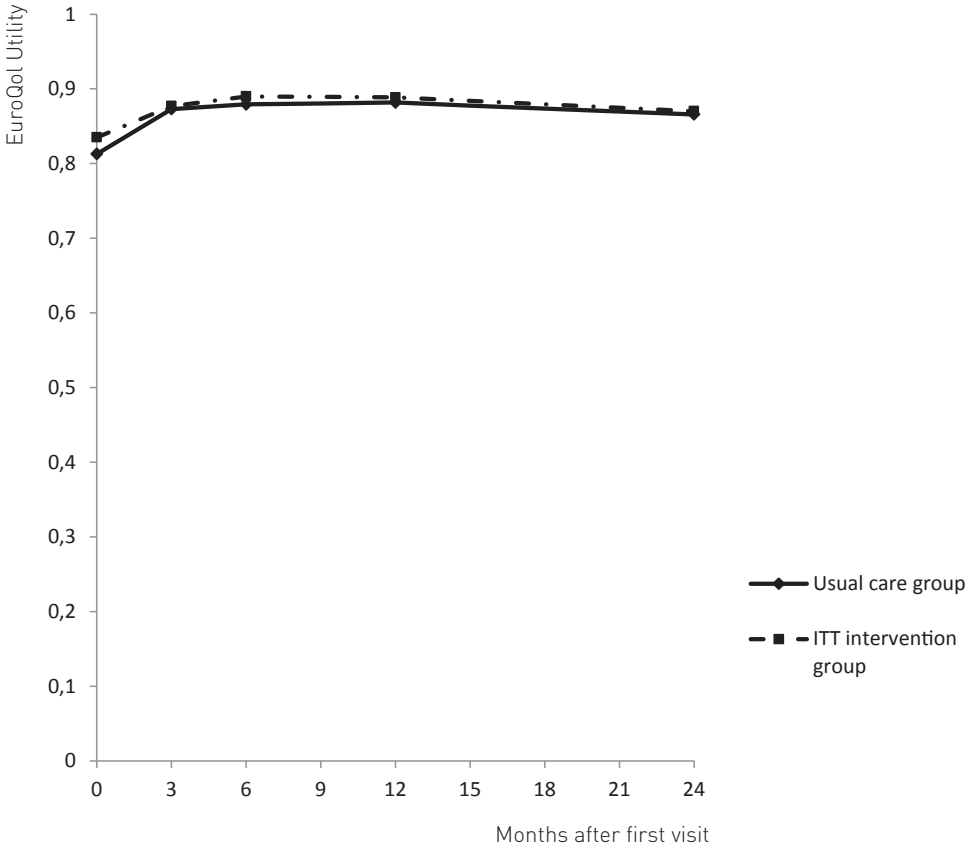


Figure S1. EuroQol Utility at t=0, t=3, t=6, t=12, and t=24 in the usual care group and the intention to treat population of the intervention group.

Abbreviations: ITT denotes intention-to-treat.

