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

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### **Citation**

Luymes, C. H. (2018, June 7). *To stop or not to stop : deprescribing preventive cardiovascular medication in low-risk general practice patients*. Retrieved from <https://hdl.handle.net/1887/63081>

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**Issue Date:** 2018-06-07

# 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**

Deprescribing 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.<sup>1-3</sup> 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.<sup>4,5</sup> 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.<sup>6-8</sup> 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.<sup>9, 10</sup> 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<sup>11</sup>, 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 %<sup>12</sup>), 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.<sup>13</sup> 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.<sup>14</sup> However, we were able to assess the average risk of developing hypertension (SBP $\geq$ 140 mmHg) and hypercholesterolemia (LDL-cholesterol level  $\geq$ 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.<sup>15</sup> 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 deprescribing

**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  $\geq 140$  mmHg after two years of follow-up was approximately 20% to 60% higher, and the risk of having a LDL-cholesterol  $\geq 2.5$  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  $\leq 140$ ;
  - 2) using preventive cardiovascular medication  $\leq 10$  years;
  - 3) using either an antihypertensive or a lipid-lowering drug (not both);
  - 4) using  $\leq 1$  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,<sup>8</sup> 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 Bremer's 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 Bremer's 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<sup>2</sup>, he has a sedentary lifestyle, and his kidney function is 55 ml/min/1.73m<sup>2</sup>. 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.<sup>16, 17</sup> 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.<sup>17</sup> Moreover, the use of population-based prediction models for recommendation of drug treatment initiation in individuals without a history of CVD is questioned.<sup>18, 19</sup> It is not even clear whether the use of CVD risk scores in general decreases the number of cardiovascular events.<sup>20</sup>

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.<sup>21, 22</sup> 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.<sup>18, 19</sup>

## 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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