CHAPTER 2

The effect of hypertension and hypercholesterolemia screening with subsequent intervention letter on the use of blood pressure and lipid lowering drugs.

Jarir Atthobari 1, Taco B.M. Monster 1, Paul E. de Jong 2, Lolkje T.W. de Jong-van den Berg 1 for the PREVEND Study Group

1 Department of Social Pharmacy, Pharmacoepidemiology & Pharmacotherapy, Groningen University Institute for Drugs Exploration (GUIDE), the Netherlands.
2 Department of Internal Medicine, Division of Nephrology University Medical Center Groningen (UMCG), the Netherlands.

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ABSTRACT

Introduction
To evaluate the effect of a letter intervention that was send to both the participants of a population screening and their general practitioners. We also tested what predicting variables influenced the GP to actually prescribe blood pressure lowering drugs (BPLD) or lipid lowering drugs (LLD).

Methods
The study design was an observational follow-up study, in PREVEND outpatient clinic in Groningen University Hospital, The Netherlands. We used the clinical data of the 8592 subjects that participated in the first screening of the PREVEND study. Data on drug use was collected from community pharmacies. Drug use was measured the year before and after the screening with the subsequent intervention letter. As control population without intervention, we used the data from the InterAction DataBase (IADB) standardized for the population characteristics of the intervention group. The letter intervention was sent to participants who had shown after screening to have either an elevated blood pressure or plasma cholesterol, and the letter contained the advice to use a BPLD or LLD. Main outcome measures were proportion of patients prescribed BPLD and/or LLD in the year before and after the intervention, and variables that influence the GP to prescribe BPLD and LLD.

Results
Data from the community pharmacy were available from 7567 (88%) subjects. 397 participants (5.2%) received a letter with advice to start a BPLD, and 326 participants (4.3%) received a letter with advice to start a LLD. The prevalence of patients who were using BPLD and LLD before the intervention was not significantly different between the intervention and control group, 16.6 (CI 95% 15.8-17.5) vs 16.0 and 4.8 (4.4-5.3) vs 4.6 respectively. After the letter intervention, the prevalence of BPLD use was higher in the intervention group compared with the control group (19.4 [18.5-20.3] vs 17.0%), as was the prevalence of LLD use (7.1 [6.5-7.7] vs 5.4%). The same held true for the incidence of BPLD (3.4 [3.0-3.8] vs 2.5%) and LLD use (2.1 [1.8-2.4] vs 1.0%), respectively, in the year after the intervention. Univariate and multivariate analysis showed that a higher blood pressure and cholesterol level, but not the presence of other cardiovascular risk factors, were associated to with a greater percentage use of a BPLD and a LLD.
Conclusions
A population survey followed by a letter of intervention to both the patient and GP are effective to improve the use of blood pressure and lipid lowering drugs as a primary prevention in patients with hypertension and hyperlipidemia. Our therapeutic advice however, was followed only in about one of the three subjects with hypertension and one of the four subjects with hyperlipidemia. The levels of blood pressure and plasma total cholesterol are important variables influencing the GP to prescribe a BPLD and/or LLD.
CHAPTER TWO

INTRODUCTION

Hypertension and hyperlipidemia occur relatively frequent and are important risk factors for cardiovascular morbidity and mortality. These risk factors can be detected easily, and effective treatment is available [1-4]. Moreover, treatment of hypertension and hyperlipidemia reduces cardio- and cerebrovascular event rates [5-7]. However, hypertension is still frequently undiagnosed and/or untreated or inadequately treated [8-9]. Strategies to reduce the cardiovascular risk of hypertension and hyperlipidemia are focused on a better detection of the risk factor, and on improving the proportion of patients receiving adequate treatment [1,4,5].

At present many programs aim to detect the presence of cardiovascular risk factors via population screening. However, how often is detection followed by the start of active treatment with adequate follow up of the subject at risk? Little attention is paid to the way the participant and his/her general practitioner should be motivated to start adequate risk factor treatment. Various intervention strategies are being applied to influence prescription behavior with the goal to obtain a higher proportion of patients receiving treatment [10]. These interventions are targeted to either the patients, the general practitioners/health provider, or both [11-12]. The letter also can be used as intervention to improving drug use [13-16]. An intervention letter is relatively inexpensive, acceptable and successful at delivering the message.

The objective of this study is to evaluate the effect of a letter intervention that was sent to both the participants of a population screening and their general practitioners. Furthermore, we studied which factors influence the general practitioner to prescribe blood pressure or lipid lowering drugs.

METHODS

Study design and population
This study is part of the ongoing PREVEND (Prevention of REnal and Vascular ENd stage Disease) study, a large part of population of Groningen (The Netherlands). We use clinical data of the first screening of the PREVEND study cohort that was performed in 1997/1998. This study has been described in detail elsewhere [17-18]. Briefly, PREVEND is designed to study the impact of microalbuminuria on cardiovascular and renal morbidity and mortality in the general population. Pregnant women and insulin using diabetic subjects were excluded. The cohort consists of 8592 subjects aged 28 to 75 years old.
Measurements
In these participants among others, body weight and length and blood pressure were measured. Also fasting blood was drawn for measurement of plasma glucose and cholesterol and two 24-hour urine samples were collected for measurement of urinary albumin excretion. All the participants also completed a questionnaire regarding demographics, smoking status, the use of blood pressure lowering, lipid lowering and oral antidiabetic drugs, the family history on cardiovascular disease, and the history on previous myocardial infarction and cerebrovascular accident.

Body weight was measured to the nearest 0.5 kg with Seca balance scale, after removal of shoes and heavy clothing. Height was measured to the nearest 0.5 cm using a stadiometer with right angle. Body mass index (BMI) was calculated as weight (in kilogram) divided by the square of height (in meters). Systolic and diastolic blood pressure were measured on two separate occasions in supine position at the right arm every minute for 10 minutes with an automatic Dinamp XL Model 9300 series device. Blood pressure was calculated as the mean of the last two measurements of the two visits. Plasma total cholesterol and plasma glucose was measured by dry chemistry (Kodak Ectachem, Rochester, NY, USA). Urinary albumin concentration was determined by nephelometry (Dade Behring diagnostics, Marburg, Germany) with a threshold of 2.3 mg/l and intra- and inter-assay coefficients of variation of less than 2.2% and 2.6%, respectively.

Pharmacy data were collected when subjects gave permission to obtain that data from their community pharmacy. Drug use was collected for at least one year prior to the participant’s visit to PREVEND outpatient unit, and for the year after that visit. The PREVEND study was approved by the local medical ethics committee and conducted according the guidelines of the declaration of Helsinki.

Definitions
Elevated blood pressure was defined as systolic blood pressure > 160 mmHg or > 95 mmHg for diastolic. Elevated plasma cholesterol was defined as total cholesterol > 8 mmol/l or > 5 mmol/l when the subjects had suffered a previous myocardial infarction. Subjects were classified as smokers if they reported current smoking or had stopped smoking less than one year before; otherwise, they were classified as nonsmokers. Subjects were defined to have experienced a myocardial infarction, cerebrovascular attack and family history of cardiovascular disease when they answered positively on the questionnaire. Definitions were described in detail elsewhere [17-18].
**Intervention letters**

In case the participant was found to have an elevated blood pressure or plasma cholesterol on the screening and had indicated on the questionnaire not to be treated with a BPLD and/or LLD, a formal letter signed by the head of PREVEND study was sent once to both the participant and his/her general practitioner. In the letter to the general practitioner, we informed them about the result of the screening (actual blood pressure and cholesterol level as well as the presence of an abnormal plasma glucose and urinary albumin excretion) and we advised to start either a BPLD and/or a LLD. We defined this group as the intervention group.

At the same time, we sent the letter to the patients. The letters encouraged the participants to go into contact with their general practitioner to discuss the result and to have the drug prescribed. The letter to the general practitioner informed him/her about the result of that individual participant and encouraged to start with a BPLD and/or LLD, although we clearly left the final decision to do so at the general practitioner.

**The control group**

We included a control group that was obtained from the InterAction DataBase (IADB), which contains pharmacy-dispensing data of a population of approximately 200,000 subjects. This database contains, among other things, the name of drug, the date the drugs were prescribed and ATC (Anatomical Therapeutical Chemical) code. The use of over the counter drugs and in-patient prescriptions are not included.

We studied the use of BPLDs or LLDs in this control (IADB) group one-year before and after July 1st 1998. The IADB contained data of 120,836 subjects between 28 to 75 years old in the year before and of 124,695 subjects of the same age in the year thereafter. As the age and sex distribution in the control population is different from the PREVEND population, we standardized and adjusted the subjects from IADB to the PREVEND age and sex distribution. Thus, we had a control population comparable in age and sex distribution to the intervention group. The study design can be seen in figure-1.
THE EFFECT OF LETTER INTERVENTION ON DRUG USE

**Statistical analysis**
Analyses were performed using SPSS 11.0. and CIA (Confidence Interval Analysis) with Wilson Score Methods. Data are presented as number or mean with standard deviation for continuous variables and as percentage of column total for categorical variables. Differences in proportion were tested using chi-square or Fischer’s exact test. A p-value <0.05 is considered statistically significant. All p-values are two tailed. Risk estimate of the dichotomous variables is performed odds ratio and 95% confidence interval, and continuous variables were tested by t-test.

Prevalence and incidence show the proportion of the patients using the drug. The prevalence include all patients who use a BPLD or LLD, while the incidence include the patients who start to use a BPLD or LLD after the intervention while not using a BPLD or LLD 1 year before the intervention or at least 180 days (for control group).

A logistic regression model was used to determine variables related to blood pressure or lipid lowering drug prescribing.

**Figure-1. Flowchart of study letter of intervention for intervention group and control**

![Flowchart](image-url)
### Table-1. Characteristics of the PREVEND study population (N=7567), stratified by type of letter intervention

<table>
<thead>
<tr>
<th></th>
<th>Received BPLD letter</th>
<th>Received LLD letter</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Yes</td>
<td>No*</td>
</tr>
<tr>
<td>N (%)</td>
<td>397 (5.2)</td>
<td>7170 (94.8)</td>
</tr>
<tr>
<td>Male (%)</td>
<td>60.2</td>
<td>48.7</td>
</tr>
<tr>
<td>Age (years)</td>
<td>63.4 ± 8.2</td>
<td>48.7 ± 12.4</td>
</tr>
<tr>
<td>Systolic Blood Pressure (mmHg)</td>
<td>179.0 ± 13.7</td>
<td>126.4 ± 16.8</td>
</tr>
<tr>
<td>Diastolic Blood Pressure (mmHg)</td>
<td>91.1 ± 9.0</td>
<td>73.2 ± 9.0</td>
</tr>
<tr>
<td>Total cholesterol level (mmol/l)</td>
<td>6.1 ± 1.1</td>
<td>5.6 ± 1.1</td>
</tr>
<tr>
<td>Glucose level (mmol/l)</td>
<td>5.6 ± 1.8</td>
<td>4.9 ± 1.2</td>
</tr>
<tr>
<td>Body Mass Index (kg/m²)</td>
<td>28.3 ± 4.3</td>
<td>26.0 ± 4.2</td>
</tr>
<tr>
<td>Median (25th-75th) UAC (mg/l)</td>
<td>27.6 (12.6-59.6)</td>
<td>9.2 (6.3-16.6)</td>
</tr>
<tr>
<td>Smoking (%)</td>
<td>33.6</td>
<td>45.3</td>
</tr>
<tr>
<td>Cardiovascular family history (%)</td>
<td>38.7</td>
<td>33.1</td>
</tr>
<tr>
<td>Cerebrovascular accident (%)</td>
<td>2.0</td>
<td>0.9</td>
</tr>
<tr>
<td>Myocardial infarction (%)</td>
<td>5.6</td>
<td>3.6</td>
</tr>
</tbody>
</table>

*BPLD = blood pressure lowering drug; LLD = lipid lowering drug. UAC = urinary albumin concentration; All variables significant (p value <.05) different versus those that received a letter, except smoking*
RESULTS

Comparison of the PREVEND groups that received or did not receive a letter
In the PREVEND study group, 1025 subjects out of the 8592 (11.9%) were excluded because no pharmacy data were available. Altogether, 7567 subjects were eligible for analysis. 397 Participants (5.2%) received the letter with an advice to start a blood pressure lowering drug (BPLD) and 326 participants (4.3%) received the letter with the advice to start a lipid lowering drug (LLD). Three patients received both letters; they have been included in both analyses. Baseline characteristics from these subjects according to predictor variables stratified by type of intervention letter are given in Table-1.

Figure-2. Patient flow on PREVEND Study and the Blood Pressure Lowering Drugs (BPLD) letter of intervention

Blood pressure lowering drugs
156 Out of 397 (39.3%) participants who received a BPLD letter already appeared to use a BPLD according to the pharmacy data, and were thus inadequately treated (Figure-2). The other 241 that received such a BPLD letter were not using a BPLD before, and were thus correctly diagnosed as new hypertensive, that is 3.2% of the entire PREVEND cohort. 71 Out of these 241 participants (29.5%) started to use a BPLD, while the other 170 subjects (70.5%) did not. This indicates that we succeeded to reduce the percent of undiagnosed and untreated hypertension from 3.2 to 2.2%.
In the group of 7170 subjects that had not received a letter to start a BPLD, 1101 were using a BPLD already, and were thus adequately treated. Of the 6069 that were not using a BPLD before the screening, 187 (3.1%) started on blood pressure lowering therapy the year after the screening.

**Lipid lowering drugs**

Fifty-one out of the 326 (14%) participants who received a LLD letter appeared to be on such treatment already according to the pharmacy data, but were thus inadequately treated (Figure-3). The other 275 that received such a letter were not using a LLD before (3.6% of the entire PREVEND population). 73 Out of the 275 participants (26.5%) started to use a LLD, while the other 202 did not. Our screening with subsequent intervention letter resulted in reduction of undiagnosed and untreated hyperlipidemia of 3.6% to 2.7%.

In the group of 7241 subjects that had not received a letter to start a LLD, 341 were using such treatment already, and were thus adequately treated. Of the remaining 6927 who were not using a LLD before the screening, 86 (1.2%) started such therapy the year after the screening.

**Figure-3.** Patient flow on PREVEND Study and the Lipid Lowering Drugs (LLD) letter of intervention
**Comparison of the PREVEND group and the control group**

Table-2 indicates the figures on the prevalence of the use of BPLDs and LLDs in the year before and after the screening for both the PREVEND and the control population. According to the pharmacy data, 1257 of the 7579 PREVEND subjects (16.6%) used BPLD before the screening, which was not different from the prevalence of 16.0% the control population. The use of BPLDs had increased in the overall PREVEND cohort in the year after the screening to 19.4% (delta 2.8%), which was significantly higher than in the control group (17% [delta 1%; p<0.001]). The incidence of those who started BPLDs in the year after the screening, was higher in the overall PREVEND group vs the control (3.4 vs 2.5%; p<0.001).

**Table-2. Prevalence and incidence of BPLD or LLD use in the PREVEND study and control population before and after the letter of intervention**

<table>
<thead>
<tr>
<th></th>
<th>PREVEND (95% CI)</th>
<th>IADB *</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Blood Pressure Lowering Drug (BPLD)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Prevalence using BPLD before intervention</td>
<td>16.6 (15.8-17.5)</td>
<td>16.0</td>
</tr>
<tr>
<td>Prevalence using BPLD after intervention</td>
<td>19.4 (18.5-20.3)</td>
<td>17.0</td>
</tr>
<tr>
<td>Delta prevalence (after-before)</td>
<td>2.8</td>
<td>1.0</td>
</tr>
<tr>
<td>Incidence using BPLD</td>
<td>3.4 (3.0-3.8)</td>
<td>2.5</td>
</tr>
<tr>
<td><strong>Lipid Lowering Drug (LLD)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Prevalence using LLD before intervention</td>
<td>4.8 (4.4-5.3)</td>
<td>4.6</td>
</tr>
<tr>
<td>Prevalence using LLD after intervention</td>
<td>7.1 (6.5-7.7)</td>
<td>5.4</td>
</tr>
<tr>
<td>Delta prevalence (after-before)</td>
<td>2.3</td>
<td>0.8</td>
</tr>
<tr>
<td>Incidence using LLD</td>
<td>2.1 (1.8-2.4)</td>
<td>1.0</td>
</tr>
</tbody>
</table>

*standardized by age and sex*

Similarly, 365 of the 7579 PREVEND subjects (4.8%) used lipid lowering treatment the year before the screening, which was not different from the prevalence in the control group (4.6%). The use of LLDs had increased in the overall PREVEND cohort in the year after the screening to 7.1% (delta 2.3%), which was significantly higher than in control group (5.4% [delta 0.8%; p<0.001]). The incidence of LLD use in the year after the screening, was also higher in the PREVEND versus the control group (2.1 vs 1.0).
Table-3. Univariate and multivariate analysis association between predictor variables and use of BPLD or LLD after the letter intervention

<table>
<thead>
<tr>
<th>Predictor Variable</th>
<th>Odds ratio (95% Confidence Interval)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Use of BPLD</td>
</tr>
<tr>
<td></td>
<td>Univariate</td>
</tr>
<tr>
<td>Male (%)</td>
<td>1.32 (0.75-2.31)</td>
</tr>
<tr>
<td>Age (years)</td>
<td>0.99 (0.95-1.02)</td>
</tr>
<tr>
<td>Systolic Blood Pressure (mmHg)</td>
<td>1.04 (1.02-1.07) ‡</td>
</tr>
<tr>
<td>Diastolic Blood Pressure (mmHg)</td>
<td>1.05 (1.02-1.09) †</td>
</tr>
<tr>
<td>Total cholesterol level (mmol/l)</td>
<td>0.84 (0.65-1.10)</td>
</tr>
<tr>
<td>Glucose level (mmol/l)</td>
<td>1.02 (0.87-1.20)</td>
</tr>
<tr>
<td>Body Mass Index (kg/m²)</td>
<td>0.98 (0.91-1.04)</td>
</tr>
<tr>
<td>Albumin urine (mg/24hr)</td>
<td>1.00 (1.00-1.01)</td>
</tr>
<tr>
<td>Smoking (%)</td>
<td>0.68 (0.37-1.23)</td>
</tr>
<tr>
<td>Family history for cardiovascular disease (%)</td>
<td>1.33 (0.74-2.38)</td>
</tr>
<tr>
<td>Cerebrovascular accident (%)</td>
<td>4.97 (0.44-55.73)</td>
</tr>
<tr>
<td>Myocardial infarction (%)</td>
<td>1.49 (0.346-6.42)</td>
</tr>
</tbody>
</table>

BPLD: Blood pressure lowering drug; LLD: Lipid lowering drug; ‡ p<0.001, † p<0.005, * p<0.05
Variables influencing the decision to follow the therapeutic advice

Both univariate and multivariate analysis showed that the level of systolic and diastolic blood pressure contributed to the decision to start BPLDs after the intervention: the higher the blood pressure, the greater the chance that the subject used a BPLD the year after detection of the elevated pressure (Table-3). However, the presence of another cardiovascular risk factor did not contribute to the decision to start such treatment. With respect to the decision to start of a LLD we found in the analysis that only the level of plasma cholesterol, but not the level of blood pressure, neither the presence of other cardiovascular risk factors was associated with the use of a LLD the year thereafter.

DISCUSSION

We showed that the screening with subsequent intervention letter to participant and general practitioner resulted in a lowering of the percent of untreated hypertension and untreated hyperlipidemia compared with a control population. However, our therapeutic advice was only followed in about one of the three subjects with hypertension and in one of the four subjects with hyperlipidemia. In the decision to follow our advice, the general practitioner was influenced by the level of the risk factor itself, but not by the presence of other cardiovascular risk factors.

Before the screening, the prevalence of subjects using blood pressure and lipid lowering treatment was comparable in our PREVEND group as in the control group, standardized for age and sex. This indicates that the PREVEND cohort, although enriched for the presence of microalbuminuria, seems an adequate representation of the general population. The figure of about 16% for the use of BPLD and 5% for LLD are slightly higher compared to other reports in the Netherlands (10-13% for BPLD [20-21] and 2.3-3.5% for LLD) [22-23]. We found the number of new prescriptions for BPLD after the screening plus intervention letter about 35% higher than in the control group. This indicates that in our study group significantly more subjects started to use BPLD than in the control population. The number of new prescriptions for lipid lowering drugs in the PREVEND cohort was even more than twice that in the control population. Our data thus indicate that our approach of screening with the subsequent intervention letter is successful to
promote prescription behavior by the general practitioner. These data are in agreement with literature \cite{13,14}. Collins et al also showed that a letter intervention is effective to increase the number of prescriptions for dypiridamole \cite{13}. Similarly, Rascati \textit{et al.} found that an intervention letter to the general practitioner is effective to change prescribing behaviour \cite{14}. In contrast, Feder \textit{et al.} found that postal prompts to patients and their general practitioners about secondary prevention after myocardial infarction did not result in a significantly better use of lipid lowering agents and beta blockers \cite{24}. However the number of patients in that study \((n=328)\) may have been too small to detect a significant difference \cite{25}.

As far as we know, our study is the first that evaluates the effectiveness of an intervention letter in addition to a population screening. We informed both participant and general practitioner to start drug treatment. This prompted the participants to visit the general practitioner and to discuss the benefits and disadvantages of drug treatment for the established risk factor. Nevertheless, in a minority of the patients our advice to start treatment was followed, possibly due to the fact that the general practitioner in general is relatively reluctant to start drug treatment in asymptomatic subjects. Many practitioners still fail to take aggressive steps in lowering blood pressure if the patient is simply feeling well \cite{26}.

In this study we followed the criteria to start treatment according to the consensus of the general practitioners, which was at that time less strict than internationally accepted criteria (systolic pressure \(>\) 140 mmHg and diastolic pressure \(>\) 90 mmHg \cite{27}). In light of this, the percentage that received drug treatment is disappointingly low. The international guidelines also advice to start drug treatment when other cardiovascular risk factors, such as diabetes, smoking, or a positive family history for cardiovascular disease are present \cite{27-30} However, none of these factors were taken into account in the decision to start the treatment in our cohort. Only the level of the risk factor itself guided the decision, which is in accordance of data in the literature \cite{31}. The finding that the treatment advice was less frequently followed in those who were smoking suggests that patient behaviour may be an important determinant of compliance to the advice to visit the general practitioner and to start BPLD.

Our study had some shortcomings. First, the PREVEND study population was enriched for the presence of microalbuminuria. However, the prevalence of using blood pressure and lipid lowering drugs before the intervention was not different from the control group. Moreover, the general practitioner did not seem influenced by the presence of microalbuminuria in his/her decision to start drug treatment. Second, we are not aware whether the patients used BPLDs for other reasons than hypertension, such as beta blocking drugs for angina, because the
IADB has no information on diagnosis. The same holds true for the control group and cannot explain the higher incidence of blood pressure lowering drug prescriptions in the PREVEND population than in the control group after the intervention letter. This moreover, cannot explain the increase in use of lipid lowering drugs that in fact are not prescribed for another indication than lipid lowering. Third, we only have a follow up of one year after the screening, and thus can not exclude that in some participant's drug treatment was started only afterwards. This is not unexpected, as the general practitioner may first have tried other non-drug approaches to correct the elevated risk factor. We also considered that probably some patients had a raised blood pressure when attending for the study visit which was subsequently lower when rechecked by the general practitioner. However if this is the case an underestimation should occur.

Our data seem robust, as we were able to compare the effect of our screening with subsequent intervention letter in the PREVEND cohort with the prescription pattern in a large cohort in the northern of the Netherlands. This seems a justified approach as the prescription behavior before the intervention appeared comparable in both cohorts. Our data moreover are not influenced by expectations from the general practitioner, as we collected the prescription data from the pharmacies, and not via the general practitioner. The pharmacist in fact was not informed on the letter that was sent to the participant and the general practitioners. An important approach in our design was the fact that we both informed the patient and general practitioner on the benefits of using drug treatment for the risk factor. This indeed, resulted in an increase in the visits of our participants to their general practitioner [32].

In conclusion, a screening of the general population on cardiovascular and renal risk factors with subsequent letter to intervene with drug treatment in hypertension and/or hyperlipidemia shows an increase in prescribing, although definitely not optimal. The level of blood pressure and plasma cholesterol, but not the presence of other cardiovascular risk factors, influences the general practitioner to prescribe a blood pressure and/or lipid-lowering drug.
REFERENCES