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

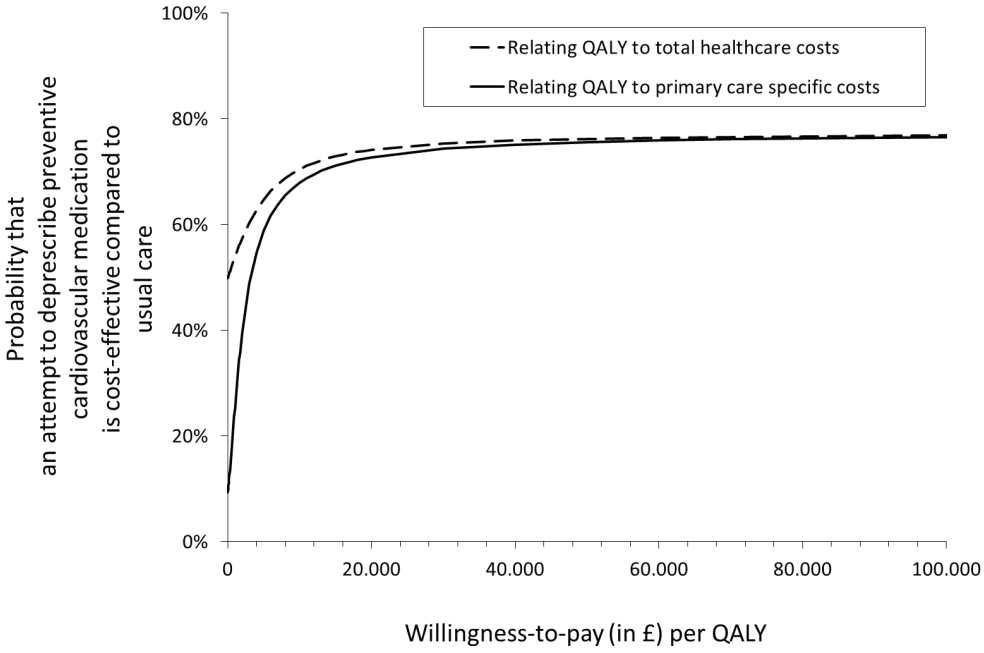
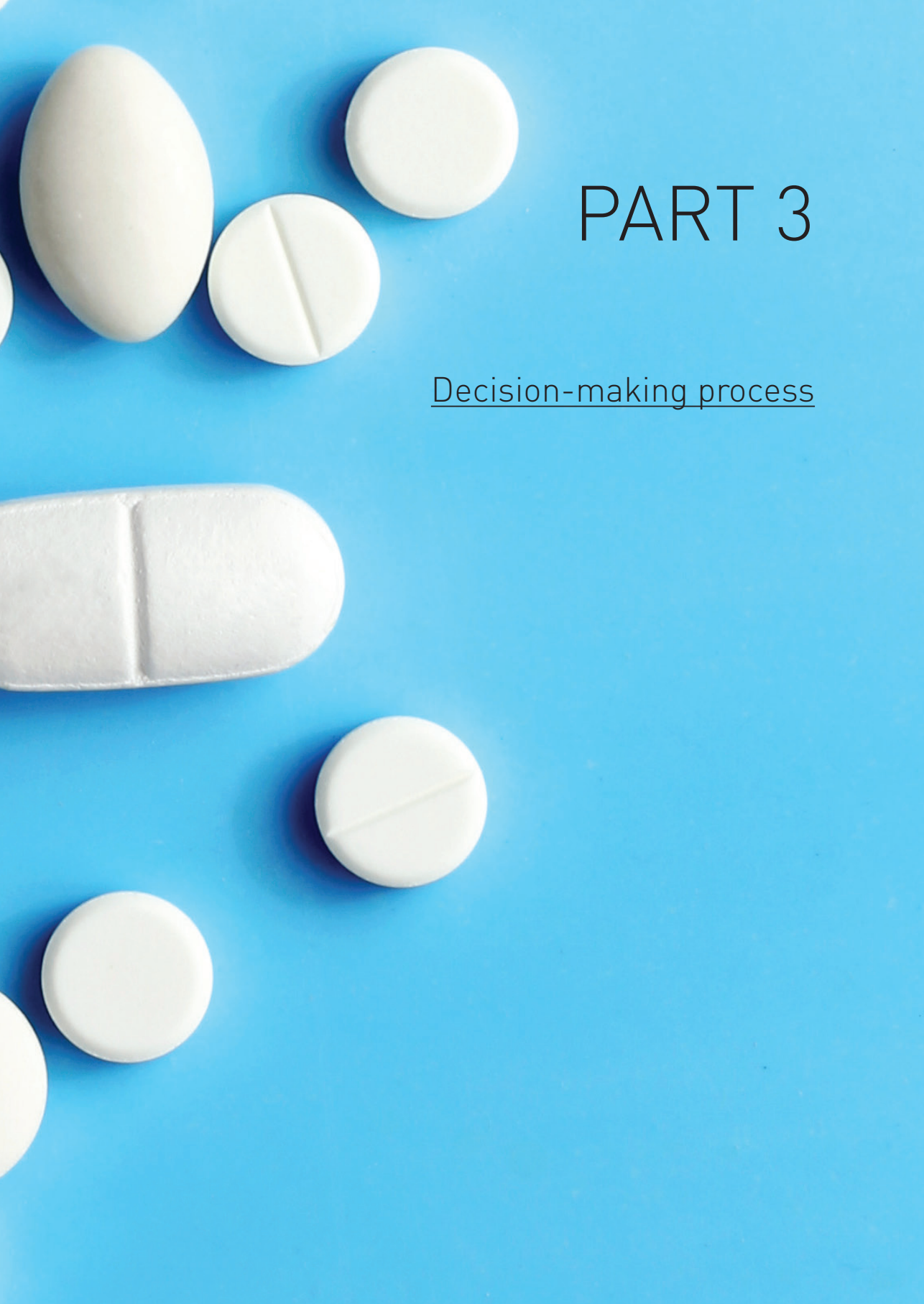


Figure S2. Cost-effectiveness acceptability curve showing the probability that an attempt to deprescribe preventive cardiovascular medication is cost-effective compared to usual care.



PART 3

Decision-making process